OH'S INTENSIVE CARE MANUAL

EIGHTH EDITION

ANDREW D. BERSTEN
JONATHAN M. HANDY

ELSEVIER

OH'S INTENSIVE CARE MANUAL

EIGHTH EDITION

This page intentionally left blank

OH'S INTENSIVE CARE MANUAL

EIGHTH EDITION

Edited by

Andrew D Bersten
MB BS MD FCICM

Director, Intensive Care Unit
Flinders Medical Centre;
Professor and Head
Department of Critical Care Medicine
Flinders University
Adelaide, SA, Australia

Jonathan M Handy
BSc MBBS FRCA EDIC FFICM

Consultant Intensivist
Royal Marsden Hospital;
Honorary Senior Lecturer
Imperial College London
London, UK

ELSEVIER

ELSEVIER

First edition 1979
Second edition 1985
Third edition 1990
Fourth edition 1997
Fifth edition 2003
Sixth edition 2009
Seventh edition 2014
Eight edition 2019

Notices
Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds or experiments described herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made. To the fullest extent of the law, no responsibility is assumed by Elsevier, authors, editors or contributors for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein.

[**FOR PRODUCTS CONTAINING ADVERTISING ONLY:** Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this publication does not constitute a guarantee or endorsement of the quality or the value of such product or the claims made of it by its manufacturer.]

ISBN: 978-0-7020-7221-5
eBook: 978-0-7020-7606-0

Printed in China
Last digit is the print number: 9 8 7 6 5 4 3 2 1

Content Strategist: Michael Houston
Content Development Specialist: Nani Clansey
Project Manager: Beula Christopher
Design: Patrick C. Ferguson
Illustration Manager: Karen Giacomucci
Marketing Manager: Melissa Fogarty

Preface

Oh's Intensive Care Manual first edition was in published 1979, when Intensive Care may not have been in its infancy but it certainly wasn't far beyond. Teik Oh, with tremendous foresight, brought together the fundamental elements of managing the critically ill in a particularly pragmatic manner, which could be considered a guideline for the development of the speciality. Thirty-nine years on, the eighth edition reflects both the maturation of that speciality and the phenomenal progress medically, technically, scientifically, ethically and educationally in all areas of management of the critically ill.

As with previous editions, each and every chapter has been updated, and there are many areas where new sections reflect the changing nature of the speciality and the subtle shifts in emphasis in the work place. A number of new authors have joined the contributor list, bringing their own expertise and a fresh look at previous chapters. We particularly want to thank 'retired' authors for their hard work and contributions; sometimes it's hard to say it much better than before, and their work has often been a firm base for the revision. New areas include chapters on fungal disease, genetics and sepsis, with the previous chapter on lung and heart transplantation now growing to two separate chapters – again reflecting the dynamic nature of the specialty.

As before, we hope that this edition will achieve several goals. It will update the previous edition in terms of the changing knowledge base; it will address emerging issues in Intensive Care; it will be of use to medical, nursing and allied health staff and students; but most importantly, it will adhere to the pragmatic and clinically useful style so effectively promulgated by Teik Oh. If a clinician can reach for it in the early hours of the morning, and can easily locate the information they require and feel ether guided or reassured, it will have served its purpose. If those passing examinations can say it helped, that will be gilding the lily.

ADB
JMH

ACKNOWLEDGEMENTS

It is a fitting time to use this opportunity to acknowledge the tremendous achievement of Teik Oh in the creation of this book back in 1979 and for the many editions that followed. It has been a massive asset in the development of the speciality, and there are hundreds – indeed thousands – of Intensivists across much of the world, including both of us, who have been the benefactors of the enthusiasm, energy and sheer work that Teik put into this book. The real beneficiaries have been the countless patients whose management was enhanced by the medical staff's access to this book, either during training or when it has been reached for on the Unit.

We also wish to acknowledge the major contribution Neil Soni made as a co-editor for the previous three editions. Neil's enthusiasm, energy, insights and breadth of vision were vital in maintaining the direction of the text. He recruited numerous leading international authors, many of whom continue to contribute, and led the development of many of the new chapters. His contributions continue in the current edition, and set a high bar for Jonathan Handy who has joined the team.

ADB
JMH

Part One
Organisation Aspects

This page intentionally left blank

1

Design and organisation of intensive care units

Vineet V Sarode, Felicity H Hawker

The intensive care unit (ICU) is a distinct organisational and geographic entity for clinical activity and care, operating in cooperation with other departments integrated in a hospital. The ICU is used to monitor and support threatened or failing vital functions in critically ill patients, who have illnesses with the potential to endanger life, so that adequate diagnostic measures and medical or surgical therapies can be performed to improve their outcome.[1] Hence intensive care patients may be:

1. Patients requiring monitoring and treatment because one or more organ functions are threatened by an acute (or an acute-on-chronic) disease (e.g. sepsis, myocardial infarction, gastrointestinal haemorrhage) or by the sequelae of surgical or other intensive treatment (e.g. percutaneous interventions) with the potential for developing life-threatening conditions.
2. Patients with existing failure of one or more organ functions such as cardiovascular, respiratory, renal, metabolic, or cerebral function but with a reasonable chance of a meaningful functional recovery. In principle, patients in known end-stages of untreatable terminal diseases should not admitted.

ICUs developed from the postoperative recovery rooms and respiratory units of the mid-20th century, when it became clear that concentrating the sickest patients in one area was beneficial. Intermittent positive-pressure ventilation (IPPV) was pioneered in the treatment of respiratory failure in the 1948–1949 poliomyelitis epidemics and particularly in the 1952 Copenhagen poliomyelitis epidemic when IPPV was delivered using an endotracheal tube and a manual bag, before the development of mechanical ventilators.[2]

As outlined later, the ICU is a department with dedicated medical, nursing and allied health staff that operates with defined policies and procedures and has its own quality improvement, continuing education and research programmes. Through its care of critically ill patients in the ICU and its outreach activities (see Chapter 2), the intensive care department provides an integrated service to the hospital, without which many programmes (e.g. cardiac surgery, trauma, emergency and transplantation) could not function.

CLASSIFICATION AND ROLE DELINEATION OF AN INTENSIVE CARE UNIT

The delineation of roles of hospitals in a region or area is necessary to rationalise services and optimise resources. Each ICU should similarly have its role in the region defined and should support the defined duties of its hospital. In general, small hospitals require ICUs that provide basic intensive care services. Critically ill patients who need complex management and sophisticated investigative back-up should be managed in an ICU located in a large tertiary referral hospital. Three levels of adult ICUs are classified as follows by the College of Intensive Care Medicine (Australia and New Zealand).[3] The European Society of Intensive Care Medicine[1] has a similar classification. The American College of Critical Care Medicine also has a similar classification but uses a reversed-numbering system.[4] Nurse staffing should be in line with accepted standards that are outlined in Chapter 6.

1. *Level I ICU*: A level I ICU has a role in small district hospitals. It should be able to provide resuscitation and short-term cardiorespiratory support of critically ill patients. It will have a major role in monitoring and preventing complications in 'at-risk' medical and surgical patients. It must be capable of providing mechanical ventilation and simple invasive cardiovascular monitoring for a period of several hours. A level I ICU should have an established relationship with a level II or a level III unit that should include mutual transfer and back transfer policies and an established joint review process. The medical director should be a certified intensive care specialist. Some training and experience in managing critically ill children, preferably with Advanced Paediatric Life Support (APLS) provider status or equivalent, is desirable for medical and nursing staff in rural ICUs.
2. *Level II ICU*: A level II ICU is located in larger general hospitals. It should be capable of providing a high standard of general intensive care, including multisystem life support, in accordance with the role

ABSTRACT

This chapter outlines the accepted standards for the design and organisation of intensive care units (ICUs) and further describes how optimising these can lead to improved well-being for patients, staff and visitors.

Examples include the effect of ICU design on spread of infection and noise levels that affect sleep for patients, and how organisational aspects can alter patient outcomes and stress levels and burnout for medical and nursing staff. It is particularly important to consider these factors when planning and resourcing the very large ICUs, often with several outreach programs, that are becoming more commonplace today.

KEYWORDS

ICU design
classification
HDU
care zones
ICU staffing
operational policies
quality improvement

of its hospital (e.g. regional centre for acute medicine, general surgery and trauma). It should have a medical officer on site and access to pharmacy, pathology and radiology facilities at all times, but it may not have all forms of complex therapy and investigations (e.g. interventional radiology, cardiac surgical service). The medical director and the majority of the other specialists should be certified intensive care specialists. Patients admitted must be referred to the attending intensive care specialist for management. Referral and transport policies should be in place with a level III unit to enable escalation of care.

3. *Level III ICU*: A level III ICU is located in a major tertiary referral hospital. It should provide all aspects of intensive care management required by its referral role for indefinite periods. These units should have a demonstrated commitment to education and research. Large ICUs should be divided into smaller 'pods' of 8–15 patients for the purpose of clinical management. A recent study in the United Kingdom showed that an increased patient to intensivist ratio of more than 7.5 was associated with increased hospital mortality.[5] The unit should be staffed by intensive care specialists with trainees, other junior medical staff, critical care nurses, allied health professionals and clerical and scientific staff. Complex investigations and imaging and support by specialists of all disciplines required by the referral role of the hospital must be available at all times. All patients admitted to the unit must be referred to the attending intensive care specialist for management.

The classification of types of ICU must not be confused with the description of intensive care beds within a hospital, as with the UK classification focused on the level of dependency that individual patients need, regardless of location.[6]

TYPE AND SIZE OF AN INTENSIVE CARE UNIT[3]

An institution may organise its intensive care beds into multiple units under separate management by single-discipline specialists (e.g. medical ICU, surgical ICU, burns ICU). Although this may be functional in some hospitals, the experience in Australia and New Zealand has favoured the development of general multidisciplinary ICUs. Thus, with the exception of dialysis units, coronary care units and neonatal ICUs, critically ill patients are admitted to the hospital's multidisciplinary ICU and are managed by intensive care specialists (or paediatric intensive care specialists in paediatric hospitals). There are good economic and operational arguments for a multidisciplinary ICU as against separate, single-discipline ICUs. Duplication of equipment and services is avoided. Critically ill patients develop the same pathophysiological processes no matter whether they are classified as medical or surgical and they require the same approaches to support of vital organs.

The ICU may constitute up to 10% of total hospital beds. This varies significantly even in developed countries, partly due to different definitions of acute care beds.[7] The number of beds required depends on the role and type of ICU. Multidisciplinary ICUs require more beds than single-specialty ICUs, especially if high-dependency beds are integrated into the unit. ICUs with fewer than four beds are considered not to be cost-effective and are too small to provide adequate clinical experience for skills maintenance for medical and nursing staff. On the other hand, the emerging trend of very large ICUs[8] can create major management problems. Consequently, as detailed previously, these units should be divided into 'pods'. Cohorting of patients in these subunits may be based on specific processes of care or the underlying clinical problem.

HIGH-DEPENDENCY UNIT[9–11]

A high-dependency unit (HDU) is a specially staffed and equipped area of a hospital that provides a level of care intermediate between intensive care and general ward care. Although HDUs may be located in or near specialty wards, increasingly they are located within or immediately adjacent to an ICU complex and are often staffed by the ICU.

The HDU provides invasive monitoring and support for patients with or at risk of developing acute (or acute-on-chronic) single-organ failure, particularly where the predicted risk of clinical deterioration is high or unknown. It may act as a 'step-up' or 'step-down' unit between the level of care delivered on a general ward and that in an ICU. Equipment should be available to manage short-term emergencies (e.g. need for mechanical ventilation). Although early studies showed conflicting results about benefits to outcome associated with the introduction of HDUs, a more recent survey in which HDU care was based on a 'single-organ failure and support model' showed that HDUs play a crucial role in management of patients and acute care beds.[11,12]

DESIGN OF AN INTENSIVE CARE UNIT[1,3,13]

The goal of design is to create a healing environment—a design that produces a measurable improvement in the physical and/or psychological states of patients, staff and visitors. Optimal ICU design helps to reduce medical errors, improve patient outcomes, reduce length of stay, increase social support for patients and can play a role in reducing costs.[13]

The layout of the ICU should allow rapid access to relevant acute areas, including operating theatres and postoperative areas, the emergency department and interventional areas such as cardiac catheterisation laboratory, endoscopy and the medical imaging department. Lines of communication in the departments and between the other departments must be available around the clock.

Safe transport of critically ill patients to and from the ICU should be facilitated by centrally located, keyed, oversized lifts and doors, and corridors should allow easy passage of beds and equipment. There should be a single entry and exit point, attended by the unit receptionist. Through-traffic of goods or people to other hospital areas must never be allowed. An ICU should have areas and rooms for public reception, patient management and support services. The total area of the unit should be 2.5–3 times the area devoted to patient care.

PATIENT CARE ZONE

An ideal patient room should incorporate three zones: a patient zone, family zone and caregiver zone.[13] Each patient bed area in an adult ICU requires a minimum floor space of 20 m^2, with single rooms being larger (at least 25 m^2), to accommodate patient, staff and equipment. There should be at least a 2.5-m traffic area beyond the bed area. Single rooms should have an optimal clearance of not less than 1.2 m at the head and the foot of the bed and not less than 1.8 m on each side. The ratio of single-room beds to open-ward beds will depend on the role and type of the ICU. Single rooms are essential for isolation; with the emergence of resistant bacterial strains in ICUs around the world, allocation of more single rooms is recommended. They have been shown to decrease acquisition of resistant bacteria and antibiotic use.[14] Isolation rooms should be equipped with an anteroom of at least 3 m^2 for hand washing, gowning and storage of isolation material. Some of those isolation rooms should be negative-pressure ventilated for contagious respiratory infections. A nonsplash hand wash basin with elbow- or foot-operated taps and a hand disinfection facility should be available for each bed.

Bedside service outlets should conform to local standards and requirements (including electrical safety and emergency supply, such as to the Australian Standard, Cardiac Protected Status AS3003).

Utilities per bed space as recommended for a level III ICU are:

- 4 oxygen
- 3 air outlets
- 3 suction inlets
- 16–20 power outlets
- A bedside light
- 4 data outlets.

Adequate and appropriate lighting for clinical observation must be available. Patients should be able to be seen at all times to allow detection of changes in status. All patient rooms should have access to natural light. Patients exposed to sunlight have been shown to experience less stress, require fewer analgesics and have improved sleep quality and quantity. Lack of natural light or outside view increases the incidence of disorientation in patients and stress levels in staff.[15,16]

Efforts should be made to reduce sound transmission and therefore noise levels. Walls and ceilings should be constructed of materials with high sound-absorbing capability; there should be acoustic baffling in the walls, soundproofing of windows and sound attenuators in the 'heating, ventilation and air conditioning' (HVAC) system.

Suitable and safe air quality should be maintained at all times. Isolation rooms (as per Australian Standard 1668.2) should have 99.99% 'high-efficiency particulate arrestance' (HEPA) filtration, along with negative pressure compared to the surrounding environment and at least 15 air changes per hour.[17] Air conditioning and heating should be provided with an emphasis on patient comfort. A clock and a calendar at each bed space are useful for patient orientation. It is widely held that transporting long-stay ICU patients outdoors is good for their morale, and access to an outside area should be considered in the design process.

The medical utility distribution systems configuration (e.g. floor column, wall mounted or ceiling pendant) depends on individual preference. There should be room to place or attach additional portable monitoring equipment, and, as far as possible, equipment should be kept off the floor. Space for charts, syringes, sampling tubes, pillows, suction catheters and patient's personal belongings should be available, often in one or more moveable bedside trolleys.

A rigorous fire safety and evacuation plan should be in place. This should include not just the basic fire safety device such as smoke detectors, automated sprinklers and fire extinguishers but also should look at design elements to minimise fire and its spread. These include selection of products and furnishing with low fire load, construction of compartments that are fire and smoke rated and protective technologies within the HVAC system to prevent the spread of smoke. It is very important to have an experienced fire safety officer involved in the ICU design process.[18]

Efficient signage is important for visitors and non–ICU staff, especially in large multi-pod ICUs.[18]

CLINICAL SUPPORT ZONE

Because critical care nursing is primarily at the bedside, staffing of a central nurse station is less important and emphasis should be on 'decentralised' stations just inside the room or patient care area or immediately outside the room, often paired to permit observation of two adjacent rooms. Nevertheless, the central station and other work areas should have adequate space for staff to allow centralised clinical management, staff interaction, mentoring and socialisation. This central station usually houses a central monitor, satellite pharmacy and drug preparation area, satellite storage of sterile and nonsterile items, telephones, computers with Internet connections, patient records, reference books and policy and procedure manuals. A dedicated computer for the

picture archive and communication system (PACS) or a multidisplay x-ray viewer should be located within the patient care area.

UNIT SUPPORT ZONE

Storage areas should take up a total floor space of at least 10 m^2 per bed.[13] They should have separate access remote from the patient area for deliveries and be no farther than 30 m from the patient area. Frequently used items (e.g. intravenous fluids and giving sets, sheets and dressing trays) should be located closer to patients than infrequently used or nonpatient items. There should be an area for storing emergency and transport equipment within the patient area with easy access to all beds.

Two separate spaces for clean (15 m^2) and dirty (25 m^2) utility rooms with separate access are necessary. Facilities for estimating blood gases, glucose, electrolytes, haemoglobin, lactate and sometimes clotting status are usually sufficient for the unit's laboratory. There should be a pneumatic tube or equivalent system to transfer specimens to pathology. Adequate arrangements for offices (receptionist, medical and nursing), doctor-on-call rooms (15 m^2), a staff lounge (with food/drinks facilities) (40 m^2 per eight beds), wash rooms and a seminar room (40 m^2) should be available and an interview room is recommended.

EQUIPMENT

The type and quantity of equipment will vary with the type, size and function of the ICU and must be appropriate to the workload of the unit. There must be a regular programme in place for checking its safety. Protocols and in-service training for medical and nursing staff must be available for the use of all equipment, including steps to be taken in the event of malfunction. There should also be a system in place for regular maintenance and service. The intensive care budget should include provision to replace old or obsolete equipment at appropriate times. A system of stock control should be in place to ensure consumables are always in adequate supply. The ICU director should have a major role in the purchase of new equipment to ensure it is appropriate for the activities of the unit. Level II and III ICUs should have an equipment officer to coordinate these activities.

FAMILY SUPPORT ZONE

For relatives, there should be a separate area of at least 10 m^2 per eight beds (two chairs per bed), and an additional facility with bed and shower as sleep or rest cubicles can be considered. There should be facilities for tea/coffee making and a water dispenser, and toilets should be located close by. Television and/or music should be provided. It is desirable to have separate entrances to the ICU for visitors and health care professionals. One or more separate areas for distressed relatives should be available.

INTENSIVE CARE UNIT ORGANISATION

STAFFING[1,3,8,13,14,16,19]

The level of staffing depends on the type of hospital, and tertiary hospital ICUs require large teams. Whatever the size of the team, it is crucial that there is clear and proper communication and collaboration among team members and a true multidisciplinary approach. Knaus et al. in a classic study[20] first showed the importance of the relationship between the degree of coordination in an ICU and the effectiveness of its care. Other studies have shown relationships between collaboration and teamwork and better outcomes for patients and staff.[21,22] Inadequate communication is the most frequent root cause of sentinel events.[23]

MEDICAL STAFF[24]

An intensive care department should have a medical director who is qualified in intensive care medicine and who coordinates the clinical, administrative and educational activities of the department. The duties of the director should involve patient care, supervision of trainees/other junior doctors, the drafting of diagnostic and therapeutic protocols, responsibility for the quality, safety and appropriateness of care provided and education, training and research. It is recommended that the director be full time in the department.

The director should be supported by a group of other specialists trained in intensive care medicine who provide patient care and contribute to nonclinical activities. In an ICU of level II or III there must be at least one specialist exclusively rostered to the unit at all times. Specialists should have a significant or full-time commitment to the ICU ahead of clinical commitments elsewhere. There should be sufficient numbers to allow reasonable working hours, protected clinical support time and leave of all types. Participation in ICU outreach activities (rapid response calls, outpatient review; see Chapter 2) has increased the workload of intensive care specialists, as well as junior staff in many hospitals, resulting in the need to increase the size of the medical team.

There should also be at least one junior doctor with an appropriate level of experience rostered exclusively to level II and III units at all times. Junior medical staff in the ICU may be intensive care medicine trainees but should ideally also include trainees of other acute disciplines (e.g. anaesthesia, medicine, surgery and emergency medicine). It is imperative that junior doctors are adequately supervised, with specialists being readily available at all times.

Medical work patterns are important for quality of treatment and should be supervised by the director. These patterns include rosters, structure of handover and daily rounds. Appropriate rostering influences satisfaction and avoids burnout syndrome in staff.[25,26] It reduces tiredness after night shifts or long shifts and consequently

improves attention and reduces errors. It also improves the quality of information transfer during handovers and daily rounds.[27]

This physician-staffing model has been used in Australia and New Zealand for many years but has not been common in the United States. A systematic review[28] has shown that when there has been mandatory intensive care specialist consultation (or closed ICU), compared with no or elective intensive care specialist consultation or open ICU, both ICU and hospital survival were improved and there was a reduced length of stay in ICU and in hospital.[29]

NURSING STAFF

Critical care nursing is covered in Chapter 6. The bedside nurse conducts the majority of patient assessment, evaluation and care in an ICU. When leave of all kinds is factored in, long-term 24-hour cover of a single bed requires a staff complement of six nurses. Nurse shortages have been shown to be associated with increased patient mortality and nurse burnout and adversely affect outcome and job satisfaction in the ICU.[30,31]

There should be a nurse manager who is appointed with authority and responsibility for the appropriateness of nursing care and who has extensive experience in intensive care nursing, as well as managerial experience. In tertiary units the nurse manager should participate in teaching, continuing education and research. Ideally, all nurses working in an ICU should have training and certification in critical care nursing.

ALLIED HEALTH

Access to physiotherapists, dietitians, speech pathologists, social workers and other therapists should also be available. A dedicated ward clinical pharmacist is invaluable and participation of a pharmacist on ward rounds has been associated with a reduction in adverse drug events. Respiratory therapists are allied health personnel trained in and responsible for the equipment and clinical aspects of respiratory therapy, a concept well established in North America but not the UK, continental Europe and Australasia. Technical support team members, either members of the ICU staff or seconded from biomedical departments, are necessary to service, repair and develop equipment.

SUPPORT STAFF

Provision should be made for adequate secretarial support.[16] Transport and 'lifting' orderly teams will reduce physical stress and possible injuries to nurses and doctors. If no mechanical system is available to transport specimens to the laboratories (e.g. air-pressurised chutes), sufficient and reliable couriers must be provided to do this day and night. The cleaning personnel should be familiar with the ICU environment and infection control protocols. There should also be a point of contact for local interpreters, chaplains, priests or officials of all beliefs when there is need for their services.

CLINICAL ACTIVITIES

OPERATIONAL POLICIES[3]

Well-defined administrative policies are vital to the functioning of an ICU. An *open* ICU has unrestricted access to multiple doctors who are allowed to admit and manage their patients. A *closed* ICU has admission, discharge and referral policies under the control of intensive care specialists. Improved cost benefits are likely with a closed ICU and patient outcomes are better, especially if the intensive care specialists have full clinical responsibilities. Consequently, ICUs should be *closed* under the charge of a medical specialist director. All patients admitted to the ICU are referred to the director and his/her specialist staff for management, although it is important for the ICU team to communicate regularly with the parent or admitting unit and to make referrals to other specialty units when appropriate.

There must be clearly defined policies for admission, discharge, management and referral of patients. Lines of responsibilities must be clearly defined for all staff members and their job descriptions defined. The director must have final overall authority for all staff and their actions, although in other respects each group may be responsible to respective hospital heads (e.g. the Director of Nursing).

Policies for the care of patients should be formulated and standardised. They should be unambiguous, periodically reviewed and familiarised by all staff. Examples include infection control and isolation policies, policies for intrafacility and interfacility transport, end-of-life policies (e.g. do not resuscitate [DNR] procedure) and sedation and restraint protocols. However, it should be noted that when protocols involve complex issues (such as weaning from mechanical ventilation), they might be less efficient than the judgment of experienced clinicians. Clinical management protocols (e.g. for feeding and bowel care) can be laminated and placed in a folder at each bed or loaded on to the intranet.

PATIENT CARE

ICU patient management should be multidisciplinary, with medical, nursing and other staff working together to provide the best care for each patient. The critical care nurse is the primary carer at the bedside and monitors, manages and supports the critically ill patient (see Chapter 6). The medical team consists of one or more registrars, residents or fellows who direct medical care with an intensive care specialist. The patient should be assessed by a formal ward round of the multidisciplinary team twice daily, usually at a time when the junior medical staff members are handing over. The nurse coordinating the floor, pharmacists and dietitians should also take part in daily rounds. Each patient should be assessed clinically (examination, observations and pathology, radiological and other investigation results), the medication chart reviewed, progress determined and a management plan developed for the immediate and longer term. The ward

round is also an opportunity to assess compliance with checklists such as the FAST HUG (Feeding, Analgesia, Sedation, Thromboembolic prophylaxis, Head of bed elevation, stress Ulcer prophylaxis, Glycaemic control). Clearly, unstable patients will require much more frequent assessment and intervention.

It is crucial that all observations, examination findings, investigations, medical orders, management plans (including treatment limitations) and important communications with other medical teams and patients' families are clearly documented in the appropriate chart or part of the medical record either electronically or in writing.

Wherever possible, clinical management should be evidence based and derived through consensus of the members of the ICU team, accepting, however, that evidence-based medicine has limitations when applied to intensive care medicine.

Well-structured collaboration among physicians, nurses and the other professionals is essential for best possible patient care, which includes presence of interprofessional clinical rounds, standardised and structured processes of handover of interdisciplinary and interprofessional information and use of clinical information systems.[1]

CARE OF FAMILIES[32]

ICU care includes sensitive handling of relatives. It is important that there are early and repeated discussions with patients' families to reduce family stress and improve consistency in communication. Ideally one senior doctor should be identified as the ICU representative to liaise with a particular family. Discussions should be interactive and honest and an attempt made to predict the likely course, especially with respect to outcome, potential complications and the duration of intensive care management required. The time, date and discussion of each interview should be recorded. Cultural factors should be acknowledged and spiritual support available, especially before, during and after a death. Open visiting hours allow families maximum contact with their loved one and promote an atmosphere of openness and transparency.

OUTREACH

ICU outreach activities are described in Chapter 2.

NONCLINICAL ACTIVITIES[2]

Nonclinical activities are very important in the ICU because they enhance the safety, quality and currency of patient care. The College of Intensive Care Medicine recommends that full-time intensive care specialists should have as protected nonclinical time three sessions per fortnight.[24] Nursing and allied health staff should also seek protected time for these activities.

QUALITY IMPROVEMENT[33,34]

It is essential that staff members promote a culture of quality improvement (QI) within the ICU, whatever its size and role. Every ICU should maintain a database that is sufficiently well structured to allow easy extraction of benchmarking, quality control and research data. All ICUs should have demonstrable and documented formal audit and review of its processes and outcomes in a regular multidisciplinary forum. Staff members who collect and process the data should have dedicated QI time.

There are three types of quality indicators:

1. *Structure*: structural indicators assess whether the ICU functions according to its operational guidelines and conforms to the policies of training and specialist bodies (e.g. clinical workload and case mix, staffing establishment and levels of supervision).
2. *Clinical processes*: clinical process indicators assess the way care is delivered. Examples include whether deep vein thrombosis prophylaxis is given, time to administration of antibiotics and glycaemic control.
3. *Outcomes*: examples of outcome measures include survival rate, quality of life of survivors and patient satisfaction.

The QI process involves *identification* of the indicator to be improved (e.g. high ventilator-associated pneumonia [VAP] rate), *development* of a method to improve it (e.g. checklist such as the FAST HUG[35]), *implementation* of the method to improve it (e.g. requirement to tick off the checklist on the morning ward round) and reevaluation of the indicator (e.g. VAP rate) to ensure the intervention has improved the outcome and finally to *ensure sustainability* (e.g. print checklist on ICU chart).

Activities that assess processes include clinical audit, compliance with protocols, guidelines and checklists and critical incident reporting. Activities that assess outcomes are calculating risk-adjusted mortality using a scoring system such as the Acute Physiology and Chronic Health Evaluation III (APACHE III) and calculation of standardised mortality ratios (see Chapter 3), measurement of rates of adverse events, and surveys.

Risk management is a closely related field. In the ICU, risks can be identified from critical incident reports, morbidity and mortality reviews and complaints from staff, patients or family members. Using similar methodology to the QI process, risks must be identified, assessed and analysed, managed and reevaluated. A major patient safety incident should result in a root cause analysis.

EDUCATION

All ICUs should have a documented orientation programme for new staff. There should be educational programmes for medical staff and a formal nursing education programme. Educational activities for intensive care trainees include lectures, tutorials, bedside teaching and trial examinations. Clinical reviews and meetings to review journals and new developments should be held regularly. Regular assessments for advanced life support and sometimes other assessments (e.g. medication safety) are often required. Increasingly, simulation centres are used to teach and assess skills and teamwork in crisis scenarios. A number of ICUs are also involved

in undergraduate medical teaching. All staff should also participate in continuing education activities outside the hospital (e.g. local, national or international meetings) and specialists should be involved in College Continuing Professional Development (CPD) activities.

RESEARCH

Level III ICUs should have an active research programme, preferably with dedicated research staff, but all units should attempt to undertake some research projects whether these are unit-based or contributions to multicentre trials.

THE FUTURE

Intensive care medicine is increasingly facing major challenges such as the aging population, increasing complexity of case mix, changing community health care and outcome expectations, increasing antibiotic resistance and also increasing stress and burnout in staff.[36] As ICUs become larger along with ICU staff numbers, it is crucial that the basic principles and standards of ICU design, staffing and clinical and nonclinical activities outlined in this chapter are maintained, but also innovative strategies to prevent multiorgan failure, antibiotic resistance in ICU patients and staff burnout need to be explored. Better screening tools for admission to ICU and tools for predicting outcomes will be essential.

REFERENCES

1. Valentin A, Ferdinande P, ESICM Working Group on Quality Improvement. Recommendations on basic requirements for intensive care units: structural and organizational aspects. *Intensive Care Med*. 2011;37(10):1575–1587.
2. Kelly FE, Fong K, Hirsch N, et al. Intensive care medicine is 60 years old: the history and future of the intensive care unit. *Clin Med (Lond)*. 2014;14(4):376–379.
3. CICM. *Minimum Standards For Intensive Care Units*; 2016. https://www.cicm.org.au/CICM_Media/CICMSite/CICM-Website/Resources/Professional%20Documents/IC-1-Minimum-Standards-for-Intensive-Care-Units_2.pdf.
4. Haupt MT, Bekes CE, Brilli RJ, et al. Guidelines on critical care services and personnel: recommendations based on a system of categorization of three levels of care. *Crit Care Med*. 2003;31(11):2677–2683.
5. Gershengorn HB, Harrison DA, Garland A, et al. Association of intensive care unit patient-to-intensivist ratios with hospital mortality. *JAMA Intern Med*. 2017;177(3):388–396.
6. Comprehensive Critical Care. Health Do, ed. *A Review of Adult Critical Care Services*. Crown; 2000.
7. Murthy S, Wunsch H. Clinical review: international comparisons in critical care - lessons learned. *Crit Care*. 2012;16(2):218.
8. Martin JM, Hart GK, Hicks P. A unique snapshot of intensive care resources in Australia and New Zealand. *Anaesth Intensive Care*. 2010;38(1):149–158.
9. Boots R, Lipman J. High dependency units: issues to consider in their planning. *Anaesth Intensive Care*. 2002;30(3):348–354.
10. CICM. *Recommendations on Standards for High Dependency Units for Training in Intensive Care Medicine*; 2013. http://cicm.org.au/CICM_Media/CICMSite/CICM-Website/Resources/Professional%20Documents/IC-13-Guidelines-on-Standards-for-High-Dependency-Units.pdf.
11. Scala R, Corrado A, Confalonieri M, et al. Increased number and expertise of Italian respiratory high-dependency care units: the second national survey. *Respir Care*. 2011;56(8):1100–1107.
12. Prin M, Harrison D, Rowan K, et al. Epidemiology of admissions to 11 stand-alone high-dependency care units in the UK. *Intensive Care Med*. 2015;41(11):1903–1910.
13. Thompson DR, Hamilton DK, Cadenhead CD, et al. Guidelines for intensive care unit design. *Crit Care Med*. 2012;40(5):1586–1600.
14. Levin PD, Golovanevski M, Moses AE, et al. Improved ICU design reduces acquisition of antibiotic-resistant bacteria: a quasi-experimental observational study. *Crit Care*. 2011;15(5):14.
15. Ulrich RS, Zimring C, Barch XZ, et al. A review of the research literature on evidence-based healthcare design. *HERD*. 2008;1(3):61–125.
16. CICM. *Administrative Services to Intensive Care Units.pdf*; 2010. https://www.cicm.org.au/CICM_Media/CICMSite/CICM-Website/Resources/Professional%20Documents/IC-7-Guidelines-on-Administrative-Services-to-Intensive-Care-Units.pdf.
17. Australia S. *The use of ventilation and airconditioning in buildings – mechanical ventilation in buildings. Mechanical ventilation of enclosures used for particular health care functions*. Sydney: SAI Global Limited; 2016.
18. Halpern NA. Innovative designs for the smart ICU: Part 2: The ICU. *Chest*. 2014;145(3):646–658.
19. Angus DC, Shorr AF, White A, et al. Critical care delivery in the United States: distribution of services and compliance with Leapfrog recommendations. *Crit Care Med*. 2006;34(4):1016–1024.
20. Knaus WA, Draper EA, Wagner DP, et al. An evaluation of outcome from intensive care in major medical centers. *Ann Intern Med*. 1986;104(3):410–418.
21. Baggs JG, Schmitt MH, Mushlin AI, et al. Association between nurse-physician collaboration and patient outcomes in three intensive care units. *Crit Care Med*. 1999;27(9):1991–1998.
22. Reader TW, Flin R, Cuthbertson BH. Team leadership in the intensive care unit: the perspective of specialists. *Crit Care Med*. 2011;39(7):1683–1691.
23. Sentinel Event Data. *Root Causes by Event Type 2004-2011*; 2012. http://www.jointcommission.org/

assets/1/18/Root_Causes_Event_Type_2004-2011.pdf.
24. CICM. *Intensive Care Specialist Practice in hospitals accredated for training in Intensive Care Medicine*; 2011. http://cicm.org.au/CICM_Media/CICMSite/CICM-Website/Resources/Professional%20Documents/IC-2-Guidelines-on-Intensive-Care-Specialist-Practice_2.pdf.
25. Garland A, Roberts D, Graff L. Twenty-four-hour intensivist presence: a pilot study of effects on intensive care unit patients, families, doctors, and nurses. *Am J Respir Crit Care Med*. 2012;185(7):738–743.
26. Moss M, Good VS, Gozal D, et al. A critical care societies collaborative statement: burnout syndrome in critical care health-care professionals. A call for action. *Am J Respir Crit Care Med*. 2016;194(1):106–113.
27. Dierk A, Vagts KKaCWM. *Organisation and Mangement of Intensive Care*. Berlin: Medizinisch Wissenschaftliche Verlagsgesellschaft; 2010.
28. Pronovost PJ, Angus DC, Dorman T, et al. Physician staffing patterns and clinical outcomes in critically ill patients: a systematic review. *JAMA*. 2002;288(17):2151–2162.
29. Vincent J-L. Evidence supports the superiority of closed ICUs for patients and families: yes. *Intensive Care Med*. 2017;43(1):122–123.
30. Tarnow-Mordi WO, Hau C, Warden A, et al. Hospital mortality in relation to staff workload: a 4-year study in an adult intensive-care unit. *Lancet*. 2000;356(9225):185–189.
31. Ulrich BT, Lavandero R, Hart KA, et al. Critical care nurses' work environments 2008: a follow-up report. *Crit Care Nurse*. 2009;29(2):93–102.
32. Davidson JE, Powers K, Hedayat KM, et al. Clinical practice guidelines for support of the family in the patient-centered intensive care unit: American College of Critical Care Medicine Task Force 2004–2005. *Crit Care Med*. 2007;35(2):605–622.
33. Curtis JR, Cook DJ, Wall RJ, et al. Intensive care unit quality improvement: a "how-to" guide for the interdisciplinary team. *Crit Care Med*. 2006;34(1):211–218.
34. CICM. *Quality Improvement*; 2010. https://www.cicm.org.au/CICM_Media/CICMSite/CICM-Website/Resources/Professional%20Documents/IC-8-Guidelines-on-Quality-Improvement.pdf.
35. Vincent JL. Give your patient a fast hug (at least) once a day. *Crit Care Med*. 2005;33(6):1225–1229.
36. Vincent J-L, Singer M. Critical care: advances and future perspectives. *Lancet*. 2010;376(9749):1354–1361.

2

Critical care outreach and rapid response systems

John R Welch, Christian P Subbe

KEY PRINCIPLES INCLUDE

- Deteriorating patients can be identified by careful monitoring of physiological signs – understanding that many hospital patients are in the last year of life.
- Timely escalation to critical care should improve outcomes.
- Effective responses to acute deterioration are often hindered by human factors.
- Rapid response systems standardise the response to at-risk and deteriorating patients, and improve process and clinical outcomes for such patients.
- Better outcomes result from multiprofessional working and effective communication, education, data collection/audit, learning from errors, and planned improvement of whole systems of care.

Outreach, rapid response or medical emergency teams providing '*critical care without walls*'[1] originated in Australia, spread to the United Kingdom, have become a standard of care across North America and many European countries, and are now deployed in the Middle East[2] and Far East,[3] and Central and South America.[4] The aim is '*equity of care for all critically ill patients irrespective of their location*'.[5]

BACKGROUND

Hospital admission criteria have become more rigorous and lengths of stay have decreased in recent years. Intensive care units (ICUs) contain relatively few beds and have high rates of occupancy. The result is that many ward patients have serious medical problems but only the most unstable are admitted to an ICU. Consequently, many high-risk patients remain in areas with staff inexpert in managing critical illness. Key tasks, such as measuring physiological signs, are often delegated to untrained personnel who may not understand the significance of abnormal values. Junior doctors are reported to be unprepared for emergency management, multidisciplinary team-working, handover and other critical roles.[6] Their training is shorter and more specialised than before, so even senior doctors may be relatively inexperienced.[7] In addition, many hospitals use temporary staff less likely to provide the continuity and team-working essential for effective care.

Comparisons of outcomes of patients admitted to an ICU from either the emergency department, operating theatre/recovery area or the wards show that those coming from wards have the highest mortality.[8] Suboptimal treatment is common before transfer to the ICU,[9–11] and is associated with worse outcomes.[9,10,12] An analysis of hospital deaths in a national database found that '*the most common incident types were failure to act on or recognise deterioration*'.[13] Crucially, differences in mortality are caused by variations in care rather than differences between the patients themselves.[12] Patients experiencing long periods of instability before there is an effective medical response are said to have suffered 'failure to rescue'. Such failures are common: in a national review of patients subsequently transferred to the ICU, many had sustained up to 72 hours physiological instability.[9] Indeed, a review of 1000 deaths in 10 hospitals concluded that 52 deaths would have had a 50% or greater chance of being prevented; although it is noteworthy that most of these were in elderly, frail patients judged to have a life expectancy of less than a year.[14] Other patients at-risk are those recently discharged from the operating theatre after major surgery or from the ICU: about one-quarter of all 'intensive care deaths' occur after transfer back to the ward.

OUTREACH, MEDICAL EMERGENCY AND RAPID RESPONSE TEAMS

Medical emergency teams (METs) were introduced in Australia in the 1990s, usually comprising critical care residents and medical registrars. These teams could be directly activated by any member of staff bypassing traditional hospital hierarchies. METs expanded the role of the cardiac arrest team to include the pre-arrest period, generally using call-out criteria based on deranged physiological values or staff concern.[15] In the United Kingdom, a review of critical care services in 2000[16] led to increased funding and the creation of critical care outreach teams largely staffed by critical care nurses. Similar services then appeared in the United States, driven by the Institute for Healthcare Improvement[17] with an

ABSTRACT

There are many ward patients with potential or actual critical illness whose care should and could be improved. The rapid response system (RRS) represents one method of addressing these issues, at the very least by highlighting defects in current ways of working and by applying what has been learned from RRS initiatives to the whole hospital.

KEYWORDS

Deterioration
early warning score
medical emergency team
rapid response

emphasis on a complete 'rapid response system' (RRS). This highlighted the principle that whole, coordinated systems are needed to reliably avoid failure to rescue.

The RRS can be divided into:

- an afferent component designed to ensure timely escalation of the deteriorating patient – usually using agreed physiological values as a trigger
- an efferent component comprising an individual or team of clinicians who can rapidly respond to deterioration
- governance and administrative structures to oversee and organise the service and its ways of working
- mechanisms to improve hospital processes.[18]

Another approach is to think of the RRS as being based on a 'chain of prevention' made up of education, monitoring, recognition, call and response.[19]

Various models and terms are used. METs are usually physician led. Critical care outreach (CCO) and rapid response teams (RRTs) are typically nurse led, but may include other allied health professionals as well as doctors. Most teams respond to defined physiological triggers, although some also work proactively with known at-risk patients, such as those discharged from the ICU. The objectives are to prevent (unnecessary) critical care admissions, to ensure timely transfer to the ICU when needed, to facilitate safe return to the ward, to share critical care skills[16] and to improve care throughout the hospital. Also, there may be a role supporting patients and their families after hospital discharge (Box 2.1).

Box 2.1 Functions of critical care outreach

- Identification of at-risk patients.
- Support for ward staff caring for at-risk patients and those recovering from critical illness.
- Referral pathways for obtaining timely, effective critical care treatments.
- Immediate availability of expert critical care and resuscitation skills when required.
- Facilitation of timely transfer to a critical care facility when needed.
- Education for ward staff in recognition of fundamental signs of deterioration, and in understanding how to obtain appropriate help promptly.
- Outpatient support to patients and their families following discharge from hospital.
- Development of systems of coordinated, collaborative, continuous care of critically ill and recovering patients across the hospital and in the community.
- Audit and improvement of basic standards of acute and critical care – and of the outreach team itself – to minimise risk and optimise treatment of the critically ill throughout the hospital.

Together, these elements comprise a system to deliver safe, quality care with proactive management of risk and timely treatment of critical illness.

RECOGNISING CRITICAL ILLNESS

Patients with potential or actual critical illness can be identified by review of the history, by examination and by investigations. Higher risks are associated with extremes of age, significant co-morbidities or serious presenting conditions.

A consensus conference on the afferent limb of the RRS reported that (1) vital sign aberrations predict risk; (2) monitoring patients more effectively may improve outcome, although some risk is random; (3) the workload implications of monitoring on the clinical workforce have not been explored, but should be investigated; and (4) the characteristics of an ideal monitoring system are identifiable, and it is possible to categorise monitoring modalities. It may also be possible to describe monitoring levels, and a system.[20]

ABNORMAL PHYSIOLOGY AND ADVERSE OUTCOME

There is a known association between abnormal physiology and adverse outcomes[21,22]: critical care scoring systems, such as APACHE II,[23] are based upon this relationship. Patients who suffer cardiac arrest or who die in hospital generally have abnormal physiological values recorded in the preceding period, as do patients requiring transfer to the ICU.[9,21,24] These findings have led to key vital signs being incorporated into early warning scoring (EWS) systems. Different systems use various combinations of parameters including respirations, oxygen saturation, pulse, blood pressure, temperature and level of consciousness as well as other indicators, such as urine output and pain.[25] The patient's measured vital signs are compared with a set of reference values, with measurements above or below designated points used as triggers for escalation. Formats vary but many use similar approaches, awarding points for varying degrees of derangement of different functions. Improvement or further deterioration can then be tracked by changes in EWS recorded over time, so that an EWS used in this way is described as a 'track and trigger system'. Many different track and trigger systems have been developed,[26,27] broadly categorised as single- or multi-parameter systems, aggregate weighted scoring systems or combinations (Box 2.2).[5] This variance has led to calls for standardisation to improve training and reliability of response, with the National Early Warning Score (NEWS) published in 2012[28] and revised in 2017 (Table 2.1) now widely used in the United Kingdom and elsewhere. It is based on the analysis of a large database of patients' vital signs recorded in different acute hospitals.[29] A different approach has been taken by Australian METs, where the escalation criteria are usually based upon single, markedly deranged physiological values, although ward staff concern is also a trigger (Box 2.3).[30]

Table 2.1 National early warning score (NEWS)[28]

	SCORE						
PHYSIOLOGICAL PARAMETERS	*3*	*2*	*1*	*0*	*1*	*2*	*3*
Respiratory rate (breaths/min)	≤8		9–11	12–20		21–24	≥25
Oxygen saturation (%)	≤91	92–93	94–95	≥96			
Any supplemental oxygen		Yes		No			
Heart rate (beats/min)	≤40		41–50	51–90	91–110	111–130	≥131
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Level of consciousness (AVPU scale)				A			V, P, U
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

AVPU, Alert, Voice, Pain, Unresponsive.

Box 2.2 Classification of track and trigger warning systems[5]

Single-parameter systems
- Tracking: periodic observation of selected basic signs
- Trigger: one or more extreme observational values

Multiple-parameter systems
- Tracking: periodic observation of selected basic vital signs
- Trigger: two or more extreme observational values

Aggregate weighted scoring systems
- Tracking: periodic observation of selected basic vital signs and the assignment of weighted scores to physiological values with the calculation of a total score
- Trigger: achieving a previously agreed trigger threshold with the total score

Combination systems
- Elements of single- or multiple-parameter systems in combination with aggregate weighted scoring

Box 2.3 Medical emergency team call-out criteria as used in the MERIT study[30]

Airway	Threatened
Breathing	Respiratory rate <5 or >36 per min
	Respiratory arrest
Circulation	Pulse rate <40 or >140 per min
	Systolic blood pressure <90 mm Hg
Neurology	Sudden fall in level of consciousness (fall in GCS of >2 points)
	Repeated or extended seizures
Other	Any patient you are seriously worried about

GCS, Glasgow Coma Scale.

As well as EWS systems based simply on acute physiology, there are methods using other data to risk-stratify patients. Systems based on laboratory parameters alone,[31] laboratory parameters in conjunction with vital sign observations,[32] or indicators of acute physiology, chronic illness and functional status[33] have all been validated. Another method is to promote the reporting of less objective but nonetheless important indicators, such as noisy breathing or changes in colour; for example, with the Dutch-Early-Nurse-Worry-Indicator-Score[34]; or to enable patients themselves – or their relatives – to activate the RRS. This method was first used in paediatric settings but also may be useful for adults.[35]

MEASURING OUTCOME

The use of RRSs is based on the premise that early detection and treatment of critical illness should improve patient outcomes. The quality of these services may be evaluated against not only such outcomes but also other indicators, including process measures (e.g. numbers of staff trained, completeness of bedside observations, timeliness of escalation and rapidity of response). The time from patient trigger to transfer to an ICU – or initiation of critical care treatment on the ward – may be a useful indicator too (i.e. the 'Score-to-Door time'[36]).

Table 2.2 shows one method that can be used to evaluate outcomes of RRS interventions 24 hours after the initial event, with outcomes classified as either positive or negative. The proportion of positive interventions provides a measure of the quality of the service. This approach has now been used in two multinational multicentre studies of RRS, enabling benchmarking and learning from others to occur. The first report – from 51 hospitals in five countries – found that, on average, urgent transfer to the ICU occurred in 24% of patient referrals, while new treatment limitations were instigated in 28% of patients not transferring to the ICU. Mortality just 24 hours after referral was 10.1%.[37]

RRSs have highlighted shortcomings in the care of ward patients, and contributed to a significant change in attitude to patients at risk. They have been instrumental in improving ward monitoring and in disseminating

Table 2.2 Matrix of possible outcomes of rapid response system intervention: the 'Multi-disciplinary Audit EvaLuating Outcomes of Rapid response' (MAELOR) tool

OUTCOMES	POSITIVE	NEGATIVE
Transfer to critical care area or operating theatre	1. Timely transfer, e.g. <4 hours after the first trigger	2. Delayed transfer, e.g. >4 hours after the first trigger
Alive on ward	3. No longer triggering	4. Still triggering
Deceased	5. On terminal care pathway/with DNACPR order	6. Following cardiopulmonary arrest
Others	7. Alive with documented treatment limitations and DNACPR order in place 8. a. Trigger from new pathology unrelated to previous call out b. Chronic condition leading to continuous trigger (e.g. tachypnoea in advanced pulmonary fibrosis) c. Discharged from hospital	9. Outcome not known/lost to follow-up

DNACPR, Do Not Attempt Cardiopulmonary Resuscitation.

From Morris A, Owen HM, Jones K, et al. Objective patient-related outcomes of rapid-response systems—a pilot study to demonstrate feasibility in two hospitals. *Crit Care Resusc.* 2013;15(1):33–39.

critical care skills. There are anecdotal reports of benefit to individuals,[38] and growing evidence of improved recognition of at-risk patients; with reduced length of stay, cardiac arrests, unplanned admissions to critical care, and morbidity and mortality.[39–42] Unfortunately, there are still relatively few high-quality studies. Positive reports include a randomised trial of phased introduction of a 24-hour outreach service to 16 wards in a general acute hospital.[43,44] The outreach team routinely followed up patients discharged from intensive care to wards and saw referrals generated by ward staff concern or the use of an EWS system. There was a statistically significant reduction in mortality in wards where the service was operational. In contrast, a large prospective, randomised trial of METs in Australia found no improvements in cardiac arrests, unplanned admissions to ICU or unexpected deaths in comparison to control hospitals in the primary analysis.[30] However, a secondary analysis showed improved outcomes in most hospitals in both the intervention and control groups, with dramatic improvements in those with the weakest baseline performance.[45] This study revealed many shortcomings in identification and care of critically ill patients, with one possible conclusion being that it is essential to take a whole systems approach to achieve timely recognition and response, and that it takes time to affect significant change across the entire hospital. An interrupted time series study of nearly 10 million patients in 232 hospitals described a progressive reduction in failure to rescue, cardiac arrests and mortality from early on, but better outcomes for the low mortality diagnostic-related group of patients only in the later years.[46,47]

Several studies have shown an inverse relation between the number of calls to the RRS and cardiac arrests.[48] This may reflect better patient assessment, more timely implementation of Do-Not-Attempt-Resuscitation orders and involvement of palliative care specialists in patients with terminal illness. This is not a negative: delivery of good palliative care can be seen as a positive outcome reinforced by an RRS.[49]

There has been less investigation of the follow-up of patients discharged from ICU, although this group is known to be at significant risk. A matched-cohort analysis of 5924 patients found follow-up by an outreach team reduced length of stay and mortality compared to historical controls and matched patients from hospitals with no outreach.[50]

SETTING UP AN OUTREACH SERVICE

Patients with potential or actual critical illness are found in every area of the hospital, so systems to identify and treat those patients need to be planned at an organisational level. Involvement of managerial and clinical staff is essential, especially from the wards. It is particularly important that there is agreement and clarity about how the outreach team or equivalent interacts with the parent/primary medical team.

KEY STEPS IN PLANNING A RAPID RESPONSE SYSTEM

- Appoint senior clinical and managerial leads to develop the service.
- Institute organisational needs analysis, audit and evaluation, asking:
  - Which patients are at risk of deterioration and where are they located?

  - Where do cardiac arrests and unexpected deaths occur?
  - What are the sources of unplanned admissions to the ICU?
  - What is the pattern of adverse events where harm can be attributed to processes of care?
  - What are the other relevant clinical governance/risk management issues or morbidity and mortality data?
- Point prevalence studies can give a snapshot view of the location of patients at risk.
- Reviewing unplanned admissions to the ICU can identify systems failings, including quality of patient management and the appropriateness and timeliness of escalation.
- Analyses should also highlight staff training needs.

Other factors to consider include:

- the patient case mix
- existing skills of ward staff
- proposed hours of service
- size of hospital – and likely demand
- existing services, such as tracheostomy specialists, respiratory specialists, renal specialists, pain teams, night teams, etc.
- training facilities
- outreach service location and equipment needs including information technology
- funding.

The Australian Commission on Safety and Quality has published a useful guide to setting up and developing an RRS, available online.[51]

THE OUTREACH TEAM

The composition and skills of the team should be designed to meet the particular needs identified by the organisation. At a minimum, the team should be capable of assessment, diagnosis, initiation of resuscitation and rapid triage of critically ill patients to higher levels of care. Such clinical competencies as airway management, venepuncture and cannulation are essential, as are skills in education, audit and research. Leadership, coordination and communication skills are also crucial. The UK Department of Health have detailed the ways of working and competencies required for care of at-risk and deteriorating patients, specifying what should be expected of junior, middle-grade and senior staff.[52]

A pragmatic, staged implementation could include:

1. Establishing an education programme in care of the deteriorating patient for ward staff so that they can recognise signs of deterioration and know how to obtain timely help.
2. Introducing a physiological track and trigger warning system with defined referral/response protocols.
3. Developing clinical bedside support – incrementally if necessary – increasing the number of clinical areas covered by the team, and the hours of work. This might include follow-up of patients discharged from critical care and responding to patients identified through the track and trigger system or by other means.[5]

It is essential that robust data are collected and used for audit and evaluation – and for feedback to ward managers and clinical staff. Successes should be highlighted and areas for improvement identified. Data may include:

- numbers of referrals and patient follow-ups
- date and time of each episode
- patient details (e.g. age, sex, date of hospital admission, location, emergency/elective admission, medical/surgical, resuscitation status)
- trigger event (e.g. early warning score, cardiac arrest call)
- significant problems identified
- interventions performed
- patient outcomes.

THE FUTURE – AND TECHNOLOGY TO MITIGATE HUMAN FACTORS

Mature RRSs experience challenges from rising demand and the charge that they deskill ward staff. One possible solution is a two-tier response system where the patient's parent team is equipped to provide a defined initial response in the first instance,[53] with the MET only activated if more severe illness is identified.[54]

It is clear that many errors causing 'failure to rescue' are due to human factors and flaws in the design of hospital systems,[55,56] as illustrated by the MERIT study finding that of patients needing escalation to the ICU – with signs that should have been reported to the MET – only 30% were actually referred.[30] Hierarchical thinking, inflexible mental modelling, unreliable performance and uncoordinated, inefficient organisation are all factors.[55,56] Even relatively simple matters, such as the documentation of vital sign recording have a role: attention to the design of charts may promote more reliable detection of deterioration.[57]

Automation has great potential to improve the reliability of some important processes. Technologies that provide continuous or semi-continuous monitoring of vital signs, automatically calculate EWS and communicate critical values, are available[58]; while checklist-based interventions might help standardise the response to deterioration.[59] The development of increasingly sophisticated expert systems will enable the analysis of patterns of physiological data that can produce specific alerts as well as prompts and advice about individual patients.

CONCLUSION

There are many ward patients with potential or actual critical illness whose care should and could be improved.

The RRS represents one method of addressing these issues, at the very least by highlighting defects in current ways of working and by applying what has been learned from RRS initiatives to the whole hospital.

REFERENCES

1. Hillman K. Critical care without walls. *Curr Opin Crit Care*. 2002;8(6):594–599.
2. Al-Qahtani S, Al-Dorzi HM, Tamim HM, et al. Impact of an intensivist-led multidisciplinary extended rapid response team on hospital-wide cardiopulmonary arrests and mortality. *Crit Care Med*. 2013;41(2):506–517.
3. Kim Y, Lee DS, Min H, et al. Effectiveness analysis of a part-time rapid response system during operation versus nonoperation. *Crit Care Med*. 2017;45(6):e592–e599.
4. Mezzaroba AL, Tanita MT, Festti J, et al. Evaluation of the five-year operation period of a rapid response team led by an intensive care physician at a university hospital. *Rev Bras Ter Intensiva*. 2016;28(3):278–284.
5. Department of Health & NHS Modernisation Agency. *The National Outreach Report 2003 [Critical Care Outreach 2003: Progress in Developing Services]*. London: Department of Health & NHS Modernisation Agency; 2003.
6. Monrouxe LV, Grundy L, Mann M, et al. How prepared are UK medical graduates for practice? A rapid review of the literature 2009-2014. *BMJ Open*. 2017;7(1):e013656.
7. Chikwe J, de Souza AC, Pepper JR. No time to train the surgeons. *BMJ*. 2004;328(7437):418–419.
8. Goldhill DR, Sumner A. Outcome of intensive care patients in a group of British intensive care units. *Crit Care Med*. 1998;26(8):1337–1345.
9. Cullinane M, Findlay G, Hargraves C, et al. *An Acute Problem?* London: National Confidential Enquiry into Patient Outcome and Death; 2005.
10. Garry DA, McKechnie SR, Culliford DJ, et al. A prospective multicentre observational study of adverse iatrogenic events and substandard care preceding intensive care unit admission (PREVENT). *Anaesthesia*. 2014;69(2):137–142.
11. Marquet K, Claes N, De Troy E, et al. One fourth of unplanned transfers to a higher level of care are associated with a highly preventable adverse event: a patient record review in six Belgian hospitals. *Crit Care Med*. 2015;43(5):1053–1061.
12. McQuillan P, Pilkington S, Allan A, et al. Confidential inquiry into quality of care before admission to intensive care. *BMJ*. 1998;316(7148): 1853–1858.
13. Donaldson LJ, Panesar SS, Darzi A. Patient-safety-related hospital deaths in England: thematic analysis of incidents reported to a national database, 2010-2012. *PLoS Med*. 2014;11(6):e1001667.
14. Hogan H, Healey F, Neale G, et al. Preventable deaths due to problems in care in English acute hospitals: a retrospective case record review study. *BMJ Qual Saf*. 2012;21(9):737–745.
15. Lee A, Bishop G, Hillman KM, et al. The medical emergency team. *Anaesth Intensive Care*. 1995;23(2):183–186.
16. Department of Health. *Comprehensive Critical Care: A Review of Adult Critical Care Services*. London: Department of Health; 2000.
17. Berwick DM, Calkins DR, McCannon CJ, et al. The 100,000 lives campaign: setting a goal and a deadline for improving health care quality. *JAMA*. 2006;295(3):324–327.
18. Devita MA, Bellomo R, Hillman K, et al. Findings of the first consensus conference on medical emergency teams. *Crit Care Med*. 2006;34(9):2463–2478.
19. Smith GB. In-hospital cardiac arrest: is it time for an in-hospital 'chain of prevention'? *Resuscitation*. 2010;81(9):1209–1211.
20. DeVita MA, Smith GB, Adam SK, et al. 'Identifying the hospitalised patient in crisis' – a consensus conference on the afferent limb of rapid response systems. *Resuscitation*. 2010;81(4):375–382.
21. Kause J, Smith G, Prytherch D, et al. A comparison of antecedents to cardiac arrests, deaths and emergency intensive care admissions in Australia and New Zealand, and the United Kingdom – the ACADEMIA study. *Resuscitation*. 2004;62(3):275–282.
22. Harrison GA, Jacques T, McLaws ML, et al. Combinations of early signs of critical illness predict in-hospital death – the SOCCER study (signs of critical conditions and emergency responses). *Resuscitation*. 2006;71(3):327–334.
23. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818–829.
24. Findlay GP, Shotton H, Kelly K, et al. *Time to Intervene? A Review of Patients Who Underwent Cardiopulmonary Resuscitation as a Result of an in-hospital Cardiorespiratory Arrest*. London: National Confidential Enquiry into Patient Outcome and Death; 2012.
25. Bright D, Walker W, Bion J. Clinical review: outreach – a strategy for improving the care of the acutely ill hospitalized patient. *Crit Care*. 2004;8(1):33–40.
26. Smith GB, Prytherch DR, Schmidt PE, et al. Review and performance evaluation of aggregate weighted 'track and trigger' systems. *Resuscitation*. 2008;77(2):170–179.
27. Smith GB, Prytherch DR, Schmidt PE, et al. A review, and performance evaluation, of single-parameter 'track and trigger' systems. *Resuscitation*. 2008;79(1): 11–21.
28. Royal College of Physicians. *National Early Warning Score (NEWS): Standardising the Assessment of Acute Illness Severity in the NHS*. Report of a working party. London: Royal College of Physicians; 2012.

29. Prytherch DR, Smith GB, Schmidt PE, et al. ViEWS – towards a national early warning score for detecting adult inpatient deterioration. *Resuscitation*. 2010;81(8):932–937.
30. Hillman K, Chen J, Cretikos M, et al. Introduction of the medical emergency team (MET) system: a cluster-randomised controlled trial. *Lancet*. 2005;365(9477):2091–2097.
31. O'Sullivan E, Callely E, O'Riordan D, et al. Predicting outcomes in emergency medical admissions – role of laboratory data and co-morbidity. *Acute Med*. 2012;11(2):59–65.
32. Churpek MM, Yuen TC, Winslow C, et al. Multicenter development and validation of a risk stratification tool for ward patients. *Am J Respir Crit Care Med*. 2014;190(6):649–655.
33. Kellett J, Deane B. The Simple Clinical Score predicts mortality for 30 days after admission to an acute medical unit. *QJM*. 2006;99(11):771–781.
34. Douw G, Huisman-de Waal G, van Zanten ARH, et al. Capturing early signs of deterioration: the Dutch-early-nurse-worry-indicator-score and its value in the Rapid Response System. *J Clin Nurs*. 2017;26(17–18):2605–2613.
35. Odell M, Gerber K, Gager M. Call 4 Concern: patient and relative activated critical care outreach. *Br J Nurs*. 2010;19(22):1390–1395.
36. Oglesby KJ, Durham L, Welch J, et al. 'Score to Door Time', a benchmarking tool for rapid response systems: a pilot multi-centre service evaluation. *Crit Care*. 2011;15(4):R180.
37. Bannard-Smith J, Lighthall GK, Subbe CP, et al. Clinical outcomes of patients seen by Rapid Response Teams: a template for benchmarking international teams. *Resuscitation*. 2016;107:7–12.
38. Park GR, McElligot M, Torres C. Outreach critical care–cash for no questions? *Br J Anaesth*. 2003;90(5):700–701.
39. Sandroni C, D'Arrigo S, Antonelli M. Rapid response systems: are they really effective? *Crit Care*. 2015;19:104.
40. Maharaj R, Raffaele I, Wendon J. Rapid response systems: a systematic review and meta-analysis. *Crit Care*. 2015;19:254.
41. Ludikhuize J, Brunsveld-Reinders AH, Dijkgraaf MG, et al. Outcomes associated with the nationwide introduction of rapid response systems in the Netherlands. *Crit Care Med*. 2015;43(12):2544–2551.
42. Solomon RS, Corwin GS, Barclay DC, et al. Effectiveness of rapid response teams on rates of in-hospital cardiopulmonary arrest and mortality: a systematic review and meta-analysis. *J Hosp Med*. 2016;11(6):438–445.
43. Priestley G, Watson W, Rashidian A, et al. Introducing Critical Care Outreach: a ward-randomised trial of phased introduction in a general hospital. *Intensive Care Med*. 2004;30(7):1398–1404.
44. Watson W, Mozley C, Cope J, et al. Implementing a nurse-led critical care outreach service in an acute hospital. *J Clin Nurs*. 2006;15(1):105–110.
45. Chen J, Bellomo R, Flabouris A, et al. The relationship between early emergency team calls and serious adverse events. *Crit Care Med*. 2009;37(1):148–153.
46. Chen J, Ou L, Flabouris A, et al. Impact of a standardized rapid response system on outcomes in a large healthcare jurisdiction. *Resuscitation*. 2016;107:47–56.
47. Pain C, Green M, Duff C, et al. Between the flags: implementing a safety-net system at scale to recognise and manage deteriorating patients in the New South Wales Public Health System. *Int J Qual Health Care*. 2017;29(1):130–136.
48. Jones D, Bellomo R, DeVita MA. Effectiveness of the Medical Emergency Team: the importance of dose. *Crit Care*. 2009;13(5):313.
49. Jones D, Moran J, Winters B, et al. The rapid response system and end-of-life care. *Curr Opin Crit Care*. 2013;19(6):616–623.
50. Harrison DA, Gao H, Welch CA, et al. The effects of critical care outreach services before and after critical care: a matched-cohort analysis. *J Crit Care*. 2010;25(2):196–204.
51. Australian Commission on Safety and Quality in Health Care. *A Guide to Support Implementation of the National Consensus Statement: Essential Elements for Recognising and Responding to Clinical Deterioration*. Sydney: ACSQHC; 2011. www.safetyandquality.gov.au/wp-content/uploads/2012/02/Nat-Consensus-Statement-PDF-Complete-Guide.pdf.
52. Department of Health. *Competencies for Recognising and Responding to Acutely Ill Patients in Hospital*. London: Department of Health; 2009. http://webarchive.nationalarchives.gov.uk/20130123195821/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_096989.
53. O'Horo JC, Sevilla Berrios RA, Elmer JL, et al. The role of the primary care team in the rapid response system. *J Crit Care*. 2015;30(2):353–357.
54. Frost SA, Chapman A, Aneman A, et al. Hospital outcomes associated with introduction of a two-tiered response to the deteriorating patient. *Crit Care Resusc*. 2015;17(2):77–82.
55. Shearer B, Marshall S, Buist MD, et al. What stops hospital clinical staff from following protocols? An analysis of the incidence and factors behind the failure of bedside clinical staff to activate the rapid response system in a multi-campus Australian metropolitan healthcare service. *BMJ Qual Saf*. 2012;21(7):569–575.
56. Mackintosh N, Sandall J. The social practice of rescue: the safety implications of acute illness trajectories and patient categorisation in medical and maternity settings. *Sociol Health Illn*. 2016;38(2):252–269.
57. Preece MH, Hill A, Horswill MS, et al. Supporting the detection of patient deterioration: observation chart design affects the recognition of abnormal

vital signs. *Resuscitation*. 2012;83(9):1111–1118.

58. Subbe CP, Duller B, Bellomo R. Effect of an automated notification system for deteriorating ward patients on clinical outcomes. *Crit Care*. 2017;21(1):52.

59. Subbe CP, Kellet J, Barach P, et al. Crisis checklists for in-hospital emergencies: expert consensus, simulation testing and recommendations for a template determined by a multi-institutional and multi-disciplinary learning collaborative. *BMC Health Serv Res*. 2017;17(1):334.

3

Severity scoring and outcome prediction

Christopher Jake Barlow, David Pilcher

INTRODUCTION

Accurate prediction of patient outcomes is a cornerstone of clinical medicine. Outcome prediction involves identifying and measuring markers of illness severity and correlating them to relevant outcomes. The discipline of intensive care medicine is concerned particularly with mortality prediction. This chapter aims to provide an introduction to severity scores, which are the family of predictive tools used to estimate risk of death. It will discuss the application of severity scoring systems in intensive care, where they are regularly used to inform clinical trials, conduct risk stratification and in benchmarking.

Many scoring systems are in current use, and this chapter does not contain an exhaustive description of each. Rather, it focuses on:

- application of severity scoring systems
- understanding the terms used to discuss severity scoring
- an overview of the principles of mortality prediction including:
  - Development of severity scores
  - Evaluation of a scoring system
  - Limitations of scoring systems
- standardised mortality ratios (SMRs) and control charts
- common mortality scores in current use
- scores used for special populations.

Many of the examples used in this chapter are derived from the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database. However, the principles illustrated may be applied throughout the world of critical care medicine.

APPLICATION OF SEVERITY SCORES

WHY USE THEM?

Many severity scoring systems have been developed in intensive care medicine. Most predict mortality in the general intensive care unit (ICU) population, including the Acute Physiology and Chronic Health Evaluation (APACHE)[1–4] series of scores, the Australia and New Zealand Risk of Death (ANZROD) model,[5] the Intensive Care National Audit and Research Centre (ICNARC) models,[6] the Simplified Acute Physiology Score (SAPS)[7–9] series, the Mortality Prediction Model (MPM)[10–12] series, and the Paediatric Index of Mortality (PIM)[13–15] series. Others have been developed for use in specific patient populations in the ICU, such as the survival after venoarterial-extracorporeal membrane oxygenation (ECMO) (SAVE)[16] and respiratory ECMO survival prediction (RESP)[17] scores for patients requiring ECMO, or for other large diagnostic categories such as trauma (Injury Severity Score[18] [ISS]), and sepsis (quick-Sepsis Organ Failure Assessment [qSOFA])[19] who commonly present to ICU.

You, a senior intensivist, arrive back at work following your holiday. On your desk, you find a letter from the Health Department. Your ICU is in the spot light!

Looking through the document, the words 'high mortality', 'outlier', 'Standardised Mortality Ratio' and 'confidence interval' leap out at you.

You stretch your mind back, trying to recall the specifics of severity scores and mortality monitoring. Surely this can't be right?

Severity scores which predict mortality are often used for:

- **Quality of care evaluation and audit**
  Severity scoring allows comparison of unit performance. Risk-adjusted scoring systems are used by many clinical quality registry organisations, including The ANZICS Centre for Outcome and Resource Evaluation (CORE), ICNARC and The Dutch National Intensive Care Evaluation registry, allowing identification of units with higher than expected mortality.
- **Resource allocation and management**
  Severity scoring systems can be used to compare predicted mortality to resource use[20] and length of stay and to potentially estimate efficiency.[21]

ABSTRACT

Accurate prediction of patient outcomes is a cornerstone of clinical medicine. Outcome prediction involves identifying and measuring markers of illness severity and correlating them to relevant outcomes. The discipline of intensive care medicine is concerned particularly with mortality prediction. This chapter provides an introduction to severity scores, which are the family of predictive tools used to estimate risk of death. It will discuss the application of severity scoring systems in intensive care, where they are regularly used to inform clinical trials, conduct risk stratification and in benchmarking.

KEYWORDS

severity scoring
APACHE
SAPS
ICNARC
ANZROD
calibration
discrimination
regression
acute physiology score
SOFA

- **Comparison of groups in research trials**
  Scoring systems allow illness severity to be compared in different arms of a research trial.

MORTALITY PREDICTION MODELS, SEVERITY SCORES, RISK OF DEATH AND SCORING SYSTEMS: WHAT'S THE DIFFERENCE?

These terms are often used interchangeably, but each is a distinct entity and they should not be confused with one another.

Prediction models use statistical techniques to estimate the chance of a particular outcome. For example, if we identify that patients admitted to the ICU with pneumonia who are aged between 65 and 70 years have a mortality of 25%, we can use this information to predict the outcome in comparable future patients.

A severity score is often a key component of MPMs.[22] A score is an arbitrary number, in which a high value typically represents a greater severity of illness and therefore chance of death. Such scores are created by weighting physiological variables and other factors, such as diagnosis or location prior to admission, and combining these to produce a total score. It is important to note that, for example, although a patient with an APACHE II score of 35 is sicker than a patient with a score of 25, neither number quantifies the actual chance of death.

The predicted mortality or 'risk of death' for a patient is the quantitative assessment of the likelihood of death. This is derived from an equation which incorporates the severity score or its components and also other factors, such as disease category, admission type, or location prior to admission. Two patients with the same severity score may have a different predicted risk of death, depending on the impact of these other factors.[23]

A scoring system refers to the combination of severity score, and the predictive equations used to derive the risk of death. For example, the APACHE III scoring system produces both the APACHE III score (incorporating age, chronic disease and physiological variables), and the APACHE III risk of death. That latter is calculated by combining weighted components of the APACHE III score, with other factors such as ICU admission diagnosis, location and time in hospital prior to ICU admission and emergency surgical status.

PRINCIPLES OF MORTALITY PREDICTION AND SEVERITY SCORES

HOW IS A SCORE OR PREDICTED RISK OF DEATH CREATED?

The first step is to identify measurable variables which have a relationship with mortality. For instance, elderly patients and those who have a particularly high or low level of serum sodium are more likely to die (Fig. 3.1). Secondly, a mathematical equation is derived which connects the measured variable to the outcome. The process of finding the best equation is known as regression analysis. The equation produced can then be used to predict the outcomes for future patients. The most common regression technique used in developing severity scores is logistic regression[24] because it is the ideal technique for 'binary' outcomes (where there are only two possible outcomes, such as 'alive or dead').

In Fig. 3.1 the relationship between age and mortality appears to be a relatively straight line. However, serum sodium, in common with many physiological variables, has a 'U'-shaped relationship with mortality, which can be divided into several sections. Many ICU scoring systems use this approach, with each section given a weighting or score based on its relationship with mortality.

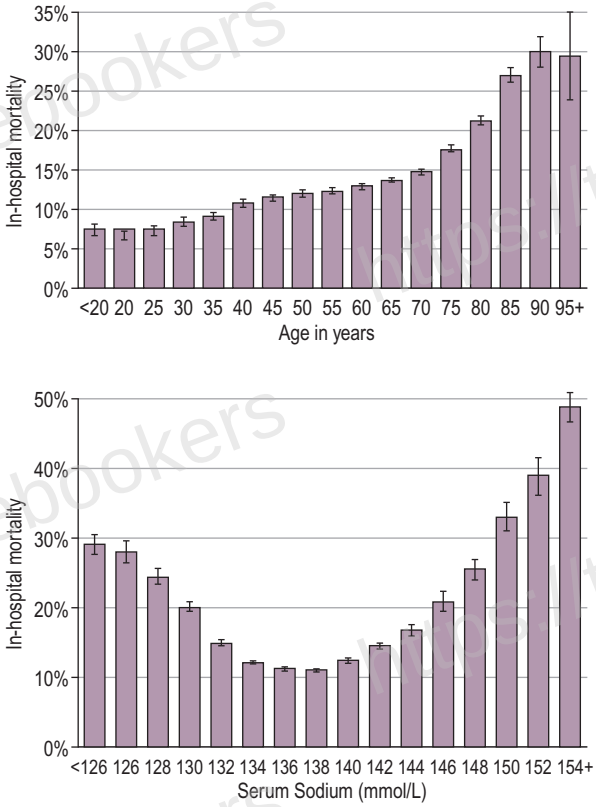


Figure 3.1 In-hospital mortality at different ages and serum sodium levels. Top pane shows the relationship between in-hospital mortality and age in years; bottom pane shows the relationship between in-hospital mortality and day 1 serum sodium level (mmol/L) for 332,409 ventilated patients admitted to 175 Australian and New Zealand Intensive Care Units (2010–2016). *ANZICS Adult Patient Database*.

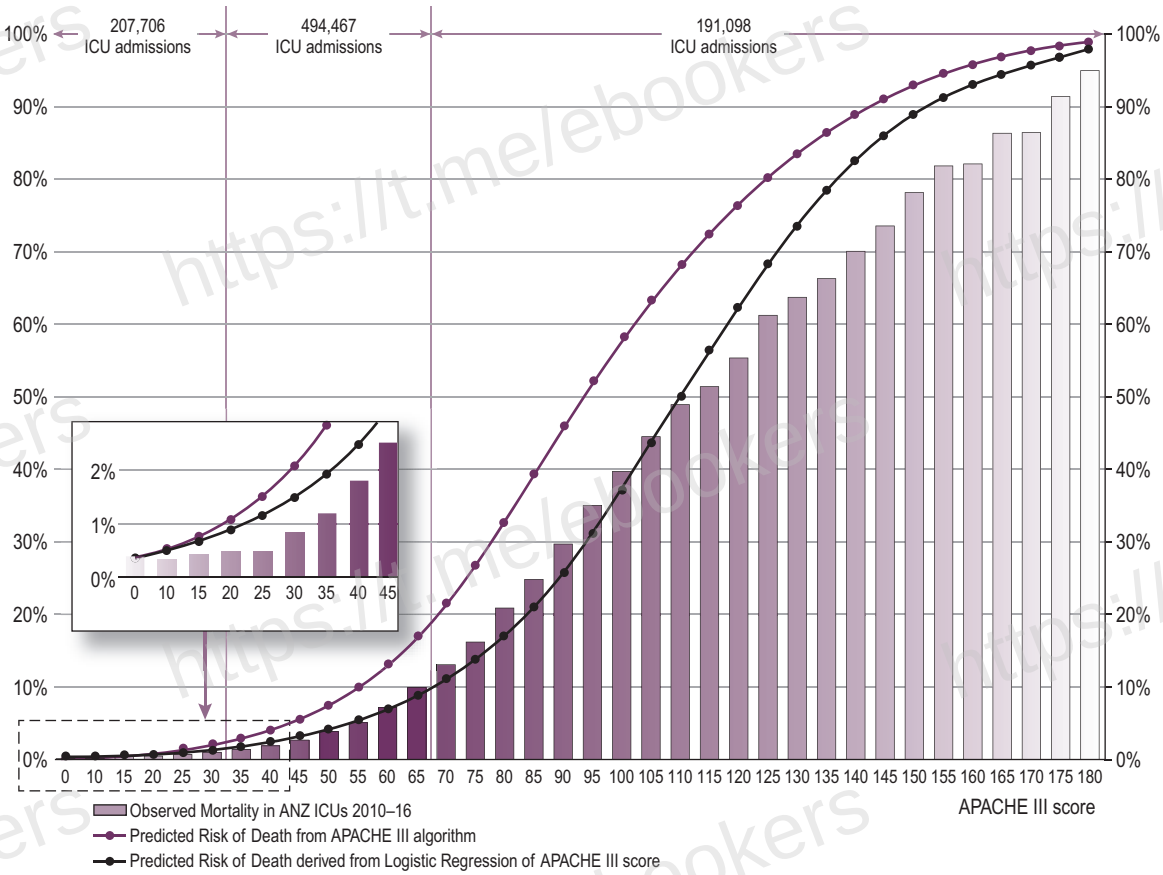


Figure 3.2 Mortality predictions derived by logistic regression. Observed and predicted mortality of 893,271 patients admitted to 176 Australian and New Zealand Intensive Care Units (ANZ ICUs) between 2010 and 2016 are plotted against Acute Physiology and Chronic Health Evaluation (APACHE) III scores. Shading of the columns represents the relative number of patients at each APACHE III score. *Purple dots/line* represent the predicted risk of death derived from the APACHE III-j algorithm at each APACHE III score. *Black dots/line* represent the predicted risk of death derived directly from logistic regression of the APACHE III score in this patient cohort. *ANZICS Adult Patient Database*.

In logistic regression the *probability* of death is calculated for each predictive variable. When the raw data are plotted on a graph, it produces an S-shaped curve. The shape of this curve means that for any given change in the predictor variable, much smaller differences in predicted mortality are found at the extreme left or right of the x-axis than in the centre of the curve. In practical terms, this means that even when overall predictions are accurate and discriminatory (see later for explanatory notes), relatively inaccurate predictions may occur for very-low-risk and very-high-risk patients (Fig. 3.2).

All common ICU MPMs incorporate multiple variables. The process of developing these models is known as multivariate regression, and the severity score is derived from the relative contribution of each of the predictor variables. Although increasing the number of variables improves predictive power, it also increases the complexity of the model and so it may be difficult to decide which variables to include. Key considerations when evaluating a variable for inclusion are the strength of the relationship with mortality, the size of the dataset used and practical aspects such as the burden of data collection. For example, the SOFA[25,26] score is relatively simple and can be 'added up by hand', whereas the predicted risk of death from APACHE IV,[4] the ICNARC model[6] or ANZROD[27] require a computer-based calculation.

EVALUATION OF A SCORING SYSTEM

It is important to know how well a scoring system relates to observed mortality and how well it performs in the specific patient groups in order to compare the outcomes of different groups of patients, in different ICUs, and across different time periods. A common statistical adage states that *'all models are wrong; the practical question is how wrong do they have to be in order to not be useful'*.[28]

Table 3.1 Comparison of published and locally assessed performance of different severity scoring systems in Australia and New Zealand

PUBLISHED PERFORMANCE		LOCAL PERFORMANCE IN ANZICS ADULT PATIENT DATABASE IN 2013			
SCORING SYSTEM	*DISCRIMINATION (AUROC)*	*DISCRIMINATION (AUROC)*	*NUMBER OF OBSERVATIONS**	*OBSERVED MORTALITY (%)*	*PREDICTED MORTALITY (%)*
APACHE II[2]	0.85	0.852 (0.848–0.856)	91,768	9.5	20.2
APACHE III[3]	0.90	0.898 (0.895–0.901)	117,397	8.5	12.0
APACHE IV[4]	0.88	Not available			
ICNARC[6]	0.86	Not applicable (UK only)			
SAPS II[8]	0.86	0.872 (0.868–0.875)	117,468	8.7	15.6
SAPS III[9,36]	0.83	Not available			
MPM-II_0[11]	0.82	Not available			
MPM-II_{24}[30]	0.84	Not available			
MPM-III[12]	0.82	Not available			
ANZROD[27]	0.91	0.911 (0.908–0.913)	125,732	8.3	8.2

*Number of observations based on application of specific exclusions for each scoring system to dataset.

ANZICS, Australian and New Zealand Intensive Care Society; *AUROC*, Area under Receiver Operator Characteristic; *APACHE*, Acute Physiology and Chronic Health Evaluation; *ICNARC*, Intensive Care National Audit and Research Centre model; *SAPS*, Simplified Acute Physiology Score; *MPM*, Mortality Prediction Model; *ANZROD*, Australian and New Zealand Risk of Death model.

Understanding how well an MPM works has three components:

- Discrimination
- Calibration
- Validity

DISCRIMINATION

Discrimination describes how well the prediction model distinguishes those who will die from those who will survive.[29] Discrimination can be displayed graphically and is represented by the area under the receiver operating characteristic curve (AUROC). Models with perfect discrimination have an AUROC of 1, whereas those where prediction performs no better than chance have an AUROC of 0.5. Models are considered to have reasonable discrimination when AUROC is greater than 0.7, strong discrimination when AUROC exceeds 0.8, and excellent discrimination if greater than 0.9. Although in principle MPMs with a greater AUROC may be considered 'better', a highly discriminatory model may have limited use if its calibration is poor (see later). A comparison of the AUROCs of common severity scoring systems can be seen in Table 3.1.

CALIBRATION

Calibration describes how close the predicted values for mortality are to the real observed values. Fig. 3.3 is an example of a well-calibrated local MPM (ANZROD) compared with a less well-calibrated model (APACHE III) for admissions to ICUs in Australia and New Zealand in 2014 and 2015. Application of a model to

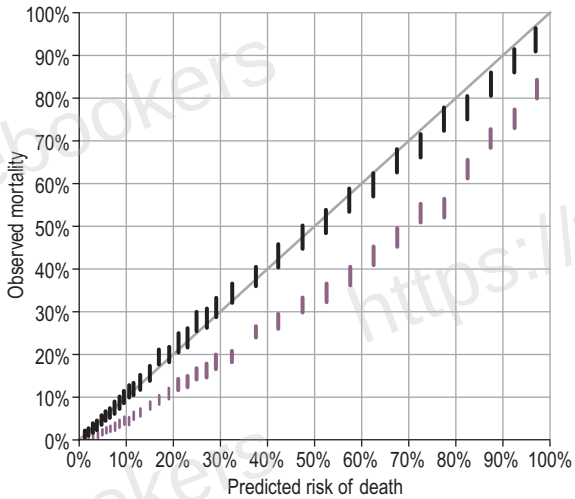


Figure 3.3 Calibration plot of predicted risk of death and observed mortality. Predicted risk of death is plotted against observed mortality for 163 Australian and New Zealand Intensive Care Units (ANZ ICUs) in 2014 and 2015. The *grey line* represents perfect prediction. The *black bars* represent 95% confidence intervals for Australian and New Zealand Risk of Death for 278,550 ICU admissions. The *purple bars* represent 95% confidence intervals for Acute Physiology and Chronic Health Evaluation for 257,278 ICU admissions. *ANZICS Adult Patient Database.*

data sets other than those used to generate it typically results in loss of calibration. This may be minimised by controlling for case mix, geographic location and time period. Many scoring systems (APACHE II, SAPS I and II, MPM I and II) exclude cardiac surgery and have poor calibration if the scores are applied in this cohort compared with use of specialised scores,[30] such as Euroscore[31–33] and the Cardiac Surgery Score (CASUS).[34] Some scoring systems, such as ANZROD and ICNARC, overcome this limitation by applying separate algorithms for specific cohorts such as cardiac surgery.[27,35]

Some systems take geography into account, as in SAPS III, which adds a variable for each region,[9,36] or create a score specifically for that region, such as ANZROD, developed specifically for Australian and New Zealand ICUs,[23] and the ICNARC model developed for England and Wales.[6] More complex modelling techniques such as mixed effects models, which treat patient level variables and ICU level or regional level variables differently in the creation of the model, are outside of the scope of this review.

Actual mortality tends to fall over time as quality of care improves, but predicted mortality remains as it was when the score was derived.[23,27] In addition, improvements over time may not be uniform across all patient groups, and the degree to which observed mortality falls below predicted may be different in specific patient subgroups. Thus the effect of variation in case mix also becomes progressively more important. When this occurs, 'recalibration' of predicted mortality should be performed.

It is worth remembering that even when mortality predictions are recalibrated and the risk of death is 're-estimated', the severity of illness score will remain unchanged. Patients with pneumonia, aged between 65 and 70 years and with APACHE II scores between 20 and 25 had a mortality of 27% in Australia and New Zealand in the early 2000s. Mortality fell to 23% between 2006 and 2010 and to 18% between 2011 and 2015: the same types of patients, with the same scores, had different mortality in different eras.

Calibration versus discrimination

A model can be well calibrated even if its discrimination is poor, and vice versa. The Baux score (age + % total body surface area burnt), which is used as a predictor of burns mortality, is a well-known example of strong discrimination (AUROC = 0.9) but poor calibration.[37,38] Patients with higher Baux scores are much more likely to die than those who score lower. However, a 50-year-old man with 50% burns does not have 100% mortality. In Australia in 2012, it was 35%.[37]

VALIDITY

Validity describes how accurately a model reflects reality and is divided into internal and external validity. Internal validity describes how well the model represents the population in which it was developed. External validity describes how reliably the model performs in other populations. Validity is a function of discrimination and calibration and with added contextual reference.

Restricting the scope of the score reduces heterogeneity and improves discrimination and calibration but also limits generalisability.[9] An example is qSOFA,[19] which was developed to identify patients who are at greater risk of death from infection and should be considered to potentially have sepsis. It is valid for use outside the ICU and in the emergency department (ED)[39] as a screening tool. However, due to its limited predictive capacity for identifying those at risk of death within the ICU, qSOFA has limited validity as a screening tool for sepsis within a critical care environment.[40] Other examples include the SAVE[16] and RESP[17] scores, which have been developed to predict mortality in patients who are already on ECMO. Although easy to calculate and potentially related to mortality, these scores are not validated for determining selection for ECMO treatment.

LIMITATIONS OF SCORING SYSTEMS

The application of severity scores is limited by the properties of the statistical methods used to generate them.

APPLICABILITY TO INDIVIDUAL PATIENTS

Severity scores predict the outcome of a cohort and are most accurate when the cohort comprises patients who are similar to each other. Models may become inaccurate when applied to an individual, so severity scores tend to be of limited benefit when making treatment decisions at the bedside. Although a patient with an APACHE II score of 8 is relatively well compared with a patient with a score of 25, the confidence interval is generally too wide to accurately predict mortality.[41]

Severity scoring systems are complex, and patients may be incorrectly scored, with one study concluding more patients are scored incorrectly than correctly.[42] At a cohort level, an approximately equal distribution of errors 'cancel each other out', but, at an individual level, incorrect scoring may result in significant changes to predicted mortality. The greatest effect occurs in the mid-range of scores because a small error in calculated score will have a large impact on predicted mortality. This is in contrast to an inherent limitation of logistic regression models where, even without any errors, predictions themselves may be inaccurate at extremes of low or high risk (see earlier).

In addition, using a score to make individual treatment decisions will change the predictive ability of the score. If treatment were withdrawn on all patients with greater than 95% predicted mortality, these patients may then have 100% mortality and the scoring system will now be inherently less accurate. This is analogous

to real-time traffic reports when driving. As congestion on one road increases, it will cause more drivers to avoid the area, paradoxically leading to less congestion on the original road but greater congestion elsewhere.

USING SEVERITY SCORES TO MONITOR INTENSIVE CARE UNIT OUTCOMES

Comparison of unadjusted death rates between ICUs lack context and can be misleading. One hospital might have twice the death rate, but their patients might also be twice as sick. Even with identical quality of care, patients who are more seriously ill, die more often. Severity scores and mortality predictions allow us to adjust for this baseline risk.

Common methods include the SMR for cross-sectional data comparing many ICUs, and control charts to monitor outcomes for a single ICU over time using exponentially weighted moving averages (EWMAs) and cumulative sum (CUSUM) charts. These standardised reporting methods produce results which are internally consistent and relatively easy to interpret.

STANDARDISED MORTALITY RATIO

The SMR is the ratio of the observed number of deaths to the predicted number of deaths, in which the latter is equal to the sum of the predicted risk of death—calculated by a severity scoring system—for all eligible patients.

$$\text{SMR} = \frac{\text{Observed number of deaths}}{\text{Predicted number of deaths}}$$

An SMR greater than 1 suggests the unit is performing worse than predicted because the observed mortality exceeds the predicted mortality.

Catches and caveats in interpreting the standardised mortality ratio

The SMR relies on an appropriate measure of observed mortality and accurate calculation of predicted mortality. Its interpretation is also dependent on knowing which groups are included. Readmission episodes to ICU and those with unknown survival outcomes are generally excluded. When reporting SMRs, some organisations either exclude patients transferred from an ICU or those transferred to another ICU.[15] SMRs for most adult ICUs consider in-hospital deaths.[1–3,6,9,27] However, it is common for paediatric ICUs to report and consider in-ICU deaths as the primary outcome.[15]

Observed mortality depends upon quality of all care delivered both within and outside the ICU. Some deaths may be inevitable, some preventable.[43] Several scoring systems account for this by excluding those admitted for organ donation or palliative care[27] (where survival is not the aim of the ICU admission) or by providing a statistical adjustment to mortality prediction for those with treatment limitations.[27] Accurate calculation of predicted mortality also relies on quality of data acquisition and the specific characteristics and calibration of the prediction model used to estimate the predicted number of deaths.

Anything which affects calibration of the MPM will also affect the calculated SMR. The annual fall in APACHE III SMRs in Australia and New Zealand is partly due to improved quality of care and better mortality outcomes. However, it has also been influenced by changes in data quality and the numbers and characteristics of contributing ICUs (Fig. 3.4).

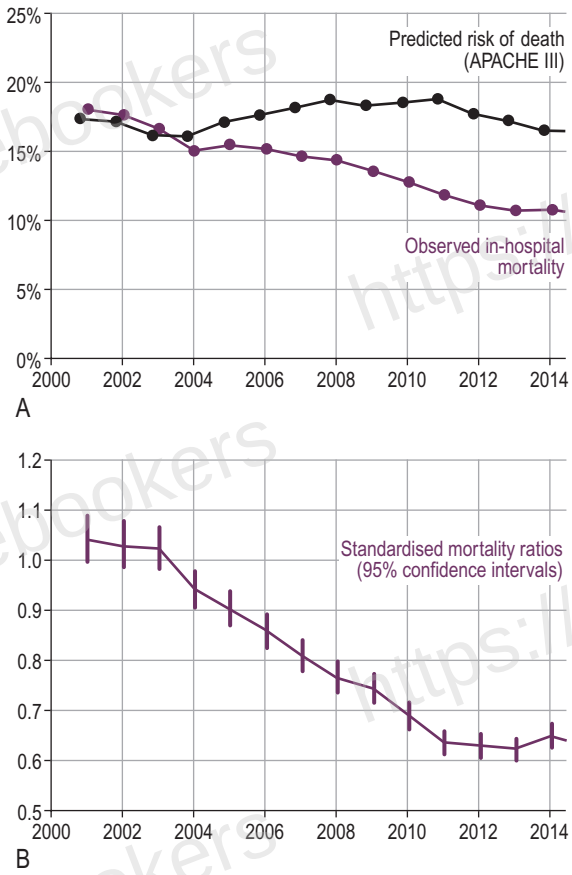


Figure 3.4 Changing standardised mortality ratio (SMR), observed mortality and predicted risk of death over time. The top panel shows observed in-hospital mortality *(purple)* and the Acute Physiology and Chronic Health Evaluation (APACHE) III predicted risk of death *(black)* for 206,770 admissions to a total 38 metropolitan Intensive Care Units (ICUs) in Australia and New Zealand between 2001 and 2014. In 2001, 22 ICUs contributed data, whereas in 2014, 36 metropolitan ICUs contributed data. The decline in SMR is partly due to mortality outcomes which have improved to be better than predicted by APACHE III but has also been influenced by improving data quality and changes in numbers and characteristics of contributing ICUs. *ANZICS Adult Patient Database.*

Sitting down with the SMR report, you use the 'Mohammed pyramid model' of investigation to try and identify the cause.[44,45]

First, you examine coding and data quality, consistency and completeness. You ensure there are no implausible values and that survivors and deaths are correctly coded. You concentrate on variables which may be systematically miscoded such as GCS.

Second, you evaluate the case mix. Are there patient groups where predicted mortality has been inaccurately estimated or where the prediction model systematically underestimates true observed mortality? Are there groups of patients where there is a true elevation of mortality above predicted?

Third, you assess clinical factors. These include staffing, bed availability and access to care, processes of care and guideline adherence and the clinicians themselves.

When ICU admission numbers are small, random variation has to be considered. Small changes in observed numbers of deaths may cause large changes in the calculated SMR. The estimate of SMR becomes more robust as the number of observed and expected deaths increase. It is important to consider the confidence intervals for an individual SMR or for the SMR of a group of ICUs (as used when a funnel plot is created—see later).

Graphing the standardised mortality ratio and identifying potential outliers

The most common graphical method used to report the SMR is a funnel plot (Fig. 3.5). Funnel plots graph the SMR for a group of ICUs over a period of time against the number of 'eligible cases' (typically number of ICU admissions or predicted number of deaths) on the x-axis.

Funnel plots also include a confidence interval derived from the mean SMR or overall number of deaths/predicted. The confidence interval indicates

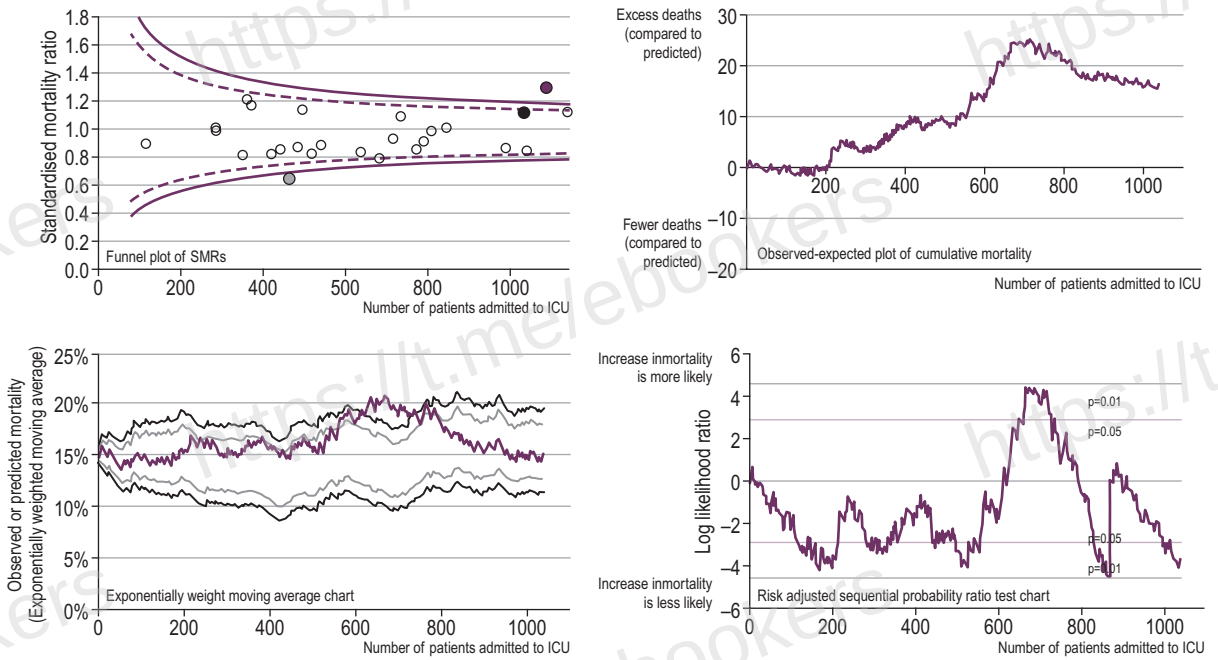


Figure 3.5 Funnel plot and continuous outcome monitoring (control) charts.
Top left: The panel shows a funnel plot of standardised mortality ratios (SMRs), with 95% (*purple* dashes) and 99% (*purple* line) confidence intervals drawn around the mean SMR of the group.
The ICU highlighted in *purple* has a higher (worse) SMR than the rest of the group. The ICU shaded in *grey* has a lower (better) SMR than the rest of the group. The ICU highlighted in *black* has an SMR within acceptable limits.
Bottom left: Exponentially weighted moving average of observed mortality (in *purple*) plotted against 2 (*grey* lines) and 3 (*black* lines) standard deviations for the predicted mortality.
Top right: Observed minus expected plot of cumulative mortality, with more deaths than predicted as the *purple* line climbs.
Bottom right: Risk adjusted sequential probability ratio test chart, with rising likelihood of an increase in mortality over predicted present as the *purple* line climbs.
Explanation: The continuous outcome monitoring (control) charts derived from the observed and predicted mortality for this (*red*) ICU are shown in the *top right*, *bottom right*, and *bottom left* panels. Despite an overall acceptable SMR, during the middle of the monitoring period, mortality outcomes appear to deteriorate. *ANZICS Adult Patient Database.*

the precision of the SMR, with its width inversely related to the number of patients. An ICU with an SMR greater than the confidence intervals of the whole group is considered a potential outlier with more deaths than predicted and may indicate poor performance.[46] Variation within the confidence limits is likely due to random noise.[47]

Funnel plots of SMR can accommodate some degree of loss of calibration in the MPM because confidence intervals are often drawn around the 'average SMR' of the group rather than around an SMR of 1. Hence the group of hospitals shown becomes the determinant of the overall acceptable performance and range of SMRs.

There are several reasons why an SMR may lie outside of the confidence interval. It may be random variation (1% of SMRs may lie outside of the 99% confidence intervals). Poor calibration of the prediction model, case mix variation (particularly important if mortality predictions are more inaccurate in one group than another) and coding errors (which can affect both observed mortality and the calculation of predicted risk of death) can commonly affect the SMR. If a funnel plot has a 'shotgun' appearance with large numbers of SMRs outside the confidence intervals (known as overdispersion), this suggests the 'risk adjustment' is inadequate and the predicted mortality rates are inaccurate (i.e. calibration is poor).

Despite these limitations, the funnel plot of SMRs is a useful screening tool to identify ICUs worthy of a 'closer look'.

EVALUATING PERFORMANCE OVER TIME FOR ONE INTENSIVE CARE UNIT: CONTINUOUS OUTCOME REPORTING

Display of outcomes over time for a single ICU typically uses CUSUM or EWMA control chart techniques. These methods compare differences in the observed and predicted outcomes at a specific ICU. Emerging trends can be identified early (possibly before a signal is seen on a funnel plot of SMRs), and clinical performance may be evaluated in real time.[48]

Cumulative sums, exponentially weighted moving averages and Variable Life-Adjusted Displays

The basic CUSUM control chart displays a running total of the difference between observed and predicted outcomes.[48] The simplest forms are called Variable Life-Adjusted Displays (VLADs) or observed-expected charts, but these often contain no control limits or confidence intervals to indicate when a trend has continued long enough to be considered significant. Risk-adjusted CUSUM and risk-adjusted sequential ratio probability charts are variants of these control charts, and sequentially assess whether an observed outcome rate is consistent with a specified baseline reference rate derived from the predicted outcome.[49]

EWMA charts are created by plotting the exponentially weighted mean of observed mortality along with a similarly weighted mean of the predicted outcome and its control limits.[48] They are able to detect small changes in mortality[50] because a small number of aberrant outcomes may reach a significance threshold. This sensitivity comes at the cost of a high false-positive rate, which can be decreased by increasing the run length of the chart.

Fig. 3.5 shows the same mortality data from one hospital displayed in three different ways, with an observed-expected chart, risk-adjusted sequential ratio probability chart and an EWMA chart.

COMMONLY USED FACTORS IN SEVERITY SCORES AND MORTALITY PREDICTION MODELS

All scoring systems rely on a limited number of patient factors to predict death (Fig. 3.6, Table 3.2). These can be loosely categorised into markers of acute physiological

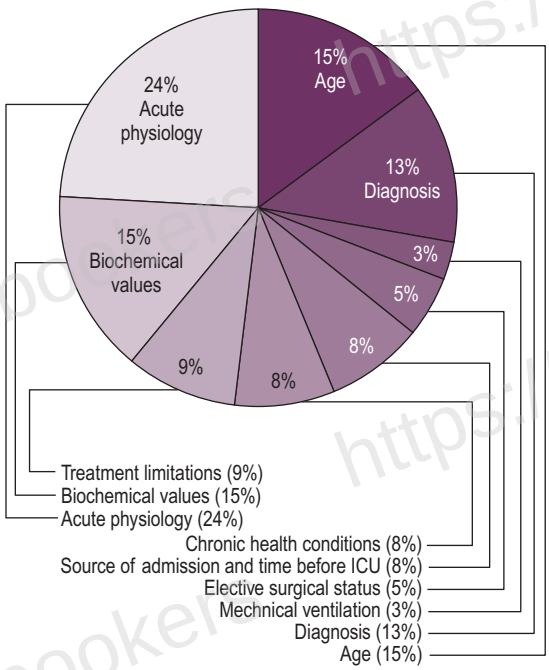


Figure 3.6 Relative contribution of variables to predicted risk of death. The figure shows the relative contributions of acute physiological disturbance ('acute physiology', 'biochemical values'), primary pathological process ('diagnosis'), physiological reserve ('age', 'chronic health conditions') and other factors ('source of admission and time before intensive care unit [ICU]', elective surgical status', 'mechanical ventilation', 'treatment limitations') to predicted risk of death in the ANZROD model. *Adapted with permission from Pilcher D, Paul E, Bailey M, Huckson S. The Australian and New Zealand Risk of Death (ANZROD) model: getting mortality prediction right for intensive care units.* Crit Care Resusc. *2014;16(1):3–4.*

Table 3.2 Factors commonly used in scoring systems

	APACHE II[2]	APACHE III[3]	APACHE IV[4]	MPM_0 III[12]	SAPS III[9,36]	ICNARC[6]	ANZROD[27]	PIM3[15]
MARKERS OF ACUTE PHYSIOLOGICAL DISTURBANCE								
Vital Signs	Yes	Yes	Yes	Yes, HR & MAP only	Yes, except RR	Yes	Yes	Yes, SBP
Arterial blood gas	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Requiring mechanical ventilation	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Glasgow Coma Score	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Creatinine	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Serum sodium	Yes	Yes	Yes	No	No	Yes	Yes	No
White blood count	Yes	Yes	Yes	No	No	Yes	Yes	No
PRIMARY PATHOLOGICAL PROCESS								
Admission type (e.g. Elective/ Emergency/ Operative)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Admission category/ diagnosis	Yes (50)	Yes (78)	Yes (433)	Yes (6)	Yes (39)	Yes (709)	Yes (124)	Yes (4 diagnostic strata)
CPR prior to admission	No	No	No	Yes	No	Yes	No	No
MARKERS OF PHYSIOLOGICAL RESERVE								
Age	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Co-morbidities	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (if more severe than admission diagnosis)
LOCATION FACTORS								
Location prior to ICU admission	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Length of hospital stay prior to admission	No	No	Yes	No	Yes	Yes	Yes	No

APACHE, Acute Physiology and Chronic Health Evaluation; *ANZROD*, Australian and New Zealand Risk of Death model; *CPR*, Cardiopulmonary Resuscitation; *HR*, heart rate; *ICNARC*, Intensive Care National Audit and Research Centre model; *ICU*, intensive care unit; *MAP*, mean arterial pressure; *MPM*, Mortality Prediction Model; *PIM*, Paediatric Index of Mortality; *RR*, respiratory rate; *SAPS*, Simplified Acute Physiology Score; *SBP*, systolic blood pressure.

disturbance, the primary pathological process driving admission, and indicators of physiological reserve (e.g. age and chronic disease state). This section will discuss the properties of these factors with respect to severity scoring.

ACUTE PHYSIOLOGICAL DISTURBANCE

Since APACHE I, measures of physiological disturbance have been used to objectively estimate severity of acute illness.[1] Initially, selection and weighting

of variables were done by expert consensus,[1] but later scores have used regression techniques to determine which variables should be included and how they should be weighted.

Commonly used markers of physiological disturbance are listed in Table 3.2. Less commonly used markers include albumin, bilirubin, urea, haematocrit, glucose, lactate, platelet count, serum potassium and urine output.[1,4,6,12,51]

SOURCES OF ERROR IN THE ACUTE PHYSIOLOGICAL CONTRIBUTION TO MORTALITY PREDICTION

Retrieval and critical care outreach services and emergency department care, as well as the impact of organ supports, will 'buff' these values and may cause a patient to be assigned a score that does not reflect the severity of their physiological derangement. Poorly performing services may have the opposite effect. This source of error occurs when treatment is initiated at a separate time to measuring physiological parameters.[52] Variables most at risk for this bias are heart rate, blood pressure, respiratory rate, blood glucose, pH and arterial partial pressure of oxygen (PaO_2).[52] Continuous variables (e.g. heart rate) are more prone to measurement bias than binary ones (e.g. presence of New York Heart Association (NYHA) III/IV heart failure).

The effect of error may be reduced by using scores such as MPM-II_0 and SAPS III[9,36] that use data from time of admission.[52] However, this strategy may also increase the proportion of missing values and reduce explanatory power and so was avoided by the APACHE scores.[53] In addition, some severity scores substitute default (normal) values for missing data, and cases with unknown outcomes are often omitted. Both of these methods bias the calculated severity score.[54]

In addition, 30% of deaths and discharges occur in the first 24 hours of ICU admission.[54] Because this provides little time to institute and see impact from ICU interventions, such 'short-stay' patients will have an SMR close to 1 irrespective of the quality of care provided.[54]

An alternative approach (used by APACHE and ANZROD) is to use the 'worst' value in the first 24 hours[3,54] following admission. This decreases the proportion of missing values, while allowing evaluation of care occurring after this period. However, this approach may disguise poorly performing units because the higher observed mortality will be attributed to increased physiological derangement which was a result of poor care in the first 24 hours of ICU stay.[53]

PRIMARY PATHOLOGICAL PROCESS

The cause of admission is an important factor[3] because the prognosis of a particular physiological insult will depend on the underlying pathology. For example, a patient presenting with severe diabetic ketoacidosis will have a comparatively low mortality compared with a patient with similarly deranged physiology due to respiratory sepsis.

It is therefore important to adjust for the primary disease process. The number of diagnostic categories used by different scoring systems vary widely: MPM III uses only 6,[12] SAPS III uses 39,[9] APACHE II uses 50,[2] ANZROD uses 177[27] and ICNARC uses 709.[6]

PHYSIOLOGICAL RESERVE

Physiological reserve is a broad term which encompasses a patient's capacity to respond to a physiological insult without significant decompensation. Several factors are commonly measured to provide an index of physiological reserve.

Age is both routinely measured and a good predictor of outcome and is included in all common scoring systems,[2–4,6,9,12,27] However, the predictive relationship is broad and a distinction should be made between chronological age and frailty. Severe chronic organ insufficiency or immunocompromise are also included in several scoring systems.[2,3,8]

Extreme physiological derangement is a strong predictor of hospital mortality on admission to and early in the ICU stay. However, with increasing ICU stay (in particular greater than 10 days) antecedent characteristics are more predictive.[55]

LOCATION AND EMERGENCY STATUS

The location from which a patient is admitted may provide an indirect measure of disease severity by the level of care required by patients in that location.[3,52] Consequently, patient location is included as a covariate in some scores. SAPS III has three locations: emergency, another ICU or 'other,'[9,36] whereas the ICNARC model has six: elective surgery, emergency surgery, ward, ICU transfer, emergency or home.[6] Although the predictive power of location may be low and its removal has almost no significant effects on model calibration and discrimination,[9] it is easily measured. In contrast, elective or emergency status can often have a large effect.[27]

SEVERITY SCORING SYSTEMS IN COMMON USE

ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION I–IV

The prototype APACHE score was derived in 1981 by Knaus, to allow evaluation of case mix in trials, compare outcomes, evaluate the efficacy of new therapies and evaluate resource use in ICUs.[1] The model was developed using data from 805 patients admitted to a university hospital ICU and a community hospital ICU within the United States. Cardiac surgery

was excluded, and the values and weightings of each variable were decided by expert consensus of five physicians.[1] APACHE I has been superseded by later versions and is the only iteration not in current use.

A revised version (APACHE II) was released in 1985.[2] Infrequently measured physiological variables were removed, as were variables which demonstrated poor predictive power. APACHE II was developed and validated using data from 5030 admissions to 13 different US ICUs. Weightings were adjusted from APACHE I but were still determined by expert consensus rather than regression modelling. The final APACHE II score is a sum of three components: the acute physiology score (from the worst values in the first 24 hours of ICU admission), a chronic health score and a score based on age. APACHE II has been the most commonly used and reported scoring system. Modern mortality outcomes are much lower than the original mortality predictions derived from the score components and admission diagnosis, an example of poor calibration.

APACHE III was released in 1991.[3] The number of hospitals involved was expanded to 40 to provide a representative sample of US ICUs, and data from 17,440 admissions was used. Of the included hospitals, 23 were selected randomly to provide a representative sample. APACHE III used multivariable regression to weight the predictive variables. A later update included estimations for cardiac surgical patients, making it the first APACHE score to do so. APACHE III represented an advance over APACHE II, with improved discrimination (AUROC 0.9, compared with 0.85) and calibration.[3] Several updates to APACHE III have been released, using alphabetical designators (e.g. the 10th update is APACHE III-j, which is publicly available).

The latest iteration is APACHE IV, derived in 2006 from 110,558 admissions from 104 ICUs in 40 different US hospitals. APACHE IV was developed due to poor calibration of APACHE III in modern patient populations.[4] It takes into account sedative effects on the ability to score the Glasgow Coma Scale (GCS) and has a more extensive admission diagnosis list. APACHE IV has good discrimination and calibration within its validation data set but may not be valid in all countries, due to poor calibration outside the United States.[5,6]

SIMPLIFIED ACUTE PHYSIOLOGY SCORE I–III

The SAPS was developed in France in 1985 and was based almost entirely on physiological variables.[7] Like APACHE I, the variables and their weightings were determined by author consensus. SAPS I was primarily designed to overcome the complexity of APACHE I and was significantly easier to complete. SAPS I demonstrated equivalent discrimination to APACHE I in the derivation cohort of 679 patients.[7] Each range of scores corresponded to a particular mortality rate.

SAPS II was an expanded version of SAPS I and was released as in 1993. Logistic regression was used to select variables for inclusion, decide on groupings for each variable and convert the severity score to a mortality prediction.[8] SAPS II was an international effort, with data used from 13,152 patients from 10 nations across Europe and North America. Burns, coronary and cardiac surgical patients were excluded. Discrimination was greatly improved over SAPS I and was equivalent to APACHE III and MPM II while still being quick to use.

SAPS III was published in 2005 and was derived from a database of 19,577 admissions to 307 ICUs across Europe; North, Central and South America; the Mediterranean and Australasia.[9,36] The equation is customised for each geographic area. Interestingly, and in contrast to the APACHE III and ICNARC scores, the majority of predictive power for SAPS 3 is from patient characteristics known prior to admission, and the circumstances surrounding admission and the acute physiological component contribute 22.5 and 27.5%, respectively.[3,6,9] Although SAPS III has poorer explanatory power than APACHE IV, it applies to a greater proportion of the world than any other scoring system available and represents a significant improvement over SAPS II.

MORTALITY PREDICTION MODEL I–III

The MPM was an evidence-based response to APACHE I and used data derived from a single US institution to compute risk of death using a logistic regression equation.[10]

MPM II was released in 2005 and consisted of two versions: MPM-II_0 (assessed at ICU admission) and MPM-II_{24} (assessed at 24 hours). MPM-II_0 and MPM-II_{24} have similar discriminatory power to SAPS II, with AUROCs of 0.82 and 0.84, respectively.

MPM III was introduced in 2007 in response to falling calibration of MPM II.[12] The score was developed on a new dataset using the same variables, with the addition of whether the patient had a 'do not resuscitate' order at the time of admission. The subsequent analysis achieved significantly better calibration than the previous iteration, with an AUROC of 0.82.

The advantage of the MPM systems are that the burdens of data collection are low because the variables are binary and all data are recorded at time of admission. However, its simplicity is counterbalanced by poorer discrimination compared with other scoring systems.

INTENSIVE CARE NATIONAL AUDIT AND RESEARCH CENTRE MODEL

The ICNARC is a UK organisation dedicated to the collection and analysis of critical care data. The ICNARC model[6] was originally published in 2007 and

derived from data which was initially collected by the ICNARC for the derivation of APACHE II, APACHE III, SAPS II and MPM II scores. It uses several of the same physiological parameters of the other scores but incorporates an expanded list of diagnostic criteria.

The first ICNARC model included data from 216,626 patients from 163 ICUs. The model is recalibrated regularly using data from the Case Mix Programme to maintain accuracy within the derivation cohort. However, like APACHE, it is based entirely on a national cohort and may not be suitable for use outside the United Kingdom.

AUSTRALIA AND NEW ZEALAND RISK OF DEATH

The ANZROD model[5] was developed by the ANZICS CORE to replace APACHE III-j, the performance of which had been deteriorating over time. Data from 450,000 ICU admissions submitted to the ANZICS Adult Patient Database between 2004 and 2009 were used to develop the initial model. In addition to the 124 diagnostic categories, to increase accuracy, eight major diagnostic groups were defined by a specific equation.[57] Patients admitted for palliative care, organ donation, or who are younger than 16 are excluded, but (unlike many other models) burns and cardiac surgery are included. The model demonstrated better calibration and discrimination than APACHE III-j in Australasian hospitals and is routinely recalibrated to maintain accuracy.

SEPSIS ORGAN FAILURE ASSESSMENT

The SOFA (later renamed Sequential Organ Failure Score) is an organ failure score. Organ failure scores can be used to predict mortality based on the number and severity of organ system failures. This is slightly different from the more general severity scores, which predict mortality from a variety of different explanatory variables.

The SOFA score was originally constructed to provide a simple, objective and reliable score for daily assessment of organ dysfunction in sepsis trials.[26] It scores the function of six organ systems (brain, cardiovascular, coagulation, renal, hepatic, respiratory) from 0 (normal) to 4 (extremely abnormal), with parameter intervals defined by experts. These parameter intervals also include the effects of treatment, including mechanical ventilation, vasoactive supports and sedation. The final score is calculated daily using the worst values for each system.

The initial role of SOFA was not to predict mortality but to quantify the sequence of events that occur in the critically ill patient.[26] SOFA has since been evaluated as a mortality prediction tool, and several derivative scores have been described for this purpose.[25,58–60] These include the mean SOFA score (sum of all SOFA scores divided by the length of stay), the highest score and Δ-SOFA (defined differently in different trials but in principle evaluating the difference between two scores[58,59]). These derivative scores demonstrate strong discrimination. However, calibration was not assessed in all instances[60] and use of SOFA as a replacement of existing severity scores is not warranted.

PAEDIATRIC INDEX OF MORTALITY[1]

The PIM is a series of severity scores covering patients younger than 16 years, who are typically excluded from other severity scoring systems. PIM1 was published in 1997, using data from seven Australian and one UK PICU.[13] Two further iterations have been released,[14,15] with the latest version (PIM3) released in 2013. PIM3 was developed from 53,112 consecutive admissions to PICUs in the United Kingdom, Ireland, Australia and New Zealand and uses several physiological and admission variables. The PIM3 model includes all individuals less than 16 admitted to a PICU, excluding those who were transferred to another ICU. The model demonstrates strong discrimination (AUC 0.88) across a range of predicted mortalities.

The PIM series are not the only paediatric-specific scoring systems; others include the Paediatric Risk of Mortality (PRISM) series of scores[61,62] and organ failure scores such as the Paediatric Logistic Organ Dysfunction Score (PELODS) series.[63,64]

SCORES FOR SPECIAL POPULATIONS

QUICK SEPSIS ORGAN FAILURE ASSESSMENT

The quick-SOFA (qSOFA) score was developed in 2016 as a bedside screening tool for patients at risk of death and with suspected infection. The score used three criteria, with one point given for low blood pressure (systolic blood pressure ≤100), respiratory rate (>22 per minute) or altered mentation (GCS <15), to a maximum of three.[19] qSOFA showed better discrimination than either SIRS and SOFA with respect to in-hospital mortality outside of the ICU (AUROC 0.81 compared with 0.76 and 0.79, respectively) but had little relationship to mortality within the ICU.[40]

INJURY SEVERITY SCORE

The ISS is an anatomically based scoring system for trauma patients, released in 1974.[18] The ISS is based on the Abbreviated Injury Scale (AIS), which classifies the severity of injury to six body regions (head and neck, face, chest, abdomen and pelvic contents, extremities or pelvic girdle, external). Injuries are graded from 1 (minor) to 6 (currently untreatable).[65] The ISS is then calculated from the sum of squares of the highest score in the three most severely injured regions.

Unlike physiological scores, which typically use data obtained close to the height of acuity, all injuries in ISS are relevant irrespective of the time at which

they were detected. Therefore injuries identified in tertiary surveys, trauma follow-up and postmortem examination are included. The ISS also has weaker discrimination as it ignores chronic disease.

Other trauma scoring systems exist. These include the Trauma Score[66] (and Revised Trauma Score[67]), which are based on age and physiological variables; and the Trauma and Injury Severity Score (TRISS) series, which combines both the Trauma Score and the ISS to give a combined anatomic and physiological scoring system.[68,69]

REFERENCES

1. Knaus WA, Zimmerman JE, Wagner DP, et al. APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. *Crit Care Med*. 1981;9(8):591–597.
2. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818–829.
3. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest*. 1991;100(6):1619–1636.
4. Zimmerman JE, Kramer AA, McNair DS, et al. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med*. 2006;34(5):1297–1310.
5. Paul E, Bailey M, Kasza J, et al. The ANZROD model: better benchmarking of ICU outcomes and detection of outliers. *Crit Care Resusc*. 2016;18(1):25–36.
6. Harrison DA, Parry GJ, Carpenter JR, et al. A new risk prediction model for critical care: the Intensive Care National Audit & Research Centre (ICNARC) model. *Crit Care Med*. 2007;35(4):1091–1098.
7. Le Gall JR, Loirat P, Alperovitch A, et al. A simplified acute physiology score for ICU patients. *Crit Care Med*. 1984;12(11):975–977.
8. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA*. 1993;270(24):2957–2963.
9. Moreno RP, Metnitz PGH, Almeida E, et al. SAPS3—from evaluation of the patient to evaluation of the intensive care unit. Part 2: development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Med*. 2005;31(10):1345–1355.
10. Lemeshow S, Teres D, Pastides H, et al. A method for predicting survival and mortality of ICU patients using objectively derived weights. *Crit Care Med*. 1985;13(7):519–525.
11. Lemeshow S, Teres D, Klar J, et al. Mortality Probability Models (MPM II) based on an international cohort of intensive care unit patients. *JAMA*. 1993;270(20):2478–2486.
12. Higgins TL, Teres D, Copes WS, et al. Assessing contemporary intensive care unit outcome: an updated Mortality Probability Admission Model (MPM0-III). *Crit Care Med*. 2007;35(3):827–835.
13. Shann F, Pearson G, Slater A, et al. Paediatric index of mortality (PIM): a mortality prediction model for children in intensive care. *Intensive Care Med*. 1997;23(2):201–207.
14. Slater A, Shann F, Pearson G. PIM2: a revised version of the Paediatric Index of Mortality. *Intensive Care Med*. 2003;29(2):278–285.
15. Straney L, Clements A, Parslow RC, et al. Paediatric index of mortality 3: an updated model for predicting mortality in pediatric intensive care. *Pediatr Crit Care Med*. 2013;14(7):673–681.
16. Schmidt M, Burrell A, Roberts L, et al. Predicting survival after ECMO for refractory cardiogenic shock: the survival after veno-arterial-ECMO (SAVE)-score. *Eur Heart J*. 2015;36(33):2246–2256.
17. Schmidt M, Bailey M, Sheldrake J, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. *Am J Respir Crit Care Med*. 2014;189(11):1374–1382.
18. Baker SP, O'Neill B, Haddon W Jr, et al. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma*. 1974;14(3):187–196.
19. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):762–774.
20. Becker RB, Zimmerman JE, Knaus WA, et al. The use of APACHE III to evaluate ICU length of stay, resource use, and mortality after coronary artery by-pass surgery. *J Cardiovasc Surg (Torino)*. 1995;36(1):1–11.
21. Straney LD, Clements A, Alexander J, et al. Measuring efficiency in Australian and New Zealand paediatric intensive care units. *Intensive Care Med*. 2010;36(8):1410–1416.
22. Bouch DC, Thompson JP. Severity scoring systems in the critically ill. *Contin Edu Anaesth Crit Care Pain*. 2008;8(5):181–185.
23. Paul E, Bailey M, Van Lint A, et al. Performance of APACHE III over time in Australia and New Zealand: a retrospective cohort study. *Anaesth Intensive Care*. 2012;40(6):980–994.
24. Bewick V, Cheek L, Ball J. Statistics review 14: logistic regression. *Crit Care*. 2005;9(1):112–118.
25. Kajdacsy-Balla Amaral AC, Andrade FM, Moreno R, et al. Use of the sequential organ failure assessment score as a severity score. *Intensive Care Med*. 2005;31(2):243–249.
26. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707–710.
27. Paul E, Bailey M, Pilcher D. Risk prediction of hospital mortality for adult patients admitted to

Australian and New Zealand intensive care units: development and validation of the Australian and New Zealand Risk of Death model. *J Crit Care*. 2013;28(6):935–941.
28. Box GEP, Draper NR. *Wiley Series in Probability and Mathematical Statistics. Empirical Model-Building and Response Surfaces*. Oxford, England: John Wiley & Sons; 1987.
29. Strand K, Flaatten H. Severity scoring in the ICU: a review. *Acta Anaesthesiol Scand*. 2008;52(4):467–478.
30. Martinez-Alario J, Tuesta ID, Plasencia E, et al. Mortality prediction in cardiac surgery patients: comparative performance of Parsonnet and general severity systems. *Circulation*. 1999;99(18):2378–2382.
31. Nashef SA, Roques F, Sharples LD, et al. EuroSCORE II. *Eur J Cardiothorac Surg*. 2012;41(4): 734–744, discussion 44–45.
32. Roques F, Michel P, Goldstone AR, et al. The logistic EuroSCORE. *Eur Heart J*. 2003;24(9):881–882.
33. Roques F, Nashef SA, Michel P, et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg*. 1999;15(6):816–822, discussion 22–23.
34. Hekmat K, Kroener A, Stuetzer H, et al. Daily assessment of organ dysfunction and survival in intensive care unit cardiac surgical patients. *Ann Thorac Surg*. 2005;79(5):1555–1562.
35. Shahin J, Ferrando-Vivas P, Power GS, et al. The Assessment of Risk in Cardiothoracic Intensive Care (ARCtIC): prediction of hospital mortality after admission to cardiothoracic critical care. *Anaesthesia*. 2016;71(12):1410–1416.
36. Metnitz PG, Moreno RP, Almeida E, et al. SAPS 3—from evaluation of the patient to evaluation of the intensive care unit. Part 1: objectives, methods and cohort description. *Intensive Care Med*. 2005;31(10): 1336–1344.
37. Moore EC, Pilcher DV, Bailey MJ, et al. The Burns Evaluation and Mortality Study (BEAMS): predicting deaths in Australian and New Zealand burn patients admitted to intensive care with burns. *J Trauma Acute Care Surg*. 2013;75(2):298–303.
38. Tsurumi A, Que YA, Yan S, et al. Do standard burn mortality formulae work on a population of severely burned children and adults? *Burns*. 2015;41(5):935–945.
39. Freund Y, Lemachatti N, Krastinova E, et al. Prognostic accuracy of sepsis-3 criteria for in-hospital mortality among patients with suspected infection presenting to the emergency department. *JAMA*. 2017;317(3):301–308.
40. Raith EP, Udy AA, Bailey M, et al. Prognostic accuracy of the sofa score, sirs criteria, and qsofa score for in-hospital mortality among adults with suspected infection admitted to the intensive care unit. *JAMA*. 2017;317(3):290–300.
41. Vincent JL, Opal SM, Marshall JC. Ten reasons why we should NOT use severity scores as entry criteria for clinical trials or in our treatment decisions. *Crit Care Med*. 2010;38(1):283–287.
42. Booth FV, Short M, Shorr AF, et al. Application of a population-based severity scoring system to individual patients results in frequent misclassification. *Crit Care*. 2005;9(5):R522–R529.
43. Girling AJ, Hofer TP, Wu J, et al. Case-mix adjusted hospital mortality is a poor proxy for preventable mortality: a modelling study. *BMJ Qual Saf*. 2012; 21(12):1052–1056.
44. Mohammed MA, Rathbone A, Myers P, et al. An investigation into general practitioners associated with high patient mortality flagged up through the Shipman inquiry: retrospective analysis of routine data. *BMJ*. 2004;328(7454):1474–1477.
45. Duckett SJ, Coory M, Sketcher-Baker K. Identifying variations in quality of care in Queensland hospitals. *Med J Aust*. 2007;187(10):571–575.
46. Spiegelhalter D. Funnel plots for institutional comparison. *Qual Saf Health Care*. 2002;11(4): 390–391.
47. Mohammed MA, Cheng KK, Rouse A, et al. Bristol, Shipman, and clinical governance: Shewhart's forgotten lessons. *Lancet*. 2001;357(9254):463–467.
48. Cook DA, Duke G, Hart GK, et al. Review of the application of risk-adjusted charts to analyse mortality outcomes in critical care. *Crit Care Resusc*. 2008;10(3):239–251.
49. Steiner SH, Cook RJ, Farewell VT. Risk-adjusted monitoring of binary surgical outcomes. *Med Decis Making*. 2001;21(3):163–169.
50. Cook DA. *The Development of Risk Adjusted Control Charts and Machine Learning Models to Monitor the Mortality Rate of Intensive Care Unit Patients*. Brisbane: University of Queensland; 2004.
51. Moreno RP, Metnitz PG, Almeida E, et al. SAPS 3—from evaluation of the patient to evaluation of the intensive care unit. Part 2: development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Med*. 2005;31(10): 1345–1355.
52. Tunnell RD, Millar BW, Smith GB. The effect of lead time bias on severity of illness scoring, mortality prediction and standardised mortality ratio in intensive care—a pilot study. *Anaesthesia*. 1998; 53(11):1045–1053.
53. Ho KM, Dobb GJ, Knuiman M, et al. A comparison of admission and worst 24-hour Acute Physiology and Chronic Health Evaluation II scores in predicting hospital mortality: a retrospective cohort study. *Crit Care*. 2006;10(1):R4.
54. Duke GJ, Pilcher DV, Shann F, et al. ANZROD, COPE 4 and PIM 3: caveat emptor. *Crit Care Resusc*. 2014;16(3):155–157.
55. Iwashyna TJ, Hodgson CL, Pilcher D, et al. Timing of onset and burden of persistent critical illness in Australia and New Zealand: a retrospective, population-based, observational study. *Lancet Respir Med*. 2016;4(7):566–573.
56. Lee H, Shon YJ, Kim H, et al. Validation of the APACHE IV model and its comparison with the APACHE II, SAPS 3, and Korean SAPS 3 models for the prediction of hospital mortality in a Korean

surgical intensive care unit. *Korean J Anesthesiol*. 2014;67(2):115–122.
57. Pilcher D, Paul E, Bailey M, et al. The Australian and New Zealand Risk of Death (ANZROD) model: getting mortality prediction right for intensive care units. *Crit Care Resusc*. 2014;16(1):3–4.
58. Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA*. 2001;286(14):1754–1758.
59. Janssens U, Graf C, Graf J, et al. Evaluation of the SOFA score: a single-center experience of a medical intensive care unit in 303 consecutive patients with predominantly cardiovascular disorders. Sequential Organ Failure Assessment. *Intensive Care Med*. 2000;26(8):1037–1045.
60. Cardenas-Turanzas M, Ensor J, Wakefield C, et al. Cross-validation of a Sequential Organ Failure Assessment score-based model to predict mortality in patients with cancer admitted to the intensive care unit. *J Crit Care*. 2012;27(6):673–680.
61. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. *Crit Care Med*. 1988;16(11): 1110–1116.
62. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated Pediatric Risk of Mortality score. *Crit Care Med*. 1996;24(5):743–752.
63. Leteurtre S, Duhamel A, Grandbastien B, et al. Paediatric logistic organ dysfunction (PELOD) score. *Lancet*. 2006;367(9514):897, author reply 900–902.
64. Leteurtre S, Duhamel A, Salleron J, et al. PELOD-2: an update of the pediatric logistic organ dysfunction score. *Crit Care Med*. 2013;41(7):1761–1773.
65. Copes WS, Champion HR, Sacco WJ, et al. The Injury Severity Score revisited. *J Trauma*. 1988; 28(1):69–77.
66. Champion HR, Sacco WJ, Carnazzo AJ, et al. Trauma score. *Crit Care Med*. 1981;9(9):672–676.
67. Champion HR, Sacco WJ, Copes WS, et al. A revision of the Trauma Score. *J Trauma*. 1989;29(5): 623–629.
68. Boyd CR, Tolson MA, Copes WS. Evaluating trauma care: the TRISS method. Trauma Score and the Injury Severity Score. *J Trauma*. 1987;27(4):370–378.
69. Schluter PJ. The Trauma and Injury Severity Score (TRISS) revised. *Injury*. 2011;42(1):90–96.

4

Transport of critically ill patients

Evan R Everest, Roy Fischer

Critical illness and injury are not necessarily defined by patient location. In addition, patients may overwhelm the level of care at their current location or require specific investigations or treatments not immediately available to them. For this reason, the transport of critically ill and injured patients occurs frequently.

Critical care patient transport has traditionally been divided into two groups; patient movement within a hospital (intrahospital) or movement between hospitals (interhospital or interfacility). In addition, a select group of critically ill or injured patients not located in a hospital facility may be managed by physician-based medical teams prior to retrieval to a hospital. Therefore, a third division (primary response or pre-hospital care) is well recognised.

The internationally widespread deployment of medical teams for critically ill patient management and retrieval from both health care facilities and pre-hospital locations has resulted in the recognition of pre-hospital and retrieval medicine as a distinct subspecialty.[1]

INTRAHOSPITAL TRANSPORT

The safest place for the critically ill patient is in the intensive care unit (ICU) connected to a modern ventilator and physiological monitoring, a nurse present to care for the patient and rapid access to nursing and medical assistance. Transports are usually required to facilitate critical investigations and interventions or to move the patient from one critical care area to another. Critically ill or injured patients with limited or no physiological reserve undergoing such transports are at risk of clinical deterioration and adverse events are well reported.[2,3] In order to reduce the mortality and morbidity associated with patient movement, a structured approach utilising high-level clinical personnel who have the correct equipment, training and sufficient planning time is required.

Moving the patient should be associated with little or no compromise in their condition. Unfortunately, this is not the case with an adverse event occurring in up to 70% of transports. One-third of these events are equipment related.[4] Deterioration in gas exchange[5] and increased rates of ventilator-associated pneumonia are common.[6] However, management is changed in 40%–50% of patients, thus justifying the risk.

Patients with unstable physiology should not be transported for nonurgent interventions or investigations. However, where the intervention or investigation is deemed critical to achieving patient stability or providing definitive management, the benefits in patient outcome will outweigh the inherent risks of transport. Therefore the transport can be seen as part of the patient's therapeutic requirement and stabilisation process. On occasions when the patient's need is so acute, or the likelihood of irreversible deterioration in transit is so high, consideration should be given to facilitating such interventions or investigations in the ICU rather than the location where these procedures would normally occur.

When preparing for intrahospital transport, the following structured approach is recommended:

- Prior planning to ensure minimal manual handling and to minimise the time away from the ICU.
- Clinical reassessment should occur swiftly, systematically and, whenever possible, with the patient already supported on the equipment that will be used during transport.
- The airway should be checked and secured, endotracheal suction performed, ventilation and oxygenation optimised, adequate and patent vascular access secured and drainage devices measured and emptied.
- Sedation and analgesic requirements should be addressed and any drugs required for transport (including additional infused agents) pre-drawn and labelled for immediate use.
- Ensure that the patient's clinical record remains with the team caring for the patient.

COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING SCANNING

Computed tomography (CT) scanning is the most common ICU diagnostic intervention requiring patient movement. Head-injury patients and those requiring previous administration of oral contrast with decreased gut motility (and thus increasing risk of aspiration) require

ABSTRACT

Critically ill patients often need to be moved within or between hospitals for investigations or treatments. Every movement is associated with an increased risk of an adverse event that may significantly impact on their chances of recovery. Transport of these patients must occur in a structured manner using experienced clinical personnel who are trained to recognise complications and to manage them in often less than desirable environments. The equipment and monitoring used during the transport is often less sophisticated and requires specific training in its use and recognition of its limitations. The transport vehicle for interhospital retrievals can be road ambulances or aircraft, either helicopter or fixed wing. Each modality has advantages and disadvantages and choice should be based on which will provide the best risk benefit.

KEYWORDS

Retrieval
transport
pre-hospital response
helicopter
equipment

extra attention. When the CT scan is booked it is vital to liaise with the radiologist and other treating teams involved to ensure that the scan will address all the clinical questions. It is important to secure adequate vascular access for the pressure injection of intravenous (IV) contrast prior to leaving ICU; standard multilumen central lines are not suitable. Specific peripherally inserted central catheter (PICC) or central venous catheter (CVC) lines that are suitable for pressure injection may be used or a secure large bore peripheral IV inserted. Single-lumen large-bore central catheters are an alternative but should be used only as a last resort.

Repeated CT scanning of head-injured patients is common. In these patients with decreased cerebral compliance, movement or changes in body position or partial pressure carbon dioxide ($PaCO_2$) can result in significant elevations in intracranial pressure (ICP). Although movement-induced changes in ICP can be reduced with sedation, very little can be done about body position. Changes in $PaCO_2$ are usually due to variation between ICU and transport ventilators. Technological improvements mean that modern transport ventilators can deliver ventilation much more accurately than older devices. However, differences in circuit design, calibration and end-tidal CO_2 ($ETCO_2$) sampling mean that it remains good practice, if time permits, to establish the patient on the transport monitor and ventilator 10–15 minutes prior to departure. This allows time to take an arterial blood gas sample to establish the relationship between $PaCO_2$ and $ETCO_2$ and define what $ETCO_2$ should be targeted. Ideally the ICP should also be measured but at times this may not be possible.

Radiation exposure for both the patient and staff needs to be considered. A stable patient who is adequately monitored with alarms activated can be observed by staff outside the room. The patient should be moved back to the ICU as soon as scanning is completed.

Magnetic resonance imaging (MRI) is increasingly used as a diagnostic and prognostic tool for a wide range of ICU patients. MRI scanning entails greater risk than CT due to the unique environment, longer duration of scans and greater need for patient immobility (potentially necessitating sedation in nonintubated patients). The major problems with MRI are the effect that the magnetic field may have on ventilators, monitors and infusion pumps, and the potential for these items to become effectively a missile by being attracted to the magnet. The last decade has seen the development of monitoring and ventilators that are MRI compatible and the acceptance of standards for equipment in the MRI. These magnetic resonance standards are: MRI safe, conditional or unsafe. Safe and unsafe are self-explanatory, while conditional relates to equipment that is safe when used under certain predetermined conditions, for example, distance from the magnet. While larger ICUs increasingly have MRI compatible transport equipment, this is not the case at every facility. More often facilities have MR safe anaesthesia machines for the provision of general anaesthesia during the MRI examination. This equipment is 'foreign' to most ICU staff and often is not used owing to lack of familiarity. The third option is to use non-MRI–compatible equipment but to keep it outside of the scan room; ventilator and infusion lines can be lengthened with long extensions and routed through openings in the wall. This then only requires a dedicated MRI monitor inside the scan room. Not all ICU patients may be suitable to undergo MRI scanning. The magnetic field of the MRI scanner may pull on some metal-containing implants or cause heating due to the radiofrequency energy; in addition, the magnetic field can cause malfunction of implanted devices (e.g. pacemakers). Prior discussion with the MRI unit must occur before the patient is moved from the ICU; this is important to ensure patient safety and to avoid denying patients the potential diagnostic benefit of MRI unnecessarily. With improving technology, some types of devices that were previously an absolute contraindication to MRI may now be suitable under some circumstances. Most MRI units will require an MRI checklist to be completed prior to scanning.

It is important to note that the magnetic field is always active and staff entering the scan room need to be screened for metallic devices either implanted or on their person that may be dangerous.

OPERATING THEATRE AND INTERVENTIONAL RADIOLOGY

Transfer to and from the operating room should be done by the anaesthetist who will be caring for the patient during the procedure. This allows handover in the controlled environment of ICU and minimises the number of people entering the sterile operating room environment. For complex interventional radiology procedures the same arrangement should occur. For diagnostic or simpler interventional procedures the ICU team undertake the transfer and care during the procedure. It is vital that the team has an understanding of the procedural requirements including patient positioning, the need for analgesia, the possible complications and the specific treatments/physiological targets required.

STAFFING

A team consisting of at least one ICU medical officer and nurse should be free from other duties. Both team members should be thoroughly familiar with the transport process, equipment and environment. The team should possess the requisite skills and knowledge to independently manage critically ill patients in transit and to deal with anticipated emergencies. The more complex and unstable the patient is, the more capable the team must be. For very unstable patients an additional nurse and more senior doctors may be required. Assistance with safe patient, trolley and equipment movement is also needed. Therefore nonclinical hospital support staff are part of the team and should be included in all briefs and contingency planning.

EQUIPMENT

Transport equipment should be regularly checked and serviceable. Powered devices should be fully charged, with power cords accessible to facilitate use of mains power in the event of delay. Where possible, equipment should be lightweight, robust and standardised throughout the ICU and hospital. In transit, equipment should be secured (not resting on the patient) but readily accessible. Dedicated transport bridges or gantries are commonly used. Dedicated transport packs or boxes ensure safe carriage of consumable items, resuscitation equipment and drugs. Equipment required for emergency airway management (e.g. bag valve mask, laryngoscope, airway devices and endotracheal tubes) must be immediately available.

MONITORING

As a minimum, intubated and ventilated patients requiring intrahospital transport should have the following monitoring instituted[7]:

- continuous $ETCO_2$
- continuous Sa_{O_2}
- continuous invasive or intermittent noninvasive BP
- continuous three-lead electrocardiography (ECG).

Ideally, a cardiac monitoring device should also provide cardiac defibrillation and external cardiac-pacing capability. Patients requiring transport with more advanced monitoring in situ should be considered on a case-by-case basis. For example, ongoing ICP monitoring is critical to ensure avoidance of profound unmonitored falls in cerebral perfusion pressure in an ICU patient with a severe head injury, whereas pulmonary artery pressure monitoring may be excluded from the transport requirements in the haemodynamically stable patient.

INTERHOSPITAL TRANSPORT

With rising expectations for high-level care by the community in both metropolitan and rural locations and with the care for critically ill and injured patients becoming increasingly centralised in large, tertiary, metropolitan ICUs, the need to transfer patients between health care facilities has also increased. Such a demand has seen the development of dedicated specialist retrieval teams. Historical models of interhospital patient transfer utilising junior medical staff as 'patient escorts' have much higher rates of hypotension, acidosis and death.[8] Thankfully this type of transport has become increasingly rare with the introduction of specialist retrieval services.

The general principles of patient transport regarding equipment, patient monitoring and clinical requirements remain the same irrespective of the physical location of the patient. Standards for transportation of the critically ill have been widely promulgated and must be followed whether it is a complex unstable patient being moved long distances or a semi-elective CT in a stable ICU patient.

RETRIEVAL CLINICAL COORDINATION AND ADVICE

Retrieval clinical coordination describes the process whereby specialist medical, nursing, paramedic and ambulance service staff are involved in direct supervision of the primary and interhospital transport or retrieval of patients. This is to ensure:

- the safe and efficient use of expensive transport and retrieval services
- that high-level clinical advice is available prior to and during transport
- the patient is delivered in a timely manner to the most appropriate receiving hospital.

Not all patients who are referred for retrieval will require transport. Of those who do, not all will require a retrieval team. To ensure that this is addressed, an integrated systems approach is required. In general, a retrieval service will be used when the complexity of the patient exceeds the ambulance service's ability to transport the patient. Tele-medicine is playing an important and increasing role in this process – not only in assisting decision making regarding retrieval activities (resulting in potential cost savings) but also in supporting remote and regional medical practitioners faced with acutely ill or injured patients, and in supporting a retrieval team before and during patient transport. For this reason, many retrieval coordination centres are co-located with ambulance service communication centres. In this way, clinical and logistic expertise is integrated. Knowing where key assets (transport platforms, such as road ambulances, helicopters and fixed-wing aircraft) and retrieval teams are at any one time is crucial to effective retrieval clinical coordination. Real-time asset tracking or mapping systems and advanced radio or phone communication networks assist in this regard.

RETRIEVAL TEAM STAFFING

The aim of the team is at least to maintain, but ideally to increase the level of care during transport. This requires a team of sufficient size and skill to provide the full complement of care for the majority of patients being transported.

The minimum team should comprise two people; occasionally a very-low-acuity stable patient may be escorted by a single person. If multiple patients are to be transported, a recommended staffing level is $n + 1$ where n equals the number of patients.[9]

Who makes up the team continues to be debated. In most cases a doctor will be one member while the other can be a person with either an acute care nursing or an ambulance background. Other requirements include the ability to work and communicate as a team, have

reasonable body habitus and physical fitness, and have no visual or auditory impairment or a susceptibility to motion sickness. In aviation transport the weight of the teams and their equipment is important as there is a maximum weight available. High team weights can limit the amount of fuel able to be carried, which may compromise some missions.

There may be some highly complex cases that will be outside of the team's capability, and supplementation of the retrieval team by additional specialist personnel may be required. For example, an obstetrician or neurosurgeon[10] may be added depending on the type of mission. It is mandatory that the specialist is added to a standard team because of the latter's familiarity with working in the retrieval environment.

TRAINING

Training should cover the following:

- standard operating procedures for the service
- the use of scenarios to teach common procedures and principles
- familiarity in the various transport platforms to be used; this would include safety briefings on aerial assets and may include helicopter underwater escape training (HUET) and crew (cockpit) resource management (CRM)
- communication procedures
- understanding of the effects of altitude and flight on patient (and team) physiology.

EQUIPMENT

GENERAL CONSIDERATIONS

Minimum equipment standards for supplies, equipment and monitoring have been published.[7] The equipment carried is often a compromise between providing for every conceivable situation and being lightweight and mobile. In some cases it is appropriate to have additional specialist packs that are taken only when warranted by the clinical situation; for example, a Sengstaken–Blakemore tube or temporary transvenous pacing wire is taken only when a gastrointestinal (GI) haemorrhage occurs in a patient who might have varices or the patient has symptomatic complete heart block. This requires good communication and a robust coordination process.

A suggested list of equipment is given in Box 4.1.

Transport monitors, infusion pumps and ventilators must work out of the transport vehicle. They must be battery powered whilst ideally allowing for utilisation of ambulance or aircraft power during transport. Batteries in most modern systems are either sealed lead acid or lithium. Battery life is quoted for new batteries and with time this value decreases. Planning on a battery life of 50% of that quoted is prudent. Spare batteries can be carried but changing them may result in temporary interruption of function. During transport the equipment must be securely stowed. There are international standards in the 'G force' that securing systems must withstand in the event of a crash. In some modern road vehicles or helicopters the requirement is 20 G. The use of a suitably engineered mount attached to the patient's stretcher to which the equipment can be secured provides the most safety.[11]

MONITORING

Clinical observation by experienced clinicians remains an important facet of monitoring.[12] However, there are significant limitations to this approach. It is difficult to auscultate adequately in a moving vehicle and impossible in a helicopter. As a minimum, ECG, pulse oximetry and noninvasive blood pressure (BP) measurement must be provided with the addition of $ETCO_2$ for any intubated patient. Noninvasive BP measurements are often subject to interference, and for critically ill patients invasive arterial access is essential, especially if the length of the transport is long.[13] Newer monitors that combine defibrillation and pacing with the monitoring aspects outlined above may be an advantage. However, noninvasive BP and defibrillation uses significant battery power and spare batteries are essential and must be carried. Portable blood gas analysers provide additional management information during long transports.

VENTILATORS

A mechanical ventilator must be used on all intubated patients as manual ventilation cannot reliably deliver constant tidal volumes and a stable $ETCO_2$.[14] However, a manual system must be available in the rare event of a ventilator failure. Transport ventilators are a compromise between portability and features. Over the last 10 years the desired features (as listed in Box 4.2) have almost been met. Small neonates often still require a specific ventilator; at the very least they require specialised circuits and ventilator software.

The provision of noninvasive ventilation (NIV) is now possible on most modern transport ventilators. An improvement with inspiratory valve-triggering technology has resulted in substantial reductions in circuit work with concurrent reduction in the work of breathing. Although Mapleson-based continuous positive airway pressure (CPAP) systems with high fresh gas flows provide the least circuit work and are optimal for patients with high work of breathing, the new transport ventilators are close enough to ideal to be used. Most patients will tolerate NIV with the modern ventilators,[15] but it does require a different approach by retrieval teams. There needs to be a period of observation prior to transport as the ability to provide advanced airway support in transit is limited. Modern NIV ventilators can at times 'chase' a circuit leak resulting in high gas consumption, and can increase the risk of depleting oxygen supplies. Gas consumption must be monitored.

In most cases, heat moisture exchangers (HMEs) will provide adequate humidification for intubated patients.

Box 4.1 Suggested equipment schedule for interhospital critical care transport

Respiratory equipment
Intubation kit:
- Endotracheal tubes and connectors – adult and paediatric sizes
- Introducers, bougies, Magill forceps
- Laryngoscopes, blades, spare globes and batteries
- Ancillaries: cuff syringe and manometer, 'gooseneck' tubing, HME/filter(s), securing ties, lubricant
- Difficult airway equipment

Alternative airways:
- Simple: Guedel and nasopharyngeal
- Supraglottic: laryngeal masks or similar
- Infraglottic: cricothyrotomy kit and tubes

Oxygen masks (including high Fi_{O_2} type), tubing, nebulisers
Suction equipment:
- Main suction system – usually vehicle mounted
- Spare (portable) suction – hand-, O_2-, or battery-powered
- Suction tubing, Yankauer, catheters and spare reservoir

Self-inflating hand ventilator, with masks and positive end expiratory pressure (PEEP) valve
Portable ventilator with disconnect and overpressure alarms, oxygen failure alarm
Ventilator circuit and spares
Capnometer/capnograph
Pleural drainage equipment:
- Intercostal catheters and cannulae
- Surgical insertion kit and sutures (see below)
- Heimlich-type valves and drainage bags

Main oxygen system (usually vehicle-mounted) of adequate capacity with flowmeters and standard wall outlets
Portable/reserve oxygen system with flowmeter and std outlet
Circulatory equipment
Monitor/defibrillator/external pacemaker, with leads, electrodes and pads
IV fluid administration equipment:
- Range of fluids: isotonic crystalloid, dextrose
- High-flow and metered flow-giving sets
- IV cannulae in range of sizes: peripheral and central/long lines
- IV extension sets, three-way taps and needle-free injection system
- Syringes, needles and drawing-up cannulae
- Skin preparation wipes, IV dressings and Band-Aid
- Pressure infusion bags (for arterial line also).
- Alternate vascular access equipment [e.g. Intra-osseous needle (IO)]

BP monitoring equipment:
- Arterial cannulae with arterial tubing and transducers
- Invasive and noninvasive (automated) BP monitors
- Aneroid (nonmercury) sphygmomanometer and range of cuffs (preferably also compatible with NIBP)

Pulse oximeter, with finger and multisite probes
Syringe/infusion pumps (minimum two) and appropriate tubing
Miscellaneous equipment
Urinary catheters and drainage/measurement bag
Gastric tubes and drainage bag
Minor surgical kit (for inter-costal catheters (ICC), CVC lines, cricothyrotomy, etc.):
- Sterile instruments: scalpels, scissors, forceps, needle holders
- Suture material and needles
- Antiseptics, skin preparation packs and dressings
- Sterile gloves (various sizes); drapes +/– gowns
- Basic thoracotomy equipment

Cervical collars, spinal immobilisation kit (e.g. Vacmat), pelvic binder, splints
Thermometer (nonmercury) and/or temperature probe for monitor
Warming equipment (e.g. reflective blanket, chemical blanket or fluid warmer)
Bandages, tapes, heavy-duty scissors (shears)
Personal protective equipment (PPE): gloves, gowns and eye protection (may need extra for pre-hospital response or aircraft, e.g. helmets, flame retardant flight suit, life vests)
Sharps and contaminated waste receptacles
Pen and folder for paperwork
Torch +/– head light
Drug/additive labels and marker pen
Nasal decongestant (for barotitis prophylaxis)
Pharmacological agents
CNS drugs:
- Narcotic and nonnarcotic analgesics
- Anxiolytics/sedatives
- Antipsychotics
- Anticonvulsants
- IV anaesthetic induction agents
- Antiemetics
- Local anaesthetics

Cardiovascular drugs:
- Antiarrhythmics
- Anticholinergics
- Inotropes/vasoconstrictors
- Nitrates
- Beta blockers
- Other hypotensives

Electrolytes and renal agents:
- Sodium bicarbonate
- Calcium (chloride)
- Magnesium
- Potassium
- Loop diuretics

Endocrine and metabolic agents:
- Glucose (concentrate) +/– glucagon
- Insulin
- Steroids

Other agents:
- Neuromuscular blockers: depolarising and nondepolarising
- Narcotic and benzodiazepine antagonists
- Bronchodilators

Box 4.1 Suggested equipment schedule for interhospital critical care transport—cont'd

- Proton pump inhibitors
- Anticoagulants
- Thrombolytics
- Vitamin K
- Antibiotics +/– antivirals
- Oxytocics
- Tocolytics
- Diluents (saline and sterile water)
- Treatment for elevated ICP (e.g. hypertonic saline or mannitol)

Additional/optional equipment

- Portable ultrasound machine
- Transvenous temporary pacing kit and pacemaker
- Blood (usually O negative) and/or blood products
- Additional infusion pumps and associated IV sets
- Obstetrics kit with neonatal equipment
- Additional paediatric equipment (depending on capability of basic kit)
- Antivenin (polyvalent or specific)
- Specific drugs or antagonists

BP, Blood pressure; *CNS*, central nervous system; *CV*, central venous; *HME*, heat moisture exchangers; *ICC*, inter-costal catheters; *ICP*, intracranial pressure; *IO*, intra-osseous; *IV*, intravenous; *NIBP*, noninvasive blood pressure; *PEEP*, positive end expiratory pressure.

Box 4.2 Features of an ideal transport ventilator

- Small, light, robust and cheap
- Not dependent on external power source
- Turbine driven (can function without high pressure oxygen)
- Easy to use and clean, with foolproof assembly
- Economical on gas consumption
- Suitable for patients from neonates through to large adults
- Fi_{O_2} continuously variable from ambient air to 100% oxygen
- Able to deliver PEEP, CPAP, synchronous intermittent mandatory ventilation (SIMV) and pressure support
- Ability to deliver noninvasive ventilation with leak compensation and low work of breathing
- Variable I:E ratios
- Flow or pressure generator modes
- Integrated monitoring and alarm functions with audio and visual signals
- Altitude compensated

A suction system and reserve are required. In most transport vehicles this can be provided by electrically powered devices with a gas-powered venturi system as a back-up.

INFUSIONS

Critically ill patients often need multiple infusions to be continued during transport. Some drugs that ideally should be given as infusions can be consolidated by combining sedation drugs, or the infusion stopped and given instead by frequent boluses. The older-style volumetric and drop-counting pumps have been superseded by lightweight syringe drivers, which should be the only method used for drug infusions in contemporary retrieval practice.

INTRA-AORTIC BALLOON PUMP AND EXTRACORPOREAL MEMBRANE OXYGENATION

Retrieval of patients with intra-aortic balloon pump (IABP) in situ has been occurring for many years and, in general, a team with some experience in troubleshooting any pump alarms can manage these patients. The IABP machines are reasonably bulky and heavy with an internal battery life of 1–2 hours. The type of transport vehicle has to be considered to ensure that the pump can be safely secured and can be connected to an external power source. Insertion of an IABP catheter requires some experience and some pre-departure consideration of the team's capabilities must be made. The addition to the standard retrieval team of an extra doctor experienced in IABP insertion should be considered.

The H1N1 influenza pandemic in 2009–2010 saw the rapid emergence of extracorporeal membrane oxygenation (ECMO) as a valid treatment for severe viral-induced respiratory failure.[16] It was recognised that ECMO should be provided in a relatively small number of institutions, and that, ideally, patients likely to need ECMO should be transferred early. However, significant numbers of patients deteriorated rapidly and rescue ECMO was instituted in many non-ECMO centres, hence requiring the patient to be transported on ECMO. Many ECMO centre staff will not be familiar with the retrieval environment. A common model to move such patients is to combine the ECMO team with a standard retrieval team. In these cases the role of the retrieval team is to assist by providing the logistical and interhospital expertise to allow the ECMO team to concentrate on caring for the patient.

MODE OF TRANSPORT

There are three common types of transport vehicle used: road vehicles, aeroplanes (fixed wing) and helicopters (rotary wing). The basic requirements are listed in Box 4.3 and their features and limitations are summarised in Table 4.1.

Box 4.3 Essential features of transport vehicles

- Readily available
- Adequate operational safety
- Capable of carrying (at least one) stretcher and mobile intensive care equipment set
- Safe seating for full medical team, including at head and side of patient
- Adequate space and patient access for observation and procedures
- Equipped with adequate supply of oxygen/other gases for duration of transports
- Fitted with medical power supply of appropriate voltage and current capacity
- Appropriate speed (coupled with) comfortable ride, without undue exposure to accelerations in any axis
- Acceptable noise and vibration levels
- Adequate cabin lighting, ventilation and climate control
- Fitted with overhead IV hooks, and sharps/biohazard waste receptacles
- Straightforward embarkation and disembarkation of patient and team
- Fitted with appropriate radios and mobile telephone

IV, Intravenous.

Ideally, dedicated vehicles should be used. Often the workload is insufficient to justify this, and nondedicated vehicles needing to be reconfigured are used. The mode of transport is based on a number of criteria:

- the availability of the transport vehicle
- the weather, especially if flying
- the distance to be travelled
- the location and capability of the retrieval team
- the urgency of the case
- the clinical capability of the referring hospital.

The coordination and tasking centre takes all these into consideration. All things being equal, the road is used for distances up to 40–80 km, rotary wing for 60–200 km and fixed wing for over 200 km.

ROAD AMBULANCE

This remains the most common form of transport and for some patients the safest – even for long distances.

FIXED WING

Both propeller-driven and jet aircraft are used. Compared with helicopters, their faster speed needs to be offset with the need for a road leg at each end of the transfer. In comparison to helicopters, fixed-wing aircraft have

Table 4.1 Properties of transport vehicles

	ROAD	HELICOPTER	FIXED WING
Launch time	3–5 min	5–10 min (more if IFR apply)	30–60 min
Speed	10–120 km/h dependent on roads and traffic	220–290 km/h, straight line	260–340 kph (piston) 420–500 kph (turboprop) 700–850 kph (jet)
Secondary transport	Not applicable	Sometimes	Inevitable
Effective range	0–100 km (longer if required)	50–300 km (longer or shorter in special cases)	200–2000 km
Noise	Low, except at high speed	Moderate to high (headsets required)	Low to moderate (cruise); higher on take-off/landing
Vibrations	Variable with speed and road surface	Moderate in most phases (varies with rotor type)	Low in cruise; moderate or high on take-off/landing
Accelerations	Variable and sometimes unpredictable in all axes	Minimal, and usually vertical only	Significant (fore/aft) on take-off and landing
Special features	Base vehicles readily available	Versatility; point to point capability	Cabin pressurisation and all-weather capability (most)
Acquisition cost	Lowest	High (US$5–15 million new, depending on capabilities)	Moderate (piston) to very high (jet)
Operating costs (per km)	Intermediate	Intermediate to high	Low to intermediate

IFR, Instrument flight rules.

lower cabin noise, the ability to pressurise the cabin (often to sea level), and the ability to fly in 'icing' conditions that increase their utility. Most aeromedical fixed-wing aircraft are specifically configured with stretcher-loading devices to assist in loading. Jets tend to be reserved for longer distance, greater than 800–1000 km.

HELICOPTERS

These remain the most high-profile and expensive vehicles used for patient transport but have been shown to be beneficial and cost effective.[9,17] Most will require significant adaption to provide a reasonable working space. The lack of space makes procedures such as intubation almost impossible. They are very noisy to work in, with conversation only possible via intercom systems. This makes communication with patients difficult. Whereas a mix of single-engine and twin-engine aircraft have been used in the past, changes by regulatory authorities in Europe and Australia mean that most helicopter transports are now being performed in more suitable, larger twin-engine aircraft. The optimal range for use is a 'donut' of 40–300 km and their main advantage is the ability to land on hospital helipads, removing an additional road leg. This, of course, requires the hospital to have a helipad. Helicopters may also have a role in the delivery of retrieval teams to trauma cases in high-traffic-density areas, such as London.

SAFETY

Any mode of transport involves some risk to patients and staff. In the aeromedical environment unfamiliar personnel perform clinical tasks poorly,[18] so teams must be appropriately trained and equipped to function effectively and safely in each mode of transport. A senior member of the professional group concerned should train and mentor new personnel on their first few trips.

A safety brief encompassing the use of safety equipment carried on the aircraft, emergency egress and actions to take during an emergency is essential. Daily meetings with helicopter flight crews can improve communication between all members of the 'team'.

Dangerous activities, such as unsafe driving and flying below safe minima, are unacceptable. For aviation missions, the decision whether a mission proceeds rests entirely with the aircraft pilot, and attempts to coerce pilots to take risks has been recognised as a contributor to air ambulance accidents.[19] The pilot should be provided with only the details of where the team needs to go. Clinical details should generally not be given as this may influence the decision to proceed with the mission.

ALTITUDE AND TRANSPORT PHYSIOLOGY

Teams need to be aware of altitude-related changes in gas, volume, temperature and partial pressures of oxygen (Table 4.2).

Patients already dependent on oxygen will be further compromised by even modest increases in height requiring further oxygen supplementation. It is the partial pressure not the percentage of oxygen that is critical. Monitoring of Sa_{O_2} during ascent is essential.

GAS EXPANSION

Expansion of trapped gas in accordance with Boyle's law occurs in physiological and pathological air spaces, and air-containing equipment such as endotracheal or tracheostomy tube cuffs, and Sengstaken–Blakemore tubes balloons. Endotracheal tube cuff pressures will need to be adjusted during flight. Delivered tidal volumes may increase spontaneously in some older ventilators, necessitating setting adjustments.

Physiological air spaces include the middle ear, nasal sinuses and GI tract. They can affect both patients and staff; consequently staff with upper respiratory tract infections or GI disturbances should not fly.

Pathological air spaces include pneumothoraces, emphysematous lung bullae, intraocular and intracranial open injuries, bowel obstructions and gas emboli. These patients need to be transported at the lowest altitude possible. Most modern fixed-wing aircraft are capable of cabin pressurisation, which decreases hypoxia and gas expansion. The pressurisation effectively replicates flying at a lower altitude – the so-called 'cabin altitude'. The difference between actual altitude and cabin altitude varies, with most air ambulances providing about 350 mm Hg (≈50 kPa) differential. This equates to a cabin pressure of 3000 ft (≈900 m) while flying at 20,000 feet (≈6000 m). Most commercial airliners fly with a cabin altitude of around 7000–9000 ft (≈2000–2700 m). Once the maximum differential is reached, a lower altitude cabin pressure can only be achieved by flying lower, which is often associated with more turbulence and increased fuel consumption. The medical team should only request a lower cabin height if clinically indicated.

The temperature falls 2°C for every 1000 ft (≈300 m) increase in height, as does the partial pressure of water, which is not corrected by cabin pressurisation. This can lead to dehydration, especially on long trips.

PREPARATION FOR TRANSPORT

The preparation phase for transport will depend on the patient's clinical condition. The ideal is to spend sufficient time, including any urgent surgery, stabilising the patient so that the transport phase is uneventful. As with intrahospital transport, this ideal may not be achievable, especially when the patient requires a time-critical intervention available only at the receiving destination. These missions are higher risk but are likely to be less futile than trying to stabilise an inevitably deteriorating patient. Prior to transport, all patients must have a secure airway, either self-maintained or intubated and ventilated, and well-secured intravenous access. External bleeding should be controlled, and investigations that may impact on the transport should be performed, if they can be done in a

Table 4.2 Changes with altitude

ALTITUDE (ft/m)	PRESSURE (mm Hg/kPa)	ALVEOLAR (ON AIR)	ALVEOLAR (100% O_2)	GAS SPACE EXPANSION (%)	STD TEMP (°C)	NOTES
Sea level	760 (≈100)	103	663	–	15	15°C is 'reference' average temperature – actual obviously varies
1000 (300)	733 (≈97)	98	636	+3.6	13	Minimum altitude above ground level for helicopter transports
2000 (600)	706 (≈94)	94	609	+8	11	Likely altitude for most visual flight rules (VFR) helicopter flights over sea-level terrain
3000 (900) 4000 (1200)	681 (≈91) 656 (≈87)	89 85	584 559	+12 +16	9 7	Likely range of *cabin* altitude for standard flights in most turboprop air ambulance craft (e.g. Raytheon–Beech King Air series)
7000 (2000)	586 (≈78)	73	489	+29	1	Standard *cabin* altitude for airliners and most jet air ambulances (e.g. Lear 35)
10,000 (3000)	523 (≈70)	61	426	+45	–5	Likely ceiling of helicopter ops and hypoxic threshold in normal individuals
15,000 (4500)	429 (≈57)	45	332	+77	–14.5	Threshold for hypoxic decompensation in nonacclimatised individuals
20,000 (6000) 25,000 (7500)	349 (≈50) 282 (≈37.5)	34 30	252 185	+117 +170	–24.5 –34	Likely upper range of cruise altitude for turboprop aircraft Decompression at these altitudes causes rapid loss of consciousness and death without O_2
40,000 (12,000)	141 (≈19)	<10	61	+439	–56	Cruise ceiling for airliners and jets Limit for survivable decompression, even with 100% O_2 for flight crew

short time-frame. Heimlich-type valves may be attached to any chest drains rather than bulky underwater seal drain devices. The patient is transferred to the stretcher and secured with the patient harness. Any equipment is also attached securely to the stretcher bridge. Any documentation and copies of investigations also need to be taken. A checklist for departure and transport is recommended and provided in Box 4.4.

During the early stages of movement, special vigilance must be employed as this is the stage when equipment disconnections or physiological decompensation is likely to occur. During transport the patient is vulnerable to hypothermia, and active warming should be considered. This can be achieved either by heating the vehicle or with a variety of commercial warming devices (e.g. blankets or fluid warmers).

HANDOVER

Handover to the receiving hospital is critical. Unless the patient needs immediate resuscitation there should be an opportunity for the retrieval team to have the exclusive attention of the receiving hospital. Various handover tools such as MIST (Mechanism of injury, Injuries suspected or found, Signs [vital signs] and Treatment given) are useful for trauma cases. ISOBAR has a wider application to all patient groups and is being promoted as the standard handover tool in many areas:

Box 4.4 Suggested pre-departure checklists

A. Before leaving hospital	
• Patient identity and next of kin	Recorded
• Consent for transport	Obtained and documented
• Paperwork and X-rays	Collected
• Drugs for transport	Present and sufficient
• Emergency drugs/ equipment	Available
• Medical equipment	Collected and repacked
• Monitors, ventilator and infusions	Connected, alarms set
• Tubes, lines, drains and catheters	Secured
• Altitude request (if applicable)	Passed to pilot
• Receiving unit	Contacted and updated
B. In vehicle and pre-departure	
• Stretcher and patient restraints	Secured and checked
• Oxygen supply	On and sufficient
• Monitors, ventilator and infusions	Working and secure
• Emergency drugs/ equipment	Stowed and accessible
• Other medical packs	Stowed
• Intravenous fluids	Hung and running
• Intravenous injection port	Accessible
• Medical power	On and connected
• Communications	Checked as applicable
• Seatbelts	On and checked
• Staff/patient headsets	On/checked (if applicable)

- I – introduction
- S – situation
- O – observations
- B – background
- A – assessment
- R – recommendations.

Retrieval teams should use the handover tool that is used in local practice. If one is not commonly used then ISOBAR will cover all the essential elements.

PRE-HOSPITAL CARE

Pre-hospital care of the acutely injured and critically ill is a complex and challenging field of medical practice. Ideally, patients should receive the most advanced required level of care at the earliest possible time, integrated with expedient transfer to the most appropriate definitive care facility. The ability to achieve this is both resource and system dependent with unique modifiers including transport platform logistics, environmental concerns and the need to integrate with other responding emergency services.

The benefits of adding a skilled critical care physician to the pre-hospital team are well recognised.[20] Service models across Australasia and Europe reflect this belief. The potential care delivered by such a team approaches or matches that only usually available in a tertiary hospital environment and may represent a 'definitive' requirement for the patient. However, the benefit of a physician and the safety and effectiveness of the team are maximised only if staff involved in such activities have the requisite skills and knowledge, and are familiar with the pre-hospital and retrieval environment.

APPROACH TO THE SCENE AND SCENE SAFETY

In any pre-hospital emergency situation safety is the primary concern. The pre-hospital retrieval (PHR) team should adopt the 'safe self, safe team, safe scene, safe patient' approach. Scene assessment is critical to ensuring team, scene and, ultimately, patient safety. It begins as soon as details of the task become available; plans for approaching the scene should be made on, or prior to, arrival.

PRE-HOSPITAL PLAN

A pre-hospital plan is a continuously evolving mental plan of action that the team will make as soon as it is activated, using the information given by the tasking agency. In many cases, this initial information is vague or incomplete, which reflects the problems experienced when receiving early phone calls about an incident. Although making a plan prior to arrival with limited information has drawbacks, there are clear benefits in arriving at the incident with a strategy for scene and patient management already in place. The plan often develops as the team travels to the scene and therefore valuable time en route should not be wasted.

When at the scene, the PHR team must have the skill to listen to all members of the emergency services and weigh up their suggestions as part of the overall plan. The ambulance service is the primary provider of pre-hospital care and paramedics are likely to be very experienced. It is worthwhile remembering that the physician-based pre-hospital teams are an extension of the ambulance service and not a replacement for them.

A generic pre-hospital plan could be:

- the scene:
  - a safe approach (self, team, scene and others)
- the patient:
  - likely requirements, need for extrication, assessment and stabilisation
- the destination:
  - triage options
  - transport platform options.

By having a pre-hospital plan, the team can add structure to their actions and, in doing so, develop a shared mental model inherent in teams that function in such high-acuity, high-consequence environments.

ENTRAPMENT AND EXTRICATION

Relative entrapment is a situation in which patients are trapped because of their injuries (e.g. a broken leg with disabling pain), location (e.g. a cave) or the ambient environment (e.g. a blizzard). If it were not for these factors, they would not require help in extricating themselves.

Actual entrapment occurs when patients are physically held in a location by the structure itself; for example, a major vehicle deformation with cabin intrusion, or a building collapse.

The aim is to remove the patient from an entrapped situation as safely and as quickly as possible. The key determinant in this plan (apart from safety) is the condition of the patient. The PHR team must decide on how to compromise between the slower, methodical extrication with total spinal control and the quicker extrication of the less stable patient. Clearly, unstable patients will need rapid extrication, but the ability to predict which patients are unsuitable for prolonged extrication due to the anticipated clinical course is more challenging. It may be better to compromise a degree of spinal protection earlier rather than have an emergency ('crash') extrication situation develop 30 minutes later.

The fire and rescue services will have access to the specialised equipment required. Without good teamwork between the services, the extrication will be significantly hindered.

ULTRASOUND IN THE FIELD

The availability of robust portable ultrasound machines has resulted in increased use in the pre-hospital or retrieval environment with good success; however, their use must be limited to people accredited in its use and must not result in undue delays in patient management.

KEY REFERENCES

1. Laird C. Prehospital and retrieval medicine. *Emerg Med J*. 2005;22(4):236.
3. Ridley S, Carter R. The effects of secondary transport on critically ill patients. *Anaesthesia*. 1989;44:822–827.
5. Marx G, Vangerow B, Hecker H, et al. Predictors of respiratory function deterioration after transfer of critically ill patients. *Intensive Care Med*. 1998;24: 1157–1162.
7. College of Intensive Care Medicine of Australia and New Zealand. *Minimum standards for inter-hospital transport of critically ill patients*. Joint Faculty of Intensive Care Medicine Policy Document IC10. Melbourne: College of Intensive Care Medicine of Australia and New Zealand; 2015.
8. Bellingan G, Olivier T, Batson S, et al. Comparison of a specialist retrieval team with current United Kingdom practice for the transport of critically ill patients. *Intensive Care Med*. 2000;26:740–744.
16. Burns BJ, Habig K, Reid C, et al. Logistics and safety of extracorporeal membrane oxygenation in medical retrieval. *Prehosp Emerg Care*. 2011;15(2): 246–253.
20. Garner A, Rashford S, Lee A, et al. Addition of physicians to paramedic helicopter services decreases blunt trauma mortality. *Aust NZ J Surg*. 1999;69:697–700.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Laird C. Prehospital and retrieval medicine. *Emerg Med J*. 2005;22(4):236.
2. Braman S, Dunn S, Amico CA, et al. Complications of intrahospital transport in critically ill patients. *Ann Intern Med*. 1987;107:469–473.
3. Ridley S, Carter R. The effects of secondary transport on critically ill patients. *Anaesthesia*. 1989;44:822–827.
4. Waydhas C. Intrahospital transport of critically ill patients. *Crit Care*. 1999;3:R83–R89.
5. Marx G, Vangerow B, Hecker H, et al. Predictors of respiratory function deterioration after transfer of critically ill patients. *Intensive Care Med*. 1998;24: 1157–1162.
6. Kollef MH, Von Harz B, Prentice D, et al. Patient transport from intensive care increases the risk of developing ventilator-associated pneumonia. *Chest*. 1997;112:765–773.
7. Australian and New Zealand College of Anaesthetists, Australasian College for Emergency Medicine, College of Intensive Care Medicine of Australia and New Zealand. *IC-10 Guidelines for Transport of Critically Ill Patients*. Melbourne: College of Intensive Care Medicine of Australia and New Zealand; 2015.
8. Bellingan G, Olivier T, Batson S, et al. Comparison of a specialist retrieval team with current United Kingdom practice for the transport of critically ill patients. *Intensive Care Med*. 2000;26:740–744.
9. Taylor C, Jan S, Curtis K, et al. The cost-effectiveness of physician staffed Helicopter Emergency Medical Service (HEMS) transport to a major trauma centre in NSW, Australia. *Injury*. 2012;43:1843–1849.
10. Gilligan JE, Griggs WM, Jelly MT, et al. Mobile intensive care services in rural South Australia 1984-1995. *Med J Aust*. 1999;171:617–620.
11. Wishaw KJ, Munford BJ, Roby HP. The CareFlight stretcher bridge: a compact mobile intensive care module. *Anaesth Intensive Care*. 1990;18:234–238.
12. Goldsmith JC. The US health care system in the year 2000. *JAMA*. 1986;256:3371–3375.
13. Rutten AJ, Isley AH, Skowronski GA, et al. A comparative study of mean arterial blood pressure using automatic oscillometers, arterial cannulation, and auscultation. *Anaesth Intensive Care*. 1986;14: 58–65.
14. Erler CJ, Rutherford WF, Rodman G, et al. Inadequate respiratory support in head injury patients. *Air Medical J*. 1993;12:223–236.
15. Coggins AR, Cummins EN, Burns B. Management of critical illness with non-invasive ventilation by an Australian HEMS. *Emerg Med J*. Published Online First: [8/11/2016]. doi:10.1136/emermed -2015-205377.
16. Burns BJ, Habig K, Reid C, et al. Logistics and safety of extracorporeal membrane oxygenation in medical retrieval. *Prehosp Emerg Care*. 2011;15(2): 246–253.
17. Desmettre T, Yeguiayan J, Coadou H, et al. Impact of emergency medical helicopter transport directly to a university hospital trauma center on mortality of severe blunt trauma patients until discharge. *Crit Care*. 2012;16:R170.
18. Harris BH. Performance of aeromedical crew members: training or experience? *Am J Emerg Med*. 1986;4:409–413.
19. *National Transportation Safety Board (US) Safety study: commercial emergency medical services helicopter operations*. SS/88/01. USA: NTSB; 1988.
20. Garner A, Rashford S, Lee A, et al. Addition of physicians to paramedic helicopter services decreases blunt trauma mortality. *Aust NZ J Surg*. 1999;69:697–700.

5

Physiotherapy in intensive care

Mandy Jones, Fiona Moffatt, Evelyn Corner

Physiotherapeutic intervention is based on clinical reasoning following the identification of physiotherapy-amenable problems, which are elucidated from a thorough systematic assessment.[1]

There is still some debate about the precise role of the physiotherapist within the intensive care unit (ICU), which may vary,[2] but the main features include:

- optimisation of cardiopulmonary function
- assistance in the weaning process utilising ventilatory support and oxygen therapy
- instigation of an early rehabilitation/mobilisation program to optimise functional independence, assist in minimising the consequences of intensive care unit-acquired weakness (ICU-AW) and improve exercise tolerance
- advice on positioning to protect joints and to minimise potential muscle and soft tissue shortening, nerve damage and to effect muscle tone in the brain-injured patient
- management of presenting musculoskeletal pathology
- advice and education of family and carers
- close interdisciplinary team working and goal setting.

CARDIOPULMONARY PHYSIOTHERAPY

TREATMENT MODALITIES TO OPTIMISE CARDIOPULMONARY FUNCTION

Patients who are critically ill may present with impaired cardiopulmonary physiology secondary to both the underlying pathology and the therapeutic interventions employed to treat them. In their approach to any individual patient, the physiotherapist may use specific treatment techniques targeted at improving ventilation/perfusion (V/Q) disturbances, increasing lung volumes, reducing the work of breathing and removing pulmonary secretions. Physiotherapy treatment modalities may differ depending on the presence of an endotracheal tube, although patient participation with treatment is encouraged and promoted at the earliest point during intubation. Each intervention is rarely used in isolation, but rather as part of an effective treatment plan. Some physiotherapeutic techniques may have short-lived beneficial effects on pulmonary function, and some have no clear evidence to validate their effectiveness.

LUNG HYPERINFLATION

Therapeutic lung hyperinflation has been used for many years by physiotherapists in the management of patients in the ICU.[3–7] Lung hyperinflation can be achieved through two techniques: manual hyperinflation (MHI) or ventilator hyperinflation (VHI).

MHI uses a self-inflating circuit to deliver a volume of gas 50% greater than tidal volume (V_T), to airway pressures up to 40 cm H_2O, via an endotracheal or tracheostomy tube. An augmented V_T may improve pulmonary compliance and aid recruitment of atelectatic lung, secondary to reduced air-flow resistance and enhanced interdependence via the collateral channels of ventilation.[8] A manometer can be included in the MHI circuit to limit augmented breaths to a predetermined pressure, where there is a risk of barotrauma. Bronchial secretions may be mobilised by the increased expiratory flow rate and/or stimulation of a cough following a quick release of pressure from the bag on expiration.[9] The aim is to achieve an expiratory flow rate 10% greater than inspiratory flow to move secretions centrally up the bronchial tree for removal via endotracheal suction.[10] The net effect can result in improved oxygenation.[8] It is possible to incorporate a positive end-expiratory pressure (PEEP) valve within the MHI circuit to maintain adequate PEEP and limit de-recruitment and atelectotrauma during intervention. However, MHI may be contraindicated in some ICU patients; therefore the use of VHI offers an alternative method to augment lung volume whilst potentially avoiding cardiopulmonary instability associated with ventilator disconnection and loss of high levels of PEEP in dependent patients. VHI involves the delivery of an augmented V_T via the ventilator (200 mL increments until a peak airway pressure of 40 cm H_2O is reached). A recent systematic review evaluating the efficacy of VHI compared to MHI, reported no statistical differences in sputum wet weight, dynamic and static pulmonary compliance and oxygenation and cardiovascular stability between VHI and MHI in adults receiving mechanical ventilation.[11]

ABSTRACT

The physiotherapist has an important and varied role within the intensive care unit/high-dependency unit (ICU/HDU) setting working as part of the interdisciplinary team to optimise cardiopulmonary function and functional ability.

The role of the physiotherapist may include: optimisation of cardiopulmonary function, assistance in the weaning process utilising ventilatory support and oxygen therapy, instigation of an early rehabilitation/mobilisation program to optimise functional independence, assist in minimising the consequences of intensive care unit-acquired weakness (ICU-AW) and improve exercise tolerance. Additionally, the physiotherapist may advise on positioning to protect joints and to minimise potential muscle and soft tissue shortening, nerve damage and to effect muscle tone in the brain-injured patient, the management of presenting musculoskeletal pathology, and the education of family and carers and the close interdisciplinary team working and goal setting.

KEYWORDS

Cardiopulmonary function
weaning
ventilatory support
early rehabilitation/mobilisation programs
intensive care unit-acquired weakness

Box 5.1 Potential advantages and complications of manual hyperinflation

Potential advantages
- Reversal of acute lobar atelectasis[8]
- Alveolar recruitment via channels of collateral ventilation[8]
- Improvement in arterial oxygenation
- Mobilisation of secretions and contents of aspiration[12]
- Improved static lung compliance[12]
- Effectiveness may be increased when combined with appropriate positioning and manual techniques[1]

Potential complications
- Absolute contraindications include undrained pneumothorax and unexplained haemoptysis
- Cardiovascular and haemodynamic instability[6]
- Loss of PEEP, inducing hypoxia and potential lung damage. This can be minimised by incorporating a PEEP valve into the circuit of a 'PEEP-dependent' patient
- Risk of volutrauma, barotrauma and pneumothorax, which can be reduced by including a manometer in the circuit
- Risk of increased intracranial pressure
- Increased patient stress and anxiety

PEEP, Positive end-expiratory pressure.

Box 5.2 Potential advantages and complications of suction

Potential advantages
- Stimulation of a cough when reflex is impaired by mechanical stimulation of the larynx, trachea or large bronchi
- Removal of secretions from central airways when cough is ineffective or absent

Potential complications
- Tracheal suction is an invasive procedure and should be undertaken only when there is a clear indication
- Absolute contraindications to suctioning are unexplained haemoptysis, severe coagulopathies, severe bronchospasm, laryngeal stridor, base of skull fracture and a compromised cardiovascular system
- Hypoxaemia can be induced secondary to suctioning. This can be limited by pre- and post-oxygenation
- Cardiac arrhythmias may be more common in the presence of hypoxia
- Tracheal stimulation may produce increased sympathetic nervous system activity or a vasovagal reflex producing cardiac arrhythmias and hypotension

In an emergency situation, an Ambu-bag and facemask can be used to perform MHI in the self-ventilating patient. However, an alternative technique, such as intermittent positive pressure breathing (IPPB), should be considered when an augmented V_T is required during a therapeutic intervention (Box 5.1).

SUCTION

Suction is used to clear secretions from central airways when a cough reflex is impaired or absent. A suction catheter is passed via an endotracheal or tracheostomy tube or via a nasal/oral airway to the carina, which may stimulate a cough in a non-paralysed patient (Box 5.2). The catheter is pulled back 1 cm before suction is applied on withdrawal. The suction catheter diameter should not be greater than 50% of the diameter of the airway through which it is inserted as large negative pressure can be generated intrathoracically without air entrainment. The use of suction following effective MHI/VHI optimises the removal of secretions.[13] Instillation of normal saline prior to suctioning remains controversial; however, it may stimulate a cough, maximising secretion mobilisation and clearance. Endotracheal suction of bronchial secretions can be achieved using either a conventional open catheter system, or via a closed-circuit suction catheter sited within the ventilator circuit. As the closed circuit catheter is intrinsic to the ventilator circuit, disconnection of the ventilator is not necessary during usage, which prevents potential spraying of respiratory secretions, additional movement of the endotracheal tube, loss of oxygenation or de-recruitment secondary to loss of PEEP.[14] However, no significant difference was found in the incidence of ventilator-associated pneumonia or mortality rates between patients treated with open or closed circuit suction.[14]

INSPIRATORY MUSCLE TRAINING

Mechanical ventilation, sepsis and the iatrogenic effects of enforced immobility may result in widespread deconditioning, including weakness or fatigue of the respiratory muscles, resulting in slow or failed weaning from ventilatory support.[15] It has been suggested that mechanical ventilation may adversely alter diaphragmatic myofibril length and function, leading to rapid atrophy.[16] Residual inspiratory muscle impairment has been demonstrated in intensive care survivors ventilated for 7 days or longer.[11,17] This residual respiratory muscle weakness may contribute to on-going dyspneoa,[17] impaired physical function[17,18] and poor quality of life in ICU survivors.[19] The instigation of inspiratory muscle training (IMT) has been shown to improve respiratory muscle strength in patients during mechanical ventilation.[20–24] Systematic reviews evaluating the effect of IMT on muscle strength in adults weaning from mechanical ventilation reported a significant increase in inspiratory muscle strength following muscle training,[25] and suggested that IMT performed prior to extubation enhances weaning success, but did not reduce rates of reintubation or survival rate.[26] More recently, IMT following successful weaning has been shown to increase inspiratory muscle strength and quality of life.[27]

MANUAL TECHNIQUES

CHEST SHAKING AND VIBRATIONS

Shaking and vibrations are oscillatory movements of large and small amplitude performed during expiration, which are thought to increase expiratory flow rate, aiding mucociliary clearance.[28] The application of chest wall shaking and vibrations is not standardised, but their effectiveness is thought to be influenced by the timing of their application within the breath cycle. Shaking and vibrations applied early in the expiratory cycle have been shown to generate high peak expiratory pressures, whereas shaking and vibrations applied late in the expiratory cycle are not effective at increasing peak expiratory flow.[29] It has been found that vibrations increased peak expiratory flow rates by more than 50% compared to relaxed, passive expiration[28] and enhances sputum clearance.[30] The application of vibrations is of particular importance to increase expiratory flow rate when using VHI compared to MHI, in the absence of a quick release of the bag. Additionally, it has been demonstrated that the application of chest wall vibration in combination with positioning was associated with a 27% reduction in rates of ventilator-acquired pneumonia.[31]

CHEST WALL COMPRESSION

Compression of the chest wall can be used to augment an expiratory manoeuvre such as a 'huff' (see section on active cycle of breathing technique [ACBT]) or a cough by providing tactile stimulation or wound support.

MANUALLY ASSISTED COUGH

Patients with neuromuscular disease (NMD) or spinal cord injury may present with inspiratory and expiratory muscle weakness and an effective cough.[32] These patients are unable to access adequate inspiratory reserve volume to produce expiratory flow rates of sufficient force to mobilise secretions or generate an effective cough.[32] A manually assisted cough can be achieved via an inward and upward compression to the anterior chest wall, costophrenic or abdominal (Heimlich type manoeuvre), during the expiratory part of the respiratory cycle.[33–35] This significantly increases peak cough flow,[36] to move secretions in a cephalad direction, prior to removal via oral or endotracheal suction.

POSITIONING

A simple change of position can have a profound effect on cardiopulmonary physiology.[37,38] As such, positioning is commonly utilised to achieve several different goals: drainage of secretions using gravity-assisted positioning (GAP), reduction of the work of breathing/breathlessness or to recruit lung units and optimise V/Q matching.

GRAVITY-ASSISTED POSITIONING

GAP facilitates the removal of excess bronchial secretions by positioning a specific bronchopulmonary segment perpendicular to gravity (Box 5.3). This technique is not used in isolation but in conjunction with augmented V_T, either via VHI, MHI or the ACBT in a spontaneously breathing patient. An individual position exists for each bronchopulmonary segment based on the anatomy of the bronchial tree[39]; however, in patients with neurological, cardiorespiratory or haemodynamic instability, these may need modification in the ICU setting. In the ICU, side lying (modified GAP) is commonly used when treating a patient with manual or VHI[40]; in this position preferential ventilation occurs in the uppermost lung, allowing filling and recruitment of slower filling alveoli, whilst facilitating the drainage of bronchial secretions, thus optimising gas exchange.[41] Research has confirmed a significantly increased sputum yield with the use of side lying in conjunction with hyperinflation.[40]

A reduction in the work of breathing/breathlessness can be achieved by putting a patient in a position that optimises the length–tension relationship of the diaphragm, promotes relaxation of the shoulder girdle and upper chest and facilitates the use of breathing control.[42] This approach to positioning is particularly effective when used in conjunction with noninvasive ventilation (NIV). Adequately supported high side lying is a useful position to promote relaxation of the breathless patient. In addition, it can discourage the overuse of accessory muscles of respiration, which may reduce energy expenditure. Some patients prefer forward lean sitting with their arms placed in front of them on a high table. In this position, the length–tension relationship of the diaphragm is optimised secondary to forward displacement of the abdominal contents.

VENTILATION/PERFUSION

Appropriate positioning of a patient can maximise V/Q.[42,43] In the self-ventilating adult, V/Q matching increases from non-dependent to dependent areas of the lung.[44] However, in adults receiving positive-pressure ventilation, lung mechanics are altered producing V/Q

Box 5.3 Potential advantages and complications of gravity-assisted positioning

Potential advantages

- Maximises removal of excess bronchial secretions when combined with the ACBT
- Allows accurate treatment of specific bronchopulmonary segments
- Self-treatment can be included in a home programme on discharge

Potential complications

- Positions need modification when used in the presence of cardiovascular/neurological instability, haemoptysis or gastric reflux

ACBT, Active cycle of breathing technique.

inequality. In this situation non-dependent areas of lung are preferentially ventilated while dependent regions are optimally perfused; as such, a regular change of position is recommended. Additionally, evidence exists to support regular turning of patients from side to side with a 40-degree lateral turn, as this may reduce the incidence of ventilator associated pneumonia (VAP).[45] In an extreme form, prone positioning has been used to improve refractory hypoxaemia in patients with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS). The mechanisms behind these improvements are complex, but probably centre around a combination of a redistribution of some pulmonary perfusion together with a more homogeneous distribution of ventilation leading to improved V/Q matching. Although prone positioning improves oxygenation in up to 70% of those with ALI/ARDS, its role in improving outcome remains controversial.[2]

ACTIVE CYCLE OF BREATHING TECHNIQUE

The ACBT is a cycle of breathing exercises used to remove excess bronchial secretions (Box 5.4).[5] The cycle can be adapted for each patient according to existing underlying pathology and presenting clinical signs. It consists of:

- breathing control × 4 to 6 breaths
- normal tidal breathing using the lower chest
- minimising the use of accessory muscles of respiration
- promoting relaxation
- lower thoracic expansion × 4 to 6 breaths
- can be used with/without an inspiratory hold
- forced expiration technique
- expiration with an open glottis ('huff'), combined with breathing control.

Box 5.4 Potential advantages and complications of active cycle of breathing technique

Potential advantages

Mobilises and clears excess bronchial secretions[28]

Improves lung function[28]

Minimises the work of breathing

Individual components of the cycle can be utilised/emphasised to target specific problems

Can be used in combination with other manual techniques, GAP, V/Q matching, positioning to reduce breathlessness, and during activities such as walking

Self-treatment can be included in a home programme

Potential complications

Without adequate periods of breathing control, bronchospasm and desaturation can occur

Poor technique can lead to ineffective treatment and unnecessary energy expenditure

GAP, Gravity-assisted positioning; *V/Q*, ventilation/perfusion.

Although mainly used in the self-ventilating patient, alert, cooperative, ventilated patients can participate with this technique. The ACBT can be delivered via MHI or VHI in sedated and ventilated patients requiring mobilisation of secretions and airway clearance.

MECHANICAL ADJUNCTS

INTERMITTENT POSITIVE-PRESSURE BREATHING

IPPB is a patient-triggered, pressure-cycled mechanical device mainly used in self-ventilating patients to increase ventilation, re-expand lung tissue, mobilise bronchial secretions and reduce the work of breathing by augmenting V_T (Table 5.1).[46] Delivered via a facemask, mouthpiece or via tracheostomy, positive airway pressure is maintained throughout inspiration; expiration is passive. IPPB requires constant adjustment of pressure and flow rates and careful patient monitoring to maintain effectiveness and cooperation. Effectiveness is increased when used in conjunction with positioning, ACBT and manual techniques (Box 5.5). Nebulised agents, such as saline or bronchodilator drugs, can be incorporated into the IPPB circuit to further facilitate airway clearance.

MECHANICAL INSUFFLATION–EXSUFFLATION

Mechanical insufflation–exsufflation is a device that initially delivers a positive inspiratory pressure above tidal volume to increase ventilation, re-expand lung tissue and mobilise bronchial secretions, followed by an expiratory negative pressure increasing expiratory flow rate and stimulating a cough.[47] In some patient groups, the use of mechanical insufflation–exsufflation may negate the requirement for tracheal suctioning[48] or delay the need for tracheostomy.[49] A manually assisted cough may also be applied by the physiotherapist during the negative, expiratory phase to further augment expiratory flow and cough stimulation.[32] This mechanical

Table 5.1 Medical Research Council sum score

MUSCLE GROUPS	SCORE
Wrist extensors Elbow flexors Shoulder abductors Foot dorsiflexors Knee extensor Hip flexors	0 = no visible/palpable contraction 1 = visible/palpable contraction without movement of the limb 2 = limb movement against, gravity counterbalanced 3 = limb movement against gravity 4 = limb movement against gravity with some resistance 5 = normal muscle strength

Box 5.5 Potential advantages and complications of intermittent positive pressure breathing, continuous positive airways pressure and non-invasive ventilation

Potential advantages
Improves lung volumes
Improves gaseous exchange
Decreases the work of breathing
IPPB and NIV can mobilise excess bronchial secretions by improving V_T
IPPB and NIV can improve lung and chest wall compliance
CPAP reduces left ventricular afterload by reducing the transmural pressure gradient
Patients can be mobilised while on CPAP and some modes of NIV; alteration of ventilator settings might be indicated to maximise patient potential/exercise tolerance during treatment
Settings can be adjusted to augment physiotherapy intervention (e.g. increased IPAP to assist removal of secretions)
Potential complications
Absolute contraindications include severe bronchospasm, undrained pneumothorax, pneumomediastinum, unexplained haemoptysis and facial fractures; use with care in pre-existing bullous lung disease
Haemodynamic/neurological instability
Risk of decreased urine output with CPAP and NIV
Risk of carbon dioxide retention with CPAP
Risk of aspiration

CPAP, Continuous positive airways pressure; *IPAP*, inspiratory positive airway pressure; *IPPB*, intermittent positive pressure breathing; *NIV*, non-invasive ventilation.

device can be applied by face mask, tracheostomy or endotracheal tube.

CONTINUOUS POSITIVE AIRWAYS PRESSURE

Continuous positive airways pressure (CPAP) maintains a positive airway pressure throughout inspiration and expiration. It is used in both intubated and self-ventilating patients to increase/normalise functional residual capacity (FRC) via recruitment of atelectatic lung. Clinically, increased FRC is associated with improved lung compliance, improved oxygenation and reduced work of breathing.[46] Effectiveness increases when used in conjunction with appropriate positioning. The self-ventilating patient must be able to generate an adequate V_T as this volume is not augmented with CPAP (Table 5.2). Research supports the application of intermittent CPAP in the treatment of acute cardiogenic pulmonary oedema[50] and type I respiratory failure secondary to postoperative atelectasis[51]; however, non-invasive bi-level ventilation (NIV or bi-level positive airway pressure [BIPAP]) has greater efficacy compared to CPAP in the reversal of atelectasis in patients post-cardiac surgery.[52]

NON-INVASIVE VENTILATION

The role of NIV in the ICU is well established. This includes the prevention of invasive ventilation in patients with hypercapnic respiratory failure secondary to chronic obstructive pulmonary disease (COPD), cardiogenic pulmonary oedema and immunocompromise, and early weaning from mechanical ventilation; however, NIV should not be used routinely for unexpected post-extubation respiratory failure.[53] Physiotherapists play a key role in the instigation and application of NIV,[51] including the selection of delivery machine and patient interface. Careful and appropriate application of NIV has been linked to increased patient tolerance and successful outcome. Physiotherapy may be instigated whilst NIV is in situ, or during rest periods if the application of NIV is intermittent. Inspiratory positive airway pressure (IPAP) may be augmented to increase V_T during physiotherapy treatment to aid the removal of secretions, or to support mobilisation of the patient (see Table 5.2). In patients with NMD, if augmentation of IPAP is not effective to clear secretions, mechanical insufflation and exsufflation and assisted cough can be used.[53] Improved oxygenation may be achieved using NIV when the patient is positioning to optimise V/Q (see Box 5.5).

LONG-TERM TRACHEOSTOMY MANAGEMENT AND WEANING

Peripheral muscle weakness and respiratory muscle weakness are inter-related and must be treated accordingly. Weaning plans must be carefully balanced with functional rehabilitation, ideally with an integrated interdisciplinary team (IDT) weekly plan in place for the long-term patient.[54] The physiotherapist plays a vital role in this IDT.

A tracheostomy is a surgical incision in the trachea, which allows the insertion of a tracheostomy tube for the purpose of: airway protection, to facilitate prolonged mechanical ventilation, to bypass obstruction and/or for secretion management.[55]

There are many different types of tracheostomy tube available:

- *Cuffed and uncuffed*: The cuff is inflated around the tracheostomy tube to reduce aspiration risk and to ensure adequate ventilation and PEEP. Uncuffed tracheostomies can be used in patients free from mechanical ventilation with sufficient airway protection.[56]
- *Single or double lumen*: Most tracheostomies in adults will be double lumen, to allow the inner tube to be removed and cleaned thus reducing the risk of airway occlusion.
- *Fenestrated and non-fenestrated*: fenestrated tracheostomies have holes in the outer cannula, which

Table 5.2 Summary of functional assessment tools for intensive care unit

The Chelsea Critical Care Physical Assessment (CPAx)[105–107]	The CPAx is a scale of function which allows grading of patients on a Guttman scale from 0 (dependent) to 5 (independent) in 10 domains to give an aggregate score out of 50. These domains are: rolling, supine to sitting on the edge of the bed, sitting balance, standing balance, sit to stand, transfers, stepping, standing balance, respiratory function, cough and grip strength. The inclusion of the respiratory components makes this scale unique
The Functional Status Scale for ICU (FSS-ICU)[108,109]	The FSS-ICU is an ordinal scale evaluating a patient's function on a scale from 0 (unable) to 7 (completely independent) to give total score out of 35. The tasks included are: rolling, transfer from spine to sit, sitting at the edge of bed, transfer from sit to stand, and walking. The patient is given an aggregate score out of 35
Physical Function in Intensive care Test scored (PFIT-s)[110,111]	The PFIT-s is an interval scale from 0 to 10. It contains four items: assistance with sit to stand (i.e. 0, 1 or 2 people), cadence (steps/min), strength of the shoulder flexors and strength of the knee extensors (as per the MRC scale). The PFIT-s can be used to prescribe an exercise programme to patients on ICU
ICU Mobility Scale (IMS)[112,113]	The ICU Mobility Scale is an ordinal measure of mobility milestones from 0 to 10. The patient is scored based on their maximal level of activity progressing from bed bound (0), to bed exercises (1), passive transfer from bed to chair (2), sitting over the edge of the bed (3), standing (4), active transfer from bed to chair (5), marching on the spot (6), and finally walking with varying degrees of assistance (7–10)

MRC, Medical Research Council.

reduce airway obstruction and allow air to pass through the upper respiratory tract (URT). These can be used to facilitate weaning; however, they can cause the formation of problematic granulation tissue and increase the risk of aspiration.[57]

Although tracheostomy insertion is often essential, the placement of a tracheostomy has many negative consequences due to altered mechanics of the URT, these are[58,59]:

- preventing the patient from speaking, as air bypasses the vocal cords
- inhibiting a normal swallow by tethering the larynx, inhibiting epiglottal closure and preventing positive subglottic pressure
- inhibiting normal cough mechanics, which are dependent on sufficient vital capacity, respiratory muscle strength, expiratory flow and epiglottal closure
- reducing smell and taste due to lack of airflow through the URT
- bypassing the natural humidification systems
- losing intrinsic PEEP leading to atelectasis
- as glottal structures contribute to the control of expiratory airflow, and thus intrathoracic and intra-abdominal pressure, the presence of a tracheostomy may also reduce postural stability and the activation of core-stabilising muscles, therefore impacting upon the patient's functional recovery.[60]

SPEAKING AND SWALLOWING VALVES

Speaking valves can be used to facilitate weaning and decannulation by helping to restore normal physiology in the URT. The Passy-Muir speaking and swallowing valve (PMSV) is a one-way valve placed on the end of a tracheostomy, or in the ventilation circuit.[59] When a PMSV is in situ, air can be inspired both through the tracheostomy tube and the mouth; at the end of inspiration the valve closes occluding the tracheostomy tube and thus preventing expiration via the tracheostomy. This means that all expired gas will travel through the URT and past the vocal cords. It is essential that the cuff is deflated when using the PMSV to allow expiration.

Use of the PMSV allows the patient to speak, eat, drink, taste and smell, which has significant psychological benefits.[61] It also facilitates normal cough mechanics, may facilitate rehabilitation by allowing recruitment of core stabilising muscles, and has been shown to facilitate weaning from mechanical ventilation. The use of the PMSV should be an IDT decision, with input from speech and language therapy.[54]

DECANNULATION

Decannulation is the process of weaning/removing the tracheostomy tube.[54] The decision to decannulate is not always a simple one and requires an integrated approach,

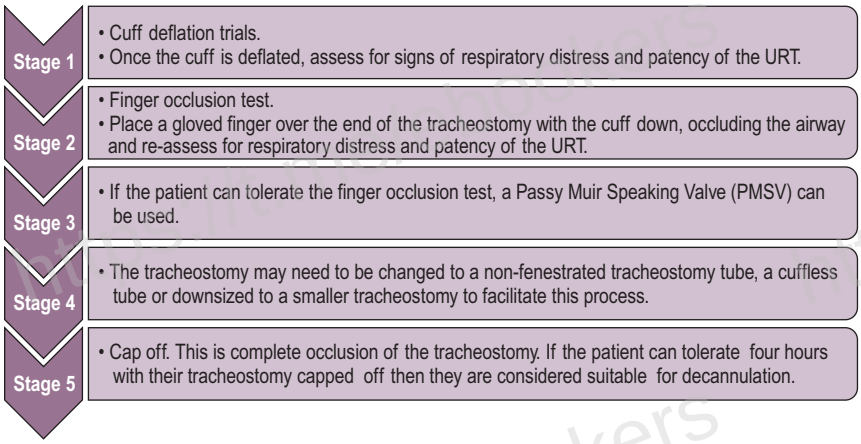


Figure 5.1 Step-wise approach to weaning and decannulation. *URT*, Upper respiratory tract.

as delays can lead to long-term complications. There are many factors that will need consideration prior to decannulation, and practice varies. A typical approach to weaning/decannulation is presented in Fig. 5.1.[56,62]

CRITICAL CARE REHABILITATION

PHYSICAL IMPAIRMENT AND INTENSIVE CARE UNIT-ACQUIRED WEAKNESS

The effects of deconditioning on the cardiovascular, respiratory and neuromusculoskeletal systems are well documented.[63–65] This phenomenon occurs as a result of restricted physical activity, and reduces the ability to perform work. Such physical impairment can occur with even relatively short periods of immobility. The addition of critical illness (which initiates a hypercatabolic response) further compounds muscle wasting and dysfunction, and often results in a state of global and persistent weakness that cannot be attributed to anything other than the critical illness itself.[66] Historically, this phenomenon of generalised weakness has been identified using a range of terminologies, but is now referred to using a clinical diagnostic label of ICU-AW.[67] A diagnosis of ICU-AW is made using, where possible, the Medical Research Council (MRC) sum score; a total score of <48/60 is considered indicative of ICU-AW.[68] Electrophysiological examination may also be used where the clinical presentation is atypical or where the patient is not awake and fully cooperative. Respiratory muscle strength should also be considered, using maximal inspiratory pressure measurement.[69,70]

The incidence of ICU-AW in patients admitted to adult ICU has been reported across studies as 9% to 86%.[71,72] A recent systematic review of 33 studies and 2686 patients reported an incidence of 40% (95% confidence interval 38%–42%) but concluded that this was influenced by the diagnostic technique used; clinical techniques were associated with a lower incidence than electrophysiological techniques.[67] The sequelae of ICU-AW are diverse, including: prolonged weaning from mechanical ventilation; increased length of ICU and hospital stay; increased hospital mortality; increased hospitalisation costs; increased 180-day mortality; persistent weakness; decreased physical functioning; and reduced quality of life post-ICU discharge.[67,70] ICU-AW may also play a contributory role in post-intensive care syndrome.[70]

ICU-AW is complex and multifactorial, involving functional and structural changes in both muscle and nerves.[66,70] Muscle atrophy results from imbalances in the breakdown and synthesis of muscle protein (especially myosin). This is thought to be directly influenced by pro-inflammatory mediators, immobility, stress-induced cytokines, nutritional deficits, impaired microcirculation and denervation.[70,73] Furthermore, other factors may impair muscle function, particularly reduced membrane excitability secondary to sodium channel dysfunction, altered excitation-contraction coupling due to changes in intracellular calcium, mitochondrial dysfunction and deficient autophagy.[70] A number of independent 'risk factors' for the development of ICU-AW have been suggested, including: sepsis; systemic inflammatory response syndrome (SIRS); multiorgan failure; severity of illness (high acute physiology and chronic health evaluation [APACHE] score); hyperglycaemia; duration of immobilisation; use of corticosteroids and neuromuscular blockade; age; and premorbid functional status.[70] Given that the consequences of ICU-AW are significant in terms of patient outcome, length of hospital stay, duration of rehabilitation and subsequent ability to function independently in the community,[74–78] there has been a paradigm shift in critical care management to reduce iatrogenic risk factors and to ensure daily screening for weakness.[66] Care bundles, such as the ABCDE approach (Awakening and Breathing coordination, Choice of sedative or analgesic exposure, Delirium monitoring

and management, Early mobility and Exercise), have been advocated in order to optimise patient recovery and outcome.[78,79]

PHYSIOTHERAPY REHABILITATION

The role of early mobility and exercise in attenuating the deleterious effects of immobility during critical illness is now widely reported.[80] Early mobilisation and/or exercise of critically ill patients via selected rehabilitation strategies has been demonstrated in certain studies to be safe and feasible, to reduce length of stay, decrease the incidence of delirium, increase the number of ventilator-free days and to improve physical function.[70,80–83] Based on growing evidence, the European Respiratory Society, the European Society of Intensive Care Medicine, and the National Institute of Health and Clinical Excellence have promoted early instigation of individualised rehabilitation programmes to prevent avoidable physical dysfunction.[84,85] Early mobilisation programmes may, however, face cultural and technological barriers.[77,86] There is certainly inconsistency in the delivery of early mobilisation practices globally.[87] As such, proponents advocate a shift from multidisciplinary 'silos' to collaborative interdisciplinary care.[78,88] The physiotherapist, possessing expertise in rehabilitation and exercise physiology, should play a key coordination role in these programmes by evaluating individual patients, devising a shared therapeutic strategy, and referring to other rehabilitative specialties (e.g. speech and language therapy, occupational therapy) as required.[84]

Careful assessment both before (and during) implementation of an early mobilisation/exercise program must be undertaken by a suitably experienced physiotherapist. A number of authors have suggested algorithms or criteria for this process.[80,83,89,90]

Traditionally, exercise rehabilitation has progressed linearly from activity in bed, then sitting, and finally to standing/walking. The model demonstrated in Fig. 5.2 represents a three-stage functional rehabilitation programme. It is supported by evidence that suggests a multimodal training regimen is required to maintain/restore both physiological and psychological performance after a period of immobility and illness.[91] The use of interlinking circles is intended to reflect the non-linear pattern of exercise progression more commonly utilised in patients with critical illness (e.g. patients may be able to stand using a tilt-table before they are able to tolerate sitting out of bed). The central shaded area represents the core components that should be addressed at every stage in the patient's recovery. The areas bordered by the broken lines represent the progression or regression from one stage to the next. During all stages, the patient's cardiopulmonary response must be closely monitored and exercise titrated accordingly. Modifications (e.g. temporarily increasing the FiO_2 and/or the level of ventilatory assistance) during exercise and in the early post-exercise

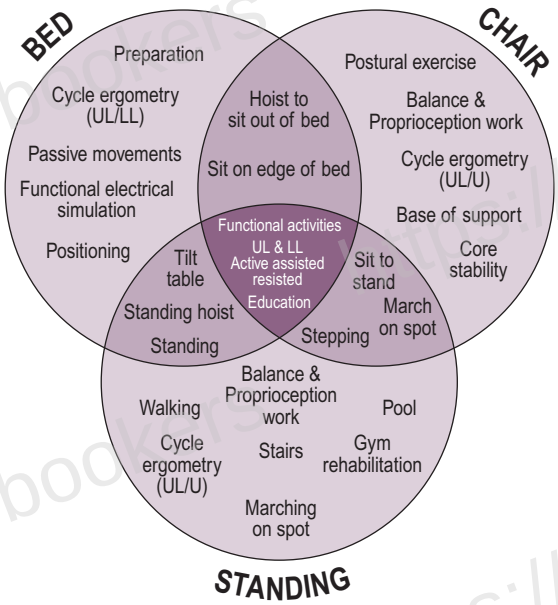


Figure 5.2 Schemata representing three-stage functional rehabilitation programme (the Nottingham Critical Care Rehabilitation Model). *LL*, Lower limb; *UL*, upper limb. *(From Douglas E. The Nottingham Critical Care Rehabilitation Model, University of Nottingham Division of Physiotherapy.)*

period may be necessary. Such modifications are commonly required as increasing physical activity often coincides with weaning from ventilatory support – both of which are significant challenges to the physiological reserve. All aspects of progressive exercise therapy should be considered, including positioning, passive and active mobilisation, aerobic training, balance and proprioceptive training and muscle strengthening.[70,84,92] Adjuncts, such as continuous passive motion, splinting, bedside cycle ergometry or functional electrical stimulation, may also be warranted.[70,92] To date, empirical data regarding the optimal timing, nature and dosage of early mobilisation remain equivocal.[87] Early mobilisation/rehabilitation of the diaphragm also should be a consideration with appropriate intervals of spontaneous breathing, and possibly IMT in the post-ICU phase.[69,70] The wealth of evidence regarding deconditioning should play a central role in planning treatment, both preventative and rehabilitative. For example, those muscle groups most adversely affected by disuse should be targeted first with a gradual, progressive regimen. During the re-mobilisation period, the IDT must be particularly mindful of those elements with delayed recovery; for example, orthostatic tolerance and bone mass (predisposition to falls and fractures), and muscle endurance (diminished exercise tolerance). It has been suggested that, in order to improve long-term outcomes for survivors of ICU (e.g. late mortality, ongoing morbidity, neurocognitive

defects, functional disability, quality of life, economic burden), critical illness and its management should be viewed on a continuum and not merely the time spent in a critical care facility.[74] As such, rehabilitation should reflect this, continuing into the community, outpatient or follow-up clinic setting.[73,93] Mitochondrial dysfunction is likely to persist well into the post-critical illness phase, impairing lactate clearance and contributing to other exercise metabolic dysfunction, thereby further adversely affecting exercise capacity.[73] Although the psychological, cardiopulmonary and functional sequelae of critical care survival may be profound, to date the optimal strategies for delivering post-critical care rehabilitation services remain unclear.[94,95] Contemporary debate suggests that individualised exercise prescription programmes, with tailored progression and patient education regarding self-monitoring of exercise, are likely to confer benefits.[73,93]

FUNCTIONAL ASSESSMENT IN INTENSIVE CARE UNIT

Clinical diagnosis and assessment of physical morbidity is an important part of the physiotherapist's role.[96] This allows the monitoring of response to physiotherapy interventions as well as tracking of functional recovery.[94]

The World Health Organisation International Classification of Functioning, Disability and Health (ICF) model categorises physical morbidity at three levels: impairment (issue with a bodily structure or function), activity limitation (functional tasks) and participation restriction (restrictions in the ability to integrate in wider societal activities).[94,97,98] In the ICU, assessment of impairment and activity limitation is the most common, that is, muscle strength, muscle mass and physical function.[97]

MUSCLE STRENGTH

Muscle strength can be assessed using the MRC sum score. This is recommended as a diagnostic tool for ICU-AW.[70,99,100] The MRC sum score is a volitional test that grades 12 major muscles groups on a scale of zero to five depending on the amount of muscle activity, giving a total score out of 60. A score of <48/60 is considered diagnostic of ICU-AW. The scale is summarised in Table 5.1. Although this is a useful clinical tool, it can lack reproducibility, and its volitional nature requires an alert and cooperative patient, which may limit its use.[70] Hand-held dynamometry and grip strength also can be used to assess muscle strength.[99]

MUSCLE MASS

Ultrasonography can be used reliably to measure the cross-sectional area of skeletal muscles as a measure of mass; this is associated with both muscle strength and ICU length of stay.[101–104] Changes in muscle mass are most commonly detected in the lower limb due to the impact of reduced mechanical loading associated with bed rest.[104]

PHYSICAL FUNCTION

There are 26 different measures of physical function that have been designed and trialled in the ICU[97]; however, the most clinimetrically robust are the Chelsea Critical Care Physical Assessment tool (CPAx),[105–107] the Functional Status Scale for ICU (FSS-ICU),[108,109] the Physical Functional Test for ICU (scored) (PFIT-s)[110,111] and the ICU Mobility Scale.[112,113] These scales are all reproducible and capable of accurately assessing function and detecting meaningful change.[97,114] Table 5.2 describes these tools in more detail.

SUMMARY

The physiotherapist has an important and varied role within the ICU/high-dependency unit (HDU) setting working as part of the IDT to optimise cardiopulmonary function and functional ability. The physiotherapist is often uniquely placed to follow and treat a patient from the acute stages at ICU admission, through the rehabilitation process to subsequent discharge from hospital and, if necessary, treatment can be continued in the outpatient setting.

There is no longer a place for routine physiotherapy treatment. Regular systematic assessment will identify physiotherapy-amenable problems that contribute to an interdisciplinary care plan. Implementation of any physiotherapy treatment should always utilise continuous analytical reassessment.

REFERENCES

1. Stiller K. Physiotherapy in intensive care. Towards an evidence-based practice. *Chest*. 2000;118: 1801–1813.
2. Norrenberg M, Vincent JL, European Society of Intensive Care Medicine. A profile of European intensive care unit physiotherapists. *Intensive Care Med*. 2000;26(7):988–994.
3. Stiller K, Geake T, Taylor R, et al. Acute lobar atelectasis: a comparison of two chest physiotherapy regimes. *Chest*. 1990;98:1336–1340.
4. Tweed W, Phua W, Chong E, et al. Tidal volume, lung hyperinflation and arterial oxygenation during general anesthesia and intensive care. *Anesth Intensive Care*. 1993;21:806–810.
5. Webber BA, Pryor JA. Physiotherapy techniques. In: Pryor JA, Webber BA, eds. *Physiotherapy for Respiratory and Cardiac Problems*. 2nd ed. Edinburgh: Churchill Livingstone; 1998:137–209.
6. Singer M, Vermaat J, Hall G, et al. Haemodynamic effects of manual hyperinflation in critically ill mechanically ventilated patients. *Chest*. 1994;106(4):1182–1187.

7. Stiller K, Jenkins S, Grant R, et al. Acute lobar atelectasis: a comparison of five physiotherapy regimes. *Physiother Pract*. 1996;12:197–207.
8. Denehy L. The use of manual hyperinflation in airway clearance. *Eur Respir J*. 1999;14(4):958–965.
9. Hodgson C, Denehy L, Ntoumenopoulos G, et al. An investigation of the early effects of manual lung hyperinflation in critically ill patients. *Anaesth Intensive Care*. 2000;28(3):255–261.
10. Maxwell L, Ellis E. Secretion clearance by manual hyperinflation: possible mechanisms. *Physiother Theory Pract*. 1998;14:189–197.
11. Anderson A, Alexanders J, Sinani C, et al. Effects of ventilator vs manual hyperinflation in adults receiving mechanical ventilation: a systematic review of randomised clinical trials. *Physiotherapy*. 2015;101(2):103–110. doi:10.1016/j.physio.2014.07.006.
12. Berney S, Denehy L. A comparison of the effects of manual and ventilator hyperinflation on static lung compliance and sputum production in intubated and ventilated intensive care patients. *Physiother Res Int*. 2002;7:100–108.
13. Choi JS, Jones AY. Effects of manual hyperinflation and suctioning on respiratory mechanics in mechanically ventilated patients with ventilator acquired pneumonia. *Austral J Physiother*. 2005;51(1):25–30.
14. Elmansoury A, Said A. Closed suction system versus open system. *Eur Respir J*. 2014;44:P2548.
15. Petrof BJ, Jaber S, Matecki S. Ventilator induced diaphragmatic dysfunction. *Curr Opin Crit Care*. 2010;16:19–25.
16. Chang AT, Boots RJ, Brown MG, et al. Reduced inspiratory muscle endurance following successful weaning from prolonged mechanical ventilation. *Chest*. 2005;128:553–559.
17. Bissett B, Leditschke IA, Neeman T, et al. Weaned but weary: one third of adult ICU patients mechanically ventilated for 7 days or more have impaired inspiratory muscle endurance after successful weaning. *Heart Lung*. 2015;44:15–20.
18. Iwashyna TJ, Ely EW, Smith DM, et al. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010;304:1787–1794. doi:10.1001/jama.2010.1553.
19. Cuthbertson BH, Roughton S, Jenkinson D, et al. Quality of life in the five years after intensive care: a cohort study. *Crit Care*. 2010;14:R6. doi:10.1186/cc8848.
20. Bissett B, Leditschke IA. Inspiratory muscle training to enhance weaning from mechanical ventilation. *Anaesth Intensive Care*. 2007;35:776–779.
21. Cader SA, Vale RG, Castro JC, et al. Inspiratory muscle training improves maximal inspiratory pressure and may assist weaning in older intubated patients: a randomized trial. *J Physiother*. 2010;56:171–177. doi:10.1016/S1836-9553(10)70022-9.
22. Martin AD, Davenport PD, Franceschi AC, et al. Use of inspiratory muscle strength training to facilitate ventilator weaning: a series of 10 consecutive patients. *Chest*. 2002;122:192–196. doi:10.1378/chest.122.1.192.
23. Martin AD, Smith BK, Davenport PD, et al. Inspiratory muscle strength training improves weaning outcome in failure to wean patients: a randomized trial. *Crit Care*. 2011;15:R84. doi:10.1186/cc10081.
24. Condessa RL, Brauner JS, Saul AL, et al. Inspiratory muscle training did not accelerate weaning from mechanical ventilation but did improve tidal volume and maximal respiratory pressures: a randomised trial. *J Physiother*. 2013;59(2):101–107.
25. Moodie L, Reeve J, Elkin M. Inspiratory muscle training increases inspiratory muscle strength in patients weaning from mechanical ventilation: a systematic review. *J Physiother*. 2011;57:213–221.
26. Elkins M, Dentice R. Inspiratory muscle training facilitates weaning from mechanical ventilation among patients in the intensive care unit: a systematic review. *J Physiother*. 2015;61:125–134. doi:10.1016/j.jphys.2015.05.016.
27. Bissett B, Leditschke I, Neeman T, et al. Inspiratory muscle training to enhance recovery from mechanical ventilation: a randomised trial. *Thorax*. 2016;71(9):812–819. doi:10.1136/thoraxjnl-2016-208279.
28. McCarren B, Alison JA, Herbert RD. Vibration and its effect on the respiratory system. *Austral J Physiother*. 2006;52(1):39–43.
29. Shannon H, Stiger R, Gregson RS, et al. Effect of chest wall vibration timing on peak expiratory flow and inspiratory pressure in a ventilator lung model. *Physiotherapy*. 2010;96(4):344–349.
30. Marik PE, Fink MP. One good turn deserves another. *Crit Care Med*. 2002;30:2146–2148.
31. Ntoumenopoulos G, Presneill J, McElholum M, et al. Chest physiotherapy for the prevention of ventilator-associated pneumonia. *Intensive Care Med*. 2002;28:850–856.
32. Bott J, Blumenthal S, Buxton M, et al. Guidelines for the physiotherapy management of the adult, medical, spontaneously breathing patient. Joint BTS/ACPRC guideline. *Thorax*. 2009;64:i1–i52. doi:10.1136/thx.2008.110726.
33. Brownlee S, Williams SJ. Physiotherapy in the respiratory care of patients with high spinal injury. *Physiotherapy*. 1987;73:148–152.
34. Bach JR. Noninvasive alternatives to tracheostomy for managing respiratory muscle dysfunction in spinal cord injury. *Top Spinal Cord Inj Rehabil*. 1997;2:49–58.
35. Massery M. Respiratory rehabilitation secondary to neurological deficits: treatment techniques. In: Frownfelter DL, ed. *Chest Physical Therapy and Pulmonary Rehabilitation. An Interdisciplinary Approach*. St Louis, MO: Mosby; 1987:529–562.
36. Seixas P, Abreu PJ, Goncalves MR. Comparison of two manually assisted coughing techniques in

patients with high spinal cord injury. *Eur Respir J*. 2006;28:731s.
37. Dean E. The effects of positioning and mobilization on oxygen transport. In: Pryor JA, Webber BA, eds. *Physiotherapy for Respiratory and Cardiac Problems*. 2nd ed. Edinburgh: Churchill Livingstone; 1998:125.
38. Jones AY, Dean E. Body position change and its effect on haemodynamic and metabolic status. *Heart Lung*. 2004;33(5):281–290.
39. Thoracic Society. The nomenclature of bronchopulmonary anatomy. *Thorax*. 1950;5: 222–228.
40. Dennis D, Jacob WJ, Samuel FD. A survey of the use of ventilator hyperinflation in Australian tertiary intensive care unit. *Crit Care Resusc*. 2010;12:262–268.
41. Hodgson C, Denehy L, Ntoumenopoulos G, et al. An investigation of the early effects of manual lung hyperinflation in critically ill patients. *Anaesth Intensive Care*. 2000;28:255–261.
42. Dean E. Effects of position on pulmonary function. *Phys Ther*. 1985;65(5):613–618.
43. Fink JB. Positioning versus postural drainage. *Respir Care*. 2002;47(7):769–777.
44. West JB. *Respiratory Physiology*. 5th ed. Baltimore: Williams & Wilkins; 1995:51–69.
45. Thomas P, Paratz J. Is there evidence to support the use of lateral positioning in intensive care? A systematic review. *Anaesth Intensive Care*. 2007;35:239–255.
46. Denehy L, Berney S. The use of positive pressure devices by physiotherapists. *Eur Respir J*. 2001;17:821–829.
47. Bach JR. New approaches in the rehabilitation of the traumatic high level quadriplegic. *Am J Phys Med Rehabil*. 1991;70:13–19.
48. Bach JR, Smith WH, Michaels J, et al. Airway secretion clearance by mechanical exsufflation for post-poliomyelitis ventilator-assisted individuals. *Arch Phys Med Rehabil*. 1993;74:170–177.
49. Bach JR. Amyotrophic lateral sclerosis: predictors for prolongation of life by noninvasive respiratory aids. *Arch Phys Med Rehabil*. 1995;76:828–832.
50. Gray A, Goodacre S, Newby DE, et al. Noninvasive ventilation in acute cardiogenic pulmonary edema. *N Engl J Med*. 2008;359:142–151.
51. Berney S, Haines K, Denehy L. Physiotherapy in critical care in Australia. *Cardiopulm Phys Ther J*. 2012;23(1):19–25.
52. Pasquina P, Merlani P, Granier JM, et al. Continuous positive airway pressure versus noninvasive pressure support ventilation to treat atelectasis after cardiac surgery. *Anesth Analg*. 2004;99:1001–1008.
53. Davidson C, Banham S, Elliott M, et al. Guidelines British Thoracic Society/Intensive Care Society Guideline for the ventilatory management of acute hypercapnic respiratory failure in adults BTS Standards of Care Committee Member, British Thoracic Society/Intensive Care Society Acute Hypercapnic Respiratory Failure Guideline Development Group, On behalf of the British Thoracic Society Standards of Care Committee. *BMJ Open Resp Res*. 2016;3:e000133. doi:10.1136/bmjresp-2016-000133.
54. Speed L, Harding K. Tracheostomy teams reduce total tracheostomy time and increase speaking valve use: a systematic review and meta-analysis. *J Crit Care*. 2013;28:216, e1–216, e10.
55. O'Connor HH, White AC. Tracheostomy Decannulation. *Respir Care*. 2010;55(8):1076–1081.
56. White AC, Kher S, O'Connor H. When to change a tracheostomy tube. *Respir Care*. 2010;55(8):1069–1075.
57. Carron MA, Kim SA, Sawhney R, et al. Airway obstruction by granulation tissue within a fenestrated trache tube: case report. *Ear Nose Throat J*. 2006;85(1):54–55.
58. Prigent H, Lejaille M, Terzi N, et al. Effect of a tracheostomy speaking valve on breathing–swallowing interaction. *Intensive Care Med*. 2012;38:85–90.
59. Passy-muir.com. *The Passy-Muir Valve*; 2017. http://www.passy-muir.com/.
60. Massery M, Hagins M, Stafford R, et al. Effect of airway control by glottal structures on postural stability. *J Appl Physiol*. 2013;115:483–490.
61. Sutt AL, Cornwell P, Mullany D, et al. The use of tracheostomy speaking valves in mechanically ventilated patients results in improved communication and does not prolong ventilation time in cardiothoracic intensive care unit patients. *J Crit Care*. 2015;30:491–494.
62. Smith KA, Matthews TW, Dubé M, et al. Changing practice and improving care using a low-risk tracheotomy clinical pathway. *AMA Otolaryngol Head Neck Surg*. 2014;140(7):630–634.
63. Convertino VA. Cardiovascular consequences of bed rest: effect on maximal oxygen uptake. *Med Sci Sports Exerc*. 1997;29:191–196.
64. Convertino VA, Bloomfield SA, Greenleaf JE. An overview of the issues: physiological effects of bed rest and restricted physical activity. *Med Sci Sports Exerc*. 1997;29:187–190.
65. Topp R, Ditmyer M, King K, et al. The effect of bed rest and potential of prehabilitation on patients in the intensive care unit. *AACN Clin Issues*. 2002;13:263–276.
66. Hodgson CL, Fan E. Intensive care unit acquired weakness. *Anaesth Intensive Care Med*. 2016;17:24–26. doi:10.1016/j.mpaic.2015.10.004.
67. Appleton RT, Kinsella J, Quasim T. The incidence of intensive care unit-acquired weakness syndromes: a systematic review. *J Intensive Care Soc*. 2015;16:126–136. doi:10.1177/1751143714563016.
68. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. *N Engl J Med*. 2014;370:1626–1635. doi:10.1056/NEJMra1209390.
69. Gosselink R, Langer D. Recovery from ICU-acquired weakness; do not forget the respiratory

muscles! *Thorax*. 2016;71(9):779–780. doi:10.1136/thoraxjnl-2016-208835.
70. Hermans G, Van den Berghe G. Clinical review: intensive care unit acquired weakness. *Crit Care*. 2015;19:274. doi:10.1186/s13054-015-0993-7.
71. Campellone JV, Lacomis D, Kramer DJ, et al. Acute myopathy after liver transplantation. *Neurology*. 1998;50:46–53.
72. Tepper M, Rakic S, Haas JA, et al. Incidence and onset of critical illness polyneuropathy in patients with septic shock. *Neth J Med*. 2000;56:211–214.
73. Wischmeyer PE, San-Millan I. Winning the war against ICU-acquired weakness: new innovations in nutrition and exercise physiology. *Crit Care*. 2015;19:S6. doi:10.1186/cc14724.
74. Angus DC, Carlet J. Brussels Roundtable Participants, 2003. Surviving intensive care: a report from the 2002 Brussels Roundtable. *Intensive Care Med*. 2002;29:368–377. doi:10.1007/s00134-002-1624-8.
75. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med*. 2003;348:683–693. doi:10.1056/NEJMoa022450.
76. Puthucheary Z, Rawal J, Ratnayake G, et al. Neuromuscular blockade and skeletal muscle weakness in critically ill patients: time to rethink the evidence? *Am J Respir Crit Care Med*. 2012;185:911–917. doi:10.1164/rccm.201107-1320OE.
77. Truong AD, Fan E, Brower RG, et al. Bench-to-bedside review: mobilizing patients in the intensive care unit – from pathophysiology to clinical trials. *Crit Care*. 2009;13:216. doi:10.1186/cc7885.
78. Vasilevskis EE, Ely EW, Speroff T, et al. Reducing iatrogenic risks: ICU-acquired delirium and weakness–crossing the quality chasm. *Chest*. 2010;138:1224–1233. doi:10.1378/chest.10-0466.
79. Pandharipande P, Banerjee A, McGrane S, et al. Liberation and animation for ventilated ICU patients: the ABCDE bundle for the back-end of critical care. *Crit Care*. 2010;14:157. doi:10.1186/cc8999.
80. Adler J, Malone D. Early mobilization in the intensive care unit: a systematic review. *Cardiopulm Phys Ther J*. 2012;23:5–13.
81. Burtin C, Clerckx B, Robbeets C, et al. Early exercise in critically ill patients enhances short-term functional recovery. *Crit Care Med*. 2009;37:2499–2505. doi:10.1097/CCM.0b013e3181a38937.
82. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. 2009;373:1874–1882. doi:10.1016/S0140-6736(09)60658-9.
83. Stiller K, Phillips A, Lambert P. The safety of mobilisation and its effect on haemodynamic and respiratory status of intensive care patients. *Physiother Theory Pract*. 2004;20:175–185. doi:10.1080/09593980490487474.
84. Gosselink R, Bott J, Johnson M, et al. Physiotherapy for adult patients with critical illness: recommendations of the European Respiratory Society and European Society of Intensive Care Medicine Task Force on Physiotherapy for Critically Ill Patients. *Intensive Care Med*. 2008;34:1188–1199. doi:10.1007/s00134-008-1026-7.
85. NICE. *Rehabilitation after critical illness in adults. Guidance and guidelines. NICE*; 2009. https://www.nice.org.uk/guidance/cg83.
86. Bailey PP, Miller RR, Clemmer TP. Culture of early mobility in mechanically ventilated patients. *Crit Care Med*. 2009;37:S429–S435. doi:10.1097/CCM.0b013e3181b6e227.
87. TEAM Study Investigators, Hodgson C, Bellomo R, et al. Early mobilization and recovery in mechanically ventilated patients in the ICU: a bi-national, multi-centre, prospective cohort study. *Crit Care*. 2015;19:81. doi:10.1186/s13054-015-0765-4.
88. Green M, Marzano V, Leditschke IA, et al. Mobilization of intensive care patients: a multidisciplinary practical guide for clinicians. *J Multidiscip Healthc*. 2016;9:247–256. doi:10.2147/JMDH.S99811.
89. Hanekom S, Gosselink R, Dean E, et al. The development of a clinical management algorithm for early physical activity and mobilization of critically ill patients: synthesis of evidence and expert opinion and its translation into practice. *Clin Rehabil*. 2011;25:771–787. doi:10.1177/0269215510397677.
90. Stiller K. Safety issues that should be considered when mobilizing critically ill patients. *Crit Care Clin*. 2007;23:35–53. doi:10.1016/j.ccc.2006.11.005.
91. Greenleaf JE. Intensive exercise training during bed rest attenuates deconditioning. *Med Sci Sports Exerc*. 1997;29:207–215.
92. Castro-Avila AC, Serón P, Fan E, et al. Effect of early rehabilitation during intensive care unit stay on functional status: systematic review and meta-analysis. *PLoS ONE*. 2015;10:e0130722. doi:10.1371/journal.pone.0130722.
93. Connolly B, Thompson A, Douiri A, et al. Exercise-based rehabilitation after hospital discharge for survivors of critical illness with intensive care unit–acquired weakness: a pilot feasibility trial. *J Crit Care*. 2015;30:589–598. doi:10.1016/j.jcrc.2015.02.002.
94. Connolly B, Denehy L, Brett S, et al. Exercise rehabilitation following hospital discharge in survivors of critical illness: an integrative review. *Crit Care*. 2012;16:226. doi:10.1186/CC11219.
95. Goddard SL, Cuthbertson BH. Rehabilitation and critical illness. *Anaesth Intensive Care Med*. 2012;13:214–216. doi:10.1016/j.mpaic.2012.02.007.

96. NICE. *Critical illness rehabilitation: NICE guideline CG83*; 2012. https://www.nice.org.uk/guidance/cg83/documents/cg83-critical-illness-rehabilitation-review-decision2.
97. Parry S, Granger CL, Berney S, et al. Assessment of impairment and activity limitations in the critically ill: a systematic review of measurement instruments and their clinimetric properties. *Intens Care Med*. 2015;41:744–762.
98. World Health Organisation. *International Classification of Functioning, Disability and Health*. Geneva: WHO; 2001.
99. Vanpee G, Hermans G, Segers J, et al. Assessment of limb muscle strength in critically ill patients: a systematic review. *Crit Care Med*. 2014;42(3):701–711.
100. Connolly B, Jones G, Curtis A, et al. Clinical predictive value of manual muscle strength testing during critical illness: an observational cohort study. *Crit Care*. 2013;17(5):R229.
101. Baldwin C, Bersten A. Alterations in respiratory and limb muscle strength and size in patients with sepsis who are mechanically ventilated. *Phys Ther*. 2014;94(1):68–82.
102. Grimm A, Teschner U, Porzelius C, et al. Muscle ultrasound for early assessment of critical illness neuromyopathy in severe sepsis. *Crit Care*. 2013; 17(5):R227.
103. Gruther W, Benesch T, Zorn C, et al. Muscle wasting in intensive care patients: ultrasound observation of the M. quadriceps femoris muscle layer. *J Rehabil Med*. 2008;40(3):185–189.
104. Turton P, Hay R, Taylor J, et al. Human limb skeletal muscle wasting and architectural remodeling during five to ten days intubation and ventilation in critical care – an observational study using ultrasound. *BMC Anesthesiol*. 2016;16:119.
105. Corner E, Soni N, Handy H, et al. Construct validity of the Chelsea critical care physical assessment tool: an observational study of recovery from critical illness. *Crit Care*. 2014;18: R55.
106. Corner E, Wood H, Englebretsen C, et al. The Chelsea critical care physical assessment tool (CPAx): validation of an innovative new tool to measure physical morbidity in the general adult critical care population; an observational proof-of-concept pilot study. *Physiotherapy*. 2013;99(1):33–41.
107. Corner EJ, Hutchins LV, Attrill K, et al. The responsiveness of the Chelsea Critical Care Physical Assessment tool in measuring functional recovery in the burns critical care population: an observational study. *Burns*. 2015;41:241–247.
108. Thrush A, Rozek M, Dekerlegand J. The clinical utility of the functional status score for the intensive care unit (FSS-ICU) at a long-term acute care hospital: a prospective cohort study. *Phys Ther*. 2012;92(12):1536–1545.
109. Huang M, Chan KS, Zanni JM, et al. Functional Status Score for the ICU: an international clinimetric analysis of validity, responsiveness and minimal important difference. *Crit Care Med*. 2016;44(12):e1115–e1164.
110. Skinner E, Berney S, Warrillow S, et al. Development of a physical function outcome measure (PFIT) and a pilot exercise training protocol for use in intensive care. *Crit Care Resusc*. 2009;11:110–115.
111. Denehy L, de Morton N, Skinner E, et al. A physical function test for use in the intensive care unit: validity, responsiveness, and predictive utility of the physical function ICU test (scored). *Phys Ther*. 2013;93(12):1636–1645.
112. Hodgson C, Needham D, Haines K, et al. Feasibility and inter-rater reliability of the ICU mobility scale. *Heart Lung*. 2014;43(1):19–24.
113. Tipping CJ, Bailey MJ, Bellomo R, et al. The ICU mobility scale has construct and predictive validity and is responsive: a multicenter observational study. *Ann Am Thorac Soc*. 2016;12(6).
114. Parry S, Denehy L, Beach LJ, et al. Functional outcomes in ICU- what should we be using? – an observational study. *Crit Care*. 2015;19:127.

6

Critical care nursing

John R Welch

NATURE AND FUNCTION OF CRITICAL CARE NURSING

Nurses are the round-the-clock constant factor for critically ill patients and their families, providing continuity and acting as the 'glue' that holds the intensive care unit (ICU) together. Nurses fine-tune, coordinate and communicate the many aspects of treatment and care needed to manage their patients '*responses to actual or potential life-threatening problems*',[1] including

- continuous, close monitoring of the patient and attached apparatus
- dynamic analysis and synthesis of complex data
- anticipation of complications
- complex decision making, and the execution and evaluation of interventions to minimise any adverse effects
- enhancement of the speed and quality of recovery
- emotional support of the patient and family, including support through the end of life.

Nursing in critical care is influenced by the essential nature of nursing as well as the specific requirements of the specialty. Key concepts for all nurses are said to include an appreciation of holism and the whole range of influences on all areas of life, and the pursuit of health rather than the treatment of illness.[2]

However, inevitably, there is an emphasis on technology in ICU: the nurses must be technically competent. Even such relatively routine tasks as titration of continuous inotrope or vasopressor infusions and maintenance of the constant flow of the drugs when syringe drivers are switched is a significant skill.[3] This means that it is all too easy to neglect the human aspects of care. Expert nurses will connect with patients both physically and psychologically,[4] but patient-centred care and emotional support can be lost when the nursing resource is reduced.[5] One ICU patient described his treatment as '*rooted in the minute analysis of charts and the balancing of chemicals, not so much in the warmth of human contact*'.[6] Others report experiencing breathlessness, voicelessness and thirst, and feelings of helplessness, anxiety, desperation, desertion and powerlessness.[7,8] ICU patients are less heavily sedated and therefore more aware than previously – '*conscious but feeling doped*'[9] – but can rarely control what happens to them during critical illness, especially in the acute phase. They usually wish to reassert their autonomy as they recover (e.g. during weaning from ventilation or when moving to a lower level of care). Nurses can enable patients to have a say in the management of these processes while still ensuring a safe progression. Essential personal care is invariably undertaken or supervised by nurses; and although important functions, such as chest physiotherapy, mobilisation and administration of nutrition, may be prescribed by other specialists, they will still be integrated and delivered by nurses.

A SYSTEMATIC APPROACH TO CARE

Nursing critically ill patients is complex. The clinical review should be structured to clarify and prioritise patient needs so that all possible problems are addressed. In acute situations, assessment in turn of the fundamental A–B–C–D–E aspects of care is a useful method:

Airway: with establishment and maintenance of airway patency (using airway adjuncts or advanced airways as necessary; humidification, removal of pulmonary secretions, etc.).

Breathing: ensuring adequacy of oxygenation and ventilation.

Circulation: assessing blood volume and pressures; perfusion of brain, heart, lungs, kidneys, gut and other organs; control of bleeding, haematology, etc.

Disability: checking consciousness and the factors that affect it, systemic and localised neurology; assessing the need for analgesia, sedation and neuromuscular blockade.

Exposure: hands-on, head-to-toe, front-and-back examination, and review of everything else; with consideration of skin and mucus membrane integrity, wounds and drains.

Treatment strategies can be prioritised using this schema, which has the additional benefit that it will be familiar to colleagues trained in advanced life support and similar systems. Further detail may be gained from the review of:

Fluid and electrolyte balance, biochemistry.

Gastrointestinal function: nutritional needs; elimination.

ABSTRACT

Nurses are the constant factor for critically ill patients, acting as the 'glue' that holds the intensive care unit (ICU) together. They must be technically competent and be able to connect with patients both physically and psychologically – providing holistic, patient-centred care – while preventing iatrogenic harm by intercepting and mitigating errors made by others. New roles include 'Advanced Critical Care Practitioners' – usually from a nursing background – who can work autonomously in defined situations.

Nurses must measure the quality of, and take responsibility for, the care they deliver; assessing the care of randomly selected patients monthly, or, better, weekly. Analysis of the data will reveal which areas of care need attention, where variations in care exist, and trends over time. It is desirable to compare data and share learning with other ICUs. Research priorities include optimisation of recovery and rehabilitation from critical illness, plus management of delirium, agitation and critical care-related stress.

KEYWORDS

Patient-centred care
staffing
safety
quality improvement
stress management
competency

History and holistic overview of the patient as a person and their sociocultural background.

Infection and infection control; microbiology – and personal hygiene.

Lines, catheters/invasive devices: utility and risks.

Medications.

Nursing and multidisciplinary teamwork: ensuring that the staff resource is sufficient for the patient's severity of illness and the physical demands of care.

Oral/dental care.

Psychology (cognition, communication and mood) – and the **p**lan of care and prognosis in the short, medium and long term.[10]

Relatives and loved ones.

More sophisticated models can be used to frame a wider impression of the patient or to reflect a particular philosophy or approach to care.[11] There is a great benefit in developing a shared vision within the department, and in articulating how agreed values will be demonstrated in practice.[12] These might include emphasising the primary importance of patient safety and well-being, ensuring that the kindness an individual would want for their own loved ones is always offered, effective teamworking, and having systems in place to achieve continuous improvement.[13] Whichever method is used, there must be explicit definitions of the patient's problems and a clear statement of measurable therapeutic goals.

NURSING AND PATIENT SAFETY

Many patients suffer iatrogenic harm in the ICU,[14] but vigilant nurses can prevent such incidents by intercepting and mitigating errors made by others.[15] No particular system of critical care nursing has been shown to be definitively superior to others,[16] but nursing surveillance is key to patient safety.[17] Insufficient staffing has been linked to increased adverse events, morbidity and mortality.[18–20] At the minimum, 5.6 nurses need to be employed for each patient requiring 1:1 care 24 hours a day.

EVOLVING ROLES OF CRITICAL CARE NURSES

Critical care nurses' range of practice has widened in recent years, partly due to progress in technology and changes in the working of other professionals, although the benefits of developing new skills must be balanced against ensuring the maintenance of essential holistic care. There is considerable variation in the array of tasks undertaken by critical care nurses in different institutions, with invasive procedures and drug prescriptions still usually performed by doctors. However, suitably trained UK nurses are enabled – in theory at least – to prescribe licensed medicines for the whole range of medical conditions, although prescribing is not yet a widespread phenomenon in the ICU. It is likely to become a routine part of nursing practice in the future.

Critical care nurses do have a rapidly increasing role in decision making regarding the adjustment, titration and troubleshooting of such key treatments as ventilation, fluid, inotrope/vasopressor administration and renal replacement therapy. The use of less invasive techniques (e.g. transoesophageal Doppler ultrasonography for cardiac output estimation) mean it is easier for nurses to institute sophisticated monitoring and then modify treatments accordingly. There is evidence that nurses can achieve good outcomes in these areas, especially with the use of clinical guidelines and protocols (e.g. by reducing the time to wean respiratory support[21]). Further development of protocols, guidelines and care pathways can be used to enhance the nursing contribution to critical care in future.

NEW NURSING ROLES IN CRITICAL CARE

Maintaining adequate numbers of staff with the experience and skills to meet the increasing needs of critically ill patients is a challenge. Nurses constitute the largest part of the workforce and represent a significant total cost. Changes in training arrangements and the demographics of nurses in general have meant that there are relatively fewer applicants for ICU posts. This has driven the development of various new ways of working to deliver both fundamental and more sophisticated aspects of care. New nursing roles include some that substitute for medical roles, as well as those that retain a nursing focus and aim to fill gaps in healthcare with nursing rather than medical practice. For example, the United Kingdom has designated a number of senior 'Nurse Consultant' posts in all areas of healthcare, but with the largest proportion in critical care, particularly in Outreach roles.[22] These are experts focusing on clinical practice but who are also required to provide professional leadership and consultancy, as well as the development of clinical and academic education and training, as well as service development, research and evaluation.

Also, there is now widespread interest in developing 'Advanced Critical Care Practitioners' (ACCPs) who can work autonomously in defined situations. ACCPs may come from a range of health care backgrounds but are usually nurses. Training typically lasts at least 2 years at a postgraduate/masters degree level and includes advanced clinical assessment skills, performance of diagnostic tests, diagnosis and clinical reasoning, initiation and management of treatment plans, invasive procedures (e.g. advanced airway techniques, central line placement) and drug prescription.[23]

Other staff – such as nursing/health care assistants – are increasingly and successfully employed to deliver what has previously been seen as core nursing care in order to support trained nurses and free them to concentrate on more advanced practice.[24] Reductions in health care funding and shortages of trained staff are likely to make such developments more common, but

it is imperative that this is a managed process to ensure the best outcomes for patients, with proper arrangements for training, support and systems of work.

CRITICAL CARE NURSING BEYOND THE ICU: CRITICAL CARE OUTREACH

Around the world, general ward staff are required to manage an increasing throughput of patients who are, on average, older than before, with more chronic disease, and more acute and critical illness. Studies of critically ill ward patients show that the majority experience substandard care and experience adverse events before transfer to the ICU.[25,26] Various factors are implicated, including knowledge deficits and failure to appreciate clinical urgency or to seek advice, which is compounded by poor organisation. It is nurses who record or supervise the recording of vital signs, but there is often poor understanding of the importance of such indicators, ineffective communication with senior staff and difficulties ensuring that appropriate treatments are prescribed and administered. Nurse-led critical care outreach teams support ward staff caring for at-risk and deteriorating patients, and facilitate transfer to ICU when appropriate.[27] They can also support the care of patients on wards after discharge from ICU,[28] and after discharge from the hospital too. Potential problems with these approaches include a loss of specialist critical care staff from the ICU, and being sure that outreach teams have the necessary skills to manage high-risk patients in less well-equipped areas, particularly when there are limitations placed on nurses prescribing and administering treatments.

NURSING IN THE MULTIDISCIPLINARY TEAM

High-quality critical care requires genuine multidisciplinary teamwork, with

- clear individual roles
- team members that share knowledge, skills, best practice and learning
- systems that enable shared clinical governance, individual and team accountability, risk analysis and management.[29]

ICUs where team performance is not so well developed are likely to have less effective processes and worse outcomes. Aspects of team leadership, coordination, communication and decision making can be measured against defined criteria, as can outcome indicators relating to patients and staff,[30] for example:

- compliance with protocols
- adverse events/critical incidents
- patient length of stay
- mortality
- staff satisfaction
- staff retention.

Identified deficiencies in teamworking can then be addressed, although some investment may be needed. One study focused on nurses as the main drivers of improvement in the ICU. Units were engaged in a structured improvement programme entailing analysis of the prevailing culture in the department, followed by tailored training in teamworking, ways of achieving safer practice, and performance measurement.[31] ICUs that completed this programme had significantly better outcomes than those that did not, even though both groups were required to use the same clinical protocols.[31]

QUALITY OF CARE AND QUALITY IMPROVEMENT

Robust audit is the foundation of quality care. Potential indicators include pressure ulcer prevalence, nosocomial infection rates, patient satisfaction and errors in drug administration.[32] Nurses must measure the quality of, and take responsibility for, the care that they deliver, although it should be appreciated that nursing care cannot be considered entirely separately from other variables that influence patient outcomes: quality care depends on a collective interdisciplinary commitment to continuous improvement,[33] and continuous 'measurement for improvement'. One approach is to assess the evidence of care of randomly selected patients every month, or, better still, weekly: some descriptors of critical care nursing quality are shown in Box 6.1. Analysis of the data will reveal which areas of care need attention, where variations in care exist and trends over time. It is desirable to compare data and to share learning with other ICUs where possible.

CRITICAL CARE NURSING MANAGEMENT

The nurse manager role is crucial to service performance. The most important priority is the challenge of attracting and retaining a flexible, effective and progressive nursing team that works well with other health care professionals to meet patient needs, but within a limited budget.

STAFFING THE CRITICAL CARE UNIT

The starting point for calculations of staffing requirements is the detailing of patient needs – and of the knowledge and skills that will be required to meet those needs – with an appreciation that there will be unpredictable variations over time (Box 6.2).

Patient need has many components, including:

- the severity and complexity of acute illness and chronic disease
- other physical characteristics (e.g. mobility, body weight, skin integrity, continence)
- consciousness and cognition
- mood and emotionality (e.g. anxiety, depression, motivation to engage in rehabilitation)

Box 6.1 Exemplar critical care nursing quality indicators[34]

Randomly select patients and check:

Airway
1. Airway management and turning/repositioning plan.
2. Emergency equipment by the bedside (for those with altered airways).

Pain
1. Pain – and nausea – score recorded hourly.
2. Plan for managing postoperative pain.
3. Is the patient in pain at the time of review?

Sedation
1. Richmond Agitation and Sedation Scale (RASS) assessed hourly.
2. If appropriate, target RASS in Care Plan.
3. Confusion Assessment Method for ICU (CAM-ICU) assessed daily.

Maintaining skin integrity
1. SSKIN (**S**kin Assessment, **S**urface, **K**eep moving, **I**ncontinence, **N**utrition assessment) completed and documented within an hour of admission.
2. Risk assessment completed every shift.
3. SSKIN bundle completed every shift.
4. Patient on the correct mattress.
5. Patient on the correct turn frequency.
6. Nurse can describe an appropriate pressure ulcer prevention plan for patient.
7. Strategies in place to prevent incontinence-associated dermatitis/moisture damage.
8. Strategies in place to prevent damage from medical devices.
9. Patient/carer understands the pressure ulcer prevention plan.
10. Manual handling assessment completed in last 24 hours.

Monitoring
1. Safe alarm limits set.
2. Fluid balance target identified.
3. Fluid challenge used as per protocol.
4. Fluid balance target achieved.
5. Invasive lines: documented evidence of insertion and removal.
6. Lines visibly clean and dressings intact.
7. Infusion lines clearly labelled and in date.

Assessment and documentation
1. Time of admission/transfer clearly documented.
2. Multidisciplinary Team care plan with problems identified and clear treatment goals.
3. Accurate A–E nursing review and evaluation on each shift.
4. Documented evening review.
5. Documented night shift review.
6. Complete Multidisciplinary Team discharge summary (when appropriate).
7. Up-to-date patient information board.

Box 6.2 Standards for nurse staffing in critical care[35]

1. Level 3 patients (requiring advanced respiratory support alone, or basic respiratory support together with support of at least two other organ systems) require a registered nurse/patient ratio of a minimum 1:1 to deliver direct care.
2. Level 2 patients (requiring more detailed observation or intervention including support for a single failing organ system or postoperative care and those 'stepping down' from higher levels of care) require a registered nurse/patient ratio of a minimum of 1:2 to deliver direct care.
3. Each designated Critical Care Unit will have an identified lead nurse with overall responsibility for the nursing elements of the service.
4. There will be a supernumerary clinical coordinator on duty 24/7. (Units with <6 beds may consider having a supernumerary clinical coordinator to cover peak activity periods; i.e. early shifts.)
5. Units with >10 beds will require additional supernumerary registered nursing staff over and above the clinical coordinator to enable the delivery of safe care. The number of additional staff per shift will be incremental depending on the size and layout of the unit (e.g. in the case of multiple single rooms), and during events, such as infection outbreaks.
6. Each Unit will have a dedicated Clinical Nurse Educator responsible for coordinating education, training and continuing professional development for nursing staff and pre-registration student allocation.
7. All nursing staff appointed to Critical Care will be allocated a period of supernumerary practice.
8. A minimum of 50% of registered nursing staff will be in possession of a post-registration award in Critical Care Nursing.
9. Units must not utilise >20% of registered nurse from bank/agency on any one shift when they are NOT their own staff.
10. Where direct care is augmented using non-registered support staff, appropriate training and competence assessment is required.

- the frequency and complexity of observation/monitoring and interventions
- the needs of relatives.

The staff resource includes members of the clinical team, the whole range of ancillary staff and the support services. Collectively, these personnel must be adequate to meet patient needs. This requires evaluation of:

- nursing numbers and skill mix
- multidisciplinary team skill mix, with consideration of variations in the availability of team members (e.g. doctors, respiratory/physiotherapists, equipment technicians out-of-hours).

The context of care is also significant; that is:

- the physical environment (e.g. the ease with which patients can be observed, whether cohorted in groups or in separate rooms)
- workload variations – peaks, troughs and overall activity in the department (e.g. admissions, discharges, transport to other areas [e.g. imaging], transfers).

The manager is also responsible for

- coordinated operational management of the area
- quality of nursing care
- management of nursing pay and non-pay budgets
- personnel management
- dealing with complaints and investigating adverse incidents.

There are always dynamic political, social and economic forces bearing on the organisational objectives and resources of the hospital and the ICU. The nurse manager needs to understand these factors and how they influence the delivery of patient care and the maintenance of a healthy environment for individual and team development. The manager must be able to communicate the key issues to the whole team in the form of an agreed strategy and a clear, regularly updated operational plan for the department. There needs to be a working system that addresses and integrates the views and needs of all users of the service, including patients and their families. Such a system should enable a shared understanding of exactly what needs to be done in practice, and where each team member fits into the plan.

Externally, the manager represents the service and ensures that other disciplines and the bigger organisation are informed about critical care issues.

Teams perform most effectively when individuals believe that they are working towards some common and worthwhile goals. The principles of shared governance can be usefully applied in this perspective, whereby staff collectively review and learn from their own practices. This has to be in the context of:

- the strategic agendas of the unit and the hospital
- the development of the service
- financial issues, budgets and budgetary restraints
- an appreciation of day-to-day working issues.

STRESS MANAGEMENT AND MOTIVATION

The ICU can be extremely stressful, demanding considerable cognitive, affective and psychomotor effort from staff. Supervisory and feedback arrangements should be in place to alleviate such demands, and to enable identification of staff members who are having difficulties at work. Studies of human resource practices in hospitals have found an association between the quantity and quality of staff appraisal and patient mortality, with organisations that emphasise training and teamworking having better outcomes.[36] Regular individual performance reviews and the formulation of development plans provide positive assurance and encouragement, and can identify specific personal requirements, such as educational needs.

Providing staff at all levels with opportunities to feel that they can influence and perhaps modify the working environment tends to decrease stress and increase motivation. Flexibility to work in different ways at different times while still meeting the overall demands of the department is important. It is the manager's job to balance and meet the needs of staff, patients and the organisation. One method is to give staff a choice regarding rostering, partly to help with work–life balance, but also so that the nurse can opt to work with particular patients for a time to practice certain skills and to promote continuity of care. This can have real benefits for patients.

NURSE EDUCATION

There are well-established educational programmes for critical care nurses, although the content and quality vary. There is a role for the study of relevant philosophy, nursing theory and research methods, but the fundamental requirement is for learning that focuses on clinical practice and practical problem solving (Box 6.3).

A competency framework can be used to structure descriptors of the skills, knowledge and attitudes needed to achieve specific patient outcomes. There needs to be consideration of how individual actions are integrated into holistic care, and the role of independent clinical judgement. Developing nurses' critical thinking and decision-making skills is also important. Appraisal of learners' performances requires assessors to observe and question the nurse in practice, although this places significant demands on hard-pressed clinical areas. It may be that high-fidelity simulators can be used to test performance away from the practice setting in future.

Frameworks to identify different levels of performance have been developed; for example, based on Benner's novice-to-expert hierarchy (Table 6.1).[4] A group of UK critical care nursing organisations have described a three-stage version of the model, suggesting that novice critical care nurses should spend up to 12 months acquiring core competencies under supervision (Stage 1), should then undertake a formal course of training (Stage 2), and finally progress to practice without direct supervision (Stage 3).[37]

CRITICAL CARE NURSING RESEARCH

Research is most valued when it is relevant to practice. The researcher is more likely to gain support for the investigation of high-risk and high-cost processes, but many everyday methods and treatments warrant examination too, particularly when there are significant variations in practice. The researcher should determine how the topic of interest might be described in a measurable

Box 6.3 Key competencies for critical care nurses[37]

- *Respiratory system*: Anatomy & Physiology, Assessment, Monitoring & Observation, Non-Invasive Ventilation, Endotracheal Intubation, Invasive Ventilation, Chest Physiotherapy, Tracheostomy Care, Chest Drain Management, Associated Pharmacology.
- *Cardiovascular system*: Anatomy & Physiology, Assessment, Monitoring & Observation, Arterial Access, Central Venous Access, Fluid Management, Sepsis Management, Shock Management, Cardiac Rhythms, Associated Pharmacology.
- *Renal system*: Anatomy & Physiology, Assessment, Monitoring & Observation, Renal Replacement Therapy, Associated Pharmacology.
- *Gastrointestinal (including liver and biliary) system*: Anatomy & Physiology, Nutrition in Critical Illness, Assessment and Management, Associated Pharmacology.
- *Neurological system*: Anatomy & Physiology, Assessment, Monitoring & Observation, Sedation & Delirium Assessment and Management, Pain Control.
- *Integumentary system*: Anatomy & Physiology, Skin Integrity, Joint Positioning & Range of Movement, Venous Thromboembolism Assessment.

Other essential areas

- Promoting a Positive Patient Experience (Psychosocial Wellbeing, Visiting in Critical Care)
- Medicines Administration
- Admission & Discharge
- End-of-Life Care
- Intra- & Interhospital Transfer
- Rehabilitation
- Communication & Teamwork
- Infection Prevention & Control
- Evidenced-Based Practice
- Professionalism
- Defensible Documentation
- (Assessment of) Mental Capacity
- Leadership.

Table 6.1 Assessment of critical care nurses' performance[4]

RATING	DEFINITION	OBSERVED BEHAVIOUR	PROMPTS
Novice	Limited skill and/or knowledge, inconsistent practice, variable interpersonal skill Limited understanding of wider context, inflexible rule-governed behaviour	Lacks coordination and confidence Potential for omissions or inaccuracies Unable to demonstrate accurate and safe performance despite repeated attempts	Requires frequent directive prompts, supervision and advice
Advanced beginner	Some skill and knowledge, generally consistent practice and interpersonal skill; variable ethical thought Some appreciation of situational influences	Coordinated and confident in fundamental tasks Easily distracted or unable to integrate other aspects of patient care	Requires occasional directive prompts and some supervision
Competent	Consistent safe, accurate and effective practice, interpersonal skill and ethical thought Conscious and deliberate planning with consideration of immediate context	Skilful, confident and coordinated patient-focused practice, with evident integration of other aspects of care Prioritisation of workload	Self-directing without supervision
Proficient	Consistent safe, accurate and effective practice, higher-level interpersonal skill and ethical reasoning Conscious and deliberate planning with consideration of long-term goals Adapts care in response to changing situations	Skilled and accomplished practice, proactive and flexible approach to care Problem solving and decision making through reflection Role model	Capable of supporting and demonstrating skills to others

Adapted from Benner P. From novice to expert. *Am J Nurs*. 1982;82(3):402–407.

way, and formulate the investigation as a question, with consideration of how answers can be obtained.

Relatively small numbers of patients are treated in the ICU, at considerable cost, although many of the methods used do not have a robust evidence base. Patient outcomes are influenced by different organisational approaches, staff characteristics, varied working practices, as well as differences between patients themselves. Therefore, a range of quantitative and qualitative investigative procedures are needed to gain an understanding of the issues. The approach chosen depends on the nature of the research question, the objectives of the researcher and the resources available. For example:

- comparing different treatments generally requires quantitative measurements of particular end-points (e.g. the dose of a drug needed to achieve a target physiological variable)
- understanding how an individual thinks or feels usually involves analysis of qualitative material (e.g. data from interviews with patients and families).

It is noteworthy that few, if any, large-scale trials of medical treatments in the ICU have shown sustained, significant benefits in recent years. At the same time, there is increasing evidence that many patients suffer severe psychological problems in the ICU[38] and posttraumatic stress disorder later on.[39] Accordingly, a recent 'ICU Priority Setting Partnership' identified three critical questions for ICU patients, carers and clinicians[40]:

1. How might patients that would benefit from critical care be identified and admitted at the optimal time?
2. How can patients and their families be helped through the often lengthy recovery and rehabilitation from critical illness?
3. How best can delirium and agitation be prevented or managed when it occurs?

Nurses have already extensively researched questions (2) and (3) in particular,[7–9,41,42] and the qualitative methods they very often use are the most appropriate for further work in these areas. There is great potential for nurses to be leaders in such matters.

REFERENCES

1. American Association of Critical-Care Nurses. *AACN Scope and Standards for Acute and Critical Care Nursing Practice*; 2015. Aliso Viejo, CA: American Association of Critical-Care Nurses. www.aacn.org/nursing-excellence/standards/aacn-scope-and-standards-for-acute-and-critical-care-nursing-practice.
2. Chinn PL, Kramer MK. *Knowledge Development in Nursing: Theory and Process*. 9th ed. St Louis, MO: Mosby; 2015.
3. Genay S, Décaudin B, Scoccia S, et al. An in vitro evaluation of infusion methods using a syringe pump to improve noradrenaline administration. *Acta Anaesthesiol Scand*. 2015;59(2):197–204.
4. Benner P. *From Novice to Expert: Excellence and Power in Clinical Nursing Practice (commemorative en)*. Upper Saddle River, NJ: Prentice-Hall; 2001.
5. Ball C, McElligot M. 'Realising the potential of critical care nurses': an exploratory study of the factors that affect and comprise the nursing contribution to the recovery of critically ill patients. *Intensive Crit Care Nurs*. 2003;19(4):226–238.
6. Watt B. *Patient: The True Story of a Rare Illness*. London: Viking; 1996.
7. Karlsson V, Bergbom I, Forsberg A. The lived experiences of adult intensive care patients who were conscious during mechanical ventilation: a phenomenological–hermeneutic study. *Intensive Crit Care Nurs*. 2012;28(1):6–15.
8. Kjeldsen CL, Hansen MS, Jensen K, et al. Patients' experience of thirst while being conscious and mechanically ventilated in the intensive care unit. *Nurs Crit Care*. 2017;doi:10.1111/nicc.12277.
9. Holm A, Dreyer P. Intensive care unit patients' experience of being conscious during endotracheal intubation and mechanical ventilation. *Nurs Crit Care*. 2017;22(2):81–88.
10. Hillman KM, Bishop G, Flabouris A. Patient examination in the intensive care unit. In: Vincent JL, ed. *Yearbook of Intensive Care and Emergency Medicine*. Berlin: Springer-Verlag; 2002: 942–950.
11. Shirey MR. Nursing practice models for acute and critical care: overview of care delivery models. *Crit Care Nurs Clin North Am*. 2008;20(4):365–373.
12. Warfield C, Manley K. Developing a new philosophy in the NDU. *Nurs Stand*. 1990;4(41):27–30.
13. University College London Hospitals NHS Foundation Trust. *UCLH vision, values and objectives*. www.uclh.nhs.uk/aboutus/wwd/Pages/Visionandobjectives.aspx.
14. Ahmed AH, Giri J, Kashyap R, et al. Outcome of adverse events and medical errors in the intensive care unit: a systematic review and meta-analysis. *Am J Med Qual*. 2015;30(1):23–30.
15. Dykes PC, Rothschild JM, Hurley AC. Medical errors recovered by critical care nurses. *J Nurs Adm*. 2010;40(5):241–246.
16. Coombs M, Lattimer V. Safety, effectiveness and costs of different models of organising care for critically ill patients: literature review. *Int J Nurs Stud*. 2007;44(1):115–129.
17. Henneman EA, Gawlinski A, Giuliano KK. Surveillance: a strategy for improving patient safety in acute and critical care units. *Crit Care Nurse*. 2012;32(2):e9–e18.
18. McGahan M, Kucharski G, Coyer F. Nurse staffing levels and the incidence of mortality and morbidity in the adult intensive care unit: a literature review. *Aust Crit Care*. 2012;25(2):64–77.
19. Checkley W, Martin GS, Brown SM, et al. Structure, process, and annual ICU mortality across 69 centers: United States Critical Illness and Injury Trials Group Critical Illness Outcomes Study. *Crit Care Med*. 2014;42(2):344–356.

20. Kelly DM, Kutney-Lee A, McHugh MD, et al. Impact of critical care nursing on 30-day mortality of mechanically ventilated older adults. *Crit Care Med*. 2014;42(5):1089–1095.
21. Chang SY, Sevransky J, Martin GS. Protocols in the management of critical illness. *Crit Care*. 2012;16(2):306.
22. Endacott R, Boulanger C, Chamberlain W, et al. Stability in shifting sands: contemporary leadership roles in critical care. *J Nurs Manag*. 2008;16(7):837–845.
23. Faculty of Intensive Care Medicine. *Curriculum for Training for Advanced Critical Care Practitioners*. 1st ed. London: Faculty of Intensive Care Medicine; 2015. www.ficm.ac.uk/sites/default/files/ACCP%20Curriculum%20v1.0%20%282015%29%20COMPLETE_0.pdf.
24. Allen K, McAleavy JM, Wright S. An evaluation of the role of the Assistant Practitioner in critical care. *Nurs Crit Care*. 2013;18(1):14–22.
25. Cullinane M, Findlay G, Hargraves C, et al. *An Acute Problem? A Report of the National Confidential Enquiry into Patient Outcome and Death*; 2005. London: National Confidential Enquiry into Patient Outcome and Death. www.ncepod.org.uk/2005aap.html.
26. Marquet K, Claes N, De Troy E, et al. One fourth of unplanned transfers to a higher level of care are associated with a highly preventable adverse event: a patient record review in six Belgian hospitals. *Crit Care Med*. 2015;43(5):1053–1061.
27. Watson W, Mozley C, Cope J, et al. Implementing a nurse-led critical care outreach service in an acute hospital. *J Clin Nurs*. 2006;15(1):105–110.
28. Harrison DA, Gao H, Welch CA, et al. The effects of critical care outreach services before and after critical care: a matched-cohort analysis. *J Crit Care*. 2010;25(2):196–204.
29. Department of Health-Emergency Care Team. *Quality Critical Care: Beyond 'Comprehensive Critical Care': A Report by the Critical Care Stakeholder Forum*; 2005. London: Department of Health-Emergency Care Team. http://webarchive.nationalarchives.gov.uk/20130123205102/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4121049.
30. Dietz AS, Pronovost PJ, Mendez-Tellez PA, et al. A systematic review of teamwork in the intensive care unit: what do we know about teamwork, team tasks, and improvement strategies? *J Crit Care*. 2014;29(6):908–914.
31. Marsteller JA, Sexton JB, Hsu YJ, et al. A multicenter, phased, cluster-randomized controlled trial to reduce central line-associated bloodstream infections in intensive care units. *Crit Care Med*. 2012;40(11):2933–2939.
32. Maben J, Morrow E, Ball J, et al. *High Quality Care Metrics for Nursing*. London: National Nursing Research Unit, King's College London; 2012. https://www.kcl.ac.uk/nursing/research/nnru/publications/Reports/High-Quality-Care-Metrics-for-Nursing----Nov-2012.pdf.
33. Curtis JR, Cook DJ, Wall RJ, et al. Intensive care unit quality improvement: a 'how-to' guide for the interdisciplinary team. *Crit Care Med*. 2006;34(1):211–218.
34. Thorpe E. *Exemplar critical care unit nursing quality indicators*; 2017. University College Hospital Critical Care Units, University College London Hospitals. Personal communication.
35. Faculty of Intensive Care Medicine & Intensive Care Society. *Guidelines for the Provision of Intensive Care Services*. 1st ed. London: Faculty of Intensive Care Medicine & Intensive Care Society; 2015. www.ficm.ac.uk/sites/default/files/gpics_-_ed.1_2015_v2.pdf.
36. West MA, Guthrie JP, Dawson JF. Reducing patient mortality in hospitals: the role of human resource management. *J Organiz Behav*. 2006;27(7):983–1002.
37. Critical Care Networks-National Nurse Leads. *National Competency Framework for Registered Nurses in Adult Critical Care*; 2015. v. 2. Critical Care Networks-National Nurse Leads. http://cc3n.org.uk/competency-framework/4577977310.
38. Wade DM, Brewin CR, Howell DC, et al. Intrusive memories of hallucinations and delusions in traumatized intensive care patients: an interview study. *Br J Health Psychol*. 2015;20(3):613–631.
39. Wade D, Hardy R, Howell D, et al. Identifying clinical and acute psychological risk factors for PTSD after critical care: a systematic review. *Minerva Anestesiol*. 2013;79(8):944–963.
40. James Lind Alliance. *Intensive Care Top 10*; 2014. Southampton: James Lind Alliance National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre. www.jla.nihr.ac.uk/priority-setting-partnerships/intensive-care/top-10-priorities.
41. Whitehorne K, Gaudine A, Meadus R, et al. Lived experience of the intensive care unit for patients who experienced delirium. *Am J Crit Care*. 2015;24(6):474–479.
42. Egerod I, Bergbom I, Lindahl B, et al. The patient experience of intensive care: a meta-synthesis of Nordic studies. *Int J Nurs Stud*. 2015;52(8):1354–1361.

7

Ethics in intensive care

Andrew Hartle, (Charlotte) Stephanie Cattlin

Ethics is a normative science, or the study of human behaviour. More specifically, it aims to characterise behaviours that are 'right' or 'wrong'. Codes of medical ethics have existed for thousands of years; for example, the Hippocratic Oath[1], which has influenced medicine in the West for some 2500 years, but has now been replaced by guidance, such as the Declaration of Geneva[2], which is more appropriate in the late 20th and early 21st century.

Conflict may arise when there is a misunderstanding or disagreement between medical staff and patients (or their relatives) about the framework within which medical practice is acceptable. If it is not possible to resolve such conflict, then decisions may ultimately rest with judges and courts, but what is ethical may not be legal (and vice versa), and human behaviour is further constrained and influenced by cultural norms, religious beliefs (or the lack thereof) and more recently by concepts of Human Rights.

Guidance on research ethics has only achieved widespread acceptance since the Codes that arose from the Nuremberg Trials following the Second World War, although there are many examples across the world (e.g. the Tuskegee syphilis study) of research ethics abuse; it was not confined to the Nazi regime. More recently, research fraud has come under closer scrutiny; even in the 21st century there is evidence of significant unethical medical practice.[3] Detailed guidance on research in critical care should be consulted before beginning any study.

ETHICAL STUDY

There are many 'schools of ethics' (utilitarianism, hedonism, deontologism, epicureanism) but more recently principalism has gained popularity, at least as an easily remembered approach to analysing ethical challenges. The four principles as proposed by Beauchamp and Childress[4] are:

Autonomy – respecting the decision-making capabilities of those who have the ability to make an informed choice

Beneficence – the primary goal of treatment should be the best interests of the patient

Non-Maleficence – the avoidance of harm, whilst appreciating that all treatment may involve some harm, that this is not disproportionate to the benefits

Justice – patients should be treated fairly and equitably.

(It is interesting that the founding principles of the UKs National Health Service were healthcare, available to all, based on clinical need free at the point of use.)[5]

Whilst principalism is helpful in discussing the different elements, it may not always resolve conflict, as autonomy often outweighs the other three principles. Those that give autonomy this elevated impact may overlook that autonomy is only ever relative in any society, and subject to the limits imposed by that society.

Before considering whether the practise of intensive care medicine is ethical, it is important to establish its purpose or the goal of treatment; the ethics of a decision is context sensitive.

WHAT IS THE PURPOSE OF INTENSIVE CARE?

1. To keep people alive long enough to recover and be discharged
2. To delay death, to prevent the unavoidable
3. To prevent death

Patients may be admitted electively in the perioperative and periprocedural period, or as an emergency, and criteria for admission may vary depending on these.

We are well versed in the criteria that patients are required to meet to merit admission to intensive care; what is often more difficult is whether the decision to admit to intensive care is in the patient's best interests or whether these best interests involve ward-based ceilings or care, or indeed palliation. This is highlighted in those patients with increasing age (both chronologically and physiologically), chronic organ dysfunction, a large number of co-morbidities and poor functional reserve. Most patients whose intensive care admission is thought to be futile would prefer to die in their own home with an emphasis on comfort care rather than undergo invasive, intensive life-prolonging treatments.[6–8]

The context of admission decisions will inevitably include resources. Intensive care as discussed in this text is available only to a minority of the world population, and there is wide variation in provision even for that minority. Patients in the United Kingdom and the United States have similar demographics, as well as hospitalisation and mortality rates, but roughly three times more patients in the United States die in a critical care environment than in the United Kingdom, at all ages,

ABSTRACT

Ethics is a normative science, or the study of human behaviour. More specifically, it aims to characterise behaviours that are 'right' or 'wrong'. Codes of medical ethics have existed for thousands of years, but despite this, ethics continues to be an area of wide discussion and sometimes of conflict, and is often highly emotive for medical professionals, patients and their families alike. Ethical considerations in intensive care cover a wide variety of circumstances from consent through to futility, withdrawal or withholding of treatment, do not attempt resuscitation (DNACPR) and end-of-life care. The conflict that these topics potentially generate may be minimised with knowledge of the ethical and legal frameworks surrounding them, alongside excellent communication between all parties with the best interests of the patient remaining paramount.

KEYWORDS

Ethics
principalism
DNACPR
end-of-life care
futility
withdrawing/withholding
best interests
limitation of treatment

and the difference is more marked in those over the age of 85.[9] There is more to this difference than just resources; although the United States has fewer hospital beds/population, it has far more critical care beds (relative and absolute numbers). Finally, US patients are more likely to die at home than those in the United Kingdom.

FUTILITY

Futility is a frequent reason for a decision not to admit to intensive care, often without defining what is futile or why. A treatment is futile if it cannot achieve its desired goal (hence the importance of defining **in advance** the purpose of admission and/or the goal of treatment).

Futility may be quantitative or qualitative: quantitative is where the likelihood of an intervention benefitting the patient is low (the patient is extremely unlikely to survive); qualitative is where the quality of benefit of an intervention is poor (the patient may survive, but their quality of life will not be acceptable to them). Futility is not a new concept; Hippocrates stated that doctors should 'refuse to treat those who are overmastered by their diseases, realising that in such cases medicine is powerless'.[10] What constitutes futility for a particular patient often lies at the heart of cases decided by courts about withholding or withdrawing intensive care treatment, and it is almost inevitably contentious.[11] Futility is a term that may have a different meaning for staff and patients/families and may be misinterpreted as 'not worth it' by some (author's opinion – AJH).

WITHHOLDING/WITHDRAWING TREATMENT

Despite admission to intensive care, some patients will reach a point when all treatment options have been explored and maximal therapeutic benefit achieved. This point, at which patients transition from illness to dying, is often only recognised in retrospect. If an escalation of treatment, or further treatment is not deemed to be in the patient's best interests (or 'futile'), it may be withheld or withdrawn. This decision is the most common precursor to death in the intensive care unit environment.[12] The rationale for reaching this decision must be explained carefully and sympathetically to the patient and/or their family with the aim of moving towards comfort care rather than active treatment.[13,14]

RELIGIOUS BELIEFS SURROUNDING END-OF-LIFE CARE

Patients, their relatives and staff, hold a wide variety of (or no) religious views and perceptions regarding aspects of care, particularly at the end of life, which in turn can influence how patients and their families approach decision making in this regard, and it is important for the medical professionals involved in their care to appreciate and take these views into consideration.[15] A detailed description of these is beyond this chapter but there are online resources, for example, about brain death and organ donation[16], and blood transfusion[17]. Often, further sympathetic exploration of their specific issues and beliefs in this area, and the early involvement of hospital chaplaincy services, will ensure a smoother transition towards end-of-life care.[18]

EUTHANASIA AND PHYSICIAN-ASSISTED SUICIDE

Euthanasia is the act of intentionally ending a person's life with the aim of relieving pain and suffering. Physician-assisted suicide is where a doctor intentionally provides a person with the knowledge or means to commit suicide.[19] This is a subject that inspires a great deal of debate worldwide and is only legal in a small number of jurisdictions; however, the availability of this is slowly increasing. There is a clear moral, ethical and legal distinction between (1) withholding or withdrawing treatment no longer deemed to be in the patient's best interest, and therefore is of no benefit to them and which may result in the patient's death; and (2) euthanasia, which has the patient's death as its primary goal.

THE ROLE OF DNACPR – DO NOT ATTEMPT CARDIOPULMONARY RESUSCITATION

Patients admitted to intensive care should be considered for all treatment options, but some limitations may be appropriate for some patients based on an assessment of their individual best interests (in accordance with the statutory, regulatory and institutional setting). One limitation of treatment is not to institute cardiopulmonary resuscitation (CPR) in the event of cardiac and or respiratory arrest – 'do not attempt cardiopulmonary resuscitation', (DNACPR), 'do not attempt resuscitation' (DNAR). It is important that everyone involved (patient, relatives, staff) understands that DNACPR is not a decision not to treat (or not to care), but to provide all treatment except CPR. Such decisions must be subject to regular review, and sensitive communication to the patient and their family, as it has been shown that patients have poor knowledge of the realities of cardiopulmonary resuscitation and what DNACPR really means.[20]

CONSENT/ADVANCED DIRECTIVES/PROXY DECISION MAKERS

No patient has absolute autonomy (see previous comments); for example, the limits to medical autonomy in the United Kingdom may be summarised as (1) patients with capacity may request but not require treatment, (2) patients must consent voluntarily to treatment, and (3) patients may make unwise decisions (such as refusing

treatment). Conversely, medical (and other) practitioners must only offer treatment **they** consider to be in the patient's best interests, or arrange for another to do so. But what of patients who, like many in intensive care, lack capacity? Patients may exercise their autonomy through an advance decision ('Advanced Directive', 'Living Will') or by nominating another person to decide for them. Details will vary in different legal systems (the situation is different in England and Wales, Scotland, and Northern Ireland – the three separate jurisdictions of the United Kingdom).[21,22] Despite this, it is thought that 16% of intensive care patients have no decision-making capacity and no surrogate decision maker.[23]

Even when such 'advanced autonomy' has been exercised, it must apply to the circumstances that pertain at the time; in the event of doubt or confusion, full active treatment must be the default until there is an opportunity for clarification. This area is littered with pitfalls, particularly over-legalistic language or terminology that is difficult to define (e.g. there is no standard definition of a 'life support machine' despite the phrase being used often in news and other broadcasts). Regardless of whether the documents themselves are sufficiently accurate or specific, they are still an indication of the patient's wishes, which deserve respect and consideration.

Decisions at the end of life are inevitably emotive for staff, patients and relatives alike. Conflict is perhaps inevitable but can be minimised by a sound knowledge of the ethical and legal principles and the medical evidence that underpins such decisions, which must be tailored to and involve the individual patient and their relatives. A structured multidisciplinary approach may aid in reducing conflict within the intensive care team. Particularly challenging cases may benefit from the involvement of independent Clinical Ethics Committees or mediation.[24]

REFERENCES

1. Edlestein L. *The Hippocratic Oath: Text Translation and Interpretation*. Baltimore, MD: Johns Hopkins Press; 1943.
2. Declaration of Geneva. *2nd General Assembly of the World Medical Association*, Geneva, Switzerland, September 1948. Latest editoral revision 173rd WMA council session.
3. Carlisle JB. Data fabrication and other reasons for non-random sampling in 5087 randomised, controlled trials in anaesthetic and general medical journals. *Anaesthesia*. 2017;72:944–952.
4. Beachamp T, Childress J. *Principles of Biomedical Ethics*. 7th ed. New York, NY: Oxford University Press; 2013.
5. Delamothe T. Founding principles. *BMJ*. 2008;336: 1216.
6. Chaudhuri D, Tanuseputro P, Herritt B, et al. Critical care at the end of life: a population-level cohort study of cost and outcomes. *Crit Care*. 2017;21(1): 124.
7. Wilson D, Cohen J, Deliens L, et al. The preferred place of last days: results of a representative population-based public survey. *J Palliat Med*. 2013;16(5):502–508.
8. Heyland DK, Dodek P, Rocker G, et al. What matters most in end-of-life care: perceptions of seriously ill patients and their family members. *Can Med Assoc J*. 2006;174(5):627–633.
9. Wunsch H, Linde-Zwirble W, Harrison D, et al. Use of intensive care services during terminal hospitalizations in England and the United States. *Am J Respir Crit Care Med*. 2009;180(9):876–880.
10. Reiser SJ, Dyck AJ, Curran WJ. *Ethics in Medicine: Historical Perspectives and Contemporary Conerns*. Cambridge: MIT press.; 1977.
11. Wilkinson D, Savulescu J. Knowing when to stop: futility in the intensive care unit. *Curr Opin Anaesthesiol*. 2011;24(2):160–165.
12. Brieva J, Cooray P, Rowley M. Withholding and withdrawal of life-sustaining therapies in intensive care: and Australian experience. *Crit Care Resusc*. 2016;11(4):266–268.
13. Cook D, Rocker G. Dying with dignity in the intensive care unit. *N Engl J Med*. 2014;370(26): 2506–2514.
14. Heyland DK, Rocker G, O'Callaghan J, et al. Dying in the ICU: perspectives of family members. *Chest*. 2003;124(1):392–397.
15. Steinberg SM. Cultural and religious aspects of palliative care. *Int J Crit Illn Inj Sci*. 2011;1(2):154–156.
16. NHS Blood and Transplant. *Organ Donation. What does my religion say?* https://www.organdonation.nhs.uk/about-donation/what-does-my-religion-say/.
17. National Institute of Health and Clinical Excellence. *Blood transfusion NICE Guideline [NG 24]*. London: NICE; 2015.
18. Erneco NC, Curlin FA, Buddadhumaruk P, et al. Health care professionals' responses to religious or spiritual statements by surrogate decision makers during goals-of-care discussions. *JAMA Intern Med*. 2015;175(10):1662–1669.
19. Emanuel EJ, Onwuteaka-Philipsen BD, Urwin JW, et al. Attitudes and practices of euthanasia and physician-assisted suicide in the United States, Canada, and Europe. *JAMA*. 2016;316(1):79–90.
20. Heyland DK, Frank C, Groll D, et al. Understanding cardiopulmonary resuscitation decision making. *Chest*. 2006;130(2):419–428.
21. Association of Anaesthetists of Great Britain and Ireland. *AAGBI: Consent for Anaesthesia*. London: AAGBI; 2017.
22. Association of Anaesthetists of Great Britain and Ireland. *Do Not Attempt Resuscitation (DNAR) Decisions in the Perioperative Period*. London: AAGBI; 2009.
23. White D, Curtis J, Luce J, et al. Decisions to limit life-sustaining treatment for critically ill patients who lack both decision-making capacity and surrogate. *Crit Care Med*. 2006;34(8):2006–2007.
24. The Right Honorable Mr Justice Francis. *Approved Judgment: Great Ormond Street Hospital and Charlie Gard*. EWHC 1909(July); 2017.

8

Common problems after intensive care unit

Carl S Waldmann, Evelyn Corner

On admission to the intensive care unit (ICU) in a state of extremis, the patient, often unbeknown to them, is about to embark on a difficult journey. In around a fifth of patients this is a journey that will end their life[1]; for the rest it will almost certainly change it.

As critical illness progresses, the physical and psychological stress that the body is put under is immense. The deleterious effects of the illness itself can lead to rapid muscle loss, delirium and organ dysfunction. Combine this with the necessary medical management – enforced bed rest, mechanical ventilation, psychoactive drugs and neuromuscular blocking agents – and the consequences may be severe.

Insomnia, incontinence, muscle weakness, post-traumatic stress disorder (PTSD), depression, unemployment, the breakdown of interpersonal relationships and sexual dysfunction are among the reported sequelae of critical illness. The term 'post-intensive care syndrome' (PICS) is now used to describe these complex phenomena.[2]

Most patients will get back to some level of normality within 1 year after discharge; however, for an unfortunate few the physical and psychological morbidity can be longstanding.

Cuthbertson and colleagues[3] demonstrated a 58% mortality rate at 3.5 years after discharge, with survivors reporting a significantly worse physical health-related quality of life (HRQoL) than the general population. These results were similar to data from a Canadian study demonstrating limited exercise tolerance and poor physical HRQoL at 5 years after acute respiratory distress syndrome (ARDS).[4]

In 1989, a Kings Fund report on intensive care services in the United Kingdom concluded that 'there is more to life than measuring death'. This was the first report of its kind that highlighted the importance of measuring morbidity as an outcome following critical illness, as well as mortality.[5] Since then, there has been greater emphasis on the long-term physical and psychological consequences of critical illness.

POST-INTENSIVE CARE SYNDROME

The range of issues seen after intensive care is vast and encompasses both physical and psychological problems.

TRACHEOSTOMY

Since percutaneous techniques performed by intensivists started to replace surgical tracheostomy in 1991, there have been an increasing number of patients tracheostomised earlier in their ICU stay with around one-quarter of patients on prolonged mechanical ventilation receiving a tracheostomy.[6] The long-term sequelae have been assessed by lung function tests, nasoendoscopy and magnetic resonance imaging (MRI) screening (Fig. 8.1). There are sometimes minor cosmetic problems, such as tethering (Fig. 8.2), which can be easily dealt with in ear, nose and throat outpatients. A less common, but more difficult to manage, complication is tracheal stenosis, defined as a 15% reduction in tracheal diameter.[7]

MOBILITY

Critically ill patients, especially those with multiorgan failure, are at high risk of developing intensive care unit-acquired weakness (ICU-AW), which is the presence of diffuse global muscle wasting, with myopathic and/or neuropathic changes. A systematic review by Appleton and colleagues[8] demonstrated a 32% incidence of ICUAW in patients requiring 7 days of mechanical ventilation. Muscle loss can be rapid, reaching up to 15% within 7 days of admission in patients with multi-organ failure.[9] ICU-AW can lead to prolonged ventilatory weaning, but also frequently both complicates and delays rehabilitation.[10] Even in the absence of trauma, patients can expect to need 9 months to 1 year to regain full mobility. This is usually due to a mixture of joint pain, stiffness and muscle weakness, but it is also linked to prior chronic health status. If questioned, patients will often report climbing stairs on all fours and descending on their bottoms (Fig. 8.3). Muscle relaxants have been implicated in the development of neuropathy,[11] but have not been shown to cause statistically significant increases in time to, and duration of, stay in the ICU.[12]

SKIN

Patients complain of a variety of nonspecific disorders, poor skin integrity, nail ridging and reports of severe alopecia.[13,14]

ABSTRACT

Since the Kings Fund Report in 1989, it was realised that in intensive care success should not be measured by mortality alone; quality of life and patient satisfaction should also be included.

As a result, intensive care units (ICUs) have started to attempt to initiate physical and psychological rehabilitation from Day 1 and continue well into the post-intensive care and hospital episodes. Many ICUs have started to run a follow-up programme, which includes seeing patients in an out-patient setting. The National Institute for Health and Care Excellence (NICE) 083 Guideline for Rehabilitation after Critical Illness has been around since 2009, but it has not been universally implemented; in 2017 the guideline was replaced by a NICE Quality Standard.

KEYWORDS

Rehabilitation after critical illness
follow up clinics
PTSD

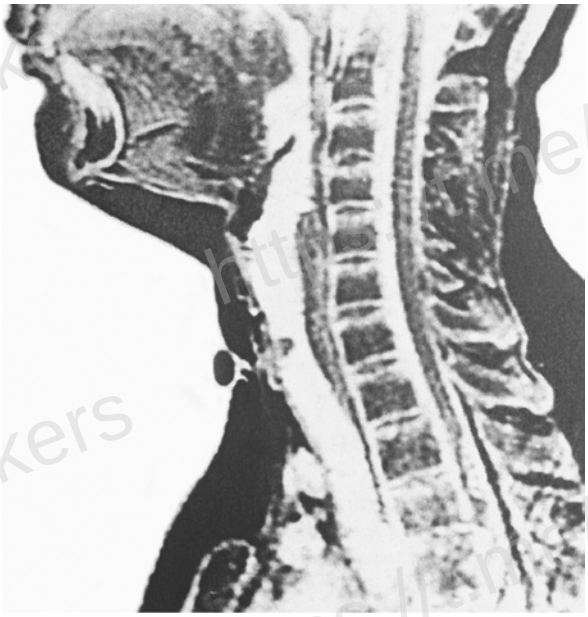


Figure 8.1 Sagittal magnetic resonance imaging demonstrating narrowing of the trachea at the site of a tracheostomy.

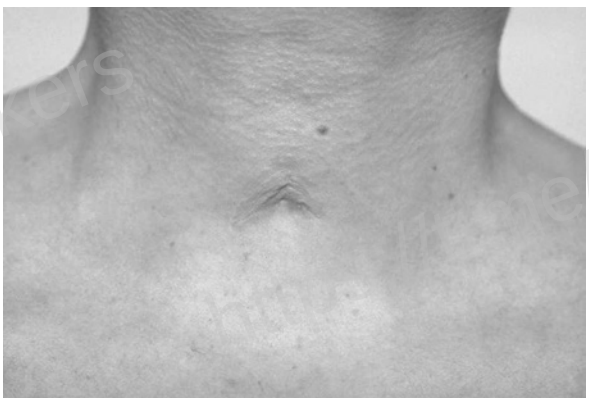


Figure 8.2 Tethering of tracheostomy.

SEXUAL DYSFUNCTION

Studies have estimated the incidence of sexual dysfunction after critical illness as high as 45%,[15,16] although in a small proportion of patients (2%) their sex life was enhanced. Sexual dysfunction improves over time, with a reported frequency of around 26% at 2 months post-ICU, down to 16% at 1 year.[17] There was no link with gender, but there was a close association with PTSD.

Withdrawing sexual intimacy can damage relationships. Often sexual dysfunction may go untreated because people are too embarrassed to mention the problem when they have recovered from a life-threatening illness. For management guidelines for erectile dysfunction, see Ralph and McNicholas.[18]

Figure 8.3 Patient climbing (A) and descending (B) stairs.

Sexual dysfunction affects both men and women. In men it usually manifests as impotence. Referral to a clinic dealing in erectile dysfunction should be considered for men, and referral for gynaecological expertise should be considered for women.

OTHER PHYSICAL PROBLEMS

A variety of other problems have been seen during follow-up:

- *Visual acuity:* particularly in patients who have been profoundly hypotensive, visual problems may occur. Occasionally, ischaemic changes may be seen on fundoscopy (Fig. 8.4A), which may be amenable to laser therapy (see Fig. 8.4B)
- *Facial scarring:* where the tape securing the endotracheal tube has been too tight; this scarring can affect the whole thickness of the cheek
- *Poor skin integrity, hair loss and nail ridging*
- *Unnecessary medication:* frequently, the medication started in the ICU as a temporary measure may have been continued (e.g. amiodarone started for sepsis-related arrhythmias).

Early mobilisation, minimising sedation, managing delirium, spontaneous breathing and early liberation from mechanical ventilation are safe and can help to mitigate the risk of long-term problems. As an international consensus, this is now established best practice, but data still suggest that these principles are delivered inconsistently, and in the case of early mobilisation, infrequently.[19–21]

PSYCHOLOGICAL PROBLEMS

Most patients admitted to the ICU have no warning of their admission (emergency admission) and these are the patients who are very much at risk of psychological sequelae post-ICU. The majority of patients do not have a structured memory of their ICU stay. Those who do

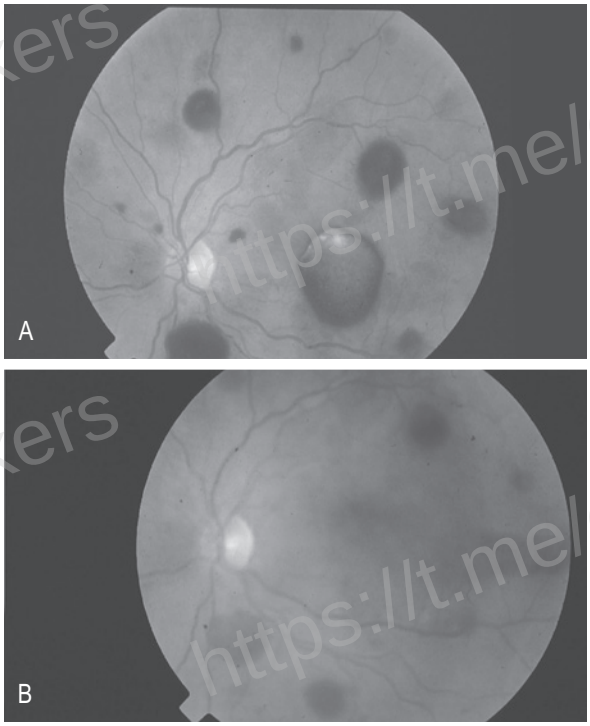


Figure 8.4 (A, B) Ischaemic changes in fundoscopy.

may have upsetting memories, which may be relatively innocuous, such as being thirsty and hearing a can of Coca-Cola being opened, or they may have memories of a far more profound nature.

A description of 'torture' experiences is not unusual when you talk to an ex-ICU patient. The psychological impact of the experience may be formidable. The memory of hearing the words 'let's bag the patient' was interpreted by the patient as if they were about to be put into a body bag rather than a physiotherapy manoeuvre, and the use of a tape measure was interpreted as being measured for a coffin and not as part of the cardiac output measurements. Previous studies demonstrate a high incidence of anxiety and depression.[22,23] It is common for patients to have memories of being trapped, of being unable to move easily, of being unable to see what is happening and of feeling intensely vulnerable. The anxiety of impending death is also reported.

Below is a typical nightmare experienced by an ICU patient:

> *I was in a tunnel knee-deep in mud. It was pitch black, but I could see light at the end. I felt a cold chill on my neck as if someone was breathing down my neck. I thought it was the grim reaper, I knew I had to get to the light.*

There may be several reasons for these experiences (Box 8.1). There is a common belief that, when on the ICU, it is better that a patient does not remember anything.

Box 8.1 Psychological issues

Illness
Sedation technique
Withdrawal
No communication aids
Lack of clear night/day
Continuous noise of alarms
Sleep disturbance – lack of rapid-eye-movement sleep

However, it is increasingly realised that false memories or delusions during an ICU stay can have a significant impact on psychological recovery, whereas factual memories of the ICU may reduce anxiety.[22,23]

It now seems likely that delusional memories of the ICU and nightmares are associated with PTSD. PTSD is the development of characteristic symptoms after being subjected to a traumatic event; this can be triggered by any memory or mention of something to do with the traumatic event and is characterised by intrusive recollections, avoidance behaviour and hyperarousal symptoms.[24] PTSD occurs in about 1% of the general population and increases to 10% in victims of road traffic accidents and 65% in prisoners of war. In the ICU, PTSD is common, with one-fifth of patients suffering from the condition 1 year after discharge.[25] In those with adult respiratory distress syndrome, the incidence increases to 27.5%.

Cognitive deficit is also common. Pandharipande and colleagues[26] found significant cognitive deficits in patients admitted to ICU in shock, with 40% demonstrating reduced global cognition at 3 months after discharge, and around one-third presenting with cognitive deficits equivalent to that of mild Alzheimer disease or moderate traumatic brain injury at 12 months.

Various strategies to deal with the psychological sequelae of an ICU stay have been tried:

- *During ICU stay:* Continuous intravenous sedation has been identified as an independent predictor of a longer duration of mechanical ventilation, ICU stay and total hospital stay.[27-29]

Kreiss and colleagues[30] demonstrated that, in 128 adults, ICU stay was reduced from an average of 7.3 to 4.9 days by the daily interruption of the sedative regimen. This regimen may have had an impact by reducing PTSD as the patients are more likely to have some recollection of their ICU stay, thus helping them to understand the reasons for their prolonged rehabilitation period. Concerns have been raised as to the type of sedative agent used in the ICU. Lorazepam has been promoted as the benzodiazepine of choice on the ICU and was preferred by a task force in the United States for adult patients in the ICU.[31] More recently, however, Panharipande and colleagues found a dose-dependent increase in delirium with the use of lorazepam.[32]

The whole concept of delirium in patients, including those who are critically ill, has now been reviewed, and the monitoring and management of delirium is now published as a National Institute of Health and Care Excellence (NICE) guidance document.[33]

- *When building or modifying ICUs:* 24-hour clocks visible to patients may help re-establish circadian rhythms, and the use of curtains to ensure patient dignity should not be forgotten. There has been some interest in appropriate colours that should be used in ICU décor, avoiding colours that cause alarm, such as red, yellow and black.

POST-INTENSIVE CARE UNIT DISCHARGE

Step down to the ward is often a difficult time for patients and relatives, and can lead to relocation stress. The RECOVER Randomized Clinical Trial investigated the use of a generic rehabilitation assistant to deliver physiotherapy, occupational therapy, dietetic, and speech and language therapy to patients on the ward after discharge from the ICU, to ensure a more cohesive approach to care.[34] The results showed no difference in functional outcome, although the sensitivity of the functional outcome used has been questioned; however, qualitatively, they showed better patient satisfaction, communication and better co-ordination of care.

ICU staff visiting patients on the ward post-ICU discharge and giving them an information booklet can also help to prepare them better for the long rehabilitation process ahead. Patient diaries have been suggested as a possible strategy to aid psychological recovery from critical illness. The diaries aim to provide a narrative of the patient's time on intensive care and fill in the memory gaps; however, a recent Cochrane review found the evidence inconclusive.[35]

POST-HOSPITAL DISCHARGE

Responsibility for the rehabilitation of patients after a critical illness has traditionally fallen between too many silos. Following multiorgan dysfunction, it is difficult to categorise a patient to an individual specialty, such as cardiac, respiratory or the stroke rehabilitation teams. Family doctors often have difficulty taking on the complexity of these patients, with the result that patients are denied vital advice and assistance, and lack an advocate with 'teeth' to ensure timely help. As a result, there has been a drive towards specialist post-ICU services in the form of rehabilitation programmes. However, until recently, few United Kingdom general ICUs were offering post-hospital rehabilitation programmes,[36] despite national clinical guidance to the contrary in the form of NICE Clinical Guideline 83 (CG83) entitled *Rehabilitation after Critical Illness*[37] and the Guidelines for Provision of Intensive Care Services published in 2015.[38] The NICE quality standard was published in 2017.[39]

SETTING UP A FOLLOW-UP SERVICE

Funding follow-up programmes has posed local problems in many trusts. Griffiths and colleagues[40] demonstrated that clinics are not widely established and show marked heterogeneity. Of those established, only two-thirds are funded, and most do not have pre-negotiated access to other outpatient services. The service at The Royal Berkshire Hospital in the United Kingdom was initially approved and funded by local, then regional, audit committees. The service is staffed by a follow-up sister who spends most of her time in this role helped by a staff nurse and an ICU consultant for the clinics held as a formal outpatient clinic 2–3 times monthly.

Invitations to patients who were in the ICU were initially extended to all patients that had been in the ICU for more than 4 days, but with time the invitation was extended to patients who have been in the ICU for a shorter time period. Patients are seen in clinic at 2 months, 6 months and 1 year after discharge and, occasionally, referrals are received from other hospitals where follow-up was not available. It is important to identify clerical and information technology support, and to achieve good collaboration with other hospital departments and general practitioners to ensure patients do not make unnecessary journeys to the hospital, by trying to coordinate the patients' visits and ensuring that transport is organised where necessary. Very often, patients will voluntarily come from long distances if they had initially been admitted from other geographical locations – out-of-area transfers.

The logistics of running the service include arranging specific tests that may be required for the visit, such as pulmonary function tests and blood/urine for creatinine clearance. There may be special tests, such as MRI for patients who had a tracheostomy during their stay in the ICU. It is important to assess patient satisfaction or dissatisfaction with their follow-up. This may be audited by questionnaires during their third visit to the follow-up clinic at 1 year post-ICU discharge.[41]

The service at The Royal Berkshire Hospital costs £30,000 annually, which, in the context of the bigger picture (£8 million annual budget for the ICU), is a small price to pay (Table 8.1). Recently the clinic visits have become funded in the same way as any other outpatient appointment and this, in part, funds the service.

Table 8.1 Budget for running a service

FOLLOW-UP CLINIC	COST (£)
Nursing	18,000
Medical	6,000
Administration	4,000
Laboratory tests and X-rays	2,000
Total	**30,000**

Box 8.2 Quality-of-life tool examples

Objective
QALY Quality of Life Years tool[5]
Subjective
HAD Hospital Anxiety and Depression[6]
PQOL Perceived Quality of Life[7]
EuroQol 'European' tool[8]
SF 36 36-item short-form survey[9]

PEER SUPPORT GROUPS AND ONLINE RESOURCES

'ICU steps' is a United Kingdom-based intensive care charity, which was set up in 2005 by ex-patients and relatives. Their aim is to support patients and relatives through and after a period of critical illness, as well as increasing recognition and awareness of PICS and involvement in research. They do this through support groups and information booklets to guide patients through their recovery; these can be downloaded in 15 languages from their website (www.icusteps.org).[42]

MEASURING OUTCOME AFTER CRITICAL ILLNESS

Measuring morbidity outcomes after critical illness is complex, due to both the multifaceted needs of critical care survivors and the innate difficulties of developing robust scales. This makes it difficult to have a clear idea of the scale of the problem, but it is also problematic in interventional trials.

There are several quality-of-life tools used in follow-up studies (Box 8.2).[43–46] However, many of the objective measurements may be too generic. Lim and colleagues[47] compared two generic HRQoL measures, the Short-Form 36 Health Survey (SF-36) and EuroQol-5D (EQ-5D), to data from semi-structured interviews exploring perceived HRQoL in critical care survivors, and found that the generic tools lacked validity in this population. There is ongoing work through The COMET (Core Outcome Measures in Effectiveness Trials) initiative, by an international body of researchers, looking at developing a core outcome set for critical care research.[48] This may change the landscape of critical care research in the coming years.

CONCLUSION

The NICE 083 Rehabilitation after Critical Illness Guideline[35] has now been around for 7 years and is currently under review; however, it still has yet to be widely implemented in the United Kingdom. In the near future, it is expected that NICE will publish its Quality Standard in Rehabilitation after critical illness. Effective follow-up of patients after their critical illness may well be a future quality indicator of a hospital's critical care service.

More work needs to be done to provide an evidence base for the impact of critical care on carers and relatives. The King's College London and the King's Fund have tested the use of patient experience interviews using experience-based co-design (EBCD).[49] In EBCD, trained interviewers interview patients and staff over several months, and then use edited films of the patient interviews to stimulate work between patients and staff to redesign services.

In a recent modification of the EBCD known as AEBCD (accelerated experience-based co-design) edited films of patients talking about their experiences of two different conditions (intensive care and lung cancer) are being used in close partnership with patients, relatives and staff in two different hospital trusts to help them plan and implement improvements in care together.[50]

It is hoped that the publication of the NICE Quality Standard in 2017 *Rehabilitation After Critical Illness* will be available to all patients that have suffered consequences of an intensive care stay.

REFERENCES

1. Kaukonen KM, Bailey M, Suzuki S, et al. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. *JAMA*. 2014;311(13):1308–1316.
2. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med*. 2012;40:502–509. http://dx.doi.org/10.1097/CCM.0b013e318232da75.
3. Cuthbertson B, Elders A, Hall S, et al. Mortality and quality of life in the five years after severe sepsis. *Crit Care*. 2013;17:R70. http://ccforum.com/content/17/2/R70.
4. Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after Acute Respiratory Distress Syndrome. *N Engl J Med*. 2011;364:1293–1304. doi:10.1056/NEJMoa1011802.
5. Kings Fund. Intensive care in the United Kingdom; a report from the Kings Fund Panel. *Anaesthesia*. 1989;44:428–430.
6. Raimondi N, Vial MR, Calleja J, et al. Evidence-based guidelines for the use of tracheostomy in critically ill patients. *J Crit Care*. 2017;38:304–331.
7. Bernau F, Waldmann CS, Meanock C, et al. Long-term follow-up of percutaneous tracheostomy using flow-loop and MRI scanning. *Intens Care Med*. 1996; 22:S295.
8. Appleton RTD, Kinsella J, Quasim T. The incidence of intensive care unit-acquired weakness syndromes: a systematic review. *J Intensive Care Soc*. 2015;16(2):126–136.
9. Puthucheary ZA, Rawal JR, McPhail M, et al. Acute skeletal muscle wasting in critical illness. *JAMA*. 2013;310(15):1591–1600.

10. Hermans G, Van den Berghe G. Clinical review: intensive care unit acquired weakness. *Crit Care*. 2015;19(1):274.
11. Barohn RJ, Jackson CE, Rogers SJ, et al. Prolonged paralysis due to non-depolarising neuromuscular blocking agents and corticosteroids. *Muscle Nerve*. 1994;17:647–654.
12. Zifko UA, Zipko HT, Bolton CF. Clinical and electrophysiological finding in critical illness polyneuropathy. *J Neurol Sci*. 1998;159:186–193.
13. Scott T, Davies M, Dutton C, et al. Intensive care follow-up in UK military casualties: a one-year pilot. *J Intensive Care Soc*. 2014;15(2):113–116.
14. Battle C, James K, Temblett P. Alopecia in survivors of critical illness. *J Intensive Care Soc*. 2016;17:270.
15. Quinlan J, Gager M, Fawcett D, et al. Sexual dysfunction after intensive care. *Br J Anaesth*. 2001; 87:348.
16. Quinlan J, Waldmann CS, Fawcett D. Sexual dysfunction after intensive care. *Br J Anaesth*. 1998; 81:809–810.
17. Griffiths J, Gager M, Alder N, et al. A self-report based study of the incidence and associations of sexual dysfunction in the survivors of intensive care treatment. *Intens Care Med*. 2006;32:445–451.
18. Ralph D, McNicholas T. UK management guidelines for erectile dysfunction. *Br Med J*. 2000;321: 499–503.
19. Morandia A, Brummel NE, Ely WE. Sedation, delirium and mechanical ventilation: the 'ABCDE' approach. *Curr Opin Crit Care*. 2011;17:43–49.
20. Nydahl P, Ruhl AP, Bartoszek G, et al. Early mobilization of mechanically ventilated patients: a 1-Day point-prevalence study in Germany. *Crit Care Med*. 2014;42(5):1178–1186.
21. The TEAM Study Investigators. Early mobilization and recovery in mechanically ventilated patients in the ICU: a bi-national, multi-centre, prospective cohort study. *Crit Care*. 2015;19(1):81. doi:10.1186/s13054-015-0765-4.
22. Nikayin A, Rabuee A, Hashem MD, et al. Anxiety symptoms in survivors of critical illness: a systematic review and meta-analysis. *Gen Hosp Psychiatry*. 2016;43:23–29.
23. Hashem MD, Nallagangula A, Nalamalapu S, et al. Patient outcomes after critical illness: a systematic review of qualitative studies following hospital discharge. *Crit Care*. 2016;20:345.
24. Jones C, Griffiths RD, Humphries G. Factual memories of intensive care may reduce anxiety post-ICU. *Br J Anaesth*. 2000;82:793.
25. Parker AM, Sricharoenchai T, Raparla S, et al. Posttraumatic stress disorder in critical illness survivors: a metaanalysis. *Crit Care Med*. 2015;43(5): 1121–1129. doi:10.1097/CCM.0000000000000882.
26. Pandharipande P, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med*. 2013;369:1306–1316. doi:10.1056/NEJMoa1301372.
27. Kollef MH, Levy NT, Ahrens TS, et al. The use of continuous IV sedation is associated with prolongation of mechanical ventilation. *Chest*. 1998; 114:541–548.
28. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock. *Intensive Care Med*. 2017;1–74. doi:10.1007/s00134-017-4683-6.
29. Shehabi Y, Bellomo R, Reade MC, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. *Am J Respir Crit Care Med*. 2012;186(8):724–731.
30. Kreiss JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000;342:1471–1477.
31. Shapiro BA, Warren J, Egol AB, et al. Practice parameters for intravenous analgesia and sedation in the intensive care unit: an executive summary. *Crit Care Med*. 1995;23:1596–1600.
32. Panharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology*. 2006;104(1):21–26.
33. *NICE Delirium guidelines*; 2010. http://guidance.nice.org.uk/CG103.
34. Walsh T, Salisbury LG, Merriweather J, et al. Increased hospital-based physical rehabilitation and information provision after intensive care unit Discharge: the RECOVER Randomized Clinical Trial. *JAMA Intern Med*. 2015;175(6):901–910.
35. Ullman AJ, Aitkin LM, Rattraye J, et al. Intensive care diaries to promote recovery for patients and families after critical illness: a Cochrane systematic review. *Int J Nurs Stud*. 2015;52:1243–1253.
36. Connolly B, Douiri A, Steier J, et al. A UK survey of rehabilitation following critical illness: implementation of NICE Clinical Guidance 83 (CG83) following hospital discharge. *BMJ Open*. 2014;4:e004963. doi:10.1136/bmjopen-2014-004963.
37. *NICE CG83*; 2009. Rehabilitation after critical illness. http://www.nice.org.uk/nicemedia/pdf/CG083NICEGuideline.pdf.
38. The Faculty of Intensive Care Medicine and the Intensive Care Society. *Guidelines for the Provision of Intensive Care Services (edition one)*; 2015. http://www.ics.ac.uk/ICS/guidelines-and-standards.aspx.
39. *NICE Quality Standard [QS158] Rehabilitation after critical illness in adults*; 2017. Online. Available: https://www.nice.org.uk/guidance/qs158.
40. Griffiths JA, Barber VS, Cuthbertson BH, et al. A national survey of intensive care follow-up clinics. *Anaesthesia*. 2006;61:950–955.
41. Hames KC, Gager M, Waldmann CS. Patient satisfaction with specialist ICU follow-up. *Br J Anaesth*. 2001;87:372.
42. *ICU steps*; 2017. Available at: www.icusteps.org.
43. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67: 361–370.

44. Patrick DL, Davis M, Southerland LI, et al. Quality of life following intensive care. *J Gen Intern Med*. 1988;3:218–223.
45. Williams A. The Euro Qol – a new facility for the measurement of health related quality of life. The EuroQol Group. *Health Policy (New York)*. 1990;16(3): 199–208.
46. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Med Care*. 1992;30: 473–481.
47. Lim WC, Black N, Lamping D, et al. Conceptualizing and measuring health-related quality of life in critical care. *J Crit Care*. 2016;31(1):183–193.
48. *MRC North West Hub for Trials Methodology*; 2017. Comet Initiative. http://www.comet-initiative.org/.
49. King's Fund. *Experience-based co-design toolkit*. 2013 London: The King's Fund. www.kingsfund.org.uk/ebcd.
50. *NIHR* project proposal*: Testing accelerated experience-based co-design: using a national archive of patient experience narrative interviews to promote rapid patient-centred service improvement*. 2014 https://njl-admin.nihr.ac.uk/document/download/2003119.

9

Clinical information systems

Phil Ward, Timothy Wigmore

The use of information technology to deliver patient care has perhaps no more obvious application than in the technology and data-rich environment of critical care. In this chapter we provide a background on relevant nomenclature, requirements, implementation and impact of critical care clinical information systems (CIS).

CONTEXT

THE DIGITAL HEALTH ECOSYSTEM

Unhelpfully, there are several inconsistently defined terms used to describe health information systems:

- Hospital information system (HIS) can be used to encompass all of an institution's information systems, but can sometimes refer just to administrative aspects of care encounters, such as scheduling or billing
- Electronic medical record (EMR), electronic patient record (EPR) and electronic health record (EHR) have overlapping definitions; EPR (used more in the United Kingdom) and EMR (used more in Asia and the United States) typically refer to the system and information pertaining to the patient and their care at a *specific* institution, whereas an EHR represents the information available across *all* institutions throughout the patient's lifetime[1]
- CIS describes a system that records, manages and displays data specific to a certain scope of clinical practice, for example, critical care

If one considers the breadth of data we utilise in making clinical decisions in critical care – a variety of vital signs, infusion rates, imaging and laboratory tests, for example – it is clear that accessing data from bedside devices and systems from other hospital services (interoperability) is key to a successful CIS. There are agreed international standards and specifications, such as HL7 ('Health Level 7') and IHE ('Integrating the Healthcare Enterprise'), which ensure that information can flow between systems both internally and externally.

An example of how these systems can be arranged is shown in Fig. 9.1. It should be noted that since the feature list of each CIS varies between vendors and depends on local procurement, an organisation may have one system meeting the needs of many departments or functions, or a multitude of products managing discrete parts of the clinical workflow (an arrangement known as 'best of breed').

INFORMATION GOVERNANCE

The transition from paper to CIS brings a host of information governance considerations. Although the same principles of access and confidentiality apply to paper clinical records, digital information potentially can be accessed from any location, as well as be shared more easily and more widely via interfacing, email or social media – either legitimately or illegitimately. Confidential data must be held and exchanged securely, and every user should undertake training in line with institutional and national policy.

NATIONAL INITIATIVES

The implementation of EMRs is increasing, but there remains disparity both geographically and in the complexity of the systems in use. The Healthcare Information Management Systems and Society (HIMSS) has developed an EMR Adoption Model, which classifies an institution on an eight-point scale depending on the capabilities and uses of its EMR. This ranges from having paper-based laboratory, radiology or pharmacy systems (level 0) through to a full EMR with data analytics (level 7), incorporating order communications, closed-loop medicines administration, clinical documentation and clinical decision support.[2]

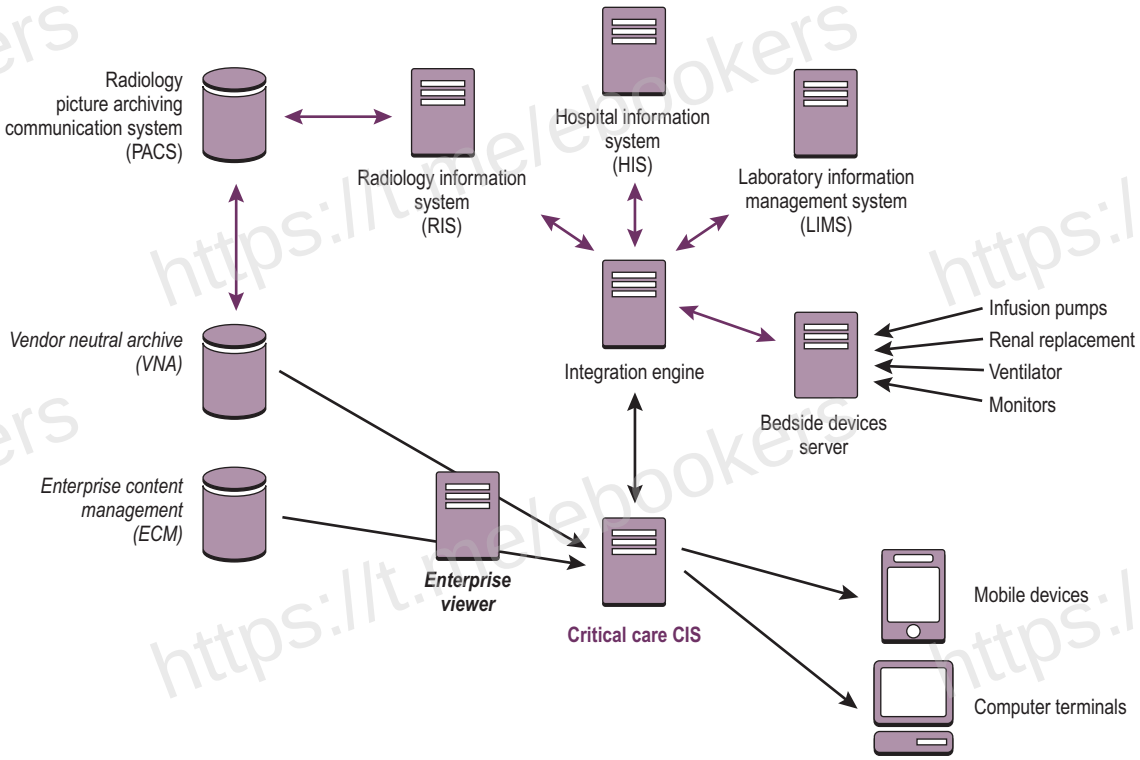
Several national projects have sought to expedite the uptake of digital health solutions. In the United States, the open-source VistA EMR is used across the Veterans Health Administration system, and under the Health Information Technology for Economic and Clinical Health (HITECH) Act, providers may receive financial incentives if they can demonstrate the use of an EMR against a timeline of requirements.[3] The UK National Health Service National Programme for Information Technology

ABSTRACT

The use of information technology to deliver patient care has perhaps no more obvious application than in the technology and data-rich environment of critical care. There are many perceived benefits, including reducing the documentation burden on staff, improving data quality through structured data entry, and improving patient safety through electronic ordering and clinical decision support. Here, we provide a clinician-orientated overview of the scope of clinical information systems, the practicalities of procurement and implementation, and the evidence base arguing their benefits – as well as disadvantages – in critical care.

KEYWORDS

Critical care
clinical information system (CIS)
electronic patient record (EPR)
eHealth
clinical decision support



System	Definition and scope
HIS	Hospital information system
LIMS	Laboratory information management system *Manages laboratory investigation orders, workflow and results*
RIS	Radiology information system *Manages radiology requests, workflow and reports*
PACS	Picture archiving and communication system *Stores images from modalities such as plain radiography or computerised tomography (CT)*
ECM	Enterprise content management *Manages scanned records such as clinic letters or investigation results from other providers, which are surfaced through an enterprise viewer*
VNA	Vendor neutral archive *Since multiple PACS may exist at one institution (e.g. cardiology, radiology), a VNA may be installed to provide a common archive, allowing all studies to be viewed together through an enterprise viewer*
Integration Engine	*Brokers exchange of data between systems*

Figure 9.1 Example critical care clinical information system and related systems architecture.

delivered a secure national healthcare network (N3) and an abbreviated national summary care record aggregated from primary care data, but was abandoned in 2011 amidst spiralling costs, slow implementation and lack of benefit in secondary and tertiary care.[4] This moved procurement of healthcare systems from regional back to the local level.

CRITICAL CARE CLINICAL INFORMATION SYSTEM REQUIREMENTS

BED STATE MANAGEMENT

A basic requirement is for users to admit, transfer and discharge patients to a virtual bed state. Along with

knowledge of elective bookings and the unit case mix, these data can be used to plan equipment and staffing allocations on a short-term basis, but by analysing trends over a longer period it also can be used to inform recruitment and procurement needs.

CLINICAL DOCUMENTATION

Arguably the most important clinical document in either a paper or a CIS-enabled unit is the bedside observation chart, and when implementing a CIS it is easy to underestimate the elegance of the paper chart that it supersedes. Many paper charts are oversized, allowing bedside staff not only to document hundreds of data points per hour but also, and more importantly, to quickly annotate and intuitively draw correlations between changes in treatments and vital signs. For example, a change in vasopressor dose and the effect on mean arterial pressure and urine output may be more difficult to identify on a chart presented on a smaller bedside display.

Regardless, a CIS can automate or mitigate a variety of manual charting processes:

- Data from bedside devices, such as vital signs, electrocardiogram waveforms, pump infusion rates, ventilator or renal replacement settings can be streamed direct to the CIS chart, removing the time and risk of error associated with manual transcription. This capability is dependent on the CIS and the bedside devices in use, and the renewal of older equipment may be necessary to realise this benefit
- Calculations (such as fluid balance and infusion concentration/dose/rate) and bedside assessment and severity scores (such as the Glasgow Coma Scale or Sequential Organ Failure Assessment [SOFA] tool) can be performed automatically
- Interfacing with other information systems and near patient analysers removes the need to transcribe results from blood gases, laboratory tests and imaging reports into the critical care record.

A CIS should provide an improvement in documentation standards, exceeding that expected by improving legibility over handwritten records alone. Acute problems, procedures, and past medical history should be coded via a standardised nomenclature, such as SNOMED (Systematized Nomenclature of Medicine) to improve audit, research and billing. A daily ward-round document can be designed with structured data fields, logic and mandatory items to ensure that key quality indicators, such as a ventilator-associated pneumonia care bundle, are consistently applied to every patient.

Finally, the CIS should provide a full audit trail for any data in the patient record. This should include the date and time that the entry was made (rather than the time on the chart it is recorded against) and the name of the user who made it. If the administration of a controlled medication requires a countersignature, then this should be catered for. If an entry is changed, then whilst the CIS should, by default, display the most recent version, it is vital that the previous entries are still accessible.

ORDER COMMUNICATIONS

Order communications (also referred to as computerised provider order entry [CPOE]) allows the caregiver to electronically request treatments, investigations and referrals. This feature may be managed by the critical care CIS or a separate institution-wide system.

Electronic prescribing of medications is often a main driver in CIS procurement. This is particularly true in critical care, where prescriptions may change frequently and are complex, involving specific quantities of diluent, weight-based dosing, or controlled rates of administration.

Investigation requests also can be enhanced by using validation logic, which can be used to ensure a minimum information standard, such as clinical findings or pregnancy status, is supplied before a request is accepted. However, the method by which results are conveyed back to the requesting team can be problematic. When a request a user has made produces an abnormal result, some systems can push messages to mobile devices or present an inbox of results, but this will depend on the CIS configuration. The feedback mechanism also needs to be flexible; as critical care providers especially work shifts, a message must be sent to a group of users to ensure it is actioned.

CLINICAL DECISION SUPPORT

Clinical decision support (CDS) describes the ability of a CIS to identify or group a constellation of information that is then used to flag potential diagnoses or requisite interventions, in order to promote adherence to unit protocols, policies or best practice. CDS can be classified as either passive or active:

- Passive CDS, where the user must proactively review information and decide its relevance to a clinical decision
- Active CDS, where the CIS applies rules to patient data in order to prompt the user with relevant alerts.

Using an example of a patient with acute respiratory failure, passive CDS might be used to present the user with a chart of a subset of patient data so that they might more easily identify a rising respiratory rate, pyrexia and inflammatory markers in the diagnosis of pneumonia. It might also include a link that displays the departmental antimicrobial prescribing guidelines in order to guide prescribing.

With active CDS, for the same patient the CIS may be configured to produce an alert when the clinical parameters exceeded their previous baseline values or an absolute limit. The alert could be displayed in the CIS user interface or routed to email or another messaging platform. When acknowledging the alert, the CIS could suggest the user order a chest radiograph and commence

antimicrobial therapy, and could use the recorded allergies in conjunction with the departmental prescribing guidelines to ensure an appropriate drug is prescribed.

REMOTE ACCESS

Data in the CIS can be accessed from outside the critical care unit or institution itself. This can provide some key logistical benefits, such as being able to prescribe remotely, allowing the intensivist to review progress whilst off site, or allowing a tertiary specialist to provide input on a case.

When used alongside videoconferencing technology, the system can be leveraged as a full critical care telemedicine solution. To date, this model of critical care delivery has been used principally in the United States, and although some studies and meta-analyses report reductions in mortality and length of stay, the findings are not uncontroverted and are based on observational before/after studies from a small number of US hospitals.[5,6]

IMPLEMENTATION

PROCUREMENT

Producing a business case for a critical care CIS begins with ascertaining the requirements of the service. This requires a detailed mapping of the clinical and information workflows, through which key stakeholders are identified. The importance of including users (both staff and patients), other relevant clinical units/services (such as radiology and pathology) and administrative services, such as billing and information, cannot be underestimated. The project budget must include the cost of seconding these staff to the project to support both the procurement and implementation phases, and backfilling their positions to prevent gaps in service.

There are two principal procurement strategies for EMRs: single vendor and 'best of breed'; a critical care CIS may be implemented as part of either. With the single vendor approach, the institution's EMR is broadly provided by the same product family. Whilst this provides a more consistent user experience and simplifies interfacing and ongoing maintenance, if the vendor cannot fully meet the requirements of a specific service, then their stakeholders will need to compromise on demands or seek a separate product, negating the single vendor approach entirely. With the 'best of breed' model, a different product may be selected based on its suitability for a particular clinical area. However, this approach brings the need to work with multiple suppliers, so this flexibility comes at a cost of more complex interfacing, contracting and maintenance requirements.

APPROACH

A successful implementation regards the CIS as a major change project, and uses it as an enabler and an opportunity to evolve existing business processes. If paper documents and forms are simply mirrored in an electronic solution, key opportunities to remove failure demand and detractors from the system will be missed.

Consideration must be also be given to data in legacy systems. The cost associated with migrating this to the new platform must be balanced against the need for the user to access two or more systems to view the complete patient record, as well as the ongoing maintenance costs of the existing data store.

CIS can be implemented across clinical areas and services incrementally, or simultaneously, as in a 'big bang' approach. Despite requiring greater support resources at the initial go-live, the latter is preferred by software vendors as incremental approaches are prone to implementation fatigue, where users become demotivated due to limited functionality and instead revert to paper-based workarounds.

RESILIENCE

Particularly in a high acuity area, such as critical care, the CIS vendor must provide assurances as to the reliability of their solution. A robust failover strategy must be in place, covering eventualities ranging from a remote server or local terminal hardware failure or power outage through to downtime associated with routine upgrades. The ability to retrieve a paper version of critical documents, such as the observations chart and drug record, is critical, and all staff should be clear of the operating procedure under such circumstances.

IMPACT

Given the disparity in global implementation and the capabilities of the products offered by different vendors, it is unsurprising that the evidence base for CIS implementation demonstrates both benefits, unintended consequences, and in some cases, harm.

DOCUMENTATION TIME

The perception of reducing documentation burden, freeing clinical staff for other aspects of patient care may not be realised. The impact varies depending on the care role, with tasks sometimes simply reallocated to other staff as part of the new digital workflow, rather than being eliminated altogether.[7,8] Time savings from automated calculations and the streaming of bedside devices data can be easily exceeded by complicating other aspects of documentation. These issues are compounded by the difficulties in training the large and transient critical care workforce.

PATIENT SAFETY

Several observational studies have looked at the effect of electronic prescribing in the ICU. Whilst reductions

in medication errors[9] and drug interactions[10] have been reported, the systems may introduce potential for new types of medication error at the same time.[11] Although there are obvious logistical benefits to remote prescribing, such as a reduction in verbal orders, to date no conclusive benefit in patient outcomes has been demonstrated, implying the reported improvements are in non-clinically significant errors.[12,13]

The evidence for CDS is particularly difficult to extrapolate to the wider ICU, given the variance in the types of intervention triggered by the system. Careful design and implementation of CDS is particularly important in the ICU, as the high prevalence of abnormal physiology and investigations may lead to 'alert fatigue', where staff dismiss advisories simply because the prompts appear too frequently. CDS has been shown to improve adherence to guidelines on mechanical ventilation,[14] sepsis[15] and antimicrobial prescribing.[16] However, systematic reviews of CDS across institutions have failed to demonstrate mortality benefit, and demonstrate only modest reductions in costs.[17–19]

UNINTENDED CONSEQUENCES

Following CIS implementation, both positive and negative behaviours can occur as users adapt to the change in their working environment. Frameworks to classify and avoid these unintended consequences have been developed.[20,21] The impact on interactions with the patient, team behaviour and the conduct of the intensive care unit (ICU) ward round also should be considered.[22]

RESEARCH AND AUDIT

An ICU CIS produces a vast dataset pertaining to each patient's stay. Acuity scores, unit activity and mandatory reporting datasets can be calculated, collected and presented automatically. When combined with data from other information systems, correlations can be drawn, for example, between the ICU visit and the surgical technique, or post-discharge patient reported outcome measures.

Also, there is an increasing requirement to submit such data sets to inform payment or as part of an externally mandated care quality and outcome assessment. An example from the United Kingdom is the ICNARC (Intensive Care National Audit & Research Centre) Case Mix Programme, to which all intensive care units must submit a quarterly dataset comprising patient demographics, acuity, treatments and outcomes for all admissions during that period.

Beyond this, the 'big data' opportunities for collaboration and machine learning are of significant interest. Although there are challenges, including appropriate anonymisation and cleansing of the dataset to exclude artefact and missing data points,[23] the last decade has seen major progress in the field. An example is the MIMIC-III (Medical Information Mart for Intensive Care) database, comprising data from over 40,000 critical care admissions to Beth Israel Deaconess Medical Center in Boston in the United States, which is freely available for research.[24]

SUMMARY

Whilst the benefits of CIS may seem many and obvious, they are far from guaranteed, and further research is required to validate their realisation as the software offerings improve and their use increases in clinical practice. The financial cost is significant and a well-planned and resourced implementation, with involvement of key clinical stakeholders from its inception through to completion, is vital to the success of the project.

REFERENCES

1. Garets D, Davis M. *Electronic medical records vs. electronic health records: yes, there is a difference*. Policy White Paper Chicago, HIMSS Analytics. 2006: 1–14.
2. Pettit L. Understanding EMRAM and how it can be used by policy-makers, hospital CIOs and their IT teams. *World Hosp Health Serv*. 2013;49:7–9.
3. Blumenthal D. Stimulating the adoption of health information technology. *N Engl J Med*. 2009;360: 1477–1479.
4. Sheikh A, Cornford T, Barber N, et al. Implementation and adoption of nationwide electronic health records in secondary care in England: final qualitative results from prospective national evaluation in "early adopter" hospitals. *BMJ*. 2011;343:d6054.
5. Lilly CM, Zubrow MT, Kempner KM, et al. Critical care telemedicine: evolution and state of the art. *Crit Care Med*. 2014;42:2429–2436.
6. Wilcox ME, Adhikari NKJ. The effect of telemedicine in critically ill patients: systematic review and meta-analysis. *Crit Care*. 2012;16:R127.
7. Poissant L, Pereira J, Tamblyn R, et al. The impact of electronic health records on time efficiency of physicians and nurses: a systematic review. *J Am Med Inform Assoc*. 2005;12:505–516.
8. Carayon P, Wetterneck TB, Alyousef B, et al. Impact of electronic health record technology on the work and workflow of physicians in the intensive care unit. *Int J Med Inform*. 2015;84:578–594.
9. Shulman R, Singer M, Goldstone J, et al. Medication errors: a prospective cohort study of hand-written and computerised physician order entry in the intensive care unit. *Crit Care*. 2005;9:R516–R521.
10. Bertsche T, Pfaff J, Schiller P, et al. Prevention of adverse drug reactions in intensive care patients by personal intervention based on an electronic clinical decision support system. *Intensive Care Med*. 2010;36:665–672.
11. Koppel R, Metlay JP, Cohen A, et al. Role of computerized physician order entry systems in

facilitating medication errors. *JAMA*. 2005;293: 1197–1203.
12. Maslove DM, Rizk N, Lowe HJ. Computerized physician order entry in the critical care environment: a review of current literature. *J Intensive Care Med*. 2011;26:165–171.
13. van Rosse F, Maat B, Rademaker CMA, et al. The effect of computerized physician order entry on medication prescription errors and clinical outcome in pediatric and intensive care: a systematic review. *Pediatrics*. 2009;123:1184–1190.
14. Eslami S, Abu-Hanna A, Schultz MJ, et al. Evaluation of consulting and critiquing decision support systems: effect on adherence to a lower tidal volume mechanical ventilation strategy. *J Crit Care*. 2012;27:425.e1–425.e8.
15. Tafelski S, Nachtigall I, Deja M, et al. Computer-assisted decision support for changing practice in severe sepsis and septic shock. *J Int Med Res*. 2010;38: 1605–1616.
16. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. *Arch Intern Med*. 2003;163: 1409–1416.
17. Moja L, Kwag KH, Lytras T, et al. Effectiveness of computerized decision support systems linked to electronic health records: a systematic review and meta-analysis. *Am J Public Health*. 2014;104:e12–e22.
18. Baysari MT, Lehnbom EC, Li L, et al. The effectiveness of information technology to improve antimicrobial prescribing in hospitals: a systematic review and meta-analysis. *Int J Med Inform*. 2016;92: 15–34.
19. Thompson G, O'Horo JC, Pickering BW, et al. Impact of the electronic medical record on mortality, length of stay, and cost in the hospital and ICU: a systematic review and metaanalysis. *Crit Care Med*. 2015;43:1276–1282.
20. Harrison MI, Koppel R, Bar-Lev S. Unintended consequences of information technologies in health care – an interactive sociotechnical analysis. *J Am Med Inform Assoc*. 2007;14:542–549.
21. Sittig DF, Singh H. A new sociotechnical model for studying health information technology in complex adaptive healthcare systems. *Qual Saf Health Care*. 2010;19(suppl 3):i68–i74.
22. Morrison C, Jones M, Blackwell A, et al. Electronic patient record use during ward rounds: a qualitative study of interaction between medical staff. *Crit Care*. 2008;12:R148.
23. Johnson AEW, Ghassemi MM, Nemati S, et al. Machine learning and decision support in critical care. *Proc IEEE Inst Electr Electron Eng*. 2016;104: 444–466.
24. Johnson AEW, Pollard TJ, Shen L, et al. MIMIC-III, a freely accessible critical care database. *Sci Data*. 2016; 3:160035.

10

Trials

Simon Finfer, Anthony Delaney

> *Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. Clinical expertise is reflected […] in the more thoughtful identification, and compassionate use of individual patients' predicaments, rights and preferences in making clinical decisions.*[1]

The most reliable evidence, and thus the best evidence for guiding clinical practice, will generally come from adequately powered and properly conducted randomised clinical trials (RCTs). It is commonly the case, however, that there are no RCTs that adequately address a particular question, so clinicians may have to assess the ability of other studies, such as cohort studies, case-control studies and systematic reviews to supplement their clinical expertise. It is important that clinicians are familiar with the underlying principles and potential sources of bias in each of these study designs, so they can incorporate evidence from reliable studies into their clinical practice and treat with appropriate caution those studies whose design makes it likely that they will produce unreliable results.

RANDOMISED CLINICAL TRIALS

The result of any clinical trial may be influenced by three factors: a true treatment effect, the effects of bias or confounding, and the play of chance. Randomised clinical trials, when properly designed, conducted and analysed, offer the optimal conditions to minimise bias and confounding, and to define the role that chance may have played in the results. As such, they represent the best study design to delineate true treatment effects under most circumstances. However, it is imperative that RCTs are designed, conducted, analysed and reported correctly. Studies that have not adhered to the principles outlined below may produce results that do not reflect a true estimate of treatment effects.

THE QUESTION TO BE ADDRESSED

Every trial should seek to answer a focused clinical question that can be clearly articulated at the outset. For example, 'we sought to assess the influence of different volume replacement fluids on outcomes of intensive care patients', is better expressed as the focused clinical question: 'we sought to address the hypothesis that when 4% albumin is compared with 0.9% sodium chloride (normal saline) for intravascular fluid resuscitation in adult patients in the intensive care unit (ICU), there is no difference in the rate of death from any cause at 28 days'.[2] The focused clinical question defines the interventions to be compared, the population to be studied and the primary outcome to be considered. This approach can be formalised using the PICO system: PICO stands for Patient, Intervention, Comparison, and Outcome. In the example above:

- Patient = adult ICU patient
- Intervention = albumin
- Comparison = saline
- Outcome = 28-day all-cause mortality.

The question that a trial is designed to address will vary somewhat depending on the stage of development of the proposed treatment. After development and testing in animal models, the testing of pharmaceutical agents in humans is generally conducted in three phases. Sometimes a fourth phase is added:

Phase I trial: testing in healthy volunteers

Phase II trial: first testing in a population of patients with disease to be modified, usually small trials focused on establishing safety and evidence of efficacy using surrogate outcome measures

Phase III: large-scale trial in patients that has sufficient statistical power to determine the effect of the treatment on the primary outcome of interest

Phase IV: post-marketing trials to confirm safety once the agent is introduced into clinical practice.

Trials may be designed to answer two quite different questions about the same treatment, and the design will be quite different depending on the questions to be answered. An 'efficacy trial' seeks to determine whether a treatment will work under optimal

ABSTRACT

The application of evidence-based medicine is a skill fundamental to the practice of critical care medicine. The best evidence to assess the risks and benefits of both new and currently used therapies will come from randomised clinical trials (RCTs). In order to conclude that the results of an RCT are reliable, it is important that bias is minimised. Key steps in minimising bias are randomisation that maintain allocation concealment, blinding whenever possible, control of confounding by assessing baseline balance and use of concomitant therapies, and complete follow up. It is also important that methods of analysis and reporting are robust and transparent. There are some questions faced by clinicians that will not be addressed by RCTs, and under these circumstances other study designs, such as cohort studies or case control studies, may provide the best available, although imperfect, evidence to guide care.

KEYWORDS

Clinical trials
evidence-based medicine
randomised clinical trial
meta-analysis
cohort study
case control study

Table 10.1 Comparison of study characteristics using either an efficacy or an effectiveness approach when designing a study

STUDY CHARACTERISTICS	EFFICACY TRIAL	EFFECTIVENESS TRIAL
Research question	Will the intervention work under ideal conditions?	Will the intervention result in more good than harm under usual practice conditions?
Setting	Restricted to specialised centres	Open to all institutions
Patient selection	Selected, well-defined patients	A wide range of patients identified using broad eligibility criteria
Study design	Smaller RCT using parallel group or factorial or other approaches (crossover design)	Large multicentre RCT using parallel groups, or factorial cluster
Baseline assessment	Elaborate and detailed	Simple and clinician-friendly
Study intervention	Tightly protocolised. Optimal therapy under optimal conditions	Less tightly protocolised. Implemented in usual clinical practice
Co-interventions	Tightly controlled protocols for many aspects of care	All therapy based on local practice/ experience/minimal control
Compliance	Compliance essential	Noncompliance expected and considered in sample size/analysis
End-points	Disease-related. Related to biological effect 'Surrogate' end-points	Patient-related, such as all-cause mortality or quality of life
Analysis	By treatment received	Intention to treat
Sample size	Generally <1000 and often <100 patients	Several thousand patients
DATA MANAGEMENT		
Data collection	Elaborate	Minimal and simple
Data monitoring*	Detailed and rigorous	Minimal
Study management	Significant interventions and support from research staff	Minimal support and interventions from research team

*Data monitoring refers to the review of source documents and adjudication/verification of outcomes.

RCT, Randomised clinical trials.

Adapted from Hébert PC, Cook DJ, Wells G, et al. The design of randomized clinical trials in critically ill patients. *Chest.* 2002;121(4):1290–1300.

conditions, whereas an 'effectiveness' trial seeks to determine the effects of the intervention when applied in normal clinical practice. A comparison of the features of efficacy and effectiveness trials is given in Table 10.1 from Hébert and colleagues.[3]

POPULATION AND SAMPLE SIZE

The population to be studied will be defined by the study question. Efficacy trials may have a very narrowly defined population, with strict eligibility criteria and many exclusion criteria. Effectiveness trials are likely to have more broad inclusion criteria and few exclusion criteria. Regardless of the design, the population to be studied should be well described. This will allow readers to assess the scientific merit of the study and allows clinicians to judge whether the results of the study could apply to their patients, to assess the 'generalisability' of the results. Trials that include only a very narrowly defined population may also face difficulties in recruiting sufficient participants to reach a definitive conclusion.

How large do trials need to be to reach a definitive conclusion? In a parallel group trial, with a dichotomous outcome (e.g. alive or dead), the number of patients required to answer a question depends on four factors:

1. The percentage of patients expected to have the outcome in the control group – the control group outcome rate
2. The expected change (usually reduction) that may result from the treatment being tested – the treatment effect
3. The level of probability to be accepted to indicate that the difference did not occur by chance (i.e., the probability level at which a treatment effect will be deemed to be real) – significance level or α (almost always 0.05)

Table 10.2 Examples of sample size calculations

CONTROL GROUP OUTCOME RATE (%)	TREATMENT GROUP OUTCOME RATE (%)	ARR	POWER (β)	TOTAL SAMPLE SIZE
50	30	20	80	206
50	30	20	90	268
30	15	15	90	348
30	20	10	90	824
30	25	5	90	3428
15	10	5	90	1914
15	12	3	90	5582
10	8	2	80	6626
10	8	2	90	8802

ARR, Absolute risk reduction.

All calculations performed with STATA 8.2, assuming a two-sided $\alpha = 0.05$.

4. The desired percentage chance of detecting a clinically important treatment effect, if one truly exists (power: usually 80% or 90%).

In the past, trials addressing issues of importance in intensive care medicine were commonly too small to detect clinically important treatment effects,[4] but fortunately this is now changing.[2,5] The conduct of underpowered trials has almost certainly given rise to a significant number of false-negative results (type II errors) leading to potentially beneficial treatments being discarded. In order to avoid these errors, clinical trials have to include a surprisingly large number of participants. Examples of sample size calculations based on different baseline incidences, different treatment effects and different statistical power are given in Table 10.2.

RANDOMISATION AND ALLOCATION CONCEALMENT

Two components of the randomisation procedure are critically important. The first is the generation of a truly random allocation sequence; modern computer programs make this relatively straightforward. The second is the concealment of this allocation sequence from the investigators, so that the investigators and participants are unaware of the treatment allocation (group) prior to each participant entering the study.

There are a number of benefits to using a random process to determine treatment allocation. First, it eliminates the possibility of bias in treatment assignment (selection bias). In order for this to be ensured, both a truly random sequence of allocation must be produced, and this sequence must not be known to the investigators prior to each participant entering the trial. Second, it reduces the chance that the trial results are affected by confounding. A clinical characteristic (such as advanced age, gender or disease severity as measured by Acute Physiology and Chronic Health Evaluation [APACHE] or Sequential Organ Failure Assessment [SOFA] scores) that is associated with the outcome is known as a confounding factor. Randomisation of a sufficient number of participants ensures that both known confounders (e.g. age and severity of illness) and unknown confounders (e.g. genetic polymorphisms) are evenly distributed between the two treatment groups. The play of chance may still result in an uneven distribution of known confounding factors between the groups, and this is particularly likely in trials with fewer than 200 participants.[6] The third benefit of randomisation is that it allows the use of the probability theory to quantify the role that chance could have played when differences are found between groups.[7] Finally, randomisation with allocation concealment facilitates blinding, which is another important component in minimising bias in clinical trials.[8]

The generation of the allocation sequence must be truly random. There are a number of approaches to generating a truly random allocation sequence, most commonly using a computer-generated sequence of random numbers. More complicated processes where randomisation is performed in blocks, or is stratified to ensure that patients from each hospital in a multicentre trial or those with certain baseline characteristics are equally distributed between treatment groups, also can be used. Allocation methods based upon predictable sequences, such as those based on medical record numbers or days of the week, do not constitute true randomisation and should be avoided. These methods allow researchers to predict to which group a participant will be allocated prior to them entering the trial, which introduces the possibility of selection bias.

Whatever method is used to produce a random allocation sequence, it is important that allocation concealment is maintained. Methods to ensure the concealment of allocation may be as simple as using sealed opaque envelopes,[9] or as complex as the centralised automated telephone-based or web-based systems commonly used in large multicentre trials. In recent years, web-based randomisation has become the predominant method of assigning trial participants to treatment groups. Appropriate attention to this aspect of a clinical trial is essential as trials with poor allocation concealment produce estimates of treatment effects that may be exaggerated by up to 40%.[10]

THE INTERVENTIONS

The intervention being evaluated in any clinical trial should be described in sufficient detail that clinicians

could implement the therapy if they so desired, or researchers could replicate the study to confirm the results. This may be a simple task if the intervention is a single drug given once at the beginning of an illness, or may be complex if the intervention being tested is the introduction of a process of care, such as the introduction of a medical emergency or rapid response team.[11] There are two additional areas with regard to the interventions delivered in clinical trials that require some thought by those conducting the trial and by clinicians evaluating the results, namely blinding and the control of concomitant interventions.

BLINDING

Blinding, also known as masking, is the practice of keeping trial participants (and, in the case of critically ill patients, their relatives or other legal surrogate decision makers), caregivers, data collectors, those adjudicating outcomes and sometimes those analysing the data and writing the study reports, unaware of which treatment is being given to individual participants. Blinding serves to reduce bias by preventing clinicians from consciously or subconsciously treating patients differently on the basis of their treatment assignment within the trial. It prevents data collectors from introducing bias when recording parameters that require a subjective assessment (e.g. pain scores, sedation scores or the Glasgow Coma Score). Although many ICU trials cannot be blinded (e.g. trials of intensive insulin therapy cannot blind treating staff who are responsible for monitoring blood glucose and adjusting insulin infusion rates), the successful blinding of the Saline versus the Albumin Fluid Evaluation trial demonstrated the possibility of blinding even large complex trials.[2] Blinded outcome assessment is also necessary when the chosen outcome measure requires a subjective judgement. In such cases, the outcome measure is said to be subject to the potential for ascertainment bias. For example, a blinded outcome assessment committee should adjudicate the diagnosis of ventilator-associated pneumonia (VAP) and blinded assessors should be used when assessing functional neurological recovery using the extended Glasgow outcome scale; both the diagnosis of VAP and the assessment of the Glasgow outcome scale require a degree of subjective assessment and are therefore prone to ascertainment bias.

It has been traditional to describe trials as single blinded, double blinded or even triple blinded. These terms, however, can be interpreted by clinicians to mean different things, and the terminology may be confusing.[12] It is recommended that reports of RCTs include a description of who was blinded and how this was achieved, rather than a simple statement that the trial was 'single blind' or 'double blind'.[13] Blinding is an important safeguard against bias in RCTs and, although not thought to be as essential as the maintenance of allocation concealment, empirical studies have shown that unblinded studies may produce results that are biased by as much as 17%.[10]

CONCOMITANT TREATMENTS

Concomitant treatments are all treatments that are administered to patients during the course of a trial other than the study treatment. With the exception of the study treatment, patients assigned to the different treatment groups should be treated equally. When one group is treated in a way that is dependent on the treatment assignment but not directly related to the treatment, there is the possibility that this third factor will confound the outcome. An example might be a trial of pulmonary artery catheters (PAC) compared with management without a PAC. If the group assigned to receive management based on the data from a PAC received an additional daily chest X-ray to confirm the position of the PAC, they could conceivably have other important complications noted earlier, such as pneumonia, pulmonary oedema or pneumothoraces, and this may affect the outcome in a fashion unrelated to the data available from the PAC. Maintenance of balance in concomitant treatments is facilitated by blinding. When trials cannot be blinded, the use of concomitant treatments that may alter the outcome should be recorded and reported.

ADAPTIVE TRIAL DESIGNS

Traditional clinical trials have followed a fixed design from the start of participant recruitment until trial completion. This approach has many advantages, including simplicity and transparency, which may make the trial results more compelling to clinicians. In recent years, interest in the use of adaptive trial designs has increased. An adaptive trial is one in which the trial design is changed while the trial is being conducted. The change may be quite simple and easy to understand, such as changing the sample size, and in practice most trials have an adaptive design as they allow early stopping for either efficacy or futility in response to recommendations from an independent data-monitoring committee. A less well-established but equally simple adaptive design is increasing the sample size due to a lower than expected event rate; an example of this is the PROWESS-SHOCK study where a predetermined increase in the sample size occurred in response to a lower than expected mortality rate in patients with septic shock.[14] More complex adaptive designs are used in other fields of medicine such as oncology,[15] where design changes may include changing drug doses or dropping or adding trial arms or drug doses, changing the proportion of patients assigned to each arm of a trial or seamlessly moving from phase II to phase III within a single trial.[15] Although such designs have been rare in critical care research, the failure of clinical trials in areas such as industry-sponsored sepsis research may see adaptive

designs becoming more accepted in future years. The evaluation of multiple interventions or strategies in a single trial, the so-called "Platform Trial" may become a more efficient strategy to assess therapies for some syndromes that commonly lead to critical illness, but these types of trials are not yet common in critical care.[16]

OUTCOME MEASUREMENT

All clinical trials should be designed to detect a difference in a single outcome. In general there are two types of outcomes, clinically meaningful outcomes and surrogate outcomes.

A clinically meaningful outcome is a measure of how patients feel, function or survive.[17] Clinically meaningful outcomes are the most credible end-points for clinical trials that seek to change clinical practice. Phase III trials should always use clinically meaningful outcomes as the primary outcome. Examples of clinically meaningful outcomes include mortality and measures of health-related quality of life. In contrast, a surrogate outcome is a substitute for a clinically meaningful outcome; a reasonable surrogate outcome would be expected to predict clinical benefits based upon epidemiological, therapeutic, pathophysiological or other scientific evidence.[17] Examples of surrogate end-points would include cytokine levels in sepsis trials, changes in oxygenation in ventilation trials, or blood pressure and urine output in a fluid resuscitation trial.

Unless a surrogate outcome has been validated, it is unwise to rely on changes in surrogate outcomes to guide clinical practice. For example, it seemed intuitively sensible that after myocardial infarction the suppression of ventricular premature beats (a surrogate outcome), which were known to be linked to mortality (the clinically meaningful outcome), would be beneficial; unfortunately the CAST trial found increased mortality in participants assigned to receive antiarrhythmic therapy.[18] The process for determining whether a surrogate outcome is a reliable indicator of clinically meaningful outcomes has been described.[19]

ANALYSIS

Even when trials are well designed and conducted, inappropriate statistical analyses may result in uncertain or erroneous conclusions. A detailed discussion of the statistical analysis of large-scale trials is beyond the scope of this chapter but certain guiding principles can be articulated:

- All trials should adhere to a predetermined statistical analysis plan because otherwise the temptation to perform multiple analyses and report only those that support the preconceived ideas of the investigators may prove irresistible
- The convention of accepting a *P* value of <.05 to indicate 'statistical significance' is based on assessment of a single outcome. Assessing multiple outcomes increases the likelihood of finding a *P* value of <.05 purely due to the play of chance. Each trial should have a single predefined primary outcome measure. If more than one primary outcome measure is used then the *P* value used to indicate statistical significance should be reduced. The simplest method is to perform a Bonferoni correction, which divides 0.05 by the number of outcomes examined to determine the new level of statistical significance. Thus for two outcomes the *P* value must be below 0.025, and for three it must be below 0.017. The *P* value may also have to be reduced further if the trial employs interim analyses.

Clinicians should pay close attention to the analysis to make certain that a true intention-to-treat analysis is presented, and that any subgroup analysis is viewed with the appropriate amount of caution.

INTENTION-TO-TREAT ANALYSIS

Trials should be analysed using the 'intention-to-treat' principle. This means that all participants are analysed in the group to which they were randomised regardless of whether they received all or any of the treatment to which they were assigned. To some readers the intention-to-treat principle may appear intuitively incorrect; it is reasonable to ask why patients who did not receive the intended treatment should be included in the analysis. The use of intention-to-treat analysis prevents bias arising from the selective exclusion of patients – termed 'attrition bias'. In an appropriately sized trial, loss of patients at random should occur equally in both groups and the inclusion of those patients will not alter the result. If loss of patients is occurring as a nonrandom event (e.g. because of protocol violations or intolerance of the treatment in one arm of the trial) then the trial result will be different if the lost patients are excluded. Consider a trial of a 5-day course of L-NMMA for the treatment of patients with septic shock; in the trial a number of patients who receive L-NMMA die in the first 24–48 hours and are excluded from the analysis as they have received only a little of the study treatment. A trial report based on the remaining patients who completed the treatment protocol (per-protocol analysis) will not give a true estimate of the effect of using L-NMMA in clinical practice. Although this is an extreme example, once a patient is included in a trial his/her outcome should always be accounted for in the study report.

SUBGROUP ANALYSIS

Particular difficulties arise from the selection, analysis and reporting of subgroups. Subgroups should be

predefined and kept to the minimum number possible. When many subgroups are examined, the likelihood of finding a subgroup where the treatment effect is different from that seen in the overall population increases. A well-known example of this was the analysis of the treatment effect of aspirin in patients with myocardial infarction in the large Second International Study of Infarct Survival (ISIS-2) trial. Overall, the trial indicated that aspirin reduced the relative risk of death at 1 month by 23%. To illustrate the unreliability of subgroup analyses, the participants were divided into subgroups according to their astrological birth signs; the analysis showed that patients born under Libra or Gemini did not benefit from treatment with aspirin.[20] Although it is easy to identify this as a chance subgroup finding, this may be much harder when the choice of the subgroup appears rational and a theoretical explanation for the findings can be advanced. For example, in the Gruppo Italiano per lo Studio della Streptochinasi nell'infarto miocardico (GISSI) trial, subgroup analysis suggested that fibrinolytic therapy did not reduce mortality in patients who had suffered a previous myocardial infarct.[21] Although this finding appears biologically plausible, subsequent trials have shown quite clearly that fibrinolytic therapy is just as effective in patients with prior infarction as in those without.[22]

The separation of patients into subgroups should be on the basis of characteristics that are apparent at the time of randomisation. The selection of subgroups using features identified after randomisation risks introducing bias as the patients have already been subjected to the different study treatments, and the subgroup analysis will therefore not be comparing like with like.

TESTS OF INTERACTION VERSUS WITHIN-SUBGROUP COMPARISONS

Even when subgroups are selected appropriately, many readers will be tempted to draw inappropriate conclusions from the results. As the trial will have been designed to examine the effect of the treatment on the primary outcome in the whole study population, the best assessment of the treatment effect in any subgroup will be the effect seen in the trial as a whole. When analysing a subgroup result, the investigators should seek to answer the following question: 'Is the treatment effect in the subgroup different from the treatment effect seen in the remaining participants?' This is a test of interaction or of heterogeneity. Often the investigators err and perform within-subgroup comparisons, which instead answer the question: 'What was the effect of treatment A versus treatment B in this subgroup?' Within-subgroup comparisons are more likely to lead to unreliable results. Journals such as the *New England Journal of Medicine* provide guidelines for the analysis and reporting of subgroup effects.[23]

REPORTING

The reporting of randomised controlled trials has been greatly improved by the work of the CONSORT (Consolidated standards of Reporting Trials) group.[13,24] The consort statement provides a framework and checklist (Table 10.3) that can be followed by investigators and authors to provide a standardised high-quality report.[24] An increasing number of journals require authors to follow the CONSORT recommendations when reporting the results of a randomised controlled trial. The group also recommends the publication of a structured diagram that documents the flow of patients through four stages of the trial – namely, enrolment, allocation, follow-up and analysis (Fig. 10.1). It is likely that the use of the CONSORT statement to guide the reporting of RCTs does lead to improvements, at least in the quality of reporting of randomised controlled trials.[25]

Trials may report results using a number of values that, taken together, will give readers a full understanding of the trial results. These may include a *P* value, confidence intervals and the number needed to treat (or harm).

- *Probabilities:* the *P* value represents the probability that a difference has arisen by chance. In very large trials, small and clinically insignificant differences may give rise to *P* value of less than .05 and, conversely, a moderately sized trial may report a clinically important difference with a *P* value that is close to or greater than .05; *P* values should not be viewed in isolation but should be assessed in combination with other measures, such as confidence intervals and the number needed to treat (or harm).
- *Confidence intervals:* these give an indication of the precision of the result. Whenever a trial reports a difference it is reporting a difference found in a finite sample of the population of interest. If the same trial is repeated, it is highly likely that a slightly or very different result will be reported. If the trial is reporting a relatively small number of patients with the outcome of interest (small number of events) then the difference between the results may be large; if the trial reports a large number of events then it is likely the two results will be quite close to each other. Confidence intervals give a range of values within which it is likely the 'true' result lies – they give an indication of the precision of the result. The most commonly quoted are the 95% confidence intervals; these are the limits within which we would expect 95% of study results to lie if the study were repeated an infinite number of times, though they are often interpreted to mean that we can be 95% confident that the 'true' result lies within these limits.
- *Number needed to treat (or harm):* a useful concept for clinicians is the number needed to treat (or harm). This is the reciprocal of the absolute difference in outcomes arising from two treatments. For example,

Table 10.3 The Consort 2010 checklist of information to include when reporting a randomised trial*

SECTION/TOPIC	ITEM NO.	CHECKLIST ITEM
TIME AND ABSTRACT		
	1a	Identification as a randomised trial in the title
	1b	Structured summary of trial design, methods, results and conclusions (for specific guidance see CONSORT for abstracts)
INTRODUCTION		
Background and objectives	2a	Scientific background and explanation of rationale
	2b	Specific objectives or hypothesis
METHODS		
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected
Interventions	5	The interventions for each group were sufficient
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed
	6b	Any changes to trial outcomes after the trial commenced, with reasons
Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses
RANDOMISATION		
Sequence generation	8a	Method used to generate the random allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps take to conceal the sequence until interventions were assigned
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
Blinding	11a	If done, who was blinded after assignment to interventions (e.g. participants, care providers, those assessing outcomes and how)
	11b	If relevant, description of the similarity of interventions
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
RESULTS		
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended

Table 10.3 The Consort 2010 checklist of information to include when reporting a randomised trial—cont'd

SECTION/TOPIC	ITEM NO.	CHECKLIST ITEM
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Harms	19	All-important harms or unintended effects in each group for (specific guidance see CONSORT for harms)
DISCUSSION		
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
Generalisability	21	Generalisability (external validity, applicability) of the trial findings
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
OTHER INFORMATION		
Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for this and for up-to-date references relevant to this checklist see www.consort-statement.org.

Reproduced with permission from Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ.* 2010;340:c332.

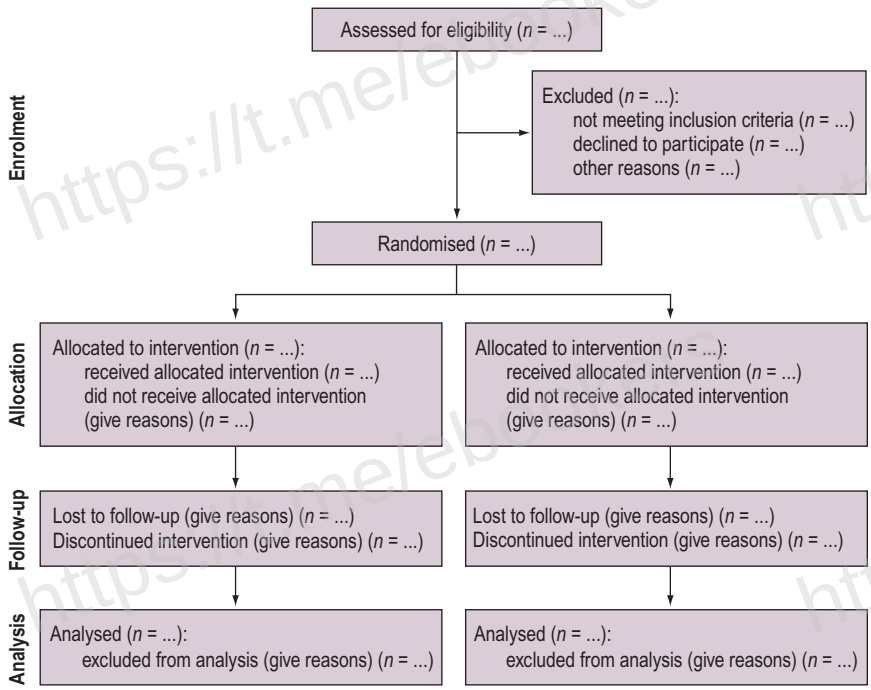


Figure 10.1 Flow diagram of the progress through the phases of a randomised trial. *From Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials.* BMJ *2010;340:c332, with permission.*

in the ISIS-2 trial, patients randomised to intravenous streptokinase had an absolute reduction in mortality of 2.8%. Thus the number needed to treat to prevent one death is 100/2.8 or 35.7 patients. As the trial was very large with a large number of events (17,187 participants and 1820 deaths), this relatively small absolute reduction in mortality (2.8%) yielded a *P* value of less than .000001. The same calculation can be performed to calculate the number needed to harm. For example, in the CRASH trial, patients with traumatic brain injury treated with high-dose steroids had a 3.4% increase in the absolute risk of death. The number needed to harm is calculated as 100/3.4, or one extra death for every 29.4 patients treated with high-dose corticosteroids. Again, as this was a large trial (10,008 participants and 1945 deaths) the *P* value is small (*P* = .00001).

ETHICAL ISSUES SPECIFIC TO CLINICAL TRIALS IN CRITICAL CARE

The ethical principles guiding the conduct of research in critical care are outlined in the International Ethical Guidelines for Health-Related Research Involving Human Subjects,[26] in addition country-specific guidelines are provided by various national bodies. The ethical principles of integrity, respect for persons, beneficence and justice, should be considered whenever research is conducted and an appropriately convened human research ethics committee or the equivalent should assess all research to ensure adherence to these principles. As the potential participants in critical care research are particularly vulnerable, owing to the nature of the conditions and the limitations to communication that exist, special consideration needs to be given to a number of areas including informed consent.

INFORMED CONSENT

That all mentally competent participants in clinical research should give informed consent prior to entering a study is an important ethical principle. This is rarely possible for people suffering critical illness, where the disease process (e.g. traumatic brain injury, encephalitis, severe hypoxaemia) or the required treatment (e.g. intubation, use of sedative medications) may make it impossible to obtain informed consent. Even awake, alert patients may not be able to give fully informed consent when they are facing stressful and potentially life-threatening situations.[27] This applies equally to surrogate decision makers. However, the treatment of critically ill patients can be improved only through the conduct of research and in many jurisdictions this has been recognised by making special provisions for consent in emergency research, including research in the critically ill. In some circumstances, it may be ethical to allow a waiver of consent for research involving treatments that must be given in a time-dependent fashion (e.g. in the setting of cardiac arrest). A waiver of consent may improve recruitment into clinical trials; it is unclear whether this approach is universally acceptable. Another approach has been to allow deferred consent or consent to continue, where patients are included in the study and consent from the patient or the relevant surrogate decision maker is sought as soon as practical. Neither approach is without problems.[28]

CRITICAL APPRAISAL

Clinicians reading reports of randomised controlled trials should use a structured framework to assess the methodological quality of the trial and the adequacy of the trial report. They should also address the magnitude and precision of reported treatment effects and ask themselves whether the results of the trial can be applied to their own clinical practice. There are a number of resources available to assist clinicians in this task, notably the Users' Guides to the Medical Literature, originally published in *JAMA* and the Critical Appraisal Skills Program from Oxford, United Kingdom, both of which are freely available on the Internet.[29,30] These resources provide a structured framework that allows any reader to perform a systematic critical appraisal of almost any piece of medical literature. A checklist is provided for the appraisal of randomised controlled trials (Box 10.1).

Box 10.1 Critical appraisal checklist for randomised controlled trials

I. Are the results of the study valid?

Primary guides: Was the assignment of patients to treatments randomised?

1. Were all patients who entered the trial properly accounted for and attributed at its conclusion?
2. Was follow-up complete?
3. Were patients analysed in the groups to which they were randomised?

Secondary guides: Were patients, health workers, and study personnel 'blind' to treatment?

1. Were the groups similar at the start of the trial?
2. Aside from the experimental intervention, were the groups treated equally?

II. What were the results?

How large was the treatment effect?

1. How precise was the estimate of the treatment effect?

III. Will the results help me in caring for my patients?

Can the results be applied to my patient care?

1. Were all clinically important outcomes considered?
2. Are the likely treatment benefits worth the potential harms and costs?

From *Centre for Health Evidence*. Users' Guides to Evidence-Based Practice. <http://www.jamaevidence.com>; 2007.

OBSERVATIONAL STUDIES

Although RCTs are the optimal study design for deciding whether or not a treatment 'works', not all research questions can be addressed with this type of study. When the disease is rare, the outcome is rare or the treatment may be associated with harm, other study designs may be more appropriate. In these circumstances a cohort study or case-control study may be used to explore potential associations between exposure to a treatment and the occurrence of outcomes.

DESCRIPTIVE STUDIES

Case reports, case series and cross-sectional studies are all examples of descriptive studies. These types of studies may be important in the initial identification of new diseases, such as HIV/AIDS[31–34] and severe acute respiratory syndrome.[35] The purpose of these studies will be to describe the 'who, when, where, what and why' of the condition, and therefore further the understanding of the epidemiology of the disease. It is important that clear and standardised definitions of cases are used, so that clinicians and researchers can identify similar cases from the information provided. Although there are some famous examples where data from simple observational studies have been used to solve particular problems,[36] in general only very limited inferences can be drawn from descriptive data. In particular, it is dangerous to draw conclusions about 'cause and effect' using data from descriptive studies alone.[37]

ANALYTICAL OBSERVATIONAL STUDIES

There are two main types of analytical observational studies: case-control studies and cohort studies.

Case-control studies are performed by identifying patients with a particular condition (the 'cases'), and a group of people who do not have the condition (the 'controls'). The researchers then look back in time to ascertain the exposure of the members of each group to the variables of interest.[38] A case-control design may be appropriate when the disease has a long latency period and is rare. Cohort studies are performed by identifying a group of people who have been exposed to a certain risk factor and a group of people who are similar in most respects apart from their exposure to the risk factor. Both groups are then followed to ascertain whether they develop the outcome of interest. Cohort studies may be the appropriate design to determine the effects of a rare exposure, and have the advantage of being able to detect multiple outcomes that are associated with the same exposure.[39]

Both types of observational studies are prone to bias. In particular, although it is possible to correct for known confounding factors using multivariate statistical techniques, it is not possible to control for unknown or unmeasured confounding factors. There are a number of other biases that may distort the results of observational studies; these include selection bias, information bias and differential loss to follow-up.[39,40] Critical appraisal guides for observational studies are available to help readers assess the validity of these studies.[41] These limitations and inherent biases mean that observational studies may not always provide reliable evidence to guide clinical practice, although it has been argued that this is not always the case.[42,43]

SYSTEMATIC REVIEWS AND META-ANALYSES

Systematic reviews have been proposed as a solution to the problem of the ever expanding medical literature.[44] A systematic review uses specific methods to identify and critically appraise all the RCTs that address a particular clinical question and, if appropriate, statistically combine the results of the primary RCTs in order to arrive at an overall estimate of the effect of the treatment. By systematically assembling all RCTs that address one specific topic, methodologically sound systematic reviews can provide a valuable overview for the busy clinician. They play an important role in providing an objective appraisal of all available evidence and may reduce the possibility that treatments with moderate effects will be discarded owing to false-negative results from small or underpowered studies.[45] The use of meta-analysis could have resulted in the earlier introduction of life-saving therapies, such as thrombolysis for acute myocardial infarction.[46] By using systematic methods, meta-analyses can provide more accurate and unbiased overviews, drawing conclusions that are often at odds with those of 'experts' and narrative reviews.[47,48]

In spite of these advantages and benefits, there are still problems with the conduct and interpretation of meta-analyses. Trial level meta-analyses may include trials that are subsequently retracted due to errors or even fabrication. Patient level meta-analyses (also known as independent patient data meta-analyses), in which researchers gather together and aggregate trial databases, may overcome these concerns but are expensive and time consuming to conduct, and not all investigators are prepared to share their trial databases. Like all research, meta-analyses need to be performed with attention to methodological detail. There are guidelines for performing and reporting systematic reviews.[49,50] It is clear that in the critical care literature these guidelines are not always followed.[51] Clinicians should critically appraise the reports of all systematic reviews and meta-analyses regardless of the source of the review, using an appropriate guide.[52,53] Problems with interpretation can arise when the results of meta-analyses are at odds with the results of large RCTs that address the same issue;[54,55] this is not uncommon, and

clinicians will have to compare the methodological quality of the meta-analyses and the RCTs included in it with the validity of the large RCT in order to decide which provides the most reliable evidence.[2,56]

KEY REFERENCES

3. Hébert PC, Cook DJ, Wells G, et al. The design of randomized clinical trials in critically ill patients. *Chest*. 2002;121(4):1290–1300.
13. Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med*. 2001;134(8):663–694.
23. Wang R, Lagakos SW, Ware JH, et al. Statistics in medicine – Reporting of subgroup analyses in clinical trials. *N Engl J Med*. 2007;357(21):2189–2194.
24. Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332.
40. MacMahon S, Collins R. Reliable assessment of the effects of treatment on mortality and major morbidity, II: observational studies. *Lancet*. 2001;357(9254):455–462.
50. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet*. 1999;354(9193):1896–1900.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Sackett DL, Evidence-based medicine. *Semin Perinatol*. 1997;21(1):3–5.
2. The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350(22):2247–2256.
3. Hébert PC, Cook DJ, Wells G, et al. The design of randomized clinical trials in critically ill patients. *Chest*. 2002;121(4):1290–1300.
4. Roberts I, Schierhout G, Alderson P. Absence of evidence for the effectiveness of five interventions routinely used in the intensive care management of severe head injury: a systematic review. *J Neurol Neurosurg Psychiatry*. 1998;65(5):729–733.
5. Edwards P, Arango M, Balica L, et al. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury – outcomes at 6 months. *Lancet*. 2005;365(9475):1957–1959.
6. Lachin JM. Properties of simple randomization in clinical trials. *Control Clin Trials*. 1988;9(4):312–326.
7. Schulz KF, Grimes DA. Generation of allocation sequences in randomised trials: chance, not choice. *Lancet*. 2002;359(9305):515–519.
8. Armitage P. The role of randomization in clinical trials. *Stat Med*. 1982;1(4):345–352.
9. Doig GS, Simpson F. Randomization and allocation concealment: a practical guide for researchers. *J Crit Care*. 2005;20(2):187–191, discussion 191–193.
10. Schulz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*. 1995;273(5):408–412.
11. Hillman K, Chen J, Cretikos M, et al. Introduction of the medical emergency team (MET) system: a cluster-randomised controlled trial. *Lancet*. 2005;365(9477):2091–2207.
12. Montori VM, Bhandari M, Devereaux PJ, et al. In the dark: the reporting of blinding status in randomized controlled trials. *J Clin Epidemiol*. 2002;55(8):787–790.
13. Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med*. 2001;134(8):663–694.
14. Ranieri VM, Thompson BT, Barie PS, et al. Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med*. 2012;366(22):2055–2064.
15. Berry DA. Adaptive clinical trials in oncology. *Nat Rev Clin Oncol*. 2012;9(4):199–207.
16. Berry SM, Connor JT, Lewis RJ. The platform trial: an efficient strategy for evaluating multiple treatments. *JAMA*. 2015;313(16):1619–1620.
17. De Gruttola VG, Clax P, DeMets DL, et al. Considerations in the evaluation of surrogate endpoints in clinical trials. Summary of a National Institutes of Health workshop. *Control Clin Trials*. 2001;22(5):485–502.
18. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med*. 1991;324(12):781–788.
19. Bucher HC, Guyatt GH, Cook DJ, et al. Users' guides to the medical literature: XIX. Applying clinical trial results. A. How to use an article measuring the effect of an intervention on surrogate end points. Evidence-Based Medicine Working Group. *JAMA*. 1999;282(8):771–788.
20. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet*. 1988;2(8607):349–360.
21. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet*. 1986;1(8478):397–402.
22. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet*. 1994;343(8893):311–322.
23. Wang R, Lagakos SW, Ware JH, et al. Statistics in medicine – reporting of subgroup analyses in clinical trials. *N Engl J Med*. 2007;357(21):2189–2194.
24. Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332.
25. Plint AC, Moher D, Morrison A, et al. Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review. *Med J Aust*. 2006;185(5):263–267.
26. Council for International Organizations of Medical Sciences. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*; 2002. https://cioms.ch/shop/product/international-ethical-guidelines-for-health-related-research-involving-humans/.
27. Wilets I, Schears RM, Gligorov N. Communicating with subjects: special challenges for resuscitation research. *Acad Emerg Med*. 2005;12(11):1060–1063.
28. Harvey SE, Elbourne D, Ashcroft J, et al. Informed consent in clinical trials in critical care: experience from the PAC-Man Study. *Intensive Care Med*. 2006;32(12):2020–2025.
29. Centre for Health Evidence. *Users' Guides to Evidence-Based Practice*; 2007. http://www.jamaevidence.com.
30. Learning and Development, Public Health Resource Unit. *Critical Appraisal Skills Programme and Evidence-Based Practice*. Oxford, 2005. https://casp-uk.net/.
31. Masur H, Michelis MA, Greene JB, et al. An outbreak of community-acquired *Pneumocystis*

carinii pneumonia: initial manifestation of cellular immune dysfunction. *N Engl J Med*. 1981;305(24): 1431–1438.
32. Gottlieb MS, Schroff R, Schanker HM, et al. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. *N Engl J Med*. 1981;305(24):1425–1431.
33. Durack DT. Opportunistic infections and Kaposi's sarcoma in homosexual men. *N Engl J Med*. 1981; 305(24):1465–1467.
34. Siegal FP, Lopez C, Hammer GS, et al. Severe acquired immunodeficiency in male homosexuals, manifested by chronic perianal ulcerative herpes simplex lesions. *N Engl J Med*. 1981;305(24):1439–1444.
35. Zhong NS, Zheng BJ, Li YM, et al. Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. *Lancet*. 2003;362(9393):1353–1358.
36. Centers for Disease Control and Prevention (CDC). 150th Anniversary of John Snow and the pump handle. *MMWR Morb Mortal Wkly Rep*. 2004;53(34):783.
37. Grimes DA, Schulz KF. Descriptive studies: what they can and cannot do. *Lancet*. 2002;359(9301): 145–149.
38. Schulz KF, Grimes DA. Case-control studies: research in reverse. *Lancet*. 2002;359(9304):431–434.
39. Grimes DA, Schulz KF. Cohort studies: marching towards outcomes. *Lancet*. 2002;359(9303):341–345.
40. MacMahon S, Collins R. Reliable assessment of the effects of treatment on mortality and major morbidity, II: observational studies. *Lancet*. 2001; 357(9254):455–462.
41. Levine M, Walter S, Lee H, et al. Users' guides to the medical literature. IV. How to use an article about harm. Evidence-Based Medicine Working Group. *JAMA*. 1994;271(20):1615–1619.
42. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med*. 2000;342(25):1878–1886.
43. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med*. 2000; 342(25):1887–1892.
44. Cook DJ, Meade MO, Fink MP. How to keep up with the critical care literature and avoid being buried alive. *Crit Care Med*. 1996;24(10):1757–1768.
45. Egger M, Smith GD. Meta-analysis. Potentials and promise. *BMJ*. 1997;315(7119):1371–1374.
46. Lau J, Antman EM, Jimenez-Silva J, et al. Cumulative meta-analysis of therapeutic trials for myocardial infarction. *N Engl J Med*. 1992; 327(4):248–254.
47. Antman EM, Lau J, Kupelnick B, et al. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction. *JAMA*. 1992; 268(2):240–248.
48. Mulrow CD. The medical review article: state of the science. *Ann Intern Med*. 1987;106(3):485–488.
49. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, UK: John Wiley; 2008.
50. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet*. 1999;354(9193):1896–1900.
51. Delaney A, Bagshaw SM, Ferland A, et al. A systematic evaluation of the quality of meta-analyses in the critical care literature. *Crit Care*. 2005;9(5):R575–R582.
52. Delaney A, Bagshaw SM, Ferland A, et al. The quality of reports of critical care meta-analyses in the Cochrane Database of Systematic Reviews: an independent appraisal. *Crit Care Med*. 2007;35(2): 589–594.
53. Oxman AD, Cook DJ, Guyatt GH. Users' guides to the medical literature. VI. How to use an overview. Evidence-Based Medicine Working Group. *JAMA*. 1994;272(17):1367–1371.
54. LeLorier J, Gregoire G, Benhaddad A, et al. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. *N Engl J Med*. 1997;337(8):536–542.
55. Villar J, Carroli G, Belizan JM. Predictive ability of meta-analyses of randomised controlled trials. *Lancet*. 1995;345(8952):772–776.
56. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ*. 1998;317(7153):235–240.

11

Palliative care

Sarah Cox, Kate Urwin

The World Health Organisation defines palliative care as an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual (Box 11.1).[1]

Palliative care clearly has a place in the care of patients identified as dying on the intensive care unit (ICU). In addition, the principles of palliative care may be appropriate for patients with life-limiting disease admitted to the ICU for treatment of reversible causes, such as neutropenic sepsis as a consequence of palliative chemotherapy. The palliative care team may also have a role in the care of patients with long-term conditions being considered for ICU admission. This chapter reviews the issues around identification and management of palliative and end-of-life care for ICU patients. It will also address some of the practical, ethical and emotional issues that arise.

PRE-ADMISSION TO INTENSIVE CARE UNIT

Admission to the ICU requires a judgement about the likelihood of benefit for the individual patient. Whilst this is often a discussion between the ICU or critical care outreach team, the usual medical team and the patient and family, the palliative care team may have an important role to play. Firstly, they can be part of a discussion about the appropriateness of aggressive treatment. Secondly, it may be helpful to underline that if ICU care is not the chosen course of action, there is another specialist team who will be involved to ensure good symptom control and emotional support. Their expertise in communication can be useful in clarifying goals aligned with the patient's wishes, if known, including access to pre-existing advance care plans from community health care teams. They can support family and ward staff with an alternative approach to care. They may become the point of contact for the family providing continuity and reassurance in what is often an emotionally fraught situation.

PATIENTS ON INTENSIVE CARE UNIT WHO ARE DYING

Around 5% of deaths in the United Kingdom and 20% of deaths in the United States occur on the ICU.[2–4] Not all of these deaths could or should be predicted, but the proportion that follow a period of treatment withdrawal is increasing in both North America and Europe.[2–4] This suggests an identifiable end-of-life phase, which could be managed with palliative care principles in mind, or as shared care with a specialist palliative care team.

There is great variability between services and cultures in identification of an end-of-life phase. Up to 90% of deaths in North American ICUs happen after decisions to limit life-sustaining treatment.[2] In northern Europe the figure is lower at around 50%, and 20% in southern Europe.[3,4] While these differences might be explained by the greater availability of ICU beds in America or less selective admission criteria, it is likely that they reflect, at least in part, cultural differences in the expectations of treatment.

Scales such as the Acute Physiology and Chronic Health Evaluation (APACHE III) have been developed to help predict outcomes of ICU intervention,[5] but they are not sufficiently precise to be helpful in end-of-life decision making for an individual.[4] Frequently, ICU admission represents a therapeutic trial with both clinicians and family sustaining hope until it is clear the trial has failed. Only then, which may be very late in the acute illness, will a transition to the goals of palliative care be considered appropriate. There may be an opportunity therefore to communicate uncertainty earlier on in the ICU stay so that active and palliative care can occur together.

What constitutes a good death depends on the views of the individual; however, there are some common themes from the literature including freedom from pain and other symptoms, and the ability to retain some degree of control, autonomy and independence.[6] For patients dying on the ICU the last three are difficult to achieve. However, they suggest delivering treatment that supports patients'

ABSTRACT

Palliative care is most obviously appropriate not only for patients who have a recognised dying phase on the intensive care unit (ICU) but also for symptom control and shared decision making in patients admitted with long-term conditions. This chapter discusses the place of palliative care for patients on the ICU, pre-admission to ICU and those dying patients who are stepped down from the ICU. The importance of excellent communication between patients, families and staff is highlighted, particularly as shared decision making results in better decisions and greater satisfaction. The assessment and management of the common symptoms seen on the ICU are explored. The ethical issues involved in withdrawing and withholding treatment are discussed. The chapter concludes with guidance around care for the dying patient and those around them.

KEYWORDS

Palliative care
end-of-life care
symptom control
shared decision making
withdrawal of treatment
care of the dying

Box 11.1 World Health Organization definition of palliative care

- Provides relief from pain and other distressing symptoms
- Affirms life and regards dying as a normal process
- Intends neither to hasten nor postpone death
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help family members cope during the patient's illness and in their own bereavement
- Uses a team approach to address the needs of patients and their families, including bereavement counselling if indicated
- Will enhance quality of life, and may also positively influence the course of illness
- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better

Based on Sepúlveda C, Marlin A, Yoshida T, Ullrich A. Palliative care: the World Health Organization's global perspective. *J Pain Sympt Manage.* 2002;24(2):91–96.

Box 11.2 Patients' and intensive care unit nurses' priorities for a good death

Patients[6]	*Intensive care unit nurses*[7]
Adequate pain and symptom management	Managing pain and other symptoms
Avoiding inappropriate prolongation of dying	Promoting earlier cessation of treatment or not initiating aggressive treatment at all
Achieving a sense of control	Knowing and following the patient's wishes for end-of-life care
Relieving burden on others	Communicating effectively as a health care team
Strengthening relationship with loved ones	

values and beliefs, including appropriate limitation of the use of aggressive treatments. Surveys of patients and ICU nurses suggest a clear overlap between them in the priority of avoiding prolongation of dying (Box 11.2).[6,7]

For relatives of patients dying on the ICU, a good death requires attention to comfort, and more particularly to pain management. Families rate whole-person concerns highly, including feeling that their relative was at peace and retained dignity and self-respect.[8] Satisfaction of families is also related to clarity around the processes of limiting treatment, with trials of treatment being explained and withdrawal or withholding of treatment occurring as expected.[9]

DECISION MAKING FOR PATIENTS AT THE END OF LIFE

INVOLVEMENT OF PATIENTS

In the 1990s, the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) study team reported their prospective observation of over 9000 seriously ill hospitalised patients.[10] The authors identified overaggressive management, inadequate pain control and poor communication amongst a significant number of those who went on to die. There was evidence that physicians were often not aware of patients' wishes around medical care.

Patients' preferences for treatment may be accessed directly in only a small minority of cases admitted to the ICU. Occasionally, a valid and applicable advance directive exists, or patients have a statement of wishes or have discussed their preferences for treatment with close family. The majority (up to 95%) of patients requiring admission to the ICU will be unable to engage in discussions about treatment choices, and most will not have discussed their wishes with relatives or recorded them in writing.[11] Offering advance care planning to individuals with chronic progressive diseases is being encouraged, but as yet has only been taken up by a small minority. Ideally, in the future, advance care planning in patients with progressive medical conditions may be helpful in respecting patient wishes around ICU care.

Where patients are able to discuss options for treatment, it should be considered that they may have a variable understanding of medical interventions. Both patients and clinicians tend to overestimate the likelihood of success, with optimism on the part of the patient and a reluctance to be pessimistic on the part of the clinicians.[12] However, discussions about treatment that include details of the likely outcome and potential burden can significantly reduce patient preferences for those treatments where the medical benefit is uncertain.[13]

INVOLVEMENT OF FAMILIES IN DECISION MAKING

The realisation that active treatment is no longer in the patient's best interests comes to health professionals, patients and families at different times. Partly this is due to experience and training and partly a sometimes unrealistic belief in what ICU treatment can achieve. Managing the different expectations is challenging. Families want to be involved in decision making, especially around value-laden decisions, such as withdrawal of life support,[14] but they will need to have clear explanations of their relative's condition and the purpose and limitations of treatment. Their role, and the role of the health care team, should be to advocate for the patient, making the decision that the patient would have made had they been able.[15] Relatives are able to identify patient preferences with agreement of 80% or greater in situations where the impact of the physical insult is either mild

or devastating.[16] However, there is a dramatic drop in agreement (down to around 60%) for more ambiguous scenarios associated with long-term physical or cognitive morbidity. In these situations, relatives are more likely than patients to identify the clinical outcome as acceptable.

Effective, frequent and timely communication with relatives increases satisfaction with care and reduces anxiety in bereavement.[17] Insufficient time spent communicating with families results in poor understanding of the diagnosis, prognosis and plan of care, and in increased conflict.[18] Time spent is not, in itself, enough, and far more important is the clinicians' ability to elicit and respond to families' views and concerns. Families judge the quality of the discussion, at least in part, by how much time they are allowed to speak rather than encouraged to listen.[19] Although the communication skills of ICU staff may be excellent, the additional resource of the palliative care team can also be useful in these situations.

INVOLVEMENT OF OTHER HEALTH PROFESSIONALS IN DECISION MAKING

ICU nurses often feel frustrated by the medical plan, especially when, in their view, conflicting or overly optimistic messages are given to patients or family members.[20] In contrast, physicians are reported to feel the burden of making decisions about limiting treatment and that 'it's a lot easier to say it than to do it'.[21]

Collaboration between these professionals has the potential to produce better-informed decisions, which can lead to greater satisfaction with care for patients, families and the professionals involved.[22,23] Not surprisingly, inconsistent messages and non-collaborative interprofessional behaviours result in family dissatisfaction.[24] Shared decision making will reduce the burden of decision making on senior ICU physicians, but it still usually remains their ultimate responsibility. Three studies of collaborative decision making involving at least nurses, physicians and family have demonstrated the additional benefits of reduced length of ICU stay and lower costs with no increase in mortality.[22,23,25]

There is much literature published on the involvement of other professionals in end-of-life decision making. Lilly et al. included a social worker and a chaplain in their model of family meetings[22]; others have suggested the importance of considering other specialists, such as physiotherapists (respiratory therapists)[26] or palliative care clinicians.[27] Involvement of clinical ethicists has been demonstrated to improve satisfaction of both health care professionals and families, and to reduce length of ICU stay and costs for patients who died.[28]

WITHHOLDING AND WITHDRAWAL OF TREATMENT

Patients identify the avoidance of inappropriate prolongation of dying in their definition of what a 'good death' might look like.[6] There is agreement in the United States and northern Europe that where treatment is not going to succeed it should be withheld or withdrawn.[4,29,30] However, there is wide variation in withholding and withdrawing treatment across countries.[4] Differences have also been measured in what ICU physicians believe they should do and what actually happens, with physicians identifying a significantly greater need for withholding or withdrawing treatment than their practice demonstrates.[5]

The ethical basis for withholding treatment is the same as that for withdrawal; however, the practice of withdrawal is often emotionally more difficult for all concerned. This may be a result of the more active nature of withdrawal.[29] It is also possible that some ICU treatments, when withdrawn, result in rapid decline and death with a greater requirement for symptomatic medication, and this temporal association presents an uncomfortable comparison with the act of euthanasia. However, allowing inevitable death and euthanasia are ethically and, in most countries, legally distinct. It is the intention behind each decision to withhold or withdraw that is critical.

Decisions to limit treatment include discontinuing monitoring vital signs, withholding cardiopulmonary resuscitation, vasopressors, antibiotics and artificial hydration, and the removal of mechanical ventilation. All decisions should be considered individually in terms of the benefit and burden to the patient, and in the context of the goals of care. In the large, prospective study of end-of-life practices in European ICUs, the Ethicus study group identified wide variation in withdrawal (5%–69%) and withholding (16%–70%) of therapy.[5]

Decisions to remove or reduce mechanical ventilation at the end of life present particularly difficult ethical and practical issues. Differing practices of weaning ventilation from rapid to prolonged are described. Proponents of the former suggest that prolonged weaning prolongs dying and therefore unnecessary suffering.[31] Those in support of prolonged weaning argue that a rapid reduction in ventilation may be associated with more dyspnoea.[29] Extubation is practised by some ICU physicians who argue that there is discomfort associated with the endotracheal tube itself and that there is no ethical justification in leaving the tube in place once a decision has been made to discontinue life-sustaining treatment.[29,32] However, there is a significant incidence of stridor and laboured breathing in extubated patients, which suggests this approach may induce more symptoms than it relieves.[32]

There has been concern about the doses of opioids and benzodiazepines required to control dyspnoea and agitation, especially in rapid weaning or extubation, and whether in fact these medications themselves bring about the patient's death. The principle of double effect holds that the unintended consequence (death) is ethically acceptable because of the intended effect (symptom control). This is a controversial position with which some are uncomfortable. In fact the principle of double effect may not be relevant as small studies in ICU

Box 11.3 Recommendations for managing the transition from active to palliative care on the intensive care unit

- Inclusive and collaborative decision making
- Consistent communication with family that begins early
- Identification of trials of therapy with timed reassessment against clinical milestones
- Concurrent attention to symptom control, spiritual and psychological support of patient and family
- Clarity about withholding and withdrawing treatment
- Guidance for 'stepping-down' to general hospital wards
- Inclusion of organ donation in consideration
- Assessment of bereavement risk for onward referral if appropriate
- Support of staff

show that the doses of opioids and sedatives required for symptom control are relatively modest[33,34] and in dying palliative care patients these drugs do not appear to hasten death.[35,36]

Given such variations in practice and the potential for different interpretations of intentions in withdrawing or withholding life-sustaining treatment, excellent communication between the multiprofessional team and the family, and clear documentation of the intent and decision-making process leading to it, are paramount (Box 11.3).

SYMPTOM CONTROL

Patients on the ICU experience a high level of symptoms including pain, dyspnoea and anxiety.[10] Symptom assessment usually involves taking a detailed history from the patient to understand the cause and severity of the symptom. In many ICU patients at the end of life this is not possible, so physiological variables and behavioural observations are used as surrogate markers, such as heart rate and respiratory rate. The use of validated pain scales, such as the Behaviour Pain Scale[37] or Pain Assessment Behaviour Scale[38] may provide more objective records of pain to direct changes in dose of symptomatic medication. Involvement of the specialist palliative care team may be useful when the situation is unclear or symptoms prove difficult to control.

Dyspnoea correlates most strongly with tachycardia and tachypnoea[39] and may be treated symptomatically with opioids with the addition of benzodiazepines to reduce anxiety if necessary. Treatments, such as oxygen, corticosteroids and diuretics, may be appropriate if they improve symptomatic control of breathlessness. Signs of agitation, anxiety or behavioural markers of pain that do not respond to opioids, and may be caused by general distress, can be treated with benzodiazepines. Specialist palliative care input may be helpful if symptoms fail to respond to usual measures.

The choice of opioid and benzodiazepine varies; it is important for units to use the particular drug most familiar to them. Morphine is first line, but it should not be used in patients with moderate to severe renal impairment as accumulation can result in additional symptoms. Fentanyl or alfentanil are common alternatives in this situation. Drug doses should be titrated against symptoms and escalated in response to documented markers of distress.

SUPPORT FOR FAMILIES AND STAFF

Patients and families will need support in the form of effective communication and they may also need psychological support. This is often provided by ICU staff, particularly the nursing staff, with whom they may have spent significant time. Offers of additional psychological support should be made to patients and family members and accessed from the specialist palliative care team and from chaplaincy.

Palliative care continues as bereavement care after the patient dies. In practice, most bereavement support from the ICU is offered immediately after death or by external agencies. Needless to say, relatives need to be informed of the death in a sensitive manner; they also need to understand the cause of death. Features of a patient's illness and death can guide identification of family members who may be at risk of complicated bereavement, alongside features of the bereaved person, such as psychological morbidity, their relationship with the deceased and their social support. Referral to a local bereavement service or requesting permission to call the family doctor and arrange an appointment may be appropriate.

Bereavement surveys suggest ways we could improve the impact of relatives' deaths on the ICU, including skilled communication during the critical illness and after death. Post-traumatic stress-related symptoms are more common among family members who felt information giving was incomplete.[40] These symptoms can subsequently translate to increased rates of anxiety and depression.

ICU staff have emotional responses to the death of their patients, which need to be addressed to avoid burnout or other negative long-term sequelae.[41,42] Support might include debriefing around deaths, a supportive environment and access to psychosocial resources. Collaborative decision making would be expected to reduce staff stress about dying patients.

ORGAN DONATION

The topic of organ donation and the ICU is more fully discussed in Chapter 102. Involvement of the palliative care team may be helpful to provide additional emotional support to the family. Also, there may be an important role in managing signs of distress, especially during

withdrawal of treatment in donation by cardiac death (DCD). In DCD, the family may wish to be with the patient whilst treatment is withdrawn. This process is an opportunity for them to say goodbye, and they may have specific wishes around prayer or cultural rituals that should be elicited and honoured as far as possible. Provision should be made for appropriate symptomatic drugs to be with the patient during DCD to treat signs of distress, as these will be unpleasant for the family, although they may not be experienced as discomfort by the patient. In some units, the palliative care team takes over the care of patients if they do not die within the timeframe for DCD, moving them to another ward or palliative care unit within the hospital.[43]

CARE PLANS TO SUPPORT END-OF-LIFE CARE ON INTENSIVE CARE UNIT

Individualised care plans and protocols have been recommended to improve the care of dying patients on the ICU.[44,45] Care plans should address appropriate assessment of symptoms, communication with the family and patient if possible, psychological and spiritual support and support with practical issues, such as open visiting and free car parking.[44] They act as a reminder to consider the appropriateness of each treatment in terms of the burden and benefit, and support the nursing staff in monitoring and maintaining comfort on an ongoing basis.

STEPPING DOWN FROM INTENSIVE CARE UNIT

Some patients are able to transfer out of the ICU for their last days, but this transition needs to be managed carefully to avoid additional family distress. The initial suggestion of stepping down from the ICU is another opportunity to utilise the palliative care team's expertise.

This transition is both a physical and emotional one for patients and families who may feel that this step away from critical care in some way seals the fate of the patient. They will be concerned about losing the skilled staff and the environment they know. Their anxiety may be compounded by the knowledge that there is not the same ratio of staff to patients outside the ICU.[46] Clear information about changes in ward and treatments may help to reduce the anxiety.

A member of the palliative care team can be helpful in providing continuity around this transition. If invited to meet the patient and family before transfer, they can begin to understand the specific needs of the patient and family members, including symptom control, emotional and spiritual issues.

The move should take place in a planned way with the family given as much forewarning as possible. Ideally, the patient should not be transferred at night or weekends if this means there is less support available. Treatments and monitoring should not be discontinued immediately before transfer, although some changes may be necessary if the 'step-down' ward does not usually care for patients with arterial lines or intravenous opioid infusions. The palliative care team can help to advise about the practicalities of continuing symptomatic medications after the move, and managing this transition seamlessly.

CONCLUSION

With advances in technology, there is likely to be an increase in trials of ICU treatment, and a corresponding increase in the transition to palliative care on the ICU. How this is managed will depend on local access to specialist palliative care resources and the focus of the ICU staff. Limitation of treatment, in whatever guise, is a difficult area and constitutes a significant part of clinical practice on the ICU. It is immensely important to patients, their relatives and clinicians and deserves to be more openly discussed. Review of ICU deaths at mortality and morbidity meetings could include consideration of the quality of the patient's end-of-life care and family support to promote learning and improve care for subsequent patients.

KEY REFERENCES

3. Sprung C, Cohen S, Sjokvist P, et al. Ethicus Study Group. End of life practices in European intensive care units – the Ethicus study. *JAMA*. 2003;290(6):790–797.
4. Carlet J, Thijs L, Antonelli M, et al. Statement of the 5th International Consensus Conference in Critical Care: Brussels, Belgium. Challenges in end-of-life care in the ICU. *Intensive Care Med*. 2004;30(5):770–784.
6. Singer P, Martin D, Kelner M. Quality end-of-life care – patients' perspectives. *JAMA*. 1999;281(2):163–168.
29. Truog R, Campbell M, Curtis R, et al. Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American College of Critical Care Medicine. *Crit Care Med*. 2008;36(3):953–963.
44. Leadership Alliance for the Care of Dying People. *One chance to get it right. [online] Leadership Alliance for the Care of Dying People*. 2014. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/323188/One_chance_to_get_it_right.pdf.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Sepúlveda C, Marlin A, Yoshida T, et al. Palliative care: the World Health Organization's global perspective. *J Pain Sympt Manage*. 2002;24(2): 91–96.
2. Prendergast T, Luce J. Increasing incidence of withholding and withdrawal of life support from the critically ill. *Am J Respir Crit Care Med*. 1997;155(1): 15–20.
3. Sprung C, Cohen S, Sjokvist P, et al. End of life practices in European intensive care units – the Ethicus study. *JAMA*. 2003;290(6):790–797.
4. Carlet J, Thijs L, Antonelli M, et al. Statement of the 5th International Consensus Conference in Critical Care: Brussels, Belgium. Challenges in end-of-life care in the ICU. *Intensive Care Med*. 2004;30(5): 770–784.
5. Sprung C, Baras M, Iapichino G, et al. The Eldicus prospective, observational study of triage decision making in European intensive care units: Part 1 – European intensive care admission triage scores. *Crit Care Med*. 2012;40(1):125–131.
6. Singer P, Martin D, Kelner M. Quality end-of-life care – patients' perspectives. *JAMA*. 1999;281(2): 163–168.
7. Bratcher J. How do critical care nurses define a "good death" in the intensive care unit? *Crit Care Nurs Quart*. 2010;33(1):87–99.
8. Mularski R, Heine C, Osborne M, et al. Quality of dying in the ICU: ratings by family members. *Chest*. 2005;128(1):280–287.
9. Keenan S, Mawdsley C, Plotkin D, et al. Withdrawal of life support: how the family feels and why. *J Palliat Care*. 2000;16(suppl):S40–S44.
10. Connors A, Dawson N, Desbiens N, et al. A controlled trial to improve care for seriously ill hospitalized-patients – the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT). *JAMA*. 1995;274(20): 1591–1598.
11. Hofman J, Wenger N, Davis R, et al. Patient preferences for communication with physicians about end-of-life decisions. *Ann Intern Med*. 1997; 127(1):1–12.
12. Fischer G, Tulsky J, Rose M, et al. Patient knowledge and physician predictions of treatment preferences after discussion of advance directives. *J Gen Intern Med*. 1998;13(7):447–454.
13. Murphy D, Burrows D, Santilli S, et al. The influence of the probability of survival on patients' preferences regarding cardiopulmonary resuscitation. *N Engl J Med*. 1994;330(8):545–549.
14. Johnson S, Bautista C, Yeon Hong S, et al. An empirical study of surrogates' preferred level of control over value-laden life support decisions in intensive care units. *Am J Respir Crit Care Med*. 2011; 183(7):915–921.
15. Mental Capacity Act. 2005. http://www.legislation.gov.uk/ukpga/2005/9/contents.
16. Fried T, Bradley E, Towle V. Valuing the outcomes of treatment. Do patients and their caregivers agree? *Arch Intern Med*. 2003;163(17):2073–2078.
17. Kirchhoff K, Walker L, Hutton A, et al. The vortex: families' experiences with death in the intensive care unit. *Am J Crit Care*. 2002;11(3):200–209.
18. Studdert D, Mello M, Burns J, et al. Conflict in the care of patients with prolonged stay in the ICU: types, sources, and predictors. *Intensive Care Med*. 2003;29(9):1489–1497.
19. McDonagh J, Elliott T, Engelberg R, et al. Family satisfaction with family conferences about end-of-life care in the intensive care unit: increased proportion of family speech is associated with increased satisfaction. *Crit Care Med*. 2004;32(7):1484–1488.
20. Beckstrand R, Kirchhoff K. Providing end-of-life care to patients: critical care nurses' perceived obstacles and supportive behaviours. *Am J Crit Care*. 2005;14(5):523–530.
21. Oberle K, Hughes D. Doctors' and nurses' perceptions of ethical problems in end-of-life decisions. *J Adv Nurs*. 2001;33(6):707–715.
22. Lilly C, Sonna L, Haley K, et al. Intensive communication: four-year follow-up from a clinical practice study. *Crit Care Med*. 2003;31(5):S394–S399.
23. Pronovost P, Berenholtz S, Dorman T, et al. Improving communication in the ICU using daily goals. *J Crit Care*. 2003;18(2):71–75.
24. Auerbach S, Kiesler D, Wartella J, et al. Optimism, satisfaction with needs met, interpersonal perceptions of the healthcare team, and emotional distress in patients' family members during critical care hospitalization. *Am J Crit Care*. 2005;14(3): 202–210.
25. Ahrens T, Yancey V, Kollef M. Improving family communications at the end-of-life: implications for length of stay in the intensive care unit and resource use. *M J Crit Care*. 2003;12(4):317–324.
26. Willms D, Brewer J. Survey of respiratory therapists attitudes and concerns regarding terminal extubation. *Resp Care*. 2005;50(8):1046–1049.
27. Billings J, Keeley A, Bauman J, et al. Merging cultures: palliative care specialists in the medical intensive care unit. *Crit Care Med*. 2006;34(11 suppl):S388–S393.
28. Schneiderman L. Effect of ethics consultations in the intensive care unit. *Crit Care Med*. 2006;34(11 suppl):S359–S363.
29. Truog R, Campbell M, Curtis R, et al. Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American College of Critical Care Medicine. *Crit Care Med*. 2008;36(3):953–963.
30. Council of Europe. *Protection of the human rights and dignity of the terminally ill and dying. Doc 8888, 7 Nov 2000, Recommendation 1418 (1999), Reply from the Committee of Ministers, adopted at the 728th meeting of the Ministers' Deputies*, 30 Oct 2000. Strasbourg: Council of Europe.
31. Gilligan T, Raffin T. Withdrawing life support: extubation and prolonged terminal weans are inappropriate. *Crit Care Med*. 1996;24(2):352–353.
32. Mayer S, Kossoff S. Withdrawal of life support in the neurological intensive care unit. *Neurology*. 1999;52(8):1602–1609.

33. Chan J, Treece P, Engelberg R, et al. Narcotic and benzodiazepine use after withdrawal of life support: association with time to death? *Chest*. 2004; 126(1):286–293.
34. Campbell M, Bizek K, Thill M. Patient responses during rapid terminal weaning from mechanical ventilation: a prospective study. *Crit Care Med*. 1999; 27(1):73–77.
35. Ventifridda V, Ripamonti C, De Conno F, et al. Symptom prevalence and control during cancer patients' last days of life. *J Palliat Care*. 1990;6(3): 7–11.
36. Thorns A, Sykes N. Opioid use in the last week of life and implications for end-of-life decision-making. *Lancet*. 2000;356(9227):398–399.
37. Payen J, Bru O, Bosson J, et al. Assessing pain in critically ill sedated patients by using a behavioural pain scale. *Crit Care Med*. 2001;29(12):2258–2263.
38. Aissaoui Y, Zeggwagh A, Zekraoui A, et al. Validation of a behavioral pain scale in critically ill, sedated, and mechanically ventilated patients. *Anesth Analg*. 2005;101(5):1470–1476.
39. Campbell M. Fear and pulmonary stress behaviours to an asphyxial threat across cognitive states. *Res Nurs Health*. 2007;30(6):572–583.
40. Azoulay E, Pochard F, Kentish-Barnes N, et al. Risk of post-traumatic stress symptoms in family members of intensive care unit patients. *Am J Respir Crit Care Med*. 2005;171:987–994.
41. Embriaco N, Azoulay E, Barrau K, et al. High level of burnout in intensivists: prevalence and associated factors. *Am J Respir Crit Care Med*. 2007; 175(11):686–692.
42. Poncet M, Toullic P, Papazian L, et al. Burnout syndrome in critical care nursing staff. *Am J Respir Crit Care Med*. 2006;175(7):698–704.
43. Kelso CM, Lyckholm LJ, Coyne PJ, et al. Palliative care consultation in the process of organ donation after cardiac death. *J Pall Med*. 2007;10(1): 118–126.
44. *Leadership Alliance for the Care of Dying People*. One chance to get it right. [online] Leadership Alliance for the Care of Dying People. 2014. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/323188/One_chance_to_get_it_right.pdf.
45. Kuschner W, Gruenewald D, Clum N, et al. Implementation of ICU Palliative Care Guidelines and Procedures: a quality improvement initiative following an investigation of alleged euthanasia. *Chest*. 2009;135(1):26–32.
46. Coyle MA. Transfer anxiety: preparing to leave intensive care. *Intensive Crit Care Nurs*. 2001;17(3): 138–143.

12

Intensive care and the elderly

Linsey Emma Christie, Richard T Keays

The proportion of the elderly population is increasing in all developed and developing nations. Medical innovation and a belief that old age and disease can be defeated by a combination of personal choice and greater resources has led to rising, often unrealistic, expectations. Increasingly, intensive care medicine is becoming a specialty largely focused on care of the elderly and the age-acquired co-morbidities of this patient group complicate their management. This chapter seeks to bring together the current information on management of the elderly presenting to critical care.

DEFINITIONS

There is no agreed definition of 'elderly'. It has been defined by chronology, social role, physical capacity, threshold life expectancy and when 'active contribution is no longer possible'. Most commonly, it is taken as the pension age – though this is an inherently fluid end-point. In 1875, the over-50s were defined as elderly, whereas now it seems around the pension age of 65, although the over-80s are also becoming an 'identifiable' group. These chronological niceties are rarely relevant from a medical perspective, as clinicians understand the poor correlation between chronological and physiological age. The medical literature has no common definition and uses a wide range of arbitrary values from 67 to 70, over-70s and, more recently, over-80s to describe population groups.[1]

DEMOGRAPHICS

More people are living longer and this trend has shown little sign of stopping. In the UK, the 2014–2015 Office for National Statistics report demonstrated that the most common age at death was now 85 for men and 89 for women.[2] In 2015, there were over half a million people aged 90 or more in the United Kingdom (0.9% of the population).[3] The proportion of the population estimated to be over 65 by 2060 is 26%[4], compared to 2011 when it was 16%[5]. Current United Nations projections predict the population of over 80s will double by 2050, representing 10% of the total population in developed countries. There are some signs this inexorable rise in life expectancy may have peaked. In the United Kingdom, overall life expectancy at birth has remained virtually unchanged in recent years.[2] For the first time in 50 years Spain reported a fall in life expectancy,[6] a finding repeated in some parts of the United States.[7] These recent declines have been attributed to familiar factors accounting for poor health: obesity, tobacco and other preventable risks.

Nevertheless, the post-war increase in longevity means many more elderly people present to critical care than previously. This greater longevity may be attributable to improved diet and better lifestyle decisions, but is also explained by improved disease management; however, the resultant gain in survival is at the price of living with morbidity. Not only are there more elderly patients but also they have more significant co-morbidity and thus a greater likelihood of developing a critical illness.

These societal changes are reflected in the intensive care unit (ICU) demographics. In Australia and New Zealand, 13% of ICU admissions were over 80 years old and the numbers had been increasing by about 5% per annum between 2000 and 2005.[8] Unsurprisingly, the chances of being admitted to the ICU are somewhat related to resource availability. In 2005 the number of ICU beds per 100,000 population was 3.3 for the United Kingdom, 7.8 in Australia, 24 in Germany and 20 in the United States.[9] A study comparing the United States with the United Kingdom in terms of hospitalisation and the elderly found that 47% of British over-85s died in hospital, whereas this figure was only 31% in the United States; however, only 1.3% of these patients received intensive care in the United Kingdom compared with 11% in the United States.[10] Of all hospital discharges, only 2.2% of patients had received intensive care in the United Kingdom compared with 19.3% in the United States.

Approaching the problem from a different direction is to consider what happens to a whole cohort of elderly people. One such longitudinal study from America following over 1 million elderly patients over a 5-year follow-up period found that over half were admitted to a higher dependency care unit at some point.[11]

THE AGEING PROCESS

Individuals accumulate co-morbidities with pathophysiological consequences as they age, but these physiological changes are both unpredictable and extremely variable across any population. Ageing is the combination of

ABSTRACT

The elderly population is increasing and presents a challenge for those working in critical care. Decisions regarding admission and ongoing management of individual patients require the intensive care unit (ICU) team to consider not only the acute reason for potential admission, but also the physiology of ageing, possible co-morbid disease, frailty, disability and pharmacology concerns (including the use of multiple medications). Outcomes for the elderly in the ICU are worse than for younger patients, yet many do have a good outcome and return home. A risk-benefit analysis, incorporating patient views if possible, is required to identify those most likely to benefit and minimise harm.

KEYWORDS

Elderly
frailty
ageing
older
reserve
co-morbidity

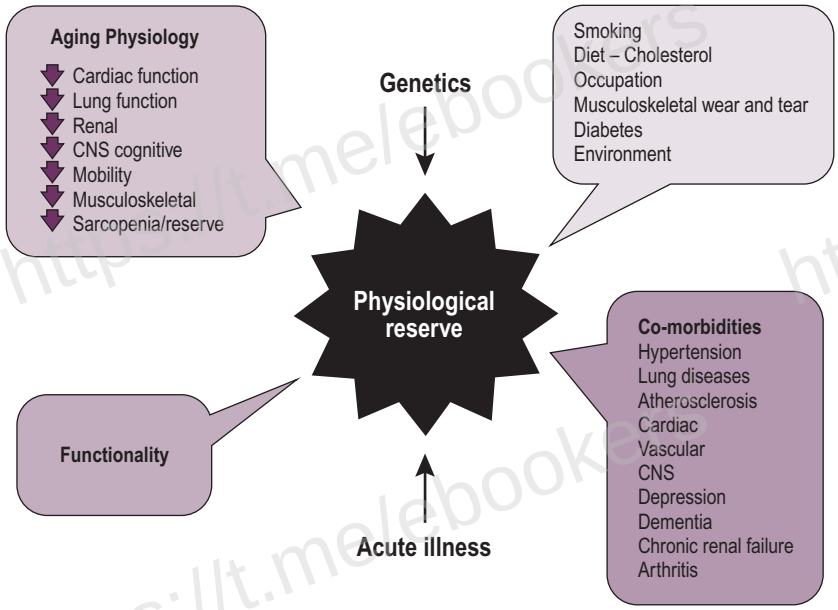


Figure 12.1 Factors affecting physiological reserve. *CNS*, Central nervous system.

physiological change and accumulated pathophysiology (Fig. 12.1). Examples of physiological changes associated with ageing include maximal oxygen uptake, cardiovascular function, muscle mass, tissue elasticity, memory and reaction time, but there are many more.[12]

THE ORGAN SYSTEMS

Each organ system undergoes age-related declines; however, in addition, there are specific disease-related organ alterations leading to a net impairment of organ function. A brief overview of changes associated with age and the impact of the more common co-morbidities follows.

CARDIOVASCULAR CHANGES

The heart has reduced contractility and overall mechanical efficiency[13] caused by:

- altered connective tissue compliance due to interstitial collagen being laid down
- reduction in myocyte numbers
- valve hardening and sclerosis, which can affect function
- fibrosis and cell loss in conduction pathways impairing conduction
- deterioration in the sinoatrial node
- ventricular hypertrophy with slower myocardial relaxation.

The result of these changes is a reduction in arterial compliance with an earlier return of the reflected wave in systole. Normally, cardiac pulsatile energy is absorbed at the arteriolar segmental level in the young but not in the elderly. Aortic impedance increases and higher blood flow organs show familiar signs of microvasculopathy. This, coupled with the tendency for pulse pressure to rise with age, means that ventricles hypertrophy and cardiac work increases. The resultant increasing oxygen demand occurs against a background fall in diastolic coronary blood flow with ventricular hypertrophy.

Both contraction and relaxation phases are slower. Diastolic filling time is reduced, which places an extra emphasis on the atrial component to maintain this filling resulting in a reversal of the E/A ratio (early-to-late diastolic-filling velocity). Subsequent atrial dilatation is more likely to lead to atrial fibrillation, significantly compromising ventricular filling. The smaller end-diastolic volume is poorly tolerated, and impaired cardiac performance ensues.

In addition to these changes, coronary flow reserve is limited, blood vessels are less easily dilated and there is a chronically elevated basal sympathetic tone. Baroreceptor reflexes are impaired and there is decreased sodium conservation.

In summary, the main ageing changes are myocardial and vascular stiffening, with impaired cardiac and vascular compliance. The blunted sympathetic responses produce the 'hyposympathetic heart' with a tendency to increased end-diastolic volume. Additionally, there is an age-related reduction in cardiac contractility. Overall cardiac reserve and flexibility of response are reduced, but are usually more than able to deal with the normal physical requirements of the elderly – though not with more excessive demands (Box 12.1).[13,14]

Box 12.1 Cardiovascular ageing

- Cellular changes: reduced excitation contraction coupling, calcium homeostasis, myocyte function and increased atrial natriuretic peptide
- Decrease in myocytes, altered connective tissues, increased ventricular wall size
- Reduction in conductive tissues and numbers of sinus node cells
- Decreased contractility, reduced ventricular compliance, increased ventricular filling pressure, blunting of β-adrenoceptor responsiveness, reduced coronary flow reserve
- Stiffer arteries, reduced elasticity
- Thicker media and intima
- Alterations in autonomic tone with reduced β-adrenoreceptor-mediated vasodilatation; reduced NO activity
- Reduced heart rate, increased end-diastolic volume, increased stroke volume, reduced peak values for ejection fraction, cardiac output
- Impaired conduction, atrial fibrillation
- Clinical effects: more arrhythmias, hypertension, reduced exercise tolerance, dyspnoea and heart failure

ACQUIRED CARDIOVASCULAR DISEASE

Atherosclerosis is detectable much earlier in life and starts to become relevant around 40 years of age in males and after menopause in females. For people older than 65 years, 40% of deaths are cardiovascular and this increases with age. Diabetes, smoking, poor blood pressure control and high cholesterol all increase the risk of death from cardiovascular disease and most become more common with age.[15] Myocardial infarction carries a higher mortality in the elderly and the risk associated with interventional treatments is also higher.[13,14] The Framingham study showed that 40% of myocardial infarctions in those over 75 were silent.[16] In addition, arrhythmias, such as atrial fibrillation, are more common as a chronic feature in the elderly but most particularly affect the postoperative patient. In one study, 22% of over-70-year-olds developed postoperative atrial fibrillation.[17] When it does occur, patients may be more at risk from hypotension, cardiac failure and myocardial infarction. The most common cause of death amongst the over-85s in the postoperative period is myocardial infarction.[18]

RESPIRATORY

Lung function decline starts at around the age of 35 years. Muscle function is impaired by a combination of reduced fast twitch fibres and muscle atrophy, so between the ages of 65 and 85 there is a decrease in maximum inspiratory pressure, maximum voluntary ventilation and forced expiratory volume-1. Impaired diaphragmatic strength impacts on force of coughing. Degeneration of elastic fibres in the lung parenchyma leads to air space enlargement. Chest wall compliance is reduced and a rise in closing volume results in increasing V/Q mismatching. This whole effect has been termed 'senile emphysema' and is often accompanied by age-related β-receptor dysfunction.

Gas transfer is also affected – diffusing capacity of the lungs for carbon monoxide (DLCO) declines with some impairment of oxygenation (about 0.5 kPa/decade) but there is no discernible effect on carbon dioxide clearance. Both the hypoxic and hypercapnic respiratory control responses are blunted. Exercise capacity, as shown by V_{max}, declines by about 1% per year after the age of 30.[18–20]

Less direct intrinsic and extrinsic changes also occur that will impair respiratory function. Diminished antioxidant defences have been observed and bronchial lavage sampling shows changes in both immunoglobulin and CD4/CD8 ratios implying chronic antigenic stimulation. There is also an increasing age-related burden of problems, such as nocturnal gastroesophageal reflux, kyphosis, vertebral collapse and sleep apnoea. The likelihood of environmental exposure to agents with the potential to cause lung damage, most particularly tobacco smoke, increases with age.

Hence it is predictable not only that more elderly patients will require respiratory support but also that ventilatory weaning is going to be more challenging. Mortality is also likely to be higher compared with younger populations. An American study confirms that the likelihood of requiring ventilation does increase with age, with an estimated 10% chance in the over-75s.[21] Amongst those who are ventilated, mortality in the over-70s is nearly double that in the under-40s,[22] and there is a high 3-year mortality in those discharged from the ICU with 57% of deaths occurring early after discharge.[23] This bleaker picture is offset to some extent in those with chronic obstructive airways disease; patients with acute exacerbations have a lower mortality at 28% compared with other causes of respiratory failure. Nevertheless, even among ICU survivors in this group the extent of premorbid problems and the need for ongoing care at discharge dictates outcome; if they were not fit to go directly home then mortality is higher[24] and a high proportion will still need help with at least one activity of daily living, and the quality of life scores are low – though not necessarily lower than they were premorbidly.

RENAL

Kidney size becomes smaller with age due to a reduction in the number of nephrons; 20% to 30% of glomeruli become sclerotic and the glomerular filtration rate may diminish by 50% by 80 years of age. However, this is neither consistent nor predictable.[25] Not only does creatinine clearance start to decline from the fourth decade of life, but renal blood flow also decreases by about 10% per decade. Tubular exchange of sodium and hydrogen

ions is also reduced, with impaired ability to handle fluid loads and acidaemia. Rarely is this ever seen as a clinical or biochemical entity, but it does represent a reduction in reserve capacity and manifests only when acute stressors are applied. In the elderly, the competing needs of the kidney versus the heart make the treatment of incipient failure of either organ problematic, and failure of one organ can cause failure of the other – this has been termed 'cardiorenal syndrome'.[26]

The risk of developing acute kidney injury increases with age and is especially associated with co-morbidities such as cardiac failure and renovascular disease, and acquired preconditions such as known nephrotoxic drugs, surgical interventions and sepsis. Obstructive uropathy may be a consequence of the increasing prevalence of prostatic disease. Many drugs have been implicated, but non-steroidal analgesics and angiotensin converting enzyme (ACE) inhibitors stand out. Surgery involves acute changes to blood pressure and volume status, but carries the additional risk of abdominal hypertension.

There is an attributable mortality associated with acute kidney injury, though it is difficult to tease out. It appears that this may be similar between the young and the old[27] and has been variously quoted at between 15% and 40%. The outcome from acute kidney injury is determined by cause and prior functional status, with drug-related renal failure doing better than most other causes. The mean survival of octogenarians after an episode of acute renal failure was 19 months, but complete recovery of renal function occurs in just over half of the survivors.[28] In one study, only 3 out of 23 biopsies of acute kidney injury showed evidence of acute tubular necrosis.[29] Those with pre-existing chronic renal failure are seven times more likely to progress to long-term dialysis.[30]

A secondary but important effect in the elderly is that there is often a reduced ability to excrete drugs. The consequence may be prolonged half-life (by a factor of 1.4), altered volumes of distribution (+24%) and reduced clearance.[31] This is probably a source of excess morbidity in the elderly.

LIVER

This is relatively unaffected and has huge intrinsic reserve so that a reduced mass of up to 30% at 80 years probably has little effect, other than loss of reserve. There is a tendency to reduced liver blood flow by up to 40% at 80 years and reduced metabolic function, in particular demethylation and the production of cholinesterase. It may have some effect on drug handling, but is rarely of clinical relevance.

It is acquired liver disease (most commonly cirrhosis) that is the potent predictor of mortality and this has a peak age of presentation in the sixth or seventh decades of life. Nevertheless, age itself is not a poor prognostic indicator in the context of patients with cirrhosis requiring intensive care.[32]

CENTRAL NERVOUS SYSTEM

There is often some decline in cognitive performance with age, though this is contentious. Memory loss is apparent in 10% of those over 70 years of age and about half of these are due to some variant of Alzheimer disease. This incidence doubles with each decade.[12] The neurocognitive decline is multifactorial but is associated with cerebral vasculopathy, decline in sex steroids, neurochemical alterations such as melatonin and sleep disorders, which are common in the elderly. Dementia has strong associations with cerebral vascular pathology and strokes, but previous head injury is also important. A new era of dementia treatment is imminent and may alter the ICU perspective about the irreversibility of this condition.

Unsurprisingly, patients with neurocognitive decline are much more likely to experience delirium. Up to two-thirds of patients aged over 65 years experience delirium in hospital and, in the ICU, one-third of patients are admitted with it and one-third develop it following admission.[33] Delirium is common after major surgery and trauma; for example, it occurs in up to 60% of patients following a hip fracture. Delirium can lead to long-term cognitive impairment[34], lengthens hospital stay and is an independent predictor of 6-monthly mortality.[35]

Age is a risk factor for persistent psychological issues and part of this may be related to post-traumatic stress disorder.

Psychological assessment of the elderly post-intensive care is in its infancy. The existing tools for assessing delirium are the Confusion Assessment Method for ICU (CAM-ICU) and Intensive Care Delirium Screening Checklist (ICDSC). An ICDSC score of more than 4 correlates with both increased mortality and, in survivors, persistent cognitive dysfunction. More recently, the 10-risk-factor assessment tool PREdiction of DELIRium in ICu patients (PRE-DELIRIC) has been validated for the ICU.[36] With increasing awareness of the problem, these scoring systems may be used more widely, and appropriate interventions implemented to both prevent and manage delirium.

METABOLIC

Over the age of 70 there is a tendency for weight loss with a general change in body composition, leading to increased fat and reduced muscle mass. This sarcopenia is manifested by a 30% reduction in main muscle group strength by the seventh decade of life.[37] With less musculoskeletal activity, there is less energy use, less heat production and a reduced calorie requirement with a 2% decrease in basal metabolic rate (BMR) per decade. Protein requirements stay broadly the same.

Malnutrition is common and calorific intake is often inadequate. This 'anorexia of ageing' is multifactorial and is not just psychosocial – there are some fundamental physiological changes: early satiation is common and gastric emptying is delayed with the feeling of fullness

suppressing ghrelin, thereby reducing appetite, as do raised cholecystokinin levels, which are also common. Dehydration and micronutrient deficiencies are also frequent. Loss of water-soluble vitamins such as thiamine occurs with diuretic therapy. B12 deficiency occurs due to atrophic gastritis and reduced intrinsic factor secretion. Calcium and vitamin D deficiency is also common in the elderly.[38]

Weight loss, frailty and reduced functional capacity will predispose to morbidity, complications, survival, and in survivors it will reduce the ability to regain independence.

SPECIAL CONSIDERATIONS

Having discussed the organ system considerations, both in terms of the physiological process of ageing and the acquisition of co-morbidities, it is notable that some elderly patients may also have additional issues, such as frailty or a disability, which can affect care. Whilst in many ways the elderly have the same requirements as any other intensive care unit patient, these other areas do require special attention.

FRAILTY

It is vital to consider in more detail the concept of 'physiological age' versus 'chronological age' – essentially frailty. Frailty has been defined as 'a condition characterised by loss of biological reserve and vulnerability to poor resolution of homeostasis following a stressor event'.[39] One method of frailty assessment is the 7-point Clinical Frailty Scale.[40] Recent studies demonstrate that assessment of frailty may be useful in predicting adverse events, morbidity and mortality post ICU.[41–43] Therefore, identification of frailty may help with prognostication, detection and intervention in this high-risk group.

DISABILITY

Some elderly patients may also have a disability that can affect care (e.g. hearing or vision loss).

PHARMACOLOGY

There are marked changes in pharmacokinetics and pharmacodynamics in the elderly. Due to the impaired ability of the kidneys to excrete drugs, drug half-lives may be prolonged. The volume of distribution may also either increase or decrease depending on the drug and the changes in body composition.[31] For example, the aminoglycosides not only may achieve higher concentrations than predicted through distribution changes, but also may remain higher for longer due to impaired excretion. Non-steroidal anti-inflammatory drugs may have profound and potentially toxic effects by the potent combination of a relatively smaller volume of distribution and the possibility of relative dehydration producing high drug levels; the associated drug-related inhibition of the prostaglandins would promote renal vasoconstriction, reducing renal blood flow and resulting in renal toxicity.

There may be changes in sensitivity to drugs, partly through altered pharmacokinetics as described, or through interaction with physiology, such as the decline in sensitivity to beta-adrenergic agonists and antagonists with age. By a similar mechanism, the incidence of orthostatic hypotension with antihypertensive drugs increases. The central nervous system, however, becomes more sensitive to centrally acting drugs.

Fluid management must incorporate some general considerations. These include the potential presence of both cardiovascular and renal impairment (cardiorenal syndrome), a reduced flexibility in cardiac output and an increasing dependence on alterations in systemic vascular resistance. This, along with changes in body composition, may alter fluid distribution. However, it is unpredictable across the population and therefore should be assessed in the individual.

The biggest single problem in the pharmacology of the elderly is poly-pharmacy. Elderly patients will often be on a panoply of medications depending on their chronic health problems. Most drugs have side effects and interactions and, as the number of medications increases, so too does the likelihood of complications from their use – especially when the patient is ill. The classic example is antihypertensive drugs in the elderly causing postural hypotension. The role of poly-pharmacy in hospital and ICU admission has two very different mechanisms: firstly, the drugs being the source of the problem and, secondly, the impact of inadvertent discontinuation of important medications.[44] It is not a minor issue, and an important part of the assessment of the elderly should be rationalisation of medication.

SURGICAL OUTCOME

Increasing numbers of elderly patients are having progressively more complex surgery performed upon them. Both operative mortality and postoperative complications are higher in the elderly and again relate to the existence of co-morbid disease, frailty and lack of physiological reserve. The fitter the patient the less likely he/she is to experience complications, and this is true for both cardiac and noncardiac surgery.[45,46] The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) published a report in 2010 called 'An Age Old Problem'. This report examined all deaths in patients aged 80 or over within 30 days of surgery within a 3-month period. Some key findings were that (1) routine daily input from Medicine for the Care of Older People is vital; (2) co-morbidity, frailty and disability are independent markers of risk; (3) delays in surgery are associated with a poor outcome; and (4) there is an ongoing need to provide level 2 and 3 perioperative care. Furthermore, over 90% of this population had co-morbid disease.[47] In the over-80s age group, it has been shown that medical patients had longer ICU lengths of stay and higher ICU and

hospital mortality than surgical patients.[48] One study in the over-80s showed that 6-month mortality rates after ICU discharge were 30% for planned surgical patients compared with 76% for emergency surgical patients.[49] Elderly patients presenting as emergencies have been eloquently described as 'a heterogeneous cohort of both potentially treatable patients and those who are dying'.[50] Distinguishing the treatable from the futile is difficult across all age groups, but is particularly so in the elderly where limited life expectancy is usual and severe, but unrecognised co-morbidity may exist. Committing patients and their families to emotional and physical hardship is clearly justifiable with a good outcome, but far harder to defend if the outcome was never likely to be good. The patient's wishes or preferences should ideally be taken into account, but frequently that is not possible. This is an area of practice that has not been studied but anecdotally it is very poorly managed.

INTENSIVE CARE UNIT OUTCOME

How the interaction between age itself, the severity of the acute illness, or the accumulated co-morbidities and declining functional status due to ageing affects ICU outcome is uncertain (Fig. 12.2). Acute Physiology and Chronic Health Evaluation (APACHE) scoring attributes only 7% of the outcome predictive power to age alone. Nevertheless, in some studies of ICU admissions, increasing age does appear to be independently associated with higher 30-day hospital mortality.[51] One study suggests that, for the over-80s, half will not survive the ICU, but half the survivors will be alive 2 years later.[52] In a study in Canada, one-quarter of patients aged 80 years or over who were admitted to the ICU survived and returned to baseline function at 1 year. This recovery was significantly associated with younger age, lower APACHE II score, lower Charlson co-morbidity score, lower frailty index, lower baseline physical function score, and specific admission diagnoses.[53] Intuitively, the pre-morbid functional status and presence of co-morbidities should significantly affect ICU outcome. Even supposedly soft indicators, such as coming from a care home, was associated with higher in-hospital mortality; also the medium-term mortality at 6 months is increased if the patient is discharged to care facilities.[23] In a study of over 15,000 elderly patients compared with non-elderly ICU admissions, the elderly were more likely to have greater co-morbid illnesses and higher illness severity scores, which led to a higher ICU mortality. These patients were more likely to be discharged to either rehabilitation or long-term care.[54] Conversely, other studies have failed to find an association between outcome and pre-existing co-morbidities or functional status.[55] Elderly (aged 65 years or over) trauma patients in the ICU may have a worse outcome than previously thought, with a recent study demonstrating a 45% in-hospital mortality and only 23% of survivors being discharged home.[56]

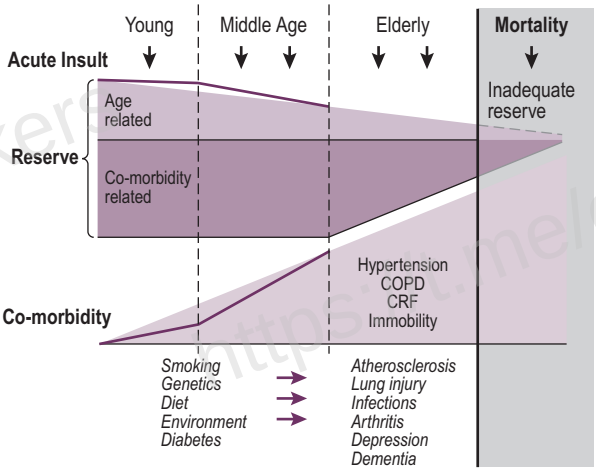


Figure 12.2 Factors affecting intensive care unit outcome. *COPD*, Chronic obstructive pulmonary disease; *CRF*, chronic renal failure.

Age itself is not a useful prognostic indicator and its use as a surrogate for general status is unpredictable. Nevertheless, it is possible to conclude that the outcome for elderly patients admitted to ICU is poorer than for younger patients, but that the outcome relates to the premorbid state (including co-morbidities and frailty), the severity of the acute illness and the presence of an underlying fatal illness, as in other populations.[52]

Quality of life is probably a more relevant factor than survival. Most patients will have significant functional disability on ICU discharge, which may improve, although the evidence is difficult to interpret. In general, those experiencing major acute events with little pre-existing co-morbidities report a substantially lower quality of life afterwards compared with those with significant pre-existing co-morbidities; this is most probably due to relatively lower expectations in the latter group. It is a contentious area with some studies showing no real impairment in quality of life, whereas others show a significant decline in quality of life.[57]

Probably the best indicators of real outcome for the elderly are measures, such as returning home, which has rarely been assessed but is often a very important consideration for the individual. Conti and colleagues assessed this with the results seen in Box 12.2; this approach is probably more relevant than mortality figures.[58] In a recent Canadian study, only 45% of medical and 41.6% of surgical emergency patients aged 80 or over were able to return home to live post-ICU.[48]

In the future, there needs to be more focus on both physical and mental functionality as an outcome measure. Patients need to be alive and have reasonable functional status, and ideally be able to return home. In order to achieve the best outcome for patients, multidisciplinary assessment, including the need for early rehabilitation, is crucial.

Box 12.2 Factors that influence elderly patients getting home from the intensive care unit

Important factors
- Over 75 years of age
- Neoplasia
- Chronic heart failure
- Neurological or neurosurgical cause for admission
- Trauma
- Respiratory failure
- Cardiology
- Neurological complication
- Cardiological complication
- Haematological complication
- Surgical complication

Less important
- Planned surgery
- Visceral surgery
- Chronic renal disease
- Living alone

From Conti M, Friolet R, Eckert P, et al. Home return 6 months after an intensive care unit admission for elderly patients. *Acta Anaesthesiol Scand*. 2011;55:387–393, with permission.

ASSESSMENT FOR ADMISSION

Premorbid functionality and the severity of co-morbid illnesses are of paramount importance when deciding on an elderly patient's suitability for admission. This must be put in the context of the acute insult and an analysis of whether the disease process is reversible, and if the patient is salvageable. If not, then the application of intensive care is likely to impose a physical and mental burden on the patient and their family that cannot be justified by the likely negative outcome. Objective decision making is problematic, and it is worth noting that physicians may overestimate the mental and functional status of patients accepted for admission and underestimate it for those whose admission is rejected.[59] Age has little role to play in this decision other than its association with physiological decline and the acquisition of co-morbidity. Further data may enable more accurate risk prediction systems to be created, thereby enhancing informed doctor–patient dialogue on the outcome. It is also worth remembering that many elderly patients will have one form or another of advanced directive.

HISTORY

This should involve speaking to the patient or, if impossible, to their relatives to make an assessment of their previous functionality physically and mentally. Establish whether co-morbidities are present and if so how severe. Determine whether the patient is living at home or in a home and how independent he/she is. Living in a nursing home may sometimes, but not always, be a surrogate for significant functional impairment.[54] In the elderly nursing home population, anaemia, cancer, heart failure, renal failure and chronic obstructive pulmonary disease (COPD) are all related to a poor 1-year outcome. For those with previous hospital admissions, a history of ventilation is also a potentially important feature. There is a need to know the physical and mental trajectory over the last few months or years, which may indicate significant functional decline. Details relating to level of activity (house, room, chair or bed bound) are powerful indicators (Box 12.3).

Box 12.3 History

Where do they live – at home or in care?
Independence – how much support?
Mobility – shopping, walking
Memory – confusion, sleeping pattern
Previous hospital admissions – in particular, ventilation or chronic renal failure
Co-morbidity – respiratory, cardiology and neurology, but also arthritis and mobility
Drugs
Patient's preferences if known

CLINICAL SIGNS

The general habitus is revealing. Posture, muscle bulk, or more often wasting, and the condition of the skin all help indicate long-term physical well-being or otherwise. Ill health is a potent cause of self-neglect, so the state of the teeth, the lower legs and the feet are very important indicators. Peripheral oedema and infection indicate potential co-morbidities, while chest wall shape may suggest chronic airways disease. Movement and agility are less easily evaluated in acute conditions, but again some impression can be gained by the factors above. Likewise, mental acuity may be difficult to assess in the acute situation.

All of these come together to provide a picture of the level of normal functionality and the degree of co-morbid illnesses, and how they may be contributing to the acute presentation. Then the acute nature of the presentation needs to be evaluated and its reversibility taken in the context of the other problems. The patient's preferences, either declared or previously informed, are a very important part of this assessment. Most importantly, no individual part of this should overwhelm all other considerations, and age itself is the least relevant factor.

TREATMENT INTENSITY

Elderly patients now present more frequently, have fewer co-morbidities and are more acutely unwell than in the past. They are also more likely to undergo more intensive treatment and are more likely to survive, although the intensity of their treatment may not match that offered to younger patients.[60,61] The conclusion is that high-intensity

treatment is appropriate and can produce good results, but careful patient selection is key. In a study that followed more than 1 million elderly patients after a diagnosis of serious illness, half were admitted to the ICU at some point and, of these, two-thirds were still alive 6 months later.[11] However, 3% of this cohort accounted for 23% of ICU usage.

In terms of cost effectiveness, a prospective, observational cohort study in Canada involving patients aged 80 or over demonstrated that the average cost of ICU admission per patient was CAN$31,679 ± $65,879.[62]

EXPECTATIONS AND PREFERENCES

Paradoxically, the aim of treating the elderly in the ICU may be more attainable than with younger patients, as they may already have adapted to a burden of co-morbid disease and disability, and have limited expectations when compared with young previously fit patients. End of life care increasingly occurs in a hospital setting, despite the fact that 86% of patients would prefer to die at home; therefore the level of medical intervention that elderly patients would want is relevant. Only 16% would take life-prolonging drugs if they made them feel worse, and most would want palliation even if it shortened life. Most would not want to be put on a ventilator to gain a week of life, and the numbers were similar if it were for a month of extra life.[63] Of those octogenarians who survived the ICU, half declared they would not want ICU treatment again if it were required.[64] However, one must be careful about making assumptions in this group of patients. The SUPPORT study showed a poor understanding by physicians of patients' preferences[65] and further declared that, despite the fact that more than half of over-70-year-olds would want cardiopulmonary resuscitation (CPR), most physicians substantially underestimated this.[66]

In 1999, Singer and colleagues identified the following as being most important to patients:

- receiving adequate pain and symptom management
- avoiding inappropriate prolongation of dying
- achieving a sense of control
- relieving burden on others
- strengthening their relationship with loved ones.[67]

END OF LIFE

Death in the ICU is usually through some form of withdrawal. Only 10% of patients dying in the ICU die through failed CPR. Limitation of life support is very common, as is withdrawing or withholding treatment. There is huge variation in practice between countries, not only in the decision process but also in the issuing of 'Do Not Resuscitate' orders, and the modes of withdrawal and withholding treatment.[68]

Patient preferences are very important, as is physician recognition of medical futility. The key to this area of management is (1) a clear view of what the ICU is intended to provide; (2) an understanding of whether the goals are achievable; and (3) acceptance that subjecting a patient and their family to the unpleasant rigors of the ICU in the sure knowledge that it will achieve no useful outcome is unacceptable. These determinations must be made objectively.

CONCLUSION

The APACHE score demonstrates that most predictive power for outcome is derived from the acute physiological condition; a much smaller component was the admission disease (13.6%) and age (approximately 7%).[51] The nature of the acute condition and the severity of co-morbid disease play a far greater part than the known physiological changes that accompany ageing, and thus absolute age itself. The reversibility of these factors should guide management, and this approach is the same for any patient of any age. It is more likely that an older patient will have advance directives and will have already voiced their personal preferences.

A simplistic view is that intensive care entails reversing an acute episode with the intention of returning the patient to the position they were in before that episode, or close to it. The majority of treatment is supportive and provides the physiological reserve that the elderly patient is likely to have lost until it can be regained. Those with less reserve will need more support. The patient will invariably need a certain amount of physical reserve to meet the challenges of the treatment and the recovery. The decision to use the ICU requires acknowledgement that the ICU has negative as well as positive aspects, and that it can be a very unpleasant experience with far-reaching sequelae, both physical and psychological, for patients and relatives. Justification is provided by a good outcome, so it is implicit that the opinion at the time of admission is that full recovery is possible or indeed probable. As in every other population, appropriate use of intensive care can produce impressive results, but inappropriate use can be disastrous for the patient and their family. Age itself is not a contraindication.

REFERENCES

1. Roebuck J. When does old age begin? The evolution of the English definition. *J Soc Hist*. 1979;12: 416–428.
2. Office for National Statistics. *National life tables, UK*; 2013–2015. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/20132015.
3. Office for National Statistics. *Estimates of the very old (including centenarians), UK*; 2002 to 2015. https://www.ons.gov.uk/peoplepopulationandcommunity/

birthsdeathsandmarriages/ageing/bulletins/estimatesoftheveryoldincludingcentenarians/2002to2015.
4. Office for Budget Responsibility. *Fiscal sustainability report*; 2012. http://budgetresponsibility.independent.gov.uk/fiscal-sustainability-report-July-2012.
5. Office for National Statistics. *What does the 2011 census tell us about older people*. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/ageing/articles/whatdoesthe2011censustellusaboutolderpeople/2013-09-06.
6. BMJ. *News, in brief*. 2012344; e772. http://www.bmj.com/content/bmj/344/bmj.e772.full.pdf.
7. Kulkarni SC, Levin-Rector A, Ezzati M, et al. Falling behind: life expectancy in US counties from 2000 to 2007 in an international context. *Popul Health Metr*. 2011;9:16.
8. Bagshaw SM, Webb SA, Delaney A, et al. Very old patients admitted to intensive care in Australia and New Zealand: a multi-centre cohort analysis. *Crit Care*. 2009;13:R45.
9. Wunsch H, Angus DC, Harrison DA, et al. Variation in critical care services across North America and Western Europe. *Crit Care Med*. 2008;36:2787–2793.
10. Wunsch H, Linde-Zwirble WT, Harrison DA, et al. Use of intensive care services during terminal hospitalizations in England and the United States. *Am J Respir Crit Care Med*. 2009;180:875–880.
11. Iwashyna TJ. Critical care use during the course of serious illness. *Am J Respir Crit Care Med*. 2004;170:981–986.
12. Martin JE, Sheaff MT. The pathology of ageing: concepts and mechanisms. *J Pathol*. 2007;211:111–113.
13. Priebe HJ. The aged cardiovascular risk patient. *Brit J Anaes*. 2000;85:763–778.
14. Suttner SW, Piper SN, Boldt J. The heart in the elderly critically ill patient. *Curr Opin Crit Care*. 2002;8:389–394.
15. Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. *N Engl J Med*. 2012;366:321–329.
16. Kannel WB, Dannenberg AL, Abbott RD. Unrecognized myocardial infarction and hypertension: the Framingham Study. *Am Heart J*. 1985;109:581–585.
17. Vaporciyan AA, Correa AM, Rice DC, et al. Risk factors associated with atrial fibrillation after noncardiac thoracic surgery: analysis of 2588 patients. *J Thorac Cardiovasc Surg*. 2004;127:779–786.
18. Menaker J, Scalea TM. Geriatric care in the surgical intensive care unit. *Crit Care Med*. 2010;38:S452–S459.
19. Marik PE. Management of the critically ill geriatric patient. *Crit Care Med*. 2006;34:S176–S182.
20. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. *Clin Interv Aging*. 2006;1:253–260.
21. Behrendt CE. Acute respiratory failure in the United States: incidence and 31-day survival. *Chest*. 2000;118:1100–1105.
22. Esteban A, Anzueto A, Frutos F, et al. Mechanical Ventilation International Study Group. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA*. 2002;287:345–355.
23. Wunsch H, Guerra C, Barnato AE, et al. Three-year outcomes for Medicare beneficiaries who survive intensive care. *JAMA*. 2010;303:849–856.
24. Garland A, Dawson NV, Altmann I, et al. SUPPORT Investigators. Outcomes up to 5 years after severe, acute respiratory failure. *Chest*. 2004;126:1897–1904.
25. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc*. 1985;33:278–285.
26. Ronco C, McCullough PA, Anker SD, et al. Acute Dialysis Quality Initiative (ADQI) consensus group. Cardiorenal syndromes: an executive summary from the consensus conference of the Acute Dialysis Quality Initiative (ADQI). *Contrib Nephrol*. 2010;165:54–67.
27. Pascual J, Liaño F. Causes and prognosis of acute renal failure in the very old. Madrid Acute Renal Failure Study Group. *J Am Geriatr Soc*. 1998;46:721–725.
28. Schiffl H, Fischer R. Five-year outcomes of severe acute kidney injury requiring renal replacement therapy. *Nephrol Dial Transplant*. 2008;2:2235–2241.
29. Akposso K, Hertig A, Couprie R, et al. Acute renal failure in patients over 80 years old: 25-years' experience. *Intensive Care Med*. 2000;26:400–406.
30. Ishani A, Xue JL, Himmelfarb J, et al. Acute kidney injury increases risk of ESRD among elderly. *J Am Soc Nephrol*. 2009;20:223–228.
31. Aymanns C, Keller F, Maus S, et al. Review on pharmacokinetics and pharmacodynamics and the aging kidney. *Clin J Am Soc Nephrol*. 2010;5:314–327.
32. Olmez S, Gümürdülü Y, Tas A, et al. Prognostic markers in cirrhotic patients requiring intensive care: a comparative prospective study. *Ann Hepatol*. 2012;11:513–518.
33. McNicoll L, Pisani MA, Zhang Y, et al. Delirium in the intensive care unit: occurrence and clinical course in older patients. *J Am Geriatr Soc*. 2003;51:591–598.
34. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med*. 2013;369:1306–1316.
35. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*. 2004;291:1753–1762.
36. van den Boogaard M, Pickkers P, Slooter AJ, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. *BMJ*. 2012;344:e420.
37. Berger MJ, Doherty TJ. Sarcopenia: prevalence, mechanisms, and functional consequences. *Interdiscip Top Gerontol*. 2010;37:94–114.
38. Elmadfa I, Meyer AL. Body composition, changing physiological functions and nutrient requirements

of the elderly. *Ann Nutr Metab*. 2008;52(suppl 1): 2–5.
39. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. *Lancet*. 2013;381(9868):752–762.
40. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173(5):489–495.
41. Hope AA, Hsieh SJ, Petti A, et al. Assessing the usefulness and validity of frailty markers in critically ill adults. *Ann Am Thorac Soc*. 2017;14(6): 952–959.
42. Pugh RJ, Thorpe CM, Subbe CP. A critical age: can we reliably measure frailty in critical care? *Crit Care*. 2017;21:121.
43. Bagshaw SM, Stelfox T, McDermid RC, et al. Association between frailty and short- and long-term outcomes among critically ill patients: a multicenter prospective cohort study. *CMAJ*. 2014;186(2):E95–E102.
44. Malhotra S, Karan RS, Pandhi P, et al. Drug related medical emergencies in the elderly: role of adverse drug reactions and non-compliance. *Postgrad Med J*. 2001;77:703–707.
45. Alexander KP, Anstrom KJ, Muhlbaier LH, et al. Outcomes of cardiac surgery in patients > or = 80 years: results from the National Cardiovascular Network. *J Am Coll Cardiol*. 2000;35:731–738.
46. Liu LL, Leung JM. Predicting adverse postoperative outcomes in patients aged 80 years or older. *J Am Geriatr Soc*. 2000;48:405–412.
47. National Confidential Enquiry into Patient Outcome and Death (NCEPOD). *An Age Old Problem: A review of the care received by elderly patients undergoing surgery*; 2010. London: http://www.ncepod.org.uk/2010report3/downloads/EESE_fullReport.pdf.
48. Ball IM, Bagshaw SM, Burns KE, et al. Outcomes of elderly critically ill medical and surgical patients: a multicenter cohort study. *Can J Anaesth*. 2017;64(3):260–269.
49. Pavoni V, Gianesello L, Paparella L, et al. Outcome and quality of life of elderly critically ill patients: an Italian prospective observational study. *Arch Gerontol Geriatr*. 2012;54:e193–e198.
50. Fassier T, Duclos A, Comte B, et al. Decision to forgo life-sustaining therapies for elderly critically ill patients is a multidisciplinary challenge. *Intensive Care Med*. 2011;37:175–176.
51. Sligl WI, Eurich DT, Marrie TJ, et al. Age still matters: prognosticating short- and long-term mortality for critically ill patients with pneumonia. *Crit Care Med*. 2010;38:2126–2132.
52. Roch A, Wiramus S, Pauly V, et al. Long-term outcome in medical patients aged 80 or over following admission to an intensive care unit. *Crit Care*. 2011;15:R36.
53. Heyland DK, Garland A, Bagshaw SM, et al. Recovery after critical illness in patients aged 80 years or older: a multi-center prospective observational cohort study. *Intensive Care Med*. 2015;41(11):1911–1920.
54. Bagshaw SM, Webb SA, Delaney A, et al. Very old patients admitted to intensive care in Australia and New Zealand: a multi-centre cohort analysis. *Crit Care*. 2009;13:R45.
55. Yende S, Angus DC, Ali IS, et al. Influence of comorbid conditions on long-term mortality after pneumonia in older people. *J Am Geriatr Soc*. 2007;55: 518–525.
56. Vogt KN, Maruscak A, Swart M, et al. Outcomes of elderly trauma patients admitted to an intensive care unit. *J Trauma Care*. 2015;1(1):1003.
57. Dowdy DW, Eid MP, Sedrakyan A, et al. Quality of life in adult survivors of critical illness: a systematic review of the literature. *Intensive Care Med*. 2005;31:611–620.
58. Conti M, Friolet R, Eckert P, et al. Home return 6 months after an intensive care unit admission for elderly patients. *Acta Anaesthesiol Scand*. 2011;55: 387–393.
59. Rodríguez-Molinero A, López-Diéguez M, Tabuenca AI, et al. Physicians' impression on the elders' functionality influences decision making for emergency care. *Am J Emerg Med*. 2010;28:757–765.
60. Lerolle N, Trinquart L, Bornstain C, et al. Increased intensity of treatment and decreased mortality in elderly patients in an intensive care unit over a decade. *Crit Care Med*. 2010;38:59–64.
61. Boumendil A, Aegerter P, Guidet B, et al. Treatment intensity and outcome of patients aged 80 and older in intensive care units: a multicenter matched-cohort study. *J Am Geriatr Soc*. 2005;53:88–93.
62. Chin-Yee N, D'Egidio G, Thavorn K, et al. Cost analysis of the very elderly admitted to intensive care units. *Crit Care*. 2017;21:109.
63. Barnato AE, Herndon MB, Anthony DL, et al. Are regional variations in end-of-life care intensity explained by patient preferences?: a study of the US Medicare population. *Med Care*. 2007;45:386–393.
64. Garrouste-Orgeas M, Timsit JF, Montuclard L, et al. Decision-making process, outcome, and 1-year quality of life of octogenarians referred for intensive care unit admission. *Intensive Care Med*. 2006;32:1045–1051.
65. The SUPPORT Principal Investigators. A controlled trial to improve care for seriously ill hospitalized patients. The study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT). *JAMA*. 1995;274:1591–1598.
66. Hamel MB, Teno JM, Goldman L, et al. Patient age and decisions to withhold life-sustaining treatments from seriously ill, hospitalized adults. SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment. *Ann Intern Med*. 1999;130:116–125.
67. Singer PA, Martin DK, Kelner M. Quality end-of-life care: patients' perspectives. *JAMA*. 1999;281:163–168.
68. Yaguchi A, Truog RD, Curtis JR, et al. International differences in end-of-life attitudes in the intensive care unit: results of a survey. *Arch Intern Med*. 2005;165:1970–1975.

13

Team-based health care delivery

Gerry O'Callaghan

The concept of health professionals working in collaboration as part of multidisciplinary teams focused on the requirements of individual patients is a well-established historical tradition.[1] This chapter outlines the benefits of team participation to the individual, the team and the health care delivery organisation, (unit or department and hospital). The characteristics of successful teams and examples of effective team-based interventions are described in the context of intensive care medicine or comparable acute care delivery settings.

The specific interventions that have been applied to the intensive care setting, the composition of intensive care teams, their function and effect on patient outcome are explored. The objective of this overview is to provide practitioners of intensive care medicine with an opportunity to reflect on the variety of ways we work in teams as part of our daily professional activities.

WHAT IS A TEAM?

> *'If you want to run fast, run alone; if you want to run far, run together.'*
>
> (An African Proverb)

Shared purpose is the foundation of team success.[2] A team is defined as a group of people with clearly defined roles and responsibilities committed to a common purpose or task. The individuals who participate in a team share common values and commit to shared behaviours, for example low-tidal-volume ventilation for acute respiratory distress syndrome (ARDS) or use of a checklist prior to a procedure. The result of their collective effort is expected to produce more than they could working as individuals. The identity of the team is visible from both within and outside (Box 13.1).

Modern intensive care medicine is undoubtedly a challenge of both skill and endurance, with the latter increasingly described as resilience. While we benefit from decades of investment in education and training focused on required knowledge, we have only recently begun to interrogate the most effective strategies for the translation of this knowledge into practice. Specifically, what workplace characteristics and evidence-based practices are of greatest benefit to both patients and practitioners? The increasing array of investigations and complex treatments for critical illness is accompanied by increases in both the number and the diversity of team members; in this context it is of value to understand the fundamentals of team dynamics. Additional factors are emerging roles for non-physician providers and participation by intensive care personnel in roles that extend beyond the traditional physical boundaries of the intensive care unit (ICU).

The introduction of advanced practice nursing roles provided insight into the lack of role clarity and understanding of both traditional and new roles within intensive care teams and has led to a deeper understanding of the workforce competencies necessary to adopt team-based practices.[3] This poses the interesting question of whether successful adoption of team-based practices at a unit level is a reflection of these pre-existing competencies of communication and appreciation of professional roles, or confirmation that such practices and behaviours can be learned and implemented by motivated professionals. There is insufficient evidence to answer this question in the intensive care context; however, it is critical to develop the necessary competencies in the workforce prior to the adoption of team-based programmes on a significant scale.

Fig. 13.1 illustrates the diversity of individuals and the skills involved in caring for critically ill patients. ICU personnel include medical and nursing staff, plus allied health including physiotherapists, respiratory therapists, dieticians and pharmacists. Support personnel include clerks, cleaners and others. External ICU is almost limitless including physicians, surgeons, infectious disease physicians and radiologists. Although local factors influence the composition and profile of these categories, the variety and complexity are constant.

The composition of critical care teams has wide regional, national and international variability. Non-physician providers are more common in North America than in the United Kingdom, Europe or Australia, where advanced nurse practitioner roles are more common. Such roles are well established in paediatric and neonatal medicine and are often an adjunct rather than an alternative to physicians in training,

ABSTRACT

Team-based practices and behaviours are now well established in the intensive care context and have delivered clear benefits to patients, health professionals and delivery organisations. This chapter explores the theory of health care teams and how they work, as well as practical examples of successful practices and how to implement them. The overview aims to increase the understanding of the variety of teams within current intensive care practice, their relevance to particular activities and how an individual practitioner might identify the optimal approach to achieve a particular outcome. Clinicians and researchers interested in team work and patient safety have turned their attention to the challenges of contemporary intensive care practice, such as the delivery of complex therapies, cognitive biases, workforce diversity, conflict, distress and burnout, and explore team structure and function as a strategy to address these issues.

KEYWORDS

Team
teamwork
communication
situational awareness
simulation
leadership
patient safety
task management
organisational change

Box 13.1 Characteristics of a team

Common goals
Shared behaviours and values
Visible identity
Clear understanding of roles and responsibilities
Greater collective than individual effectiveness or potential
Understanding of shared tools and artefacts, such as vocabulary, skills, knowledge
Mutual trust and respect: solidarity

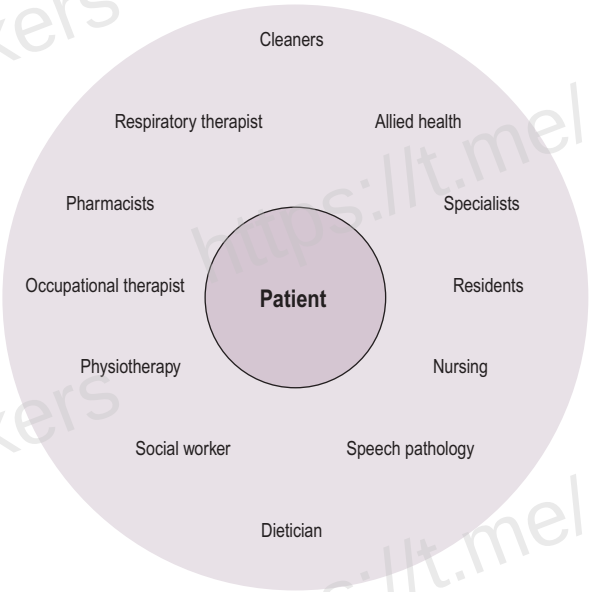


Figure 13.1 The clinical and ancillary care of patients in intensive care is provided by large diverse teams of health care workers. The size, diversity, variability and complexity of these teams make common training in non-technical skills highly desirable.

resulting in improved staffing levels and continuity of patient care.[4] More than a quarter of adult academic ICUs in the United States have physician assistants, and more than half have nurse practitioners as physician extenders.[5] They have a precisely defined scope of practice, may order tests, prescribe medications and perform diagnostic and therapeutic procedures under the supervision or on behalf of a nominated responsible physician or surgeon. Workforce planning in a recent review of the impact of non-physician providers on patient outcomes in critical care indicates this is likely to remain the case for the foreseeable future, and there is no evidence that non-physician providers are less safe or effective. Non-physician providers also contribute important increased capacity in additional areas of intensive care activity, such as quality improvement.[6]

The increasing diversity of clinical roles and complexity of therapies (e.g. extracorporeal membrane oxygenation) require frameworks for improved communication and coordination as well as role delineation. This view has been endorsed for over a decade by a wide range of professional, academic and government bodies, such as The Institute of Medicine, which recommended in *To Err is Human, Building a Safer Health System* that those who work in teams should train in teams.[7] There is an emerging literature that demonstrates improved outcomes across a range of parameters following implementation of various team-based interventions.[1] These innovations are examined later in this chapter.

Fig. 13.2 illustrates the varying and often asynchronous schedule of shift changes between nursing, resident and intensive care physicians challenging safe and effective continuity of patient care. The SBAR (situation–background–assessment–recommendation) approach to clinical handover is an early example of a shared behaviour to improve communication; it is an explicit team-based practice that facilitates continuity of care and effective transfer of information between teams.[8] Clinical handover is a common cause

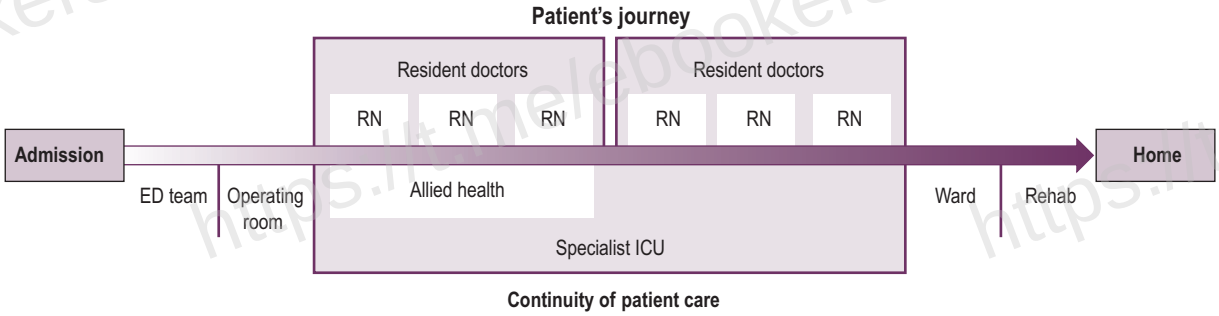


Figure 13.2 Continuity of patient care is the seamless provision of care, transfer of information and communication with relevant stakeholders over time and across multiple locations during a patient's hospitalisation or illness. *ED*, Emergency department; *ICU*, intensive care unit; *RN*, registered nurse.

of adverse events and malpractice claims. It is often of poor quality, infrequently written and generally perceived to be inadequate or unhelpful.[9] Other early examples of widely adopted team-based behaviours are the use of PDSA (plan-do-study-act) cycles and process mapping as tools in clinical practice improvement methodology, checklists, protocols, huddles and briefs.[10] The process of developing and implementing these common ways of working requires multidisciplinary collaboration and creates a shared sense of purpose and team identity. In addition, the shared mental model, which emerges from the specific context in which the proposed intervention is to be applied, consolidates team identity during the adoption process. These shared practices are now common practice in many ICUs and contribute to a shared sense of identity and purpose.

Patient safety is the main driver for adopting team-based interventions in health care following improvements in passenger safety achieved by the airline industry using a team training approach called Crew Resource Management (CRM), which is a simulation-based programme that teaches and assesses individual performance of the 'non-technical skills' necessary for effective delivery of complex technical tasks, particularly in high-stress situations. These can be defined as 'the cognitive, social and personal resource skills that complement technical skills, and contribute to safe and efficient task performance'.[11] The framework has four elements:

- *Situation awareness:* Understanding and anticipating the impact of the specific situation on the performance of workers and patient outcome. For example, requesting further information or using check-back to validate physiological information.
- *Decision making:* The ability to identify options, incorporate risk assessment and re-evaluate progress, if necessary recognising failure and changing direction in a timely way.
- *Team work and leadership:* Cooperative collaboration in complex task delivery in your assigned role; explicitly identify and claim the role that is appropriate to your level of skill and experience. This includes information sharing, seeking assistance, supporting fellow team members and coordinating efforts.
- *Task management:* Planning, preparing and prioritising the actions that need to be taken, identifying the resources necessary to achieve the planned tasks and performing them to an appropriate standard.

A training programme based on this approach has been developed for anaesthetists called Anesthetists' Non-Technical Skills (ANTS). Extensive task analysis describing the language and behaviours specific to situations encountered by anaesthetists formed the basis for identifying markers used for the assessment of good or bad performance. (For details see the website address www.abdn.ac.uk/iprc/ants.)

Rolling out a promising innovation is challenging:

1. It is essential to have a critical mass of course providers who have a sound understanding of the psychology of human performance, the methodology and language of non-technical skills and the teaching and assessment of colleagues and trainees. Where this is not the case there are unacceptable levels of inter-rater reliability and accuracy.[12]
2. Sustainability of benefit has been shown where training is provided in a similar manner to the CRM programmes in the aviation industry.[13] The authors' recommendation is for a minimum ANTS course length of 2 days to acquire sufficient knowledge and the techniques required.
3. This provides an insight as to why it is difficult to demonstrate the benefit to patient outcomes when few health care providers have the skills or experience necessary to plan and measure the quantum of team building required to address the relevant clinical issue (Box 13.2).

The quantity and quality of team interactions can be measured; face-to-face interactions are the most valuable, email or texting the least. Team behaviours and patterns of communication are consistent across different contexts and compositions (i.e. different industries including health care workers and a variety of different team sizes).[14] Individual talent and reasoning are less important than adopting successful communication patterns.

Successful teams share several defining characteristics:

1. Everyone on the team talks and listens in roughly equal measure, keeping contributions short.

Box 13.2 Characteristics of high-performing teams

Leadership that encourages participation from other team members
Effective decision making, clear, transparent, timely and consultative
Open and clear communication
Valuing diversity, welcoming diversity of experience, culture and knowledge
Mutual trust, committing to shared actions and strategies
Managing conflict – dealing with conflict openly and transparently, avoiding the gradual build-up of internal tensions and grudges
Clear goals that have personal meaning and relevance, which are supported by sharing data and resources
Defined roles and responsibilities – team members understand what they must do and must not do
Coordinative relationship, strong bonds between team members supporting frequent interactions
Positive atmosphere, team culture that is open, transparent and positive, and believes in the reality of success

Source: https://en.wikipedia.org/wiki/High-performance_teams.

2. Members face one another and their conversations and gestures are energetic.
3. Members connect directly with one another and not just with the team leader.
4. Members carry on back channel or side conversations within the team.
5. Members periodically break, go outside the team and bring information back.

Successful team participation can be learned, and advantage can be taken of the multiple opportunities that present themselves for team working. Intensive care physicians are generally expected to take on leadership roles, but few physicians receive any formal training in this area.

A simple checklist can be used for assessing team interactions with colleagues:

- Are my co-workers contributing to ward rounds and patient-centred discussions?
- Do they speak generally or just to one other person?
- Are individuals removing themselves from the group or not facing other team members when they are speaking or listening?
- Am I or the other leadership figures too dominant, speaking too much or too loudly?
- Does everyone get to finish sentences or are people interrupted and cut off?
- Am I (we) happy for any individual team member to speak on behalf of the team?

This final question is a test of mutual trust and respect within the team because it involves accepting reputational risk on behalf of co-workers.

In order for team-based interventions to positively contribute to patient safety and the wellbeing of health care workers, it is important for the host organisation (usually a hospital) to be receptive. Organisations' attempts to create a high-performance team culture may fail because of:

- Insufficient appreciation of the resolve, expertise and resources required to achieve cultural change
- Advocacy for team-based training being promotional rather than a sincere commitment
- Provision of insufficient time, opportunity, resources or executive support.

Similar issues have been demonstrated in the implementation of clinical therapeutic guidelines.

NECESSARY OR DESIRABLE ORGANISATIONAL CHARACTERISTICS THAT SUPPORT EFFECTIVE IMPROVEMENT IN CLINICAL PRACTICE AND PATIENT OUTCOMES

Bohmer characterised the four habits of high-value health care organisations[15] that perform well in terms of the ratio of long-term outcomes to costs:

1. *Specify and plan in advance:* with decisions based on predetermined explicit criteria
2. *Deliberate design of infrastructure:* including clinical microsystems that align physical environment, business process and clinical pathways in well-defined patient populations
3. *Measurement and oversight targeting:* by predefined metrics, quality and safety goals, which inculcates both accountability and performance
4. *Self-study:* using measurements so that knowledge, data and clinical information can be used not only for the assurance of best evidence-based practices but also to identify deviations. Information is shared and not considered to be the property of individuals or departments.

Organisational readiness is a prerequisite to building high-performance critical care teams.

TYPES OF TEAM

A *clinical microsystem* is the most fundamental unit of health care delivery that addresses the needs of a population of patients. It is the dynamic integration of personnel, clinical and support staff, technology, information, care and business processes.[16] The participation of all those who have direct patient care responsibilities is implicit (Fig. 13.3). Participation is compulsory; however, most participants will also be involved in other team types within this structure. The choice/volition of the individual within teams is variable. The greater the clinical focus of the team or activity

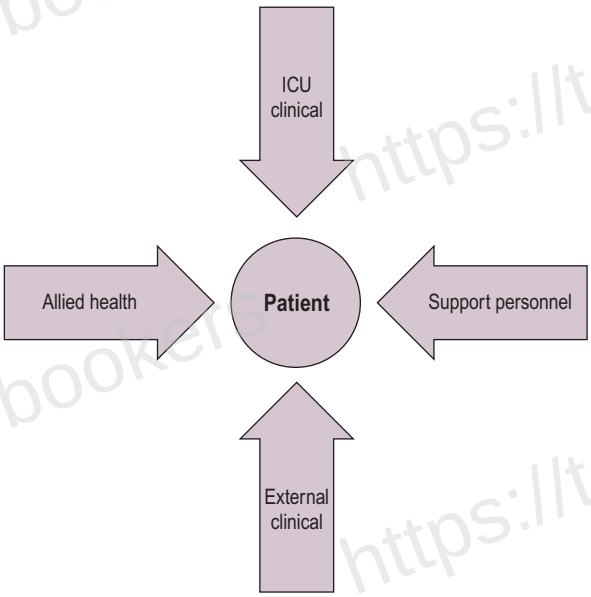


Figure 13.3 Clinical microsystems are the most fundamental units of health care delivery that address the needs of a specific population of patients. This system includes personnel, procedures, business processes and infrastructure. *ICU*, Intensive care unit.

the less choice individuals have in terms of choosing to participate. Resuscitation, diagnosis and treatment are core team activities, while research, safety and quality, and administration provide opportunity for choices that align with the interests and expertise of the individual. Collaborations beyond the immediate clinical microsystem in the hospital, professional, interdisciplinary and academic worlds have the greatest degree of choice. Team contexts are relevant to the broad understanding of health care teams.

CRITICAL INCIDENT RESPONSE TEAMS

Medical emergency teams, code and trauma teams need skills designed to meet the crisis, such as airway management, vascular access and trauma management. Teams may be nurse or physician led, are highly focused on a particular activity and often include individuals who interact infrequently owing to the rarity of certain events or rostering practices. Team membership is highly dynamic; opportunities for training are limited; and the level of familiarity with local procedures, policies and organisational characteristics varies with the individual team member (Fig. 13.4).

Leadership by an easily identifiable authority figure, who has both accountability and responsibility for the outcome, enables the application of well-defined clinical pathways or protocols. This leadership is variously described as top-down, autocratic or transactional[17] and has been demonstrated to improve both process metrics and patient outcomes (Fig. 13.5).

ACTIVITY- OR CONTEXT-RELATED TEAMS

These may be described as committees, working groups or parties with variable degrees of formality and stability. These range from ad hoc conversations or correspondence between senior clinicians to formal safety and quality committees with clear reporting protocols and accountabilities. The latter has defined terms of reference, meets regularly, involves clinical governance, keeps records and may be multidisciplinary from both within and outside the ICU. They may be temporary, such as implementing a new treatment, or consist of well-established groups responsible for monitoring and communicating clinical outcomes to their peers on a range of clinical indicators. Fig. 13.6 illustrates examples of such clinical contexts.

Critical incident and context teams (see Fig. 13.6) require and benefit from different styles of leadership. Leadership characteristics include inclusiveness, proactive mentorship of less experienced or confident team members, providing a personal example of ethical behaviour and maintaining the focus of team

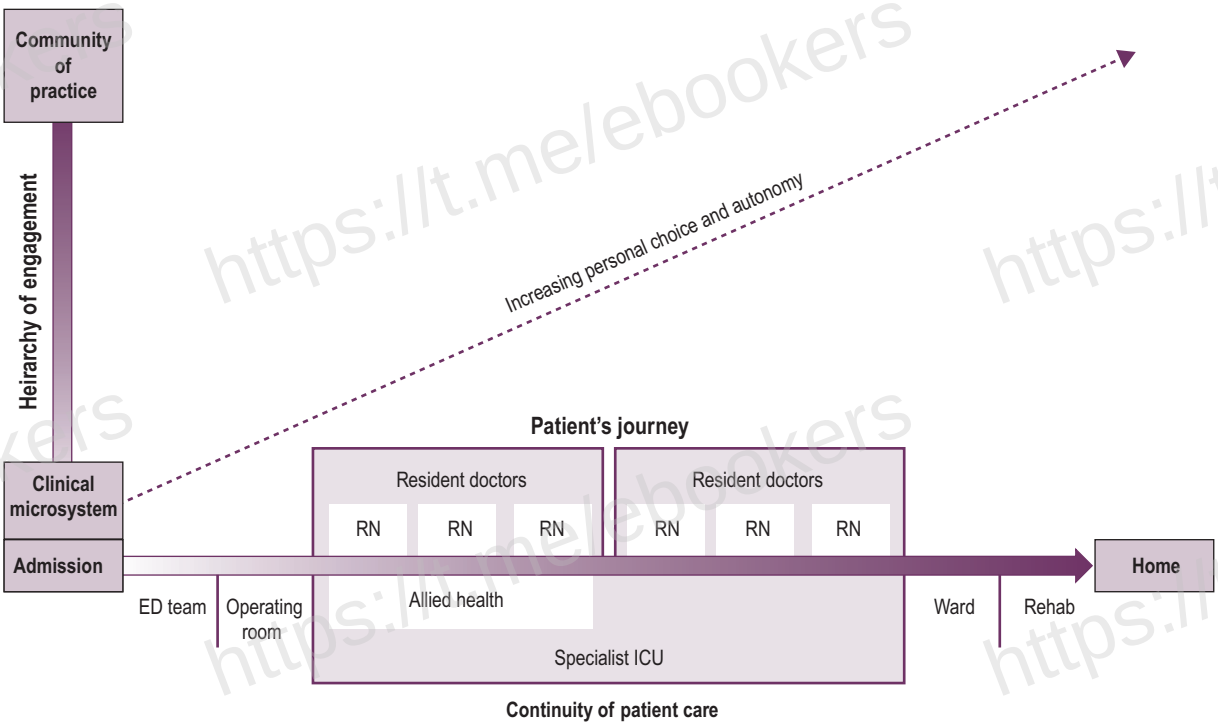


Figure 13.4 The hierarchy of individual integration of team participation represents the relationship between the interests and skills of an individual and the necessary activities that support a clinical microsystem, such as an intensive care unit *(ICU)*. Activities that are not directly related to patient care provide an opportunity for personnel to choose those activities that are of greatest professional interest. *ED*, Emergency department; *RN*, registered nurse.

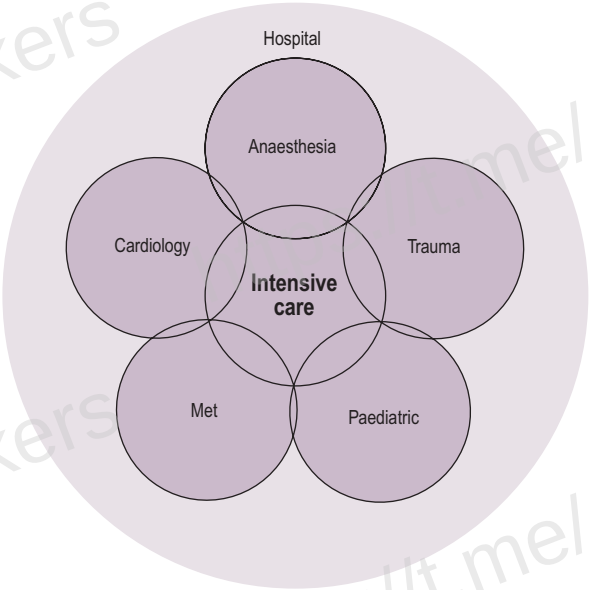


Figure 13.5 Critical incident teams are ad hoc teams of individuals from a range of clinical and professional backgrounds that assemble to meet the clinical needs of a patient experiencing acute physiological deterioration in an acute hospital setting. *Met*, Medical emergency team.

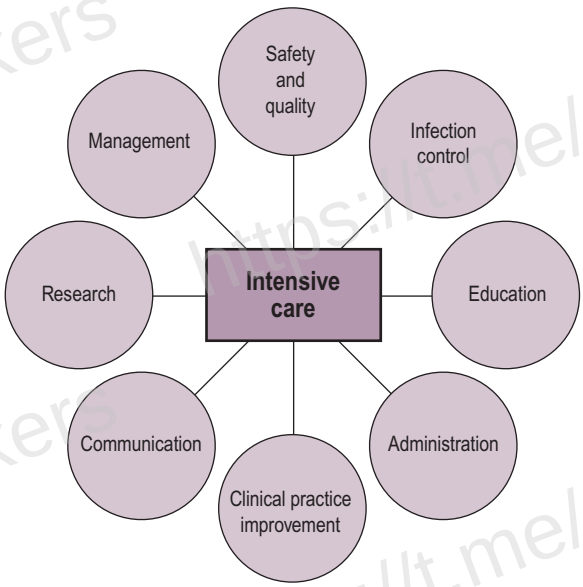


Figure 13.6 Context- or activity-based teams are comprised of individuals from a range of clinical and professional backgrounds who are collectively engaged in administrative, educational and professional activities that support clinical care.

members on the shared goal or purpose. This type of leadership is variously described as democratic, consensus driven or transformative[17] and is associated with improved staff commitment and participation in safety initiatives. The challenge is choosing the most appropriate leadership style for each situation. Adaptive leadership is the capability to deliberately move between a transactional approach for task-based time-critical goals and transformative approaches to create meaning, clarify purpose and challenge cultural assumptions or norms.

Long-term projects with outcomes over several years with strong connections to external colleagues and organisations require a different type of team. Members of these teams may not recognise themselves as participating in teams as activities are informal and self-organising, are often created by the commonality of learning activities and are consolidated through social interactions. Examples include research collaboration between clinicians working with laboratory-based scientists and other experts, often from disparate geographical locations. The Community of Practice model first described by Wenger[18] can be used to describe this type of group. The driving characteristics of working collaborations are a shared knowledge or practice domain, a workplace-based context of learning and fluctuating levels of participation. Professional development activities combined with social interaction form an ongoing mechanism that supports professional collaborations and exchange of information, such as best practice tools. This formal facilitation of social cohesion in professional groups is part of the community of practice model.

It is useful to reflect on the numerous types of teams to which intensive care practitioners may belong in order to:

- select the most suitable model for the assigned goal
- measure the overall impact on patient outcomes, staff satisfaction or other parameters
- assess and prioritise workload, taking into account the combination of team-based activities occurring in the ICU.

Effective team-based practices are most commonly described in terms of organisational characteristics or leadership responsibilities; however, this fails to emphasise the benefits of participation to individual team members. These benefits, which are summarised in Box 13.3, result in improved job satisfaction, staff retention, less sick leave, increased productivity and reduced costs.

SPECIFIC TEAM-BASED INTERVENTIONS AND INNOVATIONS

Broadly there are four categories of intervention that have been applied in critical care areas. These overlap

Box 13.3 How team members benefit from team participation

- Opportunity to be heard and for effort to be acknowledged
- Psychological safety
- Clarity of purpose resulting in clear action plans, relevant tools and strategies
- Mechanism to resolve conflict and address underperforming co-workers
- More positive work environments
- Support for professional development
- Improved performance in time-critical stressful situations
- Situational awareness

considerably depending on the programme methodology and content.

1. Leadership
2. Team building
3. Simulation
4. Organisational change.

Leaders are 'visibly responsible and accountable for achieving the goals of an organisation', and are the people on whom patients and colleagues depend to get things done. The style (autocratic vs. democratic) depends on the situation and may change as the situation demands (adaptive leadership). Leadership is the conglomeration of effective behaviours (see Box 13.2) enabling the team to achieve its goal.

In summary, leaders refine and define the team goal; they create a vision and subsequently include the team in the design of the tools and mechanisms to achieve this vision. They do not avoid hard discussions and difficult decisions; they are honest about the effort and commitment necessary. They create an environment where team members feel secure and are willing to contribute. The culture they create is one of psychological safety, which is important because within teams are hierarchies. Hierarchical discrimination is extremely variable and has a definite cultural association, so where there is a high level of respect or fear of authority individuals are extremely unlikely to either challenge or contribute without a specific request or mechanism to do so.

Explicit leadership behaviours, such as task assignment, directing co-workers and check-backs of vital signs are associated with fewer task failures and faster instigation of therapies, such as intubation and defibrillation in emergency situations. Any group implementation of training or clinical practice improvement process by definition creates leadership obligations and opportunities. There is no widespread leadership training intervention applied in the intensive care setting, although several studies demonstrate improved outcomes associated with intensive care specialist-led care.[19] Courses in leadership, management and communication as part of post-graduate training programmes, such as those now mandated by the College of Intensive Care Medicine of Australia and New Zealand, proactively develop competencies for leadership and teamwork.

For example, when the impact of multidisciplinary teams on the 30-day mortality of over 100,000 intensive care patients was assessed, intensive care specialist care combined with multidisciplinary teams was associated with a 16% reduction in mortality, which was consistent across patient cohorts and greater severity of illness.[20] This benefit was similar between intensivist-led care or mandatory consult and multidisciplinary care team input, but the greatest mortality reduction was seen when these were combined. The authors postulate that multidisciplinary rounds improve communication, enhance implementation of agreed daily goals and encourage evidence-based care (e.g. pharmacist participation may reduce drug errors). Effective communication may also reduce length of mechanical ventilation and ICU stay.

A combination of team training, coaching and checklists to instigate communication in the operating room impacted on surgical outcomes.[21] There was an 18% reduction in mortality at the hospitals that implemented the US Medical Team Training programme compared with a 7% reduction at the control hospitals; subsequently, implementation in over 187 sites in the United States resulted in the improved understanding of daily clinical goals following multidisciplinary rounds in the ICU and reduced lengths of ICU stay.[22] The programme requires ongoing support and follow-up at participating sites and mandatory executive support from site administration.

TRAINING

The TeamSTEPPS training tool is focused on improving patient safety by implementing an evidence-based teamwork system to improve communication and teamwork skills among health care professionals.[23] It has been used in paediatric, medical and surgical ICUs to train acute care teams, reducing times to placing patients on extra-corporeal membrane oxygenation (ECMO), and decreasing the nosocomial infection rate[24] Other team-based initiatives have reduced rates of ventilator-associated pneumonia[25] and reduced resuscitation time in trauma situations.[26]

Simulated scenarios can be used to explore, practice and refine the tools of communication, leadership and other team-based behaviours in a clinical context. Simulation may be high or low fidelity depending on the degree of accuracy with which the clinical scenario is replicated. Training may be stand alone, specifically designed and maintained by full-time professional educators or part of a clinical workplace. The important points are:

- participation requires an active choice to collaborate with colleagues

- simulation is an educational tool that has both strengths and limitations
- many common clinical situations in the intensive care setting are suitable for simulation-based training
- most do not require high-fidelity equipment; however, they do require expert and experienced facilitators.[27]

Using case-based or simulation-based learning, there were significant improvements in leadership, team coordination and verbalising situational information in the intervention group, and improved scores for clinical management.[28] Similar results were seen in the paediatric intensive care setting, where most found participation to be of benefit and with a highly effective impact.[29] The authors indicated that there is not only a 6- to 12-month learning curve in programme implementation, but also repeated exposure is necessary to achieve meaningful benefit.

ORGANISATIONAL CHANGE

This is the final area of intervention. It includes teamwork, simulation and leadership training; however, the context in which the team model operates is an important element of the intervention and is formally assessed as part of the change process.[30] The Integrated Team Effectiveness Model illustrates how organisational contexts, such as processes, goals and structure, have a direct effect on team effectiveness. The Breakthrough Collaborative Model uses organisational engagement and team alignment to a particular goal to achieve significant changes in clinical outcomes.[31] This has resulted in a significant increase in the rate of organ donation as measured by both donor identification and consent for donation. Teams use PDSA cycles to implement change in local practices supported by a senior clinical leader. Each team is provided with strategies and tools for change and participates in educational conferences, which allows the more successful strategies to be shared and adopted more broadly. These educational opportunities foster team development and identify clinical leaders. Although effective in accelerating clinical change, these large-scale interventions are expensive and require widespread government, professional and health care organisation support (Box 13.4).

Further consolidation of team-based practice has occurred through partnering with patients and families in the co-design of clinical pathways and other aspects of service delivery in response to national policy and regulatory settings. Similarly, collaboration with policy makers and funders in developing financially sustainable service delivery models also contributes to the habit of working in teams. Not all interprofessional interactions in the ICU conform to the idealised notion of teamwork. Alexanian and colleagues performed an ethnographic observational study in two large ICUs in North America and observed that most interprofessional interactions were more accurately described as collaboration, coordination or networking, and they raise the issue of medical dominance of decision making, which may relate to the particular legal responsibilities of physicians.[32] This study suggests that teamwork in isolation is inadequate to describe the variety of ways health professionals interact in ICU, and further analytic frameworks are required to capture the contextual factors that influence the outcome of improvement interventions.

More recently, clinicians and researchers interested in team work and patient safety have turned their attention to contemporary challenges of intensive care practice, such as cognitive bias in clinical decision making, workforce diversity, conflict, distress and burnout. Team-based practices improve communication, which has been demonstrated to reduce conflict and protect against burnout. Team diversity as described in terms of gender, experience, cultural background, range of disciplines and age groups is a marker of success for innovative thinking and avoids the cognitive trap of group think. This may be important for effective clinical diagnostic decision making. Team stability is recognised as being important to effectiveness and has clear implications for the length of clinical rotations in the ICU, rostering practices and participation in emergency response and outreach teams. All these factors should be considered in the proactive process of team composition, particularly gender balance, which has a positive impact on team performance.

A detailed exploration of the optimal size of the ICU is beyond the scope of this chapter; however, it is important to make the distinction between a social group or network and the individuals/teams embedded in the group. There are cognitive limits to the number of interpersonal relationships that can be effectively sustained by individuals, which should influence the scale or size of organisational structures. The optimal size of teams is intimately related to the nature/complexity of the tasks or activities undertaken (including learning), the stability of membership and the effectiveness of leadership. However, the team is rarely larger than six to eight participants.[33]

Box 13.4 How patients may benefit from team-based health care delivery

Improved continuity of care
Fewer adverse events
Shorter lengths of hospitalisation and mechanical ventilation
Better task delivery in emergency situations
Decreased mortality
Improved family outcomes through better communication

SUMMARY

Team-based innovation in the specific context of high-acuity environments, such as the ICU, is increasing

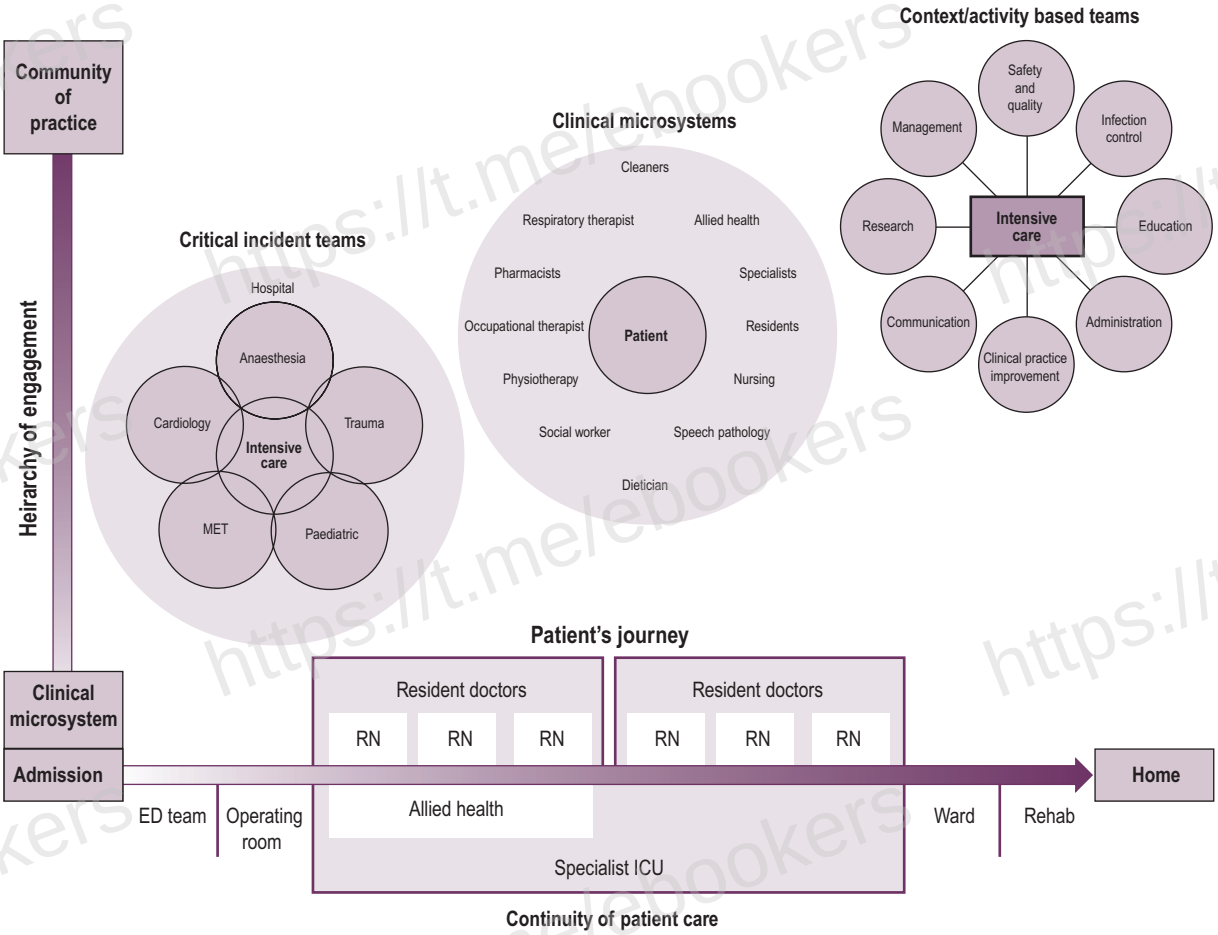


Figure 13.7 Participation in teams that provide specific aspects of clinical care, support professional development and improve quality of care are important articulations of personal preference and autonomy. Such choices are likely to represent important opportunities to increase staff satisfaction and retention, and to increase system capacity by matching skills and experience with personal interests. *ED*, Emergency department; *ICU*, intensive care unit; *MET*, medical emergency team; *RN*, registered nurse.

around the world (Fig. 13.7). There is a continuously growing evidence base that supports the following conclusions:

- Team-based interventions result in improved objective and subjective outcomes for patients, health care professionals and health care organisations.
- A broad range of well-developed tools, resources and programmes are available to implement team-based practices.
- Significant expertise, experience, commitment and resources are necessary to achieve potential benefits.
- The innovation or intervention should be prepared or adapted for the specific context in which it is to be applied.
- Sustained improvement in performance requires ongoing maintenance programmes.
- Multidisciplinary teams of intensive care health professionals are valuable assets that provide considerable dividends to the organisations in which they work.

KEY REFERENCES

2. Weled B, Adhzhigirey L. Critical care delivery: the importance of process of care and ICU structure to improved outcomes: an update from the American College of critical care medicine task force on models of critical care. *Crit Care Med*. 2015;43:1520–1525.
11. Flin R, Patey R, Glavin R, et al. Anaesthetists' non-technical skills. *Br J Anaesth*. 2010;105(1):38–44.
15. Bohmer R. The four habits of high-value health care organisations. *N Eng J Med*. 2011;365(22):2045–2047.
17. Manthous C, Hollinghead A. Team science and critical care. *Am J Resp Crit Care Med*. 2011;184:17–25.
18. Wenger E. Communities of practice. Learning as a social system. *Systems Thinker*. 1998;9(5):1–12.
27. Brattebo G. Education and training teamwork using simulation. In: Flatten H, Mureno R, Putensen C,

et al, eds. *Organisation and Management of Intensive Care*. Berlin: Medizinisch Wissenschaftliche Verlagsgesellschaft; 2010:323–334.
28. Frengley R, Weller J, Torrie J, et al. The effect of a simulation-based training intervention on the performance of established critical care unit teams. *Crit Care Med*. 2011;39:2605–2611.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Nightingale F. *Notes on Nursing: What it is and What it is Not*. London: Harrison; 1859.
2. Weled B, Adhzhigirey L. Critical care delivery: the importance of process of care and ICU structure to improved outcomes: an update from the American College of critical care medicine task force on models of critical care. *Crit Care Med*. 2015;43: 1520–1525.
3. Suter E, Arndt J, Arthur N, et al. Role understanding and effective communication as core competencies for collaborative practice. *J Interprof Care*. 2009;23(1):41–51.
4. Barnett SI, Sellers P. Neonatal critical care nurse practitioner: a new role in neonatology. *MCN Am J Matern Child Nurs*. 1979;4:279–286.
5. Moote M, Krsek C, Kleinpell R, et al. Physician assistant and nurse practitioner utilization in academic medical centres. *Am J Med Qual*. 2001;26: 452–460.
6. Gershengorn H, Johnson M, Factor P. The use of nonphysician providers in adult intensive care units. *Am J Resp Crit Care Med*. 2012;185(6):600–605.
7. Institute of Medicine. *To Err is Human: Building a Safer Health System*. Washington DC: National Academy Press; 2000.
8. Australian Commission on Safety and Quality in Healthcare. *OSSIE Guide to Clinical Handover Improvement*. 2011. <http://www.safetyandquality.gov.au/our-work/clinical-communications/clinical-handover/ossie-guide/>.
9. Institute for Healthcare Improvement. *SBAR Technique for Communication. A Situational Briefing Model*. [n.d.] <http://www.ihi.org/knowledge/Pages/Tools/SBARTechniqueforCommunicationASituationalBriefingModel.aspx>.
10. Kahn JM, Fuchs BD. Identifying and implementing quality improvement measures in the intensive care unit. *Curr Opin Crit Care*. 2007;13(6):709–713.
11. Flin R, Patey R, Glavin R, et al. Anaesthetists' non-technical skills. *Br J Anaesth*. 2010;105(1):38–44.
12. Byrne A, Greaves J. Assessment instruments used during anaesthetic simulation: review of published studies. *Br J Anaesth*. 2001;86:445–450.
13. Yee B, Naik V, Joo H, et al. Nontechnical skills in anesthesia crisis management with repeated exposure to simulation-based education. *Anesthesiology*. 2005;103:241–248.
14. Pentland S. The new science of building great teams. *Harvard Business Rev*. 2012;4:R1204C. http://hbr.org/product/the-new-science-of-building-great-teams/an/R1204C-PDF-ENG.
15. Bohmer R. The four habits of high-value health care organisations. *N Eng J Med*. 2011;365(22): 2045–2047.
16. Mohr J, Batalden P, Barach P. Integrating patient safety into the clinical microsystem. *Qual Saf Health Care*. 2004;13(suppl. ii):34–38.
17. Manthous C, Hollinghead A. Team science and critical care. *Am J Resp Crit Care Med*. 2011;184: 17–25.
18. Wenger E. Communities of practice. Learning as a social system. *Systems Thinker*. 1998;9(5):1–12.
19. Nathens A, Rivara F, Mackenzie E, et al. The impact of an intensivist-model ICU on trauma-related mortality. *Ann Surg*. 2006;244(4):545–554.
20. Michelle K, Barnato A, Angus D, et al. The effect of multidisciplinary care teams on intensive care unit mortality. *Arch Intern Med*. 2010;170(4):369–376.
21. Neily J, Mills P, Young-Xu Y, et al. Association between implantation of a medical team training program and surgical mortality. *JAMA*. 2010;304(15): 1693–1700.
22. Sun R, Marshall DC, Maruthappu M, et al. The Impact of improving teamwork on patient outcomes in surgery: a systematic review. *Int Surg*. 2018;53:171–177.
23. Agency for Healthcare Research and Quality. *Teamstepps: national implementation. US Department of Health and Human Services*. <http://teamstepps.ahrq.gov/about-2cl_3.html.
24. Mayer C, Laurie L, Wei-Ting L, et al. Evaluating efforts to optimize TeamSTEPPS implementation in surgical and paediatric intensive care units. *Jt Comm Qual Patient Saf*. 2011;37:8.
25. Berenholtz S, Pham J, Thompson D, et al. Collaborative cohort study of an intervention to reduce ventilator-associated pneumonia in the intensive care unit. *Infect Control Hosp Epidemiol*. 2011;32(4):305–314.
26. Steinmann S, Berg B, Skinner A, et al. In situ, multidisciplinary, simulation based teamwork training improves early trauma care. *J Surg Educ*. 2011;68(6):472–477.
27. Brattebo G. Education and training teamwork using simulation. In: Flatten H, Mureno R, Putensen C, et al, eds. *Organisation and Management of Intensive Care*. Berlin: Medizinisch Wissenschaftliche Verlagsgesellschaft; 2010:323–334.
28. Frengley R, Weller J, Torrie J, et al. The effect of a simulation-based training intervention on the performance of established critical care unit teams. *Crit Care Med*. 2011;39:2605–2611.
29. Stocker M, Allen M, Pool N, et al. Impact of an embedded simulation team training programme in a paediatric intensive care unit: a prospective, single-center, longitudinal study. *Intensive Care Med*. 2012;38(1):99–104.
30. Lemieux-Charles L, McGuire W. What do we know about healthcare team effectiveness? A review of the literature. *Med Care Res Rev*. 2006;63(3):263–300.
31. Schafer T, Wagner D, Chessare J, et al. Organ donation breakthrough collaborative: increasing organ donation through system redesign. *Crit Care Nurse*. 2006;26:33–48.
32. Alexanian J, Kitto S. Beyond the team: understanding interprofessional work in two North American ICUs. *Crit Care Med*. 2015;43:1880–1886.
33. Lim BC, Klein K. Team mental models and team performance: a field study of the effects of team mental model similarity and accuracy. *J Organ Behav*. 2006;27:403–418.

14

Genetics and sepsis

Jeremy Cohen, David Evans, Balasubramanian Venkatesh

INTRODUCTION

Sepsis is an enigmatic condition. Originally described by Hippocrates, it has only been in the last 50 years that the concept has been refined to describe a syndrome characterised by both an invading microorganism and the host response to it. Improvements in our understanding of the pathobiology of sepsis have led to a recent re-evaluation of how the disease is defined, leading to the current consensus definition of sepsis as 'life-threatening organ dysfunction caused by a dysregulated host response to infection'.[1] It is clear that there is substantial heterogeneity in the host response, the magnitude of which is influenced by a number of factors: patient co-morbidities, pathogen virulence, site of infection and host genetics. In the last decade, there has been substantial research into investigating the contribution that genetic variation makes to this heterogeneity and an understanding of this is an essential part of developing future management strategies. In this review we will describe how developments in genomics have led to a greater appreciation of the importance of genetic factors in the outcome of sepsis, and how this might influence future research and treatment.

BASIC DEFINITIONS AND GLOSSARY OF TERMS

A glossary of terms can be found at the end of the chapter.

Deoxyribonucleic acid (DNA) is the chemical compound inside the nucleus of a cell that carries the genetic instructions to make proteins; it contains the hereditary information that is transmitted from parents to offspring. Each DNA molecule consists of two paired strands of repeating units called nucleotides, wrapped around each other in a double helix structure (Fig. 14.1). Each nucleotide comprises a sugar molecule (deoxyribose), a phosphate group, and one of four nitrogenous bases: adenine (A), thymine (T), guanine (G) or cytosine (C). The bases of nucleotides from one strand pair with complementary bases from nucleotides on the other strand so that an 'A' nucleotide always pairs with a 'T' nucleotide, and a 'C' nucleotide always pairs with a 'G' nucleotide. The sequence of bases along the length of the DNA molecule encodes the genetic information contained within each cell and is virtually identical in all cells in an individual (gametes and some immune cells being an exception to this rule).

The DNA in the nucleus of cells is arranged into discrete linear structures called chromosomes. In each nucleus, there are 23 pairs of chromosomes, with 1 chromosome from each pair being inherited from each parent. The total amount of hereditary information encoded in the DNA sequence across all 23 pairs of chromosomes is known as an individual's genome, and consists of over 3 billion nucleotide pairs.

Within the genome are elements called genes, which are discrete segments of DNA that code for proteins. There are estimated to be around 25,000 genes in the human genome. Genes serve as templates for making messenger ribonucleic acid (mRNA) molecules through a process known as transcription. The mRNA transcripts travel out of the nucleus into the cytoplasm where they are subsequently used to make the polypeptides that form proteins, through a process known as translation.

While the vast majority of the genome (99.9%) of any two unrelated individuals is identical in terms of the DNA sequence, sequence variation can occur in a number of ways. The most commonly studied form of variation is called a single nucleotide polymorphism (SNP – see Fig. 14.1). An SNP is a DNA sequence variation that occurs when a nucleotide (A, C, T or G) is substituted for one of the others at a single position in the genome. For example, where there is typically an 'A' nucleotide at a particular location in the genome in the general population, some individuals might be found to have a 'G' nucleotide. There are over 10 million known common SNPs across the human genome. Whilst the majority of these changes produce no observable effects, some of them have measurable effects on humans, including causing, or at the very least, altering the risk of disease. For example, some SNPs in genes may produce changes in the amino-acid sequence of their corresponding proteins and therefore exert a detrimental effect on protein function.

ABSTRACT

In this chapter we outline the evidence for a genetic influence upon susceptibility and outcome from sepsis. We summarise the results of family studies and early approaches based on the candidate gene technique. We describe how advances in molecular genetic techniques have altered our approach to the study of this question and the difficulties of achieving a personalised medicine approach based upon genetic factors. We also describe the potential role of emerging techniques and future studies in the field.

KEYWORDS

Sepsis
septic shock
genome
genes
RNA
DNA
genome-wide association study
oligonucleotide array sequence analysis

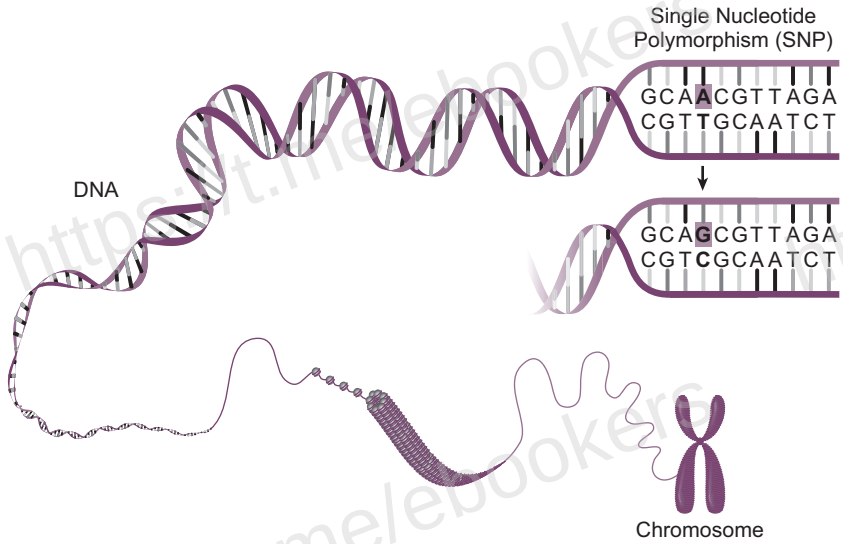


Figure 14.1 Single nucleotide polymorphism *(SNP)*. *DNA*, Deoxyribonucleic acid.

Other SNPs might produce changes in the rate at which a particular gene is transcribed. Within the context of sepsis, investigators are interested to see whether genetic changes like these may explain some of the considerable interindividual variation in risk of sepsis and/or the prognosis of individuals unfortunate enough to suffer from the condition.

In this chapter we will examine the evidence that there is a genetic basis for the susceptibility (and the response) to sepsis. We will then describe two broad strategies that have been used to try and understand the genetic basis of sepsis: genetic association studies (including candidate gene, genome-wide association studies, and whole genome sequencing studies), which attempt to find a correlation between genetic variation and risk of/response to sepsis, and studies that examine the differences in the expression of genes across the genome (including microarray-based and RNA-Seq-based studies) (Fig. 14.2).

FAMILY STUDIES

Genetic influences on lifespan have been recognised for many years.[2] In 1988 Sorenson and colleagues examined Danish adoption records and demonstrated that in adopted children whose biological parent had died before the age of 50 from an infective cause, the relative risk of death from infection was increased five-fold. There was no corresponding increase in risk to the child if it was the adoptive parent who died from the same cause.[3] This elegant study implied that genetic factors were an important determinant of outcome from infection, so they served as the foundation for future work in this field. Further analyses on this cohort suggested that genetic factors had a stronger influence upon the risk of dying from an infection compared to the risk of acquiring one – suggesting that acquisition and prognosis are likely to involve different sets of genetic and environmental risk factors.[4] Twin studies have also provided valuable information. Comparing outcomes in monozygotic twins who are genetically identical to those in dizygotic pairs who, on average, share only half their genetic material, can give an estimate of the relative contribution from hereditary factors. An increased concordance in susceptibility between monozygotic relative to dizygotic twins using this technique has been demonstrated in tuberculosis, sinusitis and *Helicobacter pylori* infections.[5–7]

CANDIDATE GENE STUDIES

Molecular genetic investigations into sepsis have been based upon two approaches. Historically the first approach, which is more widely used and simpler, is the candidate gene study. This technique relies on first identifying a gene or genes that are likely to be implicated in the pathobiology of the condition and subsequently comparing the allelic frequency of polymorphisms in those genes between cases and controls. The advantages of this sort of design are lower cost, fewer subjects are required to achieve a given level of statistical power and the analysis is less computationally intensive. As the study is hypothesis driven, any associations are likely to be biologically plausible. Given these advantages and the fact that the technology to perform genome-wide studies (see below) only

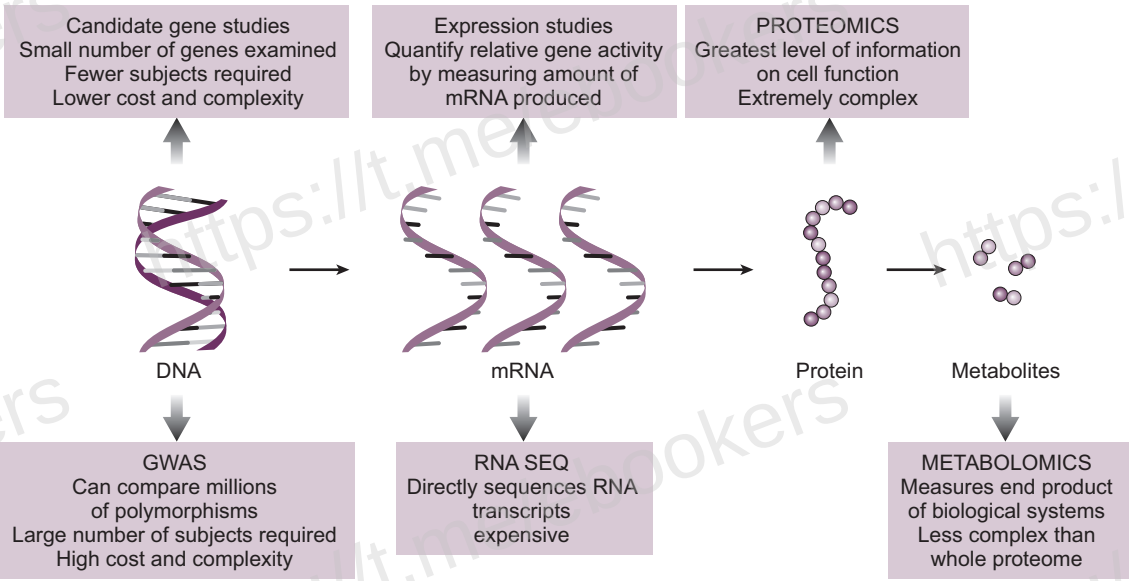


Figure 14.2 Overview of genomic, proteomic and metabolomics approach to investigation. *DNA*, Deoxyribonucleic acid; *GWAS*, genome-wide association study; mRNA, messenger ribonucleic acid.

became available a decade ago, it is unsurprising that the majority of initial studies into the genetics of sepsis have utilised the candidate gene approach. A 2006 systematic review identified 147 association studies examining 51 separate polymorphisms.[8] Many of these initial studies have reported positive associations. For example, there are reports of cases of increased mortality in sepsis associated with polymorphisms in the CRP gene,[9] the protein C gene[10] and genes for Toll-like receptors.[11] However, the candidate gene approach has many limitations, of which perhaps the most important is the low probability of correctly identifying genes of interest *a priori*. In a complex syndrome such as sepsis, there are likely to be many genes influencing the condition, some of which may be readily apparent from basic physiology, but others less so. Given that there are around 10 million common SNPs in the genome, the probability of correctly choosing one involved in risk of sepsis *a priori* is likely to be vanishingly small. Furthermore, the 2006 review identified numerous problems associated with sepsis studies in particular. Sample sizes were low, with the investigators estimating that only 7% of the studies were adequately powered to detect realistically sized associations at the 80% level. More tellingly, there was poor replication between studies, and given the undoubted heterogeneity in the condition, the effect sizes associated with genetic variants are likely to be very small.

Many of these problems are not unique to candidate gene studies of sepsis. A 2002 review found over 600 positive associations between common genetic variants and complex diseases in candidate gene studies, but noted that only six had been consistently replicated.[12] Thus it is highly likely that the majority of genetic associations reported to date in sepsis are likely to be artefactual resulting from statistical fluctuation and type I error, or latent biases producing spurious associations due to population stratification, for example.

Thus, while numerous polymorphisms have been described that appear to influence the course and outcome of sepsis,[13] none of the candidate gene studies to date have been successful in identifying reliable markers that have been used in either the stratification or identification of novel therapeutic pathways.

GENOME-WIDE ASSOCIATION STUDIES

A more recent approach is that of the genome-wide association study (GWAS). A GWAS typically utilises high-throughput microarray technologies to compare the allelic frequency of hundreds of thousands of SNPs between cases and controls. In addition, a statistical technique called imputation[14] can be used to infer genotypes at markers across the genome that have not been physically typed on the genotyping chips, meaning that literally millions of SNPs and other genetic variants can be tested for association in a GWAS. Thus, in contrast to candidate gene studies, a GWAS makes no *a priori* hypotheses as to the likely genetic mechanisms

of variability, as by their nature they examine a much larger area of the genome and have the potential to identify unanticipated associations, which could lead to novel therapeutic targets and better understanding of underlying biology. Another advantage of GWAS is that they permit statistical methods that allow investigators to detect and correct for potential underlying biases in genetic studies, like population stratification, whereas this can be difficult to do in candidate gene studies.[15] These features suggest that GWAS may be a superior technique than candidate gene studies in examining a complex multifactorial condition like sepsis. However, in order to have sufficient statistical power to detect alleles with even moderate effect sizes (e.g. allelic odds ratios of >1.3) a sample population of well over 2000 cases and controls is required.[16] This requirement is especially problematic in sepsis. Performing large-scale trials in an intensive care environment is logistically complex and expensive, and often requires multicentre, international collaborations. There are very few published critical care trials of any intervention which approach the numbers required for an adequately powered GWAS. Thus, despite the advantages that GWAS may offer, it is unsurprising that at the time of writing, there have been only two relatively small scale GWAS performed, both of which were on cohorts of patients that had been previously recruited into large-scale clinical trials.

Man and colleagues[17] examined a group of 1690 patients who had been recruited into a randomised, multicentre trial examining the effect of drotrecogin alfa in severe sepsis.[18] The primary outcome analysis was treatment response to the study drug. The authors also conducted a secondary analysis of 700 placebo patients using 28-day mortality as the primary outcome measure. The authors identified several genetic markers that may have influenced treatment response; however, as subsequent studies have failed to confirm the therapeutic efficacy of drotrecogin alfa in severe sepsis, the significance of this finding is unclear.[19] The secondary analyses failed to identify any markers associated with outcome; however, as noted, the low patient numbers suggested this analysis was underpowered.

Rautanen and colleagues performed a GWAS on over 2000 patients from three cohorts admitted to intensive care units with sepsis of pulmonary origin, including patients from two randomised, multicentre clinical trials.[20] They observed that a common variant in the *FER* gene appeared to have a significant protective effect; patients homozygous for the allele had 10% mortality at 28 days, compared to 15% for heterozygotes and 25% for the wild-type homozygous population, although the observed p value of 9.7×10^{-8} is above the commonly accepted value of $\alpha = 5 \times 10^{-8}$ for significance in a GWAS. The mechanism for the observed survival advantage is not yet clear; the *FER* gene codes for a non-transmembrane tyrosine kinase that may have a role in neutrophil chemotaxis. It is noteworthy that an attempt to replicate the findings of Rautanen and colleagues in a cohort of 740 patients with severe sepsis was unsuccessful.[21] However, this may reflect the relatively low sample size of the replication cohort and its mixed population. Pending further replication attempts, the relatively small sample size and large P-value of the Rautanen study suggest that the possibility that their findings represent a false positive association cannot be overlooked.

Given the difficulties associated with recruiting large numbers of patients into individual genetic studies, perhaps the most logical way forward will be to statistically combine the results of different sepsis GWAS in a meta-analysis.[22] This strategy has been spectacularly successful in elucidating the genetic aetiology of other complex traits and diseases,[23] although it remains to be seen how effective this will be in sepsis, given the likely underlying heterogeneity of the condition. It will also be important to differentiate between GWAS that examine risk of sepsis versus studies that investigate response to sepsis, as these may involve substantially different genetic aetiologies.

GWAS have proven to be an important tool in the investigation of inheritance. As of May 2016, the NHGRI-EBI catalogue of published genome-wide association studies contained 2437 studies and 16,617 unique SNP-trait associations.[24] However, it has become apparent that GWAS has explained only a fraction of the observed heritability of common diseases.[23,25,26] As genetic technology has advanced, next generation sequencing technology is enabling researchers to comprehensively examine the role of all genetic variations in the genome, in particular the role of rare and low-frequency variants.[27] However, whole genome sequencing studies are currently in their infancy, and the very low statistical power to detect rare variants means that sequencing studies will need to be extremely large in order to detect low frequency variants. Therefore, until the cost of sequencing a genome approaches that of a microarray chip, it is likely that GWAS will remain the method of choice for the genetic analysis of complex traits and diseases like sepsis.

GENE EXPRESSION STUDIES

Microarray technology also permits genome-wide gene expression profiling, providing a further layer of information in addition to that provided by GWAS. Typically, these studies are performed on samples of whole blood from patients, and therefore represent the combined expression of genes across many different varieties of blood cell, although it is obviously also possible to focus on specific cell types if steps are taken to purify the samples first (e.g. by flow cytometry).[28] Several studies in this area have identified

differential gene expression patterns in patients with sepsis, which may help identify individuals at a higher risk of mortality.

In 2010, Tang and colleagues published a systematic review of microarray studies performed in human patients with sepsis.[29] They identified 12 cohorts consisting of 784 individuals in total with genome-wide expression data. The largest single cohort comprised 176 individuals, with the majority of studies recruiting less than 100 patients. While a consistent finding across the studies was upregulation of receptors involved in pathogen recognition, the authors failed to observe any other consistent expression pattern relating to changes in the inflammatory response. Transcriptional changes in inflammatory genes appeared to be highly variable, and no repeatable change in the expression of genes involved in cytokine production or other inflammatory mediators were observed.

A substantial body of work has been performed in paediatric patients using these techniques. In 2009, Wong and colleagues described the results of genome-wide expression profiling using RNA derived from whole blood in 98 paediatric patients with septic shock.[30] They observed just under 7000 differentially regulated genes, and using a hierarchical cluster technique identified three subclasses of septic shock. Patients in subclass 'A' had a significantly higher sickness severity and a higher mortality rate. Of the genes that appeared to have the strongest predictive ability to identify subclasses, a majority corresponded to signalling pathways in the adaptive immune system and glucocorticoid receptor signalling. Additionally, patients in subclass 'A' appeared to have a large-scale repression of genes related to zinc biology. The authors subsequently validated their findings in a further cohort of 82 paediatric patients.[31] Of particular interest was the observation that adjunctive corticosteroid treatment was associated with a higher mortality only in the subclass of patients in whom the genes associated with glucocorticoid signalling appeared to be repressed.[32]

This observation will need to be confirmed in a prospective study, but represents the first description of a subclass of patients with septic shock in whom genetic techniques may predict the response to a specific treatment.

One of the largest and most recent studies in adult septic patients is that of Davenport and colleagues. They examined gene expression data from 265 adult patients with sepsis from community-acquired pneumonia, and identified two 'sepsis response clusters' with over 3000 differentially expressed genes.[33] Patients in the first cluster had significantly higher mortality (14-day mortality 59% vs. 29%). Gene network analysis identified the downregulation of genes associated with immune response in the first cluster, which suggested that relative immune deficiency might play a role in the outcome from sepsis.

RNA-SEQ

RNA-Seq is an emergent technique that uses deep-sequencing technologies. Its aim is to quantify the transcriptome, the complete set of transcripts in the cell. In contrast to microarray methods, which rely upon hybridisation to a set of probes, RNA-Seq directly sequences a cDNA library of fragments generated from the RNA sample of interest. It has several key advantages over microarray-based approaches, including much greater range of expression levels over which transcripts can be detected, and it is not limited to the detection of transcripts from known genomic sequences.[34]

To date there are limited data from this approach in patients with sepsis and septic shock.[35]

EPIGENETICS

Epigenetics describes the study of changes in gene expression that are not a result of modifications in the DNA sequence.[36] Potential mechanisms for epigenetic changes include DNA methylation, non-coding RNAs and modification to histones, the proteins around which the DNA double helix is wrapped. The study of how epigenetic changes may influence sepsis is in its very early stages,[37,38] but available data suggest this may be a further mechanism for explaining differences in the susceptibility and response to this condition.

FUTURE STUDIES

The ADRENAL Gene expression study (ADRENAL GEPS, NHMRC APP1085159) is an Australian National Health and Medical Council funded study, which began at the start of 2015. The aim of the study was to recruit 1500 individuals with septic shock, assay genome-wide gene expression in patients' whole blood, and endeavour to find an mRNA-based classifier that differentiates patients in terms of their response to corticosteroid therapy and risk of mortality. Blood and serum samples are also being taken from patients in order to enable future GWAS, metagenomic and other molecular studies of septic shock.

SUMMARY

Our understanding of how genetic factors may influence the development and outcome of sepsis has greatly increased over the last few decades, driven by the rapid development of new molecular genetic techniques. However, as our knowledge has increased, so has the appreciation that as a highly complex syndrome, there are unlikely to be simple genetic changes

that can serve to inform prognosis or therapy. Nevertheless, continuing research in this field may well yield the hoped for a 'personalised medicine approach', which is so essential for a disease characterised by heterogeneity.

> *'Everything should be made as simple as possible, but no simpler.'*
>
> A. Einstein

GLOSSARY

Adoption study:
A type of epidemiological study design where the similarity between parents and their biological offspring is compared to the similarity between parents and their adopted offspring.

Allele:
Alternate forms of a gene/SNP.

Candidate gene study:
A type of genetic association study where a relatively small number of genetic polymorphisms is investigated in a region of the genome that the investigator thinks is likely to be involved in the trait of interest.

Complex disease/trait:
A disease/trait that is caused by many genetic variants of small effect and environmental factors. Most of the common diseases of major public health relevance (including sepsis) are complex diseases.

Epigenetics describes the study of changes in gene expression that are not a result of modifications in the DNA sequence.

Gene:
A simple definition of a gene is a part of the genome that codes for a protein.

Genetic variant:
A part of the human genetic sequence that varies between individuals in the population.

Genome:
The entire genetic sequence of an individual.

Genome-wide association study (GWAS):
A type of genetic association study where individuals typically have hundreds of thousands of SNPs genotyped across their genomes. GWAS are typically performed using microarray technologies that may not physically capture low frequency/rare genetic variants.

Heritability:
The proportion of variation in a phenotype that is due to genetic factors.

Microarray:
Comprises a silicon chip (or other medium) containing numerous oligonucleotide probes that are complementary to specific sequences in the genome. Microarrays can be used to assay hundreds of thousands of SNPs, or measure gene expression in thousands of genes simultaneously.

Nucleotide:
A single unit of DNA consisting of a deoxyribose sugar, a phosphate group, and a nitrogenous base.

Population stratification:
Refers to the situation in genetic studies where the sample consists of individuals of different ancestries. Population stratification may lead to spurious results in genetic studies and often must be corrected for.

(Statistical) Power:
The probability of correctly rejecting the null hypothesis of no genetic association. Genome-wide association studies typically need thousands of individuals in order to have adequate power to detect true genetic associations.

Sequencing is determining the exact order of the bases in a strand of nucleotides.

Single nucleotide polymorphism (SNP):
A single base change in the sequence of the genome that varies across individuals. SNPs are the form of genetic variation that is most often tested in genome-wide association studies.

Transcription:
The process by which the DNA sequence is coded into messenger RNA.

Transcriptome:
The sum total of all the mRNA molecules expressed from the genes of an organism.

Translation:
The process whereby messenger RNA is coded into a sequence of amino acids.

Type I error:
Refers to the situation where an association is claimed but in fact no such association really exists. In genetic studies, this may arise from a number of sources including statistical fluctuation, population stratification, and the unintended inclusion of related individuals in a genetic analysis of unrelated individuals.

(Classical) Twin Study:
This sort of epidemiological study design compares the trait similarity of identical twins (who share all their genes in common) to the similarity between non-identical twins (who share, on average, half their genes in common). Excess similarity in identical twins compared to the non-identical counterparts provides evidence that a trait has a genetic aetiology.

Whole genome sequencing:
Refers to sequencing the entire genetic sequence of an individual. It is currently expensive to do.

KEY REFERENCES

1. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):801–810.
13. Nakada TA, Boyd JH, Russell JA, et al. VPS13D gene variant is associated with altered IL-6

production and mortality in septic shock. *J Innate Immun*. 2015;7(5):545–553.
17. Man M, Close SL, Shaw AD, et al. Beyond single-marker analyses: mining whole genome scans for insights into treatment responses in severe sepsis. *Pharmacogenomics J*. 2013;13(3):218–226.
19. Ranieri VM, Thompson BT, Barie PS, et al. Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med*. 2012;366(22):2055–2064.
20. Rautanen A, Mills TC, Gordon AC, et al. Genome-wide association study of survival from sepsis due to pneumonia: an observational cohort study. *Lancet Respir Med*. 2015;3(1):53–60.
21. Schoneweck F, Kuhnt E, Scholz M, et al. Common genomic variation in the FER gene: useful to stratify patients with sepsis due to pneumonia? *Intensive Care Med*. 2015;41(7):1379–1381.
23. Visscher PM, Brown MA, McCarthy MI, et al. Five years of GWAS discovery. *Am J Hum Genet*. 2012;90(1):7–24.
24. Welter D, MacArthur J, Morales J, et al. The NHGRI GWAS catalog, a curated resource of SNP-trait associations. *Nucleic Acids Res*. 2014;42(Database issue):D1001–D1006.
27. Consortium UK, Walter K, Min JL, et al. The UK10K project identifies rare variants in health and disease. *Nature*. 2015;526(7571):82–90.
28. Maslove DM, Wong HR. Gene expression profiling in sepsis: timing, tissue, and translational considerations. *Trends Mol Med*. 2014;20(4):204–213.
32. Wong HR, Cvijanovich NZ, Anas N, et al. Developing a clinically feasible personalized medicine approach to pediatric septic shock. *Am J Respir Crit Care Med*. 2015;191(3):309–315.
33. Davenport EE, Burnham KL, Radhakrishnan J, et al. Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. *Lancet Respir Med*. 2016;4(4):259–271.
35. Tsalik EL, Langley RJ, Dinwiddie DL, et al. An integrated transcriptome and expressed variant analysis of sepsis survival and death. *Genome Med*. 2014;6(11):111.
37. Ciarlo E, Savva A, Roger T. Epigenetics in sepsis: targeting histone deacetylases. *Int J Antimicrob Agents*. 2013;42(suppl):S8–S12.
38. Bomsztyk K, Mar D, An D, et al. Experimental acute lung injury induces multi-organ epigenetic modifications in key angiogenic genes implicated in sepsis-associated endothelial dysfunction. *Crit Care*. 2015;19:225.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):801–810.
2. Cohen BH. Family patterns of mortality and life span. *Q Rev Biol*. 1964;39:130–181.
3. Sorensen TI, Nielsen GG, Andersen PK, et al. Genetic and environmental influences on premature death in adult adoptees. *N Engl J Med*. 1988;318(12):727–732.
4. Petersen L, Andersen PK, Sorensen TI. Genetic influences on incidence and case-fatality of infectious disease. *PLoS ONE*. 2010;5(5):e10603.
5. Comstock GW. Tuberculosis in twins: a re-analysis of the Prophit survey. *Am Rev Respir Dis*. 1978;117(4):621–624.
6. Marshall AG, Hutchinson EO, Honisett J. Heredity in common diseases. A retrospective survey of twins in a hospital population. *Br Med J*. 1962;1(5270):1–6.
7. Malaty HM, Engstrand L, Pedersen NL, et al. *Helicobacter pylori* infection: genetic and environmental influences. A study of twins. *Ann Intern Med*. 1994;120(12):982–986.
8. Clark MF, Baudouin SV. A systematic review of the quality of genetic association studies in human sepsis. *Intensive Care Med*. 2006;32(11):1706–1712.
9. Eklund C, Huttunen R, Syrjanen J, et al. Polymorphism of the C-reactive protein gene is associated with mortality in bacteraemia. *Scand J Infect Dis*. 2006;38(11–12):1069–1073.
10. Russell JA, Wellman H, Walley KR. Protein C rs2069912 C allele is associated with increased mortality from severe sepsis in North Americans of East Asian ancestry. *Hum Genet*. 2008;123(6):661–663.
11. Wurfel MM, Gordon AC, Holden TD, et al. Toll-like receptor 1 polymorphisms affect innate immune responses and outcomes in sepsis. *Am J Respir Crit Care Med*. 2008;178(7):710–720.
12. Hirschhorn JN, Lohmueller K, Byrne E, et al. A comprehensive review of genetic association studies. *Genet Med*. 2002;4(2):45–61.
13. Nakada TA, Boyd JH, Russell JA, et al. VPS13D gene variant is associated with altered IL-6 production and mortality in septic shock. *J Innate Immun*. 2015;7(5):545–553.
14. Marchini J, Howie B, Myers S, et al. A new multipoint method for genome-wide association studies by imputation of genotypes. *Nat Genet*. 2007;39(7):906–913.
15. Devlin B, Roeder K. Genomic control for association studies. *Biometrics*. 1999;55(4):997–1004.
16. Spencer CC, Su Z, Donnelly P, et al. Designing genome-wide association studies: sample size, power, imputation, and the choice of genotyping chip. *PLoS Genet*. 2009;5(5):e1000477.
17. Man M, Close SL, Shaw AD, et al. Beyond single-marker analyses: mining whole genome scans for insights into treatment responses in severe sepsis. *Pharmacogenomics J*. 2013;13(3):218–226.
18. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med*. 2001;344(10):699–709.
19. Ranieri VM, Thompson BT, Barie PS, et al. Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med*. 2012;366(22):2055–2064.
20. Rautanen A, Mills TC, Gordon AC, et al. Genome-wide association study of survival from sepsis due to pneumonia: an observational cohort study. *Lancet Respir Med*. 2015;3(1):53–60.
21. Schoneweck F, Kuhnt E, Scholz M, et al. Common genomic variation in the FER gene: useful to stratify patients with sepsis due to pneumonia? *Intensive Care Med*. 2015;41(7):1379–1381.
22. de Bakker PI, Ferreira MA, Jia X, et al. Practical aspects of imputation-driven meta-analysis of genome-wide association studies. *Hum Mol Genet*. 2008;17(R2):R122–R128.
23. Visscher PM, Brown MA, McCarthy MI, et al. Five years of GWAS discovery. *Am J Hum Genet*. 2012;90(1):7–24.
24. Welter D, MacArthur J, Morales J, et al. The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. *Nucleic Acids Res*. 2014;42(Database issue):D1001–D1006.
25. Maher B. Personal genomes: the case of the missing heritability. *Nature*. 2008;456(7218):18–21.
26. Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. *Nature*. 2009;461(7265):747–753.
27. Consortium UK, Walter K, Min JL, et al. The UK10K project identifies rare variants in health and disease. *Nature*. 2015;526(7571):82–90.
28. Maslove DM, Wong HR. Gene expression profiling in sepsis: timing, tissue, and translational considerations. *Trends Mol Med*. 2014;20(4):204–213.
29. Tang BM, Huang SJ, McLean AS. Genome-wide transcription profiling of human sepsis: a systematic review. *Crit Care*. 2010;14(6):R237.
30. Wong HR, Cvijanovich N, Lin R, et al. Identification of pediatric septic shock subclasses based on genome-wide expression profiling. *BMC Med*. 2009;7:34.
31. Wong HR, Cvijanovich NZ, Allen GL, et al. Validation of a gene expression-based subclassification strategy for pediatric septic shock. *Crit Care Med*. 2011;39(11):2511–2517.
32. Wong HR, Cvijanovich NZ, Anas N, et al. Developing a clinically feasible personalized medicine approach to pediatric septic shock. *Am J Respir Crit Care Med*. 2015;191(3):309–315.
33. Davenport EE, Burnham KL, Radhakrishnan J, et al. Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. *Lancet Respir Med*. 2016;4(4):259–271.
34. Wang Z, Gerstein M, Snyder M. RNA-Seq: a revolutionary tool for transcriptomics. *Nat Rev Genet*. 2009;10(1):57–63.
35. Tsalik EL, Langley RJ, Dinwiddie DL, et al. An integrated transcriptome and expressed variant

analysis of sepsis survival and death. *Genome Med*. 2014;6(11):111.
36. Wu C, Morris JR. Genes, genetics, and epigenetics: a correspondence. *Science*. 2001;293(5532):1103–1105.
37. Ciarlo E, Savva A, Roger T. Epigenetics in sepsis: targeting histone deacetylases. *Int J Antimicrob Agents*. 2013;42(suppl):S8–S12.
38. Bomsztyk K, Mar D, An D, et al. Experimental acute lung injury induces multi-organ epigenetic modifications in key angiogenic genes implicated in sepsis-associated endothelial dysfunction. *Crit Care*. 2015;19:225.

Part Two
Shock

This page intentionally left blank

15

Overview of shock

Matthew J Maiden, Sandra L Peake

DEFINITION

Shock is a fundamental disease state of critical illness. Yet many who manage shocked patients, remain vague about what shock is. A commonly offered description is 'a patient with a low blood pressure', followed by some threshold blood pressure, below which, 'shock' is said to be occurring.

The reason for the uncertainty about what is an important concept, relates to the fact that the term 'shock' is used in a multitude of contexts (e.g. septic, haemorrhagic, distributive, hypovolaemic, cytotoxic, cardiogenic, anaphylactic, toxic, spinal, neurogenic, cervical, electrical and even emotional shock). Nevertheless, the unifying feature of shock, irrespective of the initiating disease or clinical features, is **acute circulatory failure associated with inadequate oxygen utilisation by the cells.**[1]

A thorough understanding of what constitutes shock is essential for all critical care practitioners. This chapter will outline the pathophysiology of shock, a classification of diseases that lead to shock and an approach to management.

CIRCULATORY PHYSIOLOGY

OXYGEN DELIVERY

Circulatory supply of oxygen is tightly regulated by the cardiovascular system. Oxygen delivery (DO_2) is the product of cardiac output (CO) and the oxygen content of arterial blood. DO_2 (mL/min) can be summarised by the following equation:

$$DO_2 = CO \times ([1.34 \times Hb \times SaO_2] + [PaO_2 \times 0.003])$$

where Hb is the haemoglobin concentration (g/L), SaO_2 is the arterial haemoglobin (Hb) oxygen saturation and PaO_2 is the arterial oxygen partial pressure. The exact value of the haemoglobin O_2-carrying capacity constant is variably listed as either 1.34 mL O_2/g Hb (directly measured) or 1.39 mL O_2/g Hb (theoretical maximum O_2 carrying capacity).

Assuming adequate arterial oxygen content, CO is the main determinant of DO_2. CO, in turn, is the product of heart rate (HR) and stroke volume (SV) with preload, afterload and myocardial contractility determining SV. Thus:

$$CO = HR \times SV\ (\text{preload, afterload, contractility})$$

Alterations in any of these determinants of CO will eventually lead to the development of different 'types' of circulatory shock (e.g. hypovolaemic, distributive, cardiogenic).

DO_2–VO_2 RELATIONSHIP

DO_2 in adults at rest is approximately 1000 mL/min, while oxygen consumption (VO_2) is about 250 mL/min. Under normal circumstances, the 'extra' O_2 being supplied is not required to meet metabolic demand and can conceptually be thought of as a 'reserve' supply (O_2 supply independency). If DO_2 decreases, VO_2 initially remains unchanged as the 'reserve' O_2 is utilised. If DO_2 falls further, oxygen extraction from Hb is increased to maintain adequate oxygen supply to the tissues. Any further reduction of DO_2 results in oxygen being maximally extracted from Hb and, at this point, VO_2 becomes dependent on DO_2 (O_2 supply dependency) and energy production in cells is limited by the supply of oxygen (Fig. 15.1).

DYSOXIA

Dysoxia occurs beyond the critical point of oxygen supply dependency (critical DO_2). Inadequate O_2 supply leads to anaerobic cellular metabolism, less efficient adenosine triphosphate (ATP) production and consequent cellular and organ dysfunction. If the process leading to shock is identified and managed early and appropriately, cellular dysfunction is limited. However, if shock persists, the ongoing limitation of oxygen supply affects cell membrane ion channels, leading to an influx of sodium and water, cellular oedema, breaching of cell membrane integrity, cell injury and eventually cell death.

The ability to withstand limited oxygen supply varies between organs. The heart and brain have high metabolic requirements with a relatively high oxygen extraction, and hence, are more vulnerable to reduced

ABTRACT

Shock is defined as acute circulatory failure associated with inadequate oxygen utilisation by the cells. It can be classified as hypovolaemic, distributive, cardiogenic or obstructive, based on the pattern of circulatory compromise. In some diseases leading to shock, such as sepsis, cells have a state of dysoxia where they have a limited ability to utilise oxygen despite an apparent increased oxygen delivery.

Not all forms of shock present with the same haemodynamic derangements. A low blood pressure is common, but is not required to define shock. Clinical characteristics will depend on the mechanisms leading to shock, the ability of the patient to mount a compensatory response, underlying comorbidities and the effect of medications.

Shock is usually lethal if untreated. The early recognition of shock, the optimisation of oxygen delivery and the prompt definite treatment of the disease triggering this condition are essential for survival. Repeated clinical assessment and monitoring of multiple haemodynamic and cellular parameters is necessary to ensure adequate management.

KEYWORDS

Shock
oxygen delivery
dysoxia
parenteral fluids
cardiovascular medications
haemodynamic monitoring
lactate

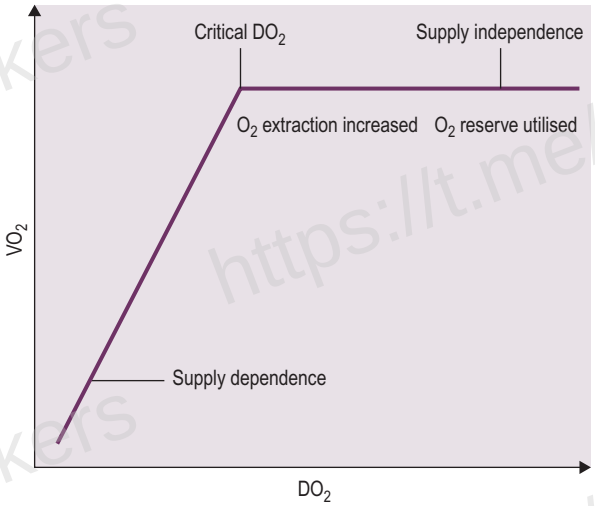


Figure 15.1 Oxygen supply and demand relationship.

oxygen supply. In contrast, the kidney and skin have relatively lower metabolic requirements and lower O_2 extraction and therefore are more tolerant of decreased DO_2. The critical DO_2 also varies between individuals and is affected by metabolic demand, age, disease states and medications.

Importantly, dysoxia may also occur despite adequate DO_2. In conditions such as sepsis and multiorgan dysfunction syndrome, DO_2 can appear to be adequate (and may even be supranormal as a result of increased CO). However, arteriolar shunting around the microvascular capillary beds prevents oxygen delivery to the cells, and inflammatory mediators can induce mitochondrial dysfunction, preventing cells from utilising available oxygen (cytotoxic shock).[2] Hence **hypotension is not required to define 'shock'.**

'TYPES' OF SHOCK

Impairment of circulatory supply of oxygen to the cells is commonly classified according to which component of the circulation is primarily disturbed, that is, hypovolaemic shock (inadequate preload), cardiogenic shock ('pump' failure), distributive or vasodilatory shock (altered vascular capacitance).[3] The classification of shock into various types is clinically useful as it has therapeutic implications – albeit this distinction is sometimes too simplistic. For example, in septic shock, hypovolaemia (decreased preload secondary to increased vascular permeability), vasodilation and myocardial dysfunction may all co-exist.

HYPOVOLAEMIC SHOCK

The total blood volume is 70 mL/kg and comprises blood cells and serum. Hypovolaemic shock occurs when acute blood loss or excessive fluid losses lead to decreased circulating blood volume (Box 15.1).

Box 15.1 Causes of hypovolaemic shock

Blood loss

Vascular injury (e.g. trauma, surgery)
Gastrointestinal bleeding (e.g. peptic ulcer, diverticular, angio-dysplasia, varices)
Obstetric bleeding (e.g. placenta praevia, postpartum haemorrhage)
Intra-abdominal haemorrhage (e.g. splenic laceration, liver injury)
Retroperitoneal (e.g. aortic aneurysm, ectopic rupture, femoral artery bleeding, pelvic fracture)
Long bone fracture
Pulmonary haemorrhage, haemothorax

Fluid loss

Vomiting
Diarrhoea
Ileostomy losses
Sweating
Polyuria (e.g. glucosuria, diabetes insipidus)
Burns
Pancreatitis

Loss of circulatory volume will reduce preload and SV. About 10% of circulating volume loss can be restored by the movement of interstitial fluid into the circulation. Blood loss beyond this invokes cardiovascular compensatory mechanisms in order to restore preload and maintain CO and systemic blood pressure. These mechanisms include:

1. *Increasing venous tone*. Venoconstriction is an early compensatory response to hypovolaemic shock. The venous system holds about 80% of blood volume and acts as a blood reservoir. The sympathetic nervous system controls venous tone and capacitance of the venous system. Reducing capacitance favours venous return to the heart in an attempt to maintain SV.
2. *Increasing arteriolar tone*. Sympathetic stimulation of arteriolar resistance vessels increases perfusion pressure to the organs. However, this does not necessarily equate with increased blood flow. The extent of change of arteriolar tone varies in order to redistribute adequate blood flow to the vital organs.
3. *Increasing HR*. To compensate for the reduction in SV, HR is increased in an attempt to maintain CO.
4. *Increasing contractility*. The heart will contract more vigorously in order to increase SV and maintain CO.

Priorities in the management of hypovolaemic shock are to (1) control the source of blood and/or volume loss, and (2) restoring the circulating volume.

Box 15.2 Causes of cardiogenic shock

Myocardial ischaemia
Acute valve dysfunction (e.g. chordae rupture, prosthetic valve thrombus)
Myocarditis
Contusion
Septal/ventricular rupture
Drugs (e.g. Ca^{2+} channel-blocker overdose, β-blocker overdose)
Extrinsic compression (e.g. tension pneumothorax, tamponade)
Pulmonary emboli, pulmonary hypertension
Bradyarrhythmias (e.g. complete heart block)
Tachyarrhythmias (e.g. atrial or ventricular tachycardias)

CARDIOGENIC SHOCK

The heart is central to the circulatory supply of oxygen and if the pump fails, then little compensatory mechanisms remain. Hence, cardiogenic shock has a very high in-hospital mortality rate ranging from 45% to 100%, depending on the aetiology.[4] Myocardial ischaemia is the most common cause of cardiogenic shock but other aetiologies must be considered (Box 15.2).

Treatment priorities in cardiogenic shock involve the urgent correction of the underlying acute cardiac disease and the consideration of afterload reduction while ensuring adequate organ perfusion.

OBSTRUCTIVE SHOCK

Mechanical obstruction to the flow of blood through the cardiac chambers will lead to a reduced cardiac output. Limitation of flow may be due to obstruction within the heart (e.g. valve thrombosis, myxoma), extrinsic compression (e.g. tension pneumothorax, cardiac tamponade) or cardiac outflow obstruction (e.g. pulmonary embolus, hypertrophic obstructive cardiomyopathy). Treatment is directed at urgent removal of the obstruction (e.g. drainage of pericardial effusion, lysis of thromboembolism).

DISTRIBUTIVE SHOCK

Arteriolar autoregulation, the autonomic nervous system and vasoactive hormones control distribution of blood around the vascular network. Distributive shock results from the failure of these mechanisms, leading to inappropriate distribution of blood (Box 15.3). Unlike other forms of shock, cardiac output may initially be increased as the heart endeavours to compensate for maldistribution of blood.

Management priorities are to identify and treat the precipitating cause and to improve organ perfusion with resuscitation fluids and vasoactive drugs.

Box 15.3 Causes of distributive shock

Septic shock
Toxic shock
Anaphylactic shock
Neurogenic shock
Adrenal/thyroid insufficiency
Toxicity (e.g. drugs)
As a component of multiorgan dysfunction syndrome

CLINICAL SIGNS

Clinical features of shock reflect an inadequate circulation and insufficient oxygen delivery and/or utilisation.

Hypotension is a typical feature of shock and often signifies circulatory failure. However, hypotension develops late as blood pressure is initially maintained by compensatory mechanisms (i.e. vascular constriction, tachycardia, increased myocardial contractility). A decline in mean arterial pressure (MAP) below the lower limit of autoregulation results in reduced perfusion to the vital organs. In a healthy adult, tissue perfusion is typically impaired with a MAP of ≤50 mm Hg. In contrast, elderly patients with pre-existing hypertension or vascular disease generally require a higher MAP to represent adequate regional blood flow.

Tachycardia is an early compensatory sign of shock. Note, however, that in some conditions bradycardia is the cause of shock (e.g. complete heart block, increased vagal tone in cervical shock, unopposed vagal tone in neurogenic shock).

Tachypnoea steadily increases with worsening shock but falls in the pre-terminal phase of shock.

Oliguria is secondary to reduced glomerular filtration and increased filtrate reabsorption. In shock, the rate of urine production may be a useful guide to adequacy of the circulation.

Altered mental status is a common feature of shock as cerebral function is very sensitive to altered oxygen delivery. During shock, mental state progressively changes from anxiety, agitation, confusion and delirium, towards drowsiness and coma.

Impaired peripheral perfusion provides a clinically useful clue regarding the likely mechanism of shock. Cool, clammy peripheries with pale or mottled skin are suggestive of hypovolaemic or cardiogenic shock, whereas warm peripheries are suggestive of distributive shock.

It is important to recognise that clinical features of shock are non-specific and will differ depending on the type of shock, the severity of the precipitating disease, the physiological reserve of the patient and the effects of medications. For example, patients on β-antagonists will not mount the same tachycardic response, and patients with pre-existing cardiac disease are less

capable of circulatory compensation, so they develop features of shock earlier. In contrast, young patients typically have greater compensatory reserves; hence clinical signs of shock in this group of patients represent profound cardiovascular compromise. Due to the non-specific and varied clinical signs of shock, repeated assessment with frequent monitoring of vital signs is essential.

MANAGEMENT

Resuscitation of shock is a medical emergency. The aim of therapy is to rapidly and effectively restore systemic DO_2 and improve tissue perfusion. History, examination and investigation (Box 15.4) must occur concurrently with resuscitation. The usual 'ABC' resuscitation principals of airway, breathing and circulation apply.

ENSURE ADEQUATE OXYGENATION

Ensure adequate FiO_2 and SaO_2, that ventilation is not impaired and that any reversible cause of pulmonary shunt is corrected (e.g. pleural collection, bronchus obstruction).

VASCULAR ACCESS

Insertion of intravenous cannulae is essential for the administration of fluids and medications. Cannula size is an important consideration as it has major implications for the rate of laminar fluid flow. Poiseuille's law describes the variables contributing to laminar flow rates.

$$Q \propto (\Delta P \times \pi r^4)/(8 \times \text{viscosity} \times \text{length})$$

This emphasises the effect of radius and cannula length on flow. Hence for rapid intravenous fluid administration, venous cannulation using short, wide-bore catheters is advised.

Flow rates achieved through different diameter intravenous cannulae are stated to range from 44 mL/min (22 G; 0.9 mm diameter) through to 286 mL/min (14 G; 2.1 mm diameter). However, the flow through cannulae is turbulent rather than laminar and actual flow rates are lower than those quoted.[5]

A central venous cannula should be considered in patients with persistent shock, particularly if they are requiring infusion of catecholamines, other cardiovascular medications or multiple infusions, or have difficult peripheral venous access.

Box 15.4 Investigations for shock (as clinically indicated)

Bedside
Haemoglobin
Arterial blood gas
Lactate
ECG
Ultrasound (e.g. FAST scan, AAA scan)
Echocardiogram

Laboratory
Full blood count, coagulation studies, D-dimer
Electrolytes, creatinine, urea, liver function tests
Cardiac enzymes, lipase
Cultures – urine, blood, sputum, pus
Toxicology assays

Radiology
Chest, abdominal X-ray
Trauma series radiology (chest, pelvis, C-spine)
CT
Angiography (e.g. coronary, visceral, pulmonary)

AAA, Abdominal aortic aneurysm; *CT*, computed tomography; *ECG*, electrocardiography; *FAST*, focused assessment with sonography for trauma.

FLUID RESUSCITATION

Fluid resuscitation is an important therapeutic strategy in the management of shock.[6] Although parenteral fluids are commonly used, there remain many questions regarding what 'dose' and type of fluid is best in shock. While hypovolaemia can contribute to states of shock, simply 'pouring in' fluids risks the development of hypervolaemia and its attendant adverse consequences and known association with mortality. Resuscitation should involve fluid administration provided in titratable aliquots, and the haemodynamic responses should be assessed before providing further fluid doses.

It is important to remember that not all patients will respond to fluid loading with a significant increase in CO. If the heart is working on the terminal (flat) portion of the Frank-Starling curve, increased preload will not result in a significant increase in SV. Furthermore, the relationship between preload and stroke volume is dynamic and is affected by many other variables extrinsic to the heart (e.g. autonomic tone, cardiovascular medications, ventilation, lung disease).[7] These need to be considered when determining the volume of fluids to administer.

TRENDELENBURG MANOEUVRE

A quick method to increase venous return is to tilt the patient's pelvis above horizontal (i.e. head down). This will 'auto-transfuse' blood from leg and pelvic veins into central veins, augmenting preload. Increases in CO, though, are minimal if venous capacitance remains high and the extra blood volume is accommodated. The haemodynamic response to passive leg raise can be used to assess whether fluid administration will enhance cardiac output.[8]

CRYSTALLOID SOLUTIONS

Crystalloid solutions comprise electrolytes (with or without dextrose) and water. These fluids cross semi-permeable membranes easily and are rapidly distributed through the intravascular and extravascular spaces. The time for fluid equilibration across the body compartments depends on: (1) osmolality of the fluid, (2) solute clearance, and (3) integrity of the vascular endothelium.

Whilst the choice of fluid should reflect the composition of the fluid lost, 0.9% saline is commonly used for initial volume replacement. Saline 0.9% is slightly hyperosmolar (300 mOsm/L) and hyperchloraemic (150 mEq/L) relative to plasma. When large volumes are used for resuscitation, hyperchloraemia can contribute to bicarbonate loss and a normal anion gap metabolic acidosis. Lactated Ringer solution (Hartmann) is isotonic and contains lactate (29 mEq/L) and electrolytes in a ratio similar to plasma. However, the calcium in Hartmann (4 mEq/L) is incompatible with certain drugs, and lactate levels may rise if hepatic function is markedly impaired, if a lot of fluid is administered or if blood is sampled from an arm receiving intravenous fluids. Other crystalloid solutions are available that contain different buffer anions and slightly different composition of electrolytes. These solutions are being studied to determine if they provide more favourable clinical outcomes.

Concentrated saline is theoretically a useful resuscitation fluid since a small volume can increase circulating volume (e.g. 250 mL 7.5% saline can increase circulating volume by 500 mL). However, the sodium also passes into the interstitial space, leading to increased interstitial fluid volume at the expense of intracellular volume.

ALBUMIN SOLUTIONS

Normal serum albumin at 4% (NSA 40 g/L; 260 mOsm/L) is iso-oncotic, and infusion rapidly increases circulating volume. Concentrated (20%) albumin is available in smaller volumes (100 mL). It increases circulating fluid volume by drawing fluid from the interstitium, but this process takes time and hence it is not a useful resuscitation fluid.

In 1998, a Cochrane review suggested that albumin use was associated with increased mortality,[9] but other reviews drew different conclusions.[10–12] To determine the safety of albumin as a resuscitation fluid, the Saline versus Albumin Fluid Evaluation (SAFE) study randomised 7000 patients to receive albumin or crystalloid as their resuscitation fluid.[13] This landmark study revealed that patients receiving albumin required less intravenous fluid, but clinical outcomes were no different to patients who received saline resuscitation. Subgroup analyses suggested that septic patients fared better with 4% NSA, while head injured patients given saline had better outcomes.

STARCH SOLUTIONS

Starch solutions contain a carbohydrate polymer (starch) as their oncotic molecule and differ according to the type and molecular size of the starch used (high starch 450,000 D, medium starch 200,000 D, low starch 70,000 D). The starch polymers undergo degradation by serum amylase with the fragments cleared by the kidney. The duration of oncotic effect is related to the size of the starch molecule and clearance rates. While starch solutions provide effective intravascular volume replacement and are convenient to administer, their use in patients with septic shock has been associated with increased risk of death, renal impairment and bleeding risk.[14,15] A recent clinical trial of 7000 intensive care unit (ICU) patients randomised to receive 6% hydroxyethyl starch (HES; 130/0.4) or 0.9% saline as resuscitation fluid found no difference in mortality; however, patients who received 6% HES had an increased need for renal replacement therapy and a greater incidence of skin reactions.[16]

RED BLOOD CELLS

The use of blood is essentially limited to shock from acute blood loss or for correcting anaemia that may be contributing to impaired oxygen delivery.

CARDIOVASCULAR MEDICATIONS

When fluid administration alone fails to restore adequate oxygen delivery, consideration should be given to augmenting the circulation with catecholamines or other agents. In extreme shock, it may be necessary to commence fluid resuscitation and vasoactive therapy concurrently. Note that increasing DO_2 *beyond* normal does not improve outcomes.[17–19]

Medications used to acutely enhance the circulation are commonly referred to as 'inotropes' as many of them increase cardiac contractility (i.e. inotropy). However, many agents have their primary effect on vascular tone rather than directly altering contractility. The choice of agent will depend on which aspect of the cardiovascular physiology is deranged, and the therapeutic effect desired.

For cardiogenic shock, medications may be required to increase contractility (e.g. dobutamine, milrinone, levosimendan), reduce afterload, maintain adequate systemic and coronary perfusion pressure, increase diastolic relaxation and increase (or decrease) HR. In distributive shock, medications are required that produce venoconstriction and restore the autoregulation of arterial flow. There is little role for cardiovascular medications in hypovolaemic shock.

The choice of which catecholamine to use in shock (i.e. noradrenaline vs. adrenaline vs. dopamine) has been the subject of considerable debate and opinion. Different catecholamines exhibit different pharmacological properties (e.g. β_1 vs. β_2 adrenergic receptor stimulation); however, the superiority of one

catecholamine over another has not been demonstrated in any large-scale clinical trials. A large, randomised trial of patients with shock reported no difference in 28-day mortality between noradrenaline and dopamine,[20] while an Australian trial found no difference between noradrenaline and adrenaline in patients with shock from any cause.[21] Similarly, in septic shock there is no mortality difference if adrenaline is used alone, or noradrenaline with dobutamine.[22] It is not surprising that there is no one 'ideal' vasoactive agent given the wide range of conditions contributing to shock and the heterogeneity of patient factors. Instead, these drugs should be chosen based on the desired therapeutic effects on the cardiovascular system.

While blood pressure is universally used as a guide to the adequacy of the circulation, and often a therapeutic target when using vasoactive agents, there are no randomised, controlled trials evaluating the ideal MAP. Choosing the ideal MAP remains empirical and should be based on the clinician's assessment of the minimum pressure thought to represent adequate blood flow. Current guidelines advocate a target MAP ≥65 mm Hg, but acknowledge that this should be altered depending on patient circumstances (e.g. chronic hypertension, penetrating trauma, head injury).[1]

MANAGE PRECIPITATING ILLNESS OR INJURY

As the circulation is being resuscitated, the cause of the circulatory disturbance needs to be identified and corrected. Time to definitive treatment of the cause of shock is related to survival. This has been clearly illustrated in cardiogenic shock (time to reperfusion),[23] haemorrhagic shock (time to haemorrhage control)[24] and septic shock (time to appropriate antibiotics).[25]

MONITORING

Outcomes from shock are greatest when it is recognised early and when the patient is managed in an environment that closely monitors clinical signs and physiological parameters (i.e. an ICU). Clinical monitoring involves frequent assessment of HR, blood pressure, respiratory rate, conscious state, urine output, peripheral perfusion and temperature. As there is no 'gold standard' measure of shock, multiple parameters should be assessed repeatedly to determine adequacy of resuscitation and treatment.[26,27]

A systemic arterial cannula is particularly useful for measuring blood pressure, while also permitting sampling for blood gas and lactate measurement. In some circumstances, the arterial waveform or its variations with ventilation can provide further insights into the haemodynamic volume status.[28]

A central venous cannula (CVC) allows measurement of central venous pressure (CVP), and is often used as an estimate of preload. However, CVP bears a variable relationship to venous volume, as it is dependent on the location of the catheter to the right atrium, intrathoracic pressures, venous compliance, position of the patient and tricuspid valve competence. Thus CVP is a guide to the *pressure* status of the venous system rather than a measure of intravascular volume and preload. The CVP does not predict whether administering a volume of fluid will change cardiac output or oxygen delivery. This has been illustrated many times, including in healthy volunteers and in patients with shock.[29–31]

There are CVCs available that contain an oximeter in the tip that measures O_2-Hb saturation of central venous blood ($ScvO_2$). This may be used as a guide to determine the O_2 demand and the adequacy of DO_2, and to help direct further resuscitation. An $ScvO_2$ ≥70% has been proposed as a resuscitation goal.[32] However, $ScvO_2$ is a general measure of global O_2 demand and does not measure the impact of coronary venous blood (from the coronary sinus). Inadequate DO_2 may still occur despite a normal or high $ScvO_2$ (e.g. anatomical shunts, microcirculation shunting). Similarly, blood sampled from a CVC and arterial cannula can be used to determine the arterial–venous difference in CO_2. Values greater than 6 mm Hg can represent increased metabolic demand, but this is not yet proven to be a reliable index to guide resuscitation.[33]

Measuring CO in patients with shock is not required routinely. For most patients, clinical assessment provides adequate information regarding CO. There is no evidence that routine monitoring of CO or targeting therapy to a specific CO improves outcomes. However, directly monitoring CO may be necessary if a patient's circulatory disturbance does not improve following initial treatment. There are an ever-increasing number of techniques available for estimating CO, all with inherent strengths and limitations. Further discussion of haemodynamic monitoring will be outlined in subsequent chapters.

Monitoring haemodynamics with ultrasound is becoming an increasingly used and recommended tool in ICU.[1,34] Echocardiography plays an important role in diagnosing the type of shock and is the recommended investigation modality if clinical examination does not lead to a clear diagnosis.[1,35] Other ultrasonic variables have been investigated to determine if they are clinically useful to guide the volume of fluid replacement. These include the size of the venae cava, the ventricular volume at end-diastole, the estimation of SV and the ejection fraction.[36] However, these techniques are operator and patient dependent, and their utility over repeated clinical assessment is unproven.

Blood gas, pH and lactate monitoring provide some guidance to the adequacy of cellular resuscitation. Inadequate oxygen delivery and/or utilisation are the most common causes of elevated serum lactate (generally defined as >2 mmol/L) in ICU patients.

Blood lactate levels, lactate clearance rates and falling base deficit are independently associated with poor outcomes[37–42] and are a better predictor of mortality than DO_2 or VO_2.[43] However, lactate is not specific for shock as elevated levels may also occur with liver failure (reduced lactate metabolism), thiamine deficiency (inhibits pyruvate dehydrogenase), lactate administration (e.g. in dialysis fluids), catecholamine administration (β-agonists) and prolonged exercise. Elevated blood lactate levels may also reflect regional dysoxia of an isolated anatomical organ or tissue (e.g. limb or bowel ischaemia) that may not necessarily be associated with a global circulatory disturbance. The role of targeting therapies to lactate clearance or base excess also remains uncertain.[44,45]

Standard ICU monitoring techniques focus on assessment of the macrocirculation. However, there is growing interest in how the microcirculation can be directly monitored. Microscopic analysis of the circulation with orthogonal polarisation spectral (OPS) imaging or near infrared spectroscopy (NIRS) provide fascinating insights into the microcirculatory status, but their use remains experimental.

KEY REFERENCES

1. Cecconi M, De Backer D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med*. 2014;40(12):1795–1815.
3. Vincent JL, De Backer D. Circulatory shock. *N Engl J Med*. 2013;369(18):1726–1734.
6. Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med*. 2013;369(13):1243–1251.
15. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012;367(2):124–134.
16. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367(20):1901–1911.
30. Marik PE, Cavallazzi R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. *Crit Care Med*. 2013;41(7):1774–1781.
33. Vallet B, Pinsky MR, Cecconi M. Resuscitation of patients with septic shock: please 'mind the gap'! *Intensive Care Med*. 2013;39(9):1653–1655.
35. McLean AS. Echocardiography in shock management. *Crit Care*. 2016;20:275.
36. McGee WT, Raghunathan K, Adler AC. Utility of functional hemodynamics and echocardiography to aid diagnosis and management of shock. *Shock*. 2015;44(6):535–541.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Cecconi M, De Backer D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med*. 2014;40(12):1795–1815.
2. Brealey D, Brand M, Hargreaves I, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. *Lancet*. 2002;360(9328):219–223.
3. Vincent JL, De Backer D. Circulatory shock. *N Engl J Med*. 2013;369(18):1726–1734.
4. Topalian S, Ginsberg F, Parrillo JE. Cardiogenic shock. *Crit Care Med*. 2008;36(1 suppl):S66–S74.
5. McPherson D, Adekanye O, Wilkes AR, et al. Fluid flow through intravenous cannulae in a clinical model. *Anesth Analg*. 2009;108(4):1198–1202.
6. Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med*. 2013;369(13):1243–1251.
7. Marr AB, Moore FA, Sailors RM, et al. Preload optimization using 'starling curve' generation during shock resuscitation: can it be done? *Shock*. 2004;21(4):300–305.
8. Cavallaro F, Sandroni C, Marano C, et al. Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies. *Intensive Care Med*. 2010;36(9):1475–1483.
9. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. Cochrane Injuries Group Albumin Reviewers. *BMJ*. 1998;317(7153):235–240.
10. Choi PT, Yip G, Quinonez LG, et al. Crystalloids vs. colloids in fluid resuscitation: a systematic review. *Crit Care Med*. 1999;27(1):200–210.
11. Wilkes MM, Navickis RJ. Patient survival after human albumin administration. A meta-analysis of randomized, controlled trials. *Ann Intern Med*. 2001;135(3):149–164.
12. Vincent JL, Navickis RJ, Wilkes MM. Morbidity in hospitalized patients receiving human albumin: a meta-analysis of randomized, controlled trials. *Crit Care Med*. 2004;32(10):2029–2038.
13. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350(22):2247–2256.
14. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008;358(2):125–139.
15. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012;367(2):124–134.
16. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367(20):1901–1911.
17. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. *N Engl J Med*. 1995;333(16):1025–1032.
18. Hayes MA, Timmins AC, Yau EH, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med*. 1994;330(24):1717–1722.
19. McKinley BA, Kozar RA, Cocanour CS, et al. Normal versus supranormal oxygen delivery goals in shock resuscitation: the response is the same. *J Trauma*. 2002;53(5):825–832.
20. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362(9):779–789.
21. Myburgh JA, Higgins A, Jovanovska A, et al. A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med*. 2008;34(12):2226–2234.
22. Annane D, Vignon P, Renault A, et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. *Lancet*. 2007;370(9588):676–684.
23. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. *JAMA*. 2006;295(21):2511–2515.
24. Cothren CC, Moore EE, Hedegaard HB, et al. Epidemiology of urban trauma deaths: a comprehensive reassessment 10 years later. *World J Surg*. 2007;31(7):1507–1511.
25. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34(6):1589–1596.
26. Pinsky MR, Payen D. Functional hemodynamic monitoring. *Crit Care*. 2005;9(6):566–572.
27. Vincent JL, Weil MH. Fluid challenge revisited. *Crit Care Med*. 2006;34(5):1333–1337.
28. Marik PE, Cavallazzi R, Vasu T, et al. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med*. 2009;37(9):2642–2647.
29. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest*. 2002;121(6):2000–2008.
30. Marik PE, Cavallazzi R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. *Crit Care Med*. 2013;41(7):1774–1781.
31. Kumar A, Anel R, Bunnell E, et al. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. *Crit Care Med*. 2004;32(3):691–699.
32. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368–1377.

33. Vallet B, Pinsky MR, Cecconi M. Resuscitation of patients with septic shock: please 'mind the gap'! *Intensive Care Med*. 2013;39(9):1653–1655.
34. Cholley BP, Vieillard-Baron A, Mebazaa A. Echocardiography in the ICU: time for widespread use! *Intensive Care Med*. 2006;32(1):9–10.
35. McLean AS. Echocardiography in shock management. *Crit Care*. 2016;20:275.
36. McGee WT, Raghunathan K, Adler AC. Utility of functional hemodynamics and echocardiography to aid diagnosis and management of shock. *Shock*. 2015;44(6):535–541.
37. Nguyen HB, Rivers EP, Knoblich BP, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med*. 2004;32(8):1637–1642.
38. Husain FA, Martin MJ, Mullenix PS, et al. Serum lactate and base deficit as predictors of mortality and morbidity. *Am J Surg*. 2003;185(5):485–491.
39. Moomey CB Jr, Melton SM, Croce MA, et al. Prognostic value of blood lactate, base deficit, and oxygen-derived variables in an LD50 model of penetrating trauma. *Crit Care Med*. 1999;27(1): 154–161.
40. Abramson D, Scalea TM, Hitchcock R, et al. Lactate clearance and survival following injury. *J Trauma*. 1993;35(4):584–588, discussion 588–589.
41. Mikkelsen ME, Miltiades AN, Gaieski DF, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med*. 2009;37(5):1670–1677.
42. Revelly JP, Tappy L, Martinez A, et al. Lactate and glucose metabolism in severe sepsis and cardiogenic shock. *Crit Care Med*. 2005;33(10):2235–2240.
43. Bakker J, Coffernils M, Leon M, et al. Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock. *Chest*. 1991;99(4):956–962.
44. Jones AE, Shapiro NI, Trzeciak S, et al. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA*. 2010;303(8):739–746.
45. Jansen TC, van Bommel J, Schoonderbeek FJ, et al. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med*. 2010; 182(6):752–761.

16

Haemodynamic monitoring

David J Sturgess, Ryan P Watts

INTRODUCTION

Haemodynamic monitoring refers to the monitoring of blood flow through the cardiovascular system. In critical care, including the intensive care unit (ICU), haemodynamic monitoring is used to detect cardiovascular insufficiency, to differentiate contributing factors and to guide therapy. Ultimately, the goal is to optimise delivery of oxygen and nutrients to the tissues.

Historically, invasive techniques prevailed. The possibility of complications and limited data demonstrating improved survival due to invasive techniques have sustained a steady trend towards less invasive monitoring in the ICU.[1]

At the bedside, the clinician must work with inexact surrogates of preload, contractility and afterload, measured or derived from arterial blood pressure (systemic or pulmonary), volume or pressure indices of cardiac filling, stroke volume or cardiac output (CO) and various markers of tissue wellbeing.

As a rough guide to the layout of this chapter, clinical observation and evaluation will be considered briefly before progressing to monitoring that is primarily concerned with the measurement of pressures (including catheterisation, equipment and techniques) and flow (CO). Functional haemodynamic monitoring, including the prediction of fluid responsiveness, will also be considered. Monitoring of perfusion in the microcirculation will be briefly mentioned also.

CLINICAL OBSERVATION AND EVALUATION

The diagnosis of acute circulatory failure should incorporate the integrated assessment of clinical, haemodynamic and laboratory data.[2]

Electrocardiographic (ECG) monitoring is almost universally indicated in the ICU. Generally, a system requiring a reduced number (<10) of electrodes is used for both patient comfort and caregiver convenience. However, it must be kept in mind that when compared to the recorded 12-lead ECG, reconstructed 12-lead ECG data appear to retain specificity but can be significantly less sensitive across a range of rhythmic and morphological abnormalities.[3]

PRESSURE-BASED CARDIOVASCULAR MONITORING

This section will discuss pressure-based monitoring techniques. Equipment, methods and supplementary variables will be discussed under the most applicable headings also.

ARTERIAL BLOOD PRESSURE

During the passage of the arterial pressure wave from the aortic root into the peripheral vasculature, there is a progressive increase in systolic blood pressure (SBP) and a reduction in diastolic blood pressure (DBP). This process, known as distal wave amplification, results from the incorporation of standing and reflected waves. Consequently, systemic arterial pressure measurements vary according to the site of measurement.

Mean arterial pressure (MAP) is arguably more relevant than either SBP or DBP for three reasons:

- MAP is least dependent on measurement site or technique (invasive vs. non-invasive).
- MAP is least altered by measurement damping.
- MAP determines tissue blood flow via autoregulation (apart from the left ventricle, which autoregulates from diastolic pressure).

NON-INVASIVE ARTERIAL BLOOD PRESSURE MEASUREMENT

In critical care, most standard non-invasive arterial blood pressure (NIBP) instruments are automated intermittent oscillometric devices. Oscillometric NIBP provides rapid, easy assessment of blood pressure and can be used alone when beat-to-beat monitoring is not required. Contraindications to NIBP are relative and influence cuff placement. It is preferable to avoid extremities with severe peripheral vascular disease, venous cannulation, arteriovenous fistula or a predisposition to lymphoedema, as may occur after lymph node clearance.

To make an oscillometric blood pressure measurement, a pneumatic cuff is inflated around a proximal limb until all oscillations in cuff pressure are extinguished. The occluding pressure is then lowered

ABSTRACT

Haemodynamic monitoring refers to the monitoring of blood flow through the cardiovascular system. In critical care, it is applied to detect cardiovascular insufficiency, differentiate contributing factors and guide therapy. Haemodynamic monitoring encompasses a broad range of evaluation and measurement techniques. It is recommended that the clinician assimilates all available information to optimise patient management. A trend towards non-invasive techniques has been propagated by a number of factors including: the risks and complications of invasive monitoring; a paucity of data relating improved outcome to the invasiveness of the technique; and increasing availability, affordability and accuracy of less invasive devices. Rather than focusing on specific devices, this chapter aims to categorise techniques and explain their underlying principles.

KEYWORDS

cardiovascular measurement
cardiovascular system
left ventricle
right ventricle
blood pressure
blood flow
stroke volume
cardiac output
catheter
non-invasive

stepwise, so that oscillations reappear over a discrete interval. Maximal oscillations concur with MAP, and proprietary algorithms compute reported pressures from the alterations in oscillatory amplitude during deflation.[4] Oscillometry overestimates low pressures and underestimates high pressures compared to intra-arterial monitoring, but for the normotensive range the 95% confidence intervals are ±15 mm Hg (2 kPa). Dysrhythmia increases the error, and reliability may be suboptimal in pregnancy and childhood. Cuff width should be 40% of the mid-circumference of the limb. Narrower cuffs overestimate and wider cuffs underestimate blood pressures. Oscillometric devices should be validated in a standard fashion and may not be automatically interchangeable. Complications are unusual. Repeated cuff inflations can cause skin ulceration, oedema and bruising – more so when the patient's consciousness is impaired by illness and sedation. Ulnar nerve injury is also possible, especially with cuff placement encroaching upon the elbow.

Continuous non-invasive blood pressure monitoring has also been developed. The benefits of such techniques may be nullified if frequent blood sampling is required for gas analysis and other tests, in which case an intra-arterial cannula is likely to be indicated.

The volume-clamp technique uses an infrared light transmission/receiving system to measure finger artery size. An inflatable pressure bladder around the finger is adjusted via a proprietary algorithm to clamp the artery to a constant size. A reference sensor is placed at heart level. The resultant changes in bladder pressure are then able to be displayed as an arterial blood pressure waveform. Manipulation of these data can produce derived haemodynamic variables, such as CO, stroke volume, stroke volume variation and systemic vascular resistance. The volume-clamp method is challenged by conditions that impair finger perfusion or plethysmography, such as vasoconstriction of finger vessels or oedema; these conditions are common in critically ill patients, but should be less of a hindrance in the perioperative setting.

Applanation tonometry is also capable of continuous measurement. The most appropriate position over the radial artery is determined by an electromechanical system, which places the sensor in such a way that the transmural pressure is zero. This allows direct measurement of the MAP and the arterial trace can be determined. Readings are easily interrupted by movement due to the patient or the care.

Original validation studies for these newer continuous techniques were not optimal. Further refinement has shown promising results.[1,5]

INVASIVE BLOOD PRESSURE MEASUREMENT

Invasive measurement is desirable in the presence of haemodynamic instability, end-organ disease requiring beat-to-beat blood pressure monitoring, during therapeutic manipulation of the cardiovascular system or if non-invasive methods fail.[2] Cannulation of a systemic artery allows continuous monitoring of the arterial pressure waveform, heart rate and blood pressure, and also facilitates blood testing. Relative contraindications include coagulopathy and vascular abnormality or disease.

To minimise the risk of infection in adults, the radial, brachial and dorsalis pedis arteries are preferred, whereas paediatric recommendations include the posterior tibial artery but not the brachial artery.[6] The radial artery is the most common site for cannulation due to ease of cannulation, relatively consistent anatomy and low complication rates (incidence of permanent ischaemic complications ~0.09%). Nothing larger than a 20-gauge cannula is advisable, and either a modified Seldinger technique or direct cannulation can be used. The modified Allen's test is sometimes employed prior to cannulation to assess for collateral flow. Evidence is lacking regarding its ability to predict ischaemic complications of radial artery cannulation.[7] Ultrasound might be a more reliable way of confirming collateral perfusion, as well as potentially improving cannulation rates with fewer attempts.

Once inserted, the cannula is usually infused with normal or heparinised saline at 3 mL/h, with a snap flush rate of 30–60 mL/h. The use of heparinised saline to prolong catheter patency must be balanced against the potential contamination of blood samples drawn through the cannula (especially activated partial thromboplastin time [APTT]) and concerns regarding sensitisation and development of heparin-induced thrombosis thrombocytopenia syndrome (HITTS).

Peripheral arterial catheters should be removed when no longer required and replaced only when clinically indicated.[6] Distal perfusion should be checked at least 8-hourly, and the cannula removed if there is persistent blanching, coolness with sluggish capillary refill, loss of pulses or evidence of raised muscle compartment pressures. Arterial cannulation may be associated with a number of complications (Table 16.1).[8]

Physical properties of clinical pressure measurement systems

In the standard setup, the arterial cannula is connected to a linearly responsive pressure transducer via fluid-filled, short, non-compliant tubing.[9] Modern disposable transducers are precalibrated using electrical signals, and are not normally calibrated further. The system is zeroed to the level of the phlebostatic axis, normally the mid-axillary line at the fourth intercostal space. Subsequent lowering of the transducer relative to this axis will cause pressure overestimation, while raising it will cause underestimation.

The *natural resonant frequency* of the system should exceed 36 Hz (>10 harmonics with allowance for optimal damping, which allows measurement of up to 67% of resonant frequency) for heart rates up to 180

Table 16.1 Complications of arterial cannulation, with suggested preventative and treatment option

COMPLICATION	PREVENTION	TREATMENT
Vascular thrombosis (ranges from 7% to 30% following radial artery cannulation). Risk factors for digital ischaemia include: shock, sepsis, embolus of air or clot, hyperlipoproteinaemia, vasculitis, female sex, prothrombotic states and accidental intra-arterial injection of drugs	Risks reduced by smaller catheter, larger artery, decreased duration of cannulation, avoiding traumatic insertion and multiple attempts. Allen's test (including modifications such as Doppler, plethysmography and digital blood pressure) is probably unhelpful	Remove cannula. Arterial thrombosis is usually self-limiting. Severe ischaemic damage estimated at <0.01%. Anticoagulation and/or vascular surgery/intervention may be necessary
Distal embolisation	Diligent catheter care and observation	As for thrombosis
Proximal embolisation of clot or air (can result in stroke)	Diligent catheter care and observation. Exclude air from pressurised system. Avoid axillary, subclavian or carotid access	Tailored to sequelae
Vascular spasm	Smaller catheter, larger artery, avoid traumatic insertion and multiple attempts	Remove cannula. Resite if necessary
Skin necrosis at catheter site	Diligent catheter care and observation	Surgical debridement and skin grafting may be necessary
Line disconnection and bleeding/exsanguination	Minimise connections. Diligent catheter care and observation	Control bleeding. Transfusion may be necessary
Accidental drug injection	Clearly label arterial line near ports	Leave cannula in situ to facilitate treatment if required. Depends on drug injected. May require papaverine or procaine, analgesia, sympathetic block of limb and anticoagulation
Infection – local or systemic	Diligent catheter care and observation	Remove cannula and send tip for culture. Resite if necessary. Immobilise and elevate affected upper limb. Start empiric antibiotics if sepsis or septic shock is present
Damage to nearby structures such as nerves, directly or due to haematoma (e.g. compartment syndrome or carpal tunnel syndrome). Arteriovenous fistula. Femoral approach can be associated with bowel damage	Careful insertion technique. Seek assistance from experienced operator	Haematomas can develop into pseudoaneurysms requiring surgery

beats/min (3 Hz), to prevent distortion of the biological signal by sine wave system oscillations. *Damping* refers to any property of an oscillatory system that reduces the amplitude of oscillations. Factors that increase oscillation in the system, such as increased tubing length, diameter or compliance, cause underdamping. Overdamping tends to smooth the waveform, causing underestimation of SBP and overestimation of DBP, while MAP tends to be preserved. Contributing factors include clots, air bubbles and loose connections.

Damping can be assessed clinically by the fast flush or square wave test. This test is performed by opening the valve, thus transmitting the pressure from the pressure bag, of the continuous flush apparatus. This is then released/closed abruptly, inducing oscillation. With appropriate damping, the measured pressure should come to reflect the biological signal within one or two oscillations.

Upstream resistance or turbulence can result in a flow-dependent pressure reduction at the cannula site that differs from damping in that the mean, systolic and diastolic pressures are all reduced. This is described as *attenuation* and is often observed in 'positional' arterial lines.

CENTRAL VENOUS CATHETERISATION

Central venous catheterisation (CVC) enables monitoring of central venous pressure (CVP) and administration of certain drugs or parenteral nutrition. In addition, it may be used as a component of transpulmonary indicator dilution systems for CO monitoring. Modified catheters are also available, which continuously monitor central venous oxygen saturation (Scv_{O2}).

Contraindications to CVC are relative and reflect potential complications of the procedure (Table 16.2).[10,11] The subclavian site is preferred to internal jugular or femoral approaches with regard to minimising the

Table 16.2 Complications of central venous catheterisation, with preventative and treatment options

COMPLICATIONS ON INSERTION		
COMPLICATION	PREVENTION	MANAGEMENT
Failure of insertion	Appropriate training, use of ultrasonography, understanding of anatomy and landmarks, appropriate site selection. Other advanced techniques may need to be employed (e.g. fluoroscopic insertion)	Appropriate training and supervision of junior staff
Damage to other structures in the region of insertion. Structures are dependent on location of insertion such as: Arteries (carotid, innominate, aorta, femoral, subclavian) Nerves (femoral, laryngeal, phrenic) Aerodigestive structures (pneumothorax, trachea, oesophagus, bowel) Other vital structures (hernial contents, thoracic duct)	Appropriate site selection, consideration of individual variation (such as prior lines, surgery, anatomical deformity). Appropriate training and understanding of insertion techniques, anatomy in the region of interest and supervision when required. Application of ultrasound	Management will depend specifically on the structure injured. Minor vascular injuries may require only local compression, however large injuries (e.g. after dilatation with a dialysis catheter) may require surgical repair. Consultation with the appropriate specialties
Damage to target vessel, including haematoma, fistula, laceration, bleeding (including massive haemorrhage)	Appropriate technique, including site selection and awareness of depth of insertion of needle. Care with stiffer catheters or equipment to avoid excessive force. Live ultrasound scanning, ensuring that the needle tip is not lost from view, may be considered	Dependent on the degree of injury. May require consultation with the appropriate specialties
Air embolism	Flushing of catheters with sterile saline prior to procedure, positioning of patient (including Trendelenberg for upper body access), cover potential sites of air ingress, monitor connections for seal. May also be a complication on removal of line	Position the patient to left lateral, 100% oxygen and initiate appropriate resuscitative manoeuvres, including CPR as necessary. Consideration may be given to attempting to aspirate air
Drug error and allergy	Confirm allergies prior to commencing procedure. Develop and implement systems to identify drug containing syringes from those with saline flush	Manage reaction as appropriate. This may include CPR or specific protocols (including local anaesthetic toxicity)
Dysrhythmia from cardiac irritation	Care with depth of insertion of wire at jugular and subclavian sites. Continuous cardiac monitoring	Removal or withdrawal of wire or catheter
Wire fracture, damage or loss	Care with insertion, avoiding resistance. Maintain control of wire at all times. Confirmation of complete wire removal at completion of procedure	May require removal via surgical or radiological intervention

Continued

Table 16.2 Complications of central venous catheterisation, with preventative and treatment options—cont'd

COMPLICATIONS ON INSERTION		
COMPLICATION	PREVENTION	MANAGEMENT
Malposition	Appropriate catheter length, depth of insertion and site selection. Patient positioning or other techniques (e.g. jugular vein compression for PICC lines) may assist with placement. Ultrasound guidance may be helpful. Confirmation during insertion, such as ultrasound scanning other related vessels (internal jugular when placing subclavian line), echocardiography or line pressure transduction. Blood gas analysis can discern arterial from venous placement. Radiological confirmation post insertion	Not using line until placement is confirmed reduces risks of complications. Readjust line, or remove and replace
LONGER TERM COMPLICATIONS		
COMPLICATION	PREVENTION	MANAGEMENT
Infection, including insertion site, remote sites such as valvular endocarditis, or sepsis	Proper insertion maintaining sterility. Use of antimicrobial/antiseptic patches, or impregnated lines. Minimising number of lumens. Surveillance of lines with removal if infection is suspected. Removal of lines that are blocked. Aseptic technique in accessing lines or ports	Removal of lines, antimicrobial therapy if appropriate
Thrombosis	Site selection (subclavian lower risk). Selection of catheters with smaller diameters. Correct placement lower SVC/high right atrium. Removal of catheter when not required. DVT prophylaxis as part of routine ICU care	Removal of line. Anticoagulation may be required. Surgical intervention or placement of caval filter may be considered
Erosion through vital structures (vena cava, atria)	Less common with modern catheters. Proper placement of line with confirmation. Removal of line when not required	Likely to require early surgical intervention
Vascular stenosis	Appropriate size catheter – smaller devices reduce vascular injury on insertion and while in place. Select appropriate location (avoid dialysis catheters in subclavian vein)	May require surgical or endovascular intervention
Line breakage, or disruption of connections with bleeding or air embolism	Minimising excess length of line outside of patient, care with line securement and avoiding kinks. Care with manipulation of lines, avoiding pulling or stress. Maintain connections	Removal and replacement of line (if required) depending on degree of disruption. Surveillance for evidence of line related infection in the case of disruption with exposure to non-sterile surroundings

Table developed from consultation of the following guidelines:

Association of Anaesthetists of Great Britain and Ireland. Safe vascular access 2016. Anaesthesia 2016; 71: 573-585

Australian and New Zealand Intensive Care Society [Internet]. Melbourne; 2012. ANZICS Safety and Quality Committee. Available from www.clabsi.com.au and www.anzics.com.au

risk of central-line-associated bloodstream infections (CLABSI).[6,11] However, routine replacement of central lines does not appear to reduce CLABSI.

Multiple societies now recommend ultrasound-guided central venous access.[12,13] Two-dimensional (2D) imaging with ultrasound can be used to localise the vein and define anatomy prior to placement of a CVC by landmark techniques. Ultrasound can also provide real-time, 2D guidance during CVC insertion, which is generally preferred.

For catheters inserted via veins draining to the superior vena cava, the right tracheobronchial angle and carina are common radiological markers of insertion depth. Ensuring that the catheter is parallel to the long axis of the vein reduces the risk of venous erosion.[14]

Many patients with chronic illness, such as malignancy, require long-term CVC (including peripherally inserted central catheters [PICC]). Complications, such as central line-associated bloodstream infection and thrombosis (concomitant risk of catheter infection, pulmonary embolus and post-thrombotic syndrome), may require ICU admission and management. The management of such complications is described in Table 16.2. In the setting of thrombosis, immediate removal is not necessarily advised.[15]

CENTRAL VENOUS PRESSURE

Jugular venous pressure, CVP and right atrial pressure are often used interchangeably. However, in situations associated with increased central venous resistance, such as central vein sclerosis and stenosis, these pressures may not be the same.

CVP is usually monitored using a fluid-filled pressure transduction system similar to that used to measure invasive arterial pressures. Waveform analysis is also possible (Table 16.3). The normal CVP in the spontaneously breathing supine patient is 0–5 mm Hg (0–0.65 kPa), while 10 mm Hg (1.3 kPa) is generally accepted as the upper limit during mechanical ventilation. In health there is a good correlation between CVP and pulmonary artery occlusion pressures (PAOPs), but this is lost in many types of critical illness involving cardiac function or pulmonary circulation. The relationship between CVP and right ventricular end-diastolic volume (RVEDV; preload) is altered in critical illness by changes in right ventricular diastolic compliance and juxta-cardiac pressures.[16]

Except at extreme values, static measures of CVP do not differentiate patients likely to respond to fluid therapy from non-responders (see Functional Haemodynamic Monitoring section). Traditionally, dynamic changes in CVP, either in response to volume loading or related to respiration, have been used to assist in evaluating volume status,[17] but these principles may be misapplied.

A steep increase in CVP following volume challenge may suggest that the heart is functioning on the plateau portion of the Frank-Starling curve. Severe hypotension with a low or normal CVP is unlikely to be solely due to acute pulmonary embolism, cardiac tamponade or tension pneumothorax.

CENTRAL VENOUS OXYGEN SATURATION

Central venous oxygen saturation (Scv_{O2}) is an additional variable that may be monitored with a central venous catheter (continuously or via blood gas analysis of samples). It has been proposed as a marker of tissue oxygen delivery (Chapter 18). Scv_{O2} rose to prominence as part of Early Goal Directed Therapy (EGDT) protocols for sepsis management but large international multicentre trials, including ARISE (Australasia), ProCESS (USA) and ProMISE (UK) and a consequent meta-analysis concluded that Scv_{O2}, as part of EGDT, is unnecessary.[18]

PULMONARY ARTERY CATHETER

Right-sided heart catheterisation using a flow-directed balloon-tipped catheter was introduced by Swan and colleagues in 1970.[19a] The ability to monitor sophisticated haemodynamic and gas exchange variables at the bedside appealed to clinicians, and the pulmonary artery catheter (PAC) was rapidly accepted into routine critical care. However, this device is potentially associated with a number of risks (Table 16.4).[19b]

Table 16.3 Analysis of central venous pressure waveform

CONDITION	PRESSURE CHANGES	WAVEFORM CHANGES
Tricuspid regurgitation	Increased RA pressure	Prominent *v* wave, *x* descent obliterated, *y* descent steep
RV infarction	RA and RV pressure elevated. RAP does not fall and may rise in inspiration	Prominent *x* and *y* descents
Constrictive pericarditis	RA, RV diastolic, PA diastolic and occlusion pressures elevated and equalised. RAP may rise in inspiration	Prominent *x* and *y* descents
Pericardial tamponade	RA, RV diastolic, PA diastolic and occlusion pressures elevated and equalised. RAP usually falls in inspiration	Y descent damped or absent

PA, Pulmonary artery; *RA,* right atrial; *RAP,* right atrial pressure; *RV,* right ventricular.

Table 16.4 Complications potentially encountered with pulmonary artery catheterisation with proposed measures for prevention and treatment

COMPLICATIONS	PREVENTION	TREATMENT
DURING INSERTION		
Damage to adjacent structures	As for central venous cannulation	As for central venous cannulation
Perforation of pulmonary artery	Ensure balloon inflated throughout insertion. Continuously monitor pulmonary artery waveform. Avoid distal PAC tip position	As for pulmonary artery rupture below
Air embolism	Raise venous pressure prior to insertion. Always occlude open ends during insertion. Use sheaths with pneumatic valve. Periodically check and tighten all connections. Remove air from fluid bag and tubing. Dress site with occlusive dressing after removal	Left lateral Trendelenburg position. Administer 100% oxygen and ventilatory support. If PAC in place tighten all connections and attempt to aspirate air from right atrium or right ventricle. Basic/advanced life support if necessary
Dysrhythmia (12.5%–70%)	Keep balloon inflated during passage from RA to PA. Minimise insertion time	For sustained ventricular tachycardia, remove PAC from right ventricle. For ventricular fibrillation, remove PAC. Advanced life support for persistent dysrhythmia
Right bundle branch block/complete heart block	Avoid PAC insertion in patients with LBBB if possible. Insert PAC with pacing electrodes in patients with LBBB	Use pacing equipment as required
Catheter knotting/ kinking/ entanglement	Minimise insertion time. Do not advance catheter against resistance. Check for waveform change from RA to RV or RV to PA after advancing 15 cm; if not withdraw catheter. Limit intravascular PAC insertion depth <60 cm. Use of fluoroscopy	Check chest X-ray. Pull knot back then remove the sheath and catheter. If no sheath used, a cut-down to vein under local anaesthesia may be required. Exploration by a vascular surgeon is indicated if unsuccessful (5% of occasions)
Valve/chordae damage (~0.9%)	Ensure balloon is inflated during forward passage through the heart and deflated prior to any retraction	Cardiothoracic consultation
DURING MAINTENANCE		
Dysrhythmia (37%)	Remove PAC when no longer required	See above
Thrombosis	As for central venous cannulation	As for central venous cannulation
Pulmonary artery rupture (0.2%)	Risk factors include pulmonary hypertension, anticoagulation and in situ duration >3 days. Maintain high level of suspicion. Avoid distal PAC tip position. Minimise wedge procedures. Continuously monitor pulmonary artery waveform – withdraw PAC if spontaneous wedging occurs, inflate with only enough air to change PA to PAOP waveform. Withdraw PAC if PAOP obtained with <1.25 mL air	Check PAC position on CXR, deflate and pull back. If applicable, stop anticoagulation therapy. Lateral position, affected side down. Selective bronchial intubation. PEEP. Surgical repair
Pulmonary infarction	As for pulmonary artery rupture	Check PAC position on CXR, deflate and pull back. Observe
Infection – including blood stream infection/ bacteraemia (1.3%–2.3%) and endocarditis (2.2%–7.1%)	As for central venous cannulation	As for central venous cannulation

Table 16.4 Complications potentially encountered with pulmonary artery catheterisation with proposed measures for prevention and treatment—cont'd

COMPLICATIONS	PREVENTION	TREATMENT
Air embolism	High suspicion of balloon rupture. Avoid repeating failed attempts to inflate	See above
Misinterpretation/ misuse of data	Anticipation and management of common pitfalls related to errors of equipment and data acquisition. Factors affecting data interpretation	Patient selection, individualisation of therapy, an understanding of potentially useful haemodynamic data, as well as an appreciation of alternative monitoring strategies are suggested

CXR, Chest X-Ray; *LBBB,* left bundle branch block; *PA,* pulmonary artery; *PAC,* pulmonary artery catheter; *PAOP,* pulmonary artery occlusion pressures; *PEEP,* positive end expiratory pressure; *RA,* right atrial; *RAP,* right atrial pressure; *RV,* right ventricular.

In 1996, a non-randomised cohort study of PAC use in American teaching hospitals appeared to show that PAC in the first 24 hours increased 30-day mortality (odds ratio, 1.24; 95% confidence interval [CI], 1.03–1.49), mean length of stay and mean cost per hospital stay.[20] An associated editorial called for a moratorium on PAC use, and for a prospective multicentre trial.[21] Although a moratorium did not eventuate, the debate contributed to clinical equipoise and paved the way for a number of randomised trials.

A recently edited Cochrane database systematic review of PAC monitoring in adult ICU patients incorporated data from 13 randomised controlled trials in adults.[22] The pooled odds ratio for mortality for the eight studies of high-risk surgery patients was 0.98 (95% CI, 0.74–1.29) and for the five studies of general intensive care patients was 1.02 (95% CI, 0.96–1.09). The authors conclude that PAC monitoring in critically ill patients is not associated with increased mortality, nor ICU or hospital length of stay.

The routine use of PAC is increasingly scrutinised. The possibility that application in specific cases might alter or guide therapy towards improved outcome remains valid. This should be balanced against the prospect of potentially serious complications and the availability of less invasive techniques that may deliver similar information.[23] Overall, the PAC still finds application in anaesthesia and critical care. It potentially offers unique insights into the right heart and pulmonary circulation.

Traditional indications for PAC monitoring have been to:

- clarify the cause of haemodynamic perturbation
- differentiate cardiogenic from non-cardiogenic pulmonary oedema
- guide use of vasoactive drugs and fluid management (including renal replacement therapy), especially when haemodynamic disturbances are coupled with increased lung water, right ventricular (RV) or left ventricular (LV) dysfunction, pulmonary hypertension and organ dysfunction.

Table 16.5 Reference range of measured and derived variables from pulmonary artery catheter

SITE	mm Hg	(kPa)
Right atrium mean	–1–7	(0.13–0.93)
Right ventricle: systolic	15–25	(2.0–3.3)
Right ventricle: diastolic	0–8	(0–1.1)
Pulmonary artery: systolic	15–25	(2.0–3.3)
Pulmonary artery: diastolic	8–15	(1.1–2.0)
Pulmonary artery: mean	10–20	(1.3–2.6)
Pulmonary artery occlusion pressure	6–15	(0.8–2.0)

Contraindications for insertion build upon those for CVC. If known in advance, atypical vascular or cardiac anatomy or electrophysiology should also be considered.

MEASURED VARIABLES

The PAC remains unique in its ability to measure right ventricular and pulmonary arterial pressures directly at the bedside. While echocardiography is a less invasive alternative, it is typically confined to intermittent 'snap-shot' evaluation, and can be technically challenging.[24] Normal pressures are given in Table 16.5.

Pulmonary artery occlusion pressure

PAOP is measured by the slow injection of air into the balloon while watching the pulmonary artery waveform. Over-wedging can lead to falsely high occlusion pressures or pulmonary arterial rupture. Less than 1.5 mL air (balloon volume) may be required.

Table 16.6 Derived haemodynamic variables

PARAMETER	ABBREVIATION	FORMULA	NORMAL RANGE	UNITS
Mean arterial pressure	MAP	DBP + 0.33 × (SBP – DBP)*	70–105	mm Hg
Mean pulmonary artery pressure	MPAP	PADP + 0.33 × (PASP – PADP)*	9–16	mm Hg
Mean right ventricular pressure	MRVP	CVP + 0.33 × (PASP – CVP)		mm Hg
LV coronary perfusion pressure	LVCCP	DBP – PAOP		mm Hg
RV coronary perfusion pressure	RVCCP	MAP – MRVP		mm Hg
Cardiac index	CI	CO/BSA	2.8–4.2	L/min/m^2
Stroke volume index	SVI	CI/HR	35–70	mL/beat/m^2
Systemic vascular resistance index	SVRI	(MAP – CVP)/CI × 79.92	1760–2600	dyn s/cm^5/m^2
Pulmonary vascular resistance index	PVRI	(PAP – PAOP)/CI × 79.92	44–225	dyn s/cm^5/m^2
Left ventricular stroke work index	LVSWI	SVI × MAP × 0.0144	44–68	g m^2/beat
Right ventricular stroke work index	RVSWI	SVI × PAP × 0.0144	4–8	g m^2/beat
Body surface area	BSA	Weight $(kg)^{0.425}$ × height $(cm)^{0.725}$ × 0.007184		m^2

*Modern monitors use a more accurate technique; they average the area under the pressure–time curve to estimate mean pressure.
CVP, Central venous pressure; *DBP,* diastolic blood pressure; *HR,* heart rate; *LV,* left ventricular; *PADP,* pulmonary artery diastolic pressure; *PAOP,* pulmonary artery occlusion pressure; *PASP,* pulmonary artery systolic pressure; *RV,* right ventricular; *SBP,* systolic blood pressure.

Deflation after PAOP measurement should re-establish the normal pulmonary arterial waveform. If not, distal migration has occurred and the catheter should be withdrawn until the waveform is re-established.

PAOP should be measured during end expiration and ideally in end diastole, using the ECG p-wave as a marker. When the catheter is wedged, it creates a static column of blood that equilibrates with downstream pressure at a site very near the left atrium. PAOP therefore closely approximates left atrial pressure (LAP), which approximates left ventricular end-diastolic pressure (LVEDP). The validity of PAOP as a surrogate of preload depends on a number of assumptions that are often incorrect in critically ill patients. The use of PAOP to reflect preload has been questioned.

Potential substitutes for pulmonary artery occlusion pressure

Measurement of PAOP requires wedging, which is associated with a number of risks. The normal pulmonary artery diastolic pressure (PADP) to PAOP gradient is less than 5 mm Hg (0.65 kPa), so that PADP may substitute as a close approximation for PAOP. However, tachycardia (>120/min) and conditions that increase pulmonary vascular resistance variably alter this gradient, invalidating direct substitution of PADP for PAOP. The relationship between PADP and PAOP tends to be stable over hours, allowing PADP to be monitored in the short term without repeated wedge manoeuvres.

B-type natriuretic peptide (BNP) is secreted by the heart in response to myocardial stretch or strain. It is potentially useful as a biomarker of heart failure. Its application to intensive care medicine has been hindered by a multitude of potential confounders.[25] BNP has not demonstrated value in the prediction of fluid responsiveness or in screening for left ventricular diastolic dysfunction.[26,27]

Echocardiographic measurements, such as transmitral flow, mitral annulus velocity (tissue Doppler) and pulmonary venous flow, can provide evidence of elevated left ventricular filling pressure (the hallmark of diastolic dysfunction).[28]

DERIVED VARIABLES

A number of variables can be derived from the measurements obtained with a standard PAC (see Table 16.5 and Table 16.6).

MIXED VENOUS OXYGEN TENSION AND SATURATION

These variables are discussed in Chapter 18.

CARDIAC OUTPUT MONITORING

Clinical estimation of CO is unreliable until extreme hypotension occurs.[29] A multitude of commercially available devices are approved for CO estimation in critical care. Most devices employ proprietary algorithms. Marketing strategies, patented/trademarked terminology and inconsistencies in nomenclature potentially contribute to confusion. A classification of techniques is presented in Table 16.7.

Table 16.7 Classification of methods for evaluating cardiac output in critical care: a variety of techniques primarily estimate stroke volume, multiplication by heart rate calculates cardiac output

CARDIAC OUTPUT	STROKE VOLUME
Fick method (O_2)	Ultrasound • 2D echocardiography (Simpson's method) • Doppler (continuous or pulsed wave)

Indirect Fick method (CO_2)
• Partial rebreathing technique
	Arterial pressure waveform analysis
	• Invasive
	• Non-invasive
	  • volume-clamp method
	  • tonometry

Indicator dilution • Thermodilution • Lithium • Indocyanine green • Ultrasound indicator dilution (saline) • Ultrasound contrast	Thoracic electrical bioimpedance

APPLICATION OF THE FICK PRINCIPLE

The Fick principle is an extension of the law of conservation of mass and states that the amount of a substance taken up by an organ (or the whole body) per unit time is the product of the arteriovenous concentration difference by the blood flow to the organ (or body).

A number of techniques used to measure CO are based upon the Fick principle. The substance measured can include oxygen (Fick method), carbon dioxide (indirect Fick method) or apply an indicator dilution method.

THE FICK METHOD

Historically the Fick principle has been applied to determine CO by analysing oxygen uptake from the lungs (direct Fick method). This method requires pulmonary artery catheterisation to sample mixed venous blood. It has been considered the 'gold standard', but in most ICU patients the stringent preconditions for accuracy are not met. Further error is introduced by the elevated oxygen consumption of inflamed lungs. Use is therefore mainly confined to cardiac laboratories.

THE INDIRECT FICK METHOD

The indirect Fick method employs carbon dioxide (CO_2) as an alternative to oxygen. The use of a partial rebreathing technique, incorporating several assumptions, can be used to eliminate the need to directly measure Cv_{CO2} with a PAC.[30] The rebreathing values are obtained by introducing an additional 150 mL of dead space into the ventilator circuit (disposable rebreathing loop) and taking measurements once a new equilibrium has been established. CO can be measured at 3-minute intervals. Assuming that the Cv_{CO2} concentration does not change significantly throughout the rebreathing period, the terms associated with Cv_{CO2} cancel each other out and are not needed to calculate CO.

Potential issues with the partial rebreathing of CO_2 method include the following:

- It is unsuitable for non-intubated patients (who have variable tidal volumes and leakage around face masks).
- Changes in mechanical ventilator settings that alter dead space or ventilation/perfusion relationships may result in an artefactual change in CO measurements. The accuracy of the technique also appears to be challenged by spontaneous mechanically assisted ventilation.
- $ETCO_2$ may not accurately reflect change in pulmonary end-capillary and $PaCO_2$, especially in chronic lung disease.
- Mathematical models rely upon a series of assumptions that may not be true under certain conditions relevant to critical care.
- There is overall lack of validation in chronic lung disease.

BOLUS THERMODILUTION CARDIAC OUTPUT

This technique utilises a PAC and is generally accepted as the clinical gold standard due to applicability at the bedside, clinician familiarity and reasonable accuracy.

A bolus injection into the right atrium of cold injectate transiently decreases blood temperature in the pulmonary artery (monitored by a thermistor proximal to the balloon). The mean decrease in temperature (calculated by integrating temperature over time) is inversely proportional to the CO, which can be determined by a modification of the Stewart–Hamilton equation:

$$Q = \frac{V \times (Tb - Ti) K1 \times K2}{Tb(t)\,dt} \quad (16.1)$$

where Q = cardiac output; V = volume injected; Tb = blood temperature; Ti = injectate temperature; $K1$ and $K2$ = corrections for specific heat and density of injectate and for blood and dead space volumes; $Tb(t)dt$ = change in blood temperature as a function of time.

This is an indicator dilution method, using lower thermal energy content as the indicator. Advantages of using thermal energy as an indicator are that it is non-toxic (temperature of injectate used does not cause thermal injury) and it does not recirculate. Repeat measurements are limited only by volume constraints and the time to regain temperature stability between

Box 16.1 Causes of inaccurate bolus thermodilution cardiac output measurements

- Catheter malposition
  - Wedge position
  - Thermistor impinging on vessel wall
- Abnormal respiratory pattern
- Intracardiac shunts
- Tricuspid regurgitation (common in mechanically ventilated patients)
- Cardiac dysrhythmias
- Incorrect recording of injectate temperature (minimised by siting an additional thermistor on the injection port)
- Rapid intravenous infusions, especially if administered via the introducer sheath
- Injectate port close to or within introducer sheath
- Abnormal haematocrit values (affecting *K*2 value)
- Extremes of cardiac output (room temperature injectate)
- Poor technique
  - Slow injection (>4 seconds)
  - Incorrect injectate volume

injections. A clinically significant change in CO cannot be diagnosed with certainty unless there is a difference of approximately 15% between the mean of three CO determinations and the previous mean.[31]

Too much or too little injectate will respectively underestimate and overestimate CO. Cold injectate (preferably 0–4°C but up to 12°C is usually accepted) improves the signal to noise ratio, but may cause a transient decrease in heart rate, reducing CO while it is being measured. Room temperature injectate introduces a small decrement in bias and precision, but has acceptable accuracy. However, the accuracy using room temperature injectate is further degraded at extremes of cardiac index, high ambient temperatures (and thus injectate temperature) or in patient hypothermia.[32]

Respiration causes fluctuations in CO and pulmonary artery temperature. Reproducibility is improved by taking measurements in expiration, though this may not reflect CO throughout the respiratory cycle. Timing can be difficult and in practice an average of three evenly spaced measurements is taken. The causes of inaccurate measurements are listed in Box 16.1.

SEMI-CONTINUOUS THERMODILUTION CARDIAC OUTPUT

This method uses the same principles as bolus thermodilution, but allows semi-continuous measurement by employing a thermal filament wrapped around the right ventricular segment of the catheter.[33] This transmits low-power pulses of heat. 'On–off' heat pulses in pseudo-random binary code are delivered in cycles. The downstream thermistor detects the heat pulses, which are then cross-correlated with the input sequence and power (to allow differentiation of thermal signal from noise).

Potential drawbacks of the technique include:

- inaccuracy during thermal disequilibrium, such as rapid infusions of cool fluids or after cardiac bypass
- delay in detecting sudden changes in CO
- magnetic resonance imaging is contraindicated (it can melt the thermal filament)
- electro-cautery can interfere with measurements.

Additional volumetric data

As well as allowing semicontinuous assessment of CO, incorporation of a rapid response thermistor into the PAC allows estimation of right ventricular ejection fraction (RVEF) and RVEDV. Thermodilution techniques appear to overestimate RVEDV and underestimate RVEF.[34] However, right ventricular geometry is complex and there are limited options for bedside volumetric evaluation.[24]

TRANSPULMONARY INDICATOR DILUTION

With this technique, thermal and other indicators injected into a central vein are detected in a systemic artery. Because the indicators pass through all chambers of the heart, as well as the entire pulmonary circulation, central blood volumes, and indices of extravascular lung water (EVLW) can be quantified (Fig. 16.1).

Transpulmonary thermodilution

A thermistor is usually positioned in the femoral artery at the tip of a modified arterial catheter.[35] CO is measured by administering a central venous bolus of cold injectate, constructing an arterial thermodilution curve and applying the Stewart–Hamilton equation. The axillary artery can also be used, but placing the sensor in more peripheral arteries causes overestimation of CO. Curves are longer and flatter than PAC curves due to thermal equilibration with intrathoracic blood and EVLW, but are unaffected by the respiratory phase of injection. Measurements are in good agreement with pulmonary thermodilution and direct Fick methods. There is a positive bias of about 5%, perhaps because of indicator loss or because transpulmonary measurements are less affected by the transient decrease in heart rate induced by cold thermodilution.

Mathematical models based on single- or double-indicator techniques allow the estimation of intrathoracic blood volume (ITBV), global end-diastolic volume (GEDV) and EVLW.[36]

Unlike CVP and PAOP, ITBV is a volumetric preload index. Interpretation is thus independent of alterations in juxta-cardiac pressures or myocardial compliance, and should be superior to conventional pressure indices. There is experimental and clinical evidence that this may be true.[37]

EVLW is a marker of the severity of illness. Following EVLW as a therapeutic end-point may reduce positive fluid balances plus ventilator and ICU days.[38]

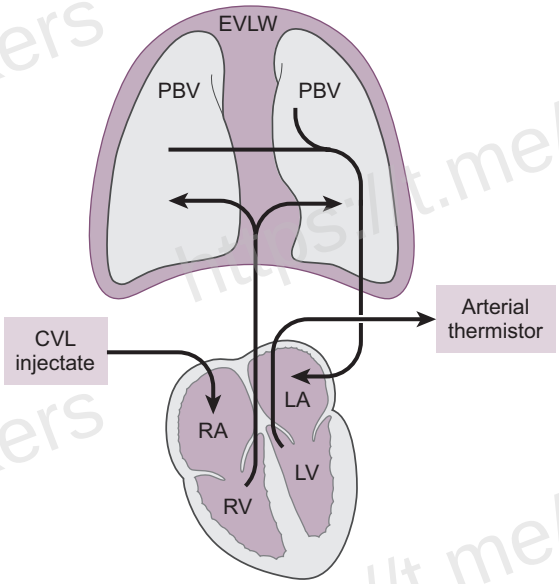


Figure 16.1 Conceptualisation of the transpulmonary mixing chambers of the cardiopulmonary system. Cardiac thermal volumes are proposed to approximate blood volumes at end diastole. *CVL*, Central venous line; *EVLW*, extravascular lung water; *LA*, left atrial thermal volume; *LV*, left ventricular thermal volume; *PBV*, pulmonary blood volume; *RA*, right atrial thermal volume; *RV*, right ventricular thermal volume. Intrathoracic thermal volume (ITTV) is the estimated total thermal volume between the points of central venous injection and peripheral arterial detection, including the EVLW. Pulmonary thermal volume (PTV) is the sum of PBV + EVLW. Intrathoracic blood volume (ITBV) is the sum of RA + RV + PBV + LA + LV, taken to be at end diastole. EVLW = ITTV – ITBV. Global end-diastolic volume (GEDV) is the sum of RAEDV + RVEDV + LAEDV + LVEDV. (With permission from PULSION Medical Systems SE, www.PULSION.com.)

EVLW also appears to offer prognostic information in sepsis and acute lung injury.

GEDV is said to represent the volume of blood in all chambers of the heart at end diastole. Like ITBV, GEDV has been shown to be a more reliable measure of cardiac preload than conventional pressure-based surrogates.[39]

LITHIUM DILUTION CARDIAC OUTPUT

Lithium can also serve as a transpulmonary indicator. The small doses of lithium required are non-toxic and easily measured with an ion-selective electrode attached to a three-way tap. A peristaltic pump limits sampling to 4 mL/min. Following injection, there is no significant first-pass loss from the circulation. After passing through the sensor, blood is discarded.

The main advantage over thermodilution is that more peripheral arteries can be used without loss of accuracy. Injection can be performed peripherally if central venous access is unavailable. The technique shows good agreement with bolus thermodilution (PAC). It is able to safely and accurately measure CO in adult and paediatric populations.

Potential limitations include the following:

- It cannot be used in patients receiving lithium therapy (background lithium concentration contributes to overestimation of CO).
- Electrode drift can occur in the presence of high-peak doses of muscle relaxants.
- Abnormal shunts can result in erroneous CO measurements (true for all indicator dilution methods).
- Ex vivo analysis requires disposal of the sampled blood.
- There is no reporting of volumetric haemodynamic variables, such as EVLW.[1]

TRANSPULMONARY DYE DILUTION

Transpulmonary indicator dilution can also be performed using injectable dye, usually indocyanine green. Dye dilution (arterial blood analysis) and pulse dye densitometry (transcutaneous fluorescent analysis) have been applied to CO measurement. Concerns exist regarding the accuracy of the transcutaneous method.[40]

ULTRASOUND INDICATOR DILUTION

Whereas transpulmonary thermodilution relies upon changes in temperature induced by injecting saline (other than body temperature), ultrasound indicator dilution relies upon resultant changes in the velocity of sound transmission. Body temperature isotonic saline is injected into a low-volume arteriovenous loop between existing arterial and central venous catheters. The measured change in ultrasound velocity (blood, 1560–1585; saline, 1533 m/s) allows the formulation of an indicator dilution curve with the calculation of CO.[41]

Another recent advance is the application of contrast-enhanced ultrasound.[42] This entails injection of an ultrasound contrast bolus while monitoring the atria using transoesophageal echocardiography. Acoustic intensity evolution over time is assessed and used to calculate indicator dilution curves. Bias exists compared to thermodilution techniques, though this method may find greater application in the future.

ARTERIAL PRESSURE WAVEFORM ANALYSIS

Estimation of stroke volume by analysis of the arterial pressure waveform, in particular various properties of the pulse pressure component, has been studied for many years.[1] It is to be recognised that pulse pressure, while proportional to stroke volume, is also dependent on aortic impedance, a value that is subject to significant inter- and intrapatient variability. Devices employ different proprietary algorithms (e.g. pulse contour

analysis)[43] to calculate CO from transduced pressure signals. Generic terminology, such as arterial pressure waveform analysis, is more broadly applicable.

A number of devices require calibration against another method, after which stroke volume can be trended continuously. Accuracy in the presence of arrhythmia has not been established.

Transpulmonary indicator dilution is the usual method of calibration. Devices that use thermodilution or lithium ion calibration are commercially available.[1]

Disadvantages of such techniques can include the following:

- Frequent recalibration is advisable to allow for changes in systemic vascular resistance. This is especially important if there is haemodynamic instability or during the administration of vasoactive drugs.
- Alterations in abdominal pressure or changes in body position, particularly in the obese, can alter aortic compliance, necessitating recalibration.
- Dependence on arterial site – clinical validation studies usually document femoral cannulation.
- Aortic aneurysms and significant aortic regurgitation are both difficult to model, and they invalidate the technique.

Proprietary algorithms for estimating stroke volume and CO from pressure-based signals without the need for calibration have been incorporated into a number of devices. The principal advantages of these techniques are ease of use and non-invasiveness. However, these devices frequently rely on the Windkessel model of the circulation, incorporating assumptions based on age, heart rate, MAP and aortic pressure waveform to estimate aortic impedance, Windkessel compliance and peripheral arterial resistance.[36] Furthermore, accuracy is impaired in the presence of major changes in vascular compliance, cardiac dysrhythmia, aortic regurgitation, or poor-quality arterial waveform transduction (under- or overdamping, attenuation).

ULTRASOUND

Ultrasound is increasingly used in the evaluation of haemodynamically unstable patients and frequently complements other monitoring techniques. Two main approaches are available to measure stroke volume (and thereby CO) using ultrasound–echocardiographic changes in ventricular volume and Doppler measurement.

ECHOCARDIOGRAPHY

Echocardiography may be used to estimate systolic and diastolic left-ventricular volumes from 2D images using Simpson's method (summation of discs). User dependence, potentially inaccurate assumptions about ventricular geometry and the cost of imaging equipment limit the usefulness of this technique for haemodynamic monitoring. Real time 3D evaluation of LV or RV volumes can be provided by state of the art transoesophageal and transthoracic echocardiography.[44] Clinical application is not yet mainstream.

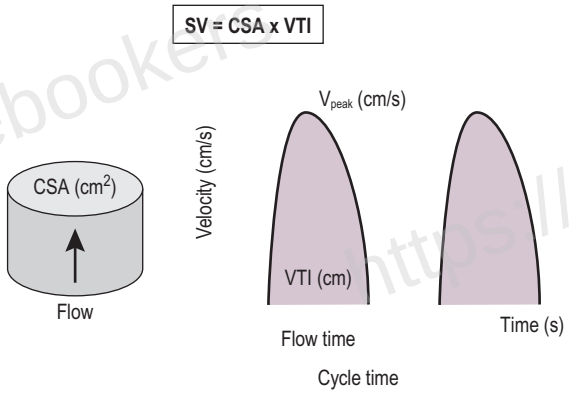


Figure 16.2 Doppler stroke volume calculation. The cross-sectional area of flow (CSA) is calculated as a circle from echocardiographic measurements or nomogram-based estimations. Velocity–time integral (VTI) is the integral of Doppler velocity with regard to time. Stroke volume (SV) is calculated as the product of CSA and VTI (mL/s in this example). Cardiac output is calculated from the product and SV and heart rate. Peak velocity of flow (V_{peak}) is also indicated.

DOPPLER TECHNIQUES

The Doppler principle states that the frequency of reflected sound is altered by a moving target, such as red blood cells.[45] This can be applied to measurement of stroke volume (Fig. 16.2). Continuous and pulsed wave Doppler are the main techniques employed to measure flow. Pulsed wave Doppler allows the site of sampling to be specified by transmitting a pulse of sound energy and then 'listening' for a period of time appropriate to catch the reflected signal. With continuous wave Doppler, a piezoelectric crystal transmits the ultrasound beam continuously, while another measures the frequency of reflected waves. The velocities of all the red blood cells moving along the path of the ultrasound beam are recorded. As a result, a continuous wave Doppler recording consists of a full spectral envelope with the outer border corresponding to the fastest moving blood cells. The flow velocity (V) of red cells can be determined from the Doppler shift in the frequency of reflected waves:

$$V = (2F_0 \times \cos\theta)^{-1} \times C\Delta F \quad (16.2)$$

where C is the speed of ultrasound in tissue (1540 m/s), ΔF is the frequency shift, F_0 is the emitted ultrasound frequency and θ is the angle of incidence. The most accurate results are obtained when the ultrasound beam is parallel to flow (θ = 0°, cosθ = 1;

$\theta = 180°$, $\cos\theta = -1$). However, angles up to 20° still yield acceptable results ($\theta = 20°$, $\cos\theta = 0.94$).

This methodology forms the basis of numerous monitoring devices. Doppler is less dependent on image quality, shows better agreement with thermodilution and demonstrates good reproducibility.

In addition to measuring stroke volume, Doppler assessment of aortic blood flow can provide additional haemodynamic information. For instance, a low duration of aortic velocity signal corrected for heart rate (corrected flow time; FTc) may prompt intravenous fluid challenge.[26,46] The peak velocity of aortic blood flow (V_{peak}) has been proposed as an index of contractility. Another index of contractility is the steepest gradient of the Doppler trace. This reflects the rate of the LV pressure rise in early systole (dP/dt max). Also, respiratory variation in V_{peak} (ΔV_{peak}) has been described as a predictor of increased CO in response to fluid challenge.[47]

Oesophageal Doppler monitoring

Oesophageal Doppler measures blood flow velocity in the descending aorta with a Doppler probe incorporated in the tip of a flexible probe.[1] The probe is positioned in the oesophagus about 30–40 cm from the teeth where the aorta runs parallel to the oesophagus and the systolic cross-sectional area varies least. The probe is rotated to obtain a characteristic aortic signal. The aortic cross-sectional area is either determined from nomograms, or calculated from a measured diameter.

Advantages of the technique include the following:

- Insertion is simple and only a short period of training is required.
- The probes (6 mm in diameter) are minimally invasive, and can be inserted nasally or orally.
- Contraindications are few. They include severe agitation, pharyngo-oesophageal pathology, aortic balloon counterpulsation, aortic dissection and severe aortic coarctation.
- Potential disadvantages include the following:
  - It assumes that the descending aortic flow remains as a fixed proportion of CO, which may not be the case in shock states or with vasoactive drug administration.
  - Flow in the aorta is not always laminar. Turbulent aortic blood flow may alter velocity measurements.
  - Assumptions that the aorta is cylindrical with a fixed systolic cross-section are not always valid. The cross-sectional area of the aorta is actually dynamic and is dependent on the pulse pressure and aortic compliance. If the aortic area is measured, errors through misplacement of the probe are compounded as the area is dependent on the square of the radius.
  - Finding and maintaining optimal probe positioning are important for consistency in trend measurements.
  - The probe may be poorly tolerated in non-sedated patients. Trends towards minimal sedation and shorter duration of endotracheal intubation might decrease the practicality of this technique in many patients.

Transcutaneous Doppler monitoring

Externally applied continuous wave Doppler can be used to monitor haemodynamics via transpulmonary (parasternal) and transaortic (suprasternal) windows. If not known or previously measured, flow diameters may be estimated by a proprietary algorithm based upon the linear association between height and cardiovascular dimensions.[48] Although this method may offer a clinically useful alternative, current data suggest limits of agreement compared to thermodilution are too wide for routine application in the critically ill.[49,50]

THORACIC ELECTRICAL BIOIMPEDANCE AND BIOREACTANCE

An alternating electrical current (high frequency, very low amplitude) is passed through the thorax. Thoracic electrical bioimpedance requires the current to be kept constant while fluctuations in electrical impedance are measured. Six electrodes are usually attached (two in the upper thorax/neck region and four in the lower thorax). These electrodes detect changes in bioimpedance and monitor cardiac electrical signals. The technique is very sensitive to any alteration in position or contact of the electrodes to the patient.

The change in aortic blood flow due to myocardial contraction (stroke volume) is measured from the changes in thoracic bioimpedance through the cardiac cycle. Other factors that contribute to a change in overall thoracic bioimpedance include changes in tissue fluid volume and changes in venous and pulmonary blood volume induced by respiration. Respiratory artefact is eliminated by averaging values over several cardiac cycles using the R–R interval (ECG) as a synchronising signal. Measuring whole body, rather than truncal, impedance by placing electrodes on wrists and ankles also appears successful.

Inaccuracies can arise from numerous sources that are prevalent in critical care. These include motion artefact, electrical interference, dysrhythmias (including frequent premature atrial contractions and atrial fibrillation) and acute change in tissue water content (such as pulmonary oedema, pleural effusions or expansion of interstitial fluid). Despite these limitations, it is clinically appealing due to its non-invasive nature.

Bioreactance has built upon the concepts of bioimpedance but, rather than changes in impedance, it measures changes in the frequency of the electrical currents traversing the chest. This potentially improves signal to noise ratio.[51]

Table 16.8 Variables described as indices of cardiac preload or fluid responsiveness in critically ill patients

STATIC	DYNAMIC
Intracardiac pressures	**Response to fluid challenge**
Central venous pressure (CVP)/right atrial pressure (RAP)	**Passive leg raising**
Pulmonary artery occlusion pressure (PAOP)	Change in aortic blood flow
CARDIOVASCULAR VOLUMES	Change in pulse pressure
Thermodilution right ventricular end-diastolic volume (RVEDV)	**Spontaneous respiratory effort**
Echocardiographic RVEDV	Inspiratory decrease in right atrial pressure (ΔRAP)
Echocardiographic left ventricular end-diastolic area (LVEDA)/volume (LVEDV)	**Mandatory mechanical ventilation**
Transpulmonary thermodilution global end-diastolic volume (GEDV)	Systolic pressure variation (SPV)
Transpulmonary thermodilution intrathoracic blood volume (ITBV)	Decrease in systolic pressure (Δ_{down})
Doppler	Pulse pressure variation (PPV)
Duration of the aortic velocity signal corrected for heart rate (FTc)	Pulse contour analysis stroke volume variation (SVV)
Respiratory variation in peak velocity of aortic blood flow (ΔV_{peak})	Respiratory variation in peak aortic blood velocity (ΔV_{peak})
	Respiratory change in the pre-ejection period (ΔPEP)
	Respiratory systolic variation test (RSVT)

Variables have been divided into static and dynamic categories. Static variables are estimates of ventricular preload at a point in time, usually end-expiration. Dynamic variables are characterised by the measurement of variation in haemodynamic measurements in response to changes in cardiac loading conditions.

From Sturgess DJ, Joyce C, Marwick TH, et al. A clinician's guide to predicting fluid responsiveness in critical illness: applied physiology and research methodology. *Anaesth Intensive Care*. 2007;35(5):669–678. Epub 2007/10/16.

FUNCTIONAL HAEMODYNAMIC MONITORING

Functional haemodynamic monitoring builds upon the observation that 'dynamic' haemodynamic variables are better predictors of response to fluid challenge than 'static' variables (Table 16.8).[52] Accurate prediction of fluid responsiveness allows rational fluid resuscitation while avoiding the consequences of excess fluid challenge; these consequences may include excess tissue and pulmonary oedema with deleterious impact upon respiratory function, wound healing and abdominal compartment syndrome.[53]

The potential value of fluid responsiveness hinges upon the ability to determine whether a patient's left ventricle is operating on the plateau (preload independent) portion of the Frank–Starling curve at the time of considering fluid challenge. Thus fluid challenge could be avoided, as it will be ineffective and potentially deleterious. Inotropic and/or vasopressor support should be considered in preference. It is crucial to appreciate that under normal conditions the left ventricle demonstrates recruitable stroke volume (ascending or 'preload dependent' portion of the Frank–Starling curve). Thus prediction of a fluid responsive state may be physiological and does not necessarily mandate fluid challenge.

It must also be appreciated that the majority of 'dynamic' variables posed as predictors of fluid responsiveness have been studied in small samples of highly selected patients under restrictive preconditions (including mandatory mechanical ventilation). In particular, techniques such as pulse pressure variation, have been validated only under a number of caveats including the absence of spontaneous respiratory effort, moderate tidal volumes and normal myocardial contractility. Assessing the response to fluid challenge or passive leg raising is more generalisable and is more commonly recommended.[54]

MONITORING THE MICROCIRCULATION

There is growing appreciation that perfusion of the microcirculation is adversely affected by many disease states directly relevant to critical care. These alterations can be related to poor outcomes. Evaluation of microvascular function at the bedside of critically ill patients remains challenging. Furthermore, many microvascular pathologies may be localised or heterogeneous, in which case the microcirculation being monitored might not offer generalisable data. Many monitoring techniques have been described, but these are currently recommended for research only.[2]

A number of techniques for evaluation of perfusion (rather than tissue oxygenation, which is discussed elsewhere) are briefly mentioned here. Clinically, mottled skin, acrocyanosis, delayed capillary refill and increased central to peripheral temperature gradients might disclose an impaired microcirculation. Biomarkers, such as plasma hyaluronan (experimental), might also indicate impairment. Laser Doppler flowmetry can be applied to a range of tissues. Microvideoscopic

techniques (nailfold videocapillaroscopy, orthogonal polarisation spectral [OPS] and sidestream darkfield [SDF] imaging techniques) can be applied to superficial capillary beds. Except at high levels, blood flow is the major determinant of venous to arterial CO_2 gradient (CO_2 gap). Alternatively, tissue CO_2 can be measured by tissue electrodes, probes or tonometry. Microdialysis and equilibrium analysis allow the measurement of molecules from the extracellular environment. These techniques are well suited to the quantification of lactate/pyruvate ratio.

REFERENCES

1. Teboul JL, Saugel B, Cecconi M, et al. Less invasive hemodynamic monitoring in critically ill patients. *Intensive Care Med*. 2016;42:1350–1359.
2. Cecconi M, De Backer D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med*. 2014;40: 1795–1815.
3. Gregg RE, Zhou SH, Lindauer JM, et al. Where do derived precordial leads fail? *J Electrocardiol*. 2008;41:546–552.
4. Benmira A, Perez-Martin A, Schuster I, et al. From Korotkoff and Marey to automatic non-invasive oscillometric blood pressure measurement: does easiness come with reliability? *Expert Rev Med Devices*. 2016;13:179–189.
5. Ameloot K, Palmers PJ, Malbrain ML. The accuracy of noninvasive cardiac output and pressure measurements with finger cuff: a concise review. *Curr Opin Crit Care*. 2015;21:232–239.
6. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis*. 2011;52: e162–e193.
7. Maniotis C, Koutouzis M, Andreou C, et al. Transradial approach for cardiac catheterization in patients with negative Allen's test. *J Invasive Cardiol*. 2015;27:416–420.
8. Durbin CG Jr. Radial arterial lines and sticks: what are the risks? *Respir Care*. 2001;46:229–231.
9. Gilbert M. Principles of pressure transducers, resonance, damping and frequency response. *Anaesth Intensive Care Med*. 2012;13:1–6.
10. Association of Anaesthetists of Great Britain and Ireland. Safe vascular access 2016. *Anaesthesia*. 2016;71:573–585.
11. Australian and New Zealand Intensive Care Society [Internet]. Melbourne; 2012. ANZICS Safety and Quality Committee. Available from: www.clabsi.com.au and www.anzics.com.au.
12. Frankel HL, Kirkpatrick AW, Elbarbary M, et al. Guidelines for the appropriate use of bedside general and cardiac ultrasonography in the evaluation of critically ill patients-part I: general ultrasonography. *Crit Care Med*. 2015;43:2479–2502.
13. National Institute for Clinical Excellence. *Guidance on the use of ultrasound locating devices for placing central venous catheters*; 2002. In: Technology Appraisal Guidance - No 49. London: National Institute for Clinical Excellence.
14. Fletcher SJ, Bodenham AR. Safe placement of central venous catheters: where should the tip of the catheter lie? *Br J Anaesth*. 2000;85:188–191.
15. Baskin JL, Pui CH, Reiss U, et al. Management of occlusion and thrombosis associated with long-term indwelling central venous catheters. *Lancet*. 2009;374:159–169.
16. Sturgess DJ, Marwick TH, Venkatesh B. Diastolic (dys)function in sepsis. In: Vincent JL, ed. *Yearbook of Intensive Care and Emergency Medicine*. Berlin Heidelberg: Springer-Verlag; 2007:444–454.
17. Magder S. Understanding central venous pressure: not a preload index? *Curr Opin Crit Care*. 2015;21:369–375.
18. Angus DC, Barnato AE, Bell D, et al. A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe investigators. *Intensive Care Med*. 2015;41: 1549–1560.

19a. Swan HJ, Ganz W, Forrester J, et al. Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. *N Engl J Med*. 1970;283:447–451.

19b. Evans DC, Doraiswamy VA, Prosciak MP, et al. Complications associated with pulmonary artery catheters: a comprehensive clinical review. *Scand J Surg*. 2009;98:199–208.

20. Connors AF Jr, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT investigators. *JAMA*. 1996;276:889–897.
21. Dalen JE, Bone RC. Is it time to pull the pulmonary artery catheter? *JAMA*. 1996;276:916–918.
22. Rajaram SS, Desai NK, Kalra A, et al. Pulmonary artery catheters for adult patients in intensive care. *Cochrane Database Syst Rev*. 2013;(2):CD003408.
23. Youssef N, Whitlock RP. The routine use of the pulmonary artery catheter should be abandoned. *Can J Cardiol*. 2017;33(1):135–141.
24. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685–713, quiz 86–88.
25. Sturgess DJ, Marwick TH, Joyce CJ, et al. B-type natriuretic peptide concentrations and myocardial dysfunction in critical illness. *Anaesth Intensive Care*. 2006;34:151–163.
26. Sturgess DJ, Pascoe RL, Scalia G, et al. A comparison of transcutaneous Doppler corrected flow time, b-type natriuretic peptide and central venous pressure as predictors of fluid responsiveness in septic shock: a preliminary evaluation. *Anaesth Intensive Care*. 2010;38:336–341.
27. Sturgess DJ, Parmar D, Dulhunty JM, et al. A preliminary evaluation of plasma b-type natriuretic

peptide as a screening test for left ventricular diastolic dysfunction in non-cardiac intensive care. *Anaesth Intensive Care*. 2013;41:591–595.
28. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016; 29:277–314.
29. Wo CC, Shoemaker WC, Appel PL, et al. Unreliability of blood pressure and heart rate to evaluate cardiac output in emergency resuscitation and critical illness. *Crit Care Med*. 1993;21:218–223.
30. Haryadi DG, Orr JA, Kuck K, et al. Partial CO_2 rebreathing indirect Fick technique for non-invasive measurement of cardiac output. *J Clin Monit Comput*. 2000;16:361–374.
31. Stetz CW, Miller RG, Kelly GE, et al. Reliability of the thermodilution method in the determination of cardiac output in clinical practice. *Am Rev Respir Dis*. 1982;126:1001–1004.
32. Lehmann KG, Platt MS. Improved accuracy and precision of thermodilution cardiac output measurement using a dual thermistor catheter system. *J Am Coll Cardiol*. 1999;33:883–891.
33. Bennett JA. Equipment review: Edwards vigilance continuous cardiac output monitor. *Am J Anesthesiol*. 1995;22:269–272.
34. Globits S, Pacher R, Frank H, et al. Comparative assessment of right ventricular volumes and ejection fraction by thermodilution and magnetic resonance imaging in dilated cardiomyopathy. *Cardiology*. 1995;86:67–72.
35. Hudson E, Beale R. Lung water and blood volume measurements in the critically ill. *Curr Opin Crit Care*. 2000;6:222–226.
36. Litton E, Morgan M. The PiCCO monitor: a review. *Anaesth Intensive Care*. 2012;40:393–409.
37. Reuter DA, Felbinger TW, Schmidt C, et al. Stroke volume variations for assessment of cardiac responsiveness to volume loading in mechanically ventilated patients after cardiac surgery. *Intensive Care Med*. 2002;28:392–398.
38. Kuzkov VV, Kirov MY, Sovershaev MA, et al. Extravascular lung water determined with single transpulmonary thermodilution correlates with the severity of sepsis-induced acute lung injury. *Crit Care Med*. 2006;34:1647–1653.
39. Hofer CK, Furrer L, Matter-Ensner S, et al. Volumetric preload measurement by thermodilution: a comparison with transoesophageal echocardiography. *Br J Anaesth*. 2005;94:748–755.
40. Reekers M, Simon MJ, Boer F, et al. Cardiovascular monitoring by pulse dye densitometry or arterial indocyanine green dilution. *Anesth Analg*. 2009;109: 441–446.
41. Lindberg L, Johansson S, Perez-de-Sa V. Validation of an ultrasound dilution technology for cardiac output measurement and shunt detection in infants and children. *Pediatr Crit Care Med*. 2014;15: 139–147.
42. Herold IH, Soliman Hamad MA, van Assen HC, et al. Pulmonary blood volume measured by contrast enhanced ultrasound: a comparison with transpulmonary thermodilution. *Br J Anaesth*. 2015; 115:53–60.
43. Godje O, Hoke K, Goetz AE, et al. Reliability of a new algorithm for continuous cardiac output determination by pulse-contour analysis during hemodynamic instability. *Crit Care Med*. 2002;30:52–58.
44. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39 e14.
45. Quinones MA, Otto CM, Stoddard M, et al. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2002;15: 167–184.
46. Hamilton MA, Cecconi M, Rhodes A. A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. *Anesth Analg*. 2011;112:1392–1402.
47. Feissel M, Michard F, Mangin I, et al. Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. *Chest*. 2001;119:867–873.
48. Nidorf SM, Picard MH, Triulzi MO, et al. New perspectives in the assessment of cardiac chamber dimensions during development and adulthood. *J Am Coll Cardiol*. 1992;19:983–988.
49. Sakka SG. Hemodynamic monitoring in the critically ill patient – current status and perspective. *Front Med (Lausanne)*. 2015;2:44.
50. Chong SW, Peyton PJ. A meta-analysis of the accuracy and precision of the ultrasonic cardiac output monitor (USCOM). *Anaesthesia*. 2012;67: 1266–1271.
51. Vincent JL, Rhodes A, Perel A, et al. Clinical review: update on hemodynamic monitoring – a consensus of 16. *Crit Care*. 2011;15:229.
52. Hadian M, Pinsky MR. Functional hemodynamic monitoring. *Curr Opin Crit Care*. 2007;13:318–323.
53. Sturgess DJ, Joyce C, Marwick TH, et al. A clinician's guide to predicting fluid responsiveness in critical illness: applied physiology and research methodology. *Anaesth Intensive Care*. 2007;35: 669–678.
54. Antonelli M, Levy M, Andrews PJ, et al. Hemodynamic monitoring in shock and implications for management. International Consensus Conference, Paris, France, 27–28 April 2006. *Intensive Care Med*. 2007;33:575–590.

17

Multiorgan dysfunction syndrome

Matthew J Maiden, Marianne J Chapman

Multiorgan dysfunction syndrome (MODS) is a complex process whereby an acute disease precipitates deranged function of a number of organ systems. MODS is encountered commonly in the intensive care unit (ICU) and accounts for 40%–50% of deaths.[1,2] Hence critical care clinicians require a sound understanding of the pathophysiology and management priorities for MODS.

HISTORY

During World War II, severely injured soldiers without thoracic trauma were noted to develop respiratory failure in the days following their initial injury. The incidence appeared related to the severity and duration of hypotension and the term 'shock lung' was used to describe the subsequent respiratory failure. While hypoperfusion was thought to initiate impaired pulmonary function, other factors including blood product transfusion, microemboli, fat emboli, endotoxin and excessive use of oxygen were postulated to contribute.[3]

Following the advent of ICU, similar patterns of 'remote' organ failures were reported in critically ill patients following trauma, surgical haemorrhage, abdominal sepsis, pneumonia and pancreatitis.[4,5] Although many pathophysiological mechanisms for this have been described, it is still not clear why only some patients develop MODS.

DEFINITION

Over 40 different names have been ascribed to the phenomenon of 'organ disease remote from the site of illness/injury'.[6] The terms 'multiple system failure' or 'multiple organ failure' have been commonly used; however, each description and definition differed.

A consensus conference in 1992 proposed the term 'multiple organ dysfunction syndrome' (MODS).[7] This term reflects a distinction between 'dysfunction' and 'failure'. 'Failure' implies a dichotomous outcome that is often irreversible, while 'dysfunction' describes a spectrum of organ impairment that may change over time. The term 'syndrome' was added to describe a pattern of multiple physiological changes that may have a similar pathogenesis.

However, this definition of MODS did not characterise or define what constitutes an organ dysfunction. Subsequently, many classifications and scoring systems have been developed in an attempt to quantify the severity of MODS. These have varied according to which organ systems are assessed, which parameters are measured and the thresholds for the organs to be considered dysfunctional.

The MODS and SOFA (sepsis-related organ failure assessment) scores were developed after the consensus definition of MODS (Table 17.1). They were primarily established to describe the severity of MODS and changes in organ function over time.[8,9] For each of six organ systems, one parameter of dysfunction was chosen. Scores for each organ were equally weighted and summed to provide an overall score. The score at ICU admission and the change in score over the course of the ICU stay correlates with the mortality rate, with both the MODS and SOFA scores performing similarly.[10,11] However, there are limitations to these scoring systems. Each organ system is assessed with only one parameter, and other features of organ dysfunction are not considered. Furthermore, organ dysfunction scores are influenced by therapies and hence may reflect the extent of treatment provided (or not provided). Nevertheless, these scores remain widely used.

AETIOLOGY OF MULTIORGAN DYSFUNCTION SYNDROME

Almost any disease that invokes tissue injury may progress to MODS (Box 17.1). It occurs most commonly following a microbial infection. Of note, the term 'sepsis-induced MODS' would now seem redundant given that the current definition of sepsis is 'infection with accompanying organ dysfunction' (Sepsis-3).[12]

Diseases without microbial infection account for a smaller number of patients developing MODS, but are an important consideration in anyone with an acute illness and organ dysfunction. For example, major trauma leads to MODS in about 30% of patients.[13] It

ABSTRACT

Multiorgan dysfunction syndrome (MODS) occurs in some patients following an acute infection, illness or injury. It is the consequence of impaired regulation of the processes involved in removing an invading pathogen and repairing injured tissue. An exaggerated inflammatory response becomes systemic, giving rise to derangement of organ function.

Many pathophysiological mechanisms contribute to the development of MODS. Disturbances to coagulation, the vascular endothelium, glycocalyx, epithelium, neuro-hormonal axis, macro- and microvascular blood flow, cell death processes, and metabolic and mitochondrial function play a role. The types of inciting acute disease, patient comorbidities and the potential harms of therapies provided are also significant factors in MODS.

Many potential therapies have targeted a range of mediators thought to promote MODS, but none have yet proved efficacious in clinical trials. Treatment priorities remain prompt recognition and definitive treatment of the acute disease, and provision of evidence-based supportive care.

KEYWORDS

Multiorgan dysfunction syndrome
severity of illness scores
sepsis
inflammation
organ support

Table 17.1 The multiorgan dysfunction syndrome and sepsis-related organ failure assessment scores: Note the similarity of the scoring systems

MODS SCORE	0	1	2	3	4
Respiratory[a] *(PO_2/FiO_2)*	>300	226–300	151–225	76–150	≤75
Renal[b] *(serum creatinine µmol/L)*	≤100	101–200	201–350	351–500	>500
Hepatic *(serum bilirubin µmol/L)*	≤20	21–60	61–120	121–240	>240
Cardiovascular[c] *(PAR)*	≤10.1	10.1–15.0	15.1–20.0	20.1–30.0	>30.0
Hematological *(platelet count × 10^3/mL)*	>120	81–120	51–80	21–50	≤20
Neurological[d] *(Glasgow Coma Score)*	15	13–14	10–12	7–9	≤6

SOFA SCORE	1	2	3	4
Respiratory *(PO_2/FiO_2)*	<400	<300	<200 With respiratory support	<100 With respiratory support
Renal *(serum creatinine µmol/L or urine output)*	110–170	171–299	300–440 or <500 mL/day	>440 or <200 mL/day
Hepatic *(serum bilirubin µmol/L)*	20–32	33–101	102–204	>204
Cardiovascular[e] *(MAP < 70 mm Hg or use of inotropes)*	MAP <70 mm Hg	Dopamine ≤5 or Dobutamine (any dose)	Dopamine >5 or Epinephrine ≤0.1 or Norepinephrine ≤0.1	Dopamine >15 or Epinephrine >0.1 or Norepinephrine >0.1
Hematological *(platelet count ×10^3/mL)*	<150	<100	<50	<20
Neurological *(Glasgow Coma Score)*	13–14	10–12	6–9	<6

[a]P/F ratio is calculated without reference to the use or mode of mechanical ventilation, and without reference to the use or level of positive end-expiratory pressure.

[b]Serum creatinine measured without reference to the use of dialysis.

[c]Pressure-adjusted heart rate (PAR) is calculated as the product of heart rate (HR) multiplied by the ratio of the right atrial (central venous) pressure (RAP) to the mean arterial pressure (MAP): PAR = HR × RAP/MAP.

[d]The Glasgow Coma Score is preferably calculated by the patient's nurse, and is scored conservatively (for the patient receiving sedation or muscle relaxant, normal function is assumed, unless there is evidence of intrinsically altered mentation).

[e]Adrenergic agents administered for at least 1 h (doses given are in µg/kg/min).

MODS, Multiorgan dysfunction syndrome; *SOFA*, sepsis-related organ failure assessment.

Box 17.1 Diseases that can progress to multiorgan dysfunction syndrome

Infection (sepsis)
No infection (nonseptic)
- Major trauma
- Burns
- Pancreatitis
- Aspiration syndromes
- Extra-corporeal circulation (e.g. cardiac bypass, ECMO)
- Large volume blood transfusion
- Ischemia-reperfusion injury
- Autoimmune disease
- Heat-induced illness
- Eclampsia
- Poisons/Toxins

occurs predominately in the first few days following injury and is most likely in patients with greater physiological derangement on presentation, and those administered more fluids and blood products.

Sepsis and the non-septic diseases associated with MODS are discussed in other chapters of this text.

PATHOGENESIS

MODS is a systemic process with complex pathophysiology. While systemic inflammation appears to be central to the development of MODS, a multitude of other factors also contribute. The pathogenesis of MODS is best conceptualised as a complex dynamic non-linear system involving a large number of variables that are highly interdependent (Fig. 17.1).[14]

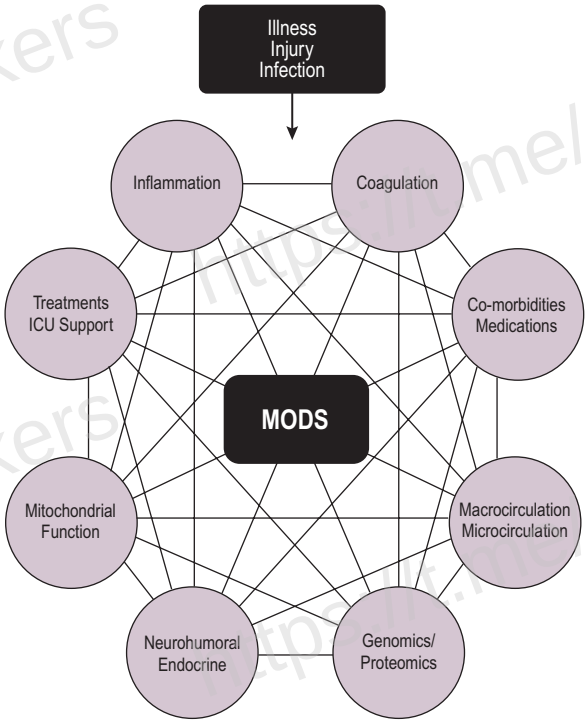


Figure 17.1 Multiorgan dysfunction syndrome *(MODS)* results from a complex interaction of a number of different pathogenic processes. *ICU,* intensive care unit.

INFLAMMATION

Inflammation is essential to contain infection, and for tissue repair. However, the inflammatory response to injury, illness or infection may become 'dysregulated', resulting in MODS and critical illness.[12,15] Increased levels of proinflammatory mediators are associated with worsening organ dysfunction[16] and MODS can be reproduced experimentally by the infusion of inflammatory cytokines.

As a systemic inflammatory response appears to be central to the development of MODS, the term systemic inflammatory response syndrome (SIRS) was defined in conjunction with the definition of MODS.[7] However SIRS is non-specific and provides little information about what is provoking the inflammation. It is important to recognise that clinical features of systemic inflammation may be an appropriate response to serious injury/infection and that most patients with these signs do not develop MODS.

Many inflammatory mediators have been identified and characterised over the last 50 years (Box 17.2). They are released from inflammatory cells and interact with the immune, endocrine and nervous systems to mediate host defence and tissue repair. With so many inflammatory molecules identified, it is not surprising they have complex interactions and that there is not one 'culprit' mediator in MODS. Given the convoluted and amplified inflammatory responses that follow injury, there has been much interest in understanding the early cellular responses to injury and infection.

Box 17.2 Some of the inflammatory mediators associated with multiorgan dysfunction syndrome

Interleukin-1β (IL-1β)
Interleukin-6 (IL-6)
Interleukin-8
Tissue necrosis factor-α (TNFα)
Interferon-γ (IFN-γ)
Colony stimulating factors
Eicosanoids/platelet aggregating factor
Soluble adhesion molecules
Complement activation
Nitric oxide
Heat shock proteins
Free radicals/reactive oxygen species
Pro-calcitonin
Angiopoietin
IL-1 receptor associated kinase (IRAK-1)

Nuclear Factor-κB (NF-κB) is a co-factor involved in the transcription of genes that encode inflammatory proteins, apoptotic signalling pathways and nitric oxide production. NF-κB is pre-formed in the cytoplasm and is activated when the inhibitory subunit (IκBα) is cleaved off, allowing NF-κB to translocate to the nucleus. NF-κB levels are increased in proportion to severity of disease.[17]

Toll-Like Receptors (e.g. TLR2, TLR4) are activated by bacterial products and necrotic cells. They in turn activate NF-κB and other factors that transcribe inflammatory mediators. The process of TLR activation differs between microbial and non-microbial precipitants.[18] Pre-clinical studies targeting the non-microbial activation pathways have yielded less organ dysfunction while maintaining antimicrobial efficacy. Mutations of TLR4 are associated with an attenuated inflammatory response.[19]

High Mobility Group Box Protein 1 (HMGB-1) is an evolutionary conserved protein that potentiates binding of inflammatory mediators to cells. It also acts as a nuclear co-factor that enhances DNA transcription of many inflammatory mediators. Plasma levels of HMGB-1 increase in sepsis and trauma in proportion to the severity of the illness or injury.[20,21] In experimental studies, anti-HMGB-1 attenuates the inflammatory response to infection, autoimmunity, ischaemia and trauma.[22]

COMPENSATORY ANTI-INFLAMMATORY RESPONSE SYNDROME

To ensure a controlled inflammatory response, mediators with anti-inflammatory effects (e.g. interleukin [IL-4, IL-10]) are increased during injury/infection.

This anti-inflammatory response has been termed the compensatory anti-inflammatory response syndrome (CARS).[23] Immunological changes include apoptosis of lymphocytes, release of IL-10, which suppresses tissue necrosis factor (TNF), decreased cytokine production and down-regulated human leucocyte antigen (HLA) receptors on monocytes.

Just as an excessive proinflammatory response may contribute to MODS, an exaggerated anti-inflammatory response, which tends to occur later in disease, can result in a state of immunosuppression and anergy.[24] Relative immunosuppression is often a feature of MODS and is thought to account for the late development of iatrogenic infections with organisms that are usually commensal or of low virulence (e.g. *Candida, Pseudomonas, Stenothrophomonas, Enterococcus*).

COAGULATION

Tissue factor, endotoxin, bacterial antigens and cytokines can trigger the clotting system. Thrombin is produced at the site of infection/injury to isolate infectious sources and initiate tissue repair. However, products of the clotting cascade are proinflammatory and the clotting system is central in the inflammatory response. For example, activation of the thrombin receptor induces transcription of NF-κB and stimulation of proinflammatory sequelae.[25]

Coagulation is normally controlled by the endogenous anticoagulant factors antithrombin III (AT-III binds to thrombin and endothelium to release endothelial prostacyclin and inhibit platelet aggregation) and protein C (complexes with Protein S to inhibit Va and VIIIa). Levels of these anticoagulants fall during critical illness proportional to the severity of MODS.[26]

ENDOTHELIUM

Vascular endothelium comprises a layer of endothelial cells and a layer of glycocalyx (Fig. 17.2). While endothelial cells comprise only a single layer of cells, they are distributed over the entire circulation and have a major influence on the integrity and function of the vascular network. The glycocalyx is a gel-like network of heparin molecules, glycoproteins and glycolipids that extend from the endothelial cell membrane into the vascular lumen. It also contributes to endothelial function including local inflammatory signalling, coagulation and detecting the shear force of the flowing blood.

The endothelium provides a dynamic barrier between the circulation and interstitial tissue. Normally the endothelium is relatively impermeable to inflammatory cells, proteins, and plasma fluid. However, following tissue injury, endothelial function and glycocalyx structure alter to permit inflammatory cells to reach the site of injury. As might be expected, the degree of disturbance to the endothelium and glycocalyx appears to be more pronounced in patients who develop MODS.[27,28] However, parameters of endothelial structure and function remain an experimental tool and their clinical utility remain to be determined.

NEURO-HUMORAL CHANGES

The autonomic system is closely intertwined with the inflammatory response. The sympathetic and parasympathetic nervous systems innervate lymphoid organs and most immune cells have neurotransmitter receptors. Neural stimulation of the immune cells inhibits cytokine release and suppresses the immune response.

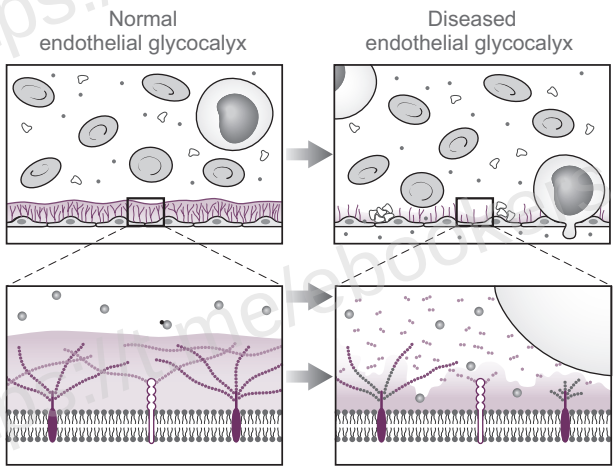


Figure 17.2 Schematic representation of the endothelium, comprising endothelial cells, and the glycocalyx. The endothelial layer normally provides a barrier between the blood and interstitium *(left image)*. In disease, the glycocalyx and endothelial structure alters allowing extravasation of inflammatory cells, proteins and plasma fluid *(right image). With permission from: Dane MJ, van den Berg BM, Lee DH, et al. A microscopic view of the renal endothelial glycocalyx.* Am J Physiol Renal Physiol. *2015;308:F956–F966.*

Some immune mediators also act as neuro-hormones providing neural feedback regarding the inflammatory state (Fig. 17.3).[29,30]

The 'stress response' to critical illness involves the release of the adrenal hormones. This is controlled by the hypothalamic secretion of corticotropin releasing hormone under direct neural control and is modulated by circulating cytokines. Inadequate hypothalamic-pituitary-adrenal response to critical illness or glucocorticoid resistance may contribute to MODS.

Changes to thyroid metabolism occur during MODS. In health, thyroxine (T4) is metabolised to the metabolically active tri-iodothyronine (T3), while during critical illness changes to the de-iodination pathways favour production of the biologically inactive reverse-T3. The consequential fall of plasma T3 levels is proportional to the severity of MODS and is independently associated with mortality.[31,32]

MACROCIRCULATORY CHANGES

Inadequate circulation of oxygenated blood can lead to cellular anaerobic metabolism and impaired organ function. While circulatory shock can initiate and perpetuate MODS, and is usually fatal if not treated, not all patients with MODS have impaired cardiac output or oxygen delivery. In fact, many patients with MODS have a preserved or increased oxygen delivery. Furthermore, attempts to prevent MODS by providing supranormal oxygen delivery by transfusing red cells or increasing cardiac output have not improved outcomes.[33]

Vascular tone is often reduced in MODS with excessive nitric oxide (NO) being a well-characterised culprit. Nitric oxide synthase (NOS) is found in endothelial cells and is induced by many inflammatory mediators. NO is toxic to micro-organisms, acts as an inflammatory signal, produces vascular smooth muscle relaxation and maintains patency of the microcirculation. However, excessive NO also leads to 'vasoplegia' with low systemic arterial pressures, venodilation and altered blood flow to the organs.

MICROCIRCULATORY CHANGES

Reduced blood flow through the microcirculation is associated with organ failure and death.[34] Microvascular thrombi, reduced red blood cell deformability and increased blood viscosity contribute to reduced microvascular flow and limited oxygen delivery to the cells.[35,36] Excessive NO alters the tone of the microcirculation contributing to mismatched microvascular flow and shunting.[37,38] Formation of interstitial oedema through endothelial permeability further restricts diffusion between the micro-circulation and cells. Images of the microcirculatory changes provide fascinating insights into the pathophysiology of MODS, but at the moment remain research tools (Fig. 17.4).

APOPTOSIS

Apoptosis is controlled cellular death that does not provoke inflammation. It is an essential process for normal coordinated control of populations of cells and

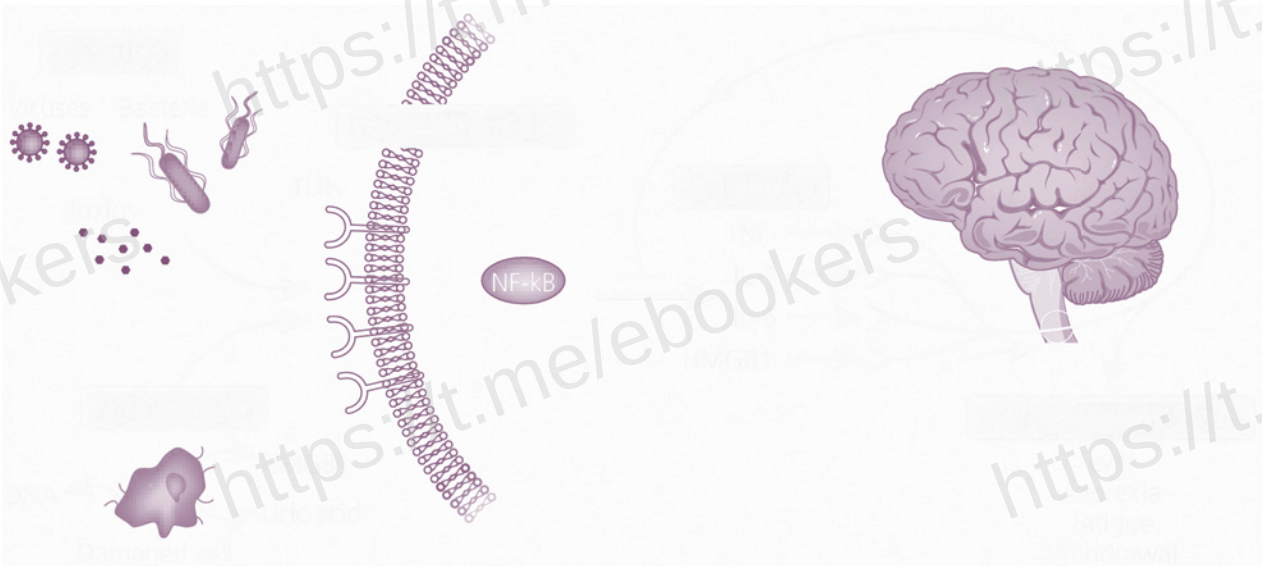


Figure 17.3 Neuro-humoral factors influence the response to illness/injury. *HMGB1*, High mobility group box protein 1; *IL*, interleukin; *NF-κB*, nuclear factor-κB; *TLR*, toll-like receptors; *TNF*, tissue necrosis factor. *Adapted from Tracey KJ. Understanding immunity requires more than immunology.* Nat Immunol. *2010;11(7):561–564.*

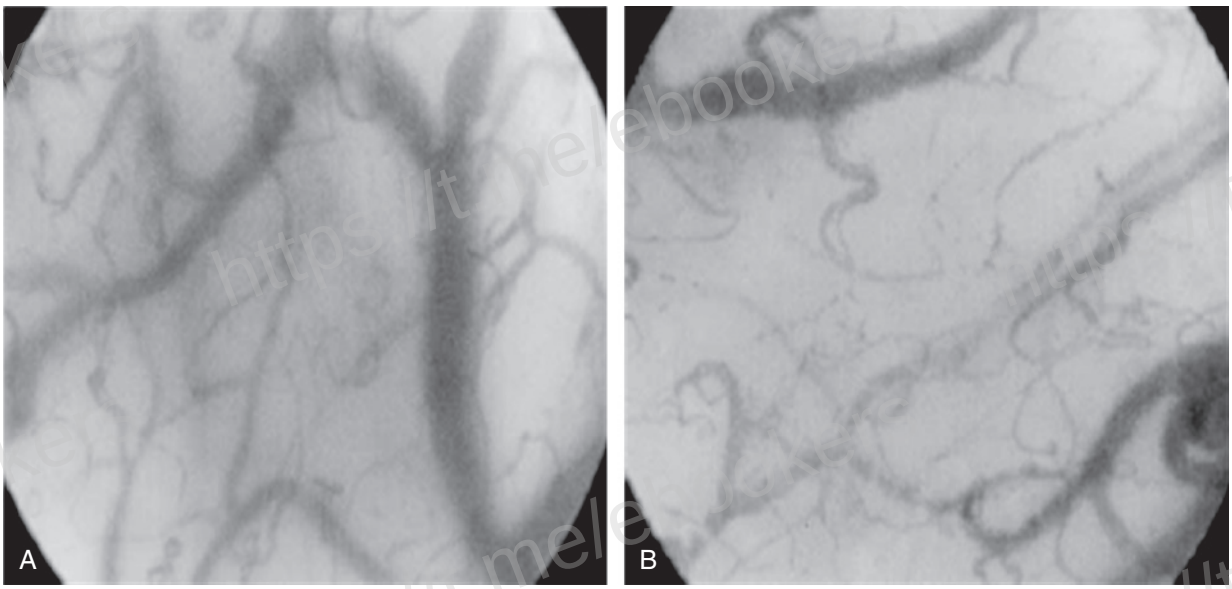


Figure 17.4 Sublingual microcirculatory changes seen in sepsis induced multiorgan dysfunction syndrome. (A) Healthy volunteer, and (B) a patient with septic shock. Note the rich density of large and small vessels in the healthy volunteer and the decrease in density of small vessels in sepsis. *Reprinted with permission of the American Thoracic Society. Copyright 2012 American Thoracic Society. Cite: DeBacker D, Creteur J, Preiser JC, Dubois MJ, Vincent JL. Microvascular blood flow is altered in patients with sepsis.* Am J Respir Crit Care Med. *2002;166:98–104. Official Journal of the American Thoracic Society.*

is involved in cell aging, immune regulation, epithelial cell turnover and resolution of inflammation. During critical illness, apoptosis is increased in lymphocytes, and in cells that typically have a barrier function (e.g. gut epithelium, vascular endothelium).[39] This increases susceptibility to further insults. In contrast, apoptosis of neutrophils is delayed and may lead to an exaggerated inflammatory response. Caspases are central in the regulation of apoptosis and may provide a therapeutic target.

Necroptosis is a recently identified mechanism of programmed cell necrosis that is mediated by receptor-integrating protein kinase-1 (RIPK1).[40,41] It can be triggered by a range of inflammatory mediators and is thought to primarily control intracellular microbial infection. Necroptosis is also seen in many other disease processes, and its role in MODS is an area of ongoing research.

MITOCHONDRIAL DYSFUNCTION

MODS appears to be primarily a functional rather than structural disorder. Overt cell necrosis is an uncommon finding in postmortem examination of organs that have failed due to MODS.[42] Mitochondrial function changes in MODS, and this may be induced by humoral factors, such as thyroid hormone, glucocorticoids, catecholamines and cytokines.[43] Cells appear to enter a state of 'hibernation' where metabolic activity is reduced and oxygen utilisation limited.[44,45] Interestingly, patients who progress to develop MODS, have a different profile of beta-oxidation, gluconeogenesis and citric acid cycle proteins.[46] This implies that there may be a metabolic predisposition to developing MODS.

CO-MORBIDITIES

An important consideration in the development of MODS is the patient's pre-morbid organ function. Patients with pre-existing organ disease are more likely to have further deterioration of organ function following an acute illness (e.g. compromised respiratory reserve in fibrotic lung disease, limited renal function in diabetic nephropathy, reduced marrow response in chronic leukaemia, impaired hepatic function in alcoholic liver disease). These patients will have a lower threshold for developing MODS.

IATROGENESIS

The recognition of MODS corresponded with the development of intensive care supports. It may be that some ICU interventions actually increase the risk of developing MODS or continue to drive the process once it is initiated. For example, the incidence of acute

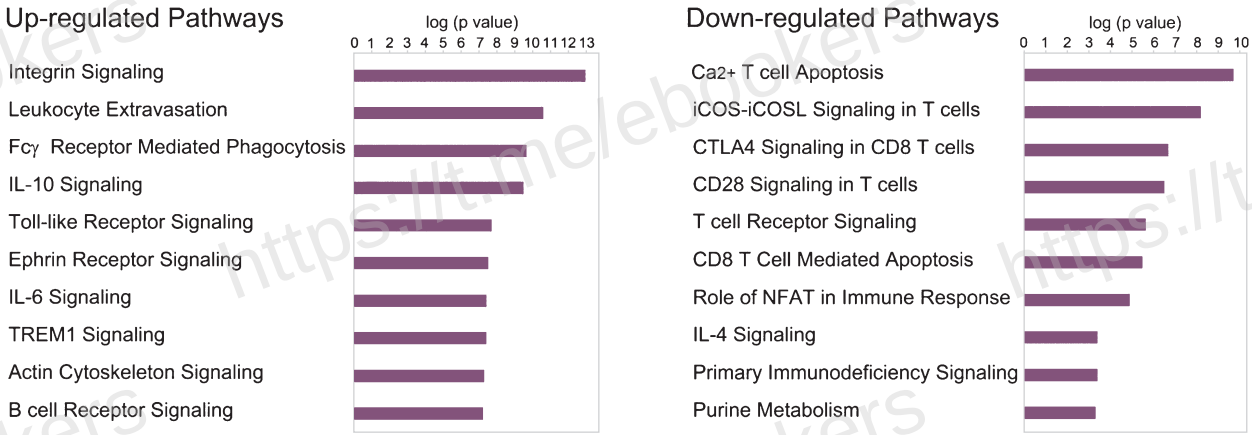


Figure 17.5 Genomic changes associated with severe blunt trauma. *With permission from from Xiao W, Mindrinos MN, Seok J, et al. A genomic storm in critically injured humans.* J Exp Med. *2011;208(13):2581–2590.*

respiratory distress syndrome (ARDS) and its mortality have reduced substantially since the recognition that larger tidal volumes and overzealous parenteral fluid administration were contributing to lung injury.[47,48] Other ICU interventions, such as parenteral fluids (type and volume), immobility, artificial cooling, extracorporeal circulatory support, catecholamines, medications, nutrition supplements and blood products may contribute. Providing evidence-based supportive care is a vital aspect of preventing MODS.

GENETICS

Genetic factors have been thought to contribute to the heterogeneity of MODS. Differences in genes coding for TNF, TLR, NF-κB, IL-1 receptor kinase and caspase-12 have been related to severity of organ dysfunction and extent of ICU supports following sepsis.[49,50] Similarly, in patients undergoing elective abdominal aortic aneurysm repair, the analysis of preoperative leucocyte genes predicted which patients subsequently developed MODS.[51]

However, recent studies suggest there is little genetic variability in the response to critical illness. An important study serially examined the leucocyte genome from patients with severe trauma, severe burns, healthy volunteers exposed to endotoxin and matched healthy controls.[52] Over 80% of the leucocyte transcriptome altered, with gene expression patterns typically representing stimulation of innate immunity and suppression of adaptive immunity (Fig. 17.5). The number of genes whose expression decreased was greater than the number of genes whose expression increased, and half of the altered gene expression had not returned to baseline by 28 days. The genomic changes were remarkably similar between major trauma, major burns and endotoxin exposure.

While the extent of genomic expression changes was independently related to disease severity, there was no gene or cluster of genes that were a unique identifier. A single genetic locus would seem unlikely to be prognostic or a therapeutic target in what appears to be a well-preserved, coordinated, reproducible genomic storm to acute severe illness.

THE GUT IN MULTIORGAN DYSFUNCTION SYNDROME

The gut and its enteric micro-organisms have been proposed to provide an inflammatory focus during critical illness. Normally, organisms in the gut remain commensal due to bowel wall integrity and maintenance of the normal microflora ecosystem. However, when normal conditions are disturbed (e.g. bowel mucosal changes, altered gastric pH, antimicrobial use, overwhelmed reticuloendothelial macrophages), the enteric organisms can invade and perpetuate an inflammatory response. Similarly, gut digestive enzymes can enter the circulation through compromised gut epithelium, contributing to the pathophysiology of MODS.[53] For these reasons, the gut has been described as the 'motor' of MODS.[54] Studies of gut decontamination in critical illness have illustrated a survival benefit, and larger trials are planned (NCT02389036).

CLINICAL FEATURES OF MULTIORGAN DYSFUNCTION SYNDROME

There is no one typical constellation or time-course of organ dysfunction that describes MODS. Some patients may develop only mild organ dysfunction, which, with supportive treatment, resolves in days, while others can develop fulminant MODS progressing rapidly to death.

Which organs become dysfunctional and the timing of their dysfunction depends on the patient's age and phenotype, the inciting injury/illness, the pre-morbid organ function, the extent and duration of physiological derangement, the treatments provided and consideration of all the pathogenesis factors discussed earlier.

Identification of MODS as a discrete clinical syndrome has been difficult due to lack of agreement about what characterises an organ dysfunction. There are many ways of measuring organ dysfunction: clinical features, monitored physiological derangement and altered biochemical markers. Each organ system can manifest dysfunction in many different ways. For example, the respiratory system can be considered dysfunctional based on hypoxia (e.g. PaO_2:FiO_2 ratio), hypercarbia, reduced compliance, radiological change, extent of ventilatory supports or lavage fluid content. The processes that lead to changes in these parameters can be quite different, and defining an organ dysfunction based on one variable alone is inadequate to describe the full spectrum of disease.

Note that criteria of SIRS are no longer recommended as diagnostic criteria for sepsis, and it is unclear if they are useful for detecting those patients who will develop MODS from other non-infectious disease processes.

THERAPIES FOR MODS

Priorities in the treatment of MODS are:

1. Early recognition of illness.
2. Early resuscitation.
3. Early definitive treatment.
4. Supportive care that is evidence based.
5. Consideration of pre-morbid disease.
6. Prevention of secondary insults.

The focus of management must be on the immediate treatment of the inflammatory focus (e.g. remove source of sepsis, repair injured tissue, control blood loss, debride burns, stabilise long bone fractures). Aspects relating to early recognition of the deteriorating patient, resuscitation, specific disease treatments and the methods of organ support are covered in other chapters.

Specific therapies that target the pathogenesis of MODS continue to be extensively studied. Each of the pathophysiological processes, described earlier, has been targeted in pre-clinical and clinical trials. However, despite promise in pre-clinical studies, no therapy has proven clinical efficacy in the treatment of MODS. The lack of a 'magic bullet' for treatment of MODS is not surprising given the complexity and variability of the pathophysiology, the lack of standardised treatments for some diseases and uncertainty regarding optimal timing of adjunctive therapy.

INFLAMMATION MODULATING THERAPIES

Proinflammatory mediators have been a logical therapeutic target. In pre-clinical studies many of these agents have provided physiological benefit, have reduced the severity of organ dysfunction and have improved mortality. However, when these therapies progressed to clinical trials, none have provided clinical benefit and some have worsened outcomes.[55] For example, pre-clinical studies of TNF-α antibodies and soluble TNF-receptors in bacteraemic primates, suggested that neutralising TNF-α improved organ function and reduced mortality.[56] However, not only did clinical trials fail to show a benefit, but higher doses increased mortality.[57] Similarly, the following agents have shown encouraging results in pre-clinical trials but no efficacy or adverse outcomes in subsequent clinical studies: endotoxin antibodies, nonsteroidal anti-inflammatory drugs, IL-1 receptor antagonists, platelet-activating factor (PAF) antagonists, bradykinin antagonists, interferon (IFN)-γ, NOS inhibition, NO antagonists, AT-III concentrate and activated protein C.

The lack of clinical efficacy of immunomodulating therapies for MODS may reflect misplaced attention on the harmful effects of cytokines rather than considering their beneficial role. While inflammatory mediators are associated with MODS, they are also vital for control of infection, tissue repair and healing. Furthermore, the proinflammatory mediators also have downstream effects that eventually attenuate inflammation. While elevated concentrations of proinflammatory cytokines are clearly associated with MODS, reduced levels are also associated with increased mortality.[58–61] The inflammatory response involves a very complex interplay of pro- and anti-inflammatory mediators, and it is not unexpected that targeting one proinflammatory mediator has not proven effective.

Future therapies to assist with recovery from MODS may aim to control excess inflammation without interfering with the essential components of the inflammatory process. Agents that modulate the inflammatory process without diminishing antimicrobial mechanisms are currently being investigated.

HUMORAL THERAPY

Glucocorticoids have been a popular experimental therapy. 'High dose' steroid treatment is known to suppress the inflammatory response, but when trialled in critically ill patients with MODS proved to be harmful. As MODS may be associated with relative adrenal insufficiency and/or glucocorticoid resistance, lower dose steroid treatment has been investigated. Initial studies suggested that septic shock patients with limited response to administered corticotropin had mortality benefit from steroid replacement.[62] However, in the CORTICUS trial, which studied a broader group of septic patients, hydrocortisone did not provide

mortality benefit.[63] Most recently, the ADRENAL study of 3800 ventilated patients with septic shock found that hydrocortisone (200 mg per day) slightly reduced the duration of catecholamine infusion but did not alter mortality.[64]

Thyroid hormone has received relatively little attention despite markedly reduced T3 concentrations during critical illness and physiological plausibility that this may contribute to cell hibernation in MODS. Clinical trials in cardiothoracic ICU patients with low T3 suggested replacement improves cardiovascular function[65]; however, in controlled experimental septic shock studies, providing supplementary T3 appeared physiologically inert.[66] Whether the cells are regulating their own T3 exposure by altering hormonal uptake or clearance is being investigated.

NUTRITION

MODS is a hypercatabolic state and nutritional support is required to ensure adequate energy, protein, fatty acids and trace elements. However, the ideal energy, protein and macronutrient composition in MODS remains unclear. Furthermore, the efficacy of supplementing feeds with amino acids (e.g. arginine, glutamine), nucleotides, fatty acids (e.g. omega-3, γ-linoleic acid) and antioxidants (e.g. selenium) is unproven. The priority is to understand how much energy to provide patients with MODS, and multi-centre studies are now underway to determine the effect on patient outcomes (NCT02306746).

OUTCOMES

Outcomes from MODS appear to have improved over time.[67,68] No specific therapies have been developed that 'treat' MODS; the improved outcomes are likely to reflect a greater awareness of the diseases that can progress to MODS, the importance of timely resuscitation, prompt treatment of the inciting disease and the application of evidence-based supportive care.

It is important to remain cognisant that many of the pathophysiological processes leading to MODS are part of a complex interdependent system that *usually* leads to the resolution of an acute illness/injury. Caution needs to be applied when considering the physiological changes that occur during a critical illness, and whether treating these changes is actually beneficial for each individual patient. Conversely, we must remain thoroughly aware that some patients are particularly sensitive to the physiological changes, or develop an exaggerated response to an acute illness/injury, progressing to MODS, permanent organ injury or death. How to identify which patients will progress to MODS and how they are best managed is a research priority.

KEY REFERENCES

12. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):801–810.
13. Minei JP, Cuschieri J, Sperry J, et al. The changing pattern and implications of multiple organ failure after blunt injury with hemorrhagic shock. *Crit Care Med*. 2012;40(4):1129–1135.
28. Ince C, Mayeux PR, Nguyen T, et al. The endothelium in sepsis. *Shock*. 2016;45(3):259–270.
32. Wang F, Pan W, Wang H, et al. Relationship between thyroid function and ICU mortality: a prospective observation study. *Crit Care*. 2012;16(1):R11.
36. De Backer D, Orbegozo Cortes D, Donadello K, et al. Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. *Virulence*. 2014;5(1):73–79.
41. Linkermann A, Green DR. Necroptosis. *N Engl J Med*. 2014;370(5):455–465.
46. Langley RJ, Tsalik EL, van Velkinburgh JC, et al. An integrated clinico-metabolomic model improves prediction of death in sepsis. *Sci Transl Med*. 2013;5(195):195ra95.
48. Hess DR, Thompson BT, Slutsky AS. Update in acute respiratory distress syndrome and mechanical ventilation 2012. *Am J Respir Crit Care Med*. 2013;188(3):285–292.
53. Altshuler AE, Kistler EB, Schmid-Schonbein GW. Autodigestion: proteolytic degradation and multiple organ failure in shock. *Shock*. 2016;45(5):483–489.
64. Venkatesh B, Finfer S, Cohen J, et al. Adjunctuve glucocorticoid therapy in patients with septic shock. *N Engl J Med*. 2018;doi:10.1056/NEJMoa1705835.
66. Maiden MJ, Chapman MJ, Torpy DJ, et al. Triiodothyronine administration in a model of septic shock: a randomized blinded placebo-controlled trial. *Crit Care Med*. 2016;44(6):1153–1160.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Mayr VD, Dunser MW, Greil V, et al. Causes of death and determinants of outcome in critically ill patients. *Crit Care*. 2006;10(6):R154.
2. Vincent JL, Nelson DR, Williams MD. Is worsening multiple organ failure the cause of death in patients with severe sepsis? *Crit Care Med*. 2011;39(5):1050–1055.
3. Fishman AP. Shock lung: a distinctive nonentity. *Circulation*. 1973;47(5):921–923.
4. Baue AE. Multiple, progressive, or sequential systems failure. A syndrome of the 1970s. *Arch Surg*. 1975;110(7):779–781.
5. Eiseman B, Beart R, Norton L. Multiple organ failure. *Surg Gynecol Obstet*. 1977;144(3):323–326.
6. Baue AE. MOF, MODS, and SIRS: what is in a name or an acronym? *Shock*. 2006;26(5):438–449.
7. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med*. 1992;20(6):864–874.
8. Marshall JC, Cook DJ, Christou NV, et al. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med*. 1995;23(10):1638–1652.
9. Vincent JL, Moreno R, Takala J, et al. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707–710.
10. Peres Bota D, Melot C, Lopes Ferreira F, et al. The multiple organ dysfunction score (MODS) versus the sequential organ failure assessment (SOFA) score in outcome prediction. *Intensive Care Med*. 2002;28(11):1619–1624.
11. Moreno R, Vincent JL, Matos R, et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Working Group on Sepsis related Problems of the ESICM. *Intensive Care Med*. 1999;25(7):686–696.
12. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):801–810.
13. Minei JP, Cuschieri J, Sperry J, et al. The changing pattern and implications of multiple organ failure after blunt injury with hemorrhagic shock. *Crit Care Med*. 2012;40(4):1129–1135.
14. Seely AJ, Christou NV. Multiple organ dysfunction syndrome: exploring the paradigm of complex nonlinear systems. *Crit Care Med*. 2000;28(7):2193–2200.
15. Marshall JC. Inflammation, coagulopathy, and the pathogenesis of multiple organ dysfunction syndrome. *Crit Care Med*. 2001;29(7 suppl):S99–S106.
16. Borrelli E, Roux-Lombard P, Grau GE, et al. Plasma concentrations of cytokines, their soluble receptors, and antioxidant vitamins can predict the development of multiple organ failure in patients at risk. *Crit Care Med*. 1996;24(3):392–397.
17. Paterson RL, Galley HF, Dhillon JK, et al. Increased nuclear factor kappa B activation in critically ill patients who die. *Crit Care Med*. 2000;28(4):1047–1051.
18. Lorne E, Dupont H, Abraham E. Toll-like receptors 2 and 4: initiators of non-septic inflammation in critical care medicine? *Intensive Care Med*. 2010;36(11):1826–1835.
19. Arbour NC, Lorenz E, Schutte BC, et al. TLR4 mutations are associated with endotoxin hyporesponsiveness in humans. *Nat Genet*. 2000;25(2):187–191.
20. Cohen MJ, Brohi K, Calfee CS, et al. Early release of high mobility group box nuclear protein 1 after severe trauma in humans: role of injury severity and tissue hypoperfusion. *Crit Care*. 2009;13(6):R174.
21. Wang H, Yang H, Czura CJ, et al. HMGB1 as a late mediator of lethal systemic inflammation. *Am J Respir Crit Care Med*. 2001;164(10 Pt 1):1768–1773.
22. Wang H, Ward MF, Sama AE. Novel HMGB1-inhibiting therapeutic agents for experimental sepsis. *Shock*. 2009;32(4):348–357.
23. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med*. 2003;348(2):138–150.
24. Boomer JS, To K, Chang KC, et al. Immunosuppression in patients who die of sepsis and multiple organ failure. *JAMA*. 2011;306(23):2594–2605.
25. Ryu J, Pyo H, Jou I, et al. Thrombin induces NO release from cultured rat microglia via protein kinase C, mitogen-activated protein kinase, and NF-kappa B. *J Biol Chem*. 2000;275(39):29955–29959.
26. Boldt J, Papsdorf M, Rothe A, et al. Changes of the hemostatic network in critically ill patients–is there a difference between sepsis, trauma, and neurosurgery patients? *Crit Care Med*. 2000;28(2):445–450.
27. Fink MP, Delude RL. Epithelial barrier dysfunction: a unifying theme to explain the pathogenesis of multiple organ dysfunction at the cellular level. *Crit Care Clin*. 2005;21(2):177–196.
28. Ince C, Mayeux PR, Nguyen T, et al. The endothelium in sepsis. *Shock*. 2016;45(3):259–270.
29. Sternberg EM. Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens. *Nat Rev Immunol*. 2006;6(4):318–328.
30. Tracey KJ. Understanding immunity requires more than immunology. *Nat Immunol*. 2010;11(7):561–564.
31. Chinga-Alayo E, Villena J, Evans AT, et al. Thyroid hormone levels improve the prediction of mortality among patients admitted to the intensive care unit. *Intensive Care Med*. 2005;31(10):1356–1361.
32. Wang F, Pan W, Wang H, et al. Relationship between thyroid function and ICU mortality: a prospective observation study. *Crit Care*. 2012;16(1):R11.
33. Heyland DK, Cook DJ, King D, et al. Maximizing oxygen delivery in critically ill patients: a

methodologic appraisal of the evidence. *Crit Care Med*. 1996;24(3):517–524.
34. Sakr Y, Dubois MJ, De Backer D, et al. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Crit Care Med*. 2004;32(9):1825–1831.
35. Piagnerelli M, Boudjeltia KZ, Brohee D, et al. Alterations of red blood cell shape and sialic acid membrane content in septic patients. *Crit Care Med*. 2003;31(8):2156–2162.
36. De Backer D, Orbegozo Cortes D, Donadello K, et al. Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. *Virulence*. 2014;5(1):73–79.
37. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. *N Engl J Med*. 2001;345(8):588–595.
38. De Backer D, Creteur J, Preiser JC, et al. Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med*. 2002;166(1): 98–104.
39. Hotchkiss RS, Schmieg RE Jr, Swanson PE, et al. Rapid onset of intestinal epithelial and lymphocyte apoptotic cell death in patients with trauma and shock. *Crit Care Med*. 2000;28(9):3207–3217.
40. Hotchkiss RS, Strasser A, McDunn JE, et al. Cell death. *N Engl J Med*. 2009;361(16):1570–1583.
41. Linkermann A, Green DR. Necroptosis. *N Engl J Med*. 2014;370(5):455–465.
42. Hotchkiss RS, Swanson PE, Freeman BD, et al. Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. *Crit Care Med*. 1999;27(7):1230–1251.
43. Singer M, De Santis V, Vitale D, et al. Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. *Lancet*. 2004;364(9433):545–548.
44. Brealey D, Brand M, Hargreaves I, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. *Lancet*. 2002;360(9328):219–223.
45. Dare AJ, Phillips AR, Hickey AJ, et al. A systematic review of experimental treatments for mitochondrial dysfunction in sepsis and multiple organ dysfunction syndrome. *Free Radic Biol Med*. 2009;47(11):1517–1525.
46. Langley RJ, Tsalik EL, van Velkinburgh JC, et al. An integrated clinico-metabolomic model improves prediction of death in sepsis. *Sci Transl Med*. 2013;5(195):195ra95.
47. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000;342(18):1301–1308.
48. Hess DR, Thompson BT, Slutsky AS. Update in acute respiratory distress syndrome and mechanical ventilation 2012. *Am J Respir Crit Care Med*. 2013; 188(3):285–292.
49. Arcaroli J, Fessler MB, Abraham E. Genetic polymorphisms and sepsis. *Shock*. 2005;24(4): 300–312.
50. Arcaroli J, Silva E, Maloney JP, et al. Variant IRAK-1 haplotype is associated with increased nuclear factor-kappaB activation and worse outcomes in sepsis. *Am J Respir Crit Care Med*. 2006;173(12):1335–1341.
51. Feezor RJ, Baker HV, Xiao W, et al. Genomic and proteomic determinants of outcome in patients undergoing thoracoabdominal aortic aneurysm repair. *J Immunol*. 2004;172(11):7103–7109.
52. Xiao W, Mindrinos MN, Seok J, et al. A genomic storm in critically injured humans. *J Exp Med*. 2011;208(13):2581–2590.
53. Altshuler AE, Kistler EB, Schmid-Schonbein GW. Autodigestion: proteolytic degradation and multiple organ failure in shock. *Shock*. 2016;45(5): 483–489.
54. Marshall JC, Christou NV, Meakins JL. The gastrointestinal tract. The 'undrained abscess' of multiple organ failure. *Ann Surg*. 1993;218(2): 111–119.
55. Vincent JL, Abraham E. The last 100 years of sepsis. *Am J Respir Crit Care Med*. 2006;173(3):256–263.
56. Tracey KJ, Fong Y, Hesse DG, et al. Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. *Nature*. 1987;330(6149):662–664.
57. Fisher CJ Jr, Agosti JM, Opal SM, et al. Treatment of septic shock with the tumor necrosis factor receptor:Fc fusion protein. The Soluble TNF Receptor Sepsis Study Group. *N Engl J Med*. 1996;334 (26):1697–1702.
58. Cabioglu N, Bilgic S, Deniz G, et al. Decreased cytokine expression in peripheral blood leukocytes of patients with severe sepsis. *Arch Surg*. 2002;137(9): 1037–1043, discussion 1043.
59. Cannon JG, Friedberg JS, Gelfand JA, et al. Circulating interleukin-1 beta and tumor necrosis factor-alpha concentrations after burn injury in humans. *Crit Care Med*. 1992;20(10):1414–1419.
60. Luger A, Graf H, Schwarz HP, et al. Decreased serum interleukin 1 activity and monocyte interleukin 1 production in patients with fatal sepsis. *Crit Care Med*. 1986;14(5):458–461.
61. Riche F, Panis Y, Laisne MJ, et al. High tumor necrosis factor serum level is associated with increased survival in patients with abdominal septic shock: a prospective study in 59 patients. *Surgery*. 1996;120(5):801–807.
62. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002;288(7):862–871.
63. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358(2):111–124.
64. Venkatesh B, Finfer S, Cohen J, et al. Adjunctuve glucocorticoid therapy in patients with septic shock. *N Engl J Med*. 2018;doi:10.1056/NEJMoa1705835.
65. Kaptein EM, Sanchez A, Beale E, et al. Clinical review: thyroid hormone therapy for postoperative nonthyroidal illnesses: a systematic review and

synthesis. *J Clin Endocrinol Metab*. 2010;95(10):4526–4534.
66. Maiden MJ, Chapman MJ, Torpy DJ, et al. Triiodothyronine administration in a model of septic shock: a randomized blinded placebo-controlled trial. *Crit Care Med*. 2016;44(6):1153–1160.
67. ARISE; ANZICS APD Management Committee. The outcome of patients with sepsis and septic shock presenting to emergency departments in Australia and New Zealand. *Crit Care Resusc*. 2007;9(1):8–18.
68. Ciesla DJ, Moore EE, Johnson JL, et al. A 12-year prospective study of postinjury multiple organ failure: has anything changed? *Arch Surg*. 2005;140(5):432–438, discussion 438-440.

18

Monitoring oxygenation

Thomas J Morgan, Balasubramanian Venkatesh

ROLES OF OXYGEN IN AEROBIC ORGANISMS[1]

- Bioenergetics. Aerobic mitochondrial respiration accounts for 90% of oxygen consumption, generating adenosine triphosphate (ATP) by oxidative phosphorylation. Oxygen is the terminal electron acceptor at Complex IV in the electron transfer cytochrome oxidase system, combining with two protons to produce water.
- Biosynthetics. Transferase systems incorporate oxygen into substrates including prostanoids, catecholamines and some neurotransmitters.
- Biodegradation and detoxification. For example, the cytochrome P-450 hydroxylases are mixed function oxidases requiring oxygen plus nicotinamide adenine dinucleotide phosphate (NADPH) as a co-substrate.
- Generation of reactive oxygen species (ROS). ROS functions include hypoxic signalling, maintenance of vascular tone and antimicrobial defence.
- Mitochondrial heat generation by 'uncoupled' oxidative phosphorylation.

HYPOXIA

The term 'hypoxia' connotes oxygen deficiency. As tissue P_{O_2} declines, a characteristic sequence is activated:

- Oxidative phosphorylation is initially supported: glycolysis accelerates; competing biosynthetic and biodegradation pathways are shut down.
- ROS released at mitochondrial Complex III activate hypoxia-inducible factor-1, up-regulating genes promoting hypoxic cell survival.[2]
- Oxidative phosphorylation ceases when intracellular $P_{O_2} < 0.1$ to 1 mm Hg.
- Low rate ATP production continues by anaerobic glycolysis.
- Cell death by apoptosis and necrosis.
- Release of ROS and reactive nitrogen species (RNS) on re-oxygenation causes oxidant stress.[3]

DYSOXIA

A suggested broader term 'dysoxia' describes any form of oxygen-limited cytochrome turnover causing progressive ATP depletion.[4]

THE DYSOXIA SPECTRUM

- 'Stagnant' hypoxia due to reduced blood flow.
- 'Hypoxaemic' hypoxia due to a low arterial oxygen tension (Pa_{O_2}).
- 'Anaemic' hypoxia due to a low haemoglobin concentration.
- 'Cytopathic' dysoxia, defined as impaired cellular oxygen utilisation despite adequate delivery and attributed to sepsis and other cytokinaemic states.[5] Multiple-organ dysfunction has been characterised as an adaptive 'hibernation' response to cytopathic dysoxia.[1]
- Oxygen toxicity: adverse effects of intentional or inadvertent hyperoxia.[6]

THE OXYGEN CASCADE

Oxygen diffuses from atmosphere to intracellular organelles down a series of partial pressure reductions known as the oxygen cascade.

Steps include:

- Inspired gas
- Alveolar gas
- Arterial blood
- Microcirculation
- Interstitium
- Mitochondria and other intracellular organelles.

Intracellular oxygenation can be jeopardised at any step. This chapter surveys current and potential monitoring options at strategic points down the cascade.

ABSTRACT

Monitoring oxygenation at strategic points along the oxygen cascade can mitigate both hypoxia and hyperoxia. Monitoring points extend from the inspired gas to individual tissues. Modalities include the distribution of ventilation by electrical impedance tomography, matching of ventilation with perfusion by the multiple inert gas elimination technique and other techniques, the A-a gradient, venous admixture, the Pi_{O_2}/Fi_{O_2} ratio, intermittent and continuous blood gas analysis and co-oximetry, dual and multiple wavelength pulse oximetry, oxygen delivery and consumption rates, mixed and central venous O_2 tensions and contents, the global CO_2 gap, regional CO_2 gaps including gastric and sublingual, dynamic circulatory imaging and near infrared spectroscopy with a functional occlusion test. Detecting dysoxic thresholds in individual tissues remains a research focus.

KEYWORDS

Oxygen cascade
lung models
DO_2
VO_2
CO_2 gaps
mixed and central venous
dynamic circulatory imaging
tissue heterogeneity

INSPIRED GAS

Regulating the inspired oxygen tension (Pi_{O_2}) can mitigate both hypoxia and hyperoxia. The Pi_{O_2} of humidified gas is determined by the fraction of inspired oxygen (Fi_{O_2}) the barometric pressure (BP) and the saturated vapour pressure of water (47 mm Hg).

$$Pi_{O_2} = Fi_{O_2} \times (BP - 47) \quad (18.1)$$

Monitoring includes:

- Gas supply and ventilator input pressures
- Oxygen concentrations (paramagnetic analysers) in inspiratory module and circuit.

TRANSFER OF INSPIRED GAS TO ALVEOLI

Open communication between oxygen delivery system and alveoli is evidenced by:

- No signs of upper airway obstruction
- Expired tidal and minute volumes and airway pressures in ventilated patients within correctly set alarm limits
- An appropriate end-tidal CO_2 waveform.

ALVEOLAR GAS

The P_{O_2} spread across individual lung units is wide, ranging from ~40 mm Hg to >600 mm Hg in a patient receiving 100% oxygen.

DISTRIBUTION OF ALVEOLAR VENTILATION

Clinicians observe chest movement, auscultate air entry, and examine plain chest radiographs. Computed tomography scanning can reveal occult overdistension, while magnetic resonance imaging (MRI) can provide regional functional lung analysis using techniques, such as oxygen-enhanced T1 mapping.[7] Both present logistic disadvantages.

Bedside monitoring techniques to track ventilation heterogeneity and recruitment responses can include:

- Electrical impedance tomography (EIT), showing promise in infants and children[8] and now adults.[9]
- Oxygen washout curves following Fi_{O_2} reductions,[10] with potential for serial monitoring of end-expiratory lung volumes and heterogeneity indices such as 'moment ratios'.

MATCHING VENTILATION AND PERFUSION

For efficient gas exchange, most lung units must receive well-matched alveolar ventilation (V) and perfusion (Q), with V/Q ratios clustered around unity. V/Q spread impairs both O_2 uptake (low V/Q) and CO_2 elimination (high V/Q).

The adult lung contains over 100,000 individual gas exchanging units,[11] with a complexity that resists simple bedside quantification. The gold standard remains the multiple inert gas elimination technique (MIGET), which models a 50-compartment lung with V/Q ratios spanning zero to infinity. Pre-equilibrated saline containing six inert gases with a range of solubilities is infused to steady state. Their measured pulmonary retention and elimination ratios are entered into software as iterative end points to compute corresponding 50 compartment distributions of ventilation and perfusion.[11,12]

Models with fewer compartments may suffice at the bedside,[13] with stepped Fi_{O_2} changes forcing measured responses in Pa_{O_2}, end-tidal P_{O_2} or Sp_{O_2} (see 'pulse oximetry').

The three-compartment model

A lung model dating from the mid-20th century[14] has just three compartments and no requirement for forcing functions, such as inert gas infusions or Fi_{O_2} switching. The trade-off is poor predictive capacity in many respiratory disorders. The compartments are:

1. 'Ideal', containing alveoli with matched perfusion and ventilation ($V/Q = 1$)
2. 'Venous admixture', containing perfused non-ventilated alveoli ($V/Q = 0$)
3. 'Dead space', containing ventilated non-perfused alveoli ($V/Q = \infty$).

The 'ideal' P_{O_2} (PA_{O_2}) is calculated from the alveolar gas equation:

$$PA_{O_2} = Pi_{O_2} - (1 - Fi_{O_2} \times (1 - R)) \times PaCO_2/R \quad (18.2)$$

R is the respiratory exchange ratio, usually assumed to be 0.8. Pi_{O_2} is calculated as in Eq. 18.1. $PaCO_2$ is arterial P_{CO_2}.

A common approximation is:

$$PA_{O_2} = Pi_{O_2} - PaCO_2/0.8$$

The A-a gradient and venous admixture calculations (see below) are derived from this minimalist model.

TRANSFER FROM ALVEOLI TO ARTERIAL BLOOD

The MIGET technique identified V/Q mismatch and right to left shunt ($V/Q = 0$) as the principal causes of reduced pulmonary oxygen transfer in critical illness.[15] The intrapulmonary shunt predominates in the acute respiratory distress syndrome (ARDS), lobar pneumonia and after cardiopulmonary bypass, whereas V/Q mismatch without shunt is prominent in chronic lung disease.[16]

TENSION-BASED INDICES

A-a gradient

The A-a gradient is calculated as $PA_{O_2} - Pa_{O_2}$, where PA_{O_2} is the 'ideal' alveolar P_{O_2} (Eq. 18.2). Hypoxaemia is then classified under two headings:

Normal A-a gradient

1. Alveolar hypoventilation (elevated PA_{CO_2})
2. Low Pi_{O_2} ($Fi_{O_2} < 0.21$, or BP <760 mm Hg).

Raised A-a gradient

1. Diffusion defect (rare)
2. V/Q mismatch
3. Right-to-left shunt (intrapulmonary or cardiac)
4. Increased oxygen extraction ($Ca_{O_2} - Cv_{O_2}$).

The A-a gradient is a component of the APACHE II, III and IV scoring systems.[17,18] Several drawbacks limit its clinical usefulness:

- Normals depend on Fi_{O_2} and age. The normal A-a gradient breathing air is 7 mm Hg in young adults and 14 mm Hg in the elderly. On 100% oxygen, values become 31 mm Hg and 56 mm Hg, respectively.
- Fi_{O_2} dependence in intrapulmonary shunt and V/Q mismatch.[19,20]

Pa_{O_2}/Fi_{O_2} ratio

The Pa_{O_2}/Fi_{O_2} ratio contributes to current ARDS diagnosis,[21] classifying severity as mild (<300 ≥ 200), moderate (<200 ≥ 100), or severe (<100). It is an input variable in Simplified Acute Physiology Score (SAPS) 2 and 3,[22] Sepsis-related organ failure assessment score (SOFA),[23] Acute physiology and chronic health evaluation score (APACHE) IV[18] and lung injury scoring systems.[24] Normal sea-level value is ≥500 mm Hg.

The advantage is simplicity. There are several disadvantages:

- Failure to distinguish hypoventilation from other causes of hypoxaemia (unlike the A-a gradient).
- Dependence on BP. A ratio of 380 mm Hg is low at sea level but unremarkable at 1600 m elevation.
- Fi_{O_2} dependence, both in right-to-left shunt and V/Q scatter.[19,20]
- Hostage to positive end-expiratory pressure (PEEP) settings and interventions such as recruitment manoeuvres and fluid balance manipulation.

Pa_{O_2}/Fi_{O_2} calculations repeated under standardised Fi_{O_2} and PEEP settings 24 hours post-intervention and stabilisation can reset ARDS classifications and improve hospital mortality prediction.[25]

CONTENT-BASED INDICES

Venous admixture (Q_s/Q_t)

Venous admixture is the proportion of mixed venous blood calculated to flow through the 'shunt' ($V/Q = 0$) compartment of the three-compartment model, which, on rejoining 'ideal' end-capillary blood flow, will reproduce the measured Pa_{O_2}. It is determined as follows:

$$\frac{\dot{Q}_s}{\dot{Q}_t} = \frac{Cc'O_2 - Ca_{O_2}}{Cc'O_2 - C\bar{v}_{O_2}} \quad (18.3)$$

Cc_{O_2}, Ca_{O_2}, and $C\bar{v}_{O_2}$ are the oxygen contents of 'ideal' end-capillary, arterial and mixed venous blood, respectively. Ca_{O_2} and Cv_{O_2} are calculated using data from arterial and mixed venous blood gas analysis and CO-oximetry (Table 18.1). Cc_{O_2} is calculated assuming $Pc_{O_2} = PA_{O_2}$ (Eq. 18.2). Sc_{O_2} is then computed from the Hb_{O_2} dissociation curve.

Advantages

- Unaffected by BP
- Unaffected by alveolar hypoventilation
- Independent of Fi_{O_2} despite variations in $Ca_{O_2} - Cv_{O_2}$ provided intrapulmonary shunt is the dominant pathology.[19,26]

Disadvantages

- Requires a pulmonary artery (PA) catheter
- Fi_{O_2} dependence in V/Q scatter without shunt, for example, in chronic obstructive pulmonary disease, virtually disappearing at $Fi_{O_2} > 0.5$.

When determined at $Fi_{O_2} = 1$, venous admixture quantifies 'true' right-to-left shunt. However, 100% oxygen exposure itself increases intrapulmonary shunt by the inhibition of hypoxic pulmonary vasoconstriction and absorption atelectasis.

Estimated shunt fraction

Assigning a fixed $Ca_{O_2} - Cv_{O_2}$ value removes the need for a PA catheter. However, because of the potential $Ca_{O_2} - Cv_{O_2}$ range (1.3–7.4 mL/dL), estimated shunt changes can be wrong in both degree and direction.[26]

ARTERIAL BLOOD

Indices of arterial oxygenation are Pa_{O_2} and Sa_{O_2}, linked by the Hb_{O_2} dissociation curve.

Hypoxaemia is defined as Pa_{O_2} <60 mm Hg or Sa_{O_2} <0.9, values near the descending portion of the Hb_{O_2} dissociation curve. A further Pa_{O_2} drop causes a marked fall in Sa_{O_2} and thus Ca_{O_2}.

BLOOD GAS ANALYSIS AND CO-OXIMETRY

Arterial blood is collected in a purpose-designed syringe containing lyophilised heparin to a final concentration of 20–50 U/mL. Pa_{O_2} is measured by a Clark electrode, and Sa_{O_2} by CO-oximetry. The Clark electrode works on polarographic principles, and a CO-oximeter computes the concentrations of haemoglobin species (Hb_{O_2}, Hb, COHb, MetHb, FHb) from light absorbance of haemolysed blood at several wavelengths.

Sa_{O_2} is 'functional' saturation, determined from concentrations of Hb_{O_2} and Hb (Table 18.1). Interference arises from substances with competing absorbance spectra, such as bilirubin, HbF, lipid emulsions and intravenous dyes. Increasing the wavelength numbers, for example, from 7 to 128, can reduce or eliminate interference.

Errors

Pre-analytic and analytic errors in P_{O_2} measurement are set out in Table 18.2.

Table 18.1 Oxygen dynamics – measured and derived indices

PARAMETER	ABBREVIATION	FORMULA	NORMAL RANGE	UNITS
Functional haemoglobin concentration	$[Hb_{funct}]$	$[Hb_{O_2}]+[Hb]$	12.0–18.0	g/dL
Arterial oxygen tension	Pa_{O_2}	Measured	95 ± 5	mm Hg
Mixed venous oxygen tension	Pv_{O_2}	Measured	40 ± 5	mm Hg
Functional saturation	S_{O_2}	$[Hb_{O_2}]/([Hb_{funct}])$		
Fractional saturation	FHb_{O_2}	$[Hb_{O_2}]/([Hb_{O_2}]+[Hb]+[COHb]+[MetHb])$		
Arterial functional saturation	Sa_{O_2}		0.97 ± 0.02	
Mixed venous functional saturation	Sv_{O_2}		0.75 ± 0.05	
Blood oxygen content	CO_2	$1.39\times[Hb_{funct}]\times S_{O_2}+0.0031\times P_{O_2}$		mL/dL
Arterial oxygen content	Ca_{O_2}		16–22	mL/dL
Mixed venous oxygen content	Cv_{O_2}		12–17	mL/dL
Cardiac index	CI	CO/BSA	2.5–4.2	L/min/m^2
Oxygen delivery index	$D_{O_2}I$	$CI\times Ca_{O_2}\times 10$	460–650	mL/min/m^2
Oxygen consumption index	$V_{O_2}I$	$CI\times(Ca_{O_2}-Cv_{O_2})\times 10$	96–170	mL/min/m^2
Oxygen extraction ratio	O_2ER	$(Ca_{O_2}-Cv_{O_2})/Ca_{O_2}$ or V_{O_2}/D_{O_2}	0.23–0.32	

BSA, Body surface area; *COHb,* carboxyhaemoglobin; *Hb,* reduced haemoglobin; Hb_{O_2}, oxyhaemoglobin; *MetHb,* methaemoglobin.

Table 18.2 Pre-analytic and analytic errors in P_{O_2} measurement

PRE-ANALYTIC	ANALYTIC
Oxygen diffusing into or out of air bubbles along tension gradients	Interanalyser variabilit. There is 7%–8% measurement variation on the same sample
Contamination with flush solution. Discard volume should be 2–3 times the internal volume of cannula and tubing	Inadequate anticoagulation, allowing protein deposits on electrodes
Pseudohypoxaemia. Oxygen consumption in vitro from extreme leukocytosis	Non-linearity at high P_{O_2} (>150 mm Hg)
Artefactual Pa_{O_2} elevations. With syringes stored on ice, the semi-permeable polypropylene allows oxygen ingress, facilitated by the cold-induced increase in oxygen solubility	Maintenance of electrode temperature within narrow limits (37 ± 0.1°C) is critical. P_{O_2} changes by 7% for every degree Celsius temperature change
	Minimal interference by nitrous oxide and volatile anaesthetic agents unless the polarising voltage of the electrode exceeds 600 mV
	Tonometry is the primary reference method. Quality control materials, such as aqueous, perfluorocarbon and bovine haemoglobin solutions, are used for convenience
	Arterial blood gas tensions fluctuate breath to breath.[27] Intermittent analysis is a snapshot

Temperature correction

All measurements are at 37°C. Temperature-corrected values can be calculated, but many clinicians prefer uncorrected data interpreted using normothermic reference ranges, except when evaluating the A-a gradient.

CONTINUOUS INTRA-ARTERIAL BLOOD GAS MONITORING[28]

Fibre-optic optodes calibrated with precision gases or solutions can be placed in the arterial stream to provide continuous measurements of pH, P_{CO_2} and P_{O_2}. Typical sensors are 0.5 mm in diameter, suitable for insertion through 20-G cannulas. Clinical trials have revealed varying bias and imprecision, with no evidence of improved outcomes. Along with expense, these factors have limited their bedside application.

Problems, such as flow and position artefact, prompted the development of monitors placed in line but ex vivo. Samples are drawn into an externally located cassette, analysed then returned, with results available in 2 minutes. In preterm neonates, this method can reduce red cell transfusion requirements.[29]

TRANSCUTANEOUS P_{O_2} AND P_{CO_2}

Continuous non-invasive assessment of blood gas tension is possible with transcutaneous P_{O_2} and P_{CO_2} monitoring. Systems incorporate integral thermistors and servo controlled heaters. P_{O_2} measurement utilises the principle of the Clark electrode, while the P_{CO_2} device is a pH sensitive glass electrode. The skin is warmed to 42–44°C for closest correlation with arterial values. Transcutaneous monitors generate reliable $PaCO_2$ values provided perfusion is unimpaired, but P_{O_2} measurements are more for trend analysis. Frequent site changes are necessary to prevent burns, and there is a need for regular recalibration. Monitoring is not recommended in haemodynamically unstable patients.

Transcutaneous monitors have a role in the prevention of neonatal hyperoxia,[30] plus monitoring potential in nocturnal noninvasive ventilation[31] and the diagnosis of sleep apnoea and hypoventilation syndromes.

PULSE OXIMETRY

Standard pulse oximetry[32] determines Sp_{O_2} from light absorbance at wavelengths 660 nm (red) and 940 nm (infrared) by capillary beds in digits, forehead, earlobes or the nasal septum. Two light-emitting diodes cycle on and off at multiples of mains frequency. A photo-diode detects transmitted light and corrects for ambient light. Subtraction of the background signal (tissue, capillary blood and venous blood) isolates the pulsatile arterial component.

Absorbance (A) for both wavelengths is determined as:

$$A = \log_{10}(I_0/I)$$

I_0 = incident light intensity, and I = emergent light intensity. For a given chromophore, A is proportional to its concentration (Beer's law) and the path length (Lambert's law). From the pulsatile (AC) and background (DC) absorbance signals at both wavelengths, a ratio (R) is derived:

$$R = (AC_{660}/DC_{660})/(AC_{940}/DC_{940})$$

Sp_{O_2} is computed using software 'look-up' tables of R versus Sa_{O_2} (FHb_{O_2} with some manufacturers) as measured in the arterial blood of volunteers breathing hypoxic gas mixtures.

Sp_{O_2} is usually displayed as a percentage. Restriction to two wavelengths necessitates an assumption that Hb_{O_2} and Hb are the sole haemoglobin species in the light path. The resulting error is trivial with normal dyshaemoglobin concentrations.

Speed of response

Sp_{O_2} is averaged over 3–6 seconds, and updated every 0.5–1 second. Forehead sensors respond to sudden Fi_{O_2} reductions within 10–15 seconds, whereas finger probe delay with peripheral vasoconstriction can exceed 1 minute.

Accuracy

In the 90%–97% saturation range, Sp_{O_2} has a mean absolute bias of <1%, and a precision (standard deviation of bias) of <3%. At Sa_{O_2} < 80% Sp_{O_2} readouts are extrapolated from higher saturation calibrations. Negative bias and imprecision progressively increase.

Error

Causes are listed in Table 18.3. A falsely high Sp_{O_2} is of greatest concern.

Unlike CO-oximetry, there is no interference from bilirubin, lipid emulsions and HbF.

Dyshaemoglobins and pulse oximetry

Dual wavelength oximeters cannot distinguish COHb from Hb_{O_2}. Sp_{O_2} therefore overestimates Sa_{O_2} when [COHb] is elevated, providing potential false reassurance for example after inhalational burn injuries.

MetHb absorbs both wavelengths. High [MetHb] causes Sp_{O_2} underestimation of Sa_{O_2} at normal saturations and overestimation at very low oxygen tensions. At [MetHb] ≥35% the R value is unity, which translates to $Sp_{O_2} = 85\%$.

Oximetric respiratory rate monitoring[33]

Opioid-induced hypoventilation can cause death or permanent injury when oxygen is administered to patients monitored by standard pulse oximetry.[34] Effective continuous respiratory rate monitoring should improve early detection. Algorithms analysing respiration-induced oximetric signal changes may supersede current methods, such as chest bands or nasal end-tidal CO_2.[33]

Table 18.3 Causes of error in Sp_{O_2} readings

FACTOR	COMMENT
COHb	Measured as Hb_{O_2}. Sp_{O_2} may be falsely high. See *Dyshaemoglobins and pulse oximetry* above
MetHb	Absorbs both wavelengths. See *Dyshaemoglobins and pulse oximetry* above
Low saturations	Progressive inaccuracy below 70%–80%, usually falsely low Sp_{O_2}
Prominent venous signal	Dependent limb, tricuspid regurgitation (venous pulsations) – falsely low Sp_{O_2}
Non-pulsatile flow	Cardiopulmonary bypass – poor signal
Vasoconstriction, limb ischaemia, shock states	Low pulsatile signal
Motion artefact	Tremor, voluntary movement – falsely low Sp_{O_2}
Ambient light	Strong sunlight, fluorescent and xenon lamps, flickering light – falsely low Sp_{O_2}
Anaemia	No effect
Dyes	Methylene blue, indocyanine green, indigo carmine – falsely low Sp_{O_2}
Black skin pigmentation	Variable precision and bias. May require separate calibration
Nail polish	Especially blue. Falsely low Sp_{O_2}. Acrylic nails do not interfere
Optical shunting	Due to inadequate probe contact – falsely low Sp_{O_2}
Radiofrequency interference	Reported with MRI scanners – falsely high Sp_{O_2}

MRI, Magnetic resonance imaging.

Importance of pulse oximetry

Pulse oximeters generate rapid real-time information without calibration. They detect unsuspected hypoxaemia during patient transport,[35] and are mandatory in highacuity areas, such as operating rooms, recovery rooms and intensive care units. They are useful screening tools.

On the down side, dual wavelength oximeters are insensitive to higher Pa_{O_2} changes (>70–100 mm Hg). They are also a common source of false alarms.

Multiwavelength pulse oximetry

The oxygen reserve index

Signal separation of venous and arterial saturations allows limited quantification of the oxygen reserve when $Sp_{O_2} \approx 100\%$ and $Pa_{O_2} = 100–200$ mm Hg.[6] Potential monitoring applications include:

- Adequacy of pre-oxygenation
- Responses to recruitment manoeuvres[36]
- Prevention of hyperoxia.

Pulse CO-oximetry[6]

Non-invasive tracking of total haemoglobin (SpHb) plus carboxyhaemoglobin (SpCO) and methaemoglobin (SpMet) concentrations is also possible with multiwavelength devices. This includes patients with low perfusion states and those requiring vasopressors. Accuracy is adequate for trend monitoring.[37]

HAEMOGLOBIN-OXYGEN AFFINITY

Haemoglobin-oxygen affinity is the relationship between the oxygen tension of blood and its oxygen content, described by the sigmoid shaped Hb_{O_2} dissociation curve. The P50 is the oxygen tension at $S_{O_2} = 0.5$. The normal adult value in humans is 26.7 mm Hg. Factors which decrease haemoglobin-oxygen affinity increase the P50. They include acidaemia (the Bohr effect), hypercarbia, increased erythrocytic 2,3-DPG and fever, whereas P50 is decreased (increased affinity) by alkalaemia, hypocarbia, low 2,3-DPG concentrations, hypothermia, COHb, MetHb and FHb.

It is possible to calculate accurate P50 values from a single measurement of blood gases and Sa_{O_2} up to $Sa_{O_2} = 0.97$. However, an impact of varying affinity on tissue oxygenation in critical illness is yet to be established.

TITRATING OXYGEN THERAPY IN CRITICAL ILLNESS

Avoidance of hypoxemia must be counterbalanced against risks of hyperoxia. The optimal oxygenation range is unclear. A 2016 single-centre, randomised, controlled trial (n = 480) supported the hypothesis that oxygen titrated to $Pa_{O_2} = 70–100$ mm Hg or $Sp_{O_2} = 94\%–98\%$ produces a lower "intensive care unit (ICU)" mortality and fewer new episodes of shock and liver failure than oxygen titrated to $Pa_{O_2} \leq 150$ mm Hg

or Sp_{O_2} = 97%–100%.[38] Results require validation in larger multicentre studies.

By contrast, two randomised controlled studies in preterm infants targeting Sp_{O_2} = 85%–89% versus Sp_{O_2} = 91%–95% to prevent retinopathy of prematurity demonstrated higher mortality in the permissive hypoxaemia groups.[39,40]

MONITORING OXYGEN DYNAMICS

Common indices are set out in Table 18.1.

D_{O_2}/V_{O_2} RELATIONSHIPS

An association reported in 1973 between hyperdynamic oxygen flow patterns and survival after high-risk non-cardiac surgery[41] led to the popular hypothesis that an induced hyperdynamic state could mitigate an acquired oxygen debt. Common goals were cardiac index (CI) > 4.5 L/min/m^2, $D_{O_2}I$ > 600 mL/min/m^2, $V_{O_2}I$ > 170 mL/min/m^2. However, the $V_{O_2}I$ targets were particularly difficult to achieve and outcomes unimproved in multicentre studies.[42,43]

Subsequent targeting of $D_{O_2}I$ values alone removed the need for PA catheterisation and was associated with reduced peri-operative morbidity.[44,45] However improved outcomes are still most likely in patients who achieve supranormal targets spontaneously.[46]

MEASURING $D_{O_2}I$

A PA catheter is not essential and normal ranges can be quoted (Table 18.1), but isolated $D_{O_2}I$ measurements are difficult to interpret due to varying oxygen demand.

MEASURING $V_{O_2}I$

Measurements can predict weaning success.[47] Two methods are the reverse Fick method (Table 18.1) and indirect calorimetry.

Reverse Fick method

This requires a PA catheter. With random errors ranging from 17% overestimation to 13% underestimation, changes <20% cannot be detected reliably. In lung inflammation, up to 20% of $V_{O_2}I$ arises directly from the lungs.

Indirect calorimetry

Indirect calorimetry has better accuracy. $V_{O_2}I$ is determined from the volumes and oxygen concentrations of inspired and expired gas. Relative errors are <5% up to Fi_{O_2} = 0.8. Higher Fi_{O_2} settings increase error.

MIXED VENOUS BLOOD

Mixed venous blood can be sampled by gentle aspiration of the distal port of an unwedged PA catheter. The distal site ensures adequate admixture of blood from superior and inferior venae cavae and the coronary sinus. Mixed venous O_2 and CO_2 tensions and content are flow-weighted averages of multiple venous effluents, insensitive to small pockets of hypoxia or hypercarbia.

MIXED VENOUS P_{O_2} (Pv_{O_2})

A Pv_{O_2} < 26 mm Hg is suggestive of cellular hypoxia.[48] Paradoxically, a normal or high Pv_{O_2} does not exclude regional dysoxia, whether cytopathic or as a result of tissue shunting.[49]

MIXED VENOUS OXYGEN SATURATION (Sv_{O_2})

Sv_{O_2} is measured either intermittently by mixed venous sampling and CO-oximetry or continuously by a PA catheter incorporating fibre-optic reflectance oximetry. Measurements have several potential applications:

- To calculate Cv_{O_2} (Table 18.1). Cv_{O_2} can then be used to determine Q_s/Q_t, $V_{O_2}I$ (reverse Fick), the oxygen extraction ratio (Table 18.1) and cardiac output (Fick).
- As an index of tissue oxygenation. Values between 0.7 and 0.8 imply but do not guarantee global oxygen supply and demand balance. Values >0.8 are seen in high flow states, such as sepsis, hyperthyroidism and severe liver disease. Lactic acidosis appears between 0.3 and 0.5,[50] although values <0.5 are surprisingly well tolerated in chronic heart failure.

Like Pv_{O_2}, Sv_{O_2} is insensitive to cytopathic dysoxia and tissue shunting. $Sv_{O_2} \geq 0.7$ as a therapeutic target failed to improve survival.[51]

CENTRAL VENOUS SATURATION (Scv_{O_2})

As with Sv_{O_2}, Scv_{O_2} can be measured either continuously using a central venous catheter modified for reflectance oximetry, or by intermittent sampling and CO-oximetry. In health, $Scv_{O_2} < Sv_{O_2}$ by 2%–3%. In shock, the difference can be reversed. Trends usually run in parallel.

Targets of $Scv_{O_2} > 0.7$ and $Sv_{O_2} > 0.65$ have equal billing in the 2012 management guidelines of the Surviving Sepsis Campaign, but at a low evidence level (1C).[52] Three subsequent randomised trials with $Scv_{O_2} > 0.7$ as part of early goal directed therapy protocols failed to show a mortality benefit, either individually or collectively.[53] Of note, targeting $Scv_{O_2} > 0.7$ has not been assessed as an individual strategy.

MIXED VENOUS-ARTERIAL P_{CO_2} GRADIENT (Pv-aCO_2), CENTRAL VENOUS-ARTERIAL P_{CO_2} GRADIENT (ΔP_{CO_2}) AND DERIVED VARIABLES

Pv-aCO_2 (normally about 6 mm Hg) increases markedly during low output states as a simple reflection of reduced CO_2 clearance. The signal is further modified by the Haldane effect, metabolic acidosis and haematocrit.[54] Similar comments apply to ΔP_{CO_2}.

A high or sudden increase in the respiratory quotient (V_{CO_2}/V_{O_2}) or in the Pv-aCO_2/arteriovenous O_2

content difference are more specific markers of tissue hypoxia and anaerobic metabolism. Corresponding ratios calculated from central venous samples (Δ cont CO_2/Δ cont O_2 and $\Delta P_{CO_2}/\Delta$ cont O_2) also show promise, with better specificity for anaerobic metabolism (defined as D_{O_2}/V_{O_2} dependence) in early septic shock than lactate concentrations or Cv_{O_2} values.[55]

REGIONAL INDICES

REGIONAL P_{CO_2}[56]

Regional P_{CO_2} reflects the balance between arterial blood CO_2 content, tissue blood flow and tissue CO_2 production. The CO_2 gap, which is regional $P_{CO_2} - PaCO_2$, controls for varying arterial CO_2 content. As tissue blood flow falls, reduced CO_2 clearance increases the CO_2 gap. Aerobic CO_2 production ceases with the onset of anaerobic metabolism, although progressive regional metabolic acidosis then generates further CO_2 by 'proton titration' of tissue and capillary HCO_3^-. A rising CO_2 gap thus signals falling tissue blood flow, but cannot identify the onset of anaerobic metabolism.[57]

GASTRIC TONOMETRY

Gastric tonometry was developed on the basis that splanchnic hypoperfusion is an early feature of circulatory shock and may persist as 'covert shock'. A gastric tonometer is a modified nasogastric tube with a silicone balloon 11.4 cm from the tip. Gastric mucosal CO_2 equilibrates with luminal CO_2, which equilibrates with (and is measured in) fluid filling the balloon. Early on, this fluid was saline. The medium was subsequently changed to air for more rapid equilibration.

Switching from pHi to the gastric mucosal-arterial CO_2 gap eliminated the questionable practice of substituting arterial for mucosal (HCO_3^-). The gastric CO_2 gap (normally 8–10 mm Hg) is an independent prognostic factor in critical illness.[58] Simultaneous end-tidal CO_2 measurement allows monitoring of the gastric to end-tidal CO_2 gap, a parameter linked to outcome in high-risk surgery.[59]

Several barriers to widespread application remain:

- The need for a nasogastric tube.
- Signal degradation by luminal contents, including feeds and blood. Feeds should be stopped 2 hours prior to measurements, jeopardising nutritional support.
  - Lack of a clear action threshold. Empiric recommendations target a CO_2 gap <25 mm Hg.
  - Gastric acidity must be suppressed to stop CO_2 back-generation by HCl titration of duodenal bicarbonate.
- Limited evidence that tonometry-guided therapy improves outcomes. A 2015 meta-analysis that included older pHi-based trials did report a composite mortality reduction.[60] Major beneficiaries were patients with normal initial pHi values, implying that the early institution of tonometry-directed management is key.

SUBLINGUAL CAPNOMETRY

The sublingual CO_2 gap tracks sublingual microcirculatory blood flow in septic shock.[61] It remains to be seen whether the technique can guide therapy. Transcutaneous ear lobe P_{CO_2} has also shown potential.[62]

DIRECT TISSUE P_{O_2} MEASUREMENT

Measurements have been recorded primarily in animal models in the brain, subcutaneous tissue, muscle and renal beds under a variety of perfusion insults. Tensions are commonly around 30–45 mm Hg, but can range from <10 mm Hg in the renal medulla to >70 mm Hg in subcutaneous tissue. This methodology is largely impractical in patients, although in vivo MRI is one possible approach.[63]

OTHER REGIONAL TECHNIQUES

DYNAMIC MICROCIRCULATORY IMAGING

Orthogonal polarisation spectroscopy (OPS) and side stream dark field (SDF) imaging allow real-time quantification of microvascular flow (0–20 µm diameter vessels) via indices such as the 'functional capillary density' and the 'mean flow index'. Image quality has improved with computer-controlled hand-held devices.[49] The sublingual circulation is most commonly evaluated. Rectal, oral, stomal and other microcirculations can be visualised.

The guiding hypothesis is that oxygen deficits are created by microcirculatory 'haemodynamic incoherence' with macrocirculatory parameters. There is a corresponding emphasis on vasodilator therapy.[49] Several derangements are described:

- Heterogeneity with functional shunting
- Obstruction from vasoconstriction (vasopressors or hyperoxia) or high venous pressures
- Haemodilution
- Tissue oedema from fluid overload and endothelial glycocalyx damage.

Of some concern, the relationship between sublingual and intestinal microcirculations may be inconsistent.[64] Moreover, clinical studies demonstrating improved outcomes in circulatory shock using microcirculatory resuscitation end-points are lacking.

NEAR-INFRARED SPECTROSCOPY[65]

Near-infrared spectroscopy (NIRS) quantifies the differential absorbance of Hb_{O_2} and Hb in muscle vessels with diameter <1 mm (arterioles, venules and capillaries) subjected to light of wavelengths 700–1000 nm. Approximately 95% of the signal is from tissue <2.4 mm in depth. Three parameters have potential

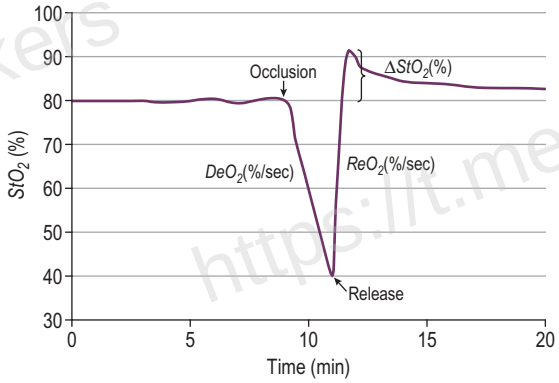


Figure 18.1 Schematic representation of a StO_2 curve measured at the thenar eminence during a vascular occlusion test. At the point marked 'occlusion' the sphygmomanometer cuff is inflated >30 mm Hg above systolic pressure and released when $StO_2 \leq 40\%$. The desaturation slope (DeO_2) reflects muscle V_{O_2}, and the resaturation slope (ReO_2) and saturation overshoot (ΔStO_2) quantify reperfusion dynamics and vascular recruitment. All decrease in sepsis and shock states.

as diagnostic and resuscitation monitoring adjuncts in hypovolaemia and shock states more generally:

- tissue haemoglobin saturation (StO_2)
- total tissue haemoglobin (TTH)
- absolute tissue haemoglobin index (THI)

The thenar eminence is normally selected for its low subcutaneous thickness and amenability to proximal vascular occlusion, although in one study of septic shock, tissue oxygen saturation measured over the knee was predictive of 14-day mortality.[66]

Vascular occlusion test

The vascular occlusion test (Fig. 18.1) detects subtle microcirculatory dysfunction, which may persist in covert shock and sepsis despite unremarkable resting StO_2 values. The sphygmomanometer cuff is inflated >30 mm Hg above systolic pressure either for 3 minutes or until StO_2 stabilises at 40%, then released:

- The desaturation slope (DeO_2) corrected for TTH is an index of muscle O_2 extraction ($\text{nir}V_{O_2}$). It is reduced in sepsis and shock states.
- On cuff release the resaturation slope (ReO_2) plus the induced StO_2 overshoot (ΔStO_2) and THI increment (reactive hyperaemia) quantify endothelial integrity, vascular recruitment and perfusion pressure. These are also decreased in sepsis and shock states.

In sepsis, DeO_2 abnormalities are associated with the development of organ failure, increased length of stay and mortality. However, for clinicians at the workface, NIRS and the vascular occlusion test may add little of value to tracking Cv_{O_2} and lactate.[67] Randomised clinical trials are awaited.

THE PROBLEM OF TISSUE HETEROGENEITY

Different tissue beds display important differences in both the magnitude and direction of responses to hypoxic or hypotensive insults,[68] and the identification of dysoxic thresholds in individual tissues remains difficult. More precise knowledge of these variables should eventually provide practical resuscitation end-points in hypoxia and shock, but at present the titration of therapy based on the monitoring of tissue oxygenation remains elusive.

REFERENCES

1. Singer M. The role of mitochondrial dysfunction in sepsis-induced multi-organ failure. *Virulence*. 2014;5(1):66–72.
2. Schumacker PT. Hypoxia-inducible factor-1 (HIF-1). *Crit Care Med*. 2005;33(12 suppl):S423–S425.
3. Hafner S, Beloncle F, Koch A, et al. Hyperoxia in intensive care, emergency, and peri-operative medicine: Dr. Jekyll or Mr. Hyde? A 2015 update. *Ann Intensive Care*. 2015;5(1):42.
4. Robin ED. Special report: dysoxia. Abnormal tissue oxygen utilization. *Arch Intern Med*. 1977;137(7): 905–910.
5. Fink MP. Cytopathic hypoxia. Is oxygen use impaired in sepsis as a result of an acquired intrinsic derangement in cellular respiration? *Crit Care Clin*. 2002;18(1):165–175.
6. Perel A. Non-invasive monitoring of oxygen delivery in acutely ill patients: new frontiers. *Ann Intensive Care*. 2015;5(1):24.
7. Biederer J, Heussel CP, Puderbach M, et al. Functional magnetic resonance imaging of the lung. *Semin Respir Crit Care Med*. 2014;35(1):74–82.
8. Durlak W, Kwinta P. Role of electrical impedance tomography in clinical practice in pediatric respiratory medicine. *ISRN Pediatr*. 2013;2013: 529038.
9. Kobylianskii J, Murray A, Brace D, et al. Electrical impedance tomography in adult patients undergoing mechanical ventilation: a systematic review. *J Crit Care*. 2016;35:33–50.
10. Bikker IG, Holland W, Specht P, et al. Assessment of ventilation inhomogeneity during mechanical ventilation using a rapid-response oxygen sensor-based oxygen washout method. *Intensive Care Med Exp*. 2014;2(1):14.
11. Wagner PD. The multiple inert gas elimination technique (MIGET). *Intensive Care Med*. 2008;34(6): 994–1001.
12. Yu G, Yang K, Baker AB, et al. The effect of bi-level positive airway pressure mechanical ventilation on gas exchange during general anaesthesia. *Br J Anaesth*. 2006;96(4):522–532.
13. Karbing DS, Kjaergaard S, Andreassen S, et al. Minimal model quantification of pulmonary gas exchange in intensive care patients. *Med Eng Phys*. 2011;33(2):240–248.
14. Riley RL, Cournand A. Analysis of factors affecting partial pressures of oxygen and carbon dioxide

in gas and blood of lungs; theory. *J Appl Physiol*. 1951;4(2):77–101.
15. D'Alonzo GE, Dantzker DR. Respiratory failure, mechanisms of abnormal gas exchange, and oxygen delivery. *Med Clin North Am*. 1983;67(3):557–571.
16. Rodriguez-Roisin R, Roca J. Mechanisms of hypoxemia. *Intensive Care Med*. 2005;31(8):1017–1019.
17. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest*. 1991;100(6):1619–1636.
18. Zimmerman JE, Kramer AA, McNair DS, et al. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med*. 2006;34(5):1297–1310.
19. Kathirgamanathan A, McCahon RA, Hardman JG. Indices of pulmonary oxygenation in pathological lung states: an investigation using high-fidelity, computational modelling. *Br J Anaesth*. 2009;103(2): 291–297.
20. Nirmalan M, Willard T, Columb MO, et al. Effect of changes in arterial-mixed venous oxygen content difference (C(a-v)O2) on indices of pulmonary oxygen transfer in a model ARDS lung. *Br J Anaesth*. 2001;86(4):477–485.
21. Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307(23):2526–2533.
22. Moreno RP, Metnitz PG, Almeida E, et al. SAPS 3 – From evaluation of the patient to evaluation of the intensive care unit. Part 2: development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Med*. 2005;31(10):1345–1355.
23. Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA*. 2001;286(14):1754–1758.
24. Murray JF, Matthay MA, Luce JM, et al. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis*. 1988;138(3):720–723.
25. Villar J, Blanco J, del Campo R, et al. Assessment of PaO(2)/FiO(2) for stratification of patients with moderate and severe acute respiratory distress syndrome. *BMJ Open*. 2015;5(3):e006812.
26. Nirmalan M, Willard T, Khan A, et al. Changes in arterial-mixed venous oxygen content difference (CaO2 - CvO2) and the effect on shunt calculations in critically ill patients. *Br J Anaesth*. 1998;80(6): 829–831.
27. Venkatesh B, Hendry SP. Continuous intra-arterial blood gas monitoring. *Intensive Care Med*. 1996; 22(8):818–828.
28. Widness JA, Madan A, Grindeanu LA, et al. Reduction in red blood cell transfusions among preterm infants: results of a randomized trial with an in-line blood gas and chemistry monitor. *Pediatrics*. 2005;115(5):1299–1306.
29. Rudiger M, Topfer K, Hammer H, et al. A survey of transcutaneous blood gas monitoring among European neonatal intensive care units. *BMC Pediatr*. 2005;5:30.
30. Storre JH, Magnet FS, Dreher M, et al. Transcutaneous monitoring as a replacement for arterial PCO(2) monitoring during nocturnal non-invasive ventilation. *Respir Med*. 2011;105(1): 143–150.
31. McMorrow RC, Mythen MG. Pulse oximetry. *Curr Opin Crit Care*. 2006;12(3):269–271.
32. Addison PS, Watson JN, Mestek ML, et al. Pulse oximetry-derived respiratory rate in general care floor patients. *J Clin Monit Comput*. 2015;29(1):113–120.
33. Lee LA, Caplan RA, Stephens LS, et al. Postoperative opioid-induced respiratory depression: a closed claims analysis. *Anesthesiology*. 2015;122(3):659–665.
34. Aust H, Kranke P, Eberhart LH, et al. Impact of medical training and clinical experience on the assessment of oxygenation and hypoxaemia after general anaesthesia: an observational study. *J Clin Monit Comput*. 2015;29(3):415–426.
35. Bouroche G, Bourgain JL. Preoxygenation and general anesthesia: a review. *Minerva Anestesiol*. 2015;81(8):910–920.
36. Barker SJ, Shander A, Ramsay MA. Continuous noninvasive hemoglobin monitoring: a measured response to a critical review. *Anesth Analg*. 2016; 122(2):565–572.
37. Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: The oxygen-ICU randomized clinical trial. *JAMA*. 2016;316(15):1583–1589.
38. Australia B-I, United Kingdom Collaborative G, Tarnow-Mordi W, et al. Outcomes of two trials of oxygen-saturation targets in preterm infants. *N Engl J Med*. 2016;374(8):749–760.
39. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Carlo WA, Finer NN, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med*. 2010;362(21):1959–1969.
40. Shoemaker WC, Montgomery ES, Kaplan E, et al. Physiologic patterns in surviving and nonsurviving shock patients. Use of sequential cardiorespiratory variables in defining criteria for therapeutic goals and early warning of death. *Arch Surg*. 1973;106(5):630–636.
41. Takala J, Meier-Hellmann A, Eddleston J, et al. Effect of dopexamine on outcome after major abdominal surgery: a prospective, randomized, controlled multicenter study. European Multicenter Study Group on Dopexamine in Major Abdominal Surgery. *Crit Care Med*. 2000;28(10):3417–3423.
42. Sandham JD, Hull RD, Brant RF, et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med*. 2003;348(1):5–14.
43. Pearse RM, Harrison DA, MacDonald N, et al. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. *JAMA*. 2014;311(21):2181–2190.

44. Grocott MP, Dushianthan A, Hamilton MA, et al. Perioperative increase in global blood flow to explicit defined goals and outcomes after surgery: a Cochrane systematic review. *Br J Anaesth*. 2013; 111(4):535–548.
45. Ackland GL, Iqbal S, Paredes LG, et al. Individualised oxygen delivery targeted haemodynamic therapy in high-risk surgical patients: a multicentre, randomised, double-blind, controlled, mechanistic trial. *Lancet Respir Med*. 2015;3(1):33–41.
46. Miwa K, Mitsuoka M, Takamori S, et al. Continuous monitoring of oxygen consumption in patients undergoing weaning from mechanical ventilation. *Respiration*. 2003;70(6):623–630.
47. Siggaard-Andersen O, Fogh-Andersen N, Gothgen IH, et al. Oxygen status of arterial and mixed venous blood. *Crit Care Med*. 1995;23(7):1284–1293.
48. Kara A, Akin S, Ince C. Monitoring microcirculation in critical illness. *Curr Opin Crit Care*. 2016;22(5): 444–452.
49. Marx G, Reinhart K. Venous oximetry. *Curr Opin Crit Care*. 2006;12(3):263–268.
50. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. *N Engl J Med*. 1995;333(16):1025–1032.
51. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41(2):580–637.
52. Angus DC, Barnato AE, Bell D, et al. A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe investigators. *Intensive Care Med*. 2015;41(9):1549–1560.
53. Viale JP. The venous-arterial partial pressure of carbon dioxide as a new monitoring of circulatory disorder: no so simple. *J Clin Monit Comput*. 2016; 30(6):757–760.
54. Mallat J, Lemyze M, Meddour M, et al. Ratios of central venous-to-arterial carbon dioxide content or tension to arteriovenous oxygen content are better markers of global anaerobic metabolism than lactate in septic shock patients. *Ann Intensive Care*. 2016;6(1):10.
55. Marik PE. Regional carbon dioxide monitoring to assess the adequacy of tissue perfusion. *Curr Opin Crit Care*. 2005;11(3):245–251.
56. Vallet B, Teboul JL, Cain S, et al. Venoarterial CO(2) difference during regional ischemic or hypoxic hypoxia. *J Appl Physiol*. 2000;89(4):1317–1321.
57. Levy B, Gawalkiewicz P, Vallet B, et al. Gastric capnometry with air-automated tonometry predicts outcome in critically ill patients. *Crit Care Med*. 2003;31(2):474–480.
58. Lebuffe G, Vallet B, Takala J, et al. A European, multicenter, observational study to assess the value of gastric-to-end tidal PCO2 difference in predicting postoperative complications. *Anesth Analg*. 2004;99(1):166–172.
59. Zhang X, Xuan W, Yin P, et al. Gastric tonometry guided therapy in critical care patients: a systematic review and meta-analysis. *Crit Care*. 2015;19:22.
60. Ospina-Tascon GA, Umana M, Bermudez WF, et al. Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock? *Intensive Care Med*. 2016;42(2):211–221.
61. Vallee F, Mateo J, Dubreuil G, et al. Cutaneous ear lobe P_{CO_2} at 37°C to evaluate microperfusion in patients with septic shock. *Chest*. 2010;138(5): 1062–1070.
62. Zaharchuk G, Busse RF, Rosenthal G, et al. Noninvasive oxygen partial pressure measurement of human body fluids in vivo using magnetic resonance imaging. *Acad Radiol*. 2006;13(8):1016–1024.
63. Edul VS, Ince C, Navarro N, et al. Dissociation between sublingual and gut microcirculation in the response to a fluid challenge in postoperative patients with abdominal sepsis. *Ann Intensive Care*. 2014;4:39.
64. Mesquida J, Gruartmoner G, Espinal C. Skeletal muscle oxygen saturation (StO_2) measured by near-infrared spectroscopy in the critically ill patients. *Biomed Res Int*. 2013;2013:502194.
65. Ait-Oufella H, Joffre J, Boelle PY, et al. Knee area tissue oxygen saturation is predictive of 14-day mortality in septic shock. *Intensive Care Med*. 2012;38(6): 976–983.
66. Mayer K, Trzeciak S, Puri NK. Assessment of the adequacy of oxygen delivery. *Curr Opin Crit Care*. 2016;22(5):437–443.
67. Dyson A, Stidwill R, Taylor V, et al. Tissue oxygen monitoring in rodent models of shock. *Am J Physiol Heart Circ Physiol*. 2007;293(1):H526–H533.
68. Pfeiffer B, Syring RS, Markstaller K, et al. The implications of arterial PO2 oscillations for conventional arterial blood gas analysis. *Anesth Analg*. 2006;102(6):1758–1764.

19

Hyperlactataemia in critical illness

David William Cosgrave, Alisa M Higgins, D Jamie Cooper, Alistair D Nichol

Hyperlactataemia is a metabolic disorder commonly observed in critically ill patients, although the precise prevalence is unknown. The definition of hyperlactataemia has changed in recent times and it is now generally considered to be clinically relevant in critical illness if the lactate concentration is greater than 2.0 mmol/L.[1,2] The previous paradigm considered lactate as a toxin, or a pure waste product, but this has been challenged as we develop a greater understanding of lactate's production and physiological function. It is probable that lactate production in humans has evolved as a substrate for metabolism within muscle and brain, and as a signalling molecule for altering metabolic processes.[3] The work of Brooks et al.,[4-7] and detailed reviews in recent publications,[3,8] have developed this understanding further and in some respects challenge the previous paradigm.

Although it has long been understood that short duration hyperlactataemia occurs during both exercise in healthy athletes and seizure activity, the concept that hyperlactataemia primarily occurs in anaerobic conditions has shifted significantly. We now understand that increased lactate production occurs in response to an increased requirement for energy, and this production occurs simultaneously with increased lactate consumption in certain tissues, such as skeletal muscle.[9]

The concept of lactic acidosis itself has also changed. Acidaemia related to hyperlactataemia tends to only occur at higher lactate levels, whereas the prognostic implications of hyperlactataemia are evident at lower levels, even in the absence of acidaemia.[10,11] It has been suggested that rather than the term lactic acidosis, reference should be made to lactate associated metabolic acidosis, or even hyperlactataemia and metabolic acidosis as two separate entities.[10]

However, despite the increasing understanding of the role of lactate in the human body in times of stress or increased energy requirements, hyperlactataemia during illness correlates with prognosis in a number of settings, most notably during shock states.[10-14]

Understanding the clinical significance of hyperlactataemia is aided by the understanding that severe hyperlactataemia and even acidosis in healthy athletes during substantive exercise is not harmful at all.[15]

LACTATE PHYSIOLOGY

Lactate is produced mainly from glucose and alanine (Fig. 19.1). The intermediate substrate is pyruvate, which exists in equilibrium with lactate and is catalysed by lactate dehydrogenase. Glucose can be metabolised to lactate via either glycolysis or the pentose-5-phosphate pathway. Pyruvate can then be converted into glucose via gluconeogenesis in the liver and kidney.[8] Pyruvate can also be converted into Acetyl-CoA for metabolism within the tricarboxylic acid cycle (TCA) cycle. During this process, adenosine triphosphate (ATP) is produced. The metabolism of lactate also generates ATP, and therefore produces significant amounts of energy, though at a slightly reduced rate.

In health, there is a continuous cycle of lactate production and metabolism. Lactate is produced at about 0.8 mmol/kg per hour, mainly in the skeletal muscle, skin, brain, intestine and red blood cells.[18] Skeletal muscle accounts for ~40% of the net production of lactate in the body.[19] The old paradigm of lactate as a waste product is changing rapidly, with publications by Brooks,[4-6] Philp[17] and Adeva-Andany,[8] leading to an understanding that lactate has multiple functions, including as a fuel and potentially as an intracellular messenger. The liver and kidneys have a major role in production of glucose from lactate. Blood flow through these organs 'clears' lactate – that is, lactate production occurs in the organ, but at a lower rate than its uptake, resulting in clearance of lactate from the blood.[8] The liver has a decisive role in lactate homeostasis and many patients who develop hyperlactataemia have decreased metabolic capacity due to acute or chronic liver disease.[20] It is thought that hyperlactataemia in critical illness may, in part at least, result from impaired clearance rather than solely through increased production.[21]

Normal lactate concentration is 1.0 ± 0.5 mmol/L.[22] Hyperlactataemia is considered to be present in the context of critical illness when lactate concentration exceeds 2.0 mmol/L.[23] However, even at 'normal' levels, relative increases in lactate concentration have been associated with worse prognosis during critical illness.[11]

ABSTRACT

Hyperlactataemia is a metabolic disorder commonly observed in critically ill patients, although the precise prevalence is unknown. The definition of hyperlactataemia has changed in recent times. The previous paradigm considered lactate as a toxin or a pure waste product, but this has been challenged as we develop a greater understanding of lactate's production and physiological function. In this chapter, we examine the emerging paradigm for lactate metabolism and review the current place for lactate in critical care practice.

KEYWORDS

Lactate
lactic acidosis

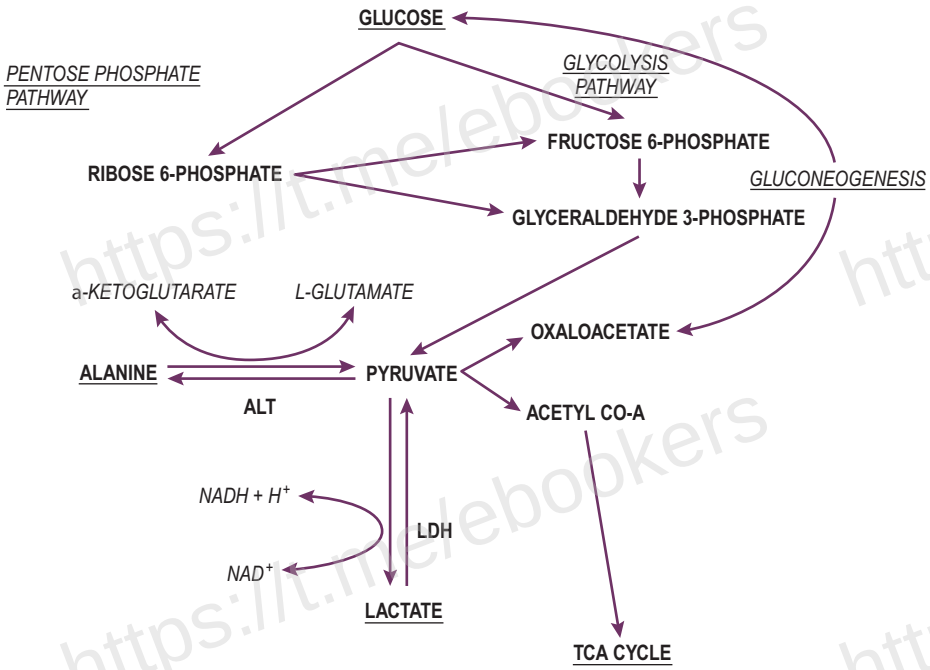


Figure 19.1 Overview of lactate metabolic pathway. *(Modified from figures in Phypers,[16] Brooks,[4-6] Philp,[17] Adeva-Andany.[8])*

In cardiogenic and hypovolaemic shock, hypoperfusion and tissue hypoxia are thought to lead to the increased lactate concentration, while decreased hepatic perfusion may contribute to the decrease in lactate clearance. In septic shock, hyperlactataemia is even more multifactorial, and contributed to by hypoperfusion by microvascular disruption causing regional hypoperfusion and by impaired mitochondrial cellular oxygen utilisation.[10] In critically ill patients, even in the absence of a lactate concentration greater than 2.0 mmol/L, higher admission, and time-weighted lactate concentrations within the normal range have been shown to correlate with poorer outcomes.[11]

The trend of lactate concentrations over time has been shown to be a good prognostic indicator in critically ill patients in numerous recent publications.[13,24-27] Nichol et al. showed significantly better performance of dynamic indices of lactate (namely time-weighted lactate and absolute change in lactate in 24 hours) as prognostic indicators in critical illness.[13]

CLASSIFICATION OF LACTIC ACIDOSIS

The Cohen and Woods classification of lactic acidosis defines two subgroups of lactic acidosis depending on the presence (type A) or absence (type B) of tissue hypoxia (Table 19.1).[28] Type A lactic acidosis due to tissue hypoxia is common in critically ill patients, although clinically, most patients have features of both type A and type B lactic acidosis, with increased lactate formation from tissue hypoxia, and decreased lactate clearance occurring together. Tissue hypoxia is most commonly due to hypoperfusion occurring due to shock (septic, cardiogenic or hypovolaemic), hypotension, cardiac arrest, acute heart failure, or regional hypoperfusion (in particular, mesenteric ischaemia), although it may also be due to reduced tissue oxygen delivery (DO_2) or utilisation due to very severe hypoxaemia, very severe anaemia or carbon monoxide poisoning. Type B lactic acidosis is subdivided into B1 (lactic acidosis occurring in association with an underlying disease), B2 (lactic acidosis due to drugs or toxins) and B3 (lactic acidosis due to inborn errors of metabolism). Given the current changing paradigm, the utility of this classification has been questioned.

SEPSIS

In sepsis, there has been much debate[29] whether the hyperlactataemia results from net increased cellular production[30] or decreased net clearance.[21] It is likely that, in these patients, the cause is multifactorial. As these patients are often haemodynamically unstable, lactate production can increase as a result of inadequate DO_2 from hypoperfusion. Other mechanisms thought to contribute to development of hyperlactataemia in sepsis include increased pyruvate production,[31] release of lactate from lung parenchyma,[32,33] decreased pyruvate dehydrogenase activity[34,35] and decreased clearance of lactate.[36,37]

Table 19.1 Classification of lactic acidosis

Type A	Shock
	Very severe hypoxaemia
	Very severe anaemia
	Carbon monoxide poisoning
Type B1 (underlying disease)	Sepsis
	Liver failure
	Thiamine deficiency
	Malignancy
	Phaeochromocytoma
	Diabetes
Type B2 (drug or toxin)	Epinephrine
	Salbutamol
	Propofol
	Nucleoside analogue reverse transcriptase inhibitor
	Ethanol
	Methanol
	Paracetamol
	Nitroprusside
	Salicylates
	Ethylene (and propylene) glycol
	Biguanides
	Fructose
	Sorbitol
	Xylitol
	Cyanide
	Isoniazid
Type B3 (rare inborn errors of metabolism)	Glucose-6-phosphatase deficiency
	Fructose-1,6 diphosphatase deficiency
	Pyruvate carboxylase deficiency
	Deficiency of enzymes of oxidative phosphorylation

Tissue hypoxia may not be a major mechanism for regional lactate production during sepsis: hyperlactataemia is thought to be linked to the severity of the septic cellular inflammatory response and hypermetabolic state.[29,38] Net lactate production from the hepatosplanchnic bed is uncommon in septic patients[39] and nuclear magnetic resonance spectroscopy suggests that hyperlactataemia may occur without tissue hypoxia.[40]

Despite this incomplete understanding of the exact cause of hyperlactataemia in sepsis, its role as a prognostic marker is clear, with mortality increasing with increasing lactate concentration.[41-43]

BRAIN INJURY

Recent research into the hypothesised astrocyte neuronal lactate shuttle has revealed that lactate may be an important energy substrate in brain metabolism.[44,45] It is hypothesised that lactate is transferred through monocarboxylate transporters as a substrate for ATP generation.[46] This process provides an alternative energy source to compensate for the decrease in glucose uptake in injured brain tissue.[47] Increased brain lactate as measured by cerebral microdialysis has been shown to be associated with improved survival,[48] leading to studies of supplemental lactate to improve outcomes after traumatic brain injury (TBI).[49-51] However, further trials are needed to confirm this potential beneficial effect.

LUNG INJURY

The lung is a primary source of lactate production in patients with acute lung injury, with pulmonary release of lactate being directly related to the severity of lung injury,[33,52] supporting the view that the primary contributors are the tissues with the most inflammation or injury. The increased lactate production by the injured lung is not only secondary to anaerobic metabolism in the hypoxic regions of the lung but also may be due to altered glucose metabolism and a direct effect of cytokines on pulmonary cells.[52]

Laboratory studies suggest that both metabolic and respiratory acidosis protect the lung against injury, whereas correction of acidosis compounds the injury.[53,54] Two ventilator trials,[55,56] which demonstrated a positive impact on mortality in acute respiratory distress syndrome (ARDS) by limiting tidal volume and airway pressures differed widely on how they regarded and managed the resultant hypercapnic acidosis. While Amato et al.[55] allowed elevation of the $PaCO_2$ (permissive hypercapnia) and resultant acidosis, the ARDSnet group[56] aggressively corrected the hypercapnic acidosis by increasing the respiratory rate and allowing administration of sodium bicarbonate. There is growing evidence that not only may hypercapnic acidosis be beneficial in lung injury,[53,57] but also the ARDSnet intervention aimed at correcting the acidosis may also be deleterious.[54,58] These findings have not only promoted a greater tolerance of acidosis during ARDS but also increased reluctance to buffer the acidosis exogenously towards 'normal' values.

ASTHMA

Hyperlactataemia often occurs in patients with acute severe asthma, and the acidosis is often attributed to

fatiguing respiratory muscles,[59] inadequate DO_2 to the respiratory muscles to meet the elevated oxygen demand[60] and liver ischaemia. However, severe hyperlactataemia also occurs in sedated, paralysed, mechanically ventilated patients who have no endogenous respiratory muscle activity.[61] Stimulation of β adrenergic receptors by β agonists, including salbutamol and epinephrine, leads to a variety of metabolic effects including an increase in glycogenolysis, gluconeogenesis and lipolysis[62] – thus contributing to hyperlactataemia. Decreasing intravenous salbutamol infusions to less than 10 mcg/min is usually associated with resolution of the acidosis. In asthma, hyperlactataemia does not have specific prognostic implications.

MESENTERIC ISCHAEMIA AND D LACTIC ACIDOSIS

The diagnosis of mesenteric ischaemia can be challenging to make in the critically ill due to lack of clinical and diagnostic signs, difficulty transferring unstable patients for diagnostic imaging and concern about the deleterious effects of inappropriately administering contrast agents. An ischaemic bowel can produce large amounts of lactate, and the presence of hyperlactataemia in the setting of acute abdominal disease has been proposed as an indicator of mesenteric ischaemia. Animal models have shown that lactate increases within 1 hour of induced intestinal ischaemia. In addition, elevated lactate at the time of diagnosis of mesenteric ischaemia is a predictor of mortality.[63] However, although plasma lactate is a very sensitive marker (100%) for detecting acute mesenteric ischaemia, the low specificity of this marker (42%) is a particular problem in the critically ill, who frequently have many plausible alternate diagnoses.

D-lactate is the isomer of lactate that is produced by intestinal bacterial metabolism and is not produced by humans.[64] Experimental work suggest that ischaemic bowel allows the translocation of D-lactate into the systemic circulation; as D-lactate is not eliminated by the liver, plasma levels may be more specific markers of mesenteric ischaemia. However, many issues need to be clarified, including the effect of antibiotic therapy on the intestinal bacteria, before D-lactate could be considered as a bedside diagnostic test.[65] It is necessary to have a high index of suspicion for mesenteric ischaemia[66] in a deteriorating patient with an elevated lactate in the absence of a convincing alternative diagnosis, as identification of mesenteric ischaemia is frequently made first at laparotomy in the critically ill.

D-lactate production also occurs in patients with short bowel syndrome, a history of jejuno-ileal bypass surgery or chronic pancreatic insufficiency. Since it was originally described in 1979,[67] there have been numerous subsequent reports.

As D-lactate is metabolised slowly, it can accumulate following a large carbohydrate load. D-lactic acidosis is characterised by a normal lactate level, as the assay for lactate only measures L-lactate and a D-lactate level must be specifically requested if D-lactic acidosis is suspected.[68]

CARDIAC PATIENTS

Of the energy requirements of the myocardium, 10%–40% are provided by pyruvate, obtained from both lactate and glucose.[69] Nonetheless, hyperlactataemia has been shown to correlate with poorer outcomes in acute heart failure,[70] acute myocardial ischaemia,[71] post coronary artery bypass grafting[72-74] and following cardiac arrest.[75] Hyperlactataemia during cardiopulmonary bypass is relatively frequent and is associated with an increased postoperative morbidity.[76] Recent work has suggested that this 'on pump' hyperlactataemia is secondary to inadequate peripheral DO_2, which creates a condition similar to cardiogenic shock, leading to both direct lactate formation by dysoxic tissues and to catecholamine release, insulin resistance and hyperglycaemia-induced lactate production.

The use of epinephrine after cardiopulmonary bypass precipitates hyperlactataemia in some patients.[77] This phenomenon is probably β-agonist mediated, is associated with increased whole body blood flow and resolves after substitution of norepinephrine. However, there is emerging evidence that the severity of hyperlactataemia following cardiac surgery is related to certain genetic polymorphisms in tumour necrosis factor and interleukin-10 genes.[78] Similar to asthma, hyperlactataemia associated with the administration of epinephrine in this setting does not have the adverse implications of hyperlactataemia associated with shock (provided that the clinical epinephrine is not an indicator of impaired cardiac function).

Similar to brain-injured patients, there is emerging evidence that supplemental hypertonic lactate infusions may improve cardiac function, without compromising other organ functions.[79,80] This early evidence requires further study before it is adopted into clinical practice.

OTHER UNDERLYING DISEASES

In patients with cancer, anaerobic glycolysis may be increased while hepatic lactate metabolism may be impaired by tumour replacement. Diabetic patients may present with shock, but in non-insulin–dependent diabetes there also may be a defect in pyruvate oxidation, and in diabetic ketoacidosis ketones may also inhibit hepatic lactate uptake. Thiamine and biotin are essential co-factors for pyruvate dehydrogenase activity and for the conversion of pyruvate to oxoaloacetate. Malnutrition (beriberi) and inadequate parental nutrition have therefore been associated with hyperlactataemia due to deficiencies of these co-factors. In

these cases, pyruvate accumulation increases lactate production.

METFORMIN-ASSOCIATED LACTIC ACIDOSIS

Metformin is an oral biguanide, which is used widely in type 2 diabetes mellitus, as it has been shown to decrease cardiovascular morbidity and mortality.[81,82] An Australian tertiary intensive care unit (ICU) reported an incidence of metformin-associated lactic acidosis (MALA) of 6 per 1000 ICU admissions, and a mortality of 29%.[83] A European study found that MALA accounted for 0.84% of all ICU admissions and was associated with a mortality of 30%.[84] In most cases, MALA occurs when the contraindications of metformin have been overlooked or, more commonly, when acute renal failure develops and leads to metformin accumulation.[81,85] Risk factors for developing hyperlactataemia while on biguanide treatment include age greater than 60 years, decreased cardiac, hepatic or renal function, diabetic ketoacidosis, surgery, respiratory failure, ethanol intoxication and fasting.[86]

A Cochrane study analysed pooled data from all prospective comparative trials and observational cohort studies up to 2009, and concluded that there was no current evidence that metformin is associated with an increased risk of hyperlactataemia compared with other antihyperglycaemic treatments.[85] However, MALA continues to be reported, frequently in ICU patients,[83,84,87,88] including in the Australian cohort described above, in which other causes of hyperlactataemia were excluded before a diagnosis of MALA was made.[83]

While the mechanism of MALA is not fully understood, it is thought that biguanides may inhibit oxidative metabolism, and increase the concentration of nicotinamide adenine dinucleotide (NADH), reduce glucogenesis, and suppress the gastrointestinal absorption of glucose.[86] A recent retrospective study comparing 10 MALA patients with 187 patients with hyperlactataemia of other origin (LAOO) found that the survival of MALA with an arterial pH less than 7.00 was significantly better (50% vs. 0%) if MALA was the underlying condition compared to LAOO.[88] These findings have since been supported by further publications.[89,90]

OTHER DRUGS AND TOXINS

The list of potential drugs and toxins that may contribute to the development of hyperlactataemia continues to grow. Nucleoside reverse transcriptase inhibitors (NRTI) used in the treatment of human immunodeficiency virus (HIV)-positive patients cause injury to the mitochondria, which can lead to hyperlactataemia. However, NRTI-induced hyperlactataemia is rare and is often associated with hepatic steatosis.[91] Acute ethanol intoxication can precipitate hyperlactataemia, as ethanol oxidation increases the conversion of pyruvate to lactate and inhibits other pathways of pyruvate accumulation. Underlying alcoholic liver disease and thiamine deficiency may exacerbate the hyperlactataemia. Propylene glycol has also been associated with hyperlactataemia as it is oxidised by alcohol dehydrogenase in the liver to lactate and pyruvate.[92] It is used as a diluent in many medications such as phenytoin, co-trimoxazole, phenobarbitol, lorazepam, diazepam, digoxin and nitroglycerine, and as such, is the most common alcohol intoxication in ICUs.[93]

CLINICAL PRESENTATION

Patients present with clinical signs appropriate to their primary disorder. Hyperlactataemia is a laboratory diagnosis. However, in critically ill patients with shock the severity of hyperlactataemia and dynamic indices of lactate concentrations can reflect a trend towards recovery from the underlying cause. Repeated measures of arterial blood gases and blood lactate are required. In hypovolaemic shock, resolving hyperlactataemia along with the clinical signs of improving perfusion is one of several indicators of successful resuscitation. Conversely, failure of hyperlactataemia to resolve in hypovolaemic shock suggests inadequate resuscitation or another undetected or unresolved clinical problem. In sepsis, the underlying cause of the hyperlactataemia is multifactorial, but slow resolution of hyperlactataemia is still associated with poorer prognosis.

Hyperlactataemia may also occur in the absence of shock. Examples include hypermetabolic states where accelerated aerobic glycolysis may contribute (trauma, burns, sepsis), conditions with increased muscle activity (seizures), labouring parturients and during exogenous lactate administration (lactate buffered haemofiltration fluid). In many of these patients (e.g. patients with seizures) very high blood lactate concentrations have no prognostic implications because the acidosis is rapidly cleared.

MANAGEMENT

GENERAL

The principles of management of patients with hyperlactataemia are to diagnose and correct the underlying condition (where possible), and restore adequate tissue DO_2. In critically ill patients, hyperlactataemia is often an indicator of major patient pathology. Therefore, the main focus is to identify and treat the cause rapidly. A clinical examination and search for occult sepsis, inadequate resuscitation, localised ischaemia or cardiovascular failure is urgently required. In each case, after diagnosis and initial management, hyperlactataemia may then be used as an ongoing monitor of disease progression or resolution. Lactate kinetics have been shown to have prognostic value

in the care of critically ill patients. Decreasing lactate levels over time have been associated with improved outcomes,[13] and appear to be independent of initial lactate values.[94]

TREAT THE PRIMARY DISORDER

Specific therapies and supports must be directed at each underlying cause. In hypovolaemic and cardiogenic shock, restoration of an adequate global DO_2 is required. Vasoconstrictors may worsen tissue perfusion and should only follow adequate intravascular volume and appropriate cardiac support. In septic shock, antibiotics appropriate to cover all likely sources of infections are a priority, and in patients with possible ischaemic gut, surgery may be required for both diagnosis and therapy. Postsurgical gastrointestinal leaks may sometimes be difficult to diagnose, may not be detectable on computed tomography and may require early laparotomy. In status epilepticus, hyperlactataemia is a result of muscle activity and the rapid use of effective anticonvulsants is indicated. In diabetic ketoacidosis, insulin, appropriate fluid and treatment of precipitants enable the resolution of all metabolic abnormalities, including associated hyperlactataemia. In thiamine deficiency, highlighted during a nationwide American shortage of multivitamins for patients receiving total parenteral nutrition,[95] high-dose intravenous thiamine corrected both the vasodilated shock and associated hyperlactataemia. In acute severe asthma, hyperlactataemia is commonly a result of high-dose intravenous β-agonist therapy.[62,77] Salbutamol dose reduction usually resolves the problem. In vasodilated patients after cardiopulmonary bypass, hyperlactataemia may also be related to β-agonist therapy and resolves after substitution of intravenous epinephrine with norepinephrine.[77] In these cases, hyperlactataemia is not related to decreased tissue perfusion, and adverse effects upon prognosis have not been noted. Patients with HIV receiving NRTI therapy have a high incidence of hyperlactataemia (8.3%), which can progress to a rapidly fatal metabolic syndrome. These patients with NRTI-induced mitochondrial dysfunction require withdrawal of the therapy (if lactate >5 mmol/L), and close monitoring.[91,96,97]

HYPERVENTILATION

Hyperventilation is a normal compensatory response to metabolic acidosis in conscious patients. Therefore, in mechanically ventilated patients with hyperlactataemia and acidosis, clinicians will usually use some hyperventilation to partially correct acidaemia. Clearly, in patients with pulmonary pathology, hyperventilation may be difficult or inappropriate, and in some patients, hyperventilation increases intrathoracic pressure, decreases venous return, decreases cardiac output and exacerbates the cause of hyperlactataemia.

BICARBONATE

Minimising bicarbonate therapy for the treatment of acidosis during hyperlactataemia is much less controversial than in the past.[2,98-100] It was thought that correction of the acidosis through the administration of bicarbonate might reverse depressed cardiac performance; however, there is no evidence in critically ill patients that hyperlactataemia depresses cardiac function, and laboratory studies report minimal depression in large animals.[101,102] Further, not all studies have actually demonstrated a rise in pH after the administration of bicarbonate.[103] One reason for these findings is that sodium bicarbonate also has adverse effects, including acute hypercapnia and ionised hypocalcaemia,[104] which outweigh the potential benefits in patients. Hypercapnia may increase intracellular acidosis (CO_2 crosses cell membranes rapidly) and hypocalcaemia decreases myocardial contractility.[105] Other side effects of bicarbonate occur because bicarbonate is a hypertonic solution; the side effects include acute intravascular volume overload and cardiac depression. In addition, bicarbonate increases lactate production by increasing the activity of the rate-limiting enzyme phosphofructokinase, shifts the haemoglobin–oxygen dissociation curve, increases oxygen affinity of haemoglobin and thereby decreases DO_2 to tissues.

While some clinicians continue to use bicarbonate in patients with a pH less than 7.20, the most recent Surviving Sepsis guidelines published in 2016 strongly recommend against the use of bicarbonate when treating hypoperfusion-induced lactic acidaemia in patients with a pH ≥7.15,[106] while others have recommended a lower target pH of 7.00 or less.[100] There are no large randomised controlled trials of the use of bicarbonate in hyperlactataemia, and the only two randomised crossover studies in critically ill patients with hyperlactataemia and shock found no improvement in cardiac function or any other beneficial effects of pH correction.[104,107] As such, bicarbonate has never been shown to be beneficial in any clinical trial of patients with hyperlactataemia, and its use in these patients is not recommended, regardless of the degree of acidaemia.[2]

However, there are two specific subgroups of patients with hyperlactataemia in whom bicarbonate should be considered. First, patients with pulmonary hypertension and right-sided heart failure (e.g. lung transplant recipients) often have pulmonary vasoconstriction, which is exacerbated by acidosis. In these patients, although there are other useful therapies, including inhaled nitric oxide, partial pH correction may improve right-sided heart function. Second, patients with significant ischaemic heart disease and hyperlactataemia with acidosis may be at increased risk of major arrhythmias because severe acidosis lowers the myocardial threshold for arrhythmias. In both of these subgroups, slow bicarbonate infusions to keep the arterial pH above 7.15 may be justified.

LACTATE AS A TREATMENT

HALF MOLAR SODIUM LACTATE

Evidence for the use of half molar lactate as a resuscitation fluid, and a treatment in specific circumstances is increasing. A growing body of evidence is emerging to support the potential benefit of infusion of hypertonic lactate in traumatic brain injury. The theory behind this research is that glucose metabolism is impaired in the injured brain, and therefore lactate provides a preferential or opportunistic energy substrate for the injured brain tissue.[46,50,51,108-111] In a pilot study of patients with acute cardiac failure, hypertonic lactate was shown to improve cardiac performance compared to compound sodium lactate.[79] In a trial comparing hypertonic lactate to compound sodium lactate post-coronary artery bypass grafting, hypertonic lactate resulted in a higher cardiac index with a lower infused fluid volume.[112] Animal studies have shown the infusion of hypertonic sodium lactate to have beneficial effects on haemodynamics and fluid balance in a pig model of endotoxic shock.[113] Whether it will become a resuscitation fluid in critical illness remains to be seen.[80]

KEY REFERENCES

Adeva-Andany M, Lopez-Ojen M, Funcasta-Calderon R, et al. Comprehensive review on lactate metabolism in human health. *Mitochondrion*. 2014;17:76–100.

Brooks GA. Cell-cell and intracellular lactate shuttles. *J Physiol*. 2009;587(Pt 23):5591–5600.

Chertoff J, Chisum M, Garcia B, et al. Lactate kinetics in sepsis and septic shock: a review of the literature and rationale for further research. *J Intensive Care*. 2015; 3:39.

Levy B. Lactate and shock state: the metabolic view. *Curr Opin Crit Care*. 2006;12(4):315–321.

van Hall G. Lactate kinetics in human tissues at rest and during exercise. *Acta Physiol (Oxf)*. 2010;199(4): 499–508.

Vincent JL, Quintairos ESA, Couto L Jr, et al. The value of blood lactate kinetics in critically ill patients: a systematic review. *Crit Care*. 2016;20(1):257.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Stacpoole PW, Wright EC, Baumgartner TG, et al. Natural history and course of acquired lactic acidosis in adults. DCA-Lactic Acidosis Study Group. *Am J Med*. 1994;97(1):47–54.
2. Forsythe SM, Schmidt GA. Sodium bicarbonate for the treatment of lactic acidosis. *Chest*. 2000;117(1): 260–267.
3. Garcia-Alvarez M, Marik P, Bellomo R. Stress hyperlactataemia: present understanding and controversy. *Lancet Diab Endocrinol*. 2014;2(4): 339–347.
4. Brooks GA. Cell-cell and intracellular lactate shuttles. *J Physiol*. 2009;587(Pt 23):5591–5600.
5. Brooks GA. Intra- and extra-cellular lactate shuttles. *Med Sci Sports Exerc*. 2000;32(4):790–799.
6. Brooks GA. The lactate shuttle during exercise and recovery. *Med Sci Sports Exerc*. 1986;18(3):360–368.
7. Gaesser GA, Brooks GA. Metabolic bases of excess post-exercise oxygen consumption. *Med Sci Sports Exerc*. 1984;16(1):29–43.
8. Adeva-Andany M, Lopez-Ojen M, Funcasta-Calderon R, et al. Comprehensive review on lactate metabolism in human health. *Mitochondrion*. 2014;17:76–100.
9. Gladden LB. Muscle as a consumer of lactate. *Med Sci Sports Exerc*. 2000;32(4):764–771.
10. Bakker J, Nijsten MWN, Jansen TC. Clinical use of lactate monitoring in critically ill patients. *Ann Intensive Care*. 2013;3:12.
11. Nichol AD, Egi M, Pettila V, et al. Relative hyperlactatemia and hospital mortality in critically ill patients: a retrospective multi-centre study. *Crit Care*. 2010;14(1):R25.
12. Nichol A, Ahmed B. Shock: causes, initial assessment and investigations. *Anaesth Intensive Care Med*. 2014; 15(2):64–67.
13. Nichol A, Bailey M, Egi M, et al. Dynamic lactate indices as predictors of outcome in critically ill patients. *Crit Care*. 2011;15(5):R242.
14. Thomas-Rueddel DO, Poidinger B, Weiss M, et al. Hyperlactatemia is an independent predictor of mortality and denotes distinct subtypes of severe sepsis and septic shock. *J Crit Care*. 2015;30(2): 439.e431–439.e436.
15. van Hall G. Lactate kinetics in human tissues at rest and during exercise. *Acta Physiol (Oxf)*. 2010;199(4): 499–508.
16. Phypers B, Pierce JMT. Lactate physiology in health and disease. Continuing education in anaesthesia. *Crit Care Pain*. 2006;6(3):128–132.
17. Philp A, Macdonald AL, Watt PW. Lactate–a signal coordinating cell and systemic function. *J Exp Biol*. 2005;208(Pt 24):4561–4575.
18. Levy B. Lactate and shock state: the metabolic view. *Curr Opin Crit Care*. 2006;12(4):315–321.
19. Consoli A, Nurjhan N, Reilly JJ, et al. Contribution of liver and skeletal muscle to alanine and lactate metabolism in humans. *Am J Physiol Endocrinol Metabol*. 1990;259(5):E677.
20. Berry MN. The liver and lactic acidosis. *Proc R Soc Med*. 1967;60(12):1260–1262.
21. Levraut J, Ciebiera JP, Chave S, et al. Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. *Am J Respir Crit Care Med*. 1998;157(4 Pt 1):1021–1026.
22. De Backer D. Lactic acidosis. *Minerva Anestesiol*. 2003;69(4):281–284.
23. Mizock BA. Lactic acidosis. *Dis Mon*. 1989;35(4): 233–300.
24. Haas SA, Lange T, Saugel B, et al. Severe hyperlactatemia, lactate clearance and mortality in unselected critically ill patients. *Intensive Care Med*. 2016;42(2):202–210.
25. Nguyen HB, Rivers EP, Knoblich BP, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med*. 2004;32(8):1637–1642.
26. Arnold RC, Shapiro NI, Jones AE, et al. Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. *Shock*. 2009;32(1):35–39.
27. Jones AE, Shapiro NI, Trzeciak S, et al. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA*. 2010;303(8):739–746.
28. Cohen RD, Woods HF. Lactic acidosis revisited. *Diabetes*. 1983;32(2):181–191.
29. Gutierrez G, Wulf ME. Lactic acidosis in sepsis: another commentary. *Crit Care Med*. 2005;33(10): 2420–2422.
30. Chiolero RL, Revelly JP, Leverve X, et al. Effects of cardiogenic shock on lactate and glucose metabolism after heart surgery. *Crit Care Med*. 2000;28(12):3784–3791.
31. Gore DC, Jahoor F, Hibbert JM, et al. Lactic acidosis during sepsis is related to increased pyruvate production, not deficits in tissue oxygen availability. *Ann Surg*. 1996;224(1):97–102.
32. Brown SD, Clark C, Gutierrez G. Pulmonary lactate release in patients with sepsis and the adult respiratory distress syndrome. *J Crit Care*. 1996;11(1): 2–8.
33. Kellum JA, Kramer DJ, Lee K, et al. Release of lactate by the lung in acute lung injury. *Chest*. 1997;111(5): 1301–1305.
34. Vary TC, Siegel JH, Nakatani T, et al. Effect of sepsis on activity of pyruvate dehydrogenase complex in skeletal muscle and liver. *Am J Physiol*. 1986;250(6 Pt 1):E634–E640.
35. Vary TC. Increased pyruvate dehydrogenase kinase activity in response to sepsis. *Am J Physiol*. 1991; 260(5 Pt 1):E669–E674.
36. Falk JL, Rackow EC, Leavy J, et al. Delayed lactate clearance in patients surviving circulatory shock. *Acute Care*. 1985;11(3–4):212–215.
37. Chrusch C, Bands C, Bose D, et al. Impaired hepatic extraction and increased splanchnic production contribute to lactic acidosis in canine sepsis. *Am J Respir Crit Care Med*. 2000;161(2 Pt 1): 517–526.

38. Mizock BA. The hepatosplanchnic area and hyperlactatemia: a tale of two lactates. *Crit Care Med*. 2001;29(2):447–449.
39. De Backer D, Creteur J, Silva E, et al. The hepatosplanchnic area is not a common source of lactate in patients with severe sepsis. *Crit Care Med*. 2001;29(2):256–261.
40. Hotchkiss RS, Karl IE. Reevaluation of the role of cellular hypoxia and bioenergetic failure in sepsis. *JAMA*. 1992;267(11):1503–1510.
41. Shapiro NI, Howell MD, Talmor D, et al. Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med*. 2005;45(5):524–528.
42. Mikkelsen ME, Miltiades AN, Gaieski DF, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med*. 2009;37(5):1670–1677.
43. Chertoff J, Chisum M, Garcia B, et al. Lactate kinetics in sepsis and septic shock: a review of the literature and rationale for further research. *J Intensive Care*. 2015;3:39.
44. Patet C, Suys T, Carteron L, et al. Cerebral lactate metabolism after traumatic brain injury. *Curr Neurol Neurosci Rep*. 2016;16(4):31.
45. van Hall G, Stromstad M, Rasmussen P, et al. Blood lactate is an important energy source for the human brain. *J Cereb Blood Flow Metab*. 2009;29(6): 1121–1129.
46. Glenn TC, Martin NA, Horning MA, et al. Lactate: brain fuel in human traumatic brain injury: a comparison with normal healthy control subjects. *J Neurotrauma*. 2015;32(11):820–832.
47. Duarte JM, Girault FM, Gruetter R. Brain energy metabolism measured by (13)C magnetic resonance spectroscopy in vivo upon infusion of [3-(13)C] lactate. *J Neurosci Res*. 2015;93(7):1009–1018.
48. Cureton EL, Kwan RO, Dozier KC, et al. A different view of lactate in trauma patients: protecting the injured brain. *J Surg Res*. 2010;159(1):468–473.
49. Bouzat P, Magistretti PJ, Oddo M. Hypertonic lactate and the injured brain: facts and the potential for positive clinical implications. *Intensive Care Med*. 2014;40(6):920–921.
50. Quintard H, Patet C, Zerlauth JB, et al. Improvement of neuroenergetics by hypertonic lactate therapy in patients with traumatic brain injury is dependent on baseline cerebral lactate/pyruvate ratio. *J Neurotrauma*. 2016;33(7):681–687.
51. Ichai C, Payen JF, Orban JC, et al. Half-molar sodium lactate infusion to prevent intracranial hypertensive episodes in severe traumatic brain injured patients: a randomized controlled trial. *Intensive Care Med*. 2013;39(8):1413–1422.
52. Iscra F, Gullo A, Biolo G. Bench-to-bedside review: lactate and the lung. *Crit Care*. 2002;6(4): 327–329.
53. Laffey JG, Honan D, Hopkins N, et al. Hypercapnic acidosis attenuates endotoxin-induced lung injury. *Am J Respir Crit Care Med*. 2004;169(1):46–56.
54. Laffey JG, Engelberts D, Kavanagh BP. Buffering hypercapnic acidosis worsens acute lung injury. *Am J Respir Crit Care Med*. 2000;161(1):141–146.
55. Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med*. 1998;338(6):347–354.
56. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301–1308.
57. Kregenow DA, Rubenfeld GD, Hudson LD, et al. Hypercapnic acidosis and mortality in acute lung injury. *Crit Care Med*. 2006;34(1):1–7.
58. Conrad SA, Zhang S, Arnold TC, et al. Protective effects of low respiratory frequency in experimental ventilator-associated lung injury. *Crit Care Med*. 2005;33(4):835–840.
59. Mountain RD, Heffner JE, Brackett NC Jr, et al. Acid-base disturbances in acute asthma. *Chest*. 1990; 98(3):651–655.
60. Stratakos G, Kalomenidis J, Routsi C, et al. Transient lactic acidosis as a side effect of inhaled salbutamol. *Chest*. 2002;122(1):385–386.
61. Manthous CA. Lactic acidosis in status asthmaticus: three cases and review of the literature. *Chest*. 2001; 119(5):1599–1602.
62. Haffner CA, Kendall MJ. Metabolic effects of beta 2-agonists. *J Clin Pharm Ther*. 1992;17(3):155–164.
63. Newman TS, Magnuson TH, Ahrendt SA, et al. The changing face of mesenteric infarction. *Am Surg*. 1998;64(7):611–616.
64. Halperin ML, Kamel KS. D-lactic acidosis: turning sugar into acids in the gastrointestinal tract. *Kidney Int*. 1996;49(1):1–8.
65. van der Voort PH. Diagnostic and scientific dilemma: the ischemic bowel. *Crit Care Med*. 2006; 34(5):1561–1562.
66. Murray MJ, Gonze MD, Nowak LR, et al. Serum D(-)-lactate levels as an aid to diagnosing acute intestinal ischemia. *Am J Surg*. 1994;167(6):575–578.
67. Oh MS, Phelps KR, Traube M, et al. D-lactic acidosis in a man with the short-bowel syndrome. *N Engl J Med*. 1979;301(5):249–252.
68. Kowlgi NG, Chhabra L. D-lactic acidosis: an underrecognized complication of short bowel syndrome. *Gastroenterol Res Pract*. 2015;2015:476215.
69. Stanley WC, Recchia FA, Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart. *Physiol Rev*. 2005;85(3): 1093–1129.
70. Lazzeri C, Valente S, Chiostri M, et al. Clinical significance of lactate in acute cardiac patients. *World J Cardiol*. 2015;7(8):483–489.
71. Attana P, Lazzeri C, Picariello C, et al. Lactate and lactate clearance in acute cardiac care patients. *Eur Heart J Acute Cardiovasc Care*. 2012;1(2):115–121.
72. Hajjar LA, Almeida JP, Fukushima JT, et al. High lactate levels are predictors of major complications

after cardiac surgery. *J Thorac Cardiovasc Surg*. 2013; 146(2):455–460.
73. Dedichen HH, Hisdal J, Aadahl P, et al. Elevated arterial lactate concentrations early after coronary artery bypass grafting are associated with increased anaerobic metabolism in skeletal muscle. *J Cardiothorac Vasc Anesth*. 2015;29(2):367–373.
74. Renew JR, Barbara DW, Hyder JA, et al. Frequency and outcomes of severe hyperlactatemia after elective cardiac surgery. *J Thorac Cardiovasc Surg*. 2016;151(3):825–830.
75. Bellomo R, Martensson J, Eastwood GM. Metabolic and electrolyte disturbance after cardiac arrest: how to deal with it. *Best Pract Res Clin Anaesthesiol*. 2015;29(4):471–484.
76. Demers P, Elkouri S, Martineau R, et al. Outcome with high blood lactate levels during cardiopulmonary bypass in adult cardiac operation. *Ann Thorac Surg*. 2000;70(6):2082–2086.
77. Totaro RJ, Raper RF. Epinephrine-induced lactic acidosis following cardiopulmonary bypass. *Crit Care Med*. 1997;25(10):1693–1699.
78. Ryan T, Balding J, McGovern EM, et al. Lactic acidosis after cardiac surgery is associated with polymorphisms in tumor necrosis factor and interleukin 10 genes. *Ann Thorac Surg*. 2002;73(6):1905–1909, discussion 1910–1911.
79. Nalos M, Leverve X, Huang S, et al. Half-molar sodium lactate infusion improves cardiac performance in acute heart failure: a pilot randomised controlled clinical trial. *Crit Care*. 2014; 18(2):R48.
80. Ichai C, Orban JC, Fontaine E. Sodium lactate for fluid resuscitation: the preferred solution for the coming decades? *Crit Care*. 2014;18(4):163.
81. Jones GC, Macklin JP, Alexander WD. Contraindications to the use of metformin. *BMJ*. 2003;326(7379):4–5.
82. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998; 352(9131):854–865.
83. Biradar V, Moran JL, Peake SL, et al. Metformin-associated lactic acidosis (MALA): clinical profile and outcomes in patients admitted to the intensive care unit. *Crit Care Resusc*. 2010;12(3):191–195.
84. Peters N, Jay N, Barraud D, et al. Metformin-associated lactic acidosis in an intensive care unit. *Crit Care*. 2008;12(6):R149.
85. Salpeter SR, Greyber E, Pasternak GA, et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2010;(4):CD002967.
86. Luft FC. Lactic acidosis update for critical care clinicians. *J Am Soc Nephrol*. 2001;12(suppl 17): S15–S19.
87. Seidowsky A, Nseir S, Houdret N, et al. Metformin-associated lactic acidosis: a prognostic and therapeutic study. *Crit Care Med*. 2009;37(7):2191–2196.
88. Friesecke S, Abel P, Roser M, et al. Outcome of severe lactic acidosis associated with metformin accumulation. *Crit Care*. 2010;14(6):R226.
89. Posma RA, Absalom AR, Touw DJ, et al. Metformin and lactic acidosis during shock: just the tip of the iceberg? *Crit Care*. 2016;20(1):158.
90. Allyn J, Vandroux D, Jabot J, et al. Prognosis of patients presenting extreme acidosis (pH <7) on admission to intensive care unit. *J Crit Care*. 2016; 31(1):243–248.
91. Lonergan JT, Behling C, Pfander H, et al. Hyperlactatemia and hepatic abnormalities in 10 human immunodeficiency virus-infected patients receiving nucleoside analogue combination regimens. *Clin Infect Dis*. 2000;31(1):162–166.
92. Brooks DE, Wallace KL. Acute propylene glycol ingestion. *J Toxicol Clin Toxicol*. 2002;40(4):513–516.
93. Kraut JA, Kurtz I. Toxic alcohol ingestions: clinical features, diagnosis, and management. *Clin J Am Soc Nephrol*. 2008;3(1):208–225.
94. Vincent JL, Quintairos ESA, Couto L Jr, et al. The value of blood lactate kinetics in critically ill patients: a systematic review. *Crit Care*. 2016;20(1):257.
95. Centers for Disease, Control and Prevention. Lactic acidosis traced to thiamine deficiency related to nationwide shortage of multivitamins for total parenteral nutrition – United States, 1997. *MMWR Morb Mortal Wkly Rep*. 1997;46(23):523–528.
96. Claessens YE, Chiche JD, Mira JP, et al. Bench-to-bedside review: severe lactic acidosis in HIV patients treated with nucleoside analogue reverse transcriptase inhibitors. *Crit Care*. 2003;7(3): 226–232.
97. Bolhaar MG, Karstaedt AS. A high incidence of lactic acidosis and symptomatic hyperlactatemia in women receiving highly active antiretroviral therapy in Soweto, South Africa. *Clin Infect Dis*. 2007;45(2):254–260.
98. Narins RG, Cohen JJ. Bicarbonate therapy for organic acidosis: the case for its continued use. *Ann Intern Med*. 1987;106(4):615–618.
99. Stacpoole PW. Lactic acidosis: the case against bicarbonate therapy. *Ann Intern Med*. 1986;105(2): 276–279.
100. Boyd JH, Walley KR. Is there a role for sodium bicarbonate in treating lactic acidosis from shock? *Curr Opin Crit Care*. 2008;14(4):379–383.
101. Cooper DJ, Herbertson MJ, Werner HA, et al. Bicarbonate does not increase left ventricular contractility during L-lactic acidemia in pigs. *Am Rev Respir Dis*. 1993;148(2):317–322.
102. Walley KR, James Cooper D, Baile EM, et al. Bicarbonate does not improve left ventricular contractility during resuscitation from hypovolemic shock in pigs. *J Crit Care*. 1992;7(1):14–21.
103. Graf H, Leach W, Arieff AI. Metabolic effects of sodium bicarbonate in hypoxic lactic acidosis in dogs. *Am J Physiol*. 1985;249(5 Pt 2):F630–F635.
104. Cooper DJ, Walley KR, Wiggs BR, et al. Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. A

prospective, controlled clinical study. *Ann Intern Med*. 1990;112(7):492–498.
105. Lang RM, Fellner SK, Neumann A, et al. Left ventricular contractility varies directly with blood ionized calcium. *Ann Intern Med*. 1988;108(4): 524–529.
106. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med*. 2017;45(3):486–552.
107. Mathieu D, Neviere R, Billard V, et al. Effects of bicarbonate therapy on hemodynamics and tissue oxygenation in patients with lactic acidosis: a prospective, controlled clinical study. *Crit Care Med*. 1991;19(11):1352–1356.
108. Bisri T, Utomo BA, Fuadi I. Exogenous lactate infusion improved neurocognitive function of patients with mild traumatic brain injury. *Asian J Neurosurg*. 2016;11(2):151–159.
109. Bouzat P, Sala N, Suys T, et al. Cerebral metabolic effects of exogenous lactate supplementation on the injured human brain. *Intensive Care Med*. 2014; 40(3):412–421.
110. Brooks GA, Martin NA. Cerebral metabolism following traumatic brain injury: new discoveries with implications for treatment. *Front Neurosci*. 2014;8:408.
111. Ichai C, Armando G, Orban JC, et al. Sodium lactate versus mannitol in the treatment of intracranial hypertensive episodes in severe traumatic brain-injured patients. *Intensive Care Med*. 2009;35(3):471–479.
112. Leverve XM, Boon C, Hakim T, et al. Half-molar sodium-lactate solution has a beneficial effect in patients after coronary artery bypass grafting. *Intensive Care Med*. 2008;34(10):1796–1803.
113. Duburcq T, Favory R, Mathieu D, et al. Hypertonic sodium lactate improves fluid balance and hemodynamics in porcine endotoxic shock. *Crit Care*. 2014;18(4):467.

This page intentionally left blank

Part Three
Acute Coronary Care

This page intentionally left blank

20

Acute cardiac syndromes, investigations and interventions

Bradley Power, Ian Seppelt

Cardiovascular disease (CVD) accounts for one in three deaths in Western industrialised society, with coronary artery disease (CAD) being responsible for about half of these.[1] Up to 70% of CAD deaths occur outside hospital as 'sudden death' from cardiac arrest.[2] In persons over age 40, acute myocardial infarction (MI) is the cause of approximately 20% of all deaths. Of those who die acutely, 50%–65% have no previous history of cardiac disease. Of patients admitted to hospital, early mortality is 5%–7% (much higher in at-risk groups) and may rise to 7%–18% by 12 months.[2–5] Improving in-hospital and longer-term CAD mortality requires rapid identification of at-risk patients and the implementation of evidence-based treatments.

MYOCARDIAL INFARCTION

MI is present when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Diagnosis involves clinical suspicion, with supportive electrocardiography (ECG), biomarkers, echocardiography or autopsy findings confirming the diagnosis.

MI can result from different pathological and epidemiological mechanisms (Box 20.1).[2,6,7] Each mechanism may have a different prognosis despite similar biomarker or ECG changes and the patterns of MI may be different in an emergency department, surgery or intensive care unit (ICU) population. This may be clinically important when applying trial results or guidelines to such populations. Small amounts of myocardial necrosis can occur with heart failure (HF), arrhythmias, pulmonary embolism or after uneventful cardiac procedures; these are better labelled 'myocardial injury' rather than MI.[6]

ACUTE CORONARY SYNDROMES

Acute coronary syndromes (ACS) describe the spectrum of patients who present with chest discomfort or other symptoms of acute myocardial ischaemia (Box 20.2). ACS can be further divided into MI and unstable angina (UA). Both are invariably caused by recent thrombus formation on pre-existing coronary artery plaque, occasionally by embolism or artery dissection. In this sense, they differ from stable angina, which is usually precipitated by increased myocardial oxygen demand with significant background coronary artery narrowing. ACS are medical emergencies and are one of the most frequent causes of hospital and coronary care unit admission.

An immediate clinical imperative is identification of patients with ST-segment elevation (STE), as rapid reperfusion therapy is strongly indicated in this group.

AETIOLOGY AND RISK FACTORS

Atheroma deposits in coronary artery walls provide the substrate for ACS. Risk factors for CVD and CAD include cigarette smoking, diabetes, dyslipidaemia, hypertension and family history.[8] About 85% of patients presenting with an initial MI have at least one risk factor.[9]

Cessation of smoking, lowering plasma cholesterol (diet and medications), weight loss and adoption of an active lifestyle can all help reduce the development of CAD.[8,10] In a large meta-analysis of trials comparing antihypertensive regimens in patients at high risk of CVD, a 10 mm Hg reduction in systolic blood pressure (SBP) resulted in a relative risk reduction (RRR) in major CVD events (20%), coronary heart disease (17%), stroke (27%) and HF (28%) with a 13% RRR in all-cause mortality.[11]

PATHOPHYSIOLOGY[11,12]

Formation of thrombus upon ruptured, fissured or eroded atheromatous plaque is the usual precipitant of an ACS (Fig. 20.1).[6,8,13] Atherosclerotic plaque formation is probably initiated by vessel wall injury that may commence as early as childhood. 'Fatty streaks' formed from lipid engorged macrophages (foam cells), and T lymphocytes, accumulate in the intima of arteries. Such cells accumulate lipid, but are also pro-inflammatory. As large amounts of lipid accumulate they may become covered by a fibromuscular

ABSTRACT

Acute coronary syndromes (ACS) are predominantly caused by acute thrombus formation upon eroded or ruptured atherosclerotic coronary plaque. They include unstable angina and myocardial infarction (MI; identification of STEMI and NSTEMI strongly guides acute therapy). History, examination, serial ECGs and cardiac biomarkers usually allow the diagnosis to be made. Atherothrombotic processes require immediate antiplatelet and antithrombotic therapy. Immediate identification of STE facilitates urgent reperfusion using coronary cardiac catheterisation (PCI) or pharmacological therapy. Serial risk scoring of NSTEMI is necessary to guide the optimal timing and nature of invasive, non-thrombolysis therapies. Clinical guidelines from controlled trials define optimal acute and long-term therapies for the management of antiplatelet, antithrombotic and 'cardiac' risk factors. ICU management indications can include heart failure, cardiogenic shock, arrhythmias and bleeding. Current knowledge of MI therapies is vital in the care of patients with a history of cardiac disease and in patients undergoing non-cardiac surgery or therapy.

KEYWORDS

Acute coronary syndromes
atherothombosis
ST-segment elevation
non–ST-segment elevation
acute myocardial infarction
unstable angina
thrombolysis
dual antiplatelet therapy
percutaneous coronary intervention angioplasty
takotsubo syndrome
apical ballooning syndrome
left ventricular failure
beta-blockers

Box 20.1 Universal classification of myocardial infarction

Type 1: Spontaneous myocardial infarction
Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring or dissection. The patient may have severe coronary artery disease (CAD) but on occasion non-obstructive or no CAD.

Type 2: Myocardial infarction secondary to an ischaemic imbalance
This occurs in instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand; for example, coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anaemia, respiratory failure, hypotension and hypertension with or without left ventricular hypertrophy (LVH).

Type 3: Myocardial infarction resulting in death when biomarker values are unavailable
Cardiac death with symptoms suggestive of myocardial ischaemia, and presumed new ischaemic changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarkers could rise or, on rare cases, biomarkers were not collected.

Type 4a: Myocardial infarction related to percutaneous coronary intervention
Significant cardiac biomarker rise from normal or by more than 20% if previously elevated. In addition, either:

i. symptoms of myocardial ischaemia, *or*
ii. new ischaemic ECG changes or LBBB, *or*
iii. angiographic loss of patency or persistent flow abnormalities, or embolisation, *or*
iv. imaging demonstration of loss of viable myocardium or regional wall motion abnormality.

Type 4b: Myocardial infarction related to stent thrombosis
Myocardial infarction associated with stent thrombosis detected by coronary angiography or autopsy in setting of myocardial ischaemia and with a significant rise and/or fall of biomarkers.

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)
Myocardial infarction associated with CABG arbitrarily defined by elevation of cardiac biomarker values from normal baseline to above 10 times the URL. In addition, either:

i. new pathological Q waves or LBBB, *or*
ii. angiographic documented new graft or new native coronary artery occlusion, *or*
iii. imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Adapted from Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33(20):2551–2567. doi:10.1093/eurheartj/ehs184. Modified with permission of Oxford University Press (UK) © European Society of Cardiology.

Box 20.2 Classification of acute coronary syndromes

Acute coronary syndrome (ACS)
A spectrum of clinical conditions characterised by acute chest pain or myocardial ischaemia. Pain is of recent origin or is more frequent, severe or prolonged than known angina, is more difficult to control with medication or occurs at rest or with minimal exertion.

ACS includes myocardial infarction with ST-segment elevation (STEMI), myocardial infarction in the absence of ST-segment elevation (NSTEMI) and unstable angina. An initial clinical subdivision of ACS is made on the presence or absence of electrocardiography ST-segment elevation.

STEMI
Patients presenting with ST-segment elevation ACS will invariably display initial or subsequent troponin elevation, although the extent of myocardial infarction and complications may be significantly moderated by intervention.

NSTEACS
Patients who present without ST-segment elevation, may later (after testing of biomarkers) be determined to have:

i. *NSTEMI:* cardiac biomarkers elevated indicating myocardial infarction
ii. *Unstable angina:* no evidence of cardiac biomarker elevation.

cap forming a 'fibrous plaque'. Plaque development is often slow but may rapidly accelerate in people with risk factors.

'Vulnerable plaque' is often rich in lipid and covered by a thin fibrin cap. Fatal MI may demonstrate plaque **rupture (75%)** or plaque **erosion (25% of cases)**. Ruptured plaque may have a thin cap, large necrotic core, inflamed and neovascularised tissue, and haemorrhage. Eroded plaque is often thin walled with a core that has less necrosis and inflammation. Both expose thrombogenic lipid and collagen, which are potent activators of platelets.

Platelet adherence and activation, and subsequent activation of the clotting cascade, result in an 'atherothrombotic processes'. Platelets aggregate to form *'white thrombus'*. The final common pathway of thrombus formation is via activation of the platelet glycoprotein (GP) IIb/IIIa receptor, which binds fibrinogen and cross-links platelets. Activation of coagulation pathways by exposed lipid and fibrin, and by activated platelets, leads to thrombin activation and fibrin clot formation. Red cells are enmeshed in this so-called *'red thrombus'* complex, which surrounds the 'white thrombus'. While *'culprit lesions'* of ST-segment elevation myocardial infarction (STEMI) can be small (<50% stenosis), studies suggest that 86% of patients had at least a moderate stenosis (>50%) and 67% had a severe stenosis (>70%).[14,15]

The pathophysiology above has immediate relevance to treatment (see Fig. 20.1).

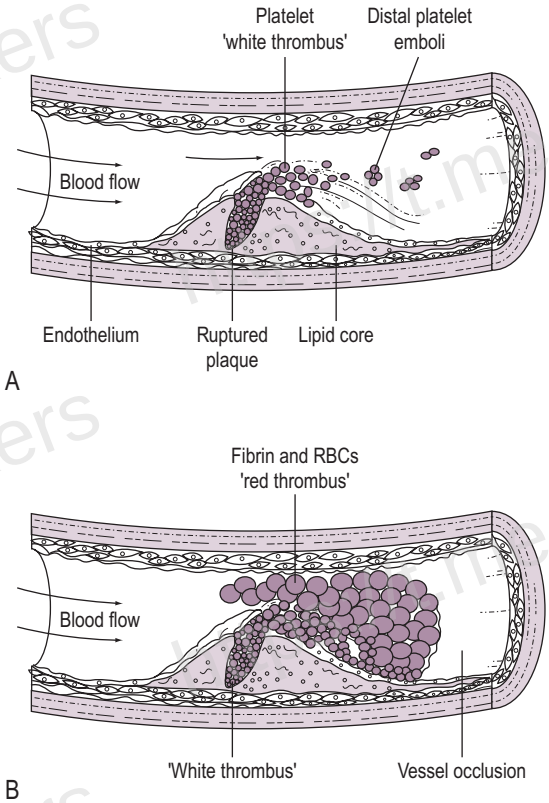


Figure 20.1 (a) Plaque rupture exposes thrombogenic lipid. 'White thrombus' is formed by adherent activated platelets. Coronary artery narrowing, distal platelet embolisation or arterial spasm can cause ischaemic myocardial pain and possible myocardial necrosis. This lesion is unstable and may lead to thrombin activation. 'White thrombus' is not removed by thrombolytic therapy. (b) Thrombin activation leads to a mesh of fibrin and red blood cells (RBCs) or 'red thrombus'. Arterial occlusion may result and, in arteries without adequate collateral circulation, myocardial necrosis follows. Complete arterial occlusion is suggested by ST-segment elevation on the electrocardiogram. Prompt reperfusion with thrombolytic therapy or with invasive coronary procedures may prevent extensive myocardial necrosis.

- **Antiplatelet agents** prevent platelet adherence, limiting and even reversing 'white thrombus' formation. Aspirin blocks thromboxane A_2 synthesis, but fails to block platelet activation by thrombin, adenosine diphosphate (ADP) and collagen. New agents may target ADP receptors (e.g. clopidogrel, prasugrel) or may inhibit cyclo-oxygenase (e.g. aspirin).
- **Fibrinolytic agents** lyse 'red thrombus' but not 'white thrombus'.
- **Antithrombin agents** (e.g. heparins) limit thrombin activation. Current fibrin-specific thrombolytic agents lyse fibrin and red cell thrombus, but paradoxically may increase surface thrombin activation.

Totally occluding thrombus causes myocardial necrosis unless there is collateral flow or rapid thrombus clearance. Occlusion is often accompanied by ECG changes of STE although this is not absolute. Non-occlusive thrombus may be asymptomatic, or may cause USA or MI, especially if spasm or distal thrombus embolisation occur. Thrombus retrieved 'early' during percutaneous coronary intervention (PCI) thrombectomy in STEMI patients surprisingly may be predominantly 'white thrombus' (up to 30% of samples), with smaller infarction. Red thrombus may be a sign of a maturing clot.

Infarct size determines

- left ventricular (LV) systolic function impairment
- stroke volume decrease
- ventricular filling pressure rise (leading to pulmonary congestion and hypotension that may impair coronary perfusion pressures and exacerbate the myocardial ischaemia)
- LV diastolic dysfunction.

CLINICAL PRESENTATION

The diagnosis of myocardial ischaemia is usually made (suspected) on the basis of clinical history and ECG.[2,4–7,16]

HISTORY[17]

Patients with myocardial ischaemia can present with chest pain or pressure, syncope, palpitations, dyspnoea, fatigue or sudden death. Prodromal USA symptoms may occur in the days preceding infarction in 20%–60% of patients although this is less likely in young patients.

Typically, the pain of acute MI:

- is severe, constant and retrosternal, spreading across the chest
- lasts greater than 20 minutes and is without a clear precipitant
- may radiate to the throat and jaw, down the ulnar aspect of both arms and to the interscapular area
- autonomic symptoms of sweating, nausea, pallor, dyspnoea, anxiety are common

The pain of USA may be similar but milder. Ischaemic features are:[4,5]

- waxing and waning
- reproducibility upon minimal exertion or emotion
- autonomic symptoms.

The pain can be atypical, leading to misdiagnosis:

- epigastric
- confined to the jaw, arms, wrists or interscapular region
- burning or a 'pressure-like' sensation.

Differential diagnosis includes may include pericarditis, aortic dissection or massive pulmonary embolism.

Atypical or silent presentations are common (25% of STEMI patients and 45% of non–ST-elevation

myocardial infarction [NSTEMI]).[7,16,18] Patients who present without classic chest discomfort are less likely to receive definitive treatment. Such presentations are more common in patients who are elderly, female, diabetic, obese or have a history of HF.

The assessment of clinical symptoms alone is insufficient for risk stratification and severity of pain does not usually correlate with the extent of infarction.

PHYSICAL EXAMINATION

Examination of patients with USA is often unremarkable. With severe ischaemia and extensive MI, autonomic activation (pallor, sweating, agitation, clamminess) as well as HF and even shock may be apparent.

LV failure (LVF) is associated with increased mortality, signs including gallop rhythm, tachycardia, tachypnoea and basal crackles.[18] A fourth heart sound is common, but a third heart sound usually indicates a large MI with extensive muscle damage. Soft systolic murmurs may be present and may be transient or persistent. These murmurs may result from mitral regurgitation (MR), due to papillary muscle dysfunction or LV dilatation.

Cardiogenic shock (CS) (poor peripheral perfusion, hypotension, oliguria and other features of 'low cardiac output') is associated with particularly poor outcome unless perfusion can be rapidly restored. Right ventricle (RV) infarction[2,19] results in hypotension and marked elevation of the jugular venous pressure, with clear lungs.

Conditions that can mimic ACS but do not benefit from thrombolysis include pericarditis and Takotsubo syndrome. Aortic dissection may be present in 1.3% of STEMI, and diagnosis may be realised during PCI. If suspected on presentation, immediate echocardiography (and possible computed tomography angiography) is indicated to confirm the diagnosis and assist with surgical planning. Coronary artery involvement may cause associated MI.

INVESTIGATIONS

The presence of MI should also be qualified by:

- anatomical location and size
- causation (e.g. MI Type 1–5) (see Box 20.1)
- time from occurrence (acute, early, late).

Technological advances in biomarker assays allows detection of very small infarcts.

ELECTROCARDIOGRAPHY[20–24]

The ECG is the initial single most cost-effective, clinically useful and predictive test for diagnosis and guidance of the emergency treatment of MI. All patients presenting with symptoms suggestive of MI should have an ECG performed and interpreted by an experienced person within 10 minutes of arrival.[25] Initial ECGs may (i) reveal significant STE-ACS, (STEACS); or (ii) suggest non-STE-ACS (NSTEACS). Serial 12-lead ECGs are necessary as STE may develop after initial assessment and changes may indicate response to therapies.

Acute and complete occlusion of a coronary artery usually leads to serial ECG changes in leads subtending the area of ischaemia, where the:

- number of leads involved broadly reflects the extent of myocardium involved
- height of initial STE is only modestly correlated with the degree of ischaemia[24]
- acute resolution of STE correlates well with reperfusion.

Recognition of STE and its evolution indicates patients in whom reperfusion therapy may interrupt, or minimise myocardial necrosis (Fig. 20.2). These changes are not stereotyped and may vary significantly but include:

- *hyperacute* (0–20 minutes): tall, peaking T-waves and progressive upward coving and elevation of ST-segments
- *acute* (minutes to hours): persisting STE, gradual loss of R-wave in the infarcted area. Progressive inversion of T-waves
- *early* (hours to days): loss of R-wave and development of pathological Q-waves in area of ischaemia. Return or fall of ST-segments to baseline. Persistence of T-wave inversion
- *indeterminate* (days to weeks): pathological Q-waves with persisting T-wave inversion. ST-segments normalise (unless there is aneurysm)
- *old* (weeks to months): persisting deep Q-waves with normalised ST-segments and T-waves.

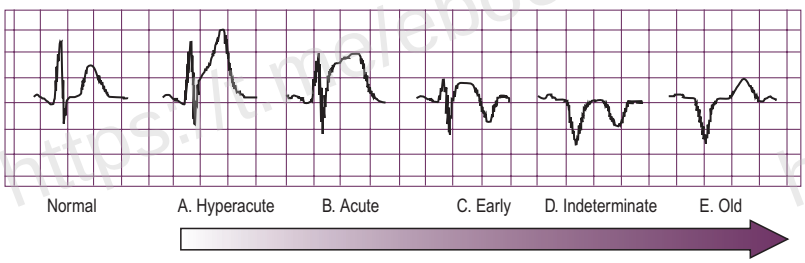


Figure 20.2 Total acute coronary occlusion leads to serial electrocardiogram changes. The evolution is variable and may be interrupted or altered by successful reperfusion. ST-segment elevation is an early and relatively specific indicator of the need for acute reperfusion in patients with acute coronary syndrome.

Clinical skill is needed to identify those ECG changes that are probably due to MI (true positive but also false negative). Other causes of STE and T-wave changes that should *not* lead to thrombolytic therapy are shown in Box 20.3.[6,26,27]

Takotsubo syndrome[28,29] may mimic an ACS and can represent up to 1%–2% of STEACS-like presentations.

Box 20.3 Electrocardiogram patterns mimicking ST-segment elevation myocardial infarction

Normal variant (non-ischaemic STE mainly V2–V3)
Early repolarisation (notched J-point mainly in anterolateral leads)
Metabolic disturbance (mainly hyperkalaemia, hypercalcaemia)
Drug toxicity
Brugada syndrome
Pre-excitation (Wolff–Parkinson–White syndrome)
Pericarditis
Myocarditis
Previous (old) myocardial infarction
Left ventricular aneurysm
Spontaneously reperfused myocardium
Apical ballooning syndrome (Takotsubo or 'broken heart') multiple causes, for example severe emotion, physical stress

Data from Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33(20):2551–2567; and Pollak P, Brady W. Electrocardiographic patterns mimicking ST segment elevation myocardial infarction. *Cardiol Clin*. 2012;30(4):601–615.

Patients with ACS but with 'non-significant STE' (NSTEACS until further subdivided by biomarker studies) are also at risk of MI and death. They commonly have active, non-occluding thrombus, or occlusion if present may be to an area with collateral flow or with poor detection of by standard lead placements. ECGs in these ACS patients may be normal or display[20–24]:

- ST-segment depression
- STE (insufficient to meet thrombolysis criteria)
- T-wave inversion or 'normalisation' of previous inverted T-waves.

LOCALISATION OF INFARCTION[20–24,30] (Fig. 20.3)

Coronary artery anatomy is displayed in Fig. 20.3. A very general relationship of ECG, MI locating leads and likely 'culprit arteries', is outlined in Table 20.1 and in cited references.[20–24] ECG 'localisation' may differ from angiography, echocardiography and autopsy findings, however, especially where there is collateral circulation or previous coronary artery bypass grafting (CABG). Approximately 40%–50% of patients may present with anterior infarctions which may be septal, anterior or lateral (Fig. 20.4a).[21] About 50% may present with acute inferior MI (see Fig. 20.4b),[20–24] which may involve extension to the lateral, posterior or RV myocardium.

Standard ECGs generally only record from anterior body leads and thus important ECG patterns that must not be missed can include.[20,22–24,31]

- **True or 'isolated' or 'strictly' posterior wall MI** (3% of MI, although posterior involvement may accompany 15% of STEMI) is important to diagnose as its amount of threatened myocardium is similar to that

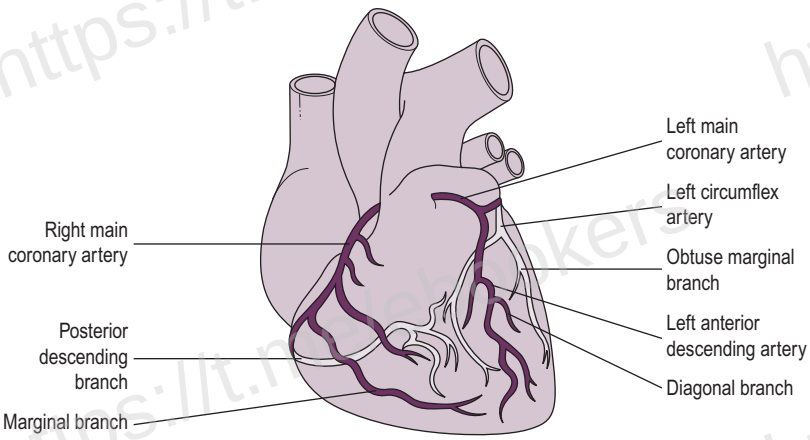


Figure 20.3 Coronary artery anatomy. The left anterior descending artery supplies the anterior two-thirds of the interventricular septum (septal perforators), anterior and lateral wall of the left ventricle (LV: diagonal branches) and sometimes part of the right ventricle (RV). Circumflex (Cx) supplies the LV lateral (anterolateral marginal branches) and posterior walls, and occasionally its inferior aspect (posterior LV arteries: 15% of patients) and the posterior septum. The right coronary artery (RCA) supplies the RV wall, and usually the posterior septum and inferior (diaphragmatic) wall of the LV (posterior LV arteries; 85% of people). The RCA is 'dominant' (as opposed to the Cx) if it gives rise to the posterior descending coronary artery and the posterior left ventricular arteries.

Table 20.1 Electrocardiogram patterns of myocardial injury

ANTERIOR WALL	ST-SEGMENT ELEVATION	
'Extensive anterior' (anterolateral)	V_1–V_6, I, aVL	Proximal LAD occlusion
Septal	V_1–V_3, disappearance of septum Q in leads V_5, V_6	LAD-septal branches
Anterior (localised or true)	V_2–V_5, I, aVL	Diagonal (supplies anterior LV wall) Occasionally marginal branch of CX
Lateral	V_5, V_6, I, aVL,	Distal LAD or circumflex
INFERIOR WALL		
Inferior (localised)	II, III, aVF	RCA (80%) or postlateral branch of CX (20%)
Inferior (extended)	II, III, aVF ***plus***	
Inferolateral	I, aVL, V_5, V_6	RCA or dominant CX
Inferoposterior	V_7, V_8, V_9 with ST depression V_1–V_2	RCA post descending branch or posterolateral branch of CX
Right ventricular	V_1, V_3R, V_4R	Proximal RCA
Posterior (localised)*	V_7, V_8, V_9. (Elevation II, III, aVF may not be marked) Initial V_1, V_2 ST depression may evolve to tall R waves	RCA

*Posterior infarctions are usually identified as lateral on angiography but guidelines suggest that the name be retained. Lack of ST elevation on standard leads may lead to failure to appreciate that they are a STEMI and will benefit from reperfusion therapy. Clinicians should also be aware of novel patterns of ischaemia and 'STEMI equivalents' that may include 'Wellens phenomenon', STE elevation in aVR, ST changes in the presence of left bundle branch block (LBBB) and the de Winter ST/T complex.

The sensitivity, specificity and predictive value of these patterns in determining the culprit artery (as subsequently determined by angiography) are not perfect. This is especially true of occlusions of the RCA and CX.

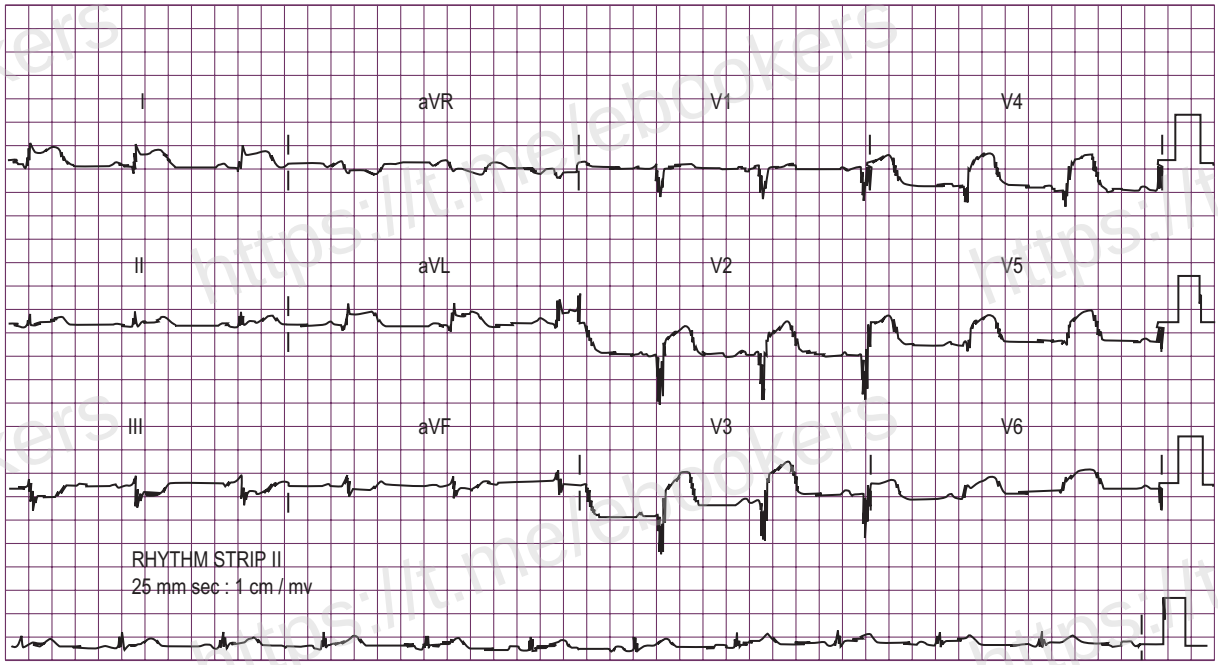
CX, Circumflex coronary artery; *LAD,* left anterior descending coronary artery; *RCA,* right coronary artery; *STEMI*, ST-elevation myocardial infarction; *VF,* ventricular fibrillation.

of inferior MI.[30] It usually causes 'mirror' changes in leads V_1–V_2 and although there might be STE in inferior leads II, III, AVF it might not have met diagnostic criteria for reperfusion. Non-standard posterior chest leads (V_7–V_9) usually show STE. Such MIs are usually lateral but the term 'posterior' is still retained.[20,22–24,31]

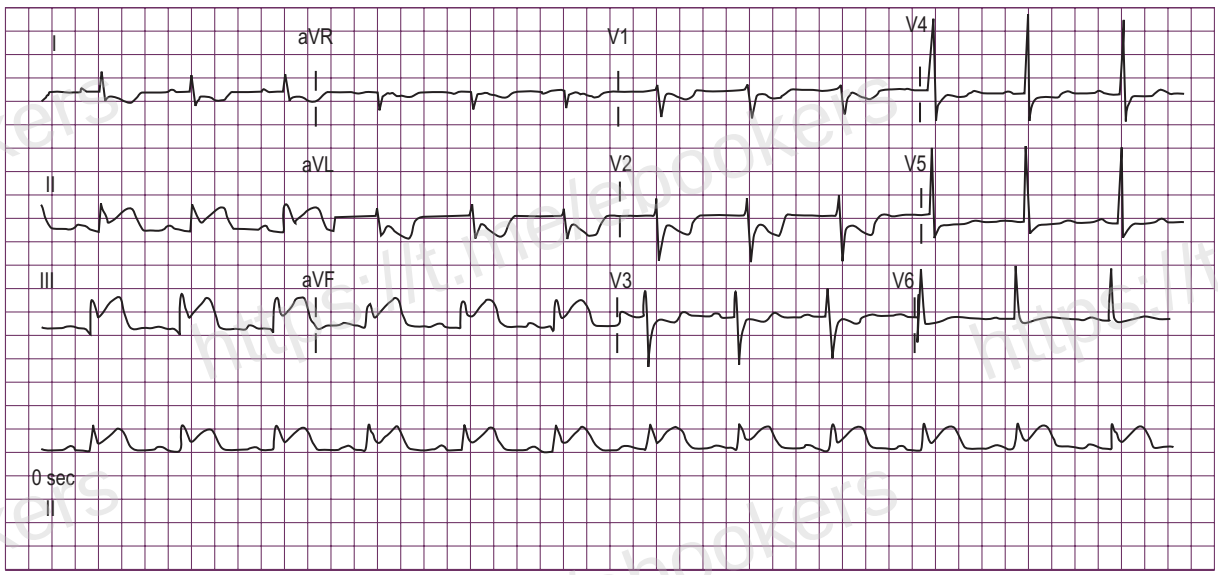
- **RV MI** is usually concurrent (20%–60%) with inferior wall MI where suspicious findings include STE in V_1 (overlies the RV), and STE lead III greater than lead II. A V_4R lead may show STE and is sensitive and specific for RV MI, although in 50% of cases it lasts less than 10 hours.[32] Sinus bradycardia and AV node block may be present.
- Resting ECG changes revealing significant ST-segment depression in six or more body surface leads coupled with STE in aVR and/or V_1 are highly suggestive of **left main coronary artery (LMCA) obstruction** or **multivessel disease** (severe 3-vessel disease or 'left main equivalent').[2,21,22] These changes may even completely disappear when the patient is asymptomatic and should not be ignored.
- The specific pattern of deep T-wave inversion in V_2–V_4 with QT interval prolongation may suggest severe **proximal left anterior descending coronary artery (LAD) disease**. It may occur **after** chest pain but be associated with imminent occlusion.[21,22]
- **A normal ECG** may be present in 15%–20% of NSTEMI, although a normal ECG during pain is unusual.[20,22–24] A small percentage of patients progressively lose R-wave height and develop evidence of Q-waves and a small number progress to CS.

CARDIAC BIOCHEMICAL MARKERS (TROPONINS)[6,7,20] (Fig. 20.5)

Cardiac troponins (cTn) can be detected in serum by monoclonal antibodies to epitopes of cTnT and cTnI. These antibodies are highly specific for myocardial, and not skeletal, muscle. Myocardial necrosis produces an initial release of cTn within the cell cytosol. Serum levels are usually detectable 4–6 hours post-MI, with a peak level at 18–24 hours. Return to normal usually occurs over 7–14 days. Renal failure prolongs excretion.



A



B

Figure 20.4 (a) Evolving anterolateral myocardial infarction. There is ST-segment elevation (STE) in anterior leads V_2–V_6 and lateral leads I, aVL. There is loss of anterior R wave height, and reciprocal ST-segment depression in leads III and aVF. If within time frames or if shocked, urgent reperfusion is indicated. (b) Acute inferior myocardial infarction (STE in the inferior leads II, III and aVF). There is ST depression in leads I, aVL, V_1 and V_2. The addition of right-sided (V_4R) and posterior leads would help identify the presence of right ventricle and posterior infarction (STE). Reciprocal ST-segment depression in leads remote from the site of infarction is a highly sensitive indicator of myocardial infarction. It may be seen in 70% of inferior and 30% of anterior infarctions.

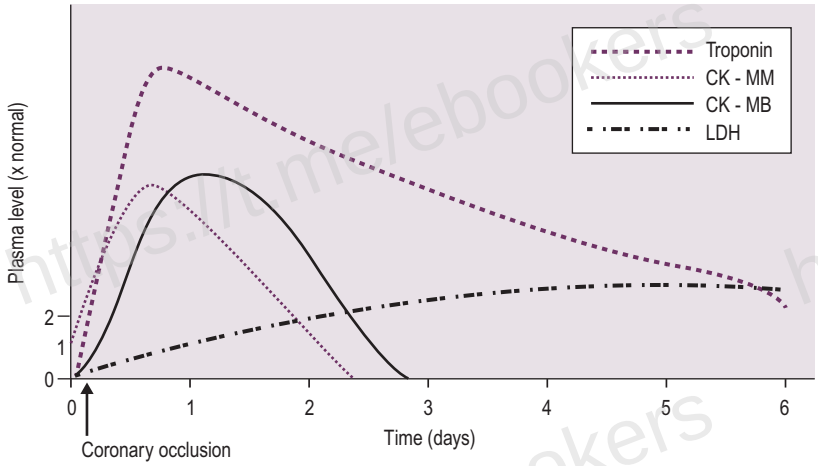


Figure 20.5 Serum biochemical marker changes after acute myocardial infarction. The sensitivity and specificity of cardiac troponins makes them useful for the early diagnosis of myocardial infarction. Their delayed fall may allow diagnosis where presentation is late. CK or CK-MB is useful if re-infarction with secondary biomarker rise is queried. *LDH*, Lactate dehydrogenase.

- High sensitivity and specificity has made cTn the gold standard for the confirming MI.[6,7]
- cTns should be measured in all patients with ACS. Levels should be taken on arrival, and at 3–6 hours. Acute rise and fall help separate ACS from other cTn elevations.
- Elevated levels of cTN in Type 1 MI (see Box 20.1), correlate well with unstable plaque, risk stratification and evidence-based therapies.
- The high sensitivity of cTn means that many people, previously diagnosed as USA, now meet diagnostic criteria for MI.[7,20,23,33]
- Troponins do not differentiate the cause of the myocardial injury (e.g. ischaemia, myocarditis, trauma), thus the clinical context must always be considered.[6]
- New markers of myocardial necrosis, including cardiac myosin binding protein C (cMyC), and soluble mRNA for vascular cell adhesion molecule-1 and interleukin-6, are currently undergoing clinical evaluation. At the time of writing, cMyC is showing promise as a rapid diagnostic test of myocardial necrosis.[34]

The importance of troponins in critical illness is discussed in Chapter 24.

ECHOCARDIOGRAPHY[35] (See Chapter 27)

Echocardiography is one of the most powerful diagnostic and monitoring tools available to assist with diagnosis and management of ACS. All tertiary ICUs should have 24-hour echocardiography access.[35] Two-dimensional transthoracic (and transoesophageal) echocardiography is used to assess presence degree of regional or global LV dysfunction. It identifies regional wall motion abnormalities (RWMAs), helping confirm or exclude the diagnosis of MI in cases where it is uncertain (e.g. left bundle branch block, or old MI with atypical presentations). RWMA and loss of wall thickening with contraction are often present in these cases if due to ischaemia.[6]

Echocardiography is useful subsequently and in ICU populations to:

- assess infarct size, especially if thrombolysis has interfered with biomarker measurement
- identify RWMA where Tn is elevated but the MI predictive value is uncertain (43% of ICU patients may have an elevated Tn when it is tested)[36]
- rapidly assist differential diagnosis (e.g. aortic dissection, pericardial effusion)
- diagnose specific complications (e.g. MR or papillary muscle rupture, pericardial effusion, myocardial rupture, ventricular septal defect)
- assess mural thrombus and thromboembolic risk
- diagnose RV infarction and infarct extension
- myocardial perfusion scanning using echocardiography is currently an experimental tool but is useful in critically ill patients where coronary angiography is logistically difficult.

OTHER STUDIES AND STRESS TESTING

Radionuclide studies have limited use in ICU patient care, although they may be useful for surgical planning in high-risk patients.[37] Exercise or dobutamine stress testing may provide information in the preoperative assessment of some vascular surgery.[38,39] High-risk CVD patients might have a small benefit but with harm in low risk. Perioperative interventions included 'monitored admission' and preoperative statins. The benefits and risks of testing asymptomatic patients, with interventions, antiplatelet therapy and its perioperative disruption are discussed on page 202. Coronary

angiography and PCI remain vital in defining and treating CAD in ICU patients, suggested by findings including echocardiography.

RISK STRATIFICATION OF ACUTE CORONARY SYNDROME (Fig. 20.6)[4,5]

STEMI

STEMI (including new or presumed new left bundle branch block [LBBB]) is the most acutely lethal form of ACS, usually due to complete occlusion of a coronary artery (>90% of patients).[33] It is an indication for immediate reperfusion therapy as successful reperfusion will significantly reduce the size of the evolving MI, although some troponin rise is inevitable. Patients who develop STE after admission should also receive thrombolytic therapy.

At the commencement of the thrombolysis era, LBBB was also recognised as gaining the largest benefit from thrombolysis. Unless the LBBB could be proven old, sentinel guideline suggestions were that it be '*presumed new*' and thrombolysis be administered.[40]

Aging populations with more co-morbid illness, see such 'not known to be old' LBBB, arrival ECGs, present in 2%–9% of ACS emergency admissions.[41–43] However, only one-third of patients presenting with LBBB are found to have a STEMI ACS (occluded culprit artery), one-third have non-ACS cardiac disease and up to one-third have non-cardiac illness.[44] Concerns of 'missed diagnosis' and of thrombolysis risk, see many referred for angiography. While 'false activations' of a catheter laboratory for ACS might be less than 14%, in this LBBB setting it may be 44%.[41] Strategies for improvement include, rapid senior cardiology review, urgent echocardiography and telemedicine or ECG reviews. The Sgarbossa ECG criteria are specific but have low sensitivity, and views on their value vary.[41,42]

Considerable variability in mortality risk exists among patients with STEMI. Readily available bedside clinical risk score tools may give insight into predicted 30-day mortality (Fig. 20.7).[45] The addition of in-hospital complications data may allow hospital discharge, longer term, 1-year prognostication after STEMI (Dynamic TIMI Risk Score).[46]

NSTEACS

Patients may have ischaemic chest pain but have 'non-specific' ECG changes (normal, ST-segment depression or minimal elevation, or T-wave inversion). After serial biomarker testing, these patients will later prove to

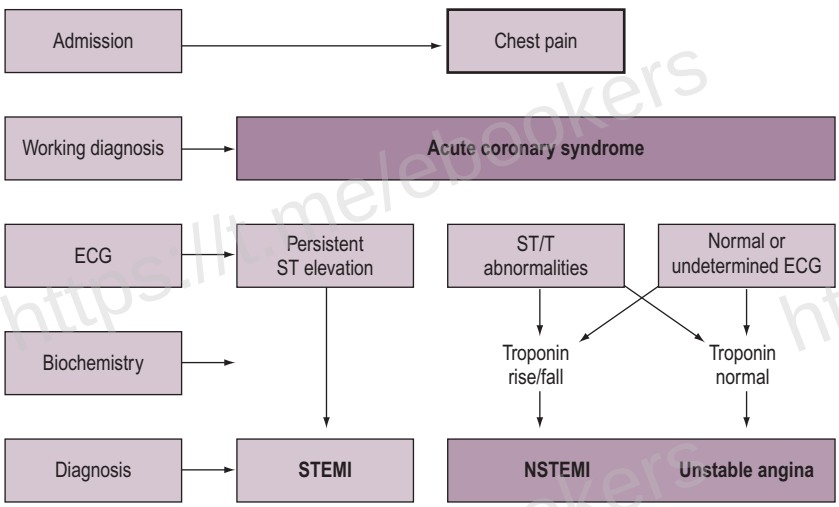
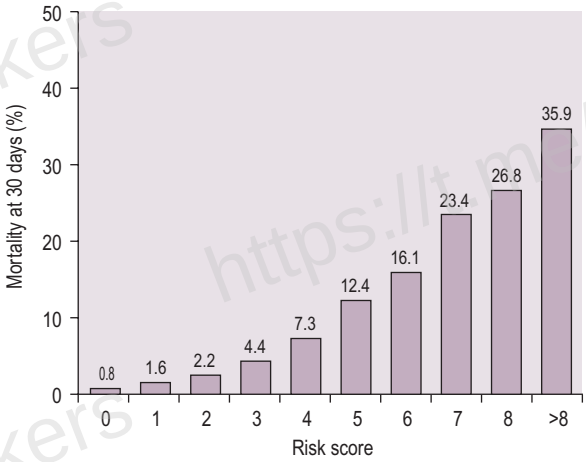


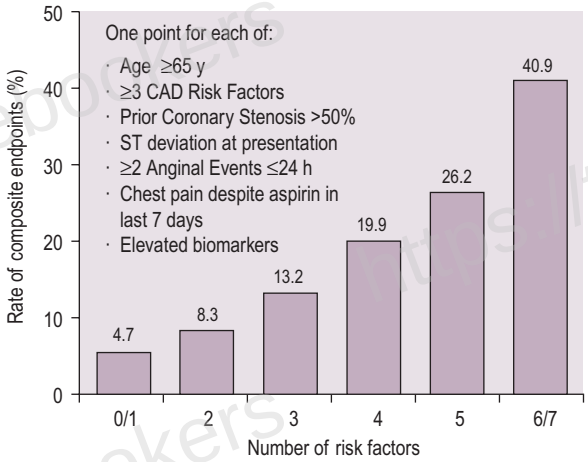
Figure 20.6 The spectrum of ACS. Physicians should obtain, interpret and stratify patients with ACS within 10 minutes of arrival. STE in this clinical setting is usually due to complete coronary occlusion and most patients will ultimately have some biomarker elevation (STEMI). Rapid and sustained coronary artery reperfusion (PCI or fibrinolytic therapy) may significantly decrease myocardial damage. Well-organised systems of care should be in place to minimise delays. In patients without STE (non-STEACS), serial biomarker measurements may define those patients with elevated levels (NSTEMI) and those with ACS but normal biomarkers (unstable angina). Clinical review and further tests may lead to a non-ischaemic cause of chest pain in some patients. Subsequent echocardiography and imaging may help define the extent of injury, coronary anatomy pathology and its clinical importance. *ACS*, Acute coronary syndrome; *ECG*, electrocardiogram; *NSTEMI*, non–ST-elevation myocardial infarction; *PCI*, percutaneous coronary intervention; *STEMI*, ST-elevation myocardial infarction. *(Adapted from Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC).* Eur Heart J. *2011;32(23):2999–3054. doi:10.1093/eurheartj/ehr236 'Adapted with permission of Oxford University Press (UK) © European Society of Cardiology'* http://www.escardio.org/guidelines.)



At risk (%)	12	22	16	16	14	9	8	3	2	1

One point each of:		
	· Age 65–74 / ≥75 years	2/3 points
	· SBP <100	3 points
	· Heart rate >100	2 points
	· Killip II–IV	2 points
	· Anterior STE or LBBB	1 point
	· Diabetes, h/o HTN or h/o angina	1 point
	· Weight <67 kg	1 point
Possible score 0–14	· Time to Rx >4 hours	1 point

Figure 20.7 STEMI-TIMI: TIMI (thrombolysis in myocardial infarction) risk score for STEMI is a simple bedside evaluation for predicting 30-day mortality. *h/o*, History of; *HTN*, hypertension; *LBBB*, left bundle branch block; *SBP*, systolic blood pressure; *STE*, ST elevation; *STEMI*, ST-elevation myocardial infarction. *(From Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation.* Circulation. *2000;102(17):2031–2037 with permission.)*



Test cohort						
Number	85	339	627	573	267	66
(%)	4.3	17.3	32.0	29.3	13.6	3.4

Figure 20.8 NSTEMI-TIMI: the thrombolysis in myocardial infarction (TIMI) score is used to estimate the risk of the composite end-point of death, myocardial infarction, or need for urgent cardiac catheterisation (vertical axis) at 14 days in patients with unstable angina or NSTEMI. Each risk factor is worth 1 point for a maximum score of 7. *CAD*, Coronary artery disease; *NSTEMI*, non-ST-elevation myocardial infarction. *(Adapted from Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making.* JAMA. *2000;284(7):835–842.)*

have either USA (Tn normal) or NSTEMI (Tn elevated). In contrast to patients with STEMI, thrombolysis in patients with ST depression or normal ECGs was associated with increased mortality.[25,40] Only 35%–75% of patients have evidence of 'significant' coronary thrombus formation.[33,40,47] Of note, some myocardial regions may have few 'facing ECG leads'; for example, 27% of inferolateral NSTEMI may actually be demonstrated to have occluded culprit arteries and, if detected, an early invasive management strategy should be established.[48]

NSTEMI therapy aligns more clinically with that of USA than with that of STEMI. These two conditions, comprising NSTEACS, represent a spectrum of disease with common treatments directed at platelet inactivation and 'plaque stabilisation'. Despite the heterogeneous nature of this group of patients, and variable prognoses, early stratification using ECGs, troponins and simple clinical variables may define risk and guide evidence-based therapy (Fig. 20.8).[49] The more severe the ischaemia, the stronger the indication for more aggressive anticoagulation and invasive procedures.

Fig. 20.9a[47,50] displays the higher mortality of STEMI patients (compared to patients presenting with and without STE) present in hospital, and at 6 months, despite lower early, in-hospital mortality in NSTEACS patients. Fig. 20.9b[47,50] shows that the subsequent rates of ongoing fatal events may be higher.

Historical 'Q-wave MI' (QWMI) and 'non–Q-wave MI' (NQWMI) correlate poorly with the clinically useful terms of STEACS and NSTEACS so that 63% of the former and 27% of the latter will have transmural infarction.[22,24] Importantly, the simple detection of STE is the most clinically useful, cost-effective and evidence-based diagnosis to make.

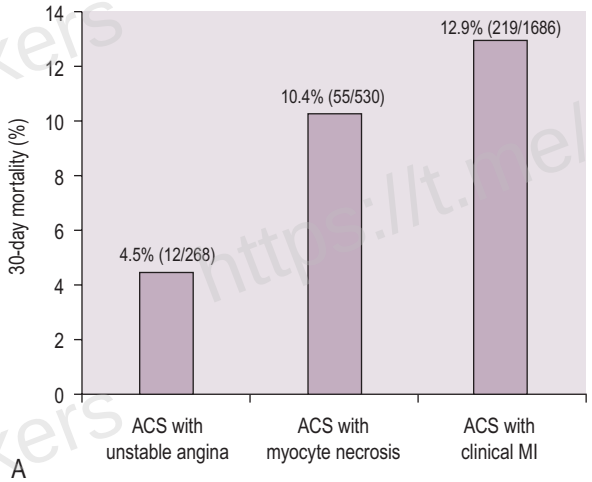
IMMEDIATE MANAGEMENT OF ACUTE CORONARY SYNDROMES

PRE-HOSPITAL CARE

Fifty per cent of deaths from MI occur within the first hour of symptom onset. These deaths are usually due to ventricular fibrillation (VF). Treatment is defibrillation.

IMMEDIATE HOSPITAL CARE

1. Cardiac monitoring.
2. Oxygen supplementation[18,51] (2–4 L/min via facemask or nasal prongs) is recommended for



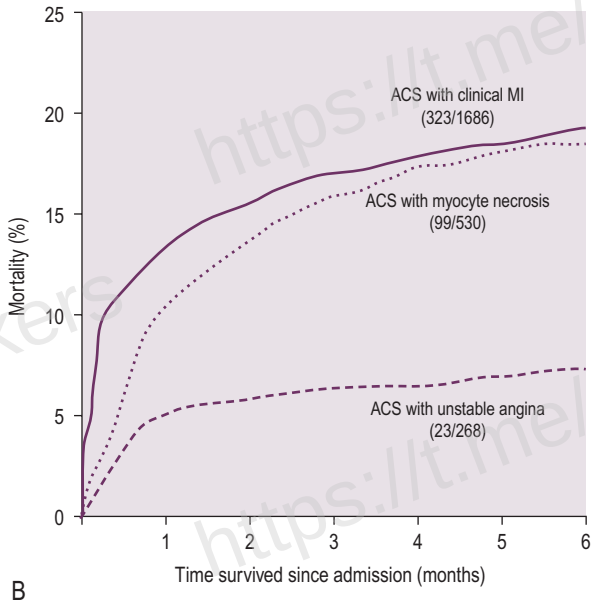


Figure 20.9 (a) Thirty-day mortality according to British Cardiac Society category. (b) Kaplan–Meier survival area curves for events from admission to 6 months. *ACS*, Acute coronary syndrome; *MI*, myocardial infarction. *(Reproduced from Das R, Kilcullen N, Morrell C, et al. The British Cardiac Society Working Group definition of myocardial infarction: implications for practice.* Heart. *2006;92:21–26, with permission.)*

breathless or hypoxic patients (<94%). Administration to non-hypoxic patients has not been shown to have a beneficial effect on 12-month all-cause mortality.[2,52,53]

3. ECG (12-lead) should be taken within 10 minutes of arrival and regularly thereafter. Pre-hospital ECGs have been shown to have a favourable effect on outcome, mediated through shorter times to thrombolysis and primary PCI.[51]
4. Aspirin at 160–325 mg (not slow release) should be chewed or dissolved, and swallowed, then continued at a dose of 100–150 mg/day. International guidelines have some differences in their recommended doses, guiding regional practice.[54] Aspirin reduces mortality and complications of MI with minimal side effects.[2,5,17,54,55] Clopidogrel or prasugrel is given if there is aspirin sensitivity or high risk.[18,33] Dual antiplatelet therapy (DAPT) with clopidogrel or prasugrel added to aspirin, may occur where regional networks anticipate primary PCI.[51]
5. Sublingual glyceryl trinitrate (GTN) given by spray may provide symptomatic relief of active chest pain. Side effects include headache. Hypotensive reactions and a hypotensive bradycardic response (the Bezold–Jarisch reflex) can occur. Recent phosphodiesterase inhibitor use (e.g. sildenafil) should be excluded.
6. Venous access is usually established.
7. Pain relief must be provided.[56] Pain produces catecholamines, which increase ischaemia. Reassurance and small incremental, titrated boluses of intravenous (IV) morphine (1–2 mg) or fentanyl (20–40 µg), can be given. A concern is that gastric emptying delay, or vomiting, may interfere with absorption of antiplatelet agents. Admission non-steroidal anti-inflammatory drugs (NSAIDs) should be ceased immediately, as use in the week prior to admission is associated with increased risk of death and cardiac complications at 6 and 30 days.[33,57] Pain relief is best served by rapid reperfusion.
8. Rapidly identify ACS patients with STE or new and presumed new LBBB (Box 20.4).[2,18,51,58] Reperfusion is critically time dependent ('time is muscle').
9. Emergent primary PCI (or rapid transfer to a PCI centre) is generally superior to thrombolytic therapy. Thrombolysis should be performed where the benefits of urgent primary PCI cannot be obtained.
10. Pulmonary oedema is treated with upright posture, sublingual or IV nitrates, and if moderate to severe, with continuous positive airway pressure (CPAP) ventilation. Response to IV furosemide has slow onset, and may be variable depending upon volume status.
11. Beta-adrenergic blockers (oral) should be commenced in haemodynamically stable patients as soon as possible (usually after thrombolytic therapy has been given or before PCI), but only where there are no contraindications.[2]
12. Prophylactic antiarrhythmics are *not* administered, but all patients should be monitored with rapid access to defibrillation.

ACUTE MANAGEMENT OF STEMI (Fig. 20.10)[2,18,59]

REPERFUSION THERAPY

Prompt 'reperfusion therapy' (mechanical or pharmacological), to establish coronary artery flow is the

Box 20.4 Typical indications for reperfusion therapy in acute myocardial infarction

Reperfusion therapy

Presentation ≤12 hours with acute coronary syndrome (ACS), unrelieved by sublingual nitroglycerine, *and*

New ST segment elevation in two or more contiguous leads with the cut-off points:

≥2 mV in men, >0.15 mV in women in leads V_2–V_3 and/or ≥1 mV in other leads, *or*

New-onset LBBB (include presumed new-onset), *or*

Posterior infarction (dominant R wave and ST depression ≥2 mV in V_1–V_2), *or*

Presentation 12–24 hours after onset of ACS with continuing pain and evidence of evolving infarction

Posterior myocardial infarction is an important presentation of STEMI where STE is not present in standard chest leads. STEMI (2%–4% of cases) may present with new or presumed new LBBB, although many such patients will not have an occluded culprit artery favouring PCI over thrombolysis. International guidelines[5,17] may vary in definitions,[54] with some having a more conservative response to LBBB.[54]

Neeland IJ, Kontos MC, de Lemos JA. Evolving considerations in the management of patients with left bundle branch block and suspected myocardial infarction. *J Am Coll Cardiol*. 2012;60(2):96–105.

'gold standard' for STEMI treatment and is far superior to non-reperfusion ('conservative') management. It should be considered for all patients presenting within 12 hours of STEMI onset.[2,18,60]

Both primary PCI and thrombolysis (fibrinolysis) are proven treatments with maximal benefit being achieved when performed early. Age is strongly related to mortality, often reflecting comorbid illness.[49,61] Underrepresentation of elderly in trials has left questions about best practice. Their large numbers (30% of ACS are >75 years) and high risk, identifies the elderly as a group where 'aggressive intervention' offers significant potential benefit.[61]

Reperfusion reduces infarct size, preserves LV function, reduces mortality and prolongs survival.[62] Strategies to achieve reperfusion can include:

- PCI (e.g. angioplasty, usually with stent insertion)
- thrombolytic (fibrinolytic) therapy
- urgent CABG.

Primary percutaneous coronary intervention[2,18,58,59]

- Primary PCI delivered in centres of excellence and without transfer delay, was far superior to thrombolysis, with reduced short-term mortality (5% vs. 7%), non-fatal re-infarction (3% vs. 7%) and stroke (1.0% vs. 2.0%). The combined trial endpoint of short-term mortality, non-fatal reinfarction and stroke was lower in the primary PCI group (8% vs. 14%)[63,64]
- Current data suggest that thrombolysis produces an ***absolute reduction*** in 30-day mortality of 4%, and that primary PCI is a further 1.5%–2% better.[60]
- Current data suggests thrombolysis has a 2% risk of stroke (number needed to harm, 50), and primary PCI technique a 1% risk of stroke.[60]

Emergency PCI can be divided into:

- primary PCI
- *rescue PCI* after failed thrombolysis.
- *pharmaco-invasive PCI* (thrombolysis with routine transfer to PCI centre for assessment)[65]

Immediate, urgent PCI when available in STEMI is strongly indicated in patients with:[18,33,59]

- presentation to cardiological centres of excellence
- contraindications to thrombolysis (e.g. bleeding risk) presentation greater than 12 hours
- uncertain diagnosis (e.g. pericarditis, LBBB)
- high-risk but predicted low benefit from thrombolytic therapy (e.g. elderly, diabetic and with presentation >3 hours)
- CS even up to 12–36 hours post MI[66]
- previous CABG.

Contraindications to primary PCI are uncommon, the major risk factor being complications from obligatory adjunctive antiplatelet or antithrombin therapy. Caution is needed in those at risk of contrast-associated renal failure.[62,67] Primary PCI is limited by the risk of abrupt vessel closure (early), and late thrombosis and stenosis. Coronary stenting reduces restenosis risk.[68]

Thrombolytic therapy

Thrombolytic therapy (in absence of contraindications) should be given to patients with STEMI and onset of ischaemic symptoms within the previous 12 hours when it is anticipated that primary PCI cannot be performed within 120 minutes of first medical contact (FMC).[2,18] Better outcomes from primary PCI have significantly decreased the percentage of people receiving thrombolysis, although in much of the world it remains a cost-effective and essential treatment.[65] Outcomes are critically dependent upon time from symptom onset ('The Golden Hour').

Thrombolytic agents (fibrinolytic agents)[69,70]

1. *Non–fibrin-specific:* these catalyse systemic fibrinolysis (e.g. streptokinase [SK]).
2. *Fibrin-specific:* these produce limited plasminogen conversion in the absence of fibrinogen. Current agents include alteplase (rt-PA), reteplase (r-PA) and tenecteplase (TNKase)

The above grouping is based on the *pharmacology* and physiology of agents. A historical grouping by *'generations'* outlines clinically driven need for agents to achieve best patient outcomes.

The ***first-generation*** fibrinolytic agent SK, formed complexes with plasminogen, releasing the protease

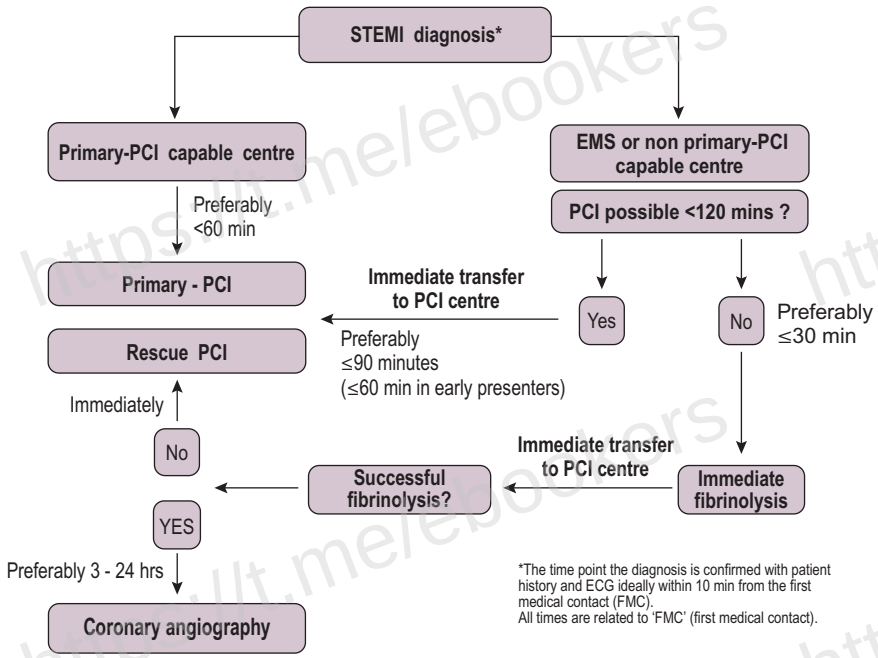


Figure 20.10 Pre-hospital and in-hospital management and reperfusion strategies within 24 hours of FMC. *Cath*, Catheterisation laboratory; *ECG*, electrocardiography; *EMS*, emergency medical system; *FMC*, first medical contact; *PCI*, percutaneous coronary intervention; *STEMI*, ST-segment elevation myocardial infarction. *(Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC).* Eur Heart J. *2012;33(20):2569–2619. doi:10.1093/eurheartj/ehs215. Modified with permission of Oxford University Press (UK) © European Society of Cardiology.)*

plasmin which created a systemic lytic state. 'Fresh' local coronary thrombus was lysed, significantly reducing mortality. Low systemic fibrinogen levels and a lytic state, however, were associated with a 0.6% incidence of lethal or disabling cerebral haemorrhage, which was higher in the elderly. SK became the agent against which newer ***second-generation* 'fibrin specific' agents,** provided more localised coronary artery clot lysis. Trials of rt-PA (alteplase) versus SK found a 1% mortality reduction (6.3% vs. 7.4%) at 30 days.[70] Outcomes were superior, but complex infusion rates and doses could be problematic. ***Third-generation*** agents have been trialled against the second-generation agents on a 'non-inferiority basis' to improve safety and efficacy. Reteplase and tenecteplase (TNKase) enjoy simpler administration, more fibrin specificity, less allergencity and more resistance to the plasminogen-activator inhibitor. The shorter duration of action of the fibrin-specific agents often requires early administration of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH).[18]

Major and minor contraindications are shown in Table 20.2.

Side-effects and choice of agent[18,62] Bleeding complications are the most serious thrombolysis complication. Approximately 1% of patients may suffer early cerebral haemorrhage but this figure can be 4% in high-risk populations. Risk factors are advanced age, significant admission systolic and diastolic hypertension, female gender, prior cerebrovascular disease and low weight. Major non-cerebral bleeds requiring transfusion or significant intervention may occur in 4%–13% of patients.

Failure to adjust the dose of fibrinolytic correctly to body weight may be associated with increased mortality and intracerebral haemorrhage. Guidelines outline similar caution with weight-based dosing of heparins.

PRIMARY PCI VERSUS THROMBOLYTIC THERAPY

Duration of symptoms, and time to achieve transfer, are critical.[62,71] Advantages of more reliable revascularisation from PCI can be lost if transfer is not expedient and if the delay is more than 60–120 minutes.[62,71] The importance of transfer for an individual patient will vary significantly depending upon the baseline risk. Many patients present to centres that do not offer primary PCI. Given the superiority of PCI over thrombolysis, transfer to such a centre has significant benefits.

- thrombolysis is a most effective treatment in patients with low bleeding risk and with arrival soon after symptom onset. Current outcomes from thrombolytic therapy in patients presenting early (≤3 hours post-onset), and PCI not on-site or immediately

Table 20.2 Contraindications and cautions for fibrinolytic use in myocardial infarction (advisory following clinical consideration)

ABSOLUTE	RELATIVE (ADVISORY FOLLOWING CLINICAL CONSIDERATION)
• Previous haemorrhagic stroke • Other stroke or cerebrovascular accident ≤6 months • Intracranial neoplasm • Active internal bleeding ≤2 weeks (menses excluded) • Aortic dissection, known or suspected	• Severe uncontrolled hypertension on presentation (≥180/110 mm Hg) • Oral anticoagulation therapy (INR >2.5); known bleeding diathesis • Recent major trauma, surgery (≤4 weeks) including head trauma • Previous allergic reaction to drug to be used • Traumatic CPR • Active peptic ulcer disease • Pregnancy • Recent streptokinase; use different agent (risk of allergy, antibodies may reduce effectiveness) • History of prior CVA or intracerebral pathology not covered in contraindications • Chronic hypertension

Specialist advice should be sought urgently where doubt exists and PCI is not available. Patients with contraindication may still benefit from urgent PCI and indeed it is usually the preferred option. PCI is generally the desired treatment in all of the above. *CPR*, Cardiopulmonary resuscitation; *CVA*, cerebrovascular accident; *INR*, international normalised ratio; *PCI*, percutaneous coronary intervention.

available, are very good as fresh clots seem more likely to be lysed.
- such benefits of thrombolysis are not present in those who present later (≥3 hours after symptom onset) or who have a high risk of bleeding or another contraindication to thrombolysis.[62,71]

Invasive strategy (PCI) is generally superior to thrombolysis if[33]:

- ineligible for thrombolytic therapy (see Table 20.2)
- CS or severe HF, Killip Class ≥3
- significant ventricular arrhythmias
- skilled PCI lab is immediately available with surgical back-up:
  - FMC-to-balloon or door-to-balloon is less than 90 minutes
  - door-to-balloon time minus door-to-needle time less than 60 minutes
- transfer can be achieved in less than 120 minutes and ideally less than 60 minutes
- diagnosis is uncertain (apical ballooning syndrome [ABS], myocarditis, aortic dissection)

Other indicators that transfer to an expert centre for PCI should be considered are:

- elevated risk from STEMI, advanced age[72]
- extensive anterior infarction with late presentation (symptom onset ≥3 hours)
- high risk of bleeding, symptom onset more than 3 hours
- previous MI or CABG

Thrombolysis may be preferred if[18,33,62]:

- transfer to a centre for primary PCI may be harmful to patients where:
  - early presentation (≤3 hours, delay to invasive strategy)
  - invasive strategy not available

COMBINATIONS OF TREATMENTS: THROMBOLYSIS AND PRIMARY PERCUTANEOUS CORONARY INTERVENTION[33,58,62,65,73,74]

In patients with failed thrombolysis, further thrombolysis is not beneficial and may cause harm.[75] Urgent transfer to a PCI centre is required, and **'rescue angioplasty'** has shown a significant, lower combined end-point of death, reinfarction and HF, but with bleeding risk.[2,18,60] Immediate, routine early PCI of all thrombolysed patients (<3 hours) could not guarantee benefit because of frequent bleeding. The transfer of all patients after thrombolysis, for reassessment and then 'optimally timed' PCI (usually within 3–24 hours or before discharge) on a case-by-case basis, is beneficial.[2,18,60,76] Trials of administration of reduced doses of thrombolytic or antithrombotic loading to 'facilitate' immediate PCI, have not shown benefit.[72,75,77–79] For patients with late onset CS, time frames for benefit from 'rescue PCI' may be extended.

ADJUNCTIVE THERAPY USED WITH REPERFUSION TREATMENTS (Fig. 20.11)[67,80]

Early adjunctive therapy is necessary with thrombolysis (and PCI) as at infusion completion, 50% of patients may not have TIMI 3 flow. Antithrombin agents facilitate ongoing 'catch-up' lysis and with antiplatelets, may decrease reocclusion of unstable arteries. The underlying coronary artery remains unstable during the following year, evidenced by angiographic reocclusion in 30% and recurrence of ischaemia in 20%.[80] Coronary arteries that have been dilated or stented, may similarly remain unstable. Immediate (early) adjunctive therapies are directed at platelet aggregation and coagulation pathways. Further therapies are directed at 'plaque stabilisation', myocardial ischaemia, and arrhythmias. Advances in adjunctive reperfusion therapies have been a major driver of outcome improvements.

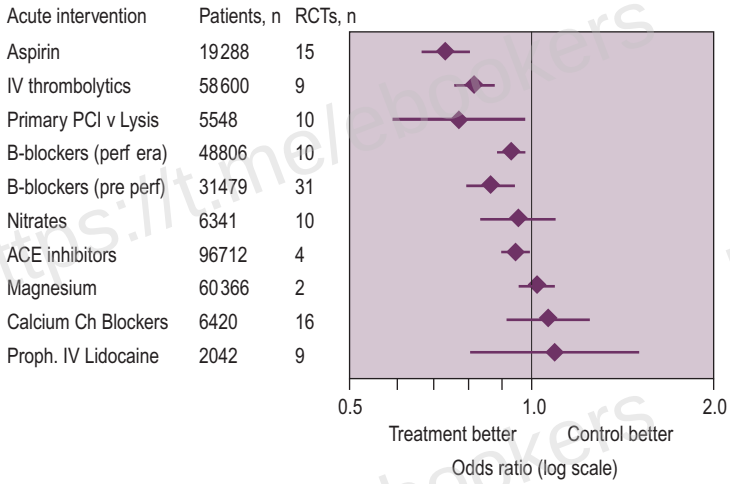


Figure 20.11 Effect of acute (early) adjunctive interventions upon mortality following MI. Results are from meta-analyses and various trials. Primary PCI has not been compared to placebo but offers superior results to thrombolysis when performed at centres within appropriate time frames. Beta blockers should only be used after exclusion of contraindications. Data graphing is indicative. *ACE*, Angiotensin-converting enzyme; *PCI*, percutaneous coronary intervention; *Proph.*, prophylactic; *RCT*, randomized controlled trial.

ASPIRIN[18,58,81,82]

Aspirin remains the most cost-effective short- and long-term treatment for STEMI and ACS. Unless contraindicated, aspirin should be administered to all patients with STEMI[2] and should be continued indefinitely.[2] In the Second International Study of Infarct survival (ISIS-2), aspirin reduced absolute mortality by 2.4% with ~50% RRR in re-infarction and stroke, and without an increase in cerebral haemorrhage or bleeds requiring transfusion.[55,83–85] Higher doses of aspirin do not provide better outcomes and may in fact be associated with higher event rates.[82,86]

Aspirin also benefits patients who have not, or cannot receive reperfusion therapy.[67] Aspirin allergic patients benefit from clopidogrel or prasugrel (avoid if the patient has had a previous transient ischaemic attack or cerebrovascular accident).

Despite the extreme value of aspirin there have been major advances in new agents and therapy.

DUAL ANTIPLATELET THERAPY[2,81,82,87]

The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) Trial[88] demonstrated the benefits of adding a second antiplatelet agent to aspirin (DAPT). The addition of clopidogrel to aspirin in USA and NSTEMI saw a 20% reduction in composite events, evident within 24 hours and continued over 12 months without prohibitive bleeding. Benefits of dual clopidogrel and aspirin have been demonstrated in STEMI patients undergoing PCI, and in thrombolysed STEMI patients, both with and without subsequent stenting.[82] The current standard of care for ACS patients includes aspirin and an ADP-receptor antagonist (subject to contraindications). Optimal agents and their duration are best chosen to balance the reduction of thrombotic and bleeding risks for individual patients.

Thus the agents used in combination with aspirin as part of DAPT may include:

A. ***Thienopyridines (e.g. clopidogrel, prasugrel, ticagrelor)***[81,87,89–91]: Oral $P2Y_{12}$ inhibitors are commonly used in DAPT, for all ACS patients during admission and for 12 months thereafter. Clopidogrel still has common use but slow onset of action (>6 hours, 3–5 days without dose loading) can be problematic if stent protection is not adequate. Prolonged half-life may increase bleeding if urgent CABG is required.[81] Prasugrel and ticagrelor have rapid and more reliable action, which favours their use in the setting of PCI; patients with high bleeding risk may need exclusion.[81,89,90]

B. ***Glycoprotein IIb/IIIa inhibitors (GPIs)***[2,5,18,60,90]: Abciximab, eptifibatide and tirofiban, developed prior to oral $P2Y_{12}$ inhibitors, were of critical importance during PCI and they still retain a role in complex lesions. Oral GPIs were disappointing with significant increases in bleeding and mortality. The safer profile of $P2Y_{12}$ inhibitors and suitability for long-term oral therapy has seen GPI use decline.

ANTITHROMBOTIC THERAPY AND NEW AGENTS[2,18,89]

Ruptured plaque activates thrombin. Antithrombin therapy is generally given in combination with fibrin-specific fibrinolytic agents. In the setting of primary or early PCI, antithrombin use is mandatory.

Four anticoagulants are currently used clinically (UFH, LMWH, bivalirudin and fondaparinux), in support of thrombolysis, PCI or their combination. Hospitals should have protocols reflecting international guidelines.

Thrombolysis[2,18] with fibrin-specific-agents requires anticoagulant therapy for at least 24–48 hours. Weight adjusted intravenous UFH may be preferred if PCI is likely. Otherwise LMWHs (e.g. enoxaparin) are preferred as reliable bioavailability removes the need for monitoring activated partial thromboplastin time. Meta-analyses suggest an advantage of enoxaparin to UFH, a lower composite end-point of death, non-fatal MI and cerebral haemorrhage, but with an increase in non-fatal bleeds.[92] Heparin-induced thrombotic thrombocytopaenia syndrome (HITTS) from previous or prolonged UFH can complicate UFH therapy.[62,92–94] LMWHs may need dose adjustment relating to age, bodyweight and renal function. Fondaparinux (pentasaccharide Factor Xa inhibitor) should not be used with PCI. Guideline recommendations and licencing for use can vary.

Primary PCI[2,18] requires 'heparin' (IV infusion or bolus dosing) prior to commencement. Agents and doses depend upon concurrent antiplatelet therapies (including GPIs), renal function, bleeding risk and stent. Intravenous loaded enoxaparin is superior to UFH in primary PCI,[18,95,96] but requires dosing adjustment for age and renal function. Bivalirudin (direct antithrombin inhibitor), is an alternative in primary PCI.[18,95] Fondaparinux is not recommended for primary PCI because of a peculiar problem of end-catheter thrombosis.[18,95]

BETA-BLOCKERS[2,18,58,97–100]

Pre-thrombolysis era trials demonstrated major benefit from early beta-blocker therapy (IV and oral), leading to their continued aggressive use. Post-thrombolysis trials of early use have demonstrated less benefit, and even harm.[2,33,58,97,99,100] Oral β-blockers should be started in all patients in the first 24 hours, subject to the absence of HF, impending shock, bradycardia, heart block or asthma.[2] In the Combination of Maintenance Methotrexate-Infliximab Trial (COMMIT),[97] early IV β-blocker therapy in MI had lower rates of recurrent MI and VF, but balanced higher rates of CS, especially on days 0 and 1,[2,97] STEMI patients undergoing primary PCI and without HF (echocardiography assisting) may benefit from cautious IV β-blockade.[101]

RENIN-ANGIOTENSIN ALDOSTERONE SYSTEM (RAAS) INHIBITORS[18]

RAAS inhibitors include angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs). Initial ACEI doses may cause hypotension, but early introduction post-STEMI (within the first 48 hours) is generally well tolerated and is associated with a small reduction in 30-day mortality, which is evident in the first week.[18] Early benefits are additive to β-blockade and antiplatelets.

OTHER THERAPIES

Nitrates may be beneficial for the treatment of recurrent angina, LVF and hypertension, but may be harmful if hypotension deters proven therapies such as ACEIs or β-blockers. Glucose–insulin–potassium therapies have not been shown to provide 'cardio-protection'.

COMPLICATIONS OF MYOCARDIAL INFARCTION

ARRHYTHMIAS[7,18,100,102] (See Chapter 22)

Arrhythmia management is discussed in detail in Chapter 22 and in modern international guidelines.[103] Post-MI arrhythmias are minimised by:

- rapid revascularisation and treatment of HF
- correct hypoxia, hypovolaemia and acid-base disturbances.
- maintain serum potassium in normal range (3.5–4.5 mmol/L) and magnesium (0.7–1.2 mmol/L).[103,104]

Rhythm disturbance is common during acute MI, especially around onset, and during reperfusion. This can include ventricular ectopy and transient tachyarrhythmias but most do not require intervention. (Ventricular tachycardia may occur in 6% of ACS in the first 48 hours.) There has been a steady decline in the incidence of VF, from approximately 4.5% to less than 2% of MI admissions.[105,106] Early β-blockers reduce the incidence of VF and are generally first-line therapy for the management of ventricular ectopy.[103] *Routine* lignocaine and magnesium have not demonstrated benefit.[7,33,103,107] When ventricular tachyarrhythmias require treatment, amiodarone and lignocaine are preferred to the class 1 agents.[102] Ventricular arrhythmias and ventricular ectopics beyond 48 hours indicate an at-risk patients needing full reassessment and likely electrophysiological studies to determine long-term management.[100,102]

POST-INFARCTION ANGINA AND RE-INFARCTION[18,25]

Angina (STEMI or NSTEMI) may occur at rest, or with minimal exertion in the 24 hours or more after MI. It is associated with increased mortality, and the reinfarction rate and can complicate MI after thrombolysis or PCI. Ischaemia may occur in the original infarct zone, or in a distant area when there is complex vessel disease. Pathology may include recurrent thrombus or vessel spasm. Tachycardia, hypertension, anaemia and fever should be corrected and aggressive treatment with antiplatelet agents, nitrates and β-blockers is indicated. The patient should be examined, angiography reviewed and repeat angiography reconsidered to exclude vessel (or stent) reocclusion. Echocardiography will assess LV function and possible mechanical complications. Refractory pain with ECG changes is indicative of high risk and is usually an indication for revascularisation.[2] Insertion of an intra-aortic balloon pump may help improve symptoms and minimise ischaemia, and may bridge for further PCI or CABG.

Table 20.3 Mechanical complications of myocardial infarction

	CVP	PAOP	CO	OTHER FINDINGS ON PAC	ECHOCARDIOGRAPHY
MECHANICAL COMPLICATIONS					
Free wall rupture	↑	↑	↓↓	Usually tamponade physiology: RA mean, RV and PA end-diastolic, and PAOP pressures are elevated and within 5 mm Hg (0.665 kPa) of one another	Pericardial effusion with tamponade and RV diastolic collapse; may visualise pseudoaneurysm
Acute ventricular septal defect	↑	↑	↓↓	Left-to-right shunt with oxygen step-up at RV level; V waves may be seen in PAOP tracing	Visualisation of left-to-right shunting with colour Doppler, can sometimes visualise defect as well
Acute mitral regurgitation	↑↑	↑↑	↓↓	V waves in PAOP tracing	Regurgitant jet apparent on colour Doppler; can diagnose papillary muscle rupture with flail leaflet
RV infarction	↑↑	↓ or normal	↓↓		RV dysfunction
Pump failure (cardiogenic shock)	↑↑	↑↑	↓↓		Decreased overall LV performance; regional wall motion abnormalities; dyskinetic or aneurysmal segments may be seen

Echocardiography has largely replaced the need for insertion of a pulmonary artery catheter although information for a PAC shown here is useful in understanding physiology. Coronary angiography and studies may be required to determine coronary anatomy and may provide additional data.
CO, Cardiac output; *CVP,* central venous pressure; *PA,* pulmonary artery; *PAC,* pulmonary artery catheterisation; *PAOP,* pulmonary artery occlusion pressure; *RA,* right atrium; *RV,* right ventricle.

Re-infarction in the 10 days following STEMI occurs in up to 5%–10% of patients.

CARDIAC FAILURE (See Chapter 24) AND CARDIOGENIC SHOCK (Table 20.3)[18,19,33,66,108–112]

LV dysfunction is the single strongest predictor of STEMI mortality. HF complicating a patient's first ACS hospitalisation ('Index HF') complicates 15% of STEMI and NSTEMI, presence rising to perhaps 25% at 1 year. In-hospital mortality is 15% compared with 3% in STEMI without HF.[112] Rates are higher in patients with previous MI. The Killip Classification documents simple bedside findings (Table 20.4)[18,109,113–115] to allow risk evaluation. Scores correlate strongly with LV function and prognosis at the time of hospitalisation.

Standard treatment for HF should include[18,108]:

- correct hypoxia, fluid balance control
- perform chest X-ray and define left ventricular ejection fraction (LVEF [Echo])
- mild HF symptoms (Killip II) require a dose of IV loop diuretics, a regular morning oral dose if necessary. Potassium-sparing diuretics, or supplements may prevent hypokalaemia. ACEI or ARB therapy (monitor potassium) should be commenced, especially if impaired LVEF or hypertension.
- In Killip Class III patients, titrate diuretics, consider oral or IV vasodilators, and also CPAP if respiratory distress is present. Avoid negative inotropes.

Table 20.4 Killip classification of severity of infarction based on clinical assessment and its correlation with hospital mortality in 1967[113] and 30-day mortality in 1993[115]

KILLIP CLASS		CASE FATALITY (%) KILLIP & KIMBALL[113]	GUSTO[115]
Class 1	No failure	6	5
Class 2	Mild to moderate heart failure (S3, rales <50% lung fields)	17	14
Class 3	Severe heart failure (S3, rales >50% lung fields)	38	32
Class 4	Cardiogenic shock	81	58

There is a strong correlation between the degree of left ventricular dysfunction and mortality in acute coronary syndrome.
Reproduced from Thompson P. *Coronary Care Manual*. 2nd ed. Sydney: Churchill Livingstone Australia; 2011, with permission.

CARDIOGENIC SHOCK[2,18,108,110,116–119]

CS is a state of inadequate tissue perfusion resulting from severe impairment of ventricular pump function in the presence of adequate intravascular volume. It is the leading cause of in-hospital STEMI mortality (40%–50%).[117,118] It may complicate 10% of STEMI but also 2%–5% of NSTEMI. Eighty per cent of cases result

from muscle necrosis and 10%–20% from MI structural disruption.[118] Late presentation or delayed reperfusion are major risk factors [117] and emergency revascularisation with PCI or emergency CABG is critical.[2,18,66,117]

The presence of shock is usually identified by[119]:

- SBP less than 90 mm Hg (11.97 kPa) or fall in mean arterial pressure 30 mm Hg below baseline
- cardiac index: less than 1.8 L/min/m^2 despite adequate filling pressures but without vasoactive drugs, or less than 2.0–2.2 L/min/m^2 with support.

Patients with CS or severe HF, or at high risk of these, should be urgently transferred to centres of excellence, regardless of time post-MI.[2,66] Improved outcomes in CS have resulted from primary PCI replacing thrombolysis, from 'rescue' of failed thrombolysis, and from PCI in NSTEMI, late onset shock. Mortality remains very high (55%–70%) in established cases, however, which is increasingly due to co-morbid illness in aging populations.[116]

CS is characterised by the failing of the heart and hypoperfused organs, initiating a vicious cycle of deterioration. Rigorous attention to all organ function is required.

- ***Reperfusion*** with PCI or CABG should always optimised. Many patients have greater than 75% stenosis of all three coronary arteries including the LAD, and 'stunned myocardium' may recover with revascularisation and support.[66,108]
- ***Respiratory assistance*** should maintain oxygenation, but also minimise cardiac demands of the work of breathing. While early intubation and mechanical ventilation is often undertaken, non-invasive ventilation (CPAP) is vital in both support and ventilator weaning (Chapter 37). Echo may monitor afterload and RV preload changes.[120,121]
- ***Haemodynamic management*** seeks to support coronary perfusion, cardiac output and organ perfusion, without increasing myocardial ischaemia.[118,119,122] The need for inotropy, vasodilation, vasoconstriction or their combination may guide therapy, although trial data are often lacking (see also Chapters 26 and 92).
- ***Mechanical cardiac support*** is of major importance and is increasingly recognised as superior to intra-aortic balloon counterpulsation, which lacks evidence of mortality benefit (see Chapter 41).
- ***Other treatments*** include seeking to maintain sinus rhythm or to 'regularise' atrial fibrillation, to consider dual chamber pacing where pacing is required, and to consider early renal support. Decision planning should always seek to involve the patient, especially where hospital discharge with good function is unlikely.

MITRAL REGURGITATION[2,33,116,118,123]

Transient 'functional' MR is common early after MI, as LV wall dysfunction or enlargement may cause subvalvular apparatus displacement and incomplete valve closure. This may be asymptomatic and silent (identified only on echocardiography in 30%). Severe MR and papillary rupture can complicate even small, 'confined MI' (50% of cases) but may not have a classical pan-systolic murmur and its presence should be sought with echocardiography in any patient with HF or shock, especially women. Incomplete chordae rupture is better tolerated haemodynamically. Posteromedial leaflet rupture is most frequent as its blood supply arises from a single coronary artery via the posterior descending coronary artery (from the right coronary artery or the circumflex coronary artery, depending upon dominance). The anterior-lateral papillary muscle has a dual blood supply but its single body or head is prone to complete rupture. A decrescendo systolic murmur may be present rather than the typical pan-systolic murmur of chronic MR.

The incidence of catastrophic MR has fallen with the introduction of primary PCI and thrombolytic therapy (1%–5% to <0.5%). It may occur early, often at days 1–4 post MI. It is usually lethal without surgery. Chronic MR can be a late complication of MI due to a combination of papillary muscle injury and ventricular remodelling. In the first instance it is best treated medically.[2]

CARDIAC RUPTURE[2,13,18,124,125]

Cardiac ruptures have fallen significantly in the PCI era and include:

- LV free wall rupture (0.5% of MI) causing tamponade, which is usually catastrophic. Subacute rupture is less common, may mimic re-infarction and have a classic 'to-and-fro' flow on echocardiography.
- Interventricular septal rupture has an incidence 0.2% in the PCI era.[125] Anterior and inferior MI are equally represented and single-vessel disease is not uncommon.[116] Patients usually rapidly develop shock and a loud systolic murmur[2] although initially the murmur may be soft with fewer symptoms. Echocardiography will help exclude mitral valve rupture. Progressive clinical deterioration is usual (untreated, mortality can be 50% at 1 week, 90% at 1 year) and requires urgent surgery in selected patients despite high mortality.[2] Better survival with later surgery may reflect selection bias. Some cases undergo percutaneous closure, usually as a bridge.[19]

SYSTEMIC EMBOLI[13,126–130]

Embolic ischaemic stroke were historically common occurring after large anterior MI (20%–55%).[127] Mural LV thrombus was frequent, often large, and strokes usually occurred early. The incidence has fallen dramatically due to primary PCI, adjuvant supportive treatments, and routine early echocardiography. Ischaemic strokes will occur with an incidence of approximately 2% in-hospital or by day 30, and up to

4% at 1 year. In-hospital mortality of ischaemic stroke can be 10%–20%.[126,127]

The highest risk of ischaemic stroke is in the first 6 months after MI and guidelines have led to early post MI 'prophylactic' anticoagulation where there is atrial fibrillation, or anterior wall mural thrombus, or the risk factor of decreased LVEF (<40%). Anticoagulation is normally continued long term for atrial fibrillation, and for 3–6 months with echo monitoring of LV mural thrombus cases. While guidelines support an indication for anticoagulation therapy because of impaired LVEF alone and without thrombus,[33] there are concerns that this does not provide benefit because of bleeding mortality.[129,130] Control of other cardiovascular risk factors is important as perhaps 50% of ischaemic strokes may not be cardioembolic.

POST-MYOCARDIAL INFARCTION INJURY SYNDROME (DRESSLER'S SYNDROME) AND PERICARDITIS[131]

A pericardial rub may develop 24–72 hours after large, usually anterior MI. Associated pain may mimic ischaemia, and biomarkers and echocardiography may be useful in excluding post-infarction angina. Dressler's syndrome is a later-presenting pericarditis (2–3 weeks after MI) thought to be an immunopathic response to myocardial necrosis. It is characterised by fever, pleuro pericardial pain and rub, arthralgia and elevated inflammatory markers, and can occasionally be recurrent. Treatment includes NSAIDs and occasionally, steroids. It is now very uncommon (<1%); fewer incidences are perhaps due to improved and earlier reperfusion, leading to smaller MIs.[131]

MANAGEMENT OF UNSTABLE ANGINA AND NSTEMI (NSTEACS)[7,25,45]

NSTEACS are now far more frequent than STEMI. Pathology is also secondary to platelet aggregation and thrombosis upon unstable plaque with elements of obstructive ischaemia, vasospasm and mircroembolisation.[25] Much acute adjuvant therapy is similar to STEMI, and secondary prevention is common to most ACS.

General principles of treatment are:

- immediate pharmacological relief of ischaemic symptoms
- immediate introduction of antiplatelet therapy, usually in conjunction with an antithrombin agent, to stabilise plaque white thrombus and prevent complete artery occlusion
- assess benefits of early invasive (PCI, vessel reopening) versus medical therapy.

Diverse causes of NSTEAC and frequent co-morbid disease, have required large trials to determine optimal interventions. Management benefits if the patients are stratified at presentation and after, into 'high risk', 'intermediate risk' and 'low risk' groups. Treatment decisions are clinically enhanced by the use of simple, validated scoring systems correlated with mortality and major adverse cardiac events (MACEs). A common system is the TIMI Risk Score for NSTEACS.[49,132]

PERCUTANEOUS CORONARY INTERVENTION AND STENTS[68,133]

PCI involves coronary artery angiography and balloon dilatation (angioplasty), now usually followed by 'stent' placement. Thrombosis from angioplasty or the presence of coronary stents requires procedural, and often long-term, antiplatelet therapy. Following angioplasty, recurrent stenosis (processes of 'pathological remodelling') was frequent,[68] initiating the development and use of bare metal stents (BMS). Although less frequent with BMS, stenosis ('neointimal inflammatory injury') was problematic (20%–30% of lesions).[68] Newer generation 'drug-eluting stents' have significantly decreased stenotic events, but have a need for often more intense or longer duration DAPT, which is problematic in patients at a high risk of bleeding. BMS thus still maintain a significant role. The ICU, in conjunction with other acute care teams, needs an understanding of the risk of stent complications where adjuvant treatment requires interruption. These can include bleeding from antiplatelet therapy and heparins, and stent thrombosis from their withdrawal.

EARLY INVASIVE VERSUS MEDICAL THERAPY IN NSTEACS[7,25]

Although medical therapy is introduced to all patients, review of ECG, biomarker changes and instability may guide the timing of PCI. Improved adjunctive agents (principally GP inhibitors) have led to the recognition that early PCI strategies can be associated with lower recurrent MI and mortality in many groups.

Risk stratification is integral to the management of patients with ACS. Scoring systems based on simple and rapidly available clinical and laboratory tests, help to guide therapy. The GRACE[5,47] and TIMI[45,49] risk scores for UA/NSTEMI predict both in-hospital and post-discharge, 6-month mortality. Emergent PCI is demonstrated to offer clinical benefit to patients with high-risk features such as elevated troponins, recurrent chest pain and recurrent ECG changes.

ANTI-ISCHAEMIC AGENTS

Initial therapy with oxygen is started if the patient is hypoxic; reassurance and analgesia is as described for all ACS.

- ***Nitrates sublingual*** may provide immediate symptom improvement, but infusions more effectively provide control of symptoms and ST segment

changes; however, data do not suggest a mortality benefit.[5,7]

- ***β-blockers***[7,134–136] should be started orally within 24 hours in patients without contraindications, but with caution. Guideline recommendations are presumed from STEMI data.[7] Risk factors for shock are common in the NSTEMI and STEMI population, and urgent therapy may cause harm in such patients. Intravenous β-blockade with monitoring in the acute setting may target specific goals (e.g. tachycardia, hypertension, ECG changes, pain).

Calcium channel blockers non-dihydropyridine agents (e.g. diltiazem or verapamil)[7,25] may provide symptom relief when β-blockers or nitrates are not tolerated, but LVF is a contraindication as cardiogenic shock may be precipitated. Combinations of calcium channel blockers and β-blocker are generally avoided. Short-acting nifedipine given in isolation may precipitate tachycardia and can be associated with increased mortality.[2]

ASPIRIN AND DUAL ANTIPLATELET THERAPY[7]

Treatment guidelines for acute, in-hospital use of aspirin and DAPT align closely with those of STEMI, and all patients without contraindications should commence DAPT regardless of whether an invasive procedure is planned or not. ADP-receptor inhibitors are a routine component of DAPT although GPIs may be administered during PCI.

ANTITHROMBINS AND ANTICOAGULANTS[4,5,25]

- Heparins are used acutely in NSTEACS to inhibit thrombin production or activity and decrease thrombus complications.[4,5] The addition of UFH to aspirin therapy produced a significant reduction in recurrent angina and subsequent MI.[25,137] LMWHs and UFH produce similar results (less difference than in STEMI)[137] but simplicity, a lack of need for monitoring and an acceptable safety profile may favour LMWH use – except perhaps where surgery is anticipated.
- Bivalirudin is an alternate anticoagulant treatment supporting early PCI. Fondaparinux if used during PCI risks end-catheter thrombosis.

ONGOING AND DISCHARGE CARE OF ACUTE CORONARY SYNDROMES (SECONDARY PREVENTION) (Fig. 20.12)

Many therapies have been studied in the long-term (secondary) treatment of ACS and have a strong evidence base. These treatments are very similar for STEMI and NSTEACS and may offer mortality and morbidity advantages for other atherothrombotic illnesses:

1. **Antiplatelet therapy. Aspirin**[2,7,84,87,138] should be continued life-long in all types of ACS and benefit has been still present at 10 years.[139] Low-dose aspirin (75–150 mg/day) is as effective as higher doses, which show no further benefit but are associated with increased bleeding.[138] DAPT is generally recommended for all ACS patients for 12 months, unless contraindicated. Longer duration DAPT, and a change in its nature should be determined on periodic review according to perceived balancing ischaemic and bleeding risks, and in accordance with

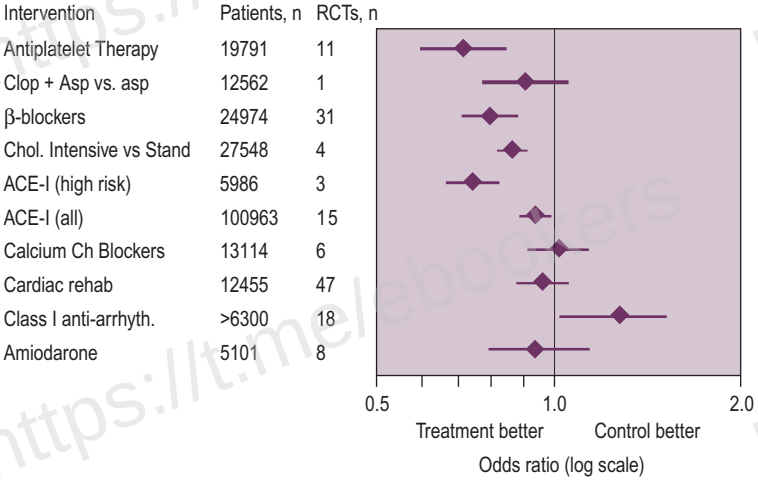


Figure 20.12 Late intervention in acute myocardial infarction. Effect of various secondary preventive treatments continued following hospital discharge. Results are from meta-analyses and various trials. Treatments may confer benefit for both STEMI and NSTEACS. DAPT benefit is dependent upon the presence and nature of stents as well as patient risk. Data graphing is indicative. *ACE-I*, Angiotensin-converting enzyme inhibitor; *Asp*, aspirin; *Calcium Ch blockers*, calcium channel blockers; *Chol Intensive*, intensive cholesterol lowering treatment; *Clop*, clopidogrel; *RCT*, randomized controlled trial.

international guidelines. Patients who discontinue aspirin despite high coronary risk, have a threefold risk of MACE, which is even higher when stents are in place.[140] Even patients who have been stable after 1 year have a high incidence of future atherothrombotic events[87] and aspirin benefits are still present at 10 years.

2. **β-blockers** historically have been recommended long term for all patients with ACS. Patients with impaired LV function (LVEF <40%) should continue long-term therapy. In asymptomatic patients with good LV function, guideline confidence levels supporting life-long therapy have fallen, perhaps due to the improvements from PCI, DAPT and ACE inhibitors. Thus such low-risk patients may derive little benefit from therapy and data suggest that where continued, lower daily doses may be as effective.[99,135,141]
3. ***Inhibitors of RAAS*** *(see Chapter 24):* Patients with anterior MI, and LVEF less than 40%, maintained on long-term ACE inhibitors may experience a sustained 20% RRR in mortality (additive to benefits of aspirin and β-blockers), and a significant reduction in the incidence of LVF.[18] Advantages may also extend to those with preserved LVEF but who are at risk of atherothrombotic disease because of concomitant hypertension, diabetes or chronic renal disease. In patients intolerant of ACE inhibitor(s), an ACE receptor blocker (ARB) may be used. Aldosterone antagonists are discussed in Chapter 24.
4. ***Lipid-lowering agents***[2,142–144]: ACS patients should commence a HMG-CoA reductase inhibitor, known as statins, in the first day after admission.[145–147] Early decreases in MACE may be due to plaque stabilisation rather than regression of stenoses. All ACS patients should continue long-term 'statin' therapy, mortality benefits being seen at 1 year. Statins reduce both vascular events and mortality, in primary and secondary settings, and benefits apply to both men and women.[143] Intensive statin therapy is superior to less-intensive lipid reduction (lower all-cause mortality)[148,149] and each 1.0 mmol/L reduction in LDL cholesterol may reduce major cardiovascular events (RRR) by 20%, major coronary events by 25%, need for coronary revascularisation by 25% and ischaemic stroke by just under 20%.[143] The benefit is maximal (and not confined only to myocardial events) in patients with elevated cholesterol and other risk factors, but the benefit is present at all cholesterol levels.

   Although statins are associated with a small risk of incidental Type 2 diabetes, this is outweighed by the reduced all-cause mortality.
5. ***Other anti-ischaemia agents*****:** Calcium channel blockers are of symptomatic use in patients intolerant of β-blockers or where there is a clinical need such as hypertension or arrhythmia but does not decrease recurrent MI or mortality.[18] Carvedilol may be of benefit in patients with ACS.
6. ***Antiarrhythmic therapy:*** Arrhythmias are discussed in Chapters 22 and 23, and in recent international guidelines.[103]
7. **Anticoagulants**[2,18,130,150]: Long-term anticoagulation is generally only indicated for specific indications. These might include atrial fibrillation, LV mural thrombus, history of embolic events, prosthetic heart valves or a prothrombotic tendency, and some with severe LV dysfunction. Increased use of DAPT has necessitated a review of INR targets, especially in the elderly. New oral anticoagulants (NOACs) have increasingly replaced warfarin, likely to continue as reversal agents improve safety.[150]
8. **Lifestyle advice:** All patients should be compliant with medication, cease smoking and receive advice on exercise and diet.[74] Tight control of blood pressure and blood sugar in diabetics is of high importance.[151] Regular medication review and confirmation of compliance are useful. A Cochrane meta-analysis found that exercise-based cardiac rehabilitation may be associated with improved outcomes.[152]

MYOCARDIAL INFARCTION IN THE INTENSIVE CARE UNIT[36,133,153–157]

MI is a common reason for admission to the ICU, often to facilitate acute management or to treat associated organ dysfunction. In patients managed acutely with STEMI or NSTEMI, primary PCI is the general treatment. Where possible, recognised guidelines should be applied.[2,5,18,60,65] However, critically ill patients are often not enrolled in clinical trials and co-morbid conditions in NSTEMI and STEMI admissions vary the risk–benefit of usual treatments. They often require continuous integrated team assessments, with further investigation and treatment on a case-by-case basis.

A difficulty in the management of 'general' ICU patients, is that cTN may be elevated in up to 40%–50%, including those with diagnoses of sepsis, pulmonary embolus and non-cardiac surgery (see Chapter 24 and Box 20.1). A presumption of ischaemic pathology ('oxygen mismatch'), would define these as Type 2 MI.[6,157] However, clinical evidence of ischaemia (voiced chest pain, ECG changes, RWMA) is often absent (perhaps in only 20% of cases) and they may now be considered as 'myocardial injury'.[156,157] Irrespective of the presence of ischaemic features, they are associated with increased early and later mortality that may often be 'non-cardiac'.[154–156] It is uncertain as to how treatment guidelines apply to such patients and how much cardiological follow-up is required. Carroll[36] indicates the value of patient team review and management with input of data from echocardiography and possible angiography. The known value of antiplatelet therapies in ACS suggests they should be introduced where possible with the support of stents following PCI on a risk–benefit judgement.

The need and nature of pre-operative investigation of high-risk surgical patients is also difficult. Data[158] in studies of major, non-cardiac surgery, found greater than 12% of patients had an elevated cTn level by post-op day 3. Mortality was 1% in patients with normal cTn but ranged from 4% to 16%, at day 30 in groups of patients in accordance with their day-3 elevation. Again, death causation was often 'non-cardiac'. Although only 50% of deaths were thought to be 'vascular', vascular investigation would seem appropriate to reduce mortality. Pre-operative exercise testing can identify patients with early positive tests, but it is unclear if revascularisation of low-risk disease patients will improve their outcomes if stent insertion requires perioperative interruption and then long-term continuation of antiplatelet therapy. Trials of perioperative beta-blockade, statin therapy or antiplatelet agents have often not shown any benefit.[159,160] Meta-analyses of statin therapy prior to CABG have not demonstrated any benefit.[161]

APICAL BALLOONING SYNDROME ('TAKOTSUBO SYNDROME')[28,29,162–165]

ABS presents with acute, reversible LV dysfunction, usually with chest pain, dyspnoea or syncope causing it to mimic an ACS (2% of such cases). Physical, pharmacological or emotional stresses may trigger 70% of cases. Up to 90% of cases occur in postmenopausal women and such cases may make up to 10% of this female demographic presenting with an initial ACS diagnosis. Biomarker or ECG changes (30% may have STE) generally necessitate coronary angiography to exclude MI, although by definition plaque rupture is absent.[28,29,164]

Echocardiography[35] reveals classical apical 'ballooning', with preserved basal contraction (the 'takotsubo' or 'Japanese octopus pot' appearance). This appearance results from a hypercontractile base of the heart with LV outflow tract obstruction, relative to a hypokinetic or akinetic apical and mid-LV ballooning myocardium; variants include a 'reverse takotsubo' appearance. The physiology of ABS is uncertain, but 'high levels of epinephrine' may paradoxically trigger cardiodepression,[166] which is most marked in apical regions because of a β_2-receptor gradient with high apical levels decreasing along the LV wall to the base.[29,165]

Major complications in severe ABS include hypotension, HF, CS, arrhythmia, LV thrombus and MR.[28] Acute mortality can be 2.4%–4.5%, and co-morbid illnesses are often the primary cause of death.[162,164] Annualised recurrence may be up to 1.5%.[164] Most cases of ABS improve with supportive treatment.[28,165] Echocardiography can help diagnose and assess response to therapy, and fluids should be administered to avoid hypovolaemia. In the presence of hypotension and shock, ideal inotropic therapy has not been defined. In severe shock, early mechanical support is often indicated as a 'bridge-to-recovery'.[28,165]

BLEEDING COMPLICATIONS AND ACUTE CORONARY SYNDROMES THERAPIES[150,167–170]

Hospital protocols and a multidisciplinary team response with skilled laboratories are required to plan major surgery and reverse major bleeding.[4,5,18,167,170,171] Treatment protocols for UFH, vitamin K antagonist and aspirin-related bleeding are generally known to clinicians.

1. **Antiplatelet agents and DAPT**[81,170]: Antiplatelet drugs have no specific reversal agents. In uncontrolled bleeding, platelets are administered and additional treatments may include DDAVP (desmopressin) and recombinant Factor VIIa (rFVIIa). The $P2Y_{12}$ oral medications have no specific 'antidotes' and treatment with these agents is also useful in this setting. The GPI abciximab can be associated with an early thrombocytopenia in 5% of patients, responsive to platelet transfusion and usually settling within a week. Tirofiban and eptifibatide have very short half-lives when renal function is normal, and antiplatelet action returns to normal 4–8 hours after discontinuation. While platelets are given, their effect is uncertain and with critical bleeding in vivo studies suggest that fresh frozen plasma (8 units) and platelets (2 units) may help reverse antiplatelet action.[171]
2. ***Antithrombins***[168]: UFH has historically been treated with dose-related protamine. Protamine treatment of LMWH is variable and incomplete, reversing perhaps only 60% of the LMWH with recommended doses. Protamine reverses 100% of the anti-IIa activity, but has far less effect on anti-Xa activity. With ongoing bleeding, rFVIIa is considered. Danaparoid, a heparinoid, is sometimes required in patients with HITTS. Its high anti-Xa/anti-IIa activity ratio168 of 20 renders it less likely to respond to protamine, and treatments have included plasmapheresis and high-dose rFVIIa. Fondaparinux has no specific antidote, but rFVIIa has been administered in severe bleeding.
3. ***Direct oral anticoagulants (DOACs)***[167,169]**:** These directly inhibit the coagulation cascade with a long-term safer profile than warfarin, but reversal of active bleeding has been extremely difficult. Dabigatran (a thrombin, Factor IIa binder) may be fully reversed by the recently licensed monoclonal antibody, idarucizumab, having been poorly responsive to cryoprecipitate, prothrombinex and rFVIIa.[150] Factor Xa inhibitors, rivaroxaban and apixaban, remain without effective reversal agents, although trials of 'decoy Factor Xa molecules' (recombinant, modified Factor Xa) that will bind to these factor agents, are encouraging.[150]
4. ***Fibrinolytic agents:*** Published studies for life-threatening bleeding have suggested large doses of cryoprecipitate (10–20 units), repletion of fibrinogen and coagulation factors (especially Factor VIII).

Fresh frozen plasma may supplement Factor V and VIII whilst platelet transfusions at high doses may replace platelets and supplement Factor V levels. ε-aminocaproic acid, loaded, followed by infusion has been suggested. Tranexamic acid might be useful.[167] Fibrinolytic reversal carries the risk of culprit coronary artery reocclusion.[171] Whilst publications may advise general advice, individual clinical scenarios and varying and multiple agents suggest considerable caution with overriding on-site multi-specialty input.

OUTCOME AFTER MYOCARDIAL INFARCTION

In-hospital mortality from MI has been steadily decreasing over the past three decades, from 15%–30% in the 1970s to approximately 10% in 1980, and now to around 8%–9% in the new millennium.[1,3–5,172] Thirty-seven per cent of the reduction of in-hospital mortality for STEMI and 21% of that for NSTEMI have been attributed to improvements in acute treatment.[1] Despite improved mortality, 60% of all deaths occur within the first hour (usually from VF) and often before reaching a medical facility.[4,5,64] Modern management of MI has undoubtedly contributed to decreased mortality. Further significant reductions in mortality must come from management strategies within the first hours of the onset of symptoms.

The most effective strategies to improve outcome are[1,18,172]:

- systems to deal with out-of-hospital VF arrest
- strategies to increase rates, and reduce time delays of PCI or thrombolysis in eligible patients
- optimise prescription and compliance with adjuvant and discharge medications.

Missed opportunities for reperfusion are a major problem. In one study, in-hospital mortality was 5.7% for those who received thrombolysis, but 14.8% for eligible patients who did not receive thrombolysis (mortality 9.3% vs. 18% in eligible women; 10.5% vs. 19% in eligible elderly). Up to 24% of eligible patients may not receive reperfusion therapy.[61,64,172,173] The role of early reperfusion and the provision of reperfusion therapy for all eligible persons, with ongoing life-long adjunctive managements, cannot be underestimated.

KEY REFERENCES

5. Roffi M, Patrono C, Collet JP, et al. [2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)]. *G Ital Cardiol (Rome)*. 2016; 17(10):831–872.
6. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33(20):2551–2567.
8. Boudoulas KD, Triposciadis F, Geleris P, et al. Coronary atherosclerosis: pathophysiologic basis for diagnosis and management. *Prog Cardiovasc Dis*. 2016;58(6):676–692.
17. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39(2):119–177.
26. Pollak P, Brady W. Electrocardiographic patterns mimicking ST segment elevation myocardial infarction. *Cardiol Clin*. 2012;30(4):601–615.
28. Lyon AR, Bossone E, Schneider B, et al. Current state of knowledge on Takotsubo syndrome: a position statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2016;18(1):8–27.
35. Lancellotti P, Price S, Edvardsen T, et al. The use of echocardiography in acute cardiovascular care: recommendations of the European Association of Cardiovascular Imaging and the Acute Cardiovascular Care Association. *Eur Heart J Cardiovasc Imaging*. 2015;16(2):119–146.
50. Husted S. Antithrombotic therapy for long-term secondary prevention of acute coronary syndrome in high-risk patients. *Ther Clin Risk Manag*. 2015;11:263–277.
54. Bainey KR, Armstrong PW. Transatlantic comparison of ST-segment elevation myocardial infarction guidelines: insights from the United States and Europe. *J Am Coll Cardiol*. 2016;67(2):216–229.
60. Chew DP, Scott IA, Cullen L, et al. National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016. *Heart Lung Circ*. 2016; 25(9):895–951.
81. Angiolillo DJ. The evolution of antiplatelet therapy in the treatment of acute coronary syndromes: from aspirin to the present day. *Drugs*. 2012;72(16):2087–2116.
133. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e326S–e350S.
167. Christos S, Naples R. Anticoagulation reversal and treatment strategies in major bleeding: update 2016. *West J Emerg Med*. 2016;17(3):264–270.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation*. 2017;135(10):e146–e603.
2. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127(4):e362–e425.
3. Montalescot G, Dallongeville J, Van Belle E, et al. STEMI and NSTEMI: are they so different? 1 year outcomes in acute myocardial infarction as defined by the ESC/ACC definition (the OPERA registry). *Eur Heart J*. 2007;28(12):1409–1417.
4. Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32(23):2999–3054.
5. Roffi M, Patrono C, Collet JP, et al. [2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)]. *G Ital Cardiol (Rome)*. 2016;17(10):831–872.
6. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33(20):2551–2567.
7. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64(24):e139–e228.
8. Boudoulas KD, Triposciadis F, Geleris P, et al. Coronary atherosclerosis: pathophysiologic basis for diagnosis and management. *Prog Cardiovasc Dis*. 2016;58(6):676–692.
9. Canto JG, Kiefe CI, Rogers WJ, et al. Number of coronary heart disease risk factors and mortality in patients with first myocardial infarction. *JAMA*. 2011;306(19):2120–2127.
10. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B):2960–2984.
11. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387(10022):957–967.
12. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289(19):2560–2572.
13. Burke AP, Virmani R. Pathophysiology of acute myocardial infarction. *Med Clin North Am*. 2007;91(4):553–572, ix.
14. Ghaffari S, Erfanparast S, Separham A, et al. The relationship between coronary artery movement type and stenosis severity with acute myocardial infarction. *J Cardiovasc Thorac Res*. 2013;5(2):41–44.
15. Fearon WF. Is a myocardial infarction more likely to result from a mild coronary lesion or an ischemia-producing one? *Circ Cardiovasc Interv*. 2011;4(6):539–541.
16. Canto AJ, Kiefe CI, Goldberg RJ, et al. Differences in symptom presentation and hospital mortality according to type of acute myocardial infarction. *Am Heart J*. 2012;163(4):572–579.
17. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39(2):119–177.
18. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). *Eur Heart J*. 2012;33(20):2569–2619.
19. Goldstein JA. Acute right ventricular infarction. *Cardiol Clin*. 2012;30(2):219–232.
20. Nikus K, Pahlm O, Wagner G, et al. Electrocardiographic classification of acute coronary syndromes: a review by a committee of the International Society for Holter and Non-Invasive Electrocardiology. *J Electrocardiol*. 2010;43(2):91–103.
21. Wagner GS, Macfarlane P, Wellens H, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part VI: acute ischemia/infarction: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. *Circulation*. 2009;119(10):e262–e270.
22. Nikus K, Birnbaum Y, Eskola M, et al. Updated electrocardiographic classification of acute coronary syndromes. *Curr Cardiol Rev*. 2014;10(3):229–236.

23. Birnbaum Y, Wilson JM, Fiol M, et al. ECG diagnosis and classification of acute coronary syndromes. *Ann Noninvasive Electrocardiol*. 2014;19(1):4–14.
24. IJkema B, Bonnier J, Schoors D, et al. Role of the ECG in initial acute coronary syndrome triage: primary PCI regardless presence of ST elevation or of non-ST elevation. *Neth Heart J*. 2014;22(11):484–490.
25. Anderson JL, Adams CD, Antman EM, et al. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011; 123(18):e426–e579.
26. Pollak P, Brady W. Electrocardiographic patterns mimicking ST segment elevation myocardial infarction. *Cardiol Clin*. 2012;30(4):601–615.
27. Nable JV, Lawner BJ. Chameleons: electrocardiogram imitators of ST-segment elevation myocardial infarction. *Emerg Med Clin North Am*. 2015; 33(3):529–537.
28. Lyon AR, Bossone E, Schneider B, et al. Current state of knowledge on Takotsubo syndrome: a position statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2016;18(1):8–27.
29. Ono R, Falcão LM. Takotsubo cardiomyopathy systematic review: pathophysiologic process, clinical presentation and diagnostic approach to Takotsubo cardiomyopathy. *Int J Cardiol*. 2016; 209:196–205.
30. Library E, Burns E. *LITFL ECG Library and clinical cases in cardiology [Internet]. LITFL • Life in the Fast Lane Medical Blog*. 2017. https://lifeinthefastlane.com/ecg-library.
31. Lawner BJ, Nable JV, Mattu A. Novel patterns of ischemia and STEMI equivalents. *Cardiol Clin*. 2012;30(4):591–599.
32. Ondrus T, Kanovsky J, Novotny T, et al. Right ventricular myocardial infarction: from pathophysiology to prognosis. *Exp Clin Cardiol*. 2013;18(1):27–30.
33. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol*. 2004;44(3):e1–e211.
34. Kaier TE, Twerenbold R, Puelacher C, et al. Direct comparison of cardiac myosin-binding protein C with cardiac troponins for the early diagnosis of acute myocardial infarction. *Circulation*. 2017;136(16):1495–1508.
35. Lancellotti P, Price S, Edvardsen T, et al. The use of echocardiography in acute cardiovascular care: recommendations of the European Association of Cardiovascular Imaging and the Acute Cardiovascular Care Association. *Eur Heart J Cardiovasc Imaging*. 2015;16(2):119–146.
36. Carroll I, Mount T, Atkinson D. Myocardial infarction in intensive care units: a systematic review of diagnosis and treatment. *J Intensive Care Soc*. 2016;17(4):314–325.
37. Stillman AE, Oudkerk M, Bluemke DB, et al. Assessment of acute myocardial infarction: current status and recommendations from the North American Society for Cardiovascular Imaging and the European Society of Cardiac Radiology. *Int J Cardiovasc Imaging*. 2010;27(1):7–24.
38. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. Developed in collaboration with the American College of Surgeons, American Society of Anesthesiologists, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Vascular Medicine Endorsed by the Society of Hospital Medicine. *J Nucl Cardiol*. 2015;22(1):162–215.
39. Wijeysundera DN, Beattie WS, Austin PC, et al. Non-invasive cardiac stress testing before elective major non-cardiac surgery: population based cohort study. *BMJ*. 2010;340.
40. Appleby P, Baigent C, Collins R, et al. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet*. 1994;343(8893):311.
41. Neeland IJ, Kontos MC, de Lemos JA. Evolving considerations in the management of patients with left bundle branch block and suspected myocardial infarction. *J Am Coll Cardiol*. 2012; 60(2):96–105.
42. Cai Q, Mehta N, Sgarbossa EB, et al. The left bundle-branch block puzzle in the 2013 ST-elevation myocardial infarction guideline: from falsely declaring emergency to denying reperfusion in a high-risk population. Are the Sgarbossa Criteria ready for prime time? *Am Heart J*. 2013;166(3):409–413.
43. Erne P, Iglesias JF, Urban P, et al. Left bundle-branch block in patients with acute myocardial infarction: presentation, treatment, and trends in outcome from 1997 to 2016 in routine clinical practice. *Am Heart J*. 2017;184:106–113.
44. Jain S, Ting HT, Bell M, et al. Utility of left bundle branch block as a diagnostic criterion

for acute myocardial infarction. *Am J Cardiol*. 2011;107(8):1111–1116.
45. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation. *Circulation*. 2000;102(17):2031–2037.
46. Amin ST, Morrow DA, Braunwald E, et al. Dynamic TIMI risk score for STEMI. *J Am Heart Assoc*. 2013;2(1):e003269.
47. Fox KAA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*. 2006;333(7578):1091–1094.
48. Wang TY, Zhang M, Fu Y, et al. Incidence, distribution, and prognostic impact of occluded culprit arteries among patients with non-ST-elevation acute coronary syndromes undergoing diagnostic angiography. *Am Heart J*. 2009;157(4):716–723.
49. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA*. 2000;284(7):835–842.
50. Husted S. Antithrombotic therapy for long-term secondary prevention of acute coronary syndrome in high-risk patients. *Ther Clin Risk Manag*. 2015;11:263–277.
51. Welsford M, Nikolaou NI, Beygui F, et al. Part 5: acute coronary syndromes: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation*. 2015;132 (16 suppl 1):S146–S176.
52. Cabello JB, Burls A, Emparanza JI, et al. Oxygen therapy for acute myocardial infarction. *Cochrane Database Syst Rev*. 2016;(12):CD007160, Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007160.pub4/abstract.
53. Hofmann R, James SK, Jernberg T, et al. Oxygen therapy in suspected acute myocardial infarction. *N Engl J Med*. 2017;377(13):1240–1249.
54. Bainey KR, Armstrong PW. Transatlantic comparison of ST-segment elevation myocardial infarction guidelines: insights from the United States and Europe. *J Am Coll Cardiol*. 2016;67(2):216–229.
55. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction. *Lancet*. 1988;2(8607): 349–360.
56. Abdikarim ABDI, Basgut B. An evidence-based review of pain management in acute myocardial infarction. *J Cardiol Clin Res*. 2016;4(4):1067.
57. Kearney PM, Baigent C, Godwin J, et al. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ*. 2006;332(7553):1302–1308.
58. Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction, Writing on Behalf of the 2004 Writing Committee. *Circulation*. 2008;117(2): 296–329.
59. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011;124(23):e574–e651.
60. Chew DP, Scott IA, Cullen L, et al. National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016. *Heart Lung Circ*. 2016; 25(9):895–951.
61. McCune C, McKavanagh P, Menown IB. A review of current diagnosis, investigation, and management of acute coronary syndromes in elderly patients. *Cardiol Ther*. 2015;4(2):95–116.
62. Boden WE, Eagle K, Granger CB. Reperfusion strategies in acute ST-segment elevation myocardial infarction: a comprehensive review of contemporary management options. *J Am Coll Cardiol*. 2007;50(10):917–929.
63. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet*. 2003;361(9351):13–20.
64. Keeley EC, Hillis LD. Primary PCI for myocardial infarction with ST-segment elevation. *N Engl J Med*. 2007;356(1):47–54.
65. Dalal JJ, Alexander T, Banerjee PS, et al. 2013 consensus statement for early reperfusion and pharmaco-invasive approach in patients presenting with chest pain diagnosed as STEMI (ST elevation myocardial infarction) in an Indian setting. *J Assoc Physicians India*. 2014;62(6):473–483.
66. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. *JAMA*. 2006;295(21):2511–2515.
67. Cohen M, Boiangiu C, Abidi M. Therapy for ST-segment elevation myocardial infarction patients who present late or are ineligible for reperfusion therapy. *J Am Coll Cardiol*. 2010;55(18): 1895–1906.

68. Simard T, Hibbert B, Ramirez FD, et al. The evolution of coronary stents: a brief review. *Can J Cardiol*. 2014;30(1):35–45.
69. Brouwer MA, Clappers N, Verheugt FW. Adjunctive treatment in patients treated with thrombolytic therapy. *Heart*. 2004;90(5):581–588.
70. Ellis SG. New fibrinolytics. *Clev Clin J Med*. 2004;71(1):20–37.
71. Ting HH, Yang EH, Rihal CS. Narrative review: reperfusion strategies for ST-segment elevation myocardial infarction. *Ann Intern Med*. 2006; 145(8):610–617.
72. Alexander KP, Newby LK, Armstrong PW, et al. Acute coronary care in the elderly, part II: ST-segment-elevation myocardial infarction: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. *Circulation*. 2007; 115(19):2570–2589.
73. Rashid MK, Guron N, Bernick J, et al. Safety and efficacy of a pharmacoinvasive strategy in ST-segment elevation myocardial infarction. A patient population study comparing a pharmacoinvasive strategy with a primary percutaneous coronary intervention strategy within a regional system. *JACC Cardiovasc Interv*. 2016;9(19): 2014–2020.
74. Wallentin L, Kristensen SD, Anderson JL, et al. How can we optimize the processes of care for acute coronary syndromes to improve outcomes? *Am Heart J*. 2014;168(5):622–631.
75. Collet JP, Montalescot G, Le May M, et al. Percutaneous coronary intervention after fibrinolysis: a multiple meta-analyses approach according to the type of strategy. *J Am Coll Cardiol*. 2006;48(7):1326–1335.
76. Madan M, Halvorsen S, Di Mario C, et al. Relationship between time to invasive assessment and clinical outcomes of patients undergoing an early invasive strategy after fibrinolysis for ST-segment elevation myocardial infarction: a patient-level analysis of the randomized early routine invasive clinical trials. *JACC Cardiovasc Interv*. 2015;8(1 Pt B):166–174.
77. Capodanno D, Dangas G. Facilitated/pharmacoinvasive approaches in STEMI. *Curr Cardiol Rev*. 2012;8(3):177–180.
78. Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. *Lancet*. 2006;367(9510):579–588.
79. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet*. 2006;367(9510):569–578.
80. Verheugt FW, Clemmensen P, Mehran R, et al. Antithrombotic outcome trials in acute coronary syndromes: seeking the optimal balance between safety and efficacy. *Eur Heart J*. 2013;34(22):1621–1629.
81. Angiolillo DJ. The evolution of antiplatelet therapy in the treatment of acute coronary syndromes: from aspirin to the present day. *Drugs*. 2012;72(16):2087–2116.
82. Singh M, Bhatt DL, Stone GW, et al. Antithrombotic approaches in acute coronary syndromes: optimizing benefit vs bleeding risks. *Mayo Clin Proc*. 2016;91(10):1413–1447.
83. Collins R, Peto R, Baigent C, et al. Aspirin, heparin, and fibrinolytic therapy in suspected acute myocardial infarction. *N Engl J Med*. 1997; 336(12):847–860.
84. Awtry EH, Loscalzo J. Aspirin. *Circulation*. 2000; 101(10):1206–1218.
85. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324(7329):71–86.
86. The CURRENT–OASIS 7 Investigators. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med*. 2010;363(10): 930–942.
87. Cavallari I, Bonaca MP. Antiplatelet therapy for secondary prevention after acute myocardial infarction. *Interv Cardiol Clin*. 2017;6(1):119–129.
88. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345(7):494–502.
89. Franchi F, Rollini F, Angiolillo DJ. Antithrombotic therapy for patients with STEMI undergoing primary PCI. *Nat Rev Cardiol*. 2017;14(6):361–379.
90. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;68(10):1082–1115.
91. Kereiakes DJ, Yeh RW, Massaro JM, et al. DAPT score utility for risk prediction in patients with or without previous myocardial infarction. *J Am Coll Cardiol*. 2016;67(21):2492–2502.
92. Murphy SA, Gibson CM, Morrow DA, et al. Efficacy and safety of the low-molecular weight heparin enoxaparin compared with unfractionated heparin across the acute coronary syndrome spectrum: a meta-analysis. *Eur Heart J*. 2007;28(17):2077–2086.
93. Eikelboom JW, Quinlan DJ, Mehta SR, et al. Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction: a meta-analysis of the randomized trials. *Circulation*. 2005;112(25):3855–3867.

94. Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med*. 2006;354(14):1477–1488.
95. Silvain J, Beygui F, Barthelemy O, et al. Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. *BMJ*. 2012;344:e553.
96. Montalescot G, Zeymer U, Silvain J, et al. Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: the international randomised open-label ATOLL trial. *Lancet*. 2011;378(9792):693–703.
97. Chen ZM, Jiang LX, Chen YP, et al. Early intravenous then oral metoprolol in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366(9497): 1622–1632.
98. Chatterjee S, Chaudhuri D, Vedanthan R, et al. Early intravenous beta-blockers in patients with acute coronary syndrome—a meta-analysis of randomized trials. *Int J Cardiol*. 2013; 168(2):915–921.
99. Kezerashvili A, Marzo K, Leon JD. Beta blocker use after acute myocardial infarction in the patient with normal systolic function: when is it "Ok" to discontinue? *Curr Cardiol Rev*. 2012;8(1):77–84.
100. Arshad A, Mandava A, Kamath G, et al. Sudden cardiac death and the role of medical therapy. *Prog Cardiovasc Dis*. 2008;50(6):420–438.
101. Elgendy IY, Elgendy AY, Mahmoud AN, et al. Intravenous β-blockers for patients undergoing primary percutaneous coronary intervention: a meta-analysis of randomized trials. *Int J Cardiol*. 2016;223:891–897.
102. Gorenek B, Blomstrom Lundqvist C, Brugada Terradellas J, et al. Cardiac arrhythmias in acute coronary syndromes: position paper from the joint EHRA, ACCA, and EAPCI task force. *EuroIntervention*. 2015;10(9):1095–2108.
103. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J*. 2015;36(41):2793–2867.
104. Goyal A, Spertus JA, Gosch K, et al. Serum potassium levels and mortality in acute myocardial infarction. *JAMA*. 2012;307(2):157–164.
105. Goldberg RJ, Yarzebski J, Spencer FA, et al. Thirty-year trends (1975-2005) in the magnitude, patient characteristics, and hospital outcomes of patients with acute myocardial infarction complicated by ventricular fibrillation. *Am J Cardiol*. 2008;102(12):1595–1601.
106. Bougouin W, Marijon E, Puymirat E, et al. Incidence of sudden cardiac death after ventricular fibrillation complicating acute myocardial infarction: a 5-year cause-of-death analysis of the FAST-MI 2005 registry. *Eur Heart J*. 2014;35(2):116–122.
107. Marti-Carvajal AJ, Simancas-Racines D, Anand V, et al. Prophylactic lidocaine for myocardial infarction. *Cochrane Database Syst Rev*. 2015; (8):CD008553.
108. Kumar A. Hemodynamically complicated ST-segment elevation myocardial infarction: presentation and treatment. *Future Cardiol*. 2010;6(5): 591–602.
109. Khot UN, Jia G, Moliterno DJ, et al. Prognostic importance of physical examination for heart failure in non-ST-elevation acute coronary syndromes: the enduring value of Killip classification. *JAMA*. 2003;290(16):2174–2181.
110. Kalavrouziotis D, Rodes-Cabau J, Mohammadi S. Moving beyond SHOCK: new paradigms in the management of acute myocardial infarction complicated by cardiogenic shock. *Can J Cardiol*. 2017;33(1):36–43.
111. Rihal CS, Naidu SS, Givertz MM, et al. 2015 SCAI/ACC/HFSA/STS clinical expert consensus statement on the use of percutaneous mechanical circulatory support devices in cardiovascular care: endorsed by the American Heart Assocation, the Cardiological Society of India, and Sociedad Latino Americana de Cardiologia Intervencion; Affirmation of Value by the Canadian Association of Interventional Cardiology-Association Canadienne de Cardiologie d'intervention. *J Am Coll Cardiol*. 2015;65(19):e7–e26.
112. Kaul P, Ezekowitz JA, Armstrong PW, et al. Incidence of heart failure and mortality after acute coronary syndromes. *Am Heart J*. 2013;165(3): 379–385, e2.
113. Killip T 3rd, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol*. 1967; 20(4):457–464.
114. Thompson P. *Coronary Care Manual*. 2nd ed. Sydney: Churchill Livingstone Australia; 2011.
115. Lee KL, Woodlief LH, Topol EJ, et al. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. GUSTO-I Investigators. *Circulation*. 1995;91(6):1659–1668.
116. Ng R, Yeghiazarians Y. Post myocardial infarction cardiogenic shock: a review of current therapies. *J Intensive Care Med*. 2013;28(3):151–165.
117. Westaby S, Kharbanda R, Banning AP. Cardiogenic shock in ACS. Part 1: prediction, presentation and medical therapy. *Nat Rev Cardiol*. 2012; 9(3):158–171.
118. Thiele H, Ohman EM, Desch S, et al. Management of cardiogenic shock. *Eur Heart J*. 2015;36(20): 1223–1230.

119. Nativi-Nicolau J, Selzman CH, Fang JC, et al. Pharmacologic therapies for acute cardiogenic shock. *Curr Opin Cardiol*. 2014;29(3):250–257.
120. Hongisto M, Lassus J, Tarvasmaki T, et al. Use of noninvasive and invasive mechanical ventilation in cardiogenic shock: a prospective multicenter study. *Int J Cardiol*. 2017;230:191–197.
121. Ho KM, Wong K. A comparison of continuous and bi-level positive airway pressure non-invasive ventilation in patients with acute cardiogenic pulmonary oedema: a meta-analysis. *Crit Care*. 2006; 10(2):R49.
122. Tharmaratnam D, Nolan J, Jain A. Management of cardiogenic shock complicating acute coronary syndromes. *Heart*. 2013;99(21):1614–1623.
123. Lung B. Management of ischaemic mitral regurgitation. *Heart*. 2003;89(4):459–464.
124. Pasotti M, Prati F, Arbustini E. The pathology of myocardial infarction in the pre- and post-interventional era. *Heart*. 2006;92(11):1552–1556.
125. Jones BM, Kapadia SR, Smedira NG, et al. Ventricular septal rupture complicating acute myocardial infarction: a contemporary review. *Eur Heart J*. 2014;35(31):2060–2068.
126. Di Tullio MR, Homma S. Mechanisms of cardioembolic stroke. *Curr Cardiol Rep*. 2002;4(2):141–148.
127. Hornung M, Franke J, Gafoor S, et al. Cardioembolic stroke and postmyocardial infarction stroke. *Cardiol Clin*. 2016;34(2):207–214.
128. Yaghi S, Pilot M, Song C, et al. Ischemic stroke risk after acute coronary syndrome. *J Am Heart Assoc*. 2016;5(7).
129. Font MÀ, Krupinski J, Arboix A. Antithrombotic medication for cardioembolic stroke prevention. *Stroke Res Treat*. 2011;2011:607852.
130. Shavadia JS, Youngson E, Bainey KR, et al. Outcomes and prognostic impact of prophylactic oral anticoagulation in anterior ST-segment elevation myocardial infarction patients with left ventricular dysfunction. *J Am Heart Assoc*. 2017;6(7):e006054.
131. Adler Y, Charron P, Imazio M, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: the task force for the diagnosis and management of pericardial diseases of the European Society of Cardiology (ESC) Endorsed by: the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2015;36(42):2921–2964.
132. Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA*. 2004;291(22):2727–2733.
133. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e326S–e350S.
134. Freemantle N, Cleland J, Young P, et al. Beta blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ*. 1999;318(7200):1730–1737.
135. Bangalore S, Makani H, Radford M, et al. Clinical outcomes with beta-blockers for myocardial infarction: a meta-analysis of randomized trials. *Am J Med*. 2014;127(10):939–953.
136. Kontos MC, Diercks DB, Ho PM, et al. Treatment and outcomes in patients with myocardial infarction treated with acute β-blocker therapy: results from the American College of Cardiology's NCDR. *Am Heart J*. 2011;161(5):864–870.
137. Eikelboom JW, Anand SS, Malmberg K, et al. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet*. 2000;355(9219): 1936–1942.
138. Berger JS. Aspirin, clopidogrel, and ticagrelor in acute coronary syndromes. *Am J Cardiol*. 2013; 112(5):737–745.
139. Baigent C, Collins R, Appleby P, et al. ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. The ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *BMJ*. 1998;316(7141):1337–1343.
140. Biondi-Zoccai GG, Lotrionte M, Agostoni P, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. *Eur Heart J*. 2006;27(22):2667–2674.
141. Goldberger JJ, Bonow RO, Cuffe M, et al. Effect of beta-blocker dose on survival after acute myocardial infarction. *J Am Coll Cardiol*. 2015;66(13):1431–1441.
142. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet*. 2016;388(10059):2532–2561.
143. Fulcher J, O'Connell R, Voysey M, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet*. 2015;385(9976):1397–1405.
144. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B):2889–2934.
145. Olsson AG, Schwartz GG. Early initiation of treatment with statins in acute coronary syndromes. *Ann Med*. 2002;34(1):37–41.
146. Cannon CP, Steinberg BA, Murphy SA, et al. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol*. 2006;48(3):438–445.
147. Angeli F, Reboldi G, Mazzotta G, et al. Statins in acute coronary syndrome: very early initia-

tion and benefits. *Ther Adv Cardiovasc Dis*. 2012; 6(4):163–174.
148. Gibson CM, Pride YB, Hochberg CP, et al. Effect of intensive statin therapy on clinical outcomes among patients undergoing percutaneous coronary intervention for acute coronary syndrome. PCI-PROVE IT: a PROVE IT-TIMI 22 (pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction 22) Substudy. *J Am Coll Cardiol*. 2009;54(24):2290–2295.
149. Serruys PW, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;287(24):3215–3222.
150. Reiffel JA, Weitz JI, Reilly P, et al. NOAC monitoring, reversal agents, and post-approval safety and effectiveness evaluation: a cardiac safety research consortium think tank. *Am Heart J*. 2016; 177:74–86.
151. Chew DP, Huynh LT, Liew D, et al. Potential survival gains in the treatment of myocardial infarction. *Heart*. 2009;95(22):1844–1850.
152. Anderson L, Oldridge N, Thompson DR, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Systematic Review and Meta-Analysis. *J Am Coll Cardiol*. 2016;67(1):1–12.
153. Dai X, Bumgarner J, Spangler A, et al. Acute ST-elevation myocardial infarction in patients hospitalized for noncardiac conditions. *J Am Heart Assoc*. 2013;2(2):e000004.
154. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators, Devereaux PJ, Chan MT, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA*. 2012;307(21):2295–2304.
155. Botto F, Alonso-Coello P, Chan MT, et al. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *Anesthesiology*. 2014;120(3):564–578.
156. Ostermann M, Lo J, Toolan M, et al. A prospective study of the impact of serial troponin measurements on the diagnosis of myocardial infarction and hospital and six-month mortality in patients admitted to ICU with non-cardiac diagnoses. *Crit Care*. 2014;18(2):R62.
157. Sandoval Y, Thygesen K. Myocardial infarction type 2 and myocardial injury. *Clin Chem*. 2017;63(1):101.
158. Devereaux PJ, Chan MT, Alonso-Coello P, et al. *JAMA*. 2012;307(21):2295–2304.
159. Devereaux PJ, Mrkobrada M, Sessler DI, et al. Aspirin in patients undergoing noncardiac surgery. *N Engl J Med*. 2014;370(16):1494–1503.
160. Wijeysundera DN, Duncan D, Nkonde-Price C, et al. Perioperative beta blockade in noncardiac surgery: a systematic review for the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol*. 2014;64(22):2406–2425.
161. Putzu A, Capelli B, Belletti A, et al. Perioperative statin therapy in cardiac surgery: a meta-analysis of randomized controlled trials. *Crit Care*. 2016;20(1): 395.
162. Deshmukh A, Kumar G, Pant S, et al. Prevalence of Takotsubo cardiomyopathy in the United States. *Am Heart J*. 2012;164(1):66–71.e1.
163. Yoshikawa T. Takotsubo cardiomyopathy, a new concept of cardiomyopathy: clinical features and pathophysiology. *Int J Cardiol*. 2015;182:297–303.
164. Akashi YJ, Nef HM, Lyon AR. Epidemiology and pathophysiology of Takotsubo syndrome. *Nat Rev Cardiol*. 2015;12(7):387–397.
165. Milinis K, Fisher M. Takotsubo cardiomyopathy: pathophysiology and treatment. *Postgrad Med J*. 2012;88(1043):530–538.
166. Paur H, Wright PT, Sikkel MB, et al. High levels of circulating epinephrine trigger apical cardiodepression in a β2-adrenergic receptor/Gi-dependent manner: a new model of Takotsubo cardiomyopathy. *Circulation*. 2012;126(6):697–706.
167. Christos S, Naples R. Anticoagulation reversal and treatment strategies in major bleeding: update 2016. *West J Emerg Med*. 2016;17(3):264–270.
168. Makris M, Van Veen JJ, Tait CR, et al. Guideline on the management of bleeding in patients on antithrombotic agents. *Br J Haematol*. 2013;160(1): 35–46.
169. Tummala R, Kavtaradze A, Gupta A, et al. Specific antidotes against direct oral anticoagulants: a comprehensive review of clinical trials data. *Int J Cardiol*. 2016;214:292–298.
170. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2017;39(3):213–260.
171. Schroeder WS, Gandhi PJ. Emergency management of hemorrhagic complications in the era of GP IIb/IIIa receptor antagonists, clopidogrel, low molecular weight heparin, and third-generation fibrinolytic agents. *Curr Cardiol Rep*. 2003; 5(4):310–317.
172. Mandelzweig L, Battler A, Boyko V, et al. The second Euro Heart Survey on acute coronary syndromes: characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. *Eur Heart J*. 2006;27(19):2285–2293.
173. Newell MC, Henry JT, Henry TD, et al. Impact of age on treatment and outcomes in ST-elevation myocardial infarction. *Am Heart J*. 2011;161(4):664–672.

21

Cardiopulmonary resuscitation (including defibrillation)

Peter Thomas Morley

Cardiac arrest is the feared end point of the deteriorating patient. In many situations this is an anticipated and inevitable conclusion of a fatal illness. However, the appropriate management of cardiac arrest does dramatically alter its natural history. Over the past decade there have been improvements in cardiac arrest outcomes in both the in-hospital[1] and out-of-hospital settings.[2,3] There are many potential reasons for these improvements, but the most likely are related to incremental improvements in the management during and after the arrest.[3] The last decade has also seen a large number of randomised controlled trials conducted in the techniques for managing the victims of cardiac arrests, and many more are in the pipeline.[4]

PREVALENCE AND OUTCOMES OF CARDIAC ARRESTS

Cardiac arrests in the community occur at approximately 50–160/100, 000 person years.[5,6]

In-hospital cardiac arrests occur at approximately 3–13/1000 admissions,[1] with a similar inclusion/exclusion effect, as the majority of in-hospital cardiac deaths are expected and occur without attempts at resuscitation.

The majority of cardiac arrests in both pre- and in-hospital settings appear to be of cardiac origin, but the underlying causes, co-morbidities and presenting rhythms vary significantly between studies.

Outcomes of cardiac arrests are critically dependent on the inclusion/exclusion criteria.[5] The best outcomes from a cardiac arrest (near 100%) occur in the electrophysiology laboratory where ventricular fibrillation (VF) is often deliberately induced. The outcomes from in-hospital cardiac arrest are variable,[7] but surprisingly good (hospital discharge as high as 52%) and are probably related to their early detection, the early arrival of the advanced life support (ALS) team and the detection and treatment of reversible causes.[8]

INTERNATIONAL REVIEW PROCESS

The International Liaison Committee On Resuscitation (ILCOR) was formed in 1992. It has facilitated a cooperative international evaluation of the resuscitation science, which resulted in the publication of international guidelines in 2000, and international consensus documents on resuscitation science in 2005, 2010 and 2015.[9] The process for the 2015 consensus on resuscitation science involved the review of 169 topics by 250 international contributors using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology[10] (completed reviews available at www.ilcor.org). The major resuscitation councils throughout the world (including the American Heart Association, and the European Resuscitation Council) used this information as the basis for the development of their published guidelines. In 2016, Australasian guidelines (co-badged by the Australian Resuscitation Council and the New Zealand Resuscitation Council) were published[11] (www.resus.org.au) under the auspices of the Australian and New Zealand Council on Resuscitation (ANZCOR).

BASIC LIFE SUPPORT

The general flow of basic life support (BLS) management is outlined in the updated Basic Life Support flow chart of ANZCOR (Fig. 21.1).

COMMENCEMENT OF CARDIOPULMONARY RESUSCITATION

The current BLS guidelines recommend that cardiopulmonary resuscitation (CPR) be commenced with compressions if the victim is unresponsive and not breathing normally. An appropriately trained ALS provider can check for a central pulse (e.g. carotid) for up to 10 seconds during this period of assessment, but this should not delay CPR.

EXTERNAL CARDIAC COMPRESSION

The delivery of high-quality CPR is believed to be a key contributor to the best possible outcomes after cardiac arrest. A number of quality factors have been proposed but the best data are for chest compression rate and depth.[12]

ABSTRACT

Outcomes from in-hospital and out-of-hospital cardiac arrest have been slowly improving over the past decade. This has been the result of incremental improvements in each phase of care: the early delivery of cardiopulmonary resuscitation, more sophisticated advanced life support (including defibrillation), and attention to detail in the post-resuscitation care. The International Liaison Committee On Resuscitation (ILCOR) oversaw the creation of the 2015 consensus on science, which, in turn, was used by the international councils to develop their revised guidelines. The residual questions about the specific role of the advanced airway, epinephrine, oxygen, carbon dioxide and targeted temperature management are likely to be settled with the publication of the trials that are currently in progress.

KEYWORDS

Cardiopulmonary resuscitation
defibrillation
heart arrest
post-resuscitation care
basic life support
advanced life support
epinephrine
targeted temperature management

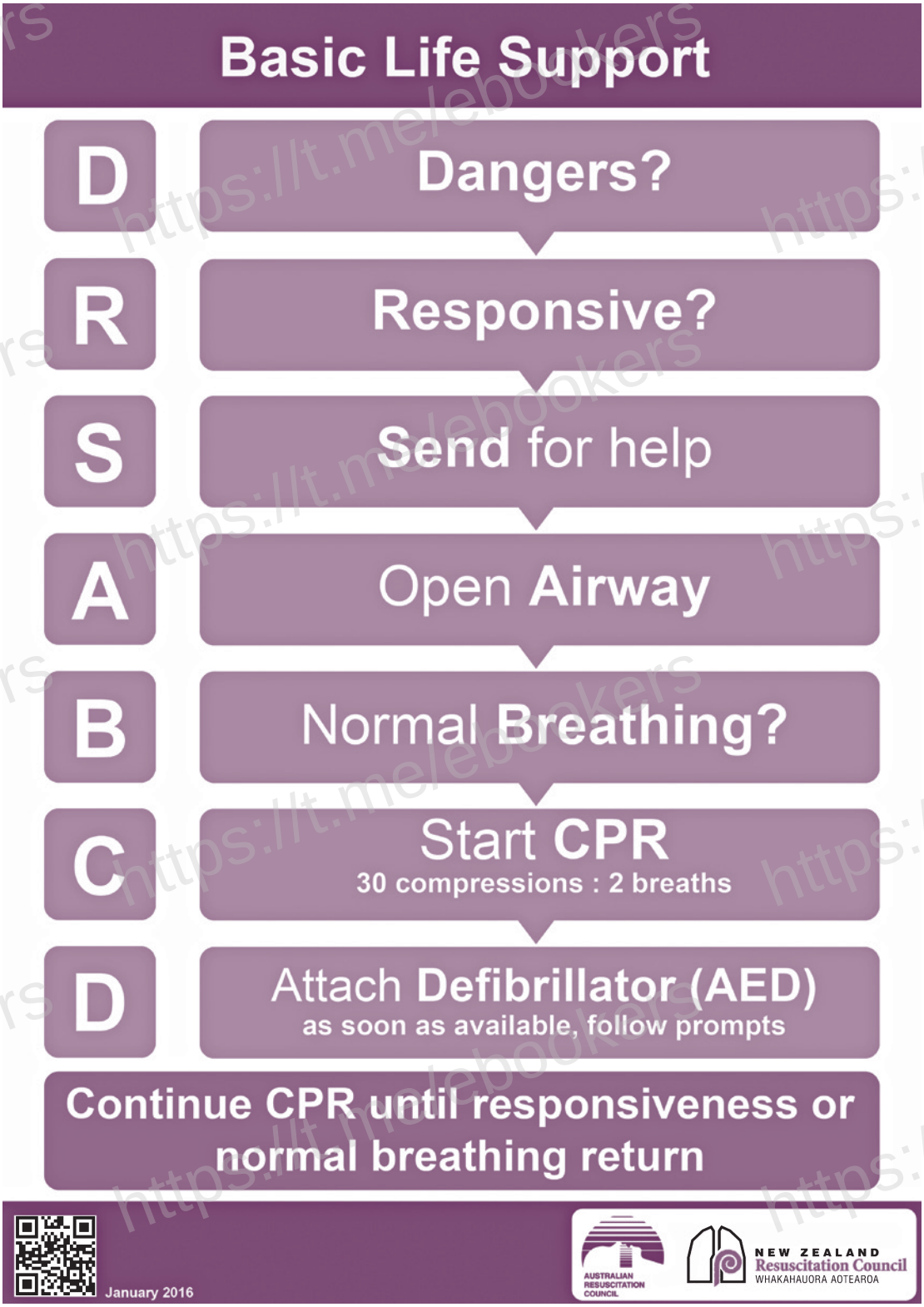


Figure 21.1 Basic life support flow chart. *(Reproduced with permission from the Australian Resuscitation Council [www.resus.org.au]).*

SITE OF COMPRESSION

The desired compression point for CPR in adults remains over the lower half of the sternum. Compressions higher than this become less effective, and compressions lower than this are also less effective and have an additional risk of damage to intra-abdominal organs.

RATE OF COMPRESSION

The optimal rate of chest compressions during cardiac arrest in adults is uncertain, but observational data allow some conclusions to be drawn.[13] The international consensus recommendation is that chest compressions should be performed at a rate of 100–120/min.[9]

DEPTH OF COMPRESSION

The optimal depth of chest compressions is uncertain. The recommended compression depth for adults is 5–6 cm. To achieve this goal, ANZCOR recommends that the chest should be compressed approximately one-third of its depth (in adults, children and infants). Compressions that are too deep may be associated with an increase in complications.[14]

MINIMISE INTERRUPTIONS TO COMPRESSIONS

Interruptions to chest compressions are common, can be prolonged, and result in a decrease in coronary perfusion pressure and reduced defibrillation success.[15] These adverse effects commence within 10 seconds of stopping CPR, but appear to be at least partially reversible with the recommencement of chest compressions. The frequency and duration of interruptions in compressions for rhythm recognition or specific interventions (such as ventilations, charging the defibrillator, defibrillation or placement of devices/equipment) should be kept to a minimum.

COMPRESSION:VENTILATION RATIO

During CPR the cardiac output is reduced to approximately one-third of normal. The minute ventilation requirements are similarly decreased. A single compression:ventilation ratio of 30:2 remains recommended for adult BLS before the airway is secured (irrespective of the number of rescuers). The tidal breath should be delivered within 1 second, and the desired tidal volume to be delivered is one that results in a visible chest rise.

MONITORING THE QUALITY OF CARDIOPULMONARY RESUSCITATION

Simple techniques to monitor the quality of CPR include observation of the rate, depth and positioning of chest compressions, the rate and depth of ventilation and palpation of central pulses. Waveform capnography should be considered for all arrests (Box 21.1). Additional monitoring (e.g. defibrillators) can be used to monitor the depth and rate of compressions and ventilation. Real-time feedback from these devices offers much promise but has limitations [16] and has not been translated into improved survival,[17,18] even when supplemented with post-arrest debriefing.[18]

Box 21.1 Utility of end-tidal carbon dioxide monitoring during cardiac arrest

Cardiovascular (absolute value of $ETCO_2$)
Falls immediately at the onset of cardiac arrest
Increases immediately with chest compressions
Provides a linear correlation with cardiac index
Allows early detection of ROSC (sudden increase)
Respiratory ($ETCO_2$ waveform)
Allows assessment of endotracheal tube placement
Allows assessment of expiratory flow limitation
Prognosis (absolute value of $ETCO_2$)
Predicts successful resuscitation

$ETCO_2$, End-tidal carbon dioxide; *ROSC*, return of spontaneous circulation.

'COMPRESSION-ONLY' CARDIOPULMONARY RESUSCITATION

Increasing anxiety about the performance of mouth-to-mouth ventilation has required the consideration of an alternative approach to traditional bystander CPR. A number of animal and human studies have suggested that ventilation may not be necessary during the initial phase of resuscitation from an arrest of a cardiac cause. Despite the limited data to support 'compression-only' CPR, it is recommended that if rescuers are unable, not trained, or unwilling to perform mouth-to-mouth ventilation (rescue breathing) then they should perform 'compression-only' CPR.

DEFIBRILLATION

Defibrillation remains the definitive treatment for shockable rhythms, such as pulseless ventricular tachycardia or VF. Successful defibrillation requires an appropriate combination of defibrillator waveform and energy level.[19]

EARLY DEFIBRILLATION VERSUS CARDIOPULMONARY RESUSCITATION BEFORE DEFIBRILLATION

The traditional approach to the treatment of a shockable rhythm during cardiac arrest has been to perform defibrillation as soon as practicable. However, in situations where VF has persisted for more than a few

minutes, an initial period of CPR does not appear to be harmful.[20]

WAVEFORM FOR DEFIBRILLATION

No specific defibrillator waveform (either monophasic or biphasic) is consistently associated with a greater incidence of return of spontaneous circulation (ROSC) or increased hospital discharge rates from cardiac arrest due to VF.[19]

ENERGY LEVELS

Recommendations for energy levels to be used for defibrillation vary according to the type of defibrillator that the rescuers are using and its specific waveform. Current recommendations are based on maximising the likelihood of success for each shock. The recommended energy level for defibrillation in adults where monophasic defibrillators are used is 360 J for all shocks. When using biphasic waveforms, the energy level should be set at 200 J for all shocks unless there is relevant clinical data for the specific defibrillator suggesting that an alternative energy level provides adequate shock success (e.g. >90%). An escalation of energy levels may be considered for subsequent shocks, though there is no evidence of a survival benefit with this approach.[19]

MANUAL DEFIBRILLATION OR AUTOMATED EXTERNAL DEFIBRILLATOR

Automated external defibrillators (AEDs) provide an opportunity for BLS providers and untrained bystanders to defibrillate a shockable rhythm. Skilled health care providers should use manual defibrillation whenever possible to avoid the delays inherent in the use of an AED.[21]

SINGLE-SHOCK TECHNIQUE

A single-shock strategy is still recommended for defibrillation (i.e. deliver a single shock and then immediately commence CPR). This strategy minimises the interruptions to chest compressions that occur during defibrillation attempts.

PADS OR PADDLES

Self-adhesive defibrillation pads are safe and effective for defibrillation and pacing. If there are concerns about contact or success of defibrillation, then paddles can be used, but they require the use of conductive gel pads and the application of sufficient firm pressure to maximise electrical contact. The default position for application of electrodes is anterior-lateral, but antero-posterior or apex-posterior can also be used (www.resus.org.au).

ADVANCED LIFE SUPPORT

ALS has an established role in the management of cardiac arrests. Although it appears obvious that the provision of ALS should improve outcomes, this has not been specifically demonstrated.

ADVANCED LIFE SUPPORT FLOW CHART

The recommended sequence of treatment to be followed is outlined in the updated 2016 Advanced Life Support ANZCOR flow chart (Fig. 21.2). This flow chart has been designed to be used as an aide memoire and a teaching tool.

PRECORDIAL THUMP

The provision of a precordial thump may be considered in a monitored arrest due to pulseless ventricular tachycardia if a defibrillator is not immediately available. The technique is not without risks and should not delay defibrillation.

CHEST COMPRESSIONS

The provision of good BLS is an essential part of the ALS management of both shockable and non-shockable rhythms. Interruptions to chest compressions for definitive procedures or interventions (such as defibrillation) should be kept to a minimum. CPR also should be commenced again immediately following defibrillation (without checking the rhythm), and continued for at least 2 minutes unless signs of life return (the victim becomes responsive or starts breathing). Even if defibrillation has successfully reverted the rhythm into one that could generate a pulse, in the vast majority of cases this is not initially associated with an output. Immediate compressions in these situations avoid the detrimental effects of prolonged interruptions in compressions and maintain the coronary perfusion. After each 2 minutes of CPR[22] (or if signs of life return), the underlying rhythm should be checked. If a rhythm compatible with a return of spontaneous circulation (ROSC) is observed at that time, then a central pulse should also be checked.

AIRWAY MANAGEMENT DURING CARDIOPULMONARY RESUSCITATION

Endotracheal intubation remains the gold standard for airway maintenance and airway protection but there are conflicting data to support its use early in a cardiac arrest.[23] There appears to be some survival benefit of endotracheal intubation over supraglottic airways in the out-of-hospital setting,[24] but no advanced airway (endotracheal or supraglottic) has been shown to be consistently better than bag-valve-mask ventilation alone.[25] Attempts at securing an advanced airway

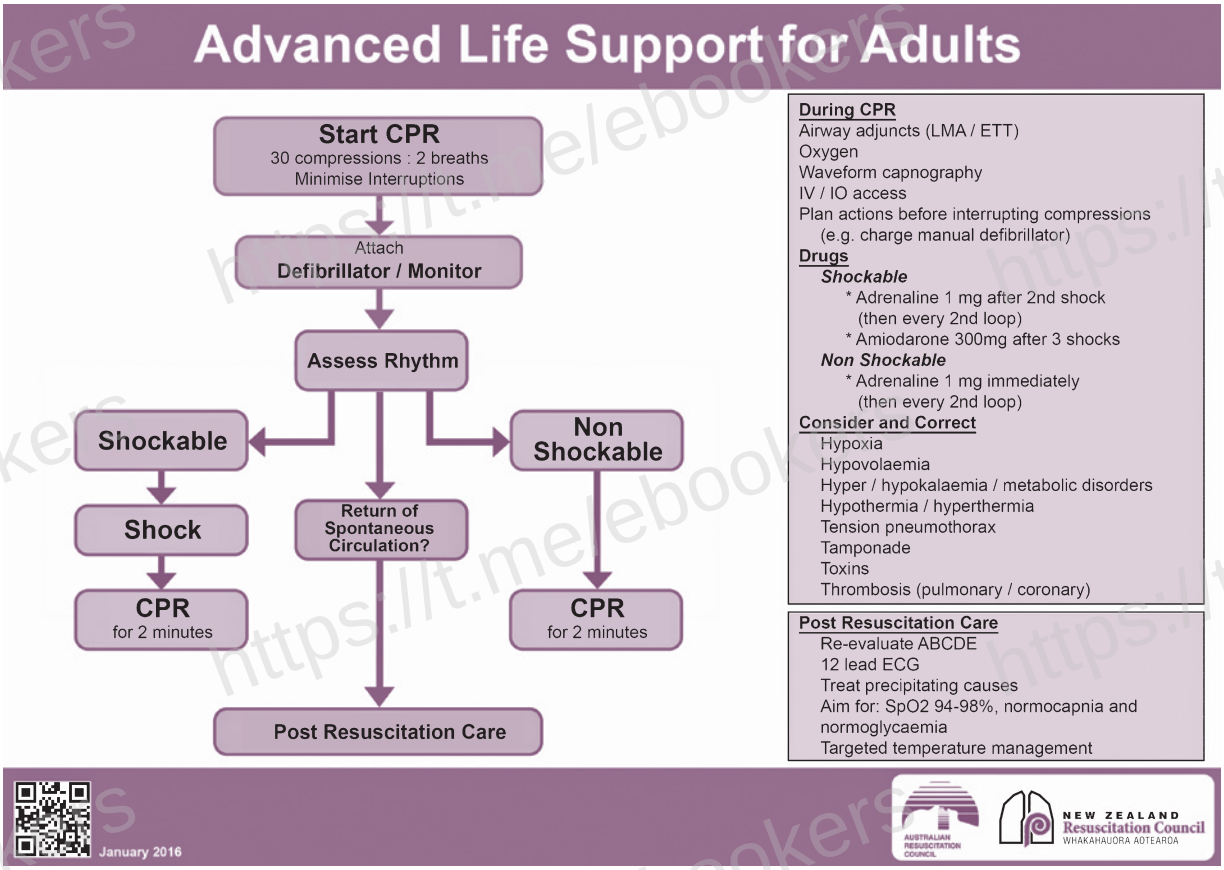


Figure 21.2 Advanced life support flow chart. *(Reproduced with permission from the Australian Resuscitation Council [www.resus.org.au]).*

should not interrupt cardiac compressions for more than 20 seconds. If an advanced airway is considered necessary, the training and experience of the resuscitation team members and the availability of devices, will determine which technique is appropriate.

VENTILATION DURING CARDIOPULMONARY RESUSCITATION

A compression:ventilation ratio of 30:2 is recommended before the airway is secured, and after the airway is secured the recommended ventilation rate is 8–10/min. One way to provide this with a secure airway, to minimise interruptions to compressions, is to use a compression:ventilation ratio of 15:1 (www.resus.org.au). The tidal volume recommended is one that results in a visible chest rise. High respiratory rates during cardiac arrest are associated with increased intrathoracic pressure, decreased coronary and cerebral perfusion, and, at least in animals, a decreased rate of ROSC.[26] If there is a concern about potential gas trapping, a period of disconnection from the ventilation circuit may be beneficial.

IDENTIFICATION OF REVERSIBLE CAUSES

Irrespective of the initial rhythm, cardiac arrests can be precipitated or perpetuated by a number of conditions that if not detected and corrected may decrease the likelihood of successful resuscitation.[8] These 'reversible causes' are categorised in the ALS algorithm as the '4Hs and 4Ts' (see Fig. 21.2). A number of techniques are available to assist in the diagnosis and exclusion of these conditions. These include a good history, a careful clinical examination and some specific investigations and interventions. Echocardiography, even in the pre-hospital setting,[27] can potentially diagnose (or help exclude) a number of cardiac and non-cardiac reversible causes (Box 21.2).[28]

MEDICATIONS DURING CARDIOPULMONARY RESUSCITATION

Although various drugs are recommended for use during the management of cardiac arrests, evidence supporting their effectiveness is quite limited. The intraosseous route should be considered for the

Box 21.2 Potentially useful diagnoses detectable by echocardiography

Hypovolaemia*
Tamponade* (pericardial)
Tension pneumothorax*
Thrombosis – pulmonary* (thromboembolism)
Thrombosis – coronary* (regional or global wall motion abnormalities, including lack of cardiac motion)
Pacemaker capture
Unexpected VF
Acute valvular insufficiency (e.g. papillary muscle rupture)
Ventricular rupture
Aortic dissection
Massive pleural effusion

*Reversible causes listed in the '4Hs and 4Ts' (www.resus.org.au) (see Fig. 21.2).
VF, Ventricular fibrillation.

administration of medications if venous access is not immediately available.[29]

VASOPRESSORS

The putative beneficial effect of vasopressors during cardiac arrest is to increase the perfusion pressure to the heart and brain. The use of intravenous epinephrine in randomised controlled trials (RCTs) enrolling out-of-hospital cardiac arrests has been associated with improved short-term survival, but not survival to hospital discharge.[30,31] Given these data, it is considered reasonable to continue to use epinephrine routinely in the management of cardiac arrests. The initial adult dose is 1 mg and this should be repeated approximately every 4 minutes. Vasopressin is an alternative drug, but studies have been unable to demonstrate any consistent benefits with its use.

ANTIARRHYTHMICS

Administration of amiodarone or lidocaine for shock refractory VF has been associated with an increased survival to hospital when compared with placebo.[32] In the largest RCT of anti-arrhythmic drugs, neither amiodarone nor lidocaine improved long-term survival when compared with placebo across the board,[33] though there was an increase in survival to discharge with amiodarone or lidocaine compared with placebo in the pre-specified subgroup of patients with a bystander-witnessed arrest.[34] Either amiodarone or lidocaine (but not both) should be considered in those patients still in VF after repeated attempts at defibrillation (including attempted defibrillation after the administration of epinephrine) have failed.

OTHER MEDICATIONS

Other medications that should be considered during cardiac arrest are those that address the detected underlying contributing factors. These include electrolytes (such as magnesium or potassium), atropine, sodium bicarbonate and other specific 'antidotes' (Table 21.1).[35]

Table 21.1 Cardiac arrest medications in specific circumstances

MEDICATION	POTENTIAL INDICATIONS
Atropine	Cholinergic/cardiac glycoside toxicity
Antivenom	Snake, funnel-web spider, box jellyfish venom
Benzodiazepines	Sympathomimetic toxicity
Calcium	Hypocalcaemia, hypermagnesaemia, hyperkalaemia, beta-blocker/calcium channel blocker toxicity
Digoxin-specific antibodies	Cardiac glycoside toxicity
Flumazenil	Benzodiazepine toxicity
Epinephrine (adrenaline)	Beta-blocker/calcium channel blocker toxicity
Glucagon	Beta-blocker/calcium channel blocker toxicity
High-dose insulin/dextrose	Beta-blocker/calcium channel blocker toxicity
Lipid emulsion	Local anaesthetic agents
Magnesium	Hypomagnesaemia, hypokalaemia, hypercalcaemia, tricyclic antidepressant/cardiac glycoside toxicity, torsade de pointes
Naloxone	Opioid toxicity
Potassium	Hypokalaemia
Pyridoxine	Isoniazid toxicity
Sodium bicarbonate	Hyperkalaemia, tricyclic antidepressant/sodium-channel-blocker toxicity

From Smith SW. Drugs and pharmaceuticals: management of intoxication and antidotes. *EXS*. 2010;100:397-460, with permission.

ADJUNCTS TO CARDIOPULMONARY RESUSCITATION

Many technologies and techniques have been evaluated as adjuncts or alternatives to CPR in an attempt to improve the management of cardiac arrests, but none have been consistently associated with improved outcomes. Mechanical CPR devices have been studied in great detail, but large RCTs have not been able to demonstrate any survival benefit with either the Lund University Cardiopulmonary Assist System (LUCAS) or AutoPulse.[36-38] The combination of active-compression decompression CPR with an impedance threshold

device was associated with improved neurological survival in an RCT in out-of-hospital cardiac arrests.[39]

However, mechanical devices (such as the LUCAS or the AutoPulse) may be useful alternatives to manual CPR in situations where traditional CPR is difficult or hazardous: during transport; during interventions (such as percutaneous coronary interventions [PCIs]); or as a bridge to extracorporeal techniques.

There has been an increased interest in extracorporeal techniques, especially as short-term rescue for refractory arrests.[40,41]

At this stage there is still insufficient supportive evidence to recommend the routine use of any of these adjunctive techniques.

POST-RESUSCITATION CARE

Survival after cardiac arrest is largely dependent on the patient's co-morbidities and the initial hypoxic insults to the heart and brain. However, survival is also influenced by subsequent complications, including secondary insults, the ensuing systemic inflammatory response[42] and differences in post-resuscitation care (Box 21.3).[1,7,43]

Box 21.3 Key factors to consider after resuscitation from cardiac arrest

Immediate tasks
- Re-evaluate Airway Breathing Circulation Disability Exposure (ABCDE)
- 12-lead electrocardiogram (ECG)
- Treat precipitating causes
- Re-evaluate oxygenation and ventilation
- Temperature control (cool)

Early goals
- Continue respiratory support
- Maintain cerebral perfusion
- Treat and prevent cardiac arrhythmias
- Determine and treat the cause of the arrest

Specific tasks
- Maintain haemodynamics (SBP >100 mm Hg [13 kPa])
- Maintain adequate oxygenation (SaO_2 94%–98%)
- Maintain normal pH and normocarbia (e.g. $PaCO_2$ 35–40 mm Hg [4.5–5.2 kPa])
- Treat hyperglycaemia (>10 mmol/L), but avoid hypoglycaemia
- Consider therapeutic hypothermia (unless contraindicated)
- Maintain appropriate sedation
- Treat seizures
- Continue search to identify underlying cause(s) and trauma related to resuscitation
- Consider specific treatment for underlying cause (e.g. percutaneous coronary intervention, thrombolytics)
- Consider prophylactic antiarrhythmics
- Consider transfer to resuscitation centre

SBP, Systolic blood pressure.

RESUSCITATION CENTRES

An increasing body of evidence suggests that there may be benefits in transporting the victims of out-of-hospital cardiac arrests to a centre that is equipped to provide all of the desired components of post-arrest care (including PCIs and therapeutic hypothermia).[1]

THERAPEUTIC HYPOTHERMIA

The international consensus recommendation is that unconscious haemodynamically stable survivors of out-of-hospital cardiac arrests due to VF should be cooled to 32–36°C for 24 hours.[44] Care should be taken if using the upper level of this range to ensure that fever is avoided.[45] A period of induced hypothermia should also be considered for cardiac arrests due to other rhythms, as well as in-hospital arrests.[44] Pre-hospital cooling with cold fluids appears not to be of benefit[44] and intra-arrest cooling with cold fluids is not indicated.[46]

ADDITIONAL FACTORS IN POST-RESUSCITATION CARE

Attention should be given to good supportive care for the patient after cardiac arrest. This includes maintenance of cerebral perfusion, provision of adequate oxygenation, ventilation, glucose control and treatment of seizures.[43]

OXYGENATION

The routine use of 100% oxygen after cardiac arrest is being questioned. Data from animal and neonatal studies have suggested that this may be associated with adverse outcomes. The adult cardiac arrest evidence regarding effects of oxygenation is accumulating, but is of low quality and remains controversial.[47] However, it seems reasonable to titrate the FiO_2 to target an acceptable SaO_2 (e.g. 94%–98%) as soon as the patient is stable.

VENTILATION

Numerous studies in animals and humans have demonstrated the potential harm of cerebral ischaemia induced by hypocapnia after cardiac arrest. Recent data suggest that mild hypercapnia may be beneficial.[48] Arterial blood gas measurements should be used to titrate ventilation in the immediate post-resuscitation period, rather than the less reliable end-tidal CO_2.

BLOOD PRESSURE CONTROL

There is limited human evidence to support specific haemodynamic goals after cardiac arrest. Hypotension appears to be detrimental,[49] but no specific target blood pressure has been identified. It is recommended to aim for a blood pressure equal to the patient's usual blood pressure or a systolic pressure greater than 100 mm Hg.

GLUCOSE CONTROL

Despite the early promise of improved outcomes with tight blood glucose control, subsequent studies have demonstrated this approach to be potentially harmful. Blood glucose should be monitored frequently after cardiac arrest. Hyperglycaemia (>10 mmol/L) should be treated with insulin, and hypoglycaemia should be avoided.

PERCUTANEOUS CORONARY INTERVENTION

The routine use of thrombolytics after cardiac arrest has not increased survival. PCIs should be considered as part of routine post-arrest care in patients with ST elevation or a new left-bundle branch block, irrespective of the neurological state. Angiography also should be considered in patients without ST-segment elevation as these patients commonly have a culprit lesion.[50]

Therapeutic hypothermia is recommended in combination with primary PCI, and should be started as early as possible, preferably prior to the initiation of PCI.

TREATMENT OF SEIZURES

Seizures are relatively common after cardiac arrest (incidence of 3%–44%), and in the post-arrest period they may be refractory to multiple medications. It is reasonable to institute prompt and aggressive treatment of seizures, but there is no definitive evidence to suggest that this approach (or preventative therapy) improves outcomes.

OTHER FACTORS

The search should be continued to identify and treat underlying causes of the arrest. Traumatic complications of resuscitation (e.g. rib fractures and sternal fractures) are relatively common, and should be identified and treated as appropriate.

It is reasonable to use an infusion of an antiarrhythmic drug that successfully restored a stable rhythm during resuscitation (e.g. lidocaine 2–4 mg/min or amiodarone 0.6 mg/kg/h for 12–24 hours). If no antiarrhythmic drug was used during resuscitation from a shockable rhythm, an antiarrhythmic drug may be considered to prevent recurrent VF.

The placement and sterility of devices inserted during the arrest should also be reviewed.

PROGNOSTICATION

It is impossible to accurately predict the potential degree of neurological recovery either during or soon after a cardiac arrest.

Accurate prediction of neurological outcome has become increasingly difficult since therapeutic hypothermia has been widely used in the post-arrest period. A number of reviews of the evidence from prognostic studies have been published.[19,51] Even the presence of myoclonus may not predict the dire outcomes it was previously associated with.[52] It is strongly recommended that decisions to limit care should not be made based on the results of a single prognostication tool, but instead the information from clinical examination, electroencephalography, neuroimaging and biochemical markers should be taken into account.

MAINTENANCE OF ALS SKILLS

Many studies have confirmed that the knowledge and skills related to ALS start to deteriorate relatively quickly after completion of ALS training (e.g. within 6 months).[53] It is recommended that ALS training includes human factors and team training, and additional simulations or education may be necessary at more frequent intervals to ensure all staff maintain their skills.

SUMMARY

Improved outcomes over the past decade are almost certainly due to a number of incremental improvements in the management of patients during and after cardiac arrests. The key to continual improvement lies with techniques to improve early delivery of good-quality BLS, as well as attention to detail in the post-resuscitation care phase and accurate prognostication. We are awaiting the publication of a number of exciting studies, and hopefully their results will inform further improvements in survival over the next decade.

REFERENCES

1. Morrison LJ, Neumar RW, Zimmerman JL, et al. Strategies for improving survival after in-hospital cardiac arrest in the United States: 2013 consensus recommendations: a consensus statement from the American Heart Association. *Circulation*. 2013; 127(14):1538–1563.
2. Chan PS, McNally B, Tang F, et al. Recent trends in survival from out-of-hospital cardiac arrest in the United States. *Circulation*. 2014;130(21):1876–1882.
3. Stromsoe A, Svensson L, Axelsson AB, et al. Improved outcome in Sweden after out-of-hospital cardiac arrest and possible association with improvements in every link in the chain of survival. *Eur Heart J*. 2015;36(14):863–871.
4. Nolan JP, Berg RA, Bernard S, et al. Intensive care medicine research agenda on cardiac arrest. *Intensive Care Med*. 2017.
5. Finn JC, Jacobs IG, Holman CD, et al. Outcomes of out-of-hospital cardiac arrest patients in Perth, Western Australia, 1996-1999. *Resuscitation*. 2001;51(3):247–255.
6. Nichol G, Thomas E, Callaway CW, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA*. 2008;300(12):1423–1431.

7. Merchant RM, Berg RA, Yang L, et al. Hospital variation in survival after in-hospital cardiac arrest. *J Am Heart Assoc*. 2014;3(1):e000400.
8. Saarinen S, Nurmi J, Toivio T, et al. Does appropriate treatment of the primary underlying cause of PEA during resuscitation improve patients' survival? *Resuscitation*. 2012;83(7):819–822.
9. Nolan JP, Hazinski MF, Aickin R, et al. Part 1: executive summary: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation*. 2015;95:e1–e31.
10. Morley PT, Lang E, Aickin R, et al. Part 2: evidence evaluation and management of conflicts of interest: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation*. 2015;95:e33–e41.
11. Leman P, Morley P. Review article: updated resuscitation guidelines for 2016: a summary of the Australian and New Zealand Committee on Resuscitation recommendations. *Emerg Med Australas*. 2016;28(4):379–382.
12. Talikowska M, Tohira H, Finn J. Cardiopulmonary resuscitation quality and patient survival outcome in cardiac arrest: a systematic review and meta-analysis. *Resuscitation*. 2015;96:66–77.
13. Idris AH, Guffey D, Pepe PE, et al. Chest compression rates and survival following out-of-hospital cardiac arrest. *Crit Care Med*. 2015;43(4):840–848.
14. Hellevuo H, Sainio M, Nevalainen R, et al. Deeper chest compression - more complications for cardiac arrest patients? *Resuscitation*. 2013;84(6):760–765.
15. Cheskes S, Schmicker RH, Verbeek PR, et al. The impact of peri-shock pause on survival from out-of-hospital shockable cardiac arrest during the Resuscitation Outcomes Consortium PRIMED trial. *Resuscitation*. 2014;85(3):336–342.
16. Lee S, Oh J, Kang H, et al. Proper target depth of an accelerometer-based feedback device during CPR performed on a hospital bed: a randomized simulation study. *Am J Emerg Med*. 2015;33(10):1425–1429.
17. Kirkbright S, Finn J, Tohira H, et al. Audiovisual feedback device use by health care professionals during CPR: a systematic review and meta-analysis of randomised and non-randomised trials. *Resuscitation*. 2014;85(4):460–471.
18. Couper K, Kimani PK, Abella BS, et al. The system-wide effect of real-time audiovisual feedback and postevent debriefing for in-hospital cardiac arrest: the cardiopulmonary resuscitation quality improvement initiative. *Crit Care Med*. 2015;43(11):2321–2331.
19. Soar J, Callaway CW, Aibiki M, et al. Part 4: advanced life support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation*. 2015;95:e71–e120.
20. Huang Y, He Q, Yang LJ, et al. Cardiopulmonary resuscitation (CPR) plus delayed defibrillation versus immediate defibrillation for out-of-hospital cardiac arrest. *Cochrane Database Syst Rev*. 2014;(9):CD009803.
21. Chan PS, Krumholz HM, Spertus JA, et al. Automated external defibrillators and survival after in-hospital cardiac arrest. *JAMA*. 2010;304(19):2129–2136.
22. Reynolds JC, Raffay V, Lang E, et al. When should chest compressions be paused to analyze the cardiac rhythm? A systematic review and meta-analysis. *Resuscitation*. 2015;97:38–47.
23. Andersen LW, Granfeldt A, Callaway CW, et al. Association between tracheal intubation during adult in-hospital cardiac arrest and survival. *JAMA*. 2017;317(5):494–506.
24. Benoit JL, Gerecht RB, Steuerwald MT, et al. Endotracheal intubation versus supraglottic airway placement in out-of-hospital cardiac arrest: a meta-analysis. *Resuscitation*. 2015;93:20–26.
25. Barr S, Smith G, Darroch S. Use of supraglottic airway devices by paramedics in the management of adult prehospital cardiac arrest patients. *Australas J Paramed*. 2017;14(1):1–10.
26. Aufderheide TP, Sigurdsson G, Pirrallo RG, et al. Hyperventilation-induced hypotension during cardiopulmonary resuscitation. *Circulation*. 2004;109(16):1960–1965.
27. Reed MJ, Gibson L, Dewar A, et al. Introduction of paramedic led echo in life support into the pre-hospital environment: the PUCA study. *Resuscitation*. 2017;112:65–69.
28. Tsou PY, Kurbedin J, Chen YS, et al. Accuracy of point-of-care focused echocardiography in predicting outcome of resuscitation in cardiac arrest patients: a systematic review and meta-analysis. *Resuscitation*. 2017;114:92–99.
29. Reades R, Studnek JR, Vandeventer S, et al. Intraosseous versus intravenous vascular access during out-of-hospital cardiac arrest: a randomized controlled trial. *Ann Emerg Med*. 2011;58(6):509–516.
30. Olasveengen TM, Sunde K, Brunborg C, et al. Intravenous drug administration during out-of-hospital cardiac arrest: a randomized trial. *JAMA*. 2009;302(20):2222–2229.
31. Jacobs IG, Finn JC, Jelinek GA, et al. Effect of adrenaline on survival in out-of-hospital cardiac arrest: a randomised double-blind placebo-controlled trial. *Resuscitation*. 2011;82(9):1138–1143.
32. Sanfilippo F, Corredor C, Santonocito C, et al. Amiodarone or lidocaine for cardiac arrest: a systematic review and meta-analysis. *Resuscitation*. 2016;107:31–37.
33. Kudenchuk PJ, Brown SP, Daya M, et al. Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. *N Engl J Med*. 2016;374(18):1711–1722.
34. Kudenchuk PJ. Antiarrhythmic drugs in out-of-hospital cardiac arrest: what counts and what doesn't? *Resuscitation*. 2016;109:A5–A7.

35. Smith SW. Drugs and pharmaceuticals: management of intoxication and antidotes. *EXS*. 2010;100: 397–460.
36. Wik L, Olsen JA, Persse D, et al. Manual vs. integrated automatic load-distributing band CPR with equal survival after out of hospital cardiac arrest. The randomized CIRC trial. *Resuscitation*. 2014;85(6):741–748.
37. Rubertsson S, Lindgren E, Smekal D, et al. Mechanical chest compressions and simultaneous defibrillation vs conventional cardiopulmonary resuscitation in out-of-hospital cardiac arrest: the LINC randomized trial. *JAMA*. 2014;311(1):53–61.
38. Perkins GD, Lall R, Quinn T, et al. Mechanical versus manual chest compression for out-of-hospital cardiac arrest (PARAMEDIC): a pragmatic, cluster randomised controlled trial. *Lancet*. 2015; 385(9972):947–955.
39. Aufderheide TP, Frascone RJ, Wayne MA, et al. Standard cardiopulmonary resuscitation versus active compression-decompression cardiopulmonary resuscitation with augmentation of negative intrathoracic pressure for out-of-hospital cardiac arrest: a randomised trial. *Lancet*. 2011;377(9762):301–311.
40. Kim SJ, Kim HJ, Lee HY, et al. Comparing extracorporeal cardiopulmonary resuscitation with conventional cardiopulmonary resuscitation: a meta-analysis. *Resuscitation*. 2016;103:106–116.
41. Stub D, Bernard S, Pellegrino V, et al. Refractory cardiac arrest treated with mechanical CPR, hypothermia, ECMO and early reperfusion (the CHEER trial). *Resuscitation*. 2015;86:88–94.
42. Nolan JP, Neumar RW, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A scientific statement from the international liaison committee on resuscitation; the American Heart Association emergency cardiovascular care committee; the council on cardiovascular surgery and anesthesia; the council on cardiopulmonary, perioperative, and critical care; the council on clinical cardiology; the council on stroke. *Resuscitation*. 2008;79(3):350–379.
43. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. *Intensive Care Med*. 2015; 41(12):2039–2056.
44. Donnino MW, Andersen LW, Berg KM, et al. Temperature management after cardiac arrest: an advisory statement by the advanced life support task force of the international liaison committee on resuscitation and the american heart association emergency cardiovascular care committee and the council on cardiopulmonary, critical care, perioperative and resuscitation. *Resuscitation*. 2016;98:97–104.
45. Bray JE, Stub D, Bloom JE, et al. Changing target temperature from 33°C to 36°C in the ICU management of out-of-hospital cardiac arrest: a before and after study. *Resuscitation*. 2017;113:39–43.
46. Bernard SA, Smith K, Finn J, et al. Induction of therapeutic hypothermia during out-of-hospital cardiac arrest using a rapid infusion of cold saline: the RINSE Trial (Rapid Infusion of Cold Normal Saline). *Circulation*. 2016;134(11):797–805.
47. Wang CH, Chang WT, Huang CH, et al. The effect of hyperoxia on survival following adult cardiac arrest: a systematic review and meta-analysis of observational studies. *Resuscitation*. 2014;85(9): 1142–1148.
48. Eastwood GM, Schneider AG, Suzuki S, et al. Targeted therapeutic mild hypercapnia after cardiac arrest: a phase II multi-centre randomised controlled trial (the CCC trial). *Resuscitation*. 2016;104: 83–90.
49. Bhate TD, McDonald B, Sekhon MS, et al. Association between blood pressure and outcomes in patients after cardiac arrest: a systematic review. *Resuscitation*. 2015;97:1–6.
50. Millin MG, Comer AC, Nable JV, et al. Patients without ST elevation after return of spontaneous circulation may benefit from emergent percutaneous intervention: a systematic review and meta-analysis. *Resuscitation*. 2016;108:54–60.
51. Oddo M, Friberg H. Neuroprognostication after cardiac arrest in the light of targeted temperature management. *Curr Opin Crit Care*. 2017;23(3): 244–250.
52. Seder DB, Sunde K, Rubertsson S, et al. Neurologic outcomes and postresuscitation care of patients with myoclonus following cardiac arrest. *Crit Care Med*. 2015;43(5):965–972.
53. Yang CW, Yen ZS, McGowan JE, et al. A systematic review of retention of adult advanced life support knowledge and skills in healthcare providers. *Resuscitation*. 2012;83(9):1055–1060.

22

Cardiac arrhythmias (combine with drugs)

Andrew William Holt

CARDIAC ELECTROPHYSIOLOGY

The electrophysiological properties of cardiac cells are important in understanding cardiac arrhythmias and their management. Cardiac cells undergo cyclical depolarisation and repolarisation to form an action potential. The shape and duration of each action potential is determined by the activity of ion channel protein complexes on the myocyte surface (Table 22.1).[1]

Ion channels are large glycoproteins that span the membrane bilayer with accessory subunits that contribute to pore structure or modulate function. The genes encoding all the major ion channels have been cloned and sequenced.

Channel activation forms pores that permit rapid transit of ions, creating ionic currents that determine the magnitude and rate of change of myocyte membrane potential.

Ion channels have two fundamental properties[2]:

ION PERMEABILITY

Channels classified on the basis of selectivity; Na^+, K^+ and Ca^{++}. Selectivity determined by size, valency and hydration energy. For example, the ration of Na^+:K^+ selectivity of Na^+ is 10:1. Channels contain multiple binding sites as ions traverse the channel and ions become dehydrated, as binding is favoured over ion-water interaction. Most have rectifying properties whereby they conduct ions more effectively in one direction.

Gating – the mechanism by which channels open and close.

Most are voltage gated and modulated by ligand binding.

Voltage-gated channels change their conductance in response to change in membrane potential. Majority of channels open in response to depolarisation, whereas pacemaker channel I_f opens in response to hyperpolarisation.

Ligand-gated channels include $I_{K\,Ach}$, the muscarinic-gated K^+ current where binding of acetylcholine mediates vagal effect by decreasing diastolic depolarisation in sinoatrial (SA) and atrioventricular (AV) pacemaker cells. $I_{K\,ATP}$ channels bind ADP activating phase 1 and 2 K^+ current to shorten the action potential matching force generation and duration to cellular energy or ADP levels. This effect is also arrhythmogenic due to shortened refractory period. The $I_{K\,ATP}$ channel is a target to break the link between ischaemia and arrhythmia. The cardioprotective effect of $I_{K\,ATP}$ plays a role in ischaemia preconditioning.

Mechanosensitive or stretch-activated channels alter action potential in response to beat-to-beat variations in pressure and volume load. Increases in load SA node pacemaker rate and action potential is increased, whereas refractory period and conduction is reduced. Sustained pressure and volume load is arrhythmogenic via these changes to the action potential.

Many of the ion channels are the molecular targets for antiarrhythmic drugs. The differential distribution of ion channel populations within the heart allows drugs to have preferential activity on different parts of the heart.

I_f 'pacemaker' channels are confined to the SA node and new drugs with specific I_f-blocking activity such as ivabradine have been shown to be beneficial in angina and heart failure by slowing the heart rate without negative effects on ventricular contractility.

I_K channels responsible for potassium ion (K^+) repolarisation currents (I_K) vary throughout the heart with the rapidly activating forms, I_{Kur}, being confined to the atrium. Vernakalant, a new K channel blocker has predominant activity on the I_{Kur} channel and therefore predominant atrial activity.

The spectrum of cardiac action potentials varies from *fast-response* cells – conducting and contractile myocytes (Fig. 22.1A) – to *slow-response* cells of pacemaker myocytes – SA and AV nodes (see Fig. 22.1B). Fast myocytes lose their characteristic action potential and behave more like slow myocytes when ischaemic. The action potential is divided into five phases and ion channel currents vary between fast- and slow-response cells (Fig. 22.2).

PHASE 0

In fast myocytes (see Fig. 22.1A), rapid depolarisation I_{Na} current occurs owing to activation of voltage-gated sodium ion (Na^+) channels. Activation is initiated in an all-or-none response once the threshold is reached. The Na^+ channels are inactivated as membrane potential

ABSTRACT

Cardiac arrhythmia is a major challenge for the critical care specialist. Cardiac electrophysiology is important to understanding arrhythmia mechanisms, accurate electrocardiographic diagnosis and guiding treatment. Acute control of arrhythmia with antiarrhythmic drugs, cardiac pacing and direct current shock are effective in avoiding haemodynamic compromise and management of cardiac arrest. Prevention and long-term control is more difficult due to lack of ideal antiarrhythmic drugs, with drug side effects outweighing antiarrhythmic benefit. Classification of antiarrhythmic drugs on the basis of their molecular targets, ion channels, receptors, ion pumps and carriers supersedes the traditional Vaughan-Williams classification. Increasingly, catheter ablation of arrhythmogenic areas of the heart is proving to be superior to antiarrhythmic drugs for long-term control. The importance of thromboembolic complications demands an evidence-based approach to anticoagulation.

KEYWORDS

Arrhythmia
cardiac electrophysiology
mechanisms
proarrhythmia
diagnosis
antiarrhythmic drugs
pharmacodynamics
ablation
sudden death

Table 22.1 Characteristics of cardiac ionic channels

ION	CHANNEL	
		INWARD CURRENT/DEPOLARISATION
Sodium Na_v	I_{Na}	• Present in atria, His–Purkinje and ventricle • Absent in SA and AV node • Generates phase 0 rapid depolarisation current • Drives action potential propagation
Calcium Ca_v	$I_{Ca\text{-}L}$	• Predominate Ca^{2+} channel • Contributes to phase 2 plateau • Produces depolarisation and propagation in SA and AV nodes • Triggers Ca^{2+} release from sarcoplasmic reticulum
	$I_{Ca\text{-}T}$	• Predominates in pacemaker cells • Contributes to later stages of phase 4 in pacemaker cells
Non-selective cation	I_f	• Predominately Na • Absent in ventricular cells • Activated by polarisation • Generates phase 4 depolarisation of pacemaker function • Strongly modulated by neurotransmitters
		OUTWARD CURRENT/REPOLARISATION
Potassium K_v	I_{to}	• Activated rapidly after depolarisation • Fast I_{to1} and slow I_{to2} variants • Responsible for phase 1 rapid early repolarisation • Predominate distribution subepicardial • Distribution creates heterogeneous repolarisation
	I_K	• Delayed rectifiers • Slow activation kinetics • Major repolarising current • Variants with slow I_{Ks}, rapid I_{Kr} and ultra-rapid I_{Kur} activation • I_K populations are not characterised in the SA node • I_{Kur} are not present in the ventricle • I_{Kur} along with I_{to} contributes to earlier repolarisation and shorter action potentials of atrial cells
	I_{K1}	• Inward rectifier • Current responsible for maintaining resting potential near K^+ equilibrium • Shuts off during depolarisation • Absence in SA node enables small currents to control pacemaker rates
	I_{Ach}	• Muscarinic-gated K^+ channel • Vagal effect by decreasing phase 4 depolarisation
	I_{KATP}	• Binds ADP • Activated in ischaemia • Activates phase 1 and 2 K^+ current to shorten action potential

AV, Atrioventricular; *SA*, sinoatrial.

rises to +30 mV and remain inactivated until repolarisation occurs. Rapidity of depolarisation determines speed of conduction. In slow-response myocytes, depolarisation does not involve Na^+ channels and the slower rate of depolarisation is due to a slow inward calcium ion (Ca^{2+}) current via $I_{Ca\text{-}L}$ and $I_{Ca\text{-}T}$ voltage-dependent Ca^{2+} channels.

PHASE 1

Early rapid incomplete repolarisation to approximately 0 mV occurs owing to activation of transient outward current from I_{TO1} and I_{TO2} K^+ channels. Slow myocytes do not exhibit phase 1 or 2 characteristics (see Fig. 22.1B).

PHASE 2

The prolonged plateau repolarisation of fast myocytes is a consequence of low membrane conductance to all ions. The decreasing inward Ca^{2+} current of $I_{Ca\text{-}L}$ and $I_{Ca\text{-}T}$ Ca^{2+} channels is initially balanced and then overcome by the outward K^+ current of the delayed rectifiers or the I_k family of K^+ channels. During this phase,

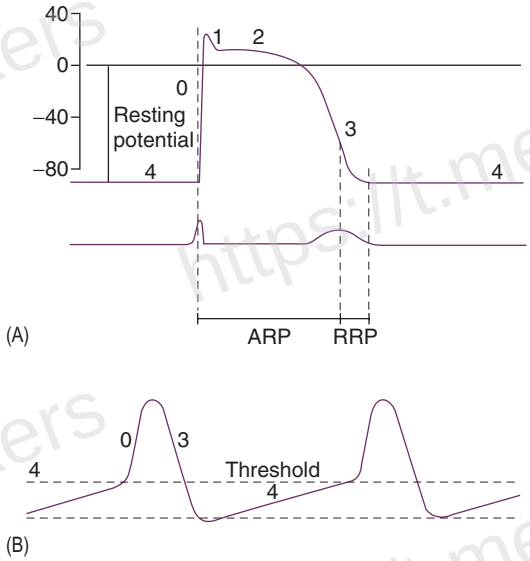


Figure 22.1 (A) Action potential in a fast-response, non-pacemaker myocyte: phases 0–4, resting membrane potential – 80 mV, absolute refractory period *(ARP)* and relative refractory period *(RRP)*. (B) Action potential in a slow-response, pacemaker myocyte. The spontaneous upward slope of phase 4, on reaching threshold potential, results in an action potential.

the rise in calcium ion concentration ($[Ca^{2+}]_i$) is the trigger to release sarcoplasmic reticulum stores of Ca^{2+} and initiate the contractile process.

PHASE 3

Relatively rapid repolarisation occurs as outward K^+ current of the delayed rectifiers increases. The I_{kr} K^+ channel, one of the I_k delayed rectifiers, is the common mechanism whereby antiarrhythmic drugs prolong the action potential and refractoriness.

PHASE 4

This is a stable electrical state in fast non-pacemaker myocytes owing to inward rectifier I_{K1} channels maintaining resting membrane potential (RMP) near K^+ equilibrium and the absence of I_f pacemaker channels. In slow pacemaker myocytes, phase 3 I_{KI} current repolarises membrane potential activating I_f channels. Subsequent pacemaker depolarisation of phase 4 to threshold occurs due to I_{K1} channel closure and I_f depolarising current (see Fig. 22.1B).

Fast-response and slow-response myocytes also have important differences in properties of refractoriness. In fast myocytes, Na^+ channels are progressively reactivated during phase 3 repolarisation as the membrane potential becomes more negative. When an extra stimulus occurs during phase 3, the magnitude of the resulting inward Na^+ current and likelihood of impulse propagation depend on the number of reactivated Na^+ channels. Refractoriness is therefore determined by the voltage-dependent recovery of Na^+ channels. The absolute refractory period (see Fig. 22.1) is that minimum time needed for recovery of sufficient Na^+ channels for a stimulus to result in impulse propagation. However, once propagation in fast myocytes occurs, conduction velocity is normal. In contrast, slow-response or Ca^{2+} channel-dependent myocytes exhibit time-dependent refractoriness. Even after full repolarisation, further time is needed before all Ca^{2+} channels are reactivated. Stimuli during this period produce reduced Ca^{2+} current and the propagation velocity of any resulting impulse is reduced. The conduction velocity independence of premature action potentials with fast-response myocytes is lost in the setting of Na^+ channel-blocking drugs or ischaemia because they behave increasingly like slow-response myocytes with resulting slowed impulse conduction.

GENETIC BASIS TO ARRHYTHMIA[1]

In the absence of structural abnormalities of the heart, primary electrical disease is associated with mutations in ion channel genes. The long-QT syndrome (LQTS) (see later), short-QT syndrome, Brugada syndrome (idiopathic ventricular fibrillation, VF), catecholaminergic polymorphic ventricular tachycardia (VT) and all causes of sudden cardiac death (SCD) in the young are examples of primary electrical disease where genetic mutations encoding for ion channel proteins have been characterised.

Inheritable forms of structural ventricular disease are associated with atrial arrhythmias and SCD. Examples include hypertrophic and dilated cardiomyopathies and arrhythmogenic right ventricular dysplasia, which are linked to mutations in sarcomeric, cytoskeletal and intercellular junction proteins, respectively.

The risk of cardiac arrhythmias and SCD in the setting of acquired structural heart disease such as ischaemic heart disease is in part genetically determined. Studies demonstrate an increased risk of SCD in patients who have a parental history of cardiac arrest.

MOLECULAR BASIS TO ARRHYTHMIA[2]

Structural and electrical remodelling in response to myocardial injury, altered haemodynamic loads and changes in neurohumoral signalling lead to alterations in:

- ion channel function
- intracellular calcium handling
- intercellular communication
- composition of intercellular matrix.

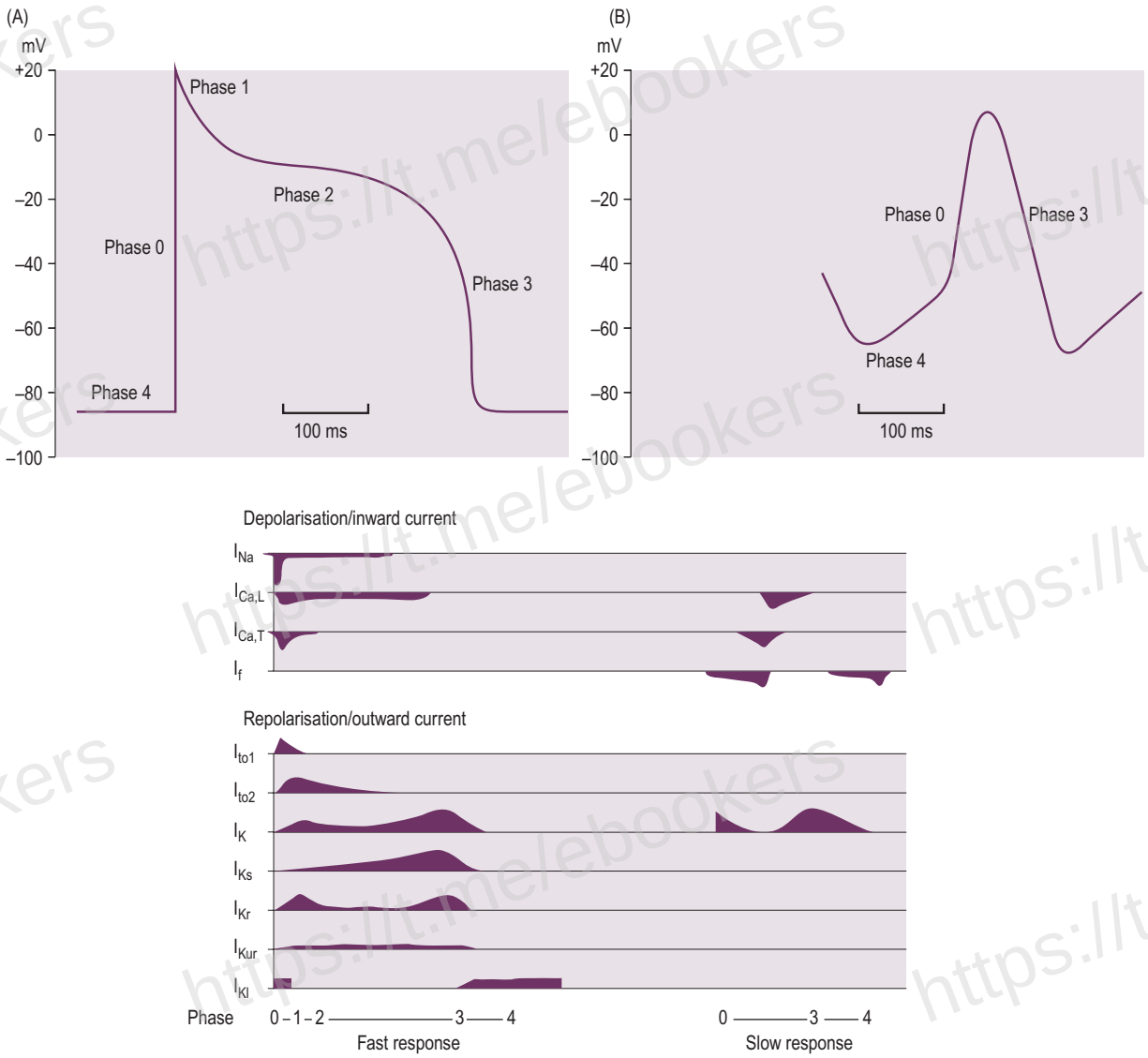


Figure 22.2 Temporal relationship between action potential and ionic channel activation for: (A) fast-response ventricular myocytes and (B) slow-response pacemaker myocytes.

All of these factors lead to heterogeneous slowing of conduction velocity and prolonged refractoriness.

Tachycardia remodelling of the atrium is associated with:

- reduced functional expression of L-type Ca^{2+} channels, intracellular Ca^{2+} overload and shortening action potential duration.

Heart failure is associated with:

- down-regulation of each of the major repolarising K^+ currents, prolonging repolarisation and resulting in susceptibility to early-after-depolarisation (EAD)-mediated arrhythmia. As these changes are heterogeneous, they also create the substrate for re-entrant arrhythmias
- reduced Na^+ channel density decreasing conduction velocity
- increased expression of Na^+–Ca^{2+} exchanger protein, leading to intracellular Ca^{2+} overload and predisposition to delayed-after-depolarisation (DAD)-mediated arrhythmia.

Intercellular ion channels or connexins at gap junctions are decreased and redistributed from the intercalated disc to lateral cell borders, slowing conduction velocity and uncoupling myocytes.

Myocardial infarction scar produces:

- heterogeneous action potential duration with zones of healing myocytes with shortened action potential and surrounding hypertrophic myocytes with prolonged action potentials
- potential anatomical circuits due to fibrous tissue separating myocyte bundles.

ARRHYTHMOGENIC MECHANISMS[4–6]

Many factors in isolation or combination give rise to the substrate of arrhythmogenesis (Fig. 22.3). Arrhythmia may arise from abnormalities of impulse generation or conduction. Table 22.2 demonstrates the relationship between mechanism and type of arrhythmia and desired antiarrhythmic effect.

ABNORMAL IMPULSE GENERATION (TABLE 22.3)

ENHANCED NORMAL AUTOMATICITY

Automaticity is the property of spontaneous impulse generation by cardiac myocytes. This results from spontaneous depolarisation during phase 4. In the SA node and subsidiary pacemaker myocytes, phase 4 spontaneous depolarisation results from an inward current, predominantly Na^+ via the non-selective cation channel I_f. SA node discharge rate is influenced by changes to channel activity. Beta-adrenergic receptor stimulation increases both I_f and $I_{Ca\text{-}T}$ conductance and rate of phase 4 depolarisation by channel phosphorylation, whereas M_2 receptor increases I_k activity during phase 3 and early phase 4 to hyperpolarise myocytes, increasing time to reach depolarisation threshold.

Enhanced normal automaticity of subsidiary atrial pacemakers, for example around pulmonary veins, is an increasingly recognised cause of atrial fibrillation (AF).

ABNORMAL AUTOMATICITY

Abnormal automaticity is the mechanism by which spontaneous impulses are generated in myocytes that are partially depolarised by a pathological process. The less negative RMP is associated with inactivation of the normal ionic currents of phase 4 depolarisation and the pacemaker current results from inward Na^+ and Ca^{2+} currents and is not readily susceptible to overdrive suppression from normal pacemaker activity. Due to this less negative membrane potential, these abnormal automatic myocytes inactivate the phase 0 fast inward Na^+ current, resulting in an impaired rate of impulse conduction (as well as contractility), which further contributes to arrhythmia. In this setting, Ca^{2+} carries the major inward current on depolarisation in these myocytes.

TRIGGERED ACTIVITY

Abnormal impulse generation from triggered activity originates from oscillations in the membrane potential that are initiated or triggered by a preceding action potential. There are two types of oscillations: EAD and DAD. EAD occurs during phase 2 or 3 of the action potential, whereas DAD occurs after the termination of depolarisation. The signal-averaged electrocardiograph (ECG) can detect after-depolarisations.

1. EADs appear as sub-threshold humps during the plateau or depolarisation phases. On reaching threshold, single or multiple action potentials can be induced. Plateau EADs are caused by an increased

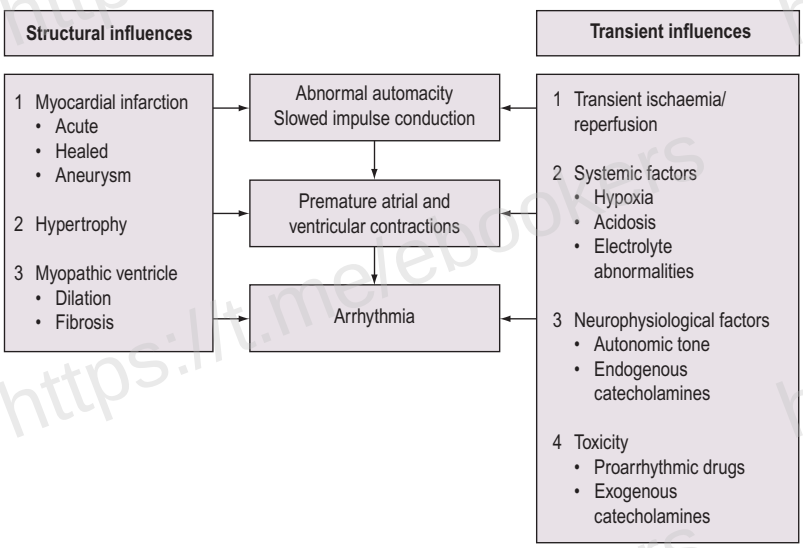


Figure 22.3 Factors that combine to form the substrate of arrhythmogenesis.

Table 22.2 Classification of mechanisms of arrhythmia and desired antiarrhythmic drug action[3]

MECHANISM OF ARRHYTHMIA	ARRHYTHMIA	ANTIARRHYTHMIC EFFECT	REPRESENTATIVE DRUGS
AUTOMATICITY ENHANCED			
Normal	Inappropriate sinus tachycardia Unifocal atrial tachycardia	Decrease phase 4 depolarisation	Beta blocker Sodium channel blockers
Abnormal	Unifocal atrial tachycardia Accelerated idioventricular rhythms VT post myocardial infarction	Hyperpolarise or decrease phase 4 depolarisation	Calcium or sodium channel blockers M_2 agonists (muscarinic receptor)
TRIGGERED ACTIVITY			
EAD	Torsade de pointes Digitalis-induced arrhythmias Some VT	Shorten action potential or suppress EAD	Increase heart rate with beta agonists or vagolytic agents, calcium channel blockers, beta blockers or magnesium
DAD		Decrease calcium overload or suppress DAD	Calcium or sodium channel blockers, beta blockers, adenosine
RE-ENTRY: SODIUM CHANNEL DEPENDENT			
Long excitable gap	Afl type 1 Circus movement tachycardia in WPW Monomorphic VT	Depress conduction and excitability	Sodium channel blockers
Short excitable gap	Afl type 2 Atrial fibrillation Circus movement tachycardia in WPW Polymorphic and monomorphic VT Bundle branch re-entry Ventricular fibrillation	Prolong refractory period	Potassium channel blockers
RE-ENTRY: CALCIUM CHANNEL DEPENDENT			
	Atrioventricular nodal re-entrant tachycardia Circus movement tachycardia in WPW VT	Depress conduction and excitability	Calcium channel blockers

DAD, Delayed after-depolarisation; *EAD*, early after-depolarisation; *VT*, ventricular tachycardia; *WPW*, Wolff–Parkinson–White syndrome.

Table 22.3 Causes of abnormal impulse generation

Enhanced normal automaticity	Adrenergic stimulation
Abnormal automaticity	Ischaemia
Early after-depolarisations	Hypoxia Hypercapnia Catecholamines Class IA antiarrhythmic drugs Class III antiarrhythmic drugs Other drugs that prolong repolarisation
Delayed after-depolarisations	Digoxin toxicity Increased intracellular Na^+ Decreased extracellular K^+ Increased intracellular Ca^{2+} Intracellular Ca^{2+} overload due to myocardial infarction or reperfusion after ischaemia

inward Ca^{2+} current (at this level of membrane potential, fast inward Na^{+} channels are inactivated) and produce slow rising and propagating action potentials. Phase 3 EADs are caused by a reduction in outward K^{+} currents and produce relatively rapidly rising and propagating action potentials. EAD amplitude and likelihood of triggered arrhythmia increase as driving rate decreases and action potential is prolonged. Tachyarrhythmia induced by EAD is more likely to occur on the background of a bradycardia.

2. DADs are produced by Na^{+}–Ca^{2+} exchanger current-induced oscillations in inward calcium current. These oscillations are caused by $[Ca^{2+}]_i$ overload saturating sarcoplasmic reticulum sequestration mechanisms, thereby leading to Ca^{2+}-induced Ca^{2+} release. Unlike EADs, DADs depend on previous rapid rhythm for their initiation.

ABNORMAL IMPULSE CONDUCTION[7]

Normal cardiac rhythm is dependent on orderly homogeneous conduction throughout atrial and ventricular tissue. This orderly homogeneity of impulse conduction can be lost by abnormal physical barriers to conduction such as infarction scars or functional disturbances in action potential leading to heterogeneity of impulse propagation. Magnitude and rate of depolarisation, presence of slow-response myocyte characteristics and rapidity of repolarisation influence speed of propagation. Functional disturbances in these properties are readily produced by channel receptor activation, ischaemia, hypertrophy and channel genetic mutation or expression.

Heterogeneity of impulse conduction may cause an arrhythmia by the phenomenon of re-entry. Re-entry describes the re-excitation of an area or entire heart by a circulating impulse. Although the classic 'bifurcating Purkinje fibre' model of Schmitt and Erlanger has given way to a much more complex picture, the essential electrophysiological requirements for re-entrant excitation remain. Requirements for re-entry are (Fig. 22.4):

- conduction block in one limb of the circuit
- slowed conduction in the other limb
- the impulse returns back along the limb initially blocked to re-enter and re-excite the pathway proximal to the block and complete the re-entry pathway.

When these properties are present, the chance of a circulating impulse producing re-entrant excitation depends on pathway geometry, the electrical properties and length of the depressed area and conduction velocity within each component. The segment of the re-entry pathway that is initially refractory and therefore blocks conduction down one limb and then recovers in time to conduct the return impulse is termed the 'excitable gap.' Therefore, the generation and subsequent maintenance of a circuit depend on this excitable gap of non-refractory tissue circulating between the advancing depolarising wave front and the repolarising tail. The resulting re-entrant impulse can be self-terminating; causing ectopic beats, or leads to atrial or ventricular tachyarrhythmia.

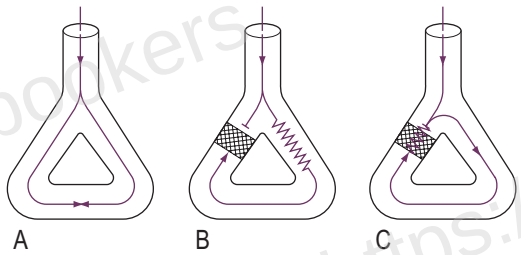


Figure 22.4 Re-entrant excitation. (A) Normal cardiac impulse conduction results in the impulse being extinguished. (B) Conduction down one limb is blocked by segment of refractory tissue (excitable gap). (C) The impulse is conducted back up the limb and arrives at the excitable gap, which has recovered from refractoriness and retrograde conduction is complete. If geometry and electrical properties are favourable, the excitable gap circulates around the re-entry loop and arrhythmia is initiated.

Risk of re-entry can be further modelled and quantified. Cardiac wavelength (λ) is the physical distance an electrical impulse travels in one refractory period; λ equals conduction velocity × refractory period (or action potential duration). Re-entry is critically dependent on the λ being shorter than the potential re-entrant pathway. If λ exceeds the path length, then the advancing impulse encroaches on the refractory tail and re-entry is terminated. Reducing λ (decreasing conduction velocity or refractory period) promotes re-entry circuits.

Re-entry may be terminated by:

- *increasing conduction velocity:* the excitable gap is abolished by the wave front arriving too early and meeting refractory tissue
- *increasing refractory period:* the excitable gap is lost
- *slowing conduction:* a unidirectional block can be converted into a complete block.

Ordered re-entry occurs along anatomical pathways which are 'macroscopic' loops (macro-re-entry), as in Wolff–Parkinson–White (WPW) syndrome. Functional circuits can be created following myocardial infarction, resulting in VT. 'Microscopic' loops (micro-re-entry) occur at the level of single fibres where antegrade and retrograde impulse propagation occurs in parallel fibres. Random re-entry refers to the generation of a circulating impulse, not from a fixed circuit but from constantly changing electrophysiologically distinct

fibres or pathways created by the circulating impulse, resulting in AF or VF.

The cellular properties that lead to impaired conduction include:

- inactivation of the phase 0 fast Na^+ channels, which reduces both the magnitude and rate of propagation of any resultant action potential
- intercellular uncoupling, which increases resistance to action potential propagation and slows conduction. Intercellular coupling is reduced by ischaemia, $[Ca^{2+}]_i$ overload, acidosis and reduced expression of intercellular ion channel connexin proteins in diseases such as chronic heart failure.

VENTRICULAR ARRHYTHMIA AND THE HIS-PURKINJE SYSTEM[8]

The Purkinje system is increasingly recognised as providing substrate for ventricular arrhythmia. Electrolyte imbalance, drugs and ischaemia during which Purkinje cells can survive in anaerobic conditions results in intracellular Ca^{++} overload, leading to enhanced automaticity and triggered arrhythmia. Triggered activity, EADs and DADs, originating in Purkinje cells during phase 2 and 3 initiate polymorphic VT and VF under these circumstances.

Recurrent ventricular arrhythmia, usually interspersed with periods of short coupling ventricular ectopics (VEs) arising from Purkinje cells allows electrical mapping of triggered activity, usually along scar borders, enabling life-saving ablation in clinical situations such as ventricular arrhythmia following acute coronary syndromes or post cardiac surgery.

The architecture of the Purkinje system in combination with areas of slowed conduction (drugs and ischaemia) can create re-entry pathways and substrate for monomorphic VT. The re-entry circuits can involve right and left bundle branches (bundle branch re-entry), single left fascicle (intrafascicle re-entry) or both left fascicles with intervening slower conducting myocardium (interfascicular re-entry). These discrete circuits can be localized by vulnerability to catheter touch and then induced or entrained by electrical pacing. The resulting VT can be terminated by programmed electrical stimulation and recurrence prevented by ablation.

ELECTROPHYSIOLOGICAL EFFECTS OF ISCHAEMIA

Both hypoxia and acidosis are implicated in the production of a less negative RMP in ischaemia. A rise in extracellular K^+ results from impairment of the adenosine triphosphate (ATP)-dependent K^+ inward channels. As $[K^+]_o/[K^+]_i$ is the major determinant of the RMP, intracellular K^+ loss results in a less negative RMP.

The consequences of this are:

- abnormal automaticity
- inactivation of the fast inward Na^+ channels, which slows the conduction velocity.

These arrhythmogenic effects of ischaemia are offset by activation of I_{KATP} K channels by ligand ADP binding, increasing phase 1 and 2 K repolarising current resulting in the antiarrhythmic action of shortening the action potential.

ELECTROLYTE ABNORMALITIES AND ARRHYTHMIA[9]

POTASSIUM

Hyper- and hypokalaemia both cause arrhythmia mediated by the resultant changes in RMP (Table 22.4). In ischaemia, hyperkalaemia at the local tissue level caused by a pathological extracellular shift of K^+ is the major factor contributing to ventricular arrhythmia in this setting. In hypokalaemia, the dispersion of pacemaker activity and the effect on repolarisation are similar to the electrophysiological effects of cardiac glycosides and beta-adrenergic agonists, and it is not surprising that a combination of these factors is associated with an increased incidence of arrhythmia. The increased risk of death in hypertensive patients treated with thiazide diuretics has been attributed

Table 22.4 Arrhythmogenic effects of potassium disturbance

	ARRHYTHMOGENIC EFFECTS	ELECTROCARDIOGRAM CHANGES	ARRHYTHMIA
HYPERKALAEMIA	Less negative RMP Inactivation of fast Na^+ channels Slowed conduction velocity	Peaked T-waves Widening of P-wave and QRS complex	Sinus node suppression Atrioventricular block Ventricular fibrillation
HYPOKALAEMIA	Prolongation of rapid repolarisation Hyperpolarisation of RMP Increased pacemaker activity in Purkinje and ventricular fibres	U-waves ST-segment and T-wave changes	Atrial and ventricular ectopy Atrial and ventricular tachyarrhythmia Ventricular fibrillation

RMP, Resting membrane potential.

to hypokalaemia (and possibly hypomagnesaemia)-induced arrhythmia (Multiple Risk Factor Intervention Trial). Thiazide-induced hypokalaemia ventricular ectopy is worsened by exercise.[10] Hypokalaemia is associated with VF and VT following acute myocardial infarction (AMI). The increased incidence of VF with a serum K^+ less than 3.5 mmol/L is clearly established and the probability of VT increases as the serum K^+ decreases. During AMI the incidence of VF/VT was 15% at 4.5 mmol/L, 38% at 3.5 mmol/L, 55% at 3.0 mmol/L and 67% at 2.5 mmol/L.[11]

MAGNESIUM

The antiarrhythmic properties of Mg^{2+} are clearly established, but a causal relationship between hypomagnesaemia and arrhythmia is largely circumstantial. Decreased extracellular Mg^{2+} by itself has little effect on the electrophysiological properties of myocytes or the ECG. Hypomagnesaemia has been implicated in the genesis of VT/VF in patients with hypertension and heart failure receiving thiazide or loop diuretics, acute alcohol intoxication or withdrawal and possibly with AMI. The product of K^+ and Mg^{2+} is the best predictor of arrhythmia in hypertensive patients taking thiazide diuretics.[12]

AUTONOMIC NERVOUS SYSTEM AND VENTRICULAR ARRHYTHMIA[13]

The parasympathetic nervous system mediates vagal effect via I_{KAch}, muscarinic-gated K channels, which hyperpolarises cell membrane and decreases phase 4 depolarisation stabilising membrane potential decreasing rate and automaticity.

The autonomic nervous system, particularly vagal tone, also has a significant effect on the occurrence of post myocardial infarction VF, as seen by the following:

- High vagal tone is associated with better outcome and less susceptibility to exercise-induced VF with new ischaemia in animal models.
- Post myocardial infarction exercise training results in an increased vagal tone, which inhibits inducible VF.
- Implantable electrical vagal stimulation and muscarinic agents, including edrophonium, are protective.
- The protection is not heart rate related, as the protection remains even when atrial pacing is used to maintain the heart rate.
- The administration of atropine increases the likelihood of developing VF.

Vagal tone can be measured by variability in the heart rate (RR interval) or blood pressure rise induced by the pressor agent phenylephrine. Heart rate variability is considered a measure of tonic vagal activity, whereas the phenylephrine method is considered a measure of magnitude of the vagal reflex in response to stimulus. A reduced vagal tone has been found post infarction in humans, which returns to normal over a 3–6-month period. There is no relationship between vagal tone and ejection fraction and the origin of reduced vagal tone post infarction appears to be due to afferent stimulation in response to necrotic tissue and impaired cardiac contractile geometry. This reduced vagal tone has also been shown to be predictive of mortality and inductility of arrhythmia at electrophysiological study (EPS).

HETEROGENEITY OF REPOLARISATION: T-WAVE ALTERNANS[14]

Regional differences in repolarisation are associated with preconditions for conduction block, re-entry and life-threatening arrhythmias. This heterogeneity is seen in settings of impaired sarcoplasmic reticulum uptake of Ca^{2+} during ischaemia, drug proarrhythmia and congenital prolonged QT syndromes. In addition to prolonged QTc, ECG changes show variability of T-waves. This variability can manifest as visible T-wave alternans (TWA), defined as a beat-to-beat alternation in the morphology and amplitude of the ST segment or T-wave (Fig. 22.5).

Computerised analytical methods for detecting non-visual TWA in the microvolt range have been developed for predicting risk of ventricular tachyarrhythmia, sudden death and need for implantable cardioverter-defibrillators. The utility of TWA appears to be better than left ventricular function. TWA can be quantified as the moving average of beat-to-beat variation in T-wave amplitude (Fig. 22.6).

TWA may find a role in guiding drug therapy as a marker of antiarrhythmic effect and proarrhythmia.

PROARRHYTHMIC EFFECTS OF ANTIARRHYTHMIC DRUGS[15,16]

Accompanying proarrhythmia with the use of antiarrhythmic drugs is increasingly recognised. The 'quinidine syncope' due to VF and polymorphic VT at therapeutic concentrations was also seen with disopyramide. The Cardiac Arrhythmia Suppression Trial (CAST) clearly defined the magnitude of this deleterious side effect in drugs that were previously perceived to be of benefit. This study, which involved flecainide, encainide and moricizine (a class IA drug), was terminated early because of adverse outcome in

Figure 22.5 Visible T-wave alternans and prolonged QT associated with heterogeneity of repolarisation.

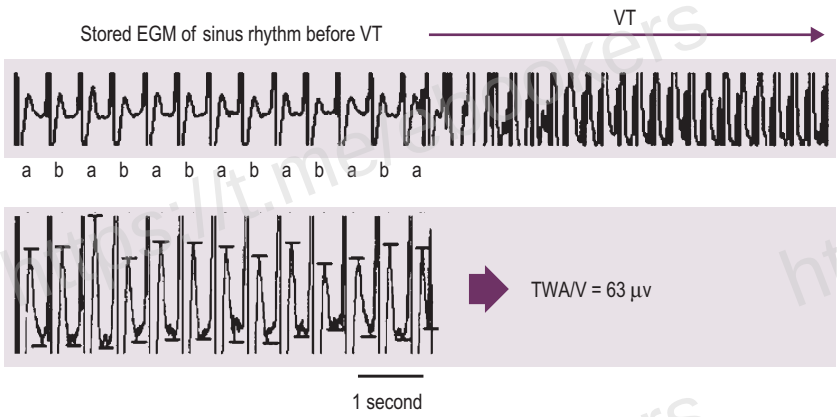


Figure 22.6 Example of heterogeneous repolarisation resulting in beat-to-beat microvolt fluctuation in T-wave amplitude measured by the Modified Moving Average method at 63 microvolts heralds the onset of ventricular tachycardia. *EGM*, Electrogram. *(From American Heart Association, with permission.)*

the flecainide and encainide groups (relative risk of arrhythmic death or non-fatal cardiac arrest of 3.6, 95% confidence interval [CI] 1.7–8.5). Proarrhythmia is reported between 5.9% and 15.8% depending on agent, clinical setting and definition of proarrhythmia, and now considered ubiquitous with all antiarrhythmic drugs.

Proarrhythmia has been defined as an increase in frequency of ventricular ectopic beat (VEB) or aggravation of the target arrhythmia on Holter monitor or exercise test. Manifestations of proarrhythmia not only include VEB, monomorphic and polymorphic VT and VF, but also bradyarrhythmias and atrial flutter (Afl) with 1:1 AV conduction. Most proarrhythmic events occur soon after starting the drug, but late arrhythmias are also a significant problem.

Proarrhythmia appears to be correlated with the degree of drug-induced QT prolongation, T-wave variability and characteristics of sodium channel blockade by the agent involved. Sodium channel-blocking agents with a long-time constant for recovery of the sodium channel blockade cause more pronounced blockade, even at slow heart rates, slow conduction to a greater extent and are associated with greater proarrhythmia. Agents with a short-time constant of sodium channel blockade, where sodium channel blockade is more pronounced at fast heart rates (e.g. class IB: lidocaine and mexiletine) are less proarrhythmic than drugs with long-time constants (e.g. class IC: flecainide and propafenone). Class III drugs and quinidine proarrhythmia correlate with degree of QT prolongation.

The mechanism of drug proarrhythmia is probably via both slowing of conduction, triggered activity and abnormal automaticity. Paradoxically, slowing conduction, which may block a re-entry circuit, may also create the very substrate needed for re-entry, unidirectional block and an excitable gap. The existence of a re-entrant circuit requires the circulating wave front of the impulse not to catch up with the refractory tissue behind the tail. Re-entry is more likely to occur with a shorter refractory period and reduced conduction velocity (Fig. 22.7).

Increasing conduction velocity is an ideal antiarrhythmic property but there are no antiarrhythmic drugs that accelerate conduction. However, antiarrhythmic drugs readily slow conduction and the degree of conduction slowing and therefore proarrhythmia tendency correlates with the potency of antiarrhythmic properties.

Prolonging the refractory period is also an ideal antiarrhythmic property, which increases the likelihood of abolishing any excitable gap by ensuring the wave front of a re-entrant circuit meets refractory tissue. The potency of class IA and III antiarrhythmic agents is dependent on the prolongation of the refractory period. This property is also protective against proarrhythmia due to re-entry mechanism. The effect of class IB agents on shortening the refractory period will contribute to proarrhythmia by this mechanism in this class.

Surface mapping of the heart has been used to quantify proarrhythmic effect. The scale of potency of proarrhythmia has been found to be:

flecainide > propafenone > quinidine > disopyramide > procainamide > mexiletine > lidocaine > sotalol

Amiodarone was not included in this study but presumably its proarrhythmic potential is similar to other class III agents and less than the class I agents.

Antiarrhythmic drugs are effective at suppressing abnormal automaticity, with the exception of triggered automaticity due to EAD. Class IA, class III and many non-antiarrhythmic drugs can produce proarrhythmia via EAD. These drugs increase not only the frequency of EAD, but also the likelihood of them leading to

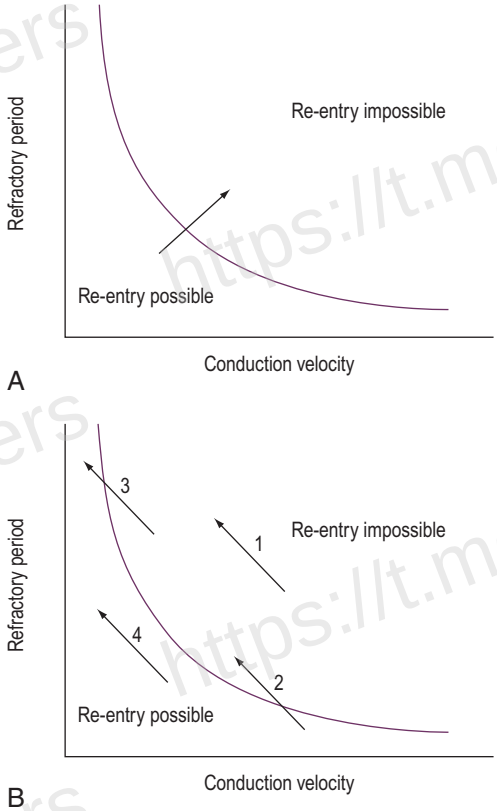


Figure 22.7 (A) Graph of refractory period of an excitable gap versus its conduction velocity around a theoretical re-entrant circuit. When conduction velocity is high enough so that refractory period of excitable gap exceeds circuit time, re-entry is impossible. *Arrow* demonstrates the action of an 'ideal' antiarrhythmic drug, which prolongs the refractory period and increases conduction velocity. (B) With antiarrhythmic drugs that increase the refractory period and slow conduction, the net effect of an antiarrhythmic drug may have no effect on proarrhythmia *(arrows 1 and 4)*, decrease proarrhythmia *(arrow 2)* or increase proarrhythmia *(arrow 3)* depending on properties of a potential re-entrant circuit. *(Adapted from Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death.* Circulation. *1992;85(suppl 1): 77–91, with permission.)*

triggered tachyarrhythmia. Slowing repolarisation, which leads to QT prolongation and slower heart rate, is central to this increased frequency and sensitivity to EAD. EAD manifests as prominent and bizarre T-U waves on the ECG and, if triggered activity results, VEB and ventricular tachyarrhythmia may occur. Torsade de pointes is the classical resulting arrhythmia, although less classical polymorphic VT and VF can result. Risk of proarrhythmia via this mechanism correlates with the degree of QT prolongation.

Box 22.1 Factors facilitating antiarrhythmic drug proarrhythmia[13]

Toxic blood levels due to excessive dose or reduced clearance from old age, heart failure, renal disease or hepatic disease
Severe left ventricular dysfunction; ejection fraction less than 35%
Pre-existing arrhythmia or arrhythmia substrate
Digoxin therapy
Hypokalaemia or hypomagnesaemia
Bradycardia
Combinations of antiarrhythmic drugs and concomitant drugs with similar toxicity

All antiarrhythmic drugs are capable of producing bradyarrhythmia via decreasing normal automaticity and slowing conduction. Digoxin can be proarrhythmic via the production of triggered activity due to DAD.

Antiarrhythmic drug proarrhythmia is facilitated by several factors which are frequently found in patients on antiarrhythmic drugs or with heart disease (Box 22.1).

MANAGEMENT OF THE PATIENT WITH A CARDIAC ARRHYTHMIA

HISTORY AND PHYSICAL EXAMINATION

A careful history is important. Specific questions should confirm or exclude palpitations, syncope, chest pain, shortness of breath, ischaemic heart disease (especially previous myocardial infarction), congestive cardiac failure, valvular heart disease, thyrotoxicosis and diuretic therapy without adequate potassium supplements. A family history is helpful for arrhythmias associated with inherited disorders (e.g. LQTS and hypertrophic obstructive cardiomyopathy). The physical examination looks for underlying structural heart disease and signs to assist diagnosis, and assesses haemodynamic consequences of the arrhythmia.

VAGAL MANOEUVRES

Vagal manoeuvres may be undertaken during examination. These reflexly increase vagal tone, thereby prolonging AV node conduction and refractoriness. The effect may be:

- transient slowing of sinus tachycardia as SA nodal discharge rate is slowed
- termination of AV nodal re-entry tachycardia (AVNRT) and AV re-entry tachycardia (AVRT)
- unmasking (but not reversion) of atrial tachycardia, flutter (Fig. 22.8) and fibrillation.

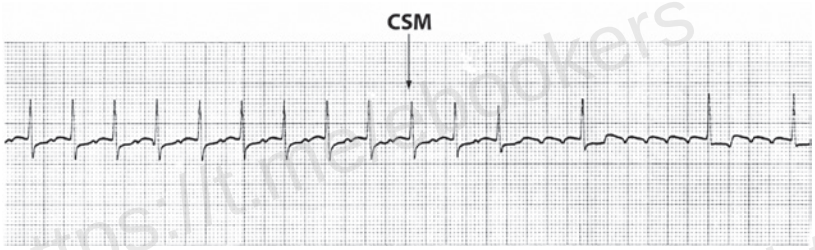


Figure 22.8 Atrial flutter with 2:1 atrioventricular (AV) block. Carotid sinus massage *(CSM)* increases AV block to 4:1, then 6:1.

VT is not affected. Carotid sinus massage has been most commonly used. Valsalva manoeuvre or iced water to the face may be useful. Eyeball pressure should be avoided as eye damage may result.

Increasingly, the Valsalva manoeuvre is recommended. Maximum vagal effect is achieved with supine positioning and a Valsalva manoeuvre of 15 seconds' duration and a pressure of 40 mm Hg (5.32 kPa) with an open glottis. An adequate Valsalva manoeuvre method can be achieved by getting the patient to blow into a 10 mL syringe in an attempt to move the plunger.

INVESTIGATIONS

A 12-lead ECG should be recorded with a longer rhythm strip (usually lead II or V_1). If P-waves are not visible, atrial activity may be recorded using an oesophageal electrode or pacing lead, or via a central venous catheter or the right atrial injectate port of a pulmonary artery catheter, using 20% saline and a bedside monitor.[17]

Holter monitoring requires prolonged (usually 24–72 hours), non-invasive, ambulatory ECG monitoring, sometimes combined with exercise testing. For infrequent symptoms suggestive of arrhythmia, implantable loop recorder can be inserted and interrogated. EPS, which involves invasive electrophysiological testing with programmed electrical stimulation, attempts to reproduce the spontaneously occurring arrhythmia.[18,19] EPS is not clearly superior to Holter monitoring in evaluating drug treatment for ventricular arrhythmias. Other investigative techniques being studied include signal-averaged ECG, heart rate variability and electrical alternans measurement.[13,20]

MANAGEMENT OF SPECIFIC ARRHYTHMIAS

Treatment has two aspects: acute termination of the arrhythmia and long-term prevention. The decision whether to treat depends on the rhythm diagnosis, haemodynamic consequences, aetiology of the arrhythmia and the prognosis (e.g. risks of sudden death or long-term complications).

ECTOPIC BEATS

These are premature impulses originating from the atria, AV junction, Purkinje system or ventricles. The coupling interval (time between the ectopic and the preceding beat) is shorter than the cycle duration of the dominant rhythm.

PREMATURE VENTRICULAR ECTOPIC BEATS

These are also known as ventricular premature beats and ventricular premature complexes. The ventricle is not activated by the normal rapidly conducting bundle branches, and a wide QRS complex results from slow ventricular conduction.

ECG

There is no preceding P-wave.

- Premature complexes occur before the next expected QRS.
- QRS is wide (>120 ms).
- T-wave of opposite polarity to the QRS (Fig. 22.9).
- VEB is not conducted retrogradely to the SA node.
- SA node is therefore not reset, and there is temporary AV dissociation with a full compensatory pause; the interval between the normal QRS complexes on either side of the VEB will usually be twice that of the dominant sinus rhythm.

Occasionally VEBs may not produce any pause, and are said to be interpolated (see Fig. 22.9). Interpolated VEBs occur when the background sinus rhythm is slow. The retrograde conduction into the AV node renders it partially refractory to the next impulse and its conduction through the AV node is slowed and the PR interval is prolonged. A VEB following each sinus beat is ventricular bigeminy. Ventricular trigeminy refers to recurring sequences of a VEB followed by two sinus beats. Two VEBs in succession are a couplet, and three, a triplet.

CLINICAL

Even when frequent, complex, or in short runs of non-sustained VT, VEBs are not associated with risk of sudden death in asymptomatic healthy adults.[21]

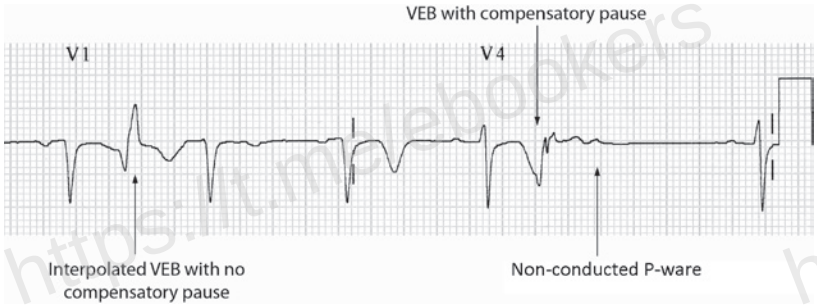


Figure 22.9 Sinus rhythm with an interpolated ventricular ectopic beat *(VEB)* without a compensatory pause and a VEB with a following non-conducted P-wave, resulting in a compensatory pause.

However, there is increased risk of cardiovascular death with:

- *exercise-induced VEB:* risk of death 2.53 (95% CI 1.65–3.88)[22]
- *AMI and VEB:* frequent and complex VEBs often precede VF or sustained VT and are a marker of risk of subsequent SCD.

Apart from ischaemic heart disease, VEB may be associated with cardiomyopathy, valvular disease, myocarditis and non-cardiac precipitating factors (e.g. electrolyte and acid-base disturbances, hypoxia and drugs such as digoxin).

TREATMENT

Drug treatment of VEB is rarely indicated and may be dangerous.

- Correct potassium and magnesium.
- Severely symptomatic patients with frequent complex VEB may benefit from judicious beta blockade.
- The underlying cause of VEB is often more clinically relevant than the arrhythmia. Following myocardial infarction, beta-adrenergic blockers, which are indicated for long-term benefit, will also likely suppress VEB.
- Prophylactic lidocaine following AMI will increase total mortality and has been abandoned.[23,24]
- Attempts at long-term VEB suppression with class IC agents (flecainide and encainide), even if successful, increase mortality.[15]

SUPRAVENTRICULAR TACHYCARDIAS (BOX 22.2)[25]

Supraventricular tachycardia (SVT) is any tachycardia that requires atrial or AV nodal tissue for initiation and maintenance.

- SVTs are usually conducted rapidly through the bundle branches so that QRS complexes are narrow.
- All narrow-complex tachycardias are SVT and wide-complex tachycardias are usually ventricular.
- However, SVT may be wide complex in the setting of bundle branch block (BBB) and pre-excitation.

Box 22.2 Classification of supraventricular tachycardia

Atrioventricular (AV) node dependent
AV nodal re-entry tachycardia: re-entry within the AV node
AV re-entry tachycardia: re-entry includes accessory pathway between atria and ventricles
Accelerated idionodal rhythm: increased automaticity of AV node
AV node independent
Afl: re-entry confined to atria
Atrial fibrillation: multiple re-entry circuits confined to atria
Unifocal atrial tachycardia: usually due to increased automaticity
Multifocal atrial tachycardia: increased automaticity or triggered activity
Others: sinus node re-entry tachycardia

Afl, Atrial flutter.

A clinically useful classification divides SVTs into AV node-dependent and AV node-independent. Distinguishing between AV node-dependent and independent SVTs can be difficult. Vagal manoeuvres or drugs that prolong AV nodal refractoriness (e.g. adenosine) may assist in diagnosis[26]:

- Temporary AV block with unchanged atrial rate indicates AV node independence.
- Slowing or reversion of the tachycardia diagnoses AV dependence.

AV NODE-DEPENDENT SVT

In these SVTs, sometimes referred to as junctional tachycardia, the re-entry circuit or ectopic focus involves the AV node or junction. Blocking the AV node with drugs such as adenosine or vagal manoeuvres will terminate these SVTs.

AV NODE-INDEPENDENT SVT

Also referred to as atrial tachycardia, the atrial tissue only is required for the initiation and maintenance of the tachycardia. Blocking the AV node will not terminate these SVTs; it will merely slow the ventricular rate.

AV NODAL RE-ENTRY TACHYCARDIA (FIG. 22.10)

Re-entry tachycardia is confined to the AV node. Antegrade conduction to the ventricles usually occurs over the slow pathway and retrograde conduction over the fast pathway.

ECG

There is regular narrow-complex tachycardia (140–220 beats/min) with abrupt onset and termination. P-waves are not usually observed as they are buried in the QRS complexes (Fig. 22.11).

CLINICAL

AVNRT is a common arrhythmia that is not usually associated with structural heart disease. The major symptom is palpitations.

TREATMENT

Vagal manoeuvres slow conduction through the AV node and may 'break' the tachycardia. If vagal manoeuvres fail, adenosine is the drug of choice and nearly all AVNRT will revert with adenosine.[24,26] Verapamil has been used in the past, but causes hypotension, which may be prolonged if cardiac function is depressed or patients are receiving beta-adrenergic blockers. Sotalol, amiodarone and flecainide may also be effective but are rarely used. Rapid atrial pacing will usually terminate AVNRT but is rarely needed.

Cardioversion is occasionally necessary when drugs are ineffective or when severe haemodynamic instability is present.

PREVENTION

Troublesome recurring episodes of AVNRT can be cured by radiofrequency ablation, using a transvenous catheter to interrupt the re-entrant circuit permanently.

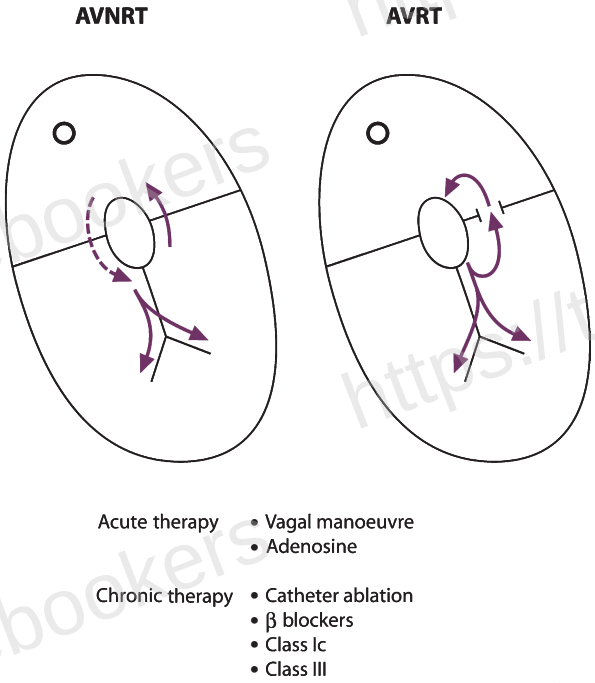


Figure 22.10 Atrioventricular nodal re-entry tachycardia *(AVNRT)* has both pathways in the AV node. The conduction occurs over the slow pathway and retrogradely over the fast pathway. AV re-entry tachycardia *(AVRT)* involves antegrade conduction through the AV node and retrograde conduction through an accessory pathway.

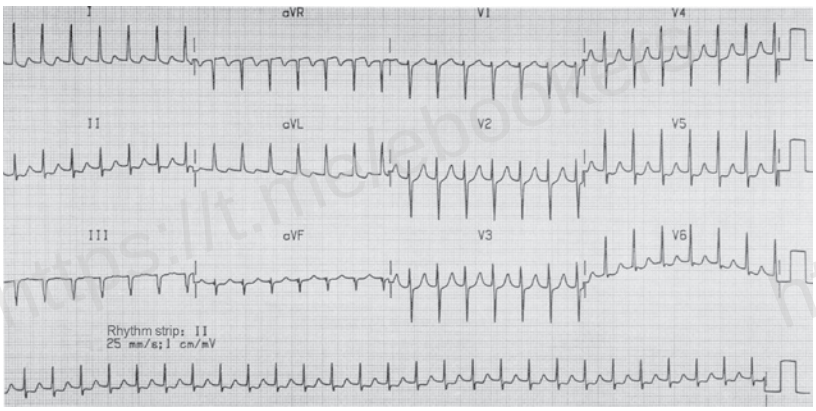


Figure 22.11 Atrioventricular nodal re-entry tachycardia. Narrow QRS tachycardia at 160 beats/min. P-waves are not apparent and are buried in the QRS complex.

AV RE-ENTRY TACHYCARDIA (SEE FIG. 22.10)

The re-entry pathway consists of the AV node and an accessory pathway, which bypasses the AV node. The accessory pathway may be evident during sinus rhythm, with the ECG showing pre-excitation: short PR interval, delta wave and widening of the QRS (see WPW, below, under Pre-excitation syndrome). However, in 25% of cases, the accessory pathway conducts only retrogradely from ventricle to atria and the ECG pre-excitation will be concealed in sinus rhythm. Orthodromic AVRT, with antegrade nodal and retrograde accessory pathway circuit, is the most common regular SVT in patients with accessory pathway.

ECG

The ECG is similar to AVNRT. The length of the re-entry circuit is, however, greater and the accessory AV pathway is some distance from the AV node. It therefore takes longer for the impulse to be conducted backwards to the atria, and so the retrograde P-wave usually occurs after the QRS, sometimes at some distance, and is inverted in leads II, III and aVF (Figs 22.12 and 22.13).

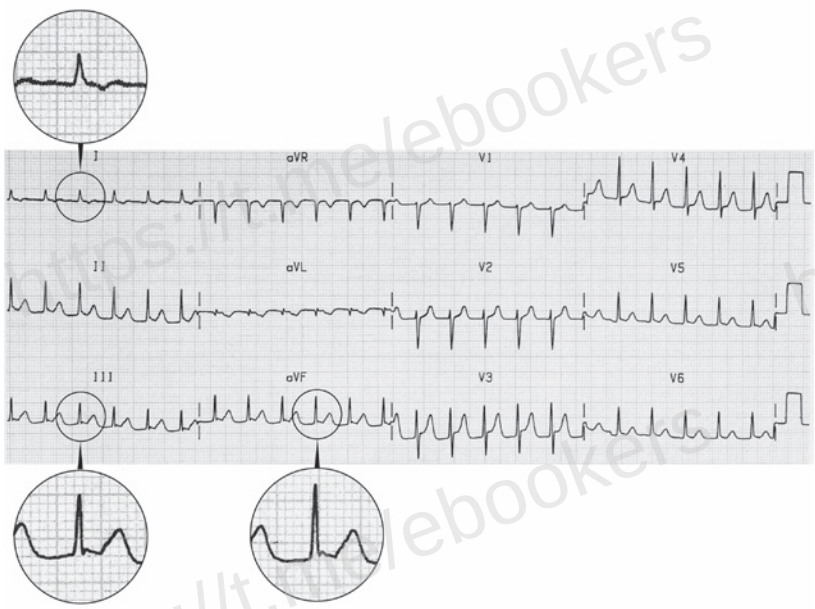


Figure 22.12 Atrioventricular re-entry tachycardia. Narrow QRS tachycardia at 135 beats/min. Inverted P-wave in leads I, II, III and aVF just following the QRS complex.

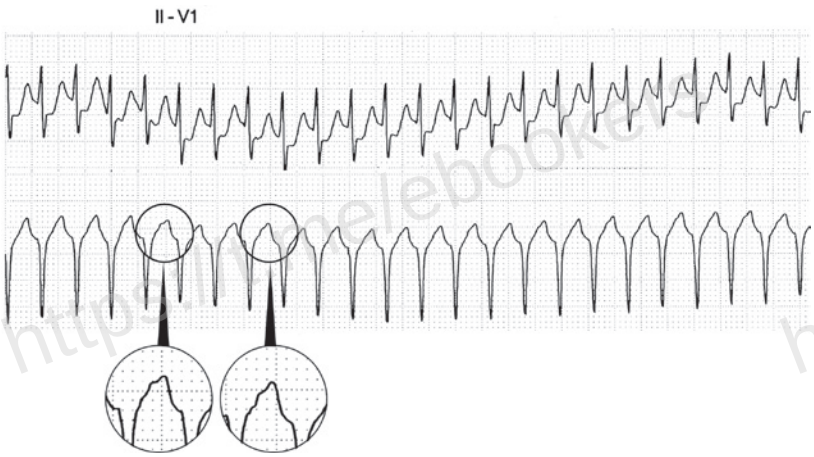


Figure 22.13 Atrioventricular re-entry tachycardia. Rate is 214 beats/min. P-wave deflection is just seen on the upslope of the T-wave in lead V_1.

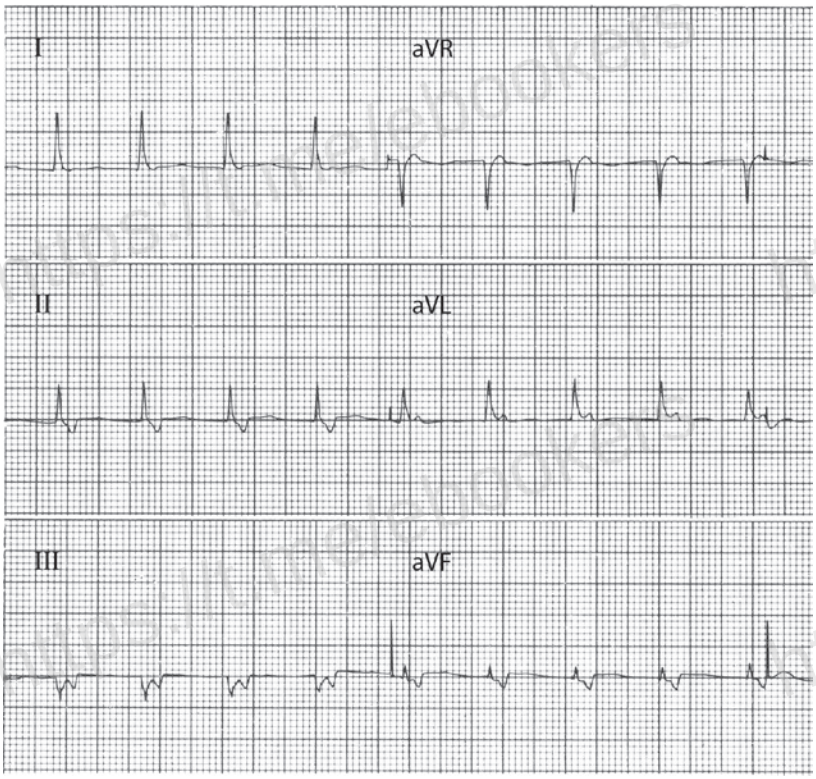


Figure 22.14 Accelerated idionodal rhythm: 105 beats/min. Inverted P-wave is immediately following the QRS complex in leads II, III and aVF.

CLINICAL
AVRT is similar to AVNRT, although antegrade conduction over the accessory pathway may be very rapid with WPW, if AF occurs.

TREATMENT[23,26]
Acute treatment is identical to AVNRT, but verapamil should be avoided in WPW syndrome, as it may block the AV node, facilitating very rapid conduction to the ventricles via the accessory pathway.[27]

PREVENTION
Drugs such as sotalol and flecainide may prevent recurrence of the tachycardia. Radiofrequency ablation of the accessory pathway is usually curative.

ACCELERATED IDIONODAL RHYTHM
Increased automaticity of the AV junction (above the inherent discharge rate of 40–60 beats/min) is the usual cause of this arrhythmia. The often-used term 'non-paroxysmal AV junctional tachycardia' is cumbersome and misleading: junctional rate is commonly 60–100 beats/min, not strictly a tachycardia. AV dissociation is often present, but there may be synchronisation of the two pacemakers – so-called isorhythmic dissociation.

ECG
There are narrow complexes on the ECG at a regular rate (60–130 beats/min) (Fig. 22.14), often with independent atrial activity. With isorhythmic dissociation, the P-wave is either fixed relative to the QRS complex (usually just after) or oscillates to and fro across the QRS in a rhythmical manner.

CLINICAL
It may be observed in normal persons, but is often associated with structural heart disease, especially following inferior myocardial infarction. Digoxin intoxication is another important cause.

TREATMENT
In most cases, the rhythm is transient and well tolerated, and no treatment is required. Treatment is otherwise directed towards the underlying cause.

UNIFOCAL ATRIAL TACHYCARDIA
This is sometimes called ectopic atrial tachycardia to distinguish it from the atrial tachycardia (referring collectively to unifocal atrial tachycardia, Afl and AF). However, it is inappropriate to call atrial tachycardia paroxysmal atrial tachycardia. Paroxysmal, by definition, indicates an abrupt onset and termination, which

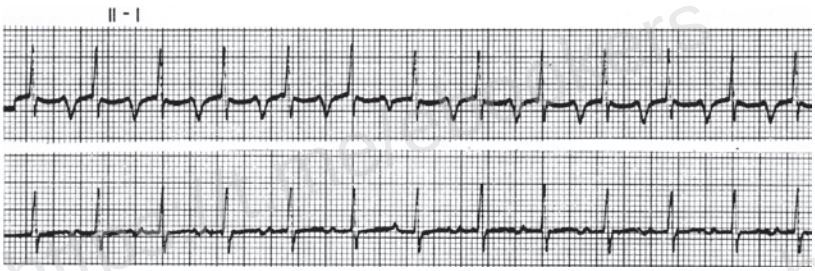


Figure 22.15 Unifocal atrial tachycardia with 1:1 atrioventricular conduction; rate is 140 beats/min. Large, inverted P-waves are seen in lead II.

applies less commonly to unifocal atrial tachycardia. Vagal manoeuvres will not terminate this arrhythmia, but AV block may be induced, or increased if already present.

ECG

P-wave morphology is abnormal but monomorphic. Atrial rate is often 130–160 beats/min, and may occasionally exceed 200 beats/min. Atrial rate distinguishes unifocal atrial tachycardia from Afl, with Afl greater than 250 beats/min. The QRS complexes will usually be narrow (Fig. 22.15). AV block is common (Fig. 22.16).

CLINICAL

Digitalis intoxication is the most common cause, especially when AV block is present. Other causes include myocardial infarction, chronic lung disease and metabolic disturbances.

TREATMENT[23]

If applicable, digitalis is stopped and the toxicity treated. Otherwise, digoxin may be used to control the ventricular rate. Beta-adrenergic blockers or amiodarone are alternatives. Rapid atrial pacing may be ineffective if the arrhythmia is due to increased automaticity, although it may increase AV block, thereby slowing ventricular rate. Synchronised DC shock may be necessary, but is avoided if digitalis intoxication is suspected.

MULTIFOCAL ATRIAL TACHYCARDIA[28]

Multifocal atrial tachycardia (MAT) is defined as an atrial rhythm with a rate greater than 100 beats/min, with organised, discrete non-sinus P-waves having at least three different forms in the same ECG trace. The baseline between P-waves is isoelectric, and the PP, PR and RR intervals are irregular. This is an uncommon arrhythmia, also known as chaotic or mixed atrial tachycardia.

ECG

There are irregular atrial rates, usually 100–130 beats/min, with varying P-wave morphology (at least three

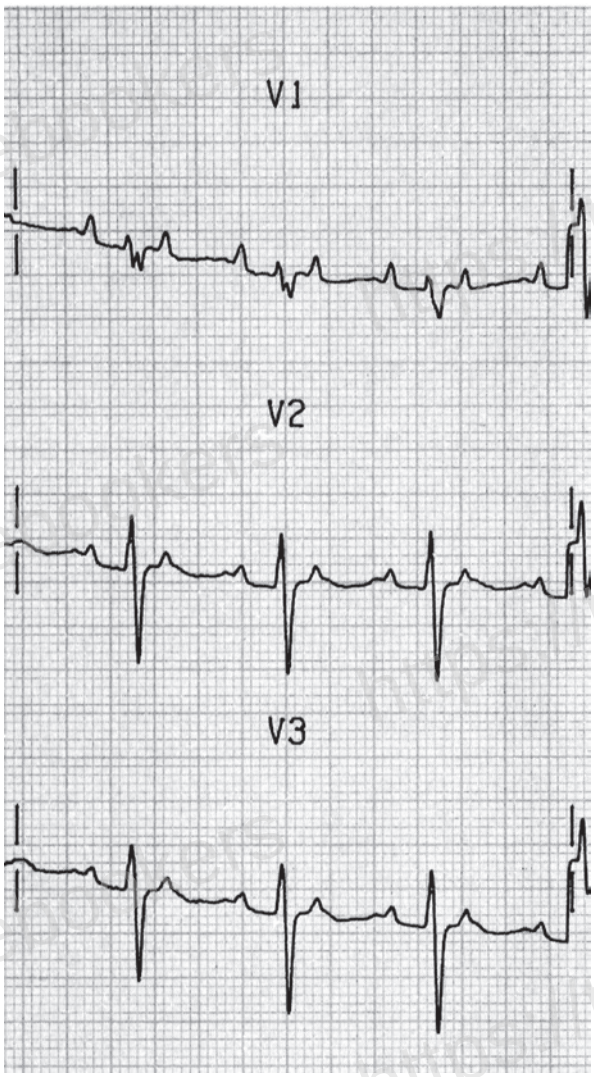


Figure 22.16 Unifocal atrial tachycardia with 2:1 atrioventricular conduction. Atrial rate is 170 beats/min.

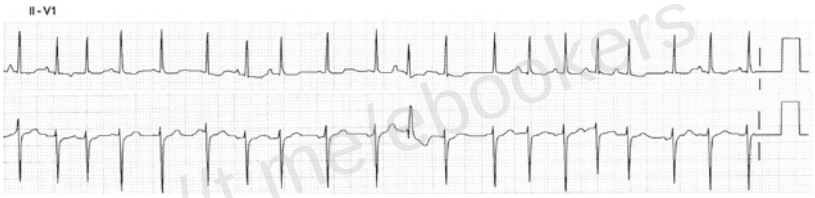


Figure 22.17 Multifocal atrial tachycardia with the rate about 130 beats/min. There is varying P-wave morphology and PR intervals. Note the wide complex preceded by a P-wave. The aberrant intraventricular conduction is related to the long-short cycle length sequence.

different P-wave morphologies and varying PR interval) and some degree of AV block (Fig. 22.17). Most P-waves are conducted to the ventricles, usually with narrow QRS complexes.

CLINICAL

MAT is often misdiagnosed and inappropriately treated as AF. This rhythm occurs most commonly in critically ill elderly patients with chronic lung disease and cor pulmonale, and is associated with a very high mortality from underlying disease. Theophylline has been implicated as a precipitating cause, and rarely, digoxin.

TREATMENT

Treatment should correct the underlying cause (e.g. treatment of cardiorespiratory failure, electrolyte and acid-base abnormalities and theophylline toxicity). Spontaneous reversion is common, and few patients require antiarrhythmic therapy. Magnesium is the drug of choice for acute control.[29] Beta blockers are probably more effective than diltiazem, but because of the common association of MAT with obstructive lung disease have limited utility. Digoxin and cardioversion are ineffective, which highlights the need to differentiate MAT from AF. Longer-term control is best achieved with diltiazem in patients with good left ventricular (LV) function and amiodarone in those without.

ATRIAL FLUTTER[30]

Afl is an intra-atrial macro-re-entrant arrhythmia with an impulse and contraction wave circulating the atrium at rates of 250–350 beats/min, and in most cases, close to 300 beats/min. Afl occurs at about one-tenth the frequency of AF, often coexisting with AF, with 56% eventually developing AF. Afl is more common in males and incidence increases with age. Conditions associated with Afl are shown in Box 22.3.

AV conduction in Afl is usually 2:1, resulting in a regular rhythm, but conduction may be irregular. Rarely 1:1 AV conduction can occur and may be lethal.

Afl is classified according to the anatomical pathway of the circuit. Right atrial cavotricuspid-isthmus-dependent flutter involving a circuit bounded by tricuspid orifice, vena cavae orifices, Eustachian and crista terminalis, is overwhelmingly most common. From a left anterior oblique view, this counterclockwise circuit makes up 90% of Afl cases and is classically referred to as 'typical.' Circuits can also be clockwise, involve the right atrium but with different circuits relating to scars or be located in the left atrium.

Box 22.3 Conditions associated with atrial flutter

- Valvular heart disease
- Myocardial infarction
- Pericardial disease
- Cardiac tumours
- Hypertrophic cardiomyopathy
- Congenital heart disease
- Post surgical repair of congenital heart disease
- Post cardiothoracic surgery
- Post major non-cardiac surgery
- Severe pulmonary disease
- Pulmonary embolus
- Thyrotoxicosis
- Acute alcohol intoxication

ECG

'Typical' Afl waves (characteristic sawtooth appearance with no isoelectric baseline) are best seen in V_1, and are negative in inferior leads with positive waves in V_1 that transition to negative in V_6 (Fig. 22.18). Rapid QRS waves may obscure typical flutter waves, and vagal manoeuvres may unmask them (see Fig. 22.8). AV conduction block (usually 2:1) is usually present, so that alternate flutter waves are conducted to the ventricles, with a ventricular rate close to 150 beats/min. Frequently flutter waves are not obvious and a ventricular rate of 150 beats/min leads to the presumption of Afl (Fig. 22.19). 'Non-typical' Afl (Type II), normally associated with scar or structural abnormalities, often results in greater atrial and ventricular rates (Fig. 22.20). Treatment with drugs that affect AV node conduction may lead to higher degrees of AV block (Fig. 22.21) and/or variable AV block with irregular QRS duration. Afl with 1:1 conduction is associated with sympathetic overactivity, class I antiarrhythmic drugs (which slow atrial discharge rate to around 200

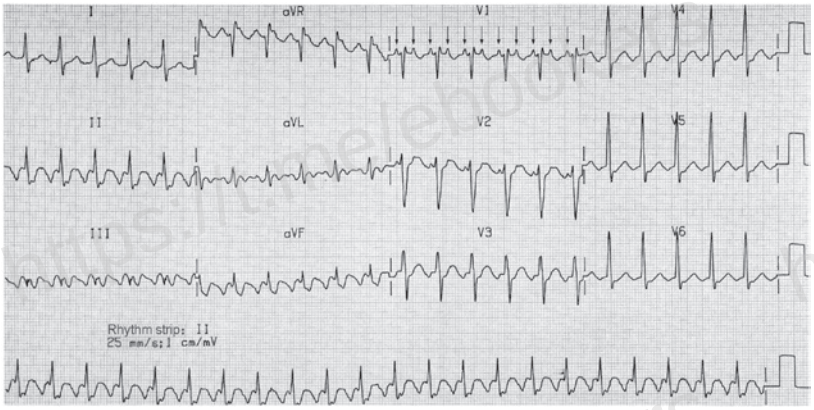


Figure 22.18 Atrial flutter with 2:1 atrioventricular conduction. Atrial rate is 270 beats/min (*arrows* V_1) and ventricular 135 beats/min. Characteristic 'sawtooth' inverted flutter waves are evident in leads II, III and aVF.

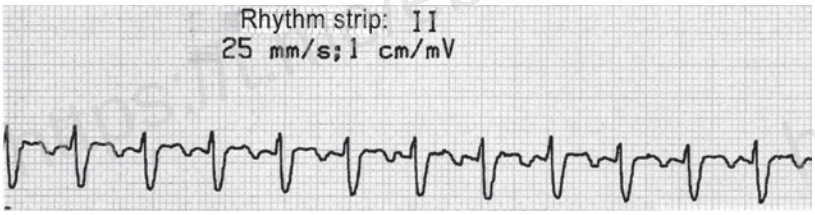


Figure 22.19 Atrial flutter (Afl) with 2:1 atrioventricular (AV) conduction. Inverted flutter waves are difficult to differentiate from T-waves. Rate of 144 beats/min confirms Afl with 2:1 AV conduction.

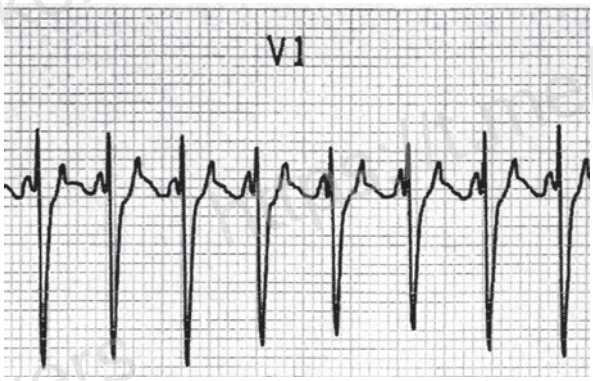


Figure 22.20 Atrial flutter (Afl) with 2:1 atrioventricular conduction. Type II Afl is confirmed by the rapid atrial rate of 380 beats/min.

beats/min, thereby allowing each atrial impulse to be conducted) or WPW syndrome and a short antegrade refractory period of the accessory pathway (Fig. 22.22). QRS complexes are usually narrow, as conduction through the bundle branches is normal.

TREATMENT[24,30]

Drug therapy has proven to be notoriously unsuccessful for Afl and large doses of AV blockers are often needed for rate control. Although no drug will reliably terminate Afl, ibutilide and dofetilide have been shown to be most likely to result in pharmacological reversion. Flecainide and procainamide may also occasionally be effective at terminating Afl. Initial attempts at slowing ventricular rate by drugs that will increase the degree of AV block are worthwhile in the first instance. Drugs such as digoxin, diltiazem, beta-adrenergic blockers, sotalol and amiodarone may be tried; the choice depends on LV function. It is important to remember class IA and IC drugs may lead to 1:1 AV conduction. Class I drugs should probably be avoided unless ventricular response has been slowed with calcium channel or beta-adrenergic blocking drugs.

Synchronised DC cardioversion, often with low energies (25–50 J), is a reliable treatment option and is often required. Rapid atrial pacing faster than the flutter rate will terminate 'typical' Afl in most patients.

Anticoagulation guidelines are the same as those for AF, although there are less supporting data.

PREVENTION

Prevention is difficult. Drugs used include sotalol and amiodarone at low doses. Class IC agents (e.g. flecainide) may be used in patients without significant structural heart disease. Increasingly, recurrent or refractory Afl may be cured by radiofrequency

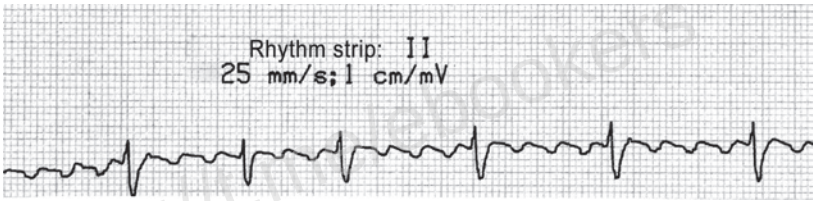


Figure 22.21 Atrial flutter varying between 3:1 and 4:1 atrioventricular (AV) conduction due to drug effect slowing AV node conduction.

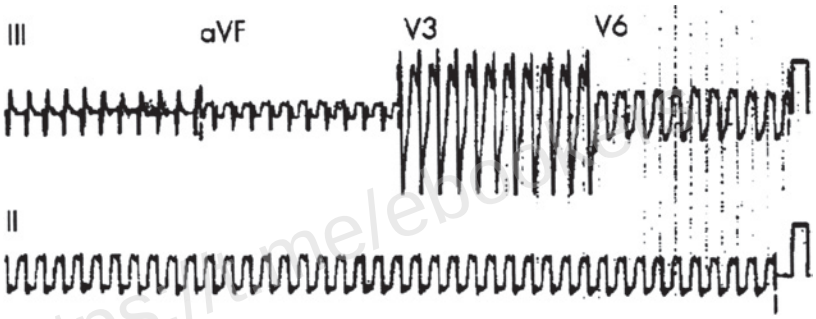


Figure 22.22 Atrial flutter with 1:1 conduction with a rate of 240 beats/min. Up-sloping of ST segment is easily mistaken as part of the QRS complex, giving the appearance of a broad QRS tachycardia in some leads. Lead III shows true narrow width of QRS complex.

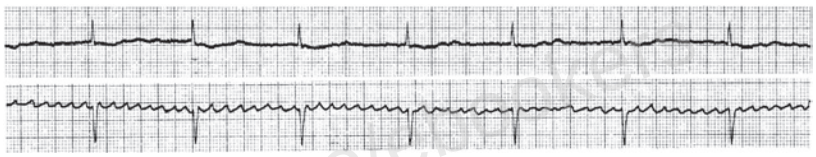


Figure 22.23 Atrial fibrillation. Irregular fibrillation waves with varying amplitude and morphology.

ablation, which creates a linear lesion between the inferior tricuspid annulus and the Eustachian ridge at the anterior margin of the inferior vena cava to interrupt the re-entry circuit.[27] 'Typical' Afl is most amendable to circuit ablation.

ATRIAL FIBRILLATION[31,32]

AF is the most common arrhythmia requiring treatment and/or hospital admission. The incidence increases with age: 5% of individuals over 70 years have this arrhythmia. There is also an age-independent increase in frequency owing to increasing obesity and obstructive sleep apnoea. LV dysfunction increases risk of AF (4.5-fold in men and 5.9 in women) with atrial stretch and fibrosis causing electrical and atrial ionic channel remodelling.

AF is common in:

- congestive cardiac failure (40%)
- coronary artery bypass grafting (CABG) (25%–50%)
- critically ill patients (15%).

Idiopathic or lone AF (i.e. with no structural heart disease or precipitating factor) in someone aged less than 60 years has an excellent prognosis; however, AF developing after cardiac surgery, for instance, is associated with increased stroke, life-threatening arrhythmias and longer hospital stays.

ECG

Atrial activity is chaotic with rapid (350–600 beats/min) and irregular depolarisation varying in amplitude and morphology (fibrillation waves). Ventricular response is irregularly irregular (Fig. 22.23). Most atrial impulses are not conducted to the ventricles, resulting in an untreated ventricular rate of 100–180 beats/min. QRS complexes will usually be narrow. When the ventricular rate is very rapid or very slow, ventricular irregularity may be missed (Fig. 22.24).

CLINICAL

The variable terminology applied to AF has been clarified by American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/

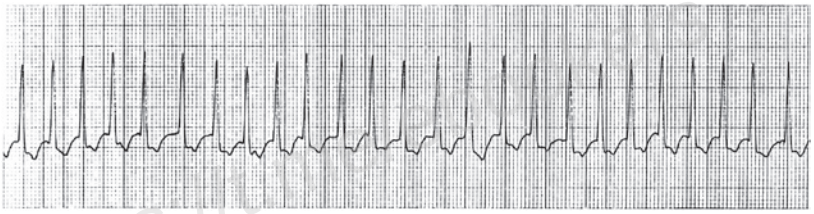


Figure 22.24 Atrial fibrillation with rapid ventricular rate. Ventricular irregularity and fibrillation waves are less evident when the rate is rapid.

Box 22.4 Definitions of atrial fibrillation

Paroxysmal AF	AF that terminates with or without treatment within 7 days of onset
Persistent AF	Continuous AF sustained for greater than 7 days
Longstanding AF	Continuous AF for greater than 12 months' duration
Permanent AF	This term is used when the patient and clinician decide to stop further attempts to restore or maintain sinus rhythm

AF, Atrial fibrillation.

Adapted from January CT, Wann LS, Alpert JS. 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014;130:2071–2104.

Box 22.5 Summary of atrial fibrillation management

- Ventricular rate control with beta blocker or non-dihydropyridine calcium channel antagonist is not inferior to pharmacological attempts to restore sinus rhythm.
- Rhythm control with antiarrhythmic agents and serial cardioversion in heart failure is not superior to rate control.
- Cardioversion is recommended to restore sinus rhythm especially if poor rate control, haemodynamic instability or pre-excitation.
- Multiple attempts at cardioversion are indicated if initial failure or meaningful periods of sinus rhythm are achieved.
- Attempts at pharmacological cardioversion with Flecainide, Dofetilide, Propafenone, intravenous Ibutilide or Amiodarone is reasonable.
- Propafenone or Flecainide ("Pill in the Pocket") to terminate AF out of hospital is reasonable once observed to be safe in a monitored setting.
- Pharmacological maintenance of sinus rhythm needs to balance risks associated with underlying heart disease, co-morbidities and antiarrhythmic drug proarrhythmia and adverse effects.
- Pharmacological maintenance of sinus rhythm is not superior to rate control.
- AF catheter ablation is indicated for symptomatic paroxysmal AF refractory or intolerant of at least one Class I or Class II agent.
- Wider application of AF ablation, prior to therapeutic trials of antiarrhythmic agents is reasonable.
- AF ablation is superior to Amiodarone in patients with NYHA Class II or III heart failure.
- AF ablation is superior to AV node ablation and bi-ventricular pacing in patients with NYHA Class II or III heart failure.

AF, Atrial fibrillation.

HRS) Guidelines (Box 22.4).[32] AF is more common in patients with underlying heart disease (particularly those with a dilated left atrium) and abnormal atrial electrophysiology. Causes include ischaemic and valvular heart disease, pericarditis, hypertension, cardiac failure, thyrotoxicosis and alcohol abuse. AF may also occur after cardiac surgery and thoracotomy. AF can be chronic, or intermittent with paroxysmal attacks. Chronic AF has a poorer prognosis.

AF is associated with:

- *adverse haemodynamic effects:* rapid ventricular rate and loss of atrial systole may increase pulmonary capillary wedge pressure, while stroke volume and cardiac output decline
- systemic embolism and stroke
- *tachycardiomyopathy:* reversible global cardiomyopathy secondary to rapid heart rate. Assessing LV function with echocardiogram before and after AV node ablation for AF refractory to medical therapy suggests that 10% of patients with AF have AF-induced tachycardiomyopathy.[33]

TREATMENT[24,34]

The goals of treatment include ventricular rate control, conversion to sinus rhythm, maintenance of sinus rhythm and anticoagulation where appropriate. Guidelines for the management of AF are multiple and extensive (Box 22.5).[32] There is increasing evidence available on the 'rate versus rhythm' control debate. Results from several recent major studies have challenged the previous belief that achievement

Table 22.5 Atrial fibrillation rate versus rhythm control debate

STUDY	NUMBER	FOLLOW-UP (MONTHS)	AGE (YEARS)	AMIODARONE USE (%)	SINUS RHYTHM (%)	WARFARIN (%)	THROMBOEMBOLISM (%)	MORTALITY (%)
AFFIRM[35]		42						
Rate control	2027		70 ± 9	10	35	85	6	21
Rhythm control	2033		70 ± 9	70	63	70	7.5	24
RACE[36]		27						
Rate control	256		68 ± 9	–	10	96	5.5	17
Rhythm control	266		68 ± 9	–	39	86	7.9	13
STAF[37]		22						
Rate control	100		65 ± 9	0	0	–	0.6	5
Rhythm control	100		66 ± 9	0	–	–	3.1	2.5
PIAF[38]		12						
Rate control	125		61 ± 9	0	10	100	–	1.6
Rhythm control	125		60 ± 10	100	56	100	–	1.6

AFFIRM, Atrial fibrillation follow-up investigation of rhythm management; *PIAF*, Pharmacological Intervention in Atrial Fibrillation; *RACE*, rate control versus electrical cardioversion of persistent atrial fibrillation; *STAF*, strategies of treatment of atrial fibrillation.

of sinus rhythm is important in the long term (Table 22.5). When comparing control of ventricular rate versus reversion to sinus rhythm, no clear survival benefit is apparent. However, composite end-points of death, stroke and recurrent hospitalisation favour rate control only.[35–38]

The possible reasons why rhythm control has not been shown to be superior include:

- trials have included predominantly elderly high-risk patients
- sinus rhythm is difficult to achieve (39%–63%)
- rate control strategies can result in sinus rhythm in up to 35% of patients
- underlying heart disease that initiates the AF persists
- there may be antiarrhythmic drug side effects
- anticoagulation is still required even if rhythm control is successful.

However, rhythm control (if possible) appears superior in patients with LV dysfunction, with both amiodarone and dofetilide reducing mortality when sinus rhythm is achieved.[35,36,39] The paucity of data in younger patients (less than 60 years) favours initial attempts at rhythm control, particularly in those with structurally normal hearts, in the hope that progressive atrial electrical and anatomical remodelling is prevented.

RECENT ONSET OR PAROXYSMAL AF

VENTRICULAR RATE CONTROL (TABLE 22.6)

The urgency of ventricular rate control depends on the clinical situation and spontaneous reversion of AF is common. Treatment may not be necessary, and a reasonable strategy is based on clinical status:

- Haemodynamically unstable with rapid ventricular rate requires immediate synchronised DC shock (in addition to drug therapy) to control rate urgently.
- Haemodynamically stable, symptomatic with depressed LV function: semi-urgent synchronised DC shock or drug therapy, digoxin or amiodarone to control ventricular rate.
- Haemodynamically stable, symptomatic, normal LV function: control of ventricular response with beta-adrenergic blockers, diltiazem, digoxin (digoxin has poor control with exertion and other settings with increased sympathetic tone), magnesium (short term), amiodarone or sotalol.
- Haemodynamically stable, with no structural heart disease and minimal or no symptoms: no immediate treatment is an option. Most cases will revert spontaneously within 24 hours. Single-dose flecainide for paroxysmal AF has been recommended (contraindicated in patients with structural heart disease).[32]

Table 22.6 Drugs for ventricular rate control in atrial fibrillation

	ACUTE	CHRONIC
STABLE	BETA BLOCKERS Metoprolol 2.5–5 mg IV bolus over 2 min – up to 3 doses Esmolol 50–200 µg/kg/min IV *NON*-DIHYDROPYRIDINE CALCIUM CHANNEL ANTAGONISTS Verapamil 0.0375–0.15 mg/kg IV over 2 min	Metoprolol ER 100–200 mg oral daily Atenolol 25–100 mg oral daily Bisoprolol 2.5–10 mg oral daily Verapamil 40 mg oral b.d. up to 360 mg ER oral daily Diltiazem 60 mg oral t.i.d. up to 360 mg ER oral daily
UNSTABLE: HYPOTENSION HEART FAILURE	Digoxin 0.5–1.0 mg IV Amiodarone 5 mg/kg IV over 1 h	Digoxin 0.125–0.50 mg oral daily Amiodarone 100–200 mg oral daily Dronedarone 400 mg oral b.d.

Table 22.7 Drugs for pharmacological conversion of recent-onset atrial fibrillation

DRUG	DOSE	FEATURES
Amiodarone	5 mg/kg IV over 1 h	Will slow ventricular rate Conversion delayed Amiodarone 80%–90%, placebo 40%–60% at 24 h Suitable structural heart disease and heart failure
Flecainide	2 mg/kg IV over 10 min 200–300 mg oral	Not suitable for structural heart disease or heart failure 67%–92% conversion at 6 h Majority within 1 h of IV dose May prolong QT Risk of Afl and 1:1 conduction
Ibutilide	1 mg IV over 10 min Further dose after 10 min	50% conversion within 90 min Risk of QT prolongation and torsades de points high
Propafenone	2 mg/kg IV over 10 min	Not suitable for structural heart disease or heart failure 41%–91% conversion within 3 h May prolong QT Risk of Afl and 1:1 conduction
Vernakalant	3 mg/kg IV over 10 min Further 2 mg/kg if required	Suitable for structural heart disease and heart failure Rapid in approximately 10 min in responders 50% conversion rate 99% of responders remain in sinus rhythm at 24 h after single dose Well tolerated

Afl, Atrial flutter.

- If pre-excitation is suspected, beta-adrenergic blockers, non-dihydropyridine calcium channel antagonists, digoxin and adenosine are contraindicated. Class I drugs are indicated. Amiodarone is no longer recommended (see Pre-excitation syndrome).

Ideal rate control can be defined as a resting heart rate of ≤80 beats/min, peak rate of ≤110 beats/min with 6-minute walk and an average of 100 beats/min.

CONVERSION TO SINUS RHYTHM

Antiarrhythmic drugs or DC shock cardioversion can be used. The likelihood of short- and long-term success depends on the clinical situation. Conversion to sinus rhythm is more important in young patients and those with heart failure. Maintenance of sinus rhythm is problematic: sinus rhythm at 1 year is 60% with amiodarone and 40% with sotalol, and associated with significant drug cardiac and extracardiac toxicities. The risk of stroke and need for antithrombotic therapy due to frequent AF recurrences, which may be asymptomatic, remain. Achieving sinus rhythm (especially greater than 60 years) is less important than previously thought.

Pharmacological conversion of recent-onset AF is variously successful depending on the clinical setting and agent used (Table 22.7). Ibutilide, propafenone and vernakalant have rapid conversion rates, compared with flecainide and amiodarone the slowest. Amiodarone, ilbutilide and vernakalent are suitable

Table 22.8 Drugs for long-term rhythm control in atrial fibrillation

DRUGS	DOSE	CONTRAINDICATIONS AND PRECAUTIONS	ECG CRITERIA FOR LOWERING DOSE OR DISCONTINUATION	AV NODE SLOWING OF PAROXYSMAL AF
Disopyramide	100–250 mg t.i.d.	Systolic heart failure QT-prolonging drugs	QT >500 ms	None
Flecainide Flecainide XL	100–200 mg b.d. 200 mg daily	Creatinine clearance <50 mL/min Coronary artery disease Reduced LV ejection fraction Conduction delay	QRS duration increase >25% over baseline	None
Propafenone Propafenone SR	150–300 mg t.i.d. 225–425 mg b.d.	Coronary artery disease Reduced LV ejection fraction Conduction delay Creatinine clearance <50 mL/min	QRS duration increase >25% over baseline	Slight
Sotalol	80–160 mg b.d.	LV hypertrophy Systolic heart failure Pre-existing QT prolongation Hypokalaemia Creatinine clearance <50 mL/min	QT >500 ms	Yes
Amiodarone	600 mg daily, 4 weeks, 400 mg daily, 4 weeks then 200 mg daily	QT prolonging drugs Warfarin dose adjustment	QT >500 ms	Yes
Dronedarone	400 mg b.d.	Heart failure NYHA Class III–IV QT prolonging drugs CYP3A4 inhibitors Creatinine clearance <30 mL/min	QT >500 ms	Yes

in heart failure. All have risk of QT prolongation and proarrhythmia, with ibutilide being the worst and vernakalant the best, although there are anecdotal case reports of ventricular arrhythmias with the latter.[40–42]

Although long-term treatment goals increasingly favour chronic rate control (see Table 22.6), antiarrhythmic drugs are still used to promote long-term rhythm control (Table 22.8). All have many contraindications and precautions, with amiodarone the best from a cardiac perspective and worst from an extracardiac point of view. The dilemma of long-term antiarrhythmic treatment in AF is highlighted by the diametrically opposite effects that dronedarone has been shown to produce in this setting.[43] In ATHENA, dronedarone decreased all cause, cardiovascular and presumed arrhythmia mortality, stroke and heart failure, whereas in PALLAS all these outcomes were worse. In PALLAS, all patients had 'permanent' AF and there was twice the baseline incidence of heart failure. Benefit would appear to be crucially dependent upon securing sinus rhythm, absence of structural substrate for proarrhythmia and cardiac reserve to tolerate the drug.

DC SHOCK CARDIOVERSION

DC shock cardioversion is indicated either before 24–48 hours or after appropriate anticoagulation protocol. Combining DC shock with antiarrhythmic drugs to promote maintenance of sinus rhythm is favoured, especially if risk factors for relapse exist. Cardioversion is less likely to be successful if:

- AF has been present for over 1 year
- left atrial size is greater than 45 mm
- untreated conditions are present (e.g. thyrotoxicosis, valvular heart disease and heart failure).

Critically ill patients who are septic, postoperative or on drugs such as catecholamines are likely to relapse.

ANTICOAGULATION AND CARDIOVERSION[44,45]

Loss of atrial contraction with AF is associated with stasis of blood flow and formation of blood clots in the left atrium, particularly the atrial appendage. Reversion to sinus rhythm and return of more effective atrial contraction may cause expulsion of any atrial clots and systemic emboli. Once AF has been present for more than 48 hours – some authors stipulate 24 hours – the risk of systemic emboli is significant and anticoagulation is required prior to DC shock cardioversion. The current recommended period of anticoagulation prior to DC shock cardioversion is 3 weeks. This 3-week period can be shortened to 1 day for heparin and 5 days for warfarin if the left atrium can be demonstrated free of clot using transoesophageal echocardiography. With this accelerated approach, heparin dose should be

titrated to an activated partial thromboplastin time 2–3 times control or warfarin to produce an international normalised ratio (INR) of 2.0–3.0. In many clinical situations such as recent surgery or other bleeding risks, anticoagulation is contraindicated and elective cardioversion should be delayed until recommended anticoagulation cover is safe. Following successful cardioversion to sinus rhythm, the risk of systemic embolism continues as the propensity to form atrial clot remains owing to atrial contractile stunning and anticoagulation should be continued for 4–6 weeks.

ATRIAL FIBRILLATION ABLATION THERAPY

Ablation techniques for AF have been continuously refined since the original Maze III surgical procedure, which involved numerous atrial incisions to form a maze-like pattern of scarring, blocking propagation of arrhythmia. The utility of this procedure was limited because it was surgical, with longer bypass times, postoperative bleeding and impaired atrial contractility. The magnitude of this original procedure was based on the belief that the entire atrium was involved in the initiation and maintenance of the fibrillatory conduction. This may be true for long-standing AF but paroxysmal AF appears to originate primarily at the junction of the left atrium and pulmonary veins. AF in 94% of patients is initiated by rapid discharges from one or more foci at or near the pulmonary vein orifices.[46] Atrial tissue in this area has heterogeneous electrophysiological properties and there is also clustering of vagal inputs, which creates substrate for rapid discharges that initiate micro-re-entrant circuits or 'rotors.' These high-frequency periodic rotors send spiral wave fronts of activation into surrounding atria. Localised ablation of a single dominant focus and rotor is inadequate, as there are usually multiple foci. Surgical excision of left atrial appendage may also be considered.

Left atrial catheter (transatrial septum) AF ablation isolating all four pulmonary veins using radiofrequency is being heralded as the possible AF cure. Results are improving, as all pulmonary veins are now isolated and the encircling lesion is clear of the pulmonary vein antrum (reducing pulmonary vein stenosis). Recently, more extensive ablation is advocated and in addition to pulmonary vein isolation, the entire left atrial posterior wall and superior vena cava is isolated as well, especially if pulmonary vein-like potentials are found. Success rates of 81% (75%–88%) free of AF and off drugs are reported. Success appears long term as any recurrence occurs early. A further 10%–20% may become responsive to antiarrhythmic drugs which were previously ineffective. Repeating the procedure can increase success to >90%, with failure only in patients found to have extensive atrial scarring (predicting and excluding patients with this extensive atrial scarring is a major future challenge). Although not yet the universal cure, the results are two- to threefold better than antiarrhythmic drugs alone. Low procedural complications are crucial to ablation having superior outcomes. While radiofrequency current ablation is the most common technique, cryoballoon ablation has been shown to be non-inferior with failure rates, recurrence of AF, occurrence of AFl or atrial tachycardia, use of antiarrhythmic drugs or repeat ablation occurring in 35% of both ablation techniques.[47] In summary:

Rhythm control is superior with ablation compared with antiarrhythmic drugs.
Ablation is indicated when rhythm control fails with antiarrhythmic drugs.
Patient outcome is superior with ablation in the setting of heart failure.[48,49]

Complication rates are falling associated with:

- intracardiac echocardiography ensuring safer transseptal puncture and positioning of isolating lesions clear of the pulmonary vein antra
- higher levels of procedural anticoagulation
- strict limitations on radiofrequency energy output.

Complications include:

- TIA, stroke
- Perforation – tamponade, oesophageal injury
- Pulmonary oedema – early from high rates of saline administration, late from pulmonary vein stenosis
- Recurrent AF
- Difficult to treat AFl

Proarrhythmia resulting from re-entrant tachycardia from incomplete ablative lesions is more common. Some are advocating ablation as first-line treatment, whereas most are selecting younger patients (less than 70 years) with paroxysmal AF for whom antiarrhythmic therapy has failed, left atrial diameter is less than 5 cm and ejection fraction is greater than 40%. Head-to-head studies comparing ablation and antiarrhythmic drugs are appearing with suggested survival benefit, improved quality of life, reduced adverse effects and cost-effectiveness after approximately 3 years with catheter AF ablation therapy.[50,51] There is renewed interest in surgical AF ablation therapy in conjunction with cardiac surgery. Complications have been reduced with energy (cryotherapy, radiofrequency) rather than incisions and the extent of lesions reduced. The minimum lesion set is now considered to be encirclement of pulmonary veins, linear lesion from the inferior pulmonary vein to mitral annulus and from the coronary sinus to the inferior vena cava.

AF and structural heart disease

The onset of AF, especially with rapid ventricular rates, often precipitates haemodynamic collapse requiring immediate control with DC shock in structural heart disease. Valvular and myopathic heart disease demands prompt preventive ablation or antiarrhythmic drugs to secure sinus rhythm.

AF in hypertrophic cardiomyopathy (HCM).[52]

AF incidence is 4–6 times greater (18%–28%) due to left atrial dilation and remodelling due to diastolic dysfunction, increase in left ventricular end diastolic pressure, primary sarcomeric atrial myopathy, left ventricular outflow tract obstruction (LVOTO) and mitral regurgitation.

AF results in four fold increase in HCM all cause mortality.

Significance mandates 24–48 hours of ambulatory monitoring every 6–12 months, especially if left atrium is greater than 45 mm. Highly sensitive troponin T predicts death and AF.

Stroke and systemic emboli are eight fold more likely than in general population AF – risk so high that CHA_2DS_2-VAScscore is not used. All are anticoagulated after one episode.

While in many settings of superiority of rhythm versus rate control continues. However with significant LVOTO, AF is so poorly tolerated that rhythm control is superior. Amiodarone is most effective to maintain sinus rhythm but long-term side effects. Disopyramide is recommended as negative inotropic action relieves symptomatic LVOTO. Must be used with AV blocking agent (beta-blocker, diltiazem or verapamil) to prevent rapid ventricular rates during AF episodes. Disopyramide dose must be decreased or ceased if QTc is greater than 480 ms. Otherwise monotherapy with Sotalol.

AF ablation is indicated for failed medical treatment although less successful than with lone AF.

If surgical myectomy is required, a MAZE procedure and left atrial appendage excision should be performed.

ANTICOAGULATION FOR CHRONIC ATRIAL FIBRILLATION[32]

VALVULAR ATRIAL FIBRILLATION

A 17-fold increased risk of embolic stroke with rheumatic mitral valve disease requires warfarin (INR 2–3). With prosthetic valves there is a similar target range of INR, though the exact level is dependent on the type of valve.

NON-VALVULAR ATRIAL FIBRILLATION

The risk of stroke has been determined by the $CHADS_2$ score (assign 1 point for congestive heart failure, hypertension, age = 75 years and diabetes mellitus, and 2 points for stroke/TIA).[53] The $CHADS_2$ score has been further developed to the CHA_2DS_2VASc score to improve risk stratification of patients at moderate risk by doubling points to 2 for age ≥75 and including vascular disease (prior myocardial infarction, peripheral artery disease determined by prior revascularisation, amputation or angiographic evidence and aortic plaque, age 65–74 and female sex) (Table 22.9).

The treatment options are discussed below.

Table 22.9 CHA_2DS_2VASc score and stroke risk stratification

RISK FACTOR	$CHA_2DS_2VAS_C$ SCORE	SCORE
Congestive heart failure Left ventricular dysfunction ejection fraction ≤40%	C	1
Hypertension	H	1
Age ≥75	A_2	2
Diabetes mellitus	D	1
Previous stroke, TIA or systemic embolism	S_2	2
Vascular disease – myocardial infarction, complex aortic plaque, prior peripheral revascularisation, amputation or angiographic evidence	V	1
Age 65–74	A	1
Female sex	S	1
Maximum score		**9**

	ADJUSTED STROKE RATE ACCORDING TO $CHA_2DS_2VAS_C$ SCORE
$CHA_2DS_2VAS_C$ SCORE	ADJUSTED STROKE RATE %/YEAR*
0	0
1	1.3
2	2.2
3	3.2
4	4.1
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

*Based on Lip GY, Frison L, Halperin JL, Lane DA. Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. *Stroke* 2010;41(12):2731–2738.
TIA, Transient ischaemic attack.

WARFARIN

Adjusted-dose warfarin reduces relative risk of stroke by 62%. The absolute risk reduction is 2.8% per year for primary and 8.4% per year for secondary prevention, although intracranial haemorrhage occurs (0.3% per year). Low-dose warfarin (INR 1.5–2.0) is less

effective than an INR of 2.0–3.0 but has fewer haemorrhagic complications. Embolic stroke rate doubles as INR falls from 2.0 to 1.7, and is markedly higher at an INR of 1.3 compared with 2.0.[44,54]

ASPIRIN

Aspirin has reduced efficacy when compared with warfarin, with a 22% relative risk reduction and an absolute risk reduction of 1.5% and 2.5% per year for primary and secondary prevention. Warfarin compared with aspirin for AF will prevent 23 strokes and result in nine additional major bleeds per 1000 patients per year.

CLOPIDOGREL PLUS ASPIRIN

Although warfarin is better under ideal circumstances, poor INR control will readily erode this benefit.

WARFARIN COMBINED WITH ANTIPLATELET THERAPY

There is no benefit over warfarin alone.

NEW ORAL ANTICOAGULANTS (NOACs) (BOX 22.6)

NOACs have an increasing role in AF anticoagulation with the benefit of fixed dosing not requiring monitoring. The evidence for superiority in non-valvular AF is oldest for dabigatran; however, other NOACs have the benefit of once-daily dosing, Rivaroxaban, and use in moderate renal failure, Apixaban. In non-valvular AF, dabigatran 150 mg b.d. had a 35% reduction in stroke and systemic embolism compared with warfarin. There was a similar rate of major bleeding, although intracranial haemorrhage was reduced by 59%. The lower dose of 110 mg b.d. had similar embolic efficacy to warfarin but with reduced bleeding. Dabigatran clearance is importantly influenced by creatinine clearance of less than 50 mL/min and rapid reversal is problematic. Apixaban (ARISTOTLE) was superior to warfarin due to reduction in haemorrhagic strokes and ischaemic strokes with haemorrhagic conversion. Rivaroxaban was non-inferior to warfarin (ROCKET-AF).

Box 22.6 New oral anticoagulants

Dabigatran
- Direct thrombin inhibitor
- 150 mg oral b.d.
- Creatinine clearance <50 mL/min decrease dose 110 mg oral b.d.
- CrCl <30 mL/min contraindicated

Rivaroxaban
- Factor Xa inhibitor
- 20 mg oral daily
- CrCl <50 mL/min decrease dose 15 mg oral daily

Apixaban
- CrCl <30 mL/min contraindicated
- Factor Xa inhibitor
- 5 mg oral b.d.
- Age >80 years, <60 kg or CrCl <50 mL/min decrease dose 2.5 mg oral b.d.
- Recommended in renal dysfunction

RECOMMENDATIONS FOR ANTICOAGULATION IN PATIENTS WITH ATRIAL FIBRILLATION

Non-valvular atrial fibrillation

INR adjusted warfarin (2.0–3.0 target 2.5) or aspirin according to CHA_2DS_2VASc score and HAS-BLED score (Tables 22.10 and 22.11).

NOACs may be substituted for warfarin, depending on risk of bleeding. Risk of bleeding can be determined by the HAS-BLED score. With a HAS-BLED score of 0–2, dabigatran 150 mg b.d. gives superior embolic prevention with reduced intracranial haemorrhage. With a HAS-BLED score of ≥3, 110 mg b.d. gives similar efficacy to warfarin, but reduced haemorrhagic complications.

Valvular atrial fibrillation

Warfarin is indicated. Direct thrombin inhibitors or Factor Xa inhibitors are yet to be studied in this situation.

Risk of haemorrhage is reduced by keeping INR = 3, systolic blood pressure <135 mm Hg (17.95 kPa) and avoiding antiplatelet drugs.

Temporary cessation of anticoagulation for AF with surgery is a common problem. Valvular AF requires

Table 22.10 Approach to thromboprophylaxis in patients with atrial fibrillation

CHA_2DS_2VASc SCORE	RECOMMENDED ANTITHROMBOTIC THERAPY
≥2	Oral anticoagulation –warfarin international normalised ratio (INR) 2.0–3.0 Target 2.5 –dabigatran –HAS-BLED score 0–2: dabigatran 150 mg b.d. <2: dabigatran 110 mg b.d.
1	Either oral anticoagulant –warfarin INR 2.0–3.0 Target 2.5 –dabigatran 110 mg b.d., *or* –aspirin 75–325 mg daily Prefer oral anticoagulation rather than aspirin
0	Either aspirin 75–325 mg daily, *or* No antithrombotic therapy Prefer no antithrombotic therapy rather than aspirin

Table 22.11 HAS-BLED bleeding risk score

H	Hypertension • systolic >160 mm Hg (21.3 kPa)	1
A	Abnormal renal or liver function (1 point each) • chronic dialysis, renal transplant or creatinine ≥200 µmol/L • cirrhosis, bilirubin >2 × upper limit of normal or liver enzymes >3 × upper limit of normal	1 or 2
S	Stroke	1
B	Bleeding • previous history of bleeding, abnormal coagulation or anaemia	1
L	Labile INRs Unstable or high INRs, poor time in therapeutic range <60%	1
E	Elderly >65 years	1
D	Drugs or alcohol • antiplatelet agents, non-steroid anti-inflammatory drugs • alcohol abuse	1 or 2
	Maximum score	9

INRs, International normalised ratios.

heparin or enoxaparin until surgery and recommencement of heparin/enoxiparin, then warfarin as soon as safely possible. Non-valvular CHA_2DS_2VASc score <2 can have anticoagulation withheld with minimal risk. Non-valvular CHA_2DS_2VASc score of ≥2 is increasingly managed as valvular AF.

Angioplasty and stenting of coronary arteries require aspirin and clopidogrel to maintain stent patency. Stenting in patients already on warfarin for AF is a common problem.

RECOMMENDATIONS FOR ATRIAL FIBRILLATION PATIENTS REQUIRING CORONARY ARTERY STENTING

- Non-valvular CHA_2DS_2VASc score <2: cease warfarin as aspirin and clopidogrel are started.
- Valvular AF and non-valvular with CHA_2DS_2VASc score ≥2: add aspirin and clopidogrel to continued warfarin treatment.

PRE-EXCITATION SYNDROME

Pre-excitation syndromes have an additional or accessory AV pathway. The term 'WPW syndrome' is usually applied when tachyarrhythmia is present.

ECG

During sinus rhythm, an atrial impulse will reach the ventricles via both the AV node and the accessory AV pathway. The latter conducts the atrial impulse to the ventricles before the AV node, resulting in ventricular pre-excitation and a short PR interval. On reaching the ventricles, the pre-excitation impulse is not conducted via the specialised conducting system. Hence, early ventricular activation will be slowed, resulting in a slurred upstroke of the QRS complex, the so-called delta (δ) wave (Fig. 22.25). The abnormal ventricular activation also gives rise to secondary S-T segment and T-wave abnormalities; δ-wave polarity in a 12-lead ECG may help localise the anatomical position of the accessory pathway. Type A WPW is characterised by upright QRS deflections in the right precordial leads (tall R-waves in V_1 and V_2) (Fig. 22.26). In type A WPW, the accessory pathway is usually situated on the left with pre-excitation of the left ventricle. Type B WPW has a dominantly negative QRS complex in V_1 and the accessory pathway tends to be on the right with pre-excitation of the right ventricle (Fig. 22.27).

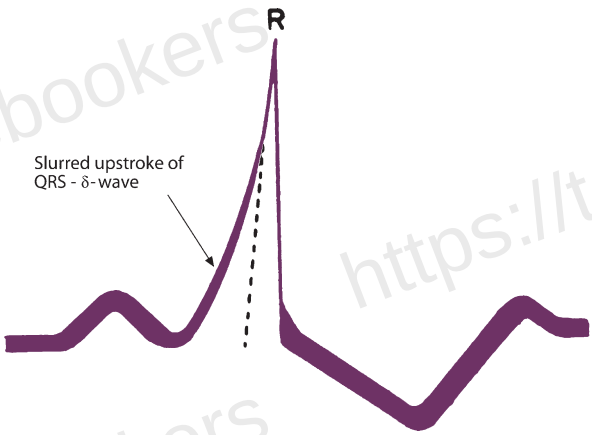


Figure 22.25 Ventricular pre-excitation via accessory pathway giving rise to a slurred upstroke and widened QRS complex.

CLINICAL

AVRT or AF can occur with WPW. During AVRT, the re-entry impulse usually travels down the AV node and back up the accessory pathway. Ventricular activation is via the normal conducting pathways and the QRS will be narrow. Occasionally, the re-entry impulse may pass in the opposite direction (down the accessory pathway and up the AV node), resulting in a wide QRS-complex tachycardia due to abnormal slow ventricular activation. Treatment is the same as for AVRT (i.e. intravenous [IV] adenosine). AF is uncommon in WPW, but may be life threatening. Most impulses are conducted via the accessory pathway, leading to wide QRS complexes. The ECG of WPW with AF usually shows rapid, irregular QRS complexes with variable QRS width (Fig. 22.28).

Ventricular response is very rapid, leading to hypotension or cardiogenic shock. This arrhythmia may degenerate to VF.

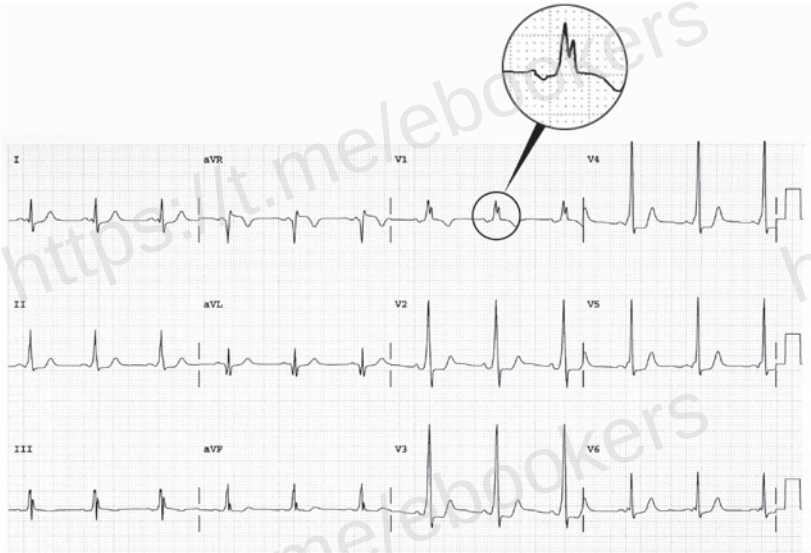


Figure 22.26 Type A Wolff–Parkinson–White syndrome with positive R-waves in the right precordial leads, short PR interval and δ-wave giving rise to a wide QRS complex.

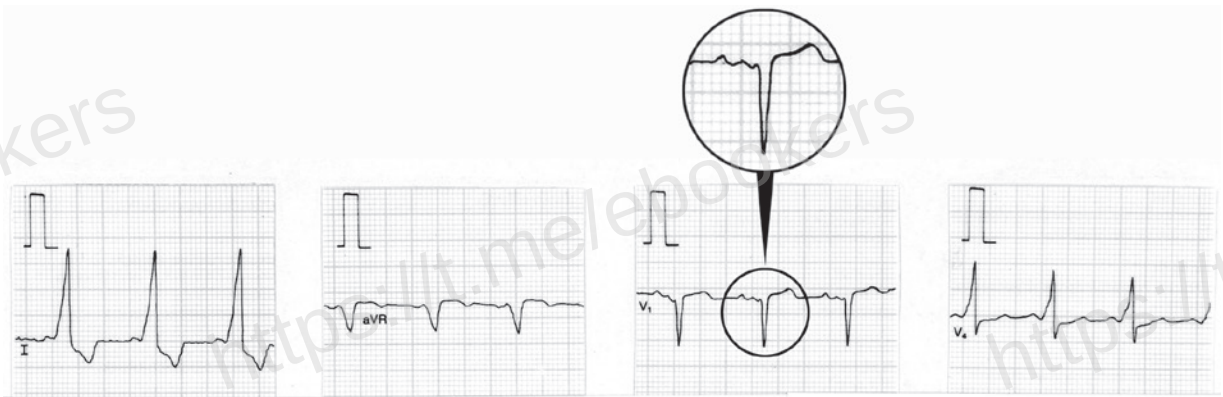


Figure 22.27 Type B Wolff–Parkinson–White syndrome with a negative QRS deflection in V_1.

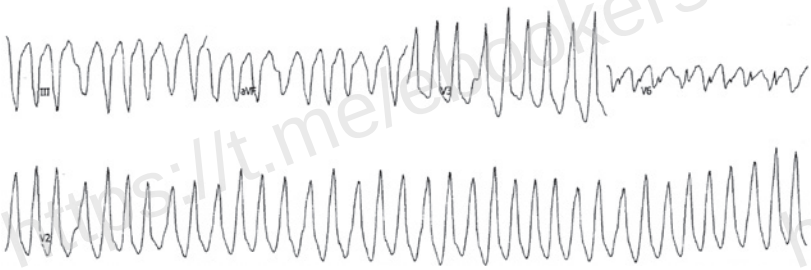


Figure 22.28 Wolff–Parkinson–White syndrome with atrial fibrillation. Rapid rate and irregularity of the broad QRS complexes help to distinguish from ventricular tachycardia.

TREATMENT[24]

Treatment usually involves synchronised DC shock if haemodynamically compromised. Antiarrhythmic drugs may be used when patients are haemodynamically stable and the ventricular rate is not excessively rapid.

- Ideal agent needs predominant action of prolonging refractory period of accessory pathway.

Agents with predominant action of slowing AV node can increase conduction rate through the accessory pathway and cause life-threatening rapid ventricular rates in the setting of AF.

Intravenous Procainamide or Ibutilide have best profile.

Amiodarone and Flecainide have been used but are not ideal due to strong AV blocking action even though they slow accessory pathway conduction.

Digoxin contraindicated as blocks AV node and increases accessory pathway conduction by shortening refractory period.

Non-dihydropyridine calcium channel blockers and adenosine may be harmful by increasing ventricular rate by blocking the AV node.

Long-term management by radiofrequency ablation of the accessory pathway is effective in selected patients.

VENTRICULAR TACHYCARDIA

VT is defined as three or more VEBs at a rate greater than 130 beats/min, and may exceed 300 beats/min. VT lasting over 30 seconds is considered to be sustained. Non-sustained VT may not cause symptoms, but is associated with increased mortality in certain patients (e.g. after myocardial infarction). VT may be monomorphic (i.e. the same QRS morphology) (Fig. 22.29) or polymorphic (varying QRS morphology).

MONOMORPHIC VENTRICULAR TACHYCARDIA

This is the most common form of VT. It is commonly associated with previous myocardial infarction, and often causes symptoms (e.g. palpitations, shortness of breath, chest pain or syncope). It may result in cardiac arrest due to the tachycardia itself or degeneration into VF. The most common mechanism is re-entry secondary to inhomogeneous activation of the myocardium and slow conduction through scar tissue from a previous myocardial infarction. AV dissociation (i.e. independent atrial and ventricular activity) (Fig. 22.30) is present in about 75% of instances, whereas retrograde ventricle-to-atrial conduction occurs in about 25%. AV dissociation is virtually diagnostic for VT during a wide-complex tachycardia, but ECG recognition of independent (and slower) atrial activity can be difficult (Fig. 22.31). VT is the most common cause of a wide-complex tachycardia (QRS >120 ms) and any such tachycardia should be considered VT until proven otherwise. Mistakes in diagnosis are common: SVT with aberrant conduction is often mistaken for VT. Inappropriate treatment based on incorrect diagnosis can have disastrous consequences.

ECG

Older criteria (e.g. QRS >140 ms and extreme electrical axis changes) are unhelpful in rhythm diagnosis.[55] ECG criteria initially proposed by Wellens and revised by Brugada et al. permit accurate diagnosis in four sequential steps (Fig. 22.32).[56–58]

The sensitivity of these four consecutive steps was 0.987, with a specificity of 0.965.

- *Step 1:* Is an RS complex present in any precordial lead? (QR, QRS, QS, monophasic R and rSR are not considered RS complexes.) If not (Fig. 22.33), the diagnosis is VT.

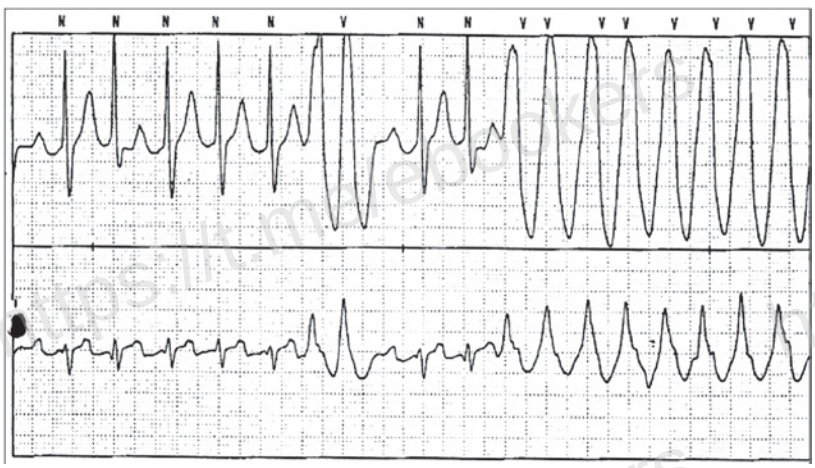


Figure 22.29 Monomorphic ventricular tachycardia preceded by a ventricular couplet.

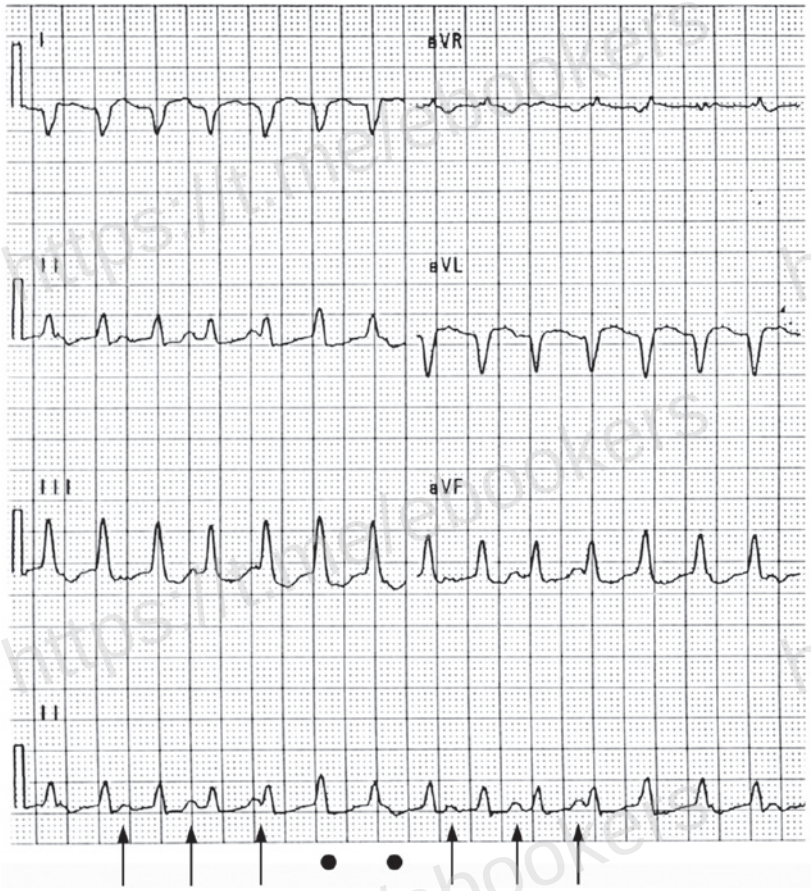


Figure 22.30 Ventricular tachycardia with obvious arteriovenous dissociation and independent P-waves are highlighted with *arrows* in lead II.

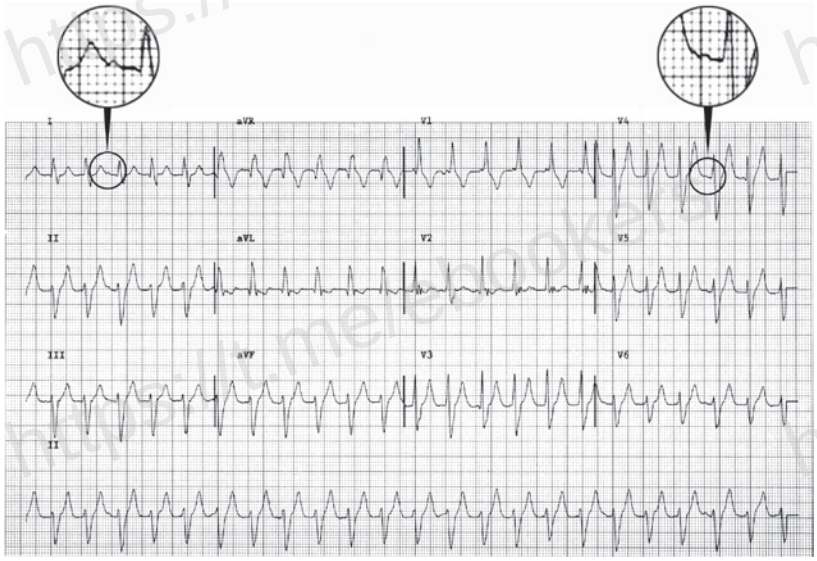


Figure 22.31 Ventricular tachycardia. Independent atrial activity can be difficult to see. Dissociated P-waves can just be seen in leads I and V_4.

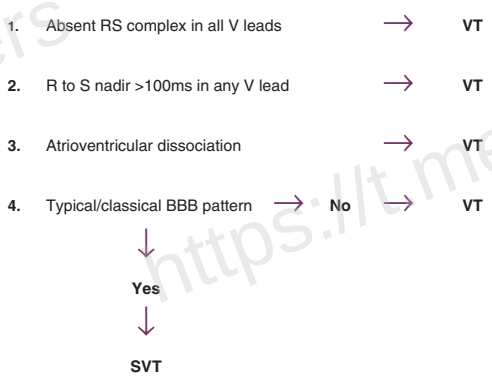


Figure 22.32 Algorithm proposed by Brugada et al.[56] to diagnose ventricular tachycardia in the setting of a broad QRS-complex tachycardia.

- *Step 2:* If an RS is present, then measure the duration of the R-to-S nadir (lowest part of the S-wave). If this duration is >100 ms in any V lead (Fig. 22.34), the rhythm is VT.
- *Step 3:* If RS <100 ms, then AV dissociation is searched for (more QRS complexes than P-waves; see Figs 22.30 and 22.31). Indirect evidence of AV dissociation such as capture or fusion beats may be present. Capture beats occur when atrial sinus impulses reach the AV node when it is no longer refractory from retrograde conduction of ventricular discharges: the AV node and ventricle are then 'captured' by the sinus impulse. The resultant QRS will occur earlier than the next expected VT complex and the QRS morphology will be that of the 'normal' underlying complexes for that patient. Similarly, a sinus impulse can penetrate the AV and 'fuse' with an

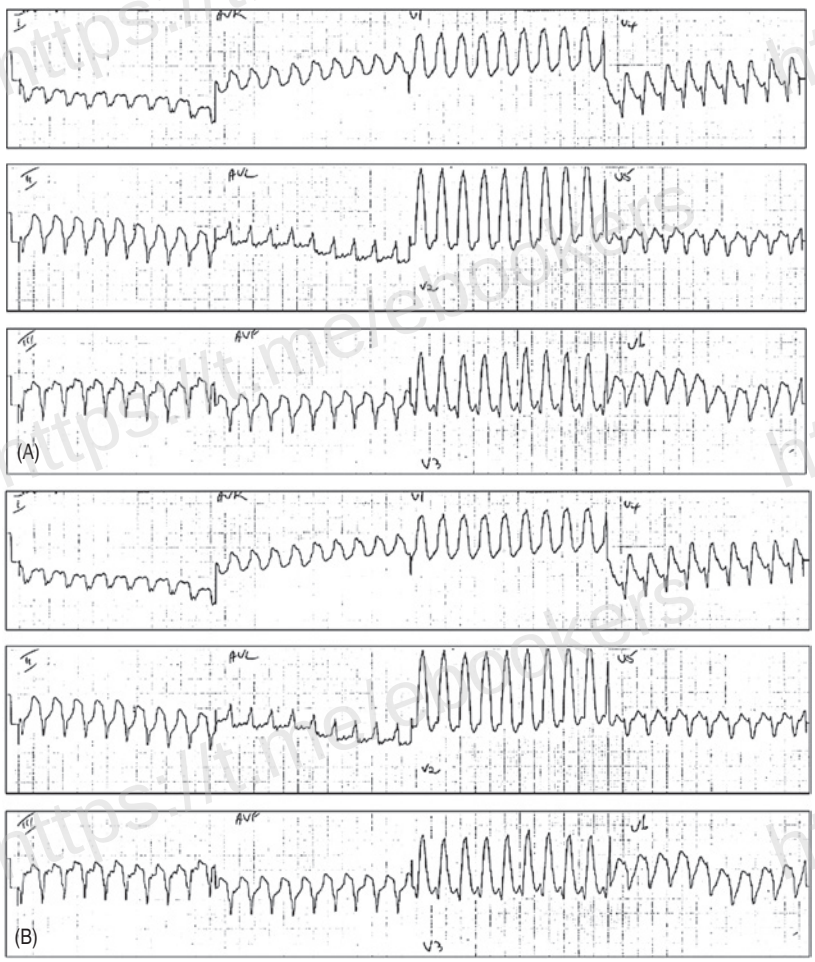


Figure 22.33 (A and B) Ventricular tachycardia. Broad QRS-complex tachycardia with absence of RS complex in all precordial leads.

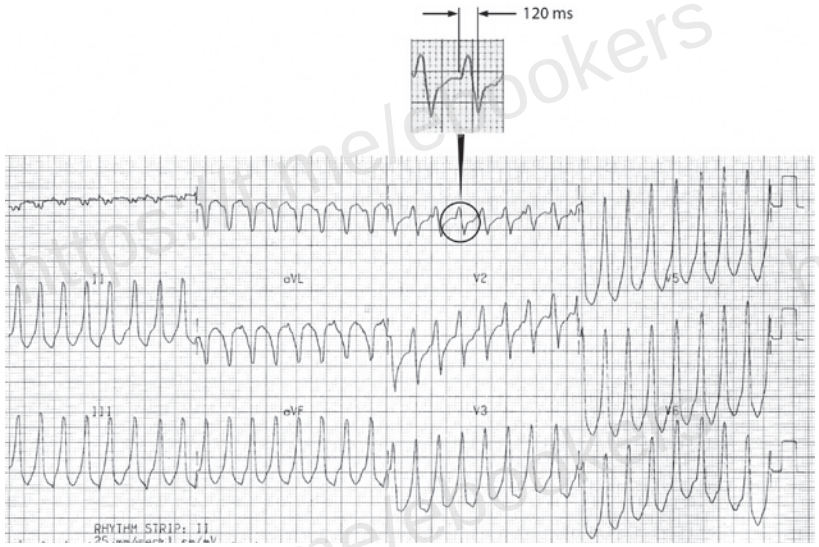


Figure 22.34 Ventricular tachycardia. Time duration of R to the nadir of the negative S-wave is 120 ms. Note also independent P-waves in lead V_1.

already depolarising ventricle from the ectopic focus initiating the VT. The resulting QRS morphology of a fusion beat will be variable and depend on the relative contribution of the supraventricular and ventricular impulses to ventricular activation. Even a single capture or fusion beat confirms AV dissociation and VT (Fig. 22.35).

- *Step 4:* If AV dissociation is not present, then decide whether the wide QRS has a right or left BBB (LBBB) pattern. If the BBB is typical in both V_1 and V_6 leads, the rhythm is supraventricular in origin (see the section on BBB). If there are any atypical features, the rhythm is considered to be VT (see Figs 22.39 and 22.40).

Termination of a wide-complex tachycardia by IV adenosine strongly suggests the arrhythmia as SVT. However, adenosine in this setting has the risk of destabilising VT when blood pressure is barely compensated by vasodilatation or acceleration of accessory pathway conduction, and is not recommended by International Liaison Committee on Resuscitation (ILCOR) as a diagnostic strategy in wide-complex tachycardia.[24] Demonstration of AV dissociation by intracardiac ECG from a central venous catheter or a transvenous pacing lead signifies VT.

CLINICAL

The major cause of VT is significant coronary artery disease. Other causes include cardiomyopathy, myocarditis and valvular heart disease. Symptoms will depend on the ventricular rate, duration of tachycardia and underlying cardiac function. There are not necessarily any haemodynamic differences between VT and SVT with aberrant conduction but haemodynamic instability mandates management as for VT.

TREATMENT[24]

DC shock is indicated if a patient is haemodynamically unstable. Antiarrhythmic drug trial is indicated in haemodynamically stable VT.

- Amiodarone may terminate VT; there is less negative inotropic action but delayed effect.
- Sotalol and procainamide are more effective than lidocaine but are associated with significant myocardial depression.
- Although traditionally indicated, there are now doubts about the efficacy of lidocaine.

If drugs are ineffective, synchronised DC shock is indicated. Rapid right ventricular pacing may also be effective.

Long-term prevention of VT and sudden death is difficult. Sotalol guided by Holter ECG or electrophysiological testing, and empirical (i.e. non-guided) amiodarone are superior to other drugs in preventing arrhythmia recurrences. Empirical beta-adrenergic blockers also have a role. Implantable defibrillators can recognise and automatically terminate VT by rapid ventricular pacing or, if this fails, by internal DC cardioversion, which may be life saving.

Catheter ablation is being increasingly used in the acute setting for VT storm. Patients with ICD and recurrent VT not controlled with amiodarone or another Class I or III agent had improved outcome with ablation compared with escalation of antiarrhythmic drugs (VANISH)[(f)][59].

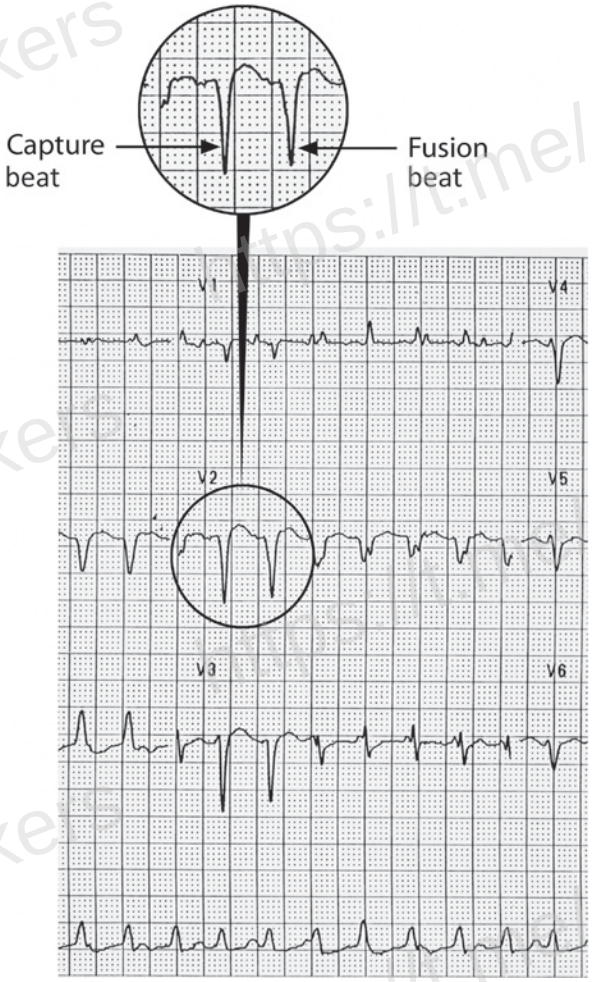


Figure 22.35 Ventricular tachycardia with a highlighted premature capture beat followed by a fusion beat showing transitional QRS morphology between the underlying normal QRS and VT complex. Note also independent P-waves.

POLYMORPHIC VENTRICULAR TACHYCARDIA AND TORSADE DE POINTES

This arrhythmia has QRS complexes at 200 beats/min or greater, which change in amplitude and axis so that they appear to twist around the baseline (Fig. 22.36). Torsade de pointes usually has prolonged QT during sinus rhythm, and U-waves are often present (see section on long-QT syndrome). However, polymorphic VT may be associated with a normal QT interval in settings such as myocardial ischaemia, infarction or post cardiac surgery.

TREATMENT

Polymorphic VT associated with a normal QT interval during sinus rhythm (e.g. following AMI) should be treated in the same way as monomorphic VT. (See section on treatment of long-QT and polymorphic VT.)

ACCELERATED IDIOVENTRICULAR RHYTHM (AIVR)

This is often inappropriately called slow VT. Increased automaticity is probably the mechanism responsible for this relatively benign arrhythmia.

ECG

There is a wide QRS with a rate of 60–110 beats/min (Fig. 22.37). Sinus rate is often only slightly slower than the arrhythmia, so the dominant rhythm may be intermittent AIVR and sinus rhythm. Fusion beats are therefore common.

CLINICAL

The rhythm is commonly encountered in inferior myocardial infarction. AIVR may be misdiagnosed as VT. Occasionally, AIVR causes haemodynamic deterioration, usually due to loss of atrial systole. Increasing the atrial rate with either atropine or atrial pacing may then be necessary.

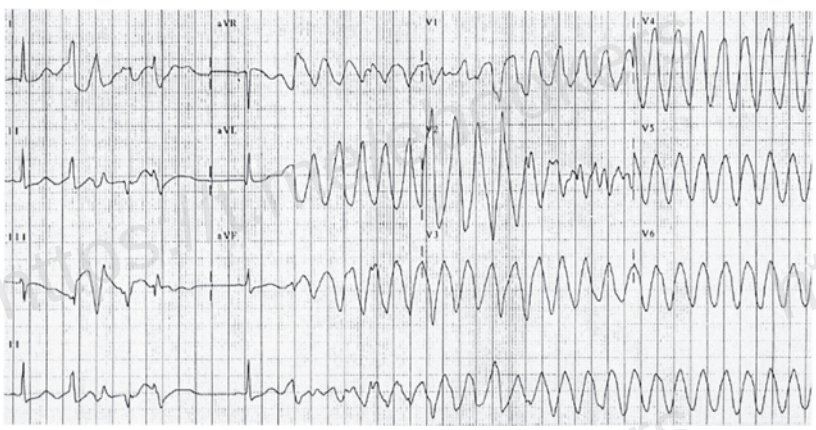


Figure 22.36 Torsade de pointes preceded by multifocal ventricular ectopic beats.

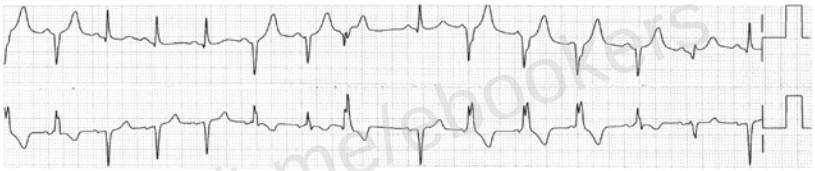


Figure 22.37 Sinus rhythm with short runs of accelerated idioventricular rhythm. Note frequent fusion beats as sinus rate is similar to the accelerated idioventricular rate.

Figure 22.38 Ventricular fibrillation with waves of varying morphology and amplitude.

VENTRICULAR FIBRILLATION

VF always causes haemodynamic collapse, loss of consciousness and death if not immediately treated. Of patients resuscitated from VF, 20%–30% have sustained an AMI, and 75% have coronary artery disease. VF (and VT) unassociated with AMI is likely to be recurrent; 50% die within 3 years.

ECG

The ECG shows irregular waves of varying morphology and amplitude (Fig. 22.38).

CLINICAL

VF is usually associated with ischaemic heart disease, although other causes include cardiomyopathy, antiarrhythmic drugs, severe hypoxia and non-synchronised DC cardioversion.

TREATMENT

Give an immediate asynchronised biphasic DC shock at 200 J. Time should not be wasted with basic life support if immediate defibrillation can be delivered.

If DC shock sequence fails, basic and advanced life support aiming to maximise coronary blood flow with chest compressions and vasopressors is crucial to cardiac success. Until recently, any role of antiarrhythmic drugs in DC shock-resistant VF has been traditional rather than proven. Recommendations have varied from lidocaine and bretylium to amiodarone. The ILCOR currently recommends consideration of a range of antiarrhythmic drugs, including amiodarone, lidocaine, magnesium and procainamide. Recent studies indicate amiodarone as the drug of choice for DC shock-resistant VF. Amiodarone (300 mg) was superior to lidocaine and, in another study, 5 mg/kg followed by 2.5 mg/kg if required was superior to lidocaine. There is an incidence of bradycardia and hypotension but no difference in adverse effect profile between lidocaine and this sizeable amiodarone dose.[60,61] After return of circulation, appropriate antiarrhythmic therapy is less clear but the role of lidocaine continues to disappear. Precipitating factors should be sought and treated (for long-term management issues, see the section on sudden cardiac death).

RIGHT BUNDLE BRANCH BLOCK (FIG. 22.39)

In right BBB (RBBB) the normal rapid coordinated depolarisation of the right ventricle is lost due to conduction block in the right branch of the bundle of His. There is normal rapid depolarisation of the septum and the initial deflection of the QRS is not altered. The activation of the free wall of the left ventricle is also normal. However, the final activation of the free wall of the right ventricle is slow and anomalous, leading to a broad QRS.

ECG

The ECG shows wide QRS (>120 ms) and the QRS morphology in the right ventricular leads V_1 and V_2 is often M shaped. This results in two R-waves, with the smaller of the R-waves being designated 'r' and the larger 'R.' The classical pattern is the M-shaped rSR in V_1 or V_2 and a broad S-wave in LV leads, especially I and V_6. In V_1 the R-wave is greater in amplitude than the R-wave. In V_6 the R-wave is greater than any S-wave present. Partial RBBB is identical, except the QRS duration is 110–120 ms.

CLINICAL

RBBB may be a normal variant, but may occur with massive pulmonary embolism, right ventricular hypertrophy, ischaemic heart disease and congenital heart disease (note that myocardial infarction can be diagnosed in the presence of RBBB).

LEFT BUNDLE BRANCH BLOCK (FIG. 22.40)

In LBBB, there is delayed and anomalous activation of the interventricular septum from right to left (i.e. in the opposite direction to normal) and the free wall of the left ventricle.

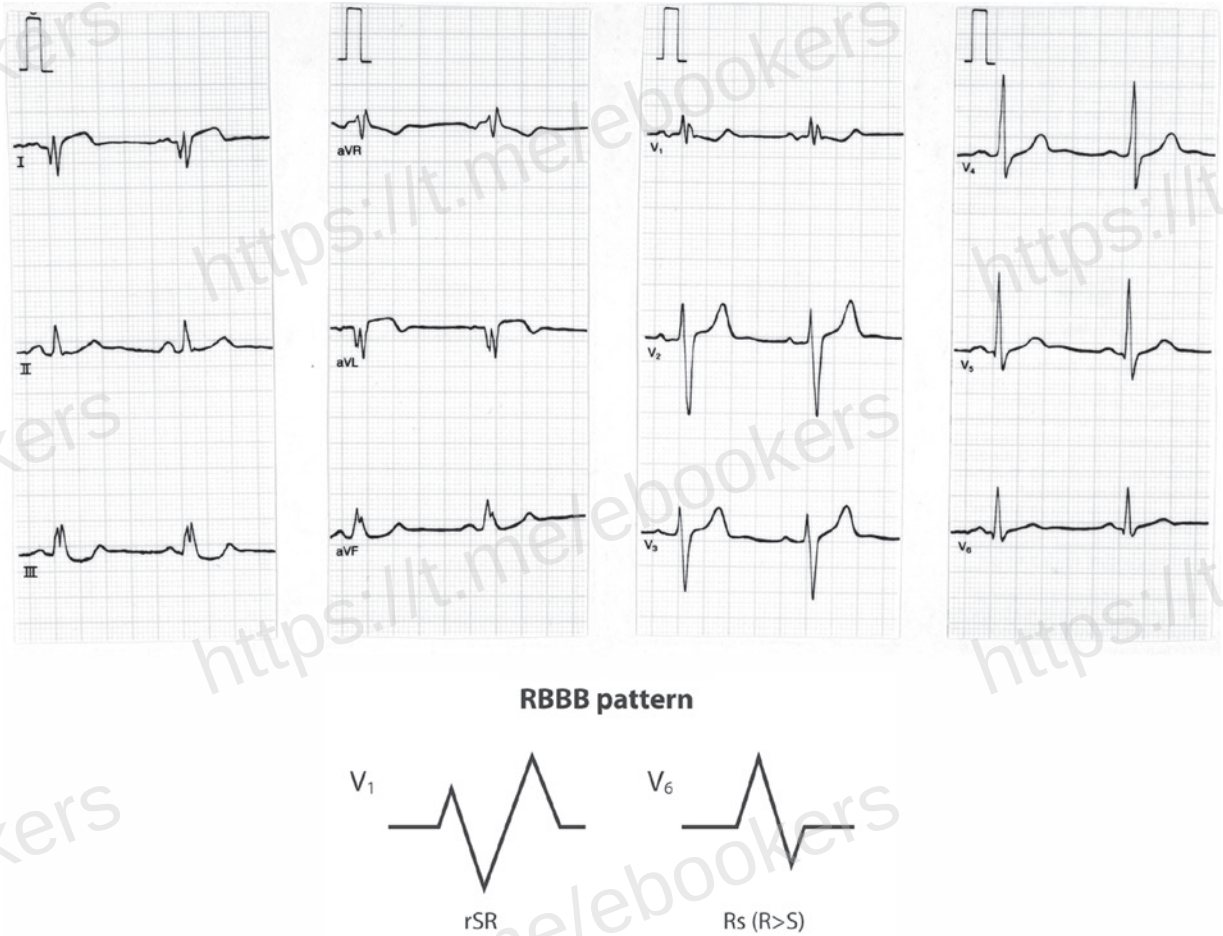


Figure 22.39 Right bundle branch block *(RBBB)* with characteristic M-shaped rSR complex in lead V_1 and Rs complex in V_6.

ECG

There is a wide QRS (>120 ms) and in V_1 the characteristic morphology shows an rS or QS. In V_6 there are primary and secondary R-waves (RR'), often resulting in M-shaped or plateau morphology. Q-waves are never seen in LV leads (V_4–V_6) (note that myocardial infarction cannot usually be diagnosed in the presence of LBBB). Partial LBBB is similar, except that the QRS duration is 110–120 ms.

CLINICAL

LBBB is often associated with heart disease such as coronary artery disease, cardiomyopathy or LV hypertrophy. LBBB makes diagnosis of myocardial infarction difficult and the development of a new LBBB fulfils ECG criteria of acute infarction.

HEMIBLOCKS

The left branch of the bundle of His divides into the left anterosuperior division supplying the anterior superior lateral wall of the left ventricle and the posteroinferior division supplying the posterior inferior diaphragmatic surface of the left ventricle. Although block can occur in either division, it is more common in the anterosuperior division, as it is more vulnerable to disease processes due to its longer course and thinner dimension. The anterosuperior division runs close to the aortic valve and tends to be involved in degenerative processes affecting this valve. The posteroinferior division is shorter and thicker and, unlike the anterosuperior division, has a double blood supply.

LEFT ANTERIOR HEMIBLOCK

There is left-axis deviation (usually lead I predominantly positive, leads II and III predominantly negative) with initial R-wave in inferior leads (II, III, aVF).

LEFT POSTERIOR HEMIBLOCK

There is usually right-axis deviation (lead I predominantly negative and lead III predominantly positive).

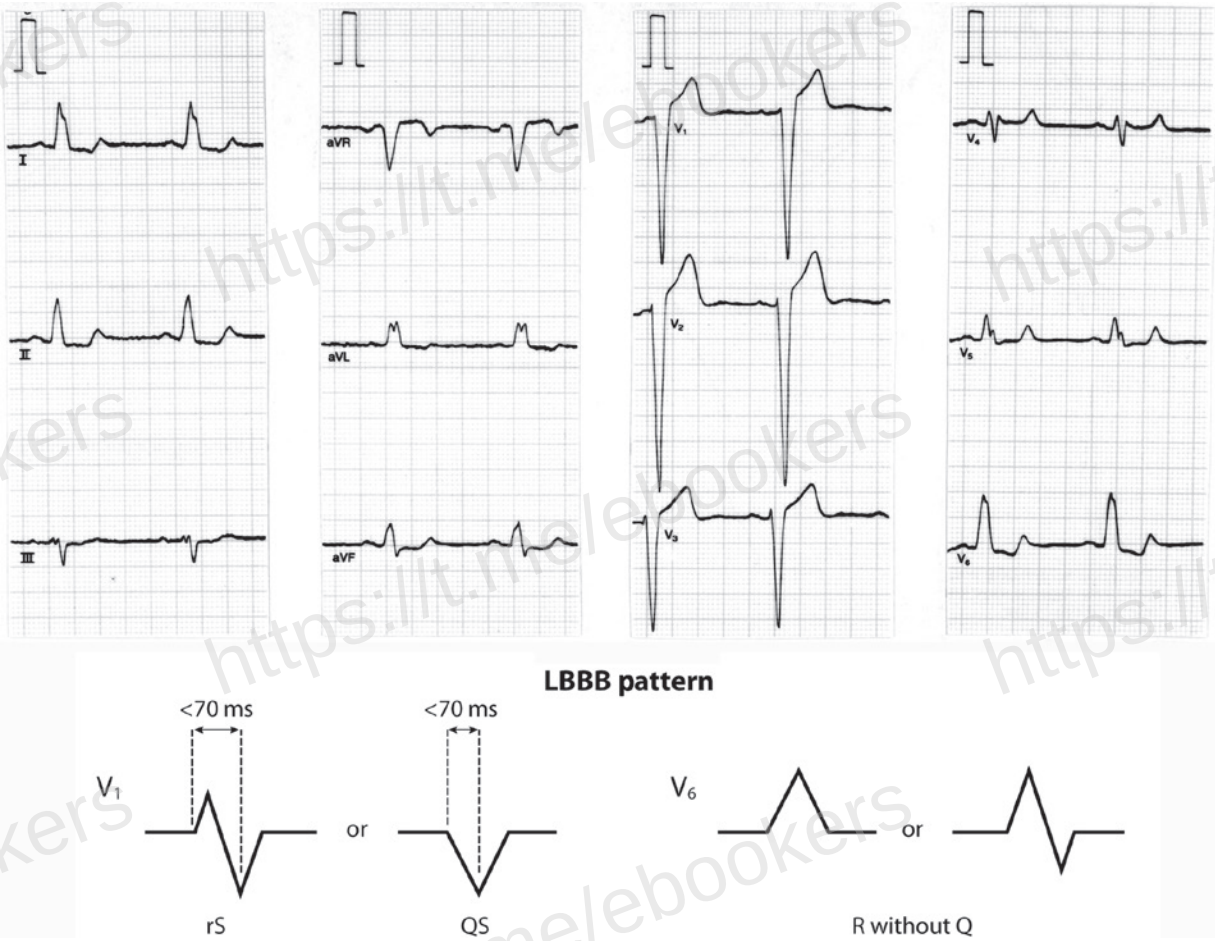


Figure 22.40 Left bundle branch block *(LBBB)*.

Other causes of right-axis deviation (e.g. right ventricular hypertrophy) need to be excluded.

CLINICAL

RBBB with either left anterior hemiblock (Fig. 22.41) or left posterior hemiblock indicates an extensive conduction defect and a poor prognosis (high risk of complete heart block), especially in AMI.

HYPERKALAEMIA

A high serum K^+ can produce ECG changes (Fig. 22.42). Early changes consist of tall peaked T-waves with reduced P-wave amplitude. Progressive widening of the QRS may be confused with BBB. Cardiac arrest may eventually occur.

ATRIOVENTRICULAR BLOCK

AV block is a delay or failure of impulse conduction from the atria to the ventricles. AV block is classified according to whether conduction of atrial impulses is delayed (first degree), blocked intermittently (second degree) or blocked completely (third degree).

FIRST-DEGREE AV BLOCK

ECG

PR interval (measured from the onset of the P-wave to the onset of the QRS) exceeds 200 ms (Fig. 22.43). Each P-wave is followed by a QRS. PR intervals may be prolonged to such a degree that the P-wave is buried in the previous T-wave or even QRS.

CLINICAL

First-degree AV block is commonly associated with increased vagal tone, and occasionally with drugs (especially digoxin), ischaemic heart disease (particularly inferior myocardial infarction) and rheumatic fever. It usually causes no symptoms and requires no treatment. If associated with digoxin, the drug should be ceased or the dose decreased.

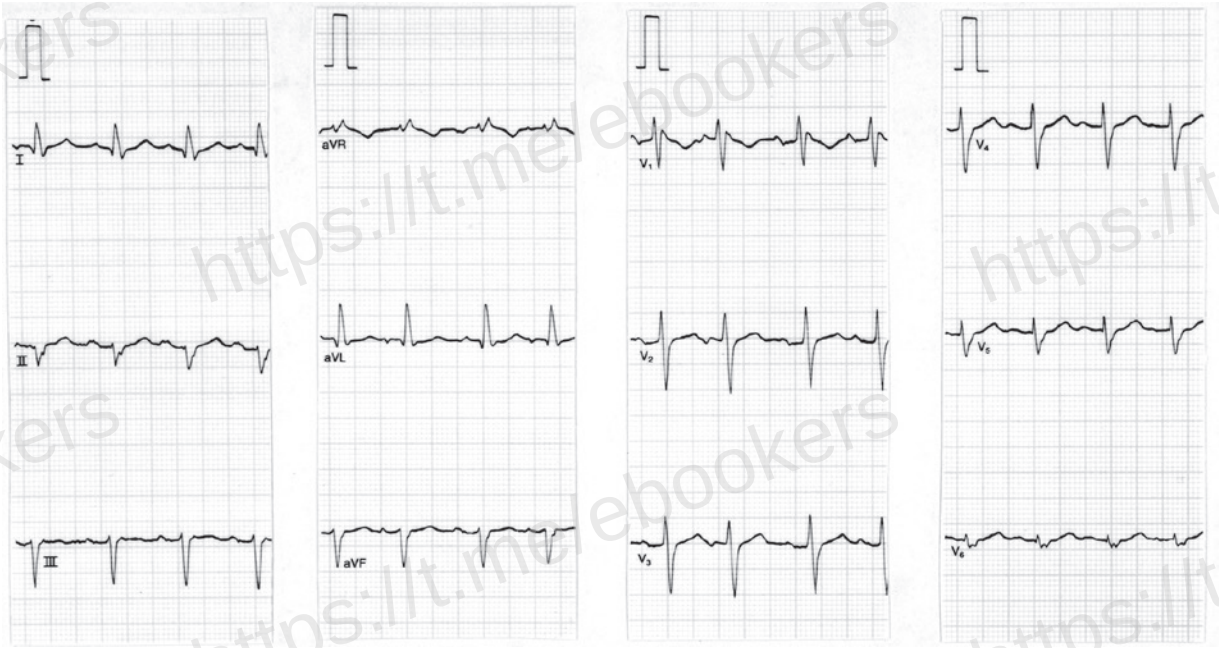


Figure 22.41 Right bundle branch block with left anterior hemiblock. There is left-axis deviation (mean frontal axis of –75°) and small R-waves in II, III and aVF.

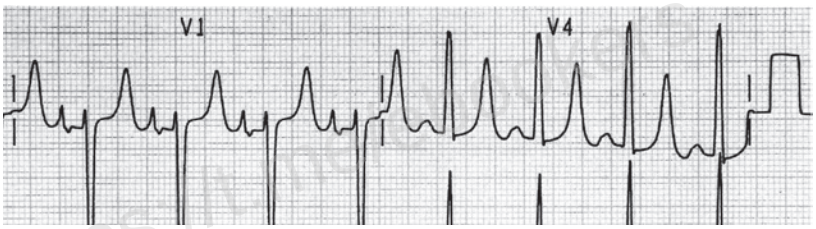


Figure 22.42 Sinus rhythm with peaked 'tent-shaped' T-waves in a patient with a serum potassium of 7.6 mmol/L.

SECOND-DEGREE AV BLOCK

Second-degree AV block is characterised by intermittent failure of AV conduction and is classified into Mobitz types I and II. Second-degree AV block can occur in SVTs; however, the conduction block is a physiological 'protective' mechanism in the setting of rapid atrial impulses.

MOBITZ TYPE I (WENCKEBACH)

Delay in AV conduction increases with each atrial impulse until an atrial impulse fails to conduct. This is usually a repetitive pattern, which may or may not begin with first-degree AV block. The level of AV block in type 1 is usually in the AV node itself and can be physiological (increased vagal tone) as well as pathological.

ECG

There is progressive lengthening of the PR interval over successive cardiac cycles, culminating in a non-conducted P-wave, resulting in a missed beat (Fig. 22.44). Type 1 is common in fit healthy people in the presence of high levels of resting vagal tone (Fig. 22.45).

CLINICAL

The condition is generally benign and does not carry the adverse likelihood of progression to complete AV block, although it may occur with inferior infarction. Treatment is rarely necessary.

MOBITZ TYPE II

There is intermittent failure of conduction of atrial impulses to the ventricles without preceding increases

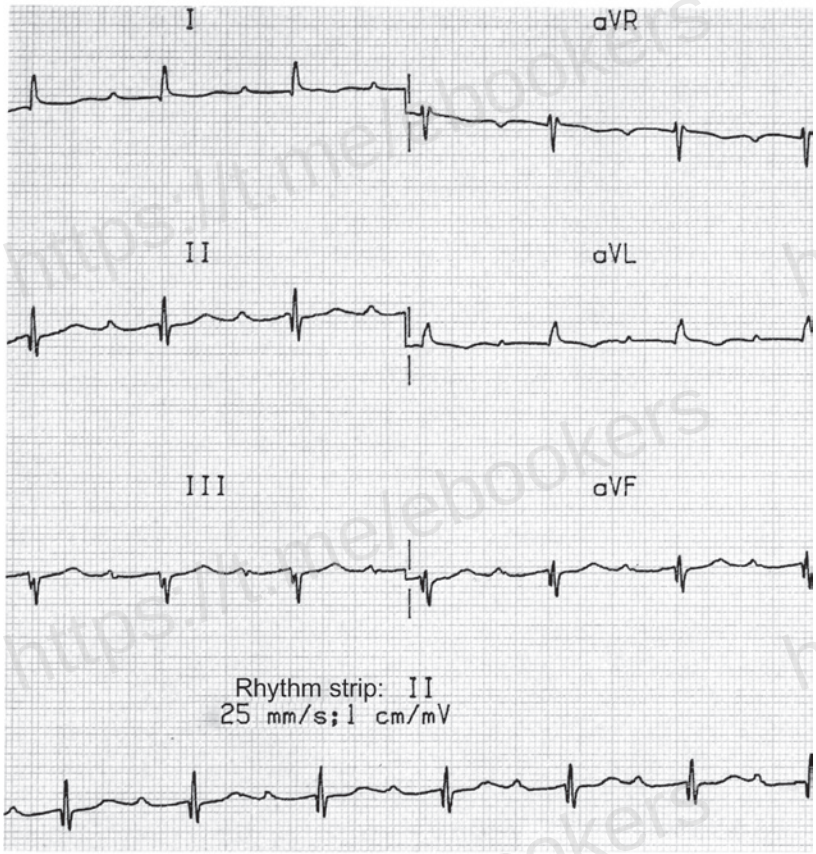


Figure 22.43 Sinus rhythm with first-degree AV block. The PR interval is 360 ms. Note inferior-wall myocardial infarction with Q-waves in II, III and aVF.

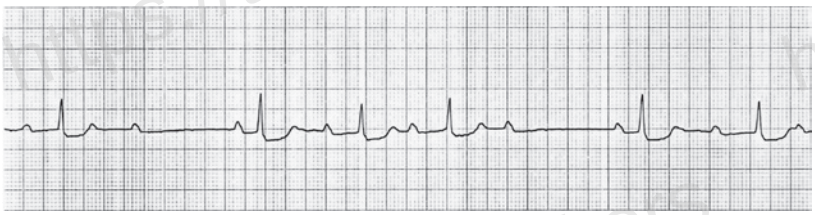


Figure 22.44 Mobitz type I (Wenckebach) second-degree arteriovenous block. Progressive lengthening of PR interval results in the failure of the second and sixth P-wave to be conducted.

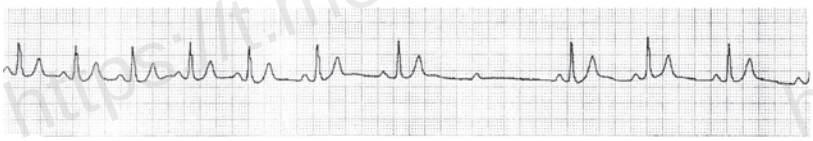


Figure 22.45 Intermittent type I second-degree arteriovenous block in a healthy male with obvious background sinus arrhythmia. Constant PR interval of 0.14 second suddenly increases to 0.22 second and next P-wave is not conducted.

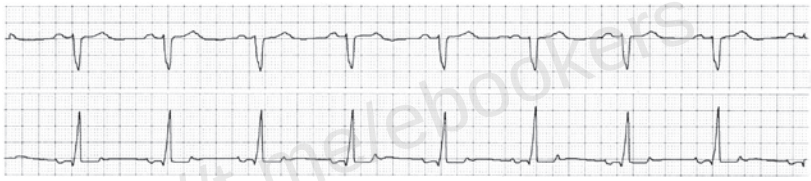


Figure 22.46 Mobitz type II second-degree arteriovenous (AV) block. Persistent 2:1 AV block with the atrial rate at 108 beats/min and the ventricular rate 54 beats/min.

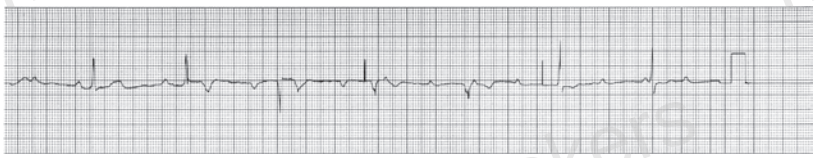


Figure 22.47 Leads I, aVR, V_1 and V_4 showing third-degree arteriovenous block. Complete dissociation of atrial activity at a rate of 107 beats/min and the ventricular rate at 46 beats/min. The escape rhythm is junctional (high up in the bundle of His) with a narrow QRS morphology.

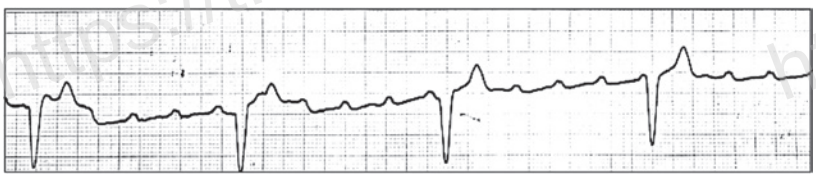


Figure 22.48 Third-degree arteriovenous block with an atrial rhythm at 135 beats/min and a broad distal ventricular escape rhythm which is unstable at a rate of 30 beats/min.

in the PR interval. The ratio of conducted to non-conducted atrial impulses varies; for example, every second or fourth atrial impulse may be conducted (i.e. 2:1 or 4:1 second-degree AV block). The lesion causing type II is usually situated in the bundle of His and is always pathological.

ECG

PR interval remains constant prior to the blocked P-wave. There is always a constant P-QRS-wave ratio: the P-waves are two (Fig. 22.46), three (rare) or four times more frequent than QRS-waves.

CLINICAL

It is likely to be associated with structural heart disease. Slower symptomatic ventricular rates may require pacing. The AV block may be intermittent or persistent. The adverse prognosis relates to the frequency of progression to complete AV block.

THIRD-DEGREE (COMPLETE) AV BLOCK

This rhythm occurs when no atrial impulses are conducted to the ventricles; atrial and ventricular contractions are dissociated. The SA node usually continues to depolarise the atria, whereas ventricular activation depends on a standby escape pacemaker located below the block. The escape pacemaker may be close to the His bundle (narrow QRS, stable pacemaker usually 40–60 beats/min) (Fig. 22.47), or more distal in ventricular tissue (wide QRS, relatively unstable pacemaker with a rate of 20–40 beats/min) (Fig. 22.48). If no ectopic escape pacemaker emerges, ventricular asystole will occur, resulting in a Stokes–Adams attack, or death if the episode is prolonged. Torsade de pointes may also occur associated with the bradycardia.

ECG

The ECG shows normal regular P-waves completely dissociated from QRS complexes. The QRS rate is always significantly slower than the P-wave rate and may be very slow at times.

CLINICAL

Idiopathic fibrosis of the conduction system is the most common cause. Other causes include myocardial infarction, valvular heart disease, cardiac surgery and a congenital form of complete heart block. Cardiac pacing is usually required to increase heart rate and cardiac output. Congenital forms often have a relatively fast escape ventricular rate, and patients may remain asymptomatic for many years.

SINUS NODE DYSFUNCTION[62]

Sinus node dysfunction (SND) results in sick sinus syndrome and or atrial arrhythmias. The incidence increases from 1 per 1000 at 45 years to 1 per 600 at 65 years. Time from development of bradycardia to SA block and sinus arrest is 13 years (range 7–29 years). SND is associated with 4.2-fold increase in AF. SND presents as AF in 40%–70% of cases. SND also presents with syncope, heart failure, other atrial tachyarrhythmia and thromboembolic events.

SND is secondary to decreased impulse generation or defective conduction out of the node resulting in bradyarrhythmia and atrial tachyarrhythmia.

Causes of SND

Intrinsic
- Interstitial fibrosis
  - Ischaemia
  - Infiltration: Amyloid
  - Inflammation: Rheumatic fever
  - Genetic mutation channellopathy: Decreased Ina propagation causing exit block

Extrinsic
- Autonomic tone
  - Drugs
  - Hypothyroid
  - Hypothermia

Sick sinus syndrome occurs in the setting of chronic SND.

Results in
- Severe sinus bradycardia
- Sinus pauses
- Sinus arrest
- SA nodal exit block

Chronotropic incompetence. Inappropriate responses to physiological demands such as exercise and stress.

Tachybradycardia. AF (most common), Afl and sinus tachycardia.

Most AF originates from left atrium and in SND the propensity of AF is explained by loss of overdrive modulation of pulmonary vein sleeves where increases in If current results in increased spontaneous activity. Impaired non-uniform conduction out of the SN also creates substrate for re-entry.

Atrial tachycardia and AF results in significant SND within 2 weeks due to down regulation of If and SND increases propensity of atrial tachyarrhythmia further.

SND recovers following AF reversion, either ablation or cardioversion.

Drug therapy is difficult in SND and tachybrady arrhythmia. If adequate chronotropic response to exercise can be demonstrated, then beta-blocker with intrinsic sympathomimetic activity can be trialled. Otherwise, all agents have negative chronotropic action and concurrent pacemaker is indicated.

Permanent pacemaker (PPM) with AAI or DDD mode reduces AF, stroke and pacemaker syndrome compared with VVI.

AF ablation improves SND, decreases bradycardia and need for pacemaker when compared to PPM and antiarrhythmic drug (Fig. 22.49).

CRITICALLY ILL PATIENTS AND ARRHYTHMIA[63]

In the general population of critically ill patients, excluding acute coronary syndromes and cardiac surgical patients, arrhythmia is common. The documented incidence is as high as 78%; however, the incidence of arrhythmia that requires treatment is much lower, at 15%–30%. SVT is by far the most common arrhythmia that requires treatment. AF, Afl and unifocal atrial tachycardias are the most frequent, in descending order. These SVTs are rarely the cause of admission but develop early in the admission, the majority by day 2. In critically ill patients, SVTs often result in:

- adverse myocardial oxygen supply–demand balance
- compromised blood pressure, cardiac output and systemic oxygen delivery
- impaired end-organ function such as oliguria and worsening gas exchange.

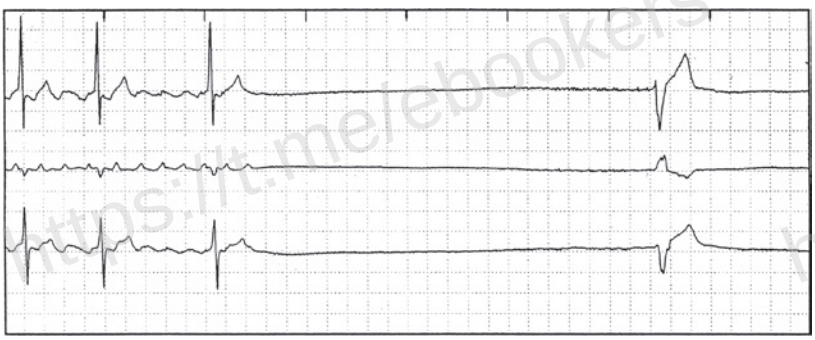


Figure 22.49 Characteristic findings in sick sinus syndrome. Episodic atrial tachycardias (atrial flutter with variable block in this instance) with periods of sinus arrest and very slow ventricular escape rhythm upon spontaneous termination in this case following carotid sinus massage.

The development of SVT in a critically ill patient is associated with a significant increase in mortality, especially in patients with sepsis and respiratory failure. Incidence of SVT is increased with:

- elderly patients
- evidence or past history of heart disease
- haemodynamic features of diastolic failure with elevated pulmonary artery occlusion pressure
- catecholamine infusion
- severe sepsis.

The actual dose of the catecholamine infusion does not appear to be important and, although electrolyte disturbances are common in critically ill patients, low plasma potassium and magnesium levels do not appear to be important predictors of SVT development. The incidence of SVT, particularly AF, is so high in elderly patients with heart disease on a catecholamine infusion that consideration of prophylactic strategies is worthwhile.

Risk of in-hospital stroke is increased in critically ill patients with new-onset AF, odds ratio 2.70 and greater focus on the need for embolic prophylaxis is needed.[64]

TREATMENT OF SUPRAVENTRICULAR TACHYCARDIA IN CRITICALLY ILL PATIENTS

Continuing arrhythmogenic and chronotropic factors make rate control difficult.

- Digoxin often results in poor rate control due to persisting endogenous and exogenous sympathomimetic tone. The inotropic and vasopressor effects of acute digitalisation are beneficial. Digoxin (10 µg/kg) has been shown to provide superior circulatory support to dopamine at 8 µg/kg per min in septic patients.[65]
- Irrespective of plasma levels, magnesium has been shown to be effective at rate control; however, hypotension due to vasodilatation can be seen.
- Amiodarone is particularly effective and has allowed reliable acute rate control over a period of days in critically ill patients with circulatory shock requiring catecholamine infusions.[66] It can cause hypotension if patients are rapidly loaded. In another study, magnesium was at least as effective as amiodarone in rate control and time to reversion to sinus rhythm.[67]
- Other agents, such as diltiazem, sotalol and procainamide, are associated with prohibitive myocardial depression and hypotension.

Urgent cardioversion is indicated in unstable patients. The likelihood of remaining in sinus rhythm in the setting of high endogenous and exogenous sympathomimetic tone is low without concomitant use of an antiarrhythmic drug. Cardioversion is best reserved for hastening onset of sinus rhythm once a drug like amiodarone has controlled rate. Cardioversion should at least be attempted within 24–48 hours of onset in the hope that embolic and anticoagulation issues are avoided.

MYOCARDIAL INFARCTION AND ARRHYTHMIA

Arrhythmia is common following AMI. While early arrhythmia contributes significantly to mortality, treatment is largely expectant and secondary to re-establishing coronary blood flow, minimising infarct size and treating ongoing ischaemia and heart failure. Late ventricular arrhythmia is particularly challenging, as selecting patients at risk is difficult and treatment options are limited.

MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION AND ARRHYTHMIA CONTROL

Modern management of AMI, although targeted to prevent or reduce infarct size, has also been very effective in reducing arrhythmia incidence and sequelae. Numerous studies have documented transient ventricular arrhythmias at the time of reperfusion resulting from thrombolysis and acute angioplasty. However, the most common arrhythmias seen in this setting are VEB, AIVR and non-sustained VT, rather than VF or sustained VT.

Meta-analysis of thrombolytic trials has shown no increase in early VF following thrombolytic therapy in the first 24 hours. The likelihood of developing VF at any time during a hospital episode is reduced following thrombolytic therapy but the risk of developing VT is increased. The mechanism of reperfusion arrhythmia is believed to be related to intracellular calcium overload and the resulting triggered activity in the form of DAD. Dipyridamole, which inhibits the cellular uptake of adenosine, has been shown to be effective in preventing and treating reperfusion ventricular arrhythmia.

Prior to the introduction of thrombolytic therapy, beta-adrenergic receptor blockers significantly reduced the incidence of early VEB and VF. However, following routine use of thrombolytic therapy, the benefit of beta blockers relates to a reduction in post-infarction ischaemia and subsequent infarction.

The early work demonstrating survival benefit of magnesium was initially thought to be due to the prevention of arrhythmia.[68] However, the Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) found the improved survival not to be related to a reduction in arrhythmia.[69] Subsequent studies in the thrombolytic era have failed to show any benefit at all with magnesium, although debate regarding optimal time of administration persists. Magnesium may have a role in patients in whom beta-adrenergic blockers or thrombolytic therapy are contraindicated.

ELECTROLYTE CONCENTRATIONS AND ARRHYTHMIA FOLLOWING ACUTE MYOCARDIAL INFARCTION

Serum potassium following AMI is negatively correlated with the incidence of VEB and VT, with the probability of VT falling until serum potassium exceeds 4.5 mmol/L.[11] There is no evidence that magnesium levels in this setting have any effect on ventricular arrhythmia. Nonetheless, ILCOR recommendations not only include the maintenance of serum potassium greater than 4.0 mmol/L, but also serum magnesium levels greater than 1.0 mmol/L.

BRADYARRHYTHMIAS POST ACUTE MYOCARDIAL INFARCTION

One-third of patients with AMI develop sinus bradycardia because of increased vagal tone. In inferior infarcts due to occlusion of the right coronary artery, bradyarrhythmia is due to ischaemia of the SA and AV nodes. Reperfusion of the right coronary artery can also lead to sinus bradycardia and heart block that is due to accumulation of adenosine in nodal tissue. Bradycardia in this setting is resistant to atropine.

Second- or third-degree AV block occurs in approximately 20% of AMI patients. High-degree AV block occurs early when present, with 42% presenting with AV block and most, 66%, developing in the first 24 hours. Similar to all post-AMI arrhythmias, thrombolytic therapy has reduced the incidence down to 12%. When present, high-degree AV block is associated with an increased mortality. However, high-degree AV block is not an independent predictor, but rather a marker of extensive infarction and LV dysfunction.

Treatment is only indicated for sinus bradycardia associated with symptoms, hypotension or signs of poor cardiac output. Most often, first- and second-degree block also do not need treatment. Mobitz type I second-degree block may require treatment and atropine is indicated. However, in Mobitz type II, atropine usually has no effect on infranodal block and may precipitate third-degree block by increasing sinus rate and enhancing block. Atropine may improve heart rate with AV block occurring at the AV node, as demonstrated by a narrow QRS complex, by improving AV conduction or accelerating escape rhythm. Atropine is not indicated for infranodal third-degree block, which is diagnosed by the presence of a new wide QRS complex. When required, atropine is administered, 0.5–1.0 mg every 3 minutes until signs or symptoms are resolved, up to a maximum of 0.03–0.04 mg/kg. If atropine is not indicated or effective, cardiac pacing is required (Box 22.7). Transcutaneous pacing is indicated for initial management as a bridge until a transvenous temporary pacing wire can be inserted safely and with appropriate sterile technique. With the ready availability of transcutaneous pacing, IV catecholamines for bradyarrhythmias are to be avoided in the setting of AMI.

Box 22.7 Indications for pacing following myocardial infarction

- Haemodynamically unstable bradycardia (<50 beats/min)
- Mobitz type II second-degree atrioventricular block
- Third-degree heart block
- Bilateral bundle branch block
- Left anterior fascicular block
- New left bundle branch block
- Bundle branch block and first-degree atrioventricular block

ATRIAL FIBRILLATION POST ACUTE MYOCARDIAL INFARCTION

New-onset AF occurs in 10%–15% of AMI. The incidence increases with age, large infarcts, LV hypertrophy and congestive cardiac failure. It is also related to atrial infarction with occlusion of the right coronary artery proximal to the sinus node branch or circumflex proximal to the left atrial circumflex branch. Later in the course of myocardial infarction, AF is related to postinfarct pericarditis.

Thrombolytic therapy has reduced the incidence of AF. In the setting of AMI, AF is usually self-limiting and requires no treatment. If rapid ventricular rates are associated with further ischaemic symptoms or haemodynamic compromise, cardioversion is indicated. Beta blockers, which are indicated in the treatment of AMI anyway, are the initial treatment of choice. Digoxin is not indicated in the setting of acute ischaemia as the likelihood of triggered activity associated with intracellular calcium overload is increased. AF following AMI is associated with an increase in mortality. Systemic emboli following AMI are three times more likely with AF and 50% occur in the first 24 hours of onset of AF. For this reason, sustained AF is an indication for anticoagulation prior to the normal 48-hour period following AMI.

VENTRICULAR ARRHYTHMIA POST ACUTE MYOCARDIAL INFARCTION[70,71]

VF/VT is the leading cause of mortality following AMI. Fifty per cent of patients dying from AMI do so pre-hospital due to VF/VT. Pre-hospital mortality is being reduced by improved community education, wider application of basic life support and availability of an automated external defibrillator (AED). Following admission to hospital, LV failure is the most common cause of death.

The major risk period for VF is the first 4 hours following onset of symptoms, with 4%–18% of patients

having VF in this period. Once admitted to hospital, 5% develop VF, mostly in this first 4-hour period. VF in this early 4-hour period is termed 'primary VF'. VF later in the course of an AMI, usually associated with LV failure or cardiogenic shock, is called 'secondary VF.'

Thrombolytic therapy has reduced VF incidence. The Gruppo Italiano per lo Studio della Streptochinasi nell'infarto miocardico (GISSI) study[70] found an incidence of primary VF of 3.6% and secondary VF of 0.6%. The overall incidence of ventricular arrhythmia in the Global Utilization of Streptokinase and Tissue plasminogen activator to treat Occluded arteries (GUSTO-1) report was VF, 4.1%, VT, 3.5% and both, 2.7%.

Primary VF increases in-hospital mortality and complications but not long-term mortality. Complex ventricular arrhythmias, defined as multiform VEB, couplets and non-sustained VT, occur in 35%–40% of patients during hospital stay. They occur equally with Q-wave and non-Q-wave infarction. Complex ventricular arrhythmia is a risk factor for subsequent VF/VT and SCD, particularly in non-Q-wave infarction. Polymorphous VT is less common after AMI and does not appear to be related to QT prolongation or electrolyte disturbances in the reported cases.

Lidocaine reduces primary VF by 33% but mortality is increased by a similar amount such that there is no net benefit and the third International Study of Infarct Survival (ISIS-3) reported an overall trend to increased mortality. Being more selective as to which patients receive lidocaine has not been possible, as only 50% of patients who develop VF have 'warning' ventricular arrhythmia. In the 'percutaneous coronary intervention or thrombolytic and beta-blocker' era of treatment of AMI, the use of prophylactic lidocaine, or any other antiarrhythmic drug, to prevent VF will have even less benefit. There are no conclusive data to support the use of lidocaine to prevent recurrent VF in those patients who have already suffered an episode of VF. Despite this, a short period of 6–24 hours of lidocaine has been advocated.

Patients who survive a late or secondary episode of VF/VT following myocardial infarction require full evaluation for preventive strategies, as do survivors of SCD. All survivors of a myocardial infarction are at an increased risk for SCD but accurate prediction is not feasible. Risk factors that have been shown to be associated with increased risk of a subsequent episode of VF/VT after myocardial infarction include:

- age
- Holter monitoring and demonstration of non-sustained VT, couplets and frequent VEB (i.e. >10 beats/min)
- impaired LV function (i.e. ejection fraction less than 30%–40%)
- signal-average ECG and detection of delayed afterpotentials. In patients presenting with SCD after myocardial infarction, 68%–87% have an abnormal signal-average ECG. However, the positive predictive value is poor, at 15%–25%
- demonstrated inducibility of VT postinfarction is associated with increased risk of SCD. However, the positive predictive value is again poor, at 20%–30%.

Combinations of these risk factors have been evaluated to predict risk after infarction. The combination of delayed potentials on signal-average ECG, LV ejection fraction of less than 40% and non-sustained VT on Holter monitor has been shown to be associated with up to 50% risk of SCD. Currently, there is no agreement on which patients require primary preventive strategies for VF/VT following myocardial infarction.

Using frequent VEB to identify patients at risk following myocardial infarction has been extensively used. There have been 54 randomised trials reported involving more than 20,000 patients using 11 different class I agents.

Class I agents showed no overall benefit on all-cause mortality and class IC agents have excess mortality despite arrhythmia suppression.

Class II antiarrhythmics, beta blockers, have an established and broadening role, with recent evidence showing significant benefit.[72]

Class III agents lack a consistent class effect. Sotalol (Survival with oral D-sotalol: SWORD) was found to increase all-cause mortality and arrhythmia deaths.[73] Amiodarone (Canadian Amiodarone Myocardial Infarction Arrhythmia Trial: CAMIAT) reduces all-cause mortality in patients with frequent VEB post myocardial infarction,[74] but another study (European Myocardial Infarction Amiodarone Trial: EMIAT) evaluated amiodarone in patients with ejection fraction less than 40% and found no effect on all-cause mortality but a 35% reduction in arrhythmia deaths.[75] Subsequent analysis of combined CAMIAT and EMIAT data has emphasised the importance of beta blockers. The combination of amiodarone and beta blockers in these post-infarct patients was better than either drug alone.[76]

CARDIOTHORACIC SURGERY AND ARRHYTHMIA

SVT AFTER CARDIOTHORACIC SURGERY[77]

AF predominates, with Afl and unifocal atrial tachyarrhythmia also commonly occurring after CABG, with an incidence of 11%–40% and in over 50% following valvular surgery. In addition to mechanisms found in non-surgical patients, pericardial inflammation or effusion, increased catecholamine production and postoperative autonomic changes are implicated. Major risk factors include:

- previous history of AF
- increasing age
- postoperative withdrawal of beta-blocker therapy.

Extent of coronary artery disease, postoperative ischaemia, duration of aortic cross-clamping or cardiopulmonary bypass and method of myocardial protection do not influence incidence. SVT post cardiothoracic surgery is not a benign event, with the major consequence being thromboembolic complications. Stroke occurs following CABG in 1%–6% of patients and postoperative atrial tachyarrhythmia increases the incidence threefold. Other adverse effects include:

- haemodynamic instability
- prolonged inotropic support
- need for intra-aortic balloon pump
- reoperation for bleeding
- longer and more expensive critical care unit and hospital episodes.

PREVENTION OF SUPRAVENTRICULAR TACHYCARDIA[78,79]

Preoperative beta-blocker treatment should be continued postoperatively. Beta blockers consistently reduce SVT across many studies with differing agents.

Amiodarone prophylaxis after elective cardiac surgery reduced postoperative AF from 53% to 25%. Diltiazem has also been shown to be effective at SVT prevention and there was associated improvement in haemodynamic variables and rates of myocardial ischaemia. Verapamil is not effective. Esmolol was found to be more effective than diltiazem. Sotalol is also effective but problematic bradycardia and hypotension are greater.[80] Atorvastatin is also effective.[81]

There is no relation between SVT incidence and serum magnesium levels and there are conflicting data relating to the efficacy of prophylactic magnesium. Digoxin has no role in prevention.

Incidence of postoperative AF are still high despite preventive strategies. In a large cohort of patients, overall AF incidence was 33% (28.1% CABG only, 33.7% valve only and 47.3% combined) despite 80% preventive beta blocker or calcium channel blocker (Cardiothoracic Surgical Trials Network[(h)]). Average onset of AF was 2.4 days (range 0–7).

TREATMENT OF SUPRAVENTRICULAR TACHYCARDIA

Treatment is aimed at control of ventricular rate, prevention of thromboembolism and cardioversion.

Similar to other settings, rhythm control not superior to rate control. Amiodarone, AV blocker and electrical cardioversion compared to AV blocker only (resting rate <100) had similar hospital length of stay, rates of anticoagulation and stable sinus rhythm at discharge, complications, including thromboembolic, stable sinus rhythm at 30 and 60 days and readmission rates.[82]

Digoxin, atenolol/metoprolol, diltiazem and magnesium are appropriate choices to control rate.

In persisting AF, the timing of electrical cardioversion is debatable. Early electrical cardioversion, inside 24–48 hours, avoids the need for anticoagulation but is associated with a significant recurrence rate as postoperative arrhythmogenic factors remain. In persistent or recurrent AF, sotalol and amiodarone, depending on myocardial function, are suitable antiarrhythmic drugs and should be continued for 6–12 weeks following cardioversion.

Timing of safe anticoagulation following cardiac surgery is also debatable. Many advocate delaying anticoagulation till 72 hours post surgery, which may be greater than 24–48 hours after onset of SVT. Most cardiac surgical patients receive aspirin and low-dose heparin in the early postoperative period, which is likely to reduce risk. However, it is worth noting that, in other AF settings, 325 mg of aspirin decreased thromboembolic events but 75 mg did not.

VENTRICULAR ARRHYTHMIA FOLLOWING CARDIAC SURGERY

Ventricular arrhythmia requiring treatment, DC shock or drug therapy is common following cardiac surgery and occurs in 23% of patients.[83] Arrhythmias requiring DC shock occur in the first 36 hours and are associated with:

- advanced age
- failure to use an internal mammary artery conduit (which is likely to reflect preoperative assessment of high risk)
- SVT.

The incidence was not related to previous myocardial infarction, ejection fraction of less than 50%, prolonged operative time, perioperative myocardial infarction or reduced number of vessels bypassed. In patients undergoing coronary artery bypass, grafting patients at high risk for sudden death, LV ejection fraction less than 36% and abnormalities on signal-averaged ECG had a 6.3% incidence of sustained VT and 4.3% VF.

VEBs are common early on return from surgery, with frequent or complex ectopy associated with adrenergic effects of emerging from anaesthesia and hypokalaemia. The threshold to treat these arrhythmias varies with clinicians. Potassium must be regularly checked and maintained above 4 mmol/L.

If there is accompanying emergent hypertension, in addition to the antiarrhythmic action, the vasodilating properties of magnesium provide an ideal profile at this stage. Patients with VT/VF reverting with DC shock who are haemodynamically stable should have prophylactic antiarrhythmic cover until adrenergic stimulation associated with awakening and weaning from mechanical ventilation is past. Lidocaine has been the agent of choice, but magnesium, amiodarone and sotalol are all more effective. Maintaining

antiarrhythmic levels of magnesium may not be conducive to weaning from ventilation. Extrapolating from post myocardial infarct data would support the conversion to beta blockers if there were no contraindications.

A smaller proportion of patients develop malignant VF/VT, most often in association with poor LV function and a postoperative low-cardiac-output state requiring catecholamine infusions. In this setting, ventricular arrhythmia is common, often initiated by short-coupling polymorphous VT (normal QT_c), due to ongoing ischaemia or reperfusion of ischaemic heart.

- High-dose amiodarone may work best in combination with antiarrhythmic levels of magnesium (1.8–2.0 mmol/L) or lidocaine.
- Many of these patients need an intra-aortic balloon pump to defend coronary artery perfusion pressure not only because of the likely poor LV function and low-output state, but also to minimise the adverse effects of antiarrhythmic drugs and recurrent DC shocks.
- Pacing may be required to counteract bradyarrhythmia associated with escalating doses of antiarrhythmic drugs. Pacing at faster rates (90–110 beats/min, which may not be ideal from a cardiac-output point of view) may be protective against recurrent episodes by promoting homogeneity of depolarisation and suppression of abnormal automaticity. The presence of epicardial or transvenous pacing wires also enables bedside-programmed stimulation and overdrive pacing for termination of recurrent VT, which has fewer deleterious effects than recurrent DC shocks.

Arrhythmia during pregnancy[84]

Cardiac arrhythmia is the most common cardiac complication during pregnancy.

Mechanism thought to result from increased plasma volume and stroke volume. Activation of stretch-activated ion channels (see above) results in EADs, shortened refractoriness and slowed conduction with spatial dispersion.

The majority of antiarrhythmic drugs are Category C (www.fda.gov). Risk cannot be ruled out. Amiodarone is teratogenic and associated with foetal hypothyroidism, growth retardation and prematurity and therefore is reserved for life-threatening arrhythmia. Dronedarone is also teratogenic and contraindicated. With other drugs, avoid use during organogenesis of first trimester. Monitor foetal growth, cardiac rhythm and uterine contractility during second and third trimesters.

Electrical cardioversion indicated for haemodynamic instability and drug refractory arrhythmia, and does not compromise blood flow to foetus and risk of foetal arrhythmia is small. Premature labour is theoretical risk only. There are rare cases of emergency caesarean section due to foetal arrhythmia and therefore foetal monitoring is advisable.

Catheter ablation is not indicated due to radiation exposure and potential haemodynamic instability.

Frequent atrial and ventricular ectopics can be intolerable. Metoprolol (Cat C), not Atenolol (Cat D), positive evidence of risk. Can be used after first trimester.

SVT is the most common sustained arrhythmia during pregnancy and 20% of patients with pre-existing SVT will have exacerbation during pregnancy. If vagal manoeuvres fail, Adenosine is safe (Cat C), with Metoprolol or Verapamil (Cat C) next in line. For SVT associated with accessory pathway (pre-excitation, stable wide-complex tachycardia) Procainamide (Cat C) indicated and Flecainide (Cat C) for prevention.

AF and AFL are less common than SVT. In new AF, pulmonary embolus and cardiomyopathy should be excluded. If unstable cardioversion is suggested, otherwise Metoprolol and or Digoxin (Cat C) for rate control. Sotalol (Cat B) or Flecainide for failure of rate control. Anticoagulation with Enoxaparin is indicated.

VT with structural heart disease, usually in the setting of acute or chronic cardiomyopathy, should be terminated with DC shock. Lidocaine (Cat C) or Procainamide if DC shock resistant. Prevention with Metoprolol or Sotalol. For VT without structural heart disease, prevention with Flecainide is indicated.

For foetal SVT, Flecainide, sotalol and Digoxin are indicated.

LONG-QT SYNDROME[85,86]

The traditional criteria of prolonged QT need to be corrected for heart rate (QT_c, Bazett's formula, QT divided by the square root of the RR interval) and a QT_c greater than 0.44 ms. Borderline QT_c is common and stems from miscalculation in the setting of atypical T-waves and prominent U-waves.[107] The recommended method to determine the end of the T-wave is by intersecting the tangent to the steepest slope of the last limb of the T-wave and the baseline (Fig. 22.50). The diagnosis of

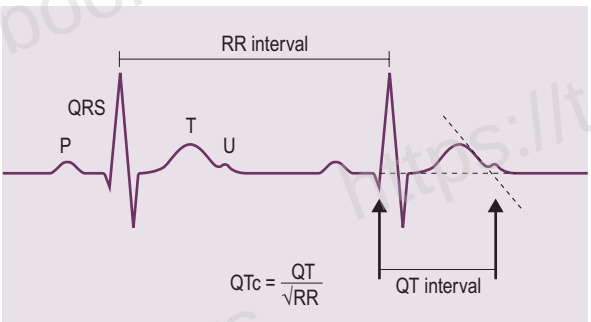


Figure 22.50 Determining QTc using the 'tangent method.'

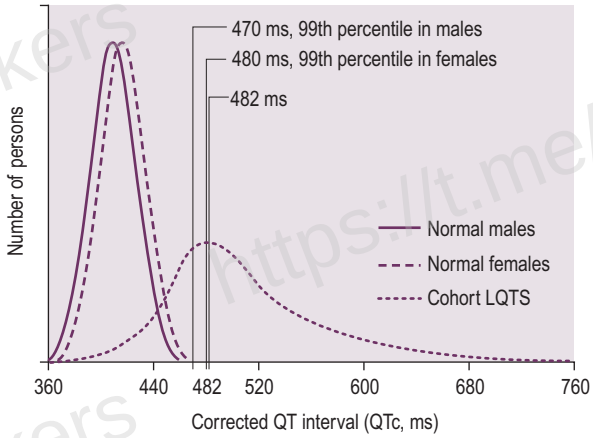


Figure 22.51 Distribution of QTc values. 99th percentile males 470 ms. 99th percentile females 480 ms. There is significant overlap of these 'normal' QTc persons and a cohort of mutation-positive patients, mean QTc 482 ms. *(Adapted from Johnson JN, Ackerman M. QTc: how long is too long?* Br J Sports Med. *2009;43:657–662; Taggart NW, Haglund CM, Tester DJ, et al. Diagnostic miscues in congenital long-QT syndrome.* Circulation. *2007;115:2613–2620, with permission.)*

'borderline LQTS' is common with QT_c in the range of 440–470 ms. QT_c should also be adjusted for age and gender with females an average 10 ms longer. There is significant overlap between the normal population and patients with congenital LQTS; 25%–35% of congenital LQTS have a QT_c <440 ms (Fig. 22.51).

The causes of LQTS can be divided into acquired and congenital (Box 22.8). Most drugs that cause LQTS do so by binding to the hERG or alpha subunit of the I_{Kr} potassium channel and reducing repolarisation current. Unlike other I_K potassium channels, the hERG subunit of I_{Kr} is very sensitive to unintended drug binding owing to aromatic amino acids positioned in such a way as to block the channel. Common to all causes is a prolongation of repolarisation, which creates the substrate for random re-entry giving rise to polymorphous VT (classically of the torsade de pointes type), particularly under conditions of acute adrenergic arousal.

Action potential prolongation results from either enhancing depolarisation (sodium [Na] channel, I_{Na}) or reducing repolarisation current (delayed rectifier potassium [K] currents, I_{Kr} and I_{Ks}).

There is less capacity to respond to additional stresses that impair repolarisation such as hypokalaemia, hypomagnesaemia and drugs with class III action.

Prolonged action potential in LQTS predisposes to arrhythmia in two ways:

1. Extended plateau phase of action potential results in susceptibility to EAD-initiated arrhythmia. EADs are due to re-opening of L-type calcium channels, the activity of which is increased by adrenergic stimulation, which explains the association between SCD and exercise and excitement in LQTS.
2. Heterogeneity of prolonged action potential creates spatial dispersion of repolarisation, leading to regions of refractory block and substrate for re-entrant arrhythmia. This mechanism appears important in pharmacological LQTS.

Box 22.8 Causes of long-QT syndrome

Acquired
Drugs
- Class IA antiarrhythmic drugs
  - Quinidine, procainamide
- Class III antiarrhythmic drugs
  - Amiodarone, sotalol
- Tricyclic antidepressants
- Macrolide antibiotics
- Phenothiazines
- Antihistamines
- Cisapride

Myocardial ischaemia/infarction
Hypokalaemia
Cardiomyopathy
Acute myocarditis
Mitral valve prolapse
Acute cerebral injury
Hypothermia
Congenital
Familial
90%
Linked to a DNA marker on the short arm of chromosome 11
Autosomal-dominant in most cases
Some cases linked to congenital deafness and autosomal-recessive
Non-familial – related to new gene mutation
Sporadic: 10%

CONGENITAL LQTS[87]

Congenital LQTS is a collection of genetically distinct arrhythmogenic disorders resulting from genetic mutations in cardiac potassium and sodium ion channels giving rise to the term 'cardiac channelopathies.' As there is overlap in QT_c between the normal population and congenital LQTS patients, a LQTS clinical probability score has been developed to determine probability of diagnosis (Table 22.12).

Congenital LQTS results from mutations in genes coding for cardiac proteins including ion channels, accessory subunits and modulatory proteins (Table 22.13).

Table 22.12 LQTS clinical probability score

FINDING	POINTS
HISTORY	
Syncope	
• without stress	1
• with stress	2
• Congenital deafness	0.5
• Family history of LQTS	1
• Unexplained sudden death in a first-degree family member <age 30	0.5
ECG	
• QTc by Bazett's formula	
• 450–459 ms in males	1
• 460–479 ms	2
• ≥480 ms	3
• Torsades de pointes	2
• T-wave alternans	1
• ≥3 leads with notched T-waves	1
• Bradycardia <2nd centile for age	0.5
PROBABILITY SCORE	
	≤1 low probability >1 to <4 intermediate probability ≥4 high probability

Schwarlz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome. An update. *Circulation*. 1993; 88:782–784.

Table 22.13 Classification of congenital LQTS

TYPE	GENE MUTATION/ PROTEIN	FEATURES
LQT1	KCNQ1 α-subunit of I_{KS}	Reduced function of I_{KS} decreases repolarising current Most common at 30%–35% but less severe When homozygous associated with congenital deafness
LQT2	KCNH2/h ERG α-subunit of I_{Kr}	Reduced function of I_{Kr} decreases repolarising current 25%–30%
LQT3	SCN5A α-subunit of I_{Na}	Increased function of I_{Na} prolonging depolarising Na current Mutations in SCN5A also cause Brugada syndrome, cardiac conduction disease and dilated cardiomyopathy
LQT4	Anchor protein ankyrin B	Ankyrin B anchors ion channels in the cell
LQT5	KCNE1 β-subunit of I_{Ks}	Reduced function of I_{Ks} Homozygous leads to Jervell and Lange–Nielson syndrome Congenital deafness
LQT6	KCNE2 β-subunit of I_{Kr}	Reduced function of I_{Kr}
LQT7	K-channel I_{Kl}	Anderson–Tawil syndrome Associated skeletal deformities
LQT8	C_{AV} CACNAlc $I_{ca\text{-}L}$	Calcium channel is distributed widely Timothy's syndrome Multiple clinical manifestations

CLINICAL FEATURES[88]

Prevalence is estimated to be 1 in 2500–5000.

Thirty per cent of patients with congenital LQTS present with unexplained syncope or aborted sudden death (which is often not the first episode). The majority (60%) are identified when family members are screened after syncope or cardiac arrest in a family member. Ten per cent are detected on routine evaluation of ECG. The majority of episodes of syncope or sudden death (60%) are precipitated by emotions, physical activity or auditory stimuli causing acute adrenergic arousal. The degree of QT_c prolongation is not predictive of syncope or sudden death.

MANAGEMENT

The first line of management of polymorphous VT with shock is DC shock, with magnesium being the antiarrhythmic of choice.[89]

- Unresponsive rhythms or recurrence despite magnesium requires pharmacological intervention (isoproterenol [isoprenaline] or epinephrine [adrenaline] depending on blood pressure) or electrical pacing.
- Factors associated with acquired LQTS need to be identified and eliminated.

Strategies for prevention of recurrence in congenital LQTS depend on the presentation. Patients who present with or have a history of syncope or aborted sudden death have a high risk of recurrence (5% per year). Beta blockers are the first line of treatment with the goal of reducing the exercise heart rate to less than 130 beats/min. Symptomatic bradycardia following adequate beta blockade requires a permanent pacemaker. Patients with recurrence despite these measures and those with an early malignant course need stellate sympathetic ganglionectomy. In 5% of these high-risk patients, triple therapy fails and an implantable defibrillator is required. Asymptomatic patients with incidental LQTS (<0.5% per year) and asymptomatic family members (0.5% per year) have a very low risk of syncope or sudden death. It is also very rare for the first episode to be fatal in these two groups, so prophylactic measures are generally not required and close follow-up is sufficient.

Class IA, IC and III drugs may increase QT interval and should be avoided in polymorphous VT and torsade de pointes.

SUDDEN CARDIAC DEATH[20]

Arrhythmic causes of SCD can be divided into three categories:

1. *VT or VF:* this is most common.
2. *SVT with a very rapid ventricular rate:* this is usually associated with the development of AF or flutter in the presence of an accessory AV connection (but can occasionally be due to enhanced conduction over the normal AV conduction system).
3. *Bradycardia or asystole:* this is usually the result of an inadequate escape pacemaker mechanism associated with either a high-degree AV block or severe sinus node dysfunction. In addition, some patients with sinus node dysfunction have paroxysmal supraventricular arrhythmia (tachycardia-bradycardia syndrome) that on termination results in an exaggerated overdrive suppression of both the sinus node and escape pacemakers such that the prolonged pause evolves into asystole or VF.

The causes of these arrhythmias can be divided into three general categories:

1. *Ischaemic heart disease:* AMI or old myocardial infarction scar
2. *Non-ischaemic heart disease:* cardiomyopathy, valvular heart disease, congenital heart disease, ventricular hypertrophy and cardiac trauma
3. *No apparent structural heart disease:* primary electrical disease, electrolyte abnormalities, LQT syndromes and drugs.

Contributing factors are often multifactorial, particularly the combination of structural heart disease, proarrhythmic drugs and electrolyte abnormalities.

EVALUATION OF A SURVIVOR OF SCD

Primary prevention of SCD has been disappointing owing to difficulties in selecting patients at risk. Regardless of the aetiology of the SCD, the reported recurrence rate is high, at least 30%–40% at 1 year. Therefore, in-hospital assessment is critical to establish the underlying cause and to guide therapy.

CORONARY ARTERY DISEASE AND SUDDEN CARDIAC DEATH

Extensive atherosclerotic coronary artery disease is the most common pathological finding in survivors and non-survivors of SCD. Fewer than 30% have evidence of a recent AMI. A larger proportion (up to 50%) has evidence of coronary artery thrombosis or plaque fissuring and rupture. In those patients not having an AMI, the majority (75%) has a coronary artery stenosis (>50% of lumen), and 60% have three-vessel disease. Approximately 50% have evidence of an old myocardial infarction. The fact that the typical pathological background for SCD is severe epicardial coronary artery disease, with or without an old myocardial infarction and evidence of a new ischaemic syndrome, underlines the central role that coronary artery disease plays in SCD.

INVESTIGATIONS[18–20]

- *Chest X-ray:* cardiac size, presence of pulmonary oedema.
- *12-lead ECG:* acute ischaemia, previous infarction, ventricular aneurysm or LV hypertrophy. Abnormalities of rate, rhythm, conduction or sinus node dysfunction. PR interval, QRS complex duration or QT interval. Changes of electrolyte abnormalities.
- *Plasma electrolytes:* potassium, magnesium and calcium. Potassium levels may be difficult to interpret after a period of resuscitation.
- *Cardiac enzymes:* serial troponin T, creatinine phosphokinase with myocardial band fractionation and lactate dehydrogenase to establish the presence of a recent AMI.
- *Plasma blood levels of drugs that affect cardiac rhythm or conduction:* while proarrhythmic effects of drugs are more likely at high levels, it should be emphasised that proarrhythmia can occur at normal or low plasma drug levels.
- *Toxicology screen:* substance abuse or drug overdose (cocaine, psychotropic drugs), particularly in patients without overt structural heart disease.
- *24-hour Holter monitor ECG:* quantitative analysis of frequency of arrhythmia and to detect silent myocardial ischaemia.
- *Assessment of LV function:* LV ejection fraction. Gated pool scan gives a better estimate of global LV systolic function, but echocardiogram will give added diagnostic information such as valvular disease and myocardial hypertrophy. Both studies will detect segmental wall motion abnormalities.
- *Exercise tolerance test:* standard exercise ECG or thallium-201 scans. Echocardiogram immediately following exercise may be as informative.
- *Signal-average ECG:* averages between 100 and 400 heart beats, for identification of low-amplitude electrical signals, such as after-depolarisations. These are found in the terminal portion of the QRS complex and cannot be seen on the 12-lead ECG. Associated with an increased risk of spontaneous and inducible ventricular arrhythmia.

- *Cardiac catheterisation and coronary angiogram:* to quantify the degree of coronary artery disease.
- *EPS:* virtually always indicated to document and characterise ventricular tachyarrhythmia. The initial baseline EPS should be performed in the absence of any antiarrhythmic drugs. Inducibility of sustained ventricular arrhythmias at EPS is associated with worse outlook, with a 5-year risk of SCD of 32% versus 24% in those without inducible arrhythmia, and is an indication for an implantable defibrillator. The inducibility of VT/VF is less common in survivors of SCD (44%) than patients who present with recurrent sustained VT. In patients with sustained monomorphic haemodynamically stable VT, EPS mapping techniques are used to determine the possibility of surgical or catheter ablation. EPS is also important in other causes of SCD other than VT/VF. Patients with ventricular pre-excitation (WPW syndrome) require localisation of the accessory pathway. Propensity to develop complete heart block can be assessed by a His-bundle ECG.

PREVENTION OF RECURRENT VENTRICULAR ARRHYTHMIA IN SURVIVORS OF SUDDEN CARDIAC DEATH

MYOCARDIAL REVASCULARISATION AND SUDDEN CARDIAC DEATH

The Coronary Artery Surgery Study (CASS) registry looked at 13,476 patients with significant operable coronary artery disease and showed an incidence of SCD of 5.2% in the medical arm compared with 1.8% in those assigned to surgery.[91] The precise mechanism of the benefit of surgery in primary prevention is unclear but is probably associated with prevention of ischaemia rather than arrhythmia control. In summary, the near-universal practice of surgical coronary revascularisation in SCD survivors with critical stenoses is based upon this primary prevention data (and the central role that ischaemia and infarction are known to play in arrhythmia substrate) rather than data demonstrating arrhythmia control.

ANTIARRHYTHMIC DRUGS AND SUDDEN CARDIAC DEATH[73–76]

The CAST study has clearly demonstrated the poor results of antiarrhythmic drug therapy alone in the prevention of arrhythmic SCD. Data from studies in survivors of SCD using amiodarone are conflicting, but generally poor, even with EPS confirmation of lack of inducibility. Certainly patients with an ejection fraction less than 30% do poorly on amiodarone alone. The primary role of antiarrhythmic drugs in the secondary prevention of SCD has all but disappeared, but amiodarone may be indicated if there is demonstrable suppression of inducible VT at EPS and the patient has an ejection fraction greater than 30%–40%.

SURGICAL AND CATHETER ABLATION TECHNIQUES AND SUDDEN CARDIAC DEATH[27]

As most sustained ventricular arrhythmias arise from a scar within the myocardium, surgical attempts were made to excise these areas completely. Catheter ablation techniques for VT are suitable for the minority of patients with haemodynamically stable VT who can withstand prolonged mapping procedures. Currently, the success rates for ablative techniques are such that a significant number still need additional preventive therapies.

IMPLANTABLE CARDIOVERTER DEFIBRILLATORS AND SUDDEN CARDIAC DEATH

The reduction in SCD and overall cardiac mortality with implantable cardioverter defibrillators (ICDs) has been so spectacular and the results of previous therapies so poor that ICDs were initially introduced with little randomised controlled data. More recently controlled studies have shown:

- reduction in 3-year mortality by 31% compared to antiarrhythmic drug therapy in SCD survivors[92]
- reduced risk of death in patients with poor LV function following myocardial infarction[93]
- improved survival in patients with HCM.[94]

However, no survival benefit was shown in high-risk patients following coronary artery bypass surgery.

Representative data from several studies are shown in Table 22.14. The benefit of ICD on survival persists for at least 8 years. Current indications are expanding, but the benefit is clear in the following groups of survivors of SCD and patients with documented VT/VF outside the early post-infarct phase:

- non-inducible VT/VF at EPS
- inducible VT/VF resistant to treatment
- VT/VF in patients with LV ejection fractions less than or equal to 30% regardless of results of EPS-directed drug therapy.

Table 22.14 Mortality data for the various treatment regimens for sudden cardiac death

	SUDDEN DEATH (%)	TOTAL MORTALITY (%)
Implantable cardioverter defibrillator	3.5	13.6
Empirical amiodarone	12	34
Electrophysiological study-directed drug treatment	14	24
Surgery	3.7	37

Further developments currently taking place include:

- transvenous catheter placement and subcutaneous patch avoiding the need for thoracotomy
- dual-chamber sensing to improve discrimination between SVT and VT that can be difficult on rate criteria alone, particularly in patients with intraventricular conduction delay
- technological advances reducing size, cost and increasing battery life.

Although one of the proposed advantages of ICD is the avoidance of antiarrhythmic drug side effects, particularly the myocardial depressant effects, current practice usually combines ICD with low-dose amiodarone. This enables improved arrhythmia control by reducing atrial tachyarrhythmia and slowing VT rate, and prolonging battery life by reducing the frequency of arrhythmia. The role of ICD in the management algorithms of SCD is shown in Figs 22.52 and 22.53. Given the current lack of available ICDs, some advocate restriction to patients less than 75 years. With wider availability of ICDs, fewer patients will be managed on drug-only strategies in the future.

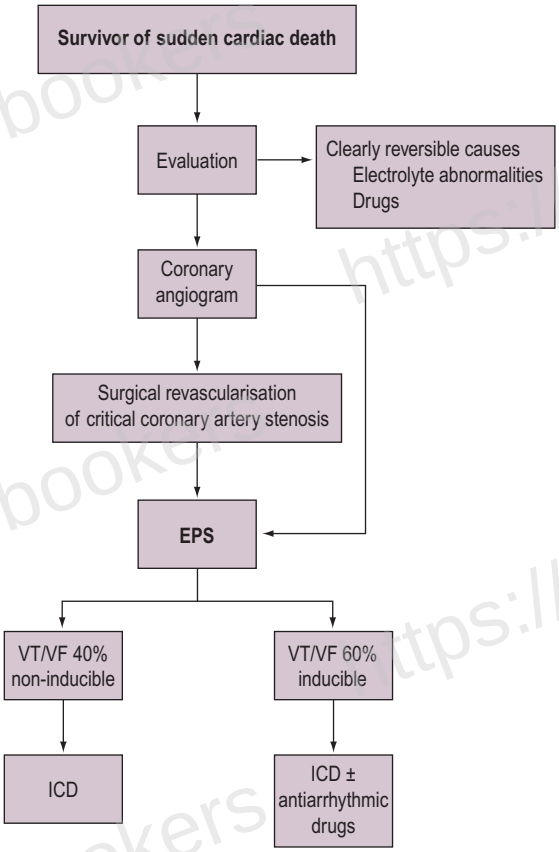


Figure 22.52 Management algorithm of a survivor of sudden cardiac death. This algorithm does not include the option of an antiarrhythmic drug alone in patients with intact left ventricular function who initially have inducible ventricular tachycardia/fibrillation *(VT/VF)* that is subsequently found to be suppressible on a drug with electrophysiological studies *(EPS)*. *ICD*, Implantable cardioverter defibrillator.

CLASSIFICATION OF ANTIARRHYTHMIC DRUGS

The time-honoured physiologically based classification of antiarrhythmic drugs is the Vaughan-Williams classification (Table 22.15), which has been modified over the years. This classification is a hybrid, with classes I and IV representing ion channel blockers, class II representing a receptor blocker and class III representing a change in an electrophysiological variable. The prolongation of repolarisation, the defining effect of class III agents, can be produced by a block of any one of several K^+ ionic channels (the delayed rectifier potassium current I_{Kr} responsible for phase 3 repolarisation is the ionic channel target of most class III agents) or from modification of Na^+ or Ca^+ channel function. This classification is also incomplete and does not include cholinergic agonists, digitalis, magnesium and adenosine. For this reason, an alternative classification has been advocated based on molecular targets for drug action that include ion channels, receptors and pumps/carriers (Table 22.16).[4]

ANTIARRHYTHMIC DRUGS

DIGOXIN

Digoxin is a muscarinic subtype 2 receptor (M_2) agonist and a highly potent Na^+/K^+-ATPase pump-blocking agent. Digoxin exerts its antiarrhythmic activity predominantly at the AV node where at lower doses conduction is slowed by the M_2 vagotonic effect. This effect is easily reversed by enhanced sympathetic tone in the setting of exercise, critical illness and postoperative state. At higher concentrations, digoxin has a direct effect on AV node conduction by the Na^+/K^+-ATPase pump blockade and is more resistant to sympathomimetic effects. The decrease in $[K^+]_i$ and increase in $[Na^+]_i$ results in hyperpolarisation, shortening of atrial action potential and an increase in AV nodal refractoriness. There is also increased availability of intracellular Na^+ for the Na^+–Ca^{2+} exchanger, increasing $[Ca^{2+}]_i$ which results in the positive inotropic effects of digoxin, making it an ideal agent in the setting of LV dysfunction. However, the positive inotropic effects of Na^+/K^+-ATPase blockade are deleterious in the setting of myocardial ischaemia and other causes of diastolic dysfunction. Digoxin also has weak vasopressor properties when administered as a slow bolus. The major

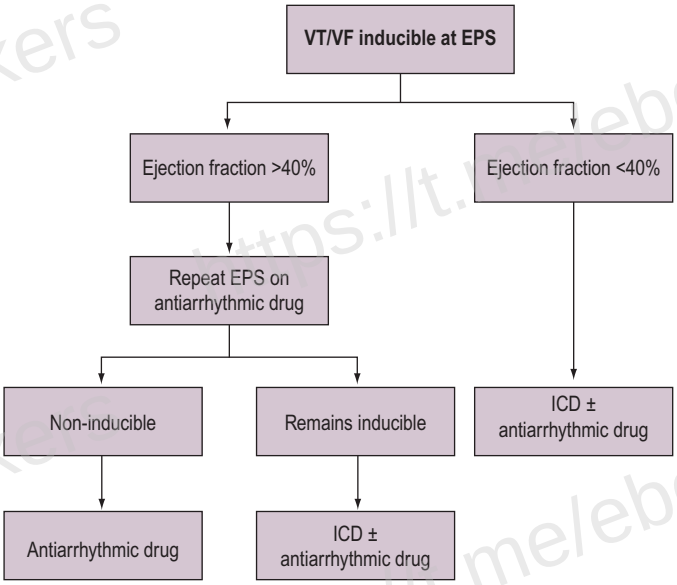


Figure 22.53 Patients found to have inducible ventricular tachycardia *(VT)* or fibrillation *(VF)* at electrophysiological studies *(EPS)*, with an ejection fraction >40% and subsequent drug suppression of their VT/VF, can be managed on antiarrhythmic drugs alone.

Table 22.15 Vaughan-Williams classification of antiarrhythmic drugs

CLASS	MECHANISM OF ACTION	EFFECT ON ACTION POTENTIAL	INDICATIVE DRUGS
Class I	Sodium channel blockers	Depresses rate of phase 0 depolarisation	
Class IA		Prolongs repolarisation	Procainamide Disopyramide Quinidine
Class IB		Shortens repolarisation	Lidocaine Mexiletine Phenytoin
Class IC		Minimal effect on repolarisation	Flecainide Encainide Propafenone
Class II	β-adrenergic receptor blockers		Propranolol Atenolol Metoprolol Esmolol
Class III	Potassium channel blockers	Prolongs repolarisation	Amiodarone Dronedarone Sotalol Ibutilide Vernakalant Bretylium
Class IV	Calcium channel blockers		Verapamil Diltiazem

ECG effects of digoxin are PR prolongation and a non-specific alteration in ventricular repolarisation with characteristic reverse-tick S-T segments.

INDICATIONS AND DOSE

- *AF:* slowing of ventricular rate only
- *Loading dose:* 15 µg/kg IV, typically administered over 30–60 minutes, but can be given faster
- *Maintenance dose:* depends on renal function.

PLASMA LEVELS

Oral bioavailability can be reduced, especially if intestinal microflora-altering antibiotics are co-administered. Therapeutic levels are 0.5–2.0 ng/mL. Plasma levels must be measured during the post-distribution phase some 6–8 hours after dose. The elimination half-life is 36 hours with normal renal function. Difference between therapeutic and toxic levels can be reduced by hypokalaemia, hypomagnesaemia, hypercalcaemia, hypoxia, cardiac surgery and myocardial ischaemia. Many drugs increase digoxin plasma levels by competing with the renal P-glycoprotein-mediated transport, or by reducing renal blood flow or function.

CONTRAINDICATIONS

Relative contraindications include myocardial ischaemia/infarction, diastolic heart failure due to hypertrophy and ischaemia, renal failure and hyperkalaemia, planned DC shock cardioversion and tachycardia–bradycardia syndromes. Co-administration with other drugs that affect AV nodal conduction, typically beta-adrenergic and calcium channel blockers, requires caution.

Table 22.16 Actions of antiarrhythmic drugs on membrane channels, receptors and ionic pumps in the heart

	CHANNELS						RECEPTORS				PUMPS
	Na^+			K^+		Ca^{2+}					
DRUG	*FAST*	*MED*	*SLOW*	I_{ks}/I_{kr}	I_{kur}		α	β	M_2	*P*	Na^+/K^+ *ATPase*
Lidocaine	+										
Mexiletine	+										
Phenytoin	+										
Procainamide		+++		++							
Disopyramide		+++		++							
Quinidine		+++		++			+		+		
Propafenone		+++						++			
Flecainide			+++	+							
Encainide			+++								
Bretylium				+++			+/–	+/–			
Sotalol				+++				+++			
Amiodarone	+			+++		+	++	++			
Dronedarone	+			+++		+	++	++			
Ibutilide				+++							
Dofetilide				+++							
Vernakalant	+				+++						
Verapamil	+					+++	++				
Diltiazem						++	+				
Propranolol	+							+++			
Metoprolol								+++			
Esmolol								+++			
Atropine									+++		
Adenosine										A	
Digoxin									A		+++
Magnesium						+					A

Sodium channel blockers are subdivided into drugs with fast-, medium- and slow-time constant for recovery from block. Receptors: α-, β-adrenoreceptors, M_2, muscarinic subtype 2; *P*, A_1 purinergic. Relative blocking potency: +, low; ++, moderate; +++, high; +/–, partial agonist/antagonist; *A*, agonist.

ADVERSE EFFECTS

The same increase in $[Ca]_i$ responsible for the positive inotropic effects of digoxin also forms the basis for toxicity arrhythmia. The increased inward calcium current is responsible for DAD-initiated arrhythmia. Digoxin toxicity can cause virtually any arrhythmia:

- DAD-related tachycardia with impairment of sinus node or AV nodal function
- unifocal atrial tachycardia with AV block is 'classic'
- ventricular bigeminy and various degrees of AV block occur.

With advanced toxicity, severe hyperkalaemia due to poisoning of Na^+/K^+-ATPase results. Profound bradycardia, which may be unresponsive to pacing, develops.

Any serious toxicity arrhythmia should be treated with antidigoxin Fab fragments. Magnesium is the drug of choice for digoxin-toxic tachyarrhythmia. Digoxin, particularly at toxic levels, increases risk of VF precipitated by DC shock. Digoxin toxicity is associated with nausea, disturbances in cognitive function and blurred or yellow vision (xanthopsia).

BETA-ADRENERGIC BLOCKERS

Beta-adrenergic blocking or class II antiarrhythmic drugs have differing properties such as relative cardioselectivity (atenolol, metoprolol), non-cardioselectivity (propranolol), intrinsic sympathomimetic activity (pindolol), lipid solubility and central activity (metoprolol, propranolol) and membrane-depressant effects (propranolol). The antiarrhythmic properties appear to be a class effect and no agent has been shown to be superior. There are data to suggest that the survival benefit of beta-adrenergic blockers post myocardial infarction may relate to some extent to the central modulation of autonomic tone of the more lipid-soluble agents. The direct membrane-stabilising or 'quinidine-like' effect of propranolol requires doses far greater than those used clinically and is of negligible clinical significance. Beta-adrenergic blockers competitively inhibit catecholamine binding at the beta-adrenergic receptor sites, which reduces the phase 4 slope of the action potential of pacemaker cells, prolongs their refractoriness and slows conduction in the AV node. Refractoriness and conduction in the His–Purkinje system are unchanged. Beta-adrenergic blockers are most effective in arrhythmia associated with increased cardiac adrenergic stimulation (postoperative states, sepsis, thyrotoxicosis, phaeochromocytoma, exercise or emotion).

INDICATIONS

Supraventricular tachycardia

Beta-adrenergic blockers may terminate SVT when the AV node is an intrinsic part of the re-entry circuit (AVNRT and AVRT); adenosine is more effective. AF and Afl do not revert with beta-adrenergic blockers, but the ventricular rate will be slowed. Beta-adrenergic blockers are effective at preventing SVT following cardiac surgery. Studies involving propranolol and atenolol have produced the best results. Beta-adrenergic blockers are effective in MAT, but, as this arrhythmia is most often seen in patients with severe chronic air-flow limitation and cor pulmonale, their utility is limited.

Ventricular arrhythmias

Beta-adrenergic blockers are ineffective for the emergency treatment of sustained VT. Empiric prophylactic administration of beta-adrenergic blockers appears to be as effective in ventricular arrhythmia prevention as electrophysiologically guided drug methods. However, ventricular arrhythmia most often occurs in the setting of poor LV dysfunction and beta-adrenergic blockers are either poorly tolerated or contraindicated.

Myocardial infarction

Survival in patients with AMI treated with thrombolytic therapy is improved by early IV beta-adrenergic blockade. Presumably this will remain the same with the current strategy of percutaneous coronary intervention. There may be other benefits such as decreased incidence of VF and relief of chest pain. Long-term beta-adrenergic blockade reduces mortality following myocardial infarction, the benefit being greatest in those at highest risk for sudden death. However, suppression of ventricular ectopy is not a requisite for benefit. Drugs with intrinsic sympathomimetic activity have not been shown to improve survival after AMI.

ATENOLOL

Atenolol does not have significant central action due to poor lipid solubility and is eliminated predominantly by the kidneys with an elimination half-life of 7–9 hours. Care is required in patients with poor or deteriorating renal function.

- *Loading dose IV:* 2.5 mg over 2.5 minutes, repeat every 5 minutes, maximum 10 mg
- *Loading dose oral:* 50–100 mg
- *Maintenance dose oral:* 50–200 mg/day
- *ISIS-1 post-MI regimen:* 5 mg IV over 5 minutes, repeated 10 minutes later if heart rate exceeds 60 beats/min. If heart rate exceeds 40 beats/min 10 minutes later, oral 50 mg atenolol and continue at 100 mg daily
- *SVT prophylaxis following cardiac surgery:* 5 mg IV within 3 hours of surgery, repeated 24 hours later, followed by oral 50 mg daily for 6 days.

METOPROLOL

Metoprolol is lipid-soluble and has significant central action. It is eliminated by the liver with an elimination half-life of 3–4 hours.

- *Loading dose IV:* 1–2 mg at 1 mg/minute, repeat every 5 minutes, maximum dose 15–20 mg
- *Loading dose oral:* 100–200 mg
- *Maintenance dose oral:* 50–100 mg/12-hourly.

PROPRANOLOL

Propranolol has been one of the most studied beta-adrenergic blockers for SVT prophylaxis following cardiac surgery.

- *Dose:* 10 mg orally 6-hourly starting the morning after surgery.

ESMOLOL

Esmolol is an ultrashort-acting cardioselective beta-adrenergic blocker, which is especially useful for rapid control of ventricular rate in AF or Afl. Esmolol has also been shown to prevent postoperative SVT. The distribution half-life is 2 minutes and the elimination half-life is 9 minutes. Esmolol is rapidly metabolised by hydrolysis of the ester linkage, chiefly by the esterases

in the cytosol of red blood cells and not by plasma cholinesterases or red cell membrane acetyl-cholinesterase:

- *Loading dose IV:* 500 µg/kg over 1 minute
- *Maintenance dose IV:* 50 µg/kg per minute for 4 minutes. If satisfactory rate control is not achieved, the loading dose should be repeated and the maintenance dose increased to 100 µg/kg per minute. If control is still not achieved after a further 4 minutes, then the procedure is repeated with 50 µg/kg per minute increments in the maintenance infusion until maximum dose of 200 µg/kg per minute is reached. Further increases in infusion rate are unlikely to be successful.

CONTRAINDICATIONS

Reversible airways disease and poor LV function are two common relative contraindications, which limit the utility of beta-adrenergic blockers in patients with cardiac disease. Beta-adrenergic blockers may also be poorly tolerated in diabetics and patients with severe peripheral vascular disease.

ADVERSE EFFECTS

Beta-adrenergic blockers, particularly those that are centrally acting, are often poorly tolerated in the long term. These effects include fatigue, hypotension, bradycardia, dry mouth, dizziness, headache and cold extremities.

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers or class IV antiarrhythmic drugs block the slow calcium channels in cardiac tissue. Verapamil and diltiazem have similar electrophysiological properties. The dihydropyridine group of calcium channel blockers, which include nifedipine, does not have any significant electrophysiological properties. Calcium channel blockers depress the slope of diastolic depolarisation in the SA node cells, the rate of rise of the phase 0 and action potential amplitude in the SA and AV nodal cells. They also slow conduction and prolong the refractory period of the AV node, which results in their main antiarrhythmic actions. Refractoriness of atrial, ventricular and accessory pathway tissue is unchanged. The sinus rate does not usually change significantly because calcium channel blockers induce peripheral vasodilatation, which causes reflex sympathetic stimulation of SA node. Verapamil particularly has marked negative inotropic actions and hypotension is often seen; however, cardiac index is generally maintained because of afterload reduction. Diltiazem has a less negative inotropic effect than verapamil.

INDICATIONS

- *SVT:* calcium channel blockers are effective if the AV node is an integral part of the arrhythmia circuit. Verapamil has been superseded by adenosine for the first line of treatment for these with AVNRT and AVRT
- *AF and Afl:* slow ventricular response in AF and Afl, but termination of the arrhythmia is uncommon. Verapamil may prolong episodes of AF through a proarrhythmic effect
- *MAT:* calcium channel blockers are effective[31]
- *SVT following cardiac surgery:* diltiazem has been shown not only to reduce, but also to decrease incidence of ventricular arrhythmia and postoperative ischaemia
- *AF associated with the WPW syndrome:* calcium channel blockers may increase the ventricular response and should be avoided if this is suspected.[28]

In general, calcium channel blockers should not be given to patients with a wide-complex tachycardia not only because of the risk of accelerating accessory pathway conduction, but also because their myocardial depressant effects can result in cardiovascular collapse in the setting of VT and pre-existing myocardial dysfunction.

VERAPAMIL

Verapamil is cleared by the liver with an elimination half-life of 3–8 hours. Therapeutic plasma concentration is 0.1–0.15 mg/L. With the availability of adenosine and the better tolerance of diltiazem, the use of verapamil has fallen substantially:

- *Loading dose IV:* 5–10 mg, maximum 0.15 mg/kg over 2 minutes. If poor response after 30 minutes repeat dose of up to 10 mg, 0.15 mg/kg to a maximum of 20 mg.
- *Maintenance dose IV:* infusion up to 10 mg/hour titrated to effect.
- *Maintenance dose oral:* 80–120 mg 6–8-hourly.

DILTIAZEM

Diltiazem is cleared by the liver with an elimination half-life of 3.5 hours. There is reduced oral absorption and extensive first-pass hepatic metabolism: only 40% of oral dose is available compared with IV:

- *Loading dose IV:* 0.25 mg/kg, followed by 0.35 mg/kg if required
- *Maintenance dose IV:* infusion up to 10 mg/hour titrated to effect
- *Maintenance dose oral:* 60–120 mg 6–8-hourly
- *SVT prophylaxis following cardiac surgery:* 0.1 mg/kg per hour, starting at onset of bypass and continuing for 24 hours. The dose can be titrated up for blood pressure control.

MAGNESIUM

Magnesium is an emerging antiarrhythmic agent with a range of indications, however, as an antiarrhythmic agent, magnesium has largely defied classification. Magnesium has many reported electrophysiological effects, including blocking voltage-dependent L-type

Ca^{2+} channels. Magnesium is a necessary cofactor for the membrane enzyme Na^+/K^+-ATPase that provides energy for the membrane Na/K channels.[95] Consequences of magnesium deficiency are as follows:

- Intracellular potassium falls and intracellular sodium rises, leading to a reduction in RMP.
- Intracellular sodium is elevated, increasing the availability of sodium for the Na/Ca counter transport mechanism.
- The resulting elevation in intracellular calcium predisposes to DAD-triggered activity.

Magnesium administration reduces the availability of intracellular Na^+ and therefore this Ca^{2+} inward current. The dependency of normal membrane potassium gradients on magnesium is demonstrated by the inability to correct intracellular potassium deficiency with the administration of potassium in the setting of hypomagnesaemia. The antiarrhythmic properties of supranormal levels of magnesium associated with pharmacological doses of magnesium appear to be largely due to augmentation of this physiological role of magnesium. Therefore, magnesium may be best classified as a Na/K pump agonist.

Magnesium in pharmacological doses decreases RMP, resulting in a reduction in automaticity. However, once depolarisation occurs, the maximum rate of depolarisation and action potential amplitude is increased, thereby improving conduction. Action potential duration is increased, thereby increasing the absolute refractory period and reducing relative refractory period. The net result is a reduction in the vulnerable period and more synchronous conduction. All of these electrophysiological effects are augmented in the setting of increased extracellular potassium. It is not surprising that the utility of magnesium appears greatest in the setting of ischaemia where loss of potassium from the cell is a major consequence. A secondary effect is the reduction in the availability of intracellular sodium to contribute to inward calcium flux, producing triggered activity. Magnesium has also been shown to elevate VF and ectopy threshold.[96]

INDICATIONS

- Acute rate control of AF, and has been shown to be as effective as amiodarone in the short term[67]
- Prevent postoperative SVT following cardiac surgery with varying efficacy
- Acute control of MAT
- Ventricular arrhythmia associated with triggered activity, such as torsade de pointes and digoxin toxicity[89]
- Drug-induced polymorphous VT, particularly that caused by class I agents, can also be terminated with magnesium
- Appears very effective at controlling transient ventricular arrhythmia in the setting of ischaemia such as post-infarct and cardiac surgery.

DOSE

- *AF rate and MAT control:* magnesium sulphate, 0.15 mmol/kg, in an adult 10–20 mmol (2.5–5.0 g) over 5–10 minutes. If no response after 15 minutes dose can be repeated. Subsequent dose recommendations over 24 hours have varied from 0.1 mmol/kg/hour to a total dose of 60 mmol
- *SVT prophylaxis following cardiac surgery:* 20–25 mmol per day for 4 days
- *Transient ventricular arrhythmia:* 10 mmol as a slow IV push, repeated if required
- *LIMIT-2 post myocardial infarction dose:* 8 mmol bolus over 5 minutes, followed by 65 mmol over 24 hours. Mean plasma level 1.55 (SD 0.44) mmol/L.[69]

PLASMA LEVELS

Observational data would suggest that plasma levels of magnesium required for potent antiarrhythmic action are at least 1.8 mmol/L.

ADVERSE EFFECTS

- When administered too rapidly, magnesium can cause hypotension by excessive peripheral vasodilatation; this is associated with an unpleasant hot-flush sensation.
- Prolonged administration or excessive dosing can produce plasma levels associated with skeletal muscle weakness, which can be clinically significant in acute-on-chronic respiratory failure.
- Excessive action can be seen if magnesium is used in the setting of hyperkalaemia, resulting in bradyarrhythmia and heart block.

PROCAINAMIDE

Procainamide is a class IA antiarrhythmic drug with potent Na^+ channel-blocking activity and intermediate K^+ channel-blocking activity. The Na^+ channel-blocking action has an intermediate time constant of recovery. Procainamide has similar electrophysiological and ECG effects to quinidine but lacks vagolytic and alpha-adrenergic blocking activity:

- decreases automaticity
- increases refractory period
- slows conduction.

Procainamide is metabolised to *N*-acetyl procainamide. *N*-acetyl procainamide lacks Na^+ channel-blocking activity, but is equipotent in K^+ channel blockade and prolongation of action potential. The increasing effect of greater refractoriness and QT prolongation with chronic procainamide therapy relates to increased contribution of *N*-acetyl procainamide.

CLINICAL USE

Procainamide is used to treat both atrial and ventricular arrhythmias.

- Intravenous procainamide is more effective than lidocaine for terminating VT.

- Procainamide controls ventricular rate in AF and Afl.
- It is effective for conversion of AVNRT, AVRT and possibly AF and Afl.
- It controls rapid ventricular rate owing to accessory pathway conduction in pre-excitation syndromes and for wide-complex tachycardia that cannot be distinguished as being SVT or VT.

The need to infuse slowly to avoid hypotension is the major barrier to wider use in life-threatening arrhythmia. Maintenance therapy with procainamide is not widely used due to its side-effect profile:

- *Loading dose IV:* 15 to 18 mg/kg at 20 mg/minute until there is arrhythmia control, hypotension ensues or QRS duration increases by more than 50%. Up to 50 mg/min has been used in urgent situations
- *Maintenance dose IV:* 1–4 mg/minute. Reduce maintenance dose by 30%–60% for moderate to severe renal or cardiac impairment.
- *Plasma levels: N*-acetyl procainamide has a longer duration of action
- *Adverse effects:* as with quinidine, the ventricular response may be accelerated if given for SVT; QT-interval prolongation and torsade de pointes may also occur.

A reversible lupus-like syndrome develops in 20%–30% of patients receiving procainamide long term. Other side effects include gastrointestinal disturbances (less common than with quinidine), central nervous system manifestations and cardiac depression.

LIDOCAINE

Lidocaine, long considered an important antiarrhythmic drug for ventricular tachyarrhythmia, is now relegated to lower-choice options or missing from most treatment algorithms. Na^+ channel-blocking effect is increased in myocardial ischaemia and is unproven outside acute ischaemia settings. It has no effect on SA node automaticity, but it depresses automaticity in other pacemaker tissues. Normally, lidocaine has little or no effect on conduction. The ECG shows no changes in sinus rate, PR interval, QRS width or QT interval with lidocaine.

CLINICAL USE

Lidocaine has reducing importance.

- It is ineffective against SVT.
- Amiodarone has taken over as the antiarrhythmic of choice for DC shock-resistant VF.[62,63]
- Lidocaine increases the current required for defibrillation, increases the likelihood of post DC shock asystole and therefore is detrimental during an episode of VF.
- Prophylaxis to prevent VF in AMI can no longer be recommended.

Extensive first-pass hepatic metabolism precludes oral use of lidocaine; IV dose should be reduced by 30%–50% in severe liver disease or heart failure. The distribution half-life is about 8 minutes, and the elimination half-life is 1.5 hours in normal patients (but may be increased >10 hours in severe heart failure or shock). An initial bolus of IV lidocaine 50–100 mg (0.7–1.4 mg/kg) over 1–2 minutes. A further dose may be repeated if initial is ineffectual. Thereafter an infusion of 4 mg/min for 1 hours, then 2 mg/min for 2 hours, and thereafter 1–2 mg/min, is recommended. Increasing the maintenance infusion rate without an additional bolus requires about 6 hours (four elimination half-lives) to reach a steady state. If the initial bolus is ineffective, another bolus of 1 mg/kg may be given after 5 minutes. Another dosage regimen is 0.7–1.4 mg/kg initially, and 0.8 mg/kg at 8-minute intervals for three doses (i.e. three distribution half-lives), and thereafter 1–2 mg/min by infusion. The half-life of lidocaine increases after 24–48 hours as the drug in effect inhibits its own hepatic metabolism and dose reduction is required.

ADVERSE EFFECTS

Central nervous system toxicity with high plasma concentrations is the most common adverse effect (e.g. dizziness, paraesthesia, confusion, and coma and convulsions). Uncommonly, AV block or cardiac depression may occur. Cimetidine reduces lidocaine clearance, potentially causing toxic drug concentrations.

FLECAINIDE

Flecainide exhibits rate-dependent Na^+ channel blockade with slow-time constant of recovery, with marked slowing of conduction in all cardiac tissue, and little prolongation of refractoriness.

CLINICAL USE

- May revert AVNRT and AVRT, although adenosine and verapamil are more widely used
- Useful in SVT, including AF and possibly Afl, particularly in the setting of accessory pathway syndromes
- Flecainide has been given in life-threatening VT.

Flecainide can be administered IV or orally. If flecainide is deemed necessary for prophylaxis of ventricular arrhythmias, therapy should start with ECG monitoring. In CAST, suppression of VEBs after myocardial infarction with flecainide was associated with increased mortality:

- *Dose:* IV loading 2 mg/kg at 10 mg/min
- *Oral maintenance:* 100–200 mg 12-hourly.

ADVERSE EFFECTS

- Depression of cardiac contractility – flecainide is usually contraindicated in patients with abnormal

LV function as it can worsen or precipitate heart failure.
- Conduction block – avoid in high-degree AV block unless a pacemaker is in situ.
- Flecainide increases pacing capture threshold.
- Proarrhythmic events are common, especially in patients with depressed LV function, and may be life threatening.
- Torsade de pointes may occur, even in patients without structural heart disease.
- Incessant VT may be induced, unresponsive to any therapy, including cardioversion.
- Although flecainide depresses intracardiac conduction, a paradoxical increase in ventricular rate may occur with Afl or AF.
- Central nervous system effects include visual disturbances, dizziness and nausea.

PROPAFENONE

Propafenone is a class IC agent and has a structure similar to flecainide. The electrophysiological, haemodynamic and side-effect profile is also similar to flecainide and encainide. The I_{Na} blocking profile of propafenone has a fast time-constant resulting in greater activity at faster rates and less risk of bradycardia. In addition, propafenone has non-selective beta-blocking properties and can produce bronchoconstriction. Similar to flecainide, propafenone could be considered in both ventricular and SVT arrhythmia in the setting of normal LV function. Use of long-term propafenone should probably be limited because of its class IC profile, even though it was not included in the CAST study and contraindicated in structural heart disease because of proarrhythmia.

Propafenone is metabolised by the liver and the rate can vary significantly between patients. The short terminal half-life requires at least t.i.d. administration.

- *Dose:* Conversion of AF to SR, IV 2 mg/kg over 10 minutes, oral dose 150–600 mg stat. Oral maintenance dose 150 mg t.i.d. immediate release tablets or 225 mg b.i.d. for slow release.

AMIODARONE

Amiodarone is a potent antiarrhythmic agent with a complex electrophysiological and pharmacological profile. The appealing broad spectrum and haemodynamic stability of amiodarone have resulted in it emerging as the most frequently used antiarrhythmic in critically ill patients. In this setting short-term use predominates and the formidable side-effect profile is much less significant. Amiodarone:

- prolongs action potential duration
- increases the refractoriness of all cardiac tissue
- has Na^+ channel blockade (class I), antiadrenergic (class II), calcium channel blockade (class IV) and antifibrillatory effects. The Na^+ channel blockade of amiodarone has a fast time-constant for recovery
- QT prolongation reflects a global prolongation of repolarisation and is closely associated with its antiarrhythmic effects.

When given IV, amiodarone has little immediate class III effect: the major action is on the AV node, causing a delay in intranodal conduction and a prolongation of refractoriness. This probably explains why IV amiodarone controls the ventricular rate in recent-onset AF, but is less effective for termination of this arrhythmia. Administration IV causes some cardiac depression, the magnitude depending on rate of administration and pre-existing LV function. Cardiac index is often unchanged because of its vasodilator properties.

CLINICAL USE

It is effective in suppressing both supraventricular and ventricular tachyarrhythmia.

SUPRAVENTRICULAR TACHYCARDIA

Amiodarone is effective in terminating and suppressing recurrences of AVNRT and AVRT tachycardia, although adenosine (for acute reversion) or verapamil (acute termination and long-term prophylaxis) is superior. Amiodarone IV is less effective in reverting Afl or AF, but the ventricular rate will slow. Administration over a longer time span (days to weeks) may be more effective in reverting recent-onset AF. In preventing recurrence of AF after reversion, amiodarone is comparable in efficacy to quinidine and flecainide but superior to sotalol and propafenone.[42]

DOSE

- Lower doses than that required for ventricular arrhythmia are usually sufficient
- *AVNRT and AVRT reversion or AF and Afl rate control:* 5–7 mg/kg over 30–60 minutes depending on blood pressure and myocardial function. Alternatively for a adult, 150 mg over 10 minutes followed by 0.5–1.0 mg/minute up to maximum of 1.2–1.8 g per 24 hours. Poor rate control can be improved with additional 1–2 mg/kg boluses
- *Postoperative AF prophylaxis:* 200 mg orally 8-hourly for 5 days, followed by daily until hospital discharge
- *Long-term SVT control or AF rate control:* 100–200 mg/day orally will usually suffice.

VENTRICULAR TACHYARRHYTHMIAS

Amiodarone IV may be effective in treating life-threatening ventricular tachyarrhythmia refractory to other drugs, especially in myocardial infarction and poor LV function. Amiodarone's efficacy in DC shock-resistant VF further confirms a prominent role in this setting.[62,63] Long-term oral amiodarone is useful in controlling symptomatic VT and VF, especially when other

conventional antiarrhythmics have failed. The absence of negative inotropic effect is useful in those with severely depressed LV function, but its many adverse effects limit widespread use. The Cardiac Arrest in Seattle, Conventional versus Amiodarone Drug Evaluation (CASCADE) study demonstrated that empirical amiodarone treatment was superior to guided (non-invasive Holter or EPS) class I drugs in survivors of VF not associated with AMI. Amiodarone prevented arrhythmia recurrence and decreased the incidence of sudden death. Amiodarone, presumably because it is better tolerated in patients with poor LV function and having less proarrhythmia, can be considered as first-line drug to prevent life-threatening ventricular tachyarrhythmias.[74–76] The rate of arrhythmia control is often slower with ventricular arrhythmia and may take several days to achieve. This delay appears to be independent of dose. The pharmacodynamic basis for this relates to the fact that much of the class III or K^+ channel-blocking activity is due to the amiodarone metabolite, desethylamiodarone, whereas the predominant actions of acute administration of amiodarone are due to its class I and class II activity. The full potency of the class III activity requires several days, at least, for the effects of desethylamiodarone to appear.

DOSE

- *Haemodynamically stable VT:* 5–7 mg/kg over 30–60 minutes, followed by 0.5–1.0/minute.
- *DC shock-resistant VF:* 5 mg/kg, followed by 2.5 mg/kg if required[61]
- *Long-term prevention of ventricular arrhythmia:* oral loading with 1200 mg/day for 1–2 weeks, reducing to 400–600 mg/day and then 100–400 mg/day after 2–3 months. The dose should probably not be reduced below 400 mg/day with life-threatening ventricular arrhythmia.

MYOCARDIAL INFARCTION

Data are limited at present, but amiodarone may improve long-term survival in patients after myocardial infarction.

PHARMACOKINETICS

Oral bioavailability of amiodarone is variable at 40%–70%, with a delayed onset of action (days to weeks); however, loading doses reduce this interval. The kinetics of amiodarone has been modelled to four compartments when given acutely. Following a slow IV bolus over 15 minutes, amiodarone is rapidly distributed to the active compartment ($t_{1/2}\alpha$ = 4.2 minutes), with demonstrable prolongation of QTc and antiarrhythmic effect within 2–5 minutes. Subsequently, amiodarone is progressively redistributed to 'deeper' compartments ($t_{1/2}\beta$ = 36.6 minutes, $t_{1/2}\gamma$ = 4.5 hours and $t_{1/2}\delta$ = 33.6 hours).[97] This is in contrast to the very prolonged terminal half-life – greater than 50 days – after long-term treatment. This redistribution of amiodarone explains why repeated boluses are often required in the first 24–48 hours of treatment. Transient loading-dose hypotension due to myocardial depression or vasodilatation is dose-, rate- and patient-dependent. A loading dose of 5 mg/kg over 20 minutes resulted in significant further myocardial depression and a fall in cardiac index, whereas in patients without evidence of heart failure, 5 mg/kg over 1 minute resulted in hypotension due to systemic vasodilatation and an increase in cardiac index.[98,99]

MONITORING

Plasma amiodarone concentrations have poor correlation with arrhythmia control, and therapeutic levels, 1.0–2.5 mg/L, have the greatest utility for avoidance of adverse effects in long-term treatment.

ADVERSE EFFECTS

Adverse effects will occur in the majority of patients if they receive amiodarone for long enough. Most are reversible when the drug is discontinued. Adverse effects include:

- *Dermatological:* photosensitivity, bluish/grey skin discoloration (slate-blue skin)
- *Eye:* corneal microdeposits (almost 100%) with little or no clinical significance
- *Gastrointestinal disturbances*
- *Hypo- and hyperthyroidism*
- *Liver dysfunction:* asymptomatic increases in liver enzymes are common, and do not require amiodarone cessation unless enzymes are 2–3 times normal; hepatitis is rare
- *Neuropathy, myopathy and cerebellar abnormalities*
- *Pulmonary toxicity:* unexpected acute respiratory distress syndrome has been reported in patients on amiodarone undergoing procedures such as uncomplicated cardiopulmonary bypass surgery and pulmonary angiography. These observations suggest that amiodarone may predispose the lung to acute injury. Pulmonary toxicity is the most serious adverse effect, with a reported incidence of 10% at 3 years. Amiodarone pulmonary toxicity has been reported in one case after 13 days and 11.2 g cumulative dose and 11.2 g over 2 weeks in another. Patients on long-term amiodarone need regular respiratory function testing and decreased carbon monoxide diffusion of 15% below baseline requires dose modification or cessation. The severe syndrome of shortness of breath, cough and fever with pulmonary crepitations and widespread pulmonary infiltrates on chest X-ray has a mortality of 10%. Immediate discontinuation is necessary. Use of steroids is controversial.

Amiodarone interacts with other drugs, potentiating warfarin, digoxin and other antiarrhythmic agents. When administered concurrently, doses of these drugs should be reduced accordingly. On the positive side,

long-term amiodarone is unlikely to precipitate or worsen heart failure and proarrhythmia is uncommon.

DRONEDARONE[44,100]

Dronedarone is an amiodarone analogue designed to reduce the lipophilicity of the molecule to reduce the pharmacokinetic complexity and toxicity. The iodine moieties have also been eliminated to prevent thyroid dysfunction.

Dronedarone is a multi-channel blocker, blocking I_{Na}, I_K and $I_{Ca\text{-}L}$ channels with a predominant electrophysiological effect of prolonging repolarisation or class III. It also has antiadrenergic properties.

Dronedarone decreases the recurrence of AF, controls rate with recurrences (heart reduction of 12.3 beats/min compared with placebo), especially with exercise. Sequential major studies evaluating dronedarone highlight the importance of variable outcome in differing patient populations. In comparing dronedarone with placebo, the ATHENA study found dronedarone reduced all-cause mortality, cardiovascular admissions by 24%, death from cardiac arrhythmias, HR 0.55 (0.34–0.88) and stroke rate in addition to delaying recurrence of AF/Afl. Whereas in the PALLAS study (patients with permanent AF), all these outcomes were worse and the ANDROMEDA study (patients with poor LV function) was stopped due to increased mortality due to worsening heart failure. Meta-analysis of all placebo-controlled trials does show dronedarone has reduced mortality, but maintenance of sinus rhythm and absence of LV dysfunction is important to confer this mortality benefit. Dronedarone is currently contraindicated in patients with New York Heart Association (NYHA) class III or IV heart failure.

In comparing dronedarone to amiodarone, the picture is even less clear. In the DIONYSOS study (post electrical cardioversion) there was increased AF recurrence, dronedarone 63.5% and amiodarone 42% at 7 months, although drug discontinuation was higher with amiodarone. Meta-analysis of studies comparing the two drugs confirms greater efficacy for amiodarone maintaining sinus rhythm (HR 0.49; 0.37–0.63) but greater drug discontinuation rates and a trend to increased all-cause mortality with amiodarone. Dronedarone may have reduced torsade de pointes arrhythmia. The increased efficacy of amiodarone may relate to its lipophilicity giving higher tissue levels or the increased activity of its major metabolite, desethylamiodarone compared with *N*-debutyldronedarone.

Dronedarone has poor oral bioavailability, 15%, which can be variable, increasing by a factor of three if taken with food. It is extensively metabolised by cytochrome P450 CYP3A4 (inhibitors can result in marked elevation in plasma levels) to the metabolite *N*-debutyldronedarone, which is much less potent. The elimination half-life is 24 hours. Serum digoxin levels are increased due to inhibition of P-glycoprotein-mediated intestinal and renal excretion.

- *Dose:* 400 mg oral b.d. with steady state in 7 days.

Although long-term data are lacking, there has been no evidence of thyroid dysfunction or pulmonary toxicity.

SOTALOL

Sotalol prolongs action potential duration, thereby prolonging the effective refractory period in the atria, ventricles, AV node and accessory AV pathways. It is also a potent non-cardio-selective beta-adrenergic blocker (class II). Sotalol also has antifibrillatory actions that are superior to those of conventional beta blockers. It can worsen heart failure in patients with depressed LV function. The negative inotropic beta-blocking effect is slightly offset by a weak positive inotropic effect owing to prolongation of the action potential (resulting in more time for calcium influx into contracting myocardial cells).

CLINICAL USE

Higher doses of sotalol are required to prolong cardiac repolarisation than to cause beta blockade. Sotalol may be administered IV or orally, and is excreted by the kidneys (elimination half-life 15 hours); Should only be used if QTc is less than 450 ms. If QTc increases to greater than 500 ms during treatment, dose should be reduced or ceased. IV dose is 75 mg (0.5–1.5 mg/kg) over 5 hours. C_{max} for 75 mg IV over 5 hours equivalent to 80 mg oral. Oral therapy is initiated at 80 mg 12-hourly and increased to 160 mg 12-hourly, although doses of 320 mg 12-hourly have been administered. Maintenance dosing is dependent on renal function. If CrCl is less than 40 mL/minute long term Sotalol is contraindicated, 40–60 mL/min once daily dosing and greater than 60 mL/min b.i.d. dosing.

SUPRAVENTRICULAR TACHYCARDIA

- Effective in AVNRT and AVRT, although adenosine and verapamil are superior. Long-term sotalol will prevent recurrences of these arrhythmias
- Probably ineffective for reversion of AF/Afl, but is effective in preventing recurrence of AF after cardioversion. If AF recurs, heart rate is likely to be well controlled with sotalol
- Prevents postoperative SVT.

VENTRICULAR ARRHYTHMIAS

Sotalol is superior to lidocaine to terminate sustained VT, and should be considered a first-line drug in patients without heart failure. Oral sotalol is more effective than class I drugs for the long-term prevention of VT or VF. Guided (Holter or EPS) sotalol and empirical amiodarone are first-line drugs to prevent recurrences of VT and VF over the long term; however,

the worse outcome with sotalol in SWORD has significantly reduced the role of sotalol in this setting.[73]

ADVERSE EFFECTS

Side effects of sotalol are mainly due to beta blockade (e.g. bronchospasm, heart failure or AV conduction problems) and prolongation of QT proarrhythmia (e.g. torsade de pointes, similar 2% incidence as quinidine, which may occur early during drug titration or later during long-term treatment).

IBUTILIDE

Ibutilide is an I_{Kr} K^+ channel blocker, which prolongs action potential and increases the refractory period. This agent, with class III effect, is recommended for acute pharmacological conversion of AF and Afl, or as an adjunct to improve success of DC shock cardioversion. The success rate for ibutilide alone is higher for Afl (50%–70%) than that with AF (30%–50%) and, as expected, efficacy is greatest in short-term AF/Afl without structural heart disease. The major role of ibutilide appears to be cardioversion pretreatment to facilitate reversion to sinus rhythm from AF.[46] Ibutilide has minimal effect on blood pressure and heart rate and the major adverse effect is proarrhythmia, with torsade de pointes occurring in 3%–6% of patients. For this reason, patients should be monitored for at least 6 hours after administration. Ibutilide has a short duration of action and other antiarrhythmic drugs are required to maintain sinus rhythm.

DOSE

For patients weighing more than 60 kg, 1 mg over 10 minutes, which can be repeated 10 minutes later if unsuccessful. In patients weighing less than 60 kg, 0.01 mg/kg is given as initial dose.

DOFETILIDE

Dofetilide is one of the latest class III I_{Kr} K^+ channel blockers being investigated in the hope of finding an antiarrhythmic drug for long-term use with amiodarone's efficacy but without its side-effect profile. Dofetilide's emerging role is again in pharmacological cardioversion of AF and Afl (superior to sotalol, similar to amiodarone but inferior to ibutilide) in about 30% of patients. Prevention of recurrence is similar to amiodarone and long-term oral therapy is not associated with increased mortality in post-MI and heart failure patients. It also appears safe in patients with LV dysfunction. Early (first 3 days) proarrhythmia (3.3% of patients developed torsade de pointes) also necessitates monitoring with commencement of therapy.[42,101,102,103]

DOSE

Recommended dose is 500 mg orally 12-hourly. Dose requires adjustment for renal function and QT-interval monitoring for a minimum of 3 days. First dose is based on renal function. CrCl less than 20 mL/minute dofetilide is contraindicated. CrCl 20–40 mL/minute, 125 mg b.i.d., 40–60, 250 mg b.i.d. and greater than 60 500 mg b.i.d. Second dose is based on QTc increase. QTc increase less than 15% continue same dose. Increase greater than 15% dose is decreased. QTc interval greater than 500 ms necessitates cessation.

VERNAKALANT[104]

Vernakalant, a pyrrolidine compound, is a new multichannel blocker with I_K- and I_{Na}-blocking activity, with I_K blockade predominating (class III agent). The unique profile of vernakalant I_K blockade is the relative specificity for the atria and minimal effect on the ventricle. This specificity relates to differential activity on the various I_K channel isoforms, with I_{Kur} blockade being much greater compared with the modest activity at I_{Kr} channels. I_{Kur} channels are the 'ultra-rapid' I_K channels confined to the atria that are responsible for the fast early phase of repolarisation that results in the shorter action potential of atrial cells. Vernakalant therefore specifically prolongs atrial refractory period and slows atrial conduction with a rate-dependent profile.

Vernakalant in non-surgical, short-duration AF (ACT I and ACT III studies, duration less than 7 days) achieved sinus rhythm in 51.7% and 51.2% (placebo 4 and 3.6%) within 90 minutes, generally less than 10 minutes (median time to conversion 10 and 11 minutes). The IV dose of 3 mg/kg over 10 minutes, followed by a further 2 mg/kg over 10 minutes if conversion did not occur within 15 minutes of the first dose, produced not only rapid but durable conversion with 99% of responders remaining in sinus rhythm at 24 hours. Vernakalant was not effective in Afl, with a conversion rate of only 7%.

A similar cohort (AVRO study) comparing vernakalant (same dose as ACT I and III) with amiodarone (5 mg/kg over 1 hour followed by 50 mg over the next hour), again in recent-onset AF, found vernakalant again superior at 90 minutes with a conversion rate of 51.7 versus 5.2%. However, at 4 hours amiodarone was catching up with 21.6% versus 54.4% conversion, with amiodarone recognised to have a longer onset of action.

In post-cardiac surgical patients who developed AF, having been in sinus rhythm preoperatively (ACT II study), vernakalant was superior to placebo with rapid conversion rates (47% vs. 14%) and times (median time 12.4 minutes). However, unlike non-surgical patients, in this cohort responders were less durable with only 60% remaining in sinus rhythm at 24 hours. In all studies vernakalant had no effect on success rates with subsequent attempts at electrical cardioversion.

Vernakalant is extensively metabolised by the liver and subsequently excreted in the urine. The acute

kinetics of vernakalant is not affected by congestive cardiac failure, renal or hepatic impairment.

Vernakalant is well tolerated with serious side effects of hypotension and bradycardia during infusion infrequent (7.6%, placebo 5.1%), slightly higher than the rates of hypotension with amiodarone.

Although vernakalant may be seen as agent of choice for rapid pharmacological conversion of recent onset of AF, <7 days (the greater efficacy of ibutilide is eroded by risk of polymorphous ventricular arrhythmia), the superior conversion rate over amiodarone would appear to be lost at 24 hours and beyond, with amiodarone also likely to be a better agent to control ventricular rate in non-responders with greater AV-blocking activity.

ADENOSINE

Adenosine stimulates specific A_1 receptors present on the surface of cardiac cells, thereby influencing adenosine-sensitive K^+ channel cyclic adenosine monophosphate production. It slows the sinus rate and prolongs AV node conduction, usually causing transient high-degree AV block. The half-life of adenosine is usually less than 2 minutes as it is taken up by red blood cells and deaminated in the plasma. This ultrashort half-life is a major advantage over other antiarrhythmic drugs. The effects of adenosine, both antiarrhythmic and haemodynamic, can be antagonised by methylxanthines, especially theophylline and caffeine. Dipyridamole, an adenosine uptake blocker, potentiates the effect of adenosine. Adenosine effects are prolonged in patients on carbamazepine and in denervated transplanted hearts.

CLINICAL USE

- *AVNRT and AVRT tachycardia:* adenosine is the drug of choice. Expected reversion rates exceed 90%.[26] The AV nodal-blocking actions of adenosine may unmask atrial activity (e.g. flutter waves in Afl).
- Diagnosis of a wide-complex tachycardia may be assisted by the use of adenosine.
- SVT with intraventricular conduction block will terminate with adenosine, whereas few VTs will revert. Whether adenosine should be used routinely to discriminate between VT and SVT with aberrant conduction in haemodynamically stable wide-complex tachycardia is unclear. Potential for haemodynamic collapse in VT is real and ILCOR advises against.

Adenosine will not revert AF. Ventricular rate may transiently increase when AF is associated with the WPW syndrome.

Adenosine is given as a rapid bolus through a large peripheral or central vein followed by a saline flush, at intervals less than 60 seconds. The usual dose is 6 mg, followed by 12 mg if response is ineffective. Another 18 mg can be given if the last dose was well tolerated.

ADVERSE EFFECTS

Most patients experience transient side effects such as flushing, shortness of breath and chest discomfort. Adenosine should not be given to asthmatic patients as bronchospasm may result.

DIRECT CURRENT CARDIOVERSION[105]

DC cardioversion/defibrillation is an important treatment option in tachyarrhythmia. In addition to its emergency role in cardiac arrest from VF or VT, urgent DC cardioversion is indicated in haemodynamically unstable VT and sustained SVT that precipitate angina, heart failure or hypotension. More elective DC cardioversion is indicated in haemodynamically stable VT following a trial of antiarrhythmic drug therapy. Cardioversion is most commonly used in AF/Afl once potential precipitants have been eliminated and, again, usually after antiarrhythmic drug treatment to prevent further episodes. Digoxin toxicity is a relative contraindication to DC cardioversion, which should also be used with care in patients on digoxin.

MECHANISM OF ACTION

DC shocks need to produce a current density that depolarises a critical mass of myocardium, thereby leaving insufficient myocardium to maintain the re-entrant tachycardia and prevent recurrence. For VF and AF, the critical mass involves the entire ventricles or atria, whereas for the more organised tachyarrhythmia, VT and Afl, which involve specific re-entrant circuits, regional depolarisation in the path of their circulating wave fronts is all that is required. DC shocks also prolong the refractoriness of myocardium and this effect will contribute to the arrhythmia termination and prevention of immediate recurrence.

ELECTRICAL ENERGY

Even though the goal is to achieve a certain current through the entire heart, atria or a region depending on the arrhythmia, DC shocks are prescribed as energy measured in joules (J) or watt-seconds. Obviously it would make more sense to be able to deliver a set current. This would prevent delivering inappropriately low currents in patients with high impedance and excessive current flow causing myocardial damage in patients with low impedance. Clinical studies to determine current doses are under way for defibrillation and cardioversion. The optimal current for VF using monophasic damped sinusoidal (MDS) waveform for cardioversion waveform appears to be 30–40 A. Current dosage for biphasic waveform is not available.

CURRENT WAVEFORM

Modern defibrillators deliver a current, the magnitude of which depends on the prescribed energy and

thoracic impedance. This current can be delivered in a number of different waveforms.

MDS defibrillators deliver current that is in a single direction or polarity. They can be further characterised by the rate at which the current pulse returns to zero. MDS waveforms return to zero gradually, whereas truncated exponential waveforms return instantaneously. Biphasic waveform for cardioversion (BTE) has superseded monophasic waveforms, achieving equivalent efficacy at lower electrical energies. BTE is a sequence of two current pulses generated with the polarity of the second in the direction opposite to the first. Biphasic waveforms with lower shock energies are associated with fewer ST-segment changes and less post-resuscitation myocardial dysfunction and has an ILCOR class IIa recommendation.

THORACIC IMPEDANCE

The magnitude of current flow is dependent on the resistance to current flow or thoracic impedance. The average adult thoracic impedance is 70–80 Ω. Factors that determine thoracic impedance include:

- energy selection
- electrode size
- electrode composition
- paddle-to-skin coupling
- distance between electrodes
- number of previous shocks
- time interval between previous and present shock
- pressure on electrodes
- phase of ventilation
- patient's body build
- recent sternotomy.

Conductive gel reduces impedance, while hair trapping air between skin and paddle and self-adhesive monitor/defibrillator electrode pads may increase it. There is no clear relationship between body size and energy requirements but compensation for patient-to-patient differences in impedance can be achieved by changes in duration and voltage of shocks, or by a process called burping, which involves releasing the residual membrane charge.

PADDLE POSITION AND SIZE

ILCOR recommends standard placement of the sternum paddle just to the right of the upper sternal border below the clavicle and the apex paddle to the left of the nipple, with the centre of the paddle in the mid-axillary line. Permanent pacemakers and ICDs must be avoided as shock may cause malfunction or block current going to the heart. Inevitably, some current passes down the pacemaker lead and it is necessary to check pacing threshold post-shock. Other alternative paddle placements can enable avoidance of pacemakers and ICDs or perhaps improve current direction. Using self-adhesive electrodes, the sternum electrode can be placed posterior to the heart on the right infrascapular region and the apex on the left precordium. The use of right parasternal and left posterior infrascapula has been advocated for AF because this configuration provides an optimal vector of current delivery to the atria. Large electrodes or paddles have less impedance; however, excessively large electrodes may result in less transmyocardial current flow. The minimum recommended electrode size is 50 cm^2, with the sum of both electrodes exceeding 150 cm^2.

SYNCHRONISED CARDIOVERSION

With cardioversion of atrial tachyarrhythmia and VT, when time permits, synchronisation of DC shock with the R-wave of the QRS complex is required to reduce the possibility of inducing VF by delivering the shock during the relatively refractory portion of the T-wave of the cardiac cycle. Synchronisation in VT may be difficult and misleading because of the wide complex or polymorphous nature. Synchronisation should not delay DC shock in pulseless VT or VT associated with unconsciousness, hypotension or severe pulmonary oedema.

DIRECT CURRENT SHOCK DOSAGE

Recommendations for energy doses are changing, as biphasic waveform generators become more widely available. Where studied, BTE shocks have been consistently as effective as higher-energy MDS shocks. Recommended doses are always a balance between the energy likely to generate a critical current flow and that not likely to cause functional and morphological damage. Electrical energies greater than 400 J have been reported to cause myocardial necrosis.

- *VF and pulseless VT:* BTE shock at 200 J. Evidence for sequential escalation of the energy dose is not strong and repeated shocks at the same energy result in increasing current delivery as impedance falls. Repeated non-escalating lower-energy BTE shocks, in the range of 150–175 J, are as effective as escalating MDS recommendations.
- *VT:* energy dose for cardioversion of VT depends on morphology and rate. For monomorphic VT, synchronised 100 J BTE is the starting energy. For polymorphic VT, synchronised if possible, 200 J BTE is the starting energy and for both stepwise increases if the first shock fails.
- *AF:* initial energy is synchronised 100–200 J BTE and stepwise increases if first shock fails. Despite obvious concerns for myocardial injury, mega dose energy at 720 J MDS has been used with success in large patients with AF refractory to 360 J, without evidence of myocardial injury. Constant-current,

rectilinear biphasic waveforms, BTE appear to be more effective in cardioverting AF. This biphasic waveform at the low energy of 120 J was superior to 200 J MDS.

- *Afl, AVNRT and AVRT:* these atrial tachyarrhythmias require least energy and the initial recommended energy is synchronised 50–100 J BTE.

SEDATION

A separate doctor expert in managing the airway must perform sedation for cardioversion. The dose of the sedating agent is titrated on the basis of patient factors and type of arrhythmia. Patients with poor myocardial function not only need reduced dose but also onset time is slower because of low cardiac output. Sensitive tachyarrhythmias such as Afl require only low doses, whereas AF is likely to need higher and repeated doses as higher energy and repeated shocks may be necessary. Cardioversions should be performed with standard resuscitation equipment available and pre-oxygenation is crucial.

DIGOXIN AND CARDIOVERSION

Digoxin toxicity results in a significant reduction in the threshold for inducing ventricular arrhythmia with DC shock. If digoxin toxicity is a possibility, then reconsideration of the need for cardioversion or at least careful titration of energy is required. Clinical experience would suggest the latter procedure of starting with 10 J BTE, and a stepwise increase thereafter increases safety of DC shock in this setting.

ANTICOAGULATION FOR CARDIOVERSION[105]

Cardioversion of AF and, to a lesser extent, Afl is associated with catastrophic thromboembolism, especially stroke. Early studies suggested an incidence of up to 6.3% without anticoagulation. It is accepted that the likelihood of clots forming in the left atrium after 48 hours in AF and for these to be dislodged when sinus rhythm is restored is so high that anticoagulation is indicated prior to cardioversion in AF.

Anticoagulation for 3–4 weeks before cardioversion reduced the risk of embolism by 80%. The risk of thromboembolism following cardioversion continues for a period.

- Echocardiographic findings suggestive of atrial thrombi formation occur in up to 35% of patients post cardioversion.
- Left atrial appendage emptying velocities often decrease despite the development of coordinated electrical activity after cardioversion, presumably because of stunning of mechanical function.

Prolonged AF greater than 48 hours requires anticoagulation for 3 weeks prior to cardioversion and warfarin therapy for at least another 4 weeks depending on risk of recurrence of AF.

Transoesophageal echocardiography, which allows detection of thrombi in the left atrial appendage with much greater accuracy, has been found to be a safe means of expediting cardioversion. Anticoagulation with heparin for 1 day or warfarin for 5 days prior to demonstrating the left atrium to be free of thrombi by transoesophageal echocardiography, then 4 weeks of warfarin following cardioversion, was as effective in preventing emboli as the conventional longer anticoagulation regimen. However, there was a significant reduction in major haemorrhagic events in the transoesophageal echocardiography-guided, shorter lead-in anticoagulation strategy.

KEY REFERENCES

1. Nerbonne JM, Kass RS. Molecular physiology of cardiac repolarization. *Physiol Rev*. 2005;85:1205–1253.
2. Grant AO. Cardiac ion channels. *Circ Arrhythm Electrophysiol*. 2009;2:185–194.
4. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. The Sicilian gambit: a new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. *Circulation*. 1991;84:1831–1851.
30. Lee KW, Yang Y, Scheinman MM, et al. Atrial flutter: a review of its history, mechanisms, clinical features and current therapy. *Curr Probl Cardiol*. 2005;30:121–168.
32. January CT, Wann LS, Alpert JS. 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:2071–2104.
64. Walkey AJ, Wiener RS, Ghobrial JM, et al. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA*. 2011;306:2248–2255.
86. Johnson JN, Ackerman M. QTc: how long is too long? *Br J Sports Med*. 2009;43:657–662.
100. Dobrev D, Nattel S. New antiarrhythmic drugs for treatment of atrial fibrillation. *Lancet*. 2010;375:1212–1223.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Nerbonne JM, Kass RS. Molecular physiology of cardiac repolarization. *Physiol Rev*. 2005;85: 1205–1253.
2. Grant AO. Cardiac ion channels. *Circ Arrhythm Electrophysiol*. 2009;2:185–194.
3. Shah M, Akar FG, Tomaselli GF. Molecular basis of arrhythmias. *Circulation*. 2005;112:2517–2529.
4. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. The Sicilian gambit: a new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. *Circulation*. 1991;84:1831–1851.
5. Hoffman BF, Rosen MR. Cellular mechanisms for cardiac arrhythmias. *Circ Res*. 1981;49:1–15.
6. Binah O, Rosen MR. Mechanisms of ventricular arrhythmias. *Circulation*. 1992;85(suppl 1): 25–31.
7. Wit AL, Cranefield PF. Reentrant excitation as a cause of cardiac arrhythmias. *Am J Physiol*. 1978;235: H1–H17.
8. Haissaguerre M, Vigmond E, Stuyvers B, et al. Ventricular arrhythmias and the His-Purkinje system. *Nat Rev Cardiol*. 2016;13:155–166.
9. Gettes LS. Electrolyte abnormalities underlying lethal and ventricular arrhythmias. *Circulation*. 1992;85(suppl 1):70–76.
10. Hollifield JW. Thiazide treatment of hypertension: effects of thiazide diuretics on serum potassium, magnesium and ventricular ectopy. *Am J Med*. 1986;80:8–12.
11. Nordrehaug JE, Johannessen K-A, von der Lippe G. Serum potassium concentration as a risk factor of ventricular arrhythmias early in acute myocardial infarction. *Circulation*. 1985;71:645–649.
12. Hollifield JW. Thiazide treatment of systemic hypertension: effects on serum magnesium and ventricular ectopic activity. *Am J Cardiol*. 1989;63: G22–G25.
13. Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death. *Circulation*. 1992;85(suppl 1):77–91.
14. Verrier RL, Nieminen T. T-wave alternans as a therapeutic marker for antiarrhythmic agents. *J Cardiovasc Pharmacol*. 2010;55:544–554.
15. Campbell TJ. Proarrhythmic actions of antiarrhythmic drugs: a review. *Aust N Z J Med*. 1990;20: 275–282.
16. Dhein S, Muller A, Gerwin R, et al. Comparative study on the proarrhythmic effects of some antiarrhythmic agents. *Circulation*. 1993;87:617–630.
17. Donovan KD, Power BM, Hockings BE, et al. Usefulness of atrial electrograms recorded via central venous catheters in the diagnosis of complex cardiac arrhythmias. *Crit Care Med*. 1993;21: 532–537.
18. Mason JW. A comparison of electrophysiologic testing with Holter monitoring to predict antiarrhythmic drug efficacy for ventricular tachyarrhythmias. *N Engl J Med*. 1993;329:445–451.
19. Buxton AE, Lee KL, DiCarlo L, et al. Electrophysiologic testing to identify patients with coronary artery disease who are at risk of sudden death. *N Engl J Med*. 2000;342:1937–1945.
20. Gilman JK, Jalal S, Naccarelli GV. Predicting and preventing sudden cardiac death from cardiac causes. *Circulation*. 1994;90:1083–1092.
21. Kennedy HL, Whitlock JA, Spraugue MK, et al. Long-term follow up of asymptomatic healthy subjects with frequent and complex ventricular ectopy. *N Engl J Med*. 1985;312:193–197.
22. Jouven X, Zuriek M, Desnos M, et al. Long-term outcome in asymptomatic men with exercise-induced premature ventricular depolarisations. *N Engl J Med*. 2000;343:826–833.
23. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction: an overview of results from randomized controlled trials. *JAMA*. 1993;270: 1589–1595.
24. Field JM, Hazinski MF, Sayre MR, et al. Part 1: executive summary: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122:S640–S656.
25. Ganz LI, Friedman PL. Supraventricular tachycardia. *N Engl J Med*. 1995;322:162–173.
26. Camm AJ, Garratt CJ. Adenosine and supraventricular tachycardia. *N Engl J Med*. 1991;325:1621–1629.
27. Garratt C, Antoniou A, Ward D, et al. Misuse of verapamil in pre-existent atrial fibrillation. *Lancet*. 1989;1:367–369.
28. Scher DL, Arsura EL. Multifocal atrial tachycardia: mechanisms, clinical correlates and treatment. *Am Heart J*. 1989;118:574–580.
29. McCord JK, Borzak S, Davis T, et al. Usefulness of intravenous magnesium for multifocal atrial tachycardia in patients with chronic obstructive pulmonary disease. *Am J Cardiol*. 1998;81:91–93.
30. Lee KW, Yang Y, Scheinman MM, et al. Atrial flutter: a review of its history, mechanisms, clinical features and current therapy. *Curr Probl Cardiol*. 2005;30:121–168.
31. Falk RH. Medical progress: atrial fibrillation. *N Engl J Med*. 2001;344:1067–1078.
32. January CT, Wann LS, Alpert JS. 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:2071–2104.
33. Ozcon C, Jahangir A, Frudman PA, et al. Significant effects of atrioventricular node ablation and pacemaker implantation on left ventricular function and long-term survival in patients with atrial fibrillation and left ventricular dysfunction. *Am J Cardiol*. 2003;92:33–37.
34. Prystowski EN, Benson DW, Fuster V, et al. Management of patients with atrial fibrillation.

A statement for healthcare professionals. From the subcommittee on electrocardiography and electrophysiology: American Heart Association. *Circulation*. 1996;93:1262–1277.
35. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825–1833.
36. Rienstra M, Van Veldhiusen DJ, Crijns HJ, et al. Enhanced cardiovascular morbidity and mortality during rhythm control treatment in persistent atrial fibrillation in hypertensives: data of the RACE study. *Eur Heart J*. 2007;6:741–751.
37. Carlsson J, Miketic S, Windeler J, et al. Randomized trial of rate-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. *J Am Coll Cardiol*. 2003;41:1690–1696.
38. Holmloser S, Kuick K, Lilienthal J. Rhythm or rate control in atrial fibrillation: Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomized trial. *Lancet*. 2000;356:1789–1794.
39. Deedwandia PC, Singh B, Ellenbogen K, et al. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the Veterans Affairs Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT). *Circulation*. 1998;98:2574–2579.
40. Oral H, Souza JJ, Michaud GF, et al. Facilitating transthoracic cardioversion of atrial fibrillation with Ibutilide pre-treatment. *N Engl J Med*. 1999;340:1849–1854.
41. McCellan KJ, Markham A. Dofetilide: a review of its use in atrial fibrillation and atrial flutter. *Drugs*. 1999;58:1043–1059.
42. Roy D, Talajie M, Dorian P, et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *N Engl J Med*. 2000;342:913–920.
43. Nattel S. Dronedarone in atrial fibrillation—Jekyll and Hyde? *N Engl J Med*. 2011;365:2321–2322.
44. Hylek EM, Skates SJ, Sheehan MA, et al. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with non-rheumatic atrial fibrillation. *N Engl J Med*. 1996;335:540–546.
45. Klein AL, Grimm RA, Murray RD, et al. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med*. 2001;344:1411–1420.
46. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beat originating in the pulmonary veins. *N Engl J Med*. 1998;339:659–666.
47. Kuck K-H, Brugada J, Furnkranz A, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med*. 2016;374:2235–2245.
48. Koplan BA, Stevenson WG. Atrial fibrillation in heart failure, Should catheter ablation play a larger role? *Circulation*. 2016;133:1631–1633.
49. Khan MN, Jais P, Cummings J, et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med*. 2008;359:1778–1785.
50. Verma A, Natale A. Why atrial fibrillation ablation should be considered first-line therapy for some patients. *Circulation*. 2005;112:1214–1221.
51. Pappone C, Rosamo S, Augello G, et al. Mortality, morbidity and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. *J Am Coll Cardiol*. 2003;42:185–197.
52. MacIntyer C, Lakdawala NK. Management of atrial fibrillation in hypertrophic cardiomyopathy. *Circulation*. 2016;133:1901–1905.
53. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870.
54. Hart RG, Benavente O, McBride R, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med*. 1999;131:492–501.
55. Wellens HJJ, Bar FWHM, Lie KL. The value of the electrocardiogram in the differential diagnosis of a tachycardia with a wide QRS complex. *Am J Med*. 1978;64:27–33.
56. Brugada P, Brugada J, Mont L, et al. A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex. *Circulation*. 1991;83:1649–1659.
57. Antunes E, Brugada J, Steurer G, et al. The differential diagnosis of a regular tachycardia with a wide QRS complex on the 12-lead ECG: ventricular tachycardia, supraventricular tachycardia with aberrant intraventricular conduction, and supraventricular tachycardia with anterograde conduction over an accessory pathway. *Pacing Clin Electrophysiol*. 1994;17:1515–1524.
58. Griffith MJ, Garratt CJ, Mounsey P, et al. Ventricular tachycardia as a default diagnosis in broad complex tachycardia. *Lancet*. 1994;343:386–388.
59. Sapp JL, Wells GA, Parkash R, et al. Ventricular tachycardia ablation versus escalation of antiarrhythmic drugs. *N Engl J Med*. 2016;375:111–121.
60. Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med*. 1999;341:871–878.
61. Dorian P, Cass D, Schwartz B, et al. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med*. 2000;346:884–890.
62. John RM, Kumar S. Sinus node and atrial arrhythmias. *Circulation*. 2016;133:1892–1900.
63. Artucio H, Pereira M. Cardiac arrhythmias in critically ill patients: epidemiologic study. *Crit Care Med*. 1990;18:1383–1388.
64. Walkey AJ, Wiener RS, Ghobrial JM, et al. Incident stroke and mortality associated with new-onset

atrial fibrillation in patients hospitalized with severe sepsis. *JAMA*. 2011;306:2248–2255.
65. Nasraway SA, Rackow EC, Astiz ME, et al. Inotropic response to digoxin and dopamine in patients with severe sepsis, cardiac failure and systemic hypoperfusion. *Chest*. 1989;95:612–615.
66. Holt AW. Hemodynamic responses to amiodarone in critically ill patients receiving catecholamine infusions. *Crit Care Med*. 1989;17:1270–1276.
67. Moran JL, Gallagher J, Peake SL, et al. Parenteral magnesium sulfate versus amiodarone in the therapy of atrial tachyarrhythmias: a prospective, randomized study. *Crit Care Med*. 1995;23:1816–1824.
68. Horner SM. Efficacy of intravenous magnesium in acute myocardial infarction in reducing arrhythmias and mortality: meta-analysis of magnesium in acute myocardial infarction. *Circulation*. 1992;86:774–779.
69. Woods KL, Fletcher S, Roffe C, et al. Intravenous magnesium sulphate in suspected acute myocardial infarction: results of the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet*. 1992;339:1553–1558.
70. Maggioni AP, Zuanetti G, Franzosi MG, et al. Prevalence and prognostic significance of ventricular arrhythmias after acute myocardial infarction in the thrombolytic era: GISSI-2 results. *Circulation*. 1993;87:312–321.
71. Solomon SD, Ridker PM, Antman EM. Ventricular arrhythmias in trials of thrombolytic therapy for acute myocardial infarction: a meta-analysis. *Circulation*. 1993;88:2575–2581.
72. Radford MJ, Krumholz HM. Beta-blockers after myocardial infarction – for few patients, or many? *N Engl J Med*. 1998;339:551–553.
73. Waldo AL, Camm AJ, de Ruyter H, et al. Effect of D-sotalol on mortality in patients with left ventricular dysfunction after recent or remote myocardial infarction. The SWORD investigators. Survival with oral D-sotalol. *Lancet*. 1996;348:7–12.
74. Cairns JA, Connolly SJ, Roberts R, et al. Randomized trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarizations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial investigators. *Lancet*. 1997;349:675–682.
75. Julian DG, Camm AJ, Frangin G, et al. Randomized trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarction Amiodarone Trial investigators. *Lancet*. 1997;349:667–674.
76. Boutitie F, Boissel JP, Connolly SJ, et al. Amiodarone interaction with beta-blockers: analysis of merged EMIAT (European Myocardial Infarction Amiodarone Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Arrhythmia Trial) databases. The EMIAT and CAMIAT investigators. *Circulation*. 1999;99:2268–2275.
77. Ommen SR, Odell JA, Stanton MS. Atrial arrhythmias after cardiothoracic surgery. *N Engl J Med*. 1997;336:1429–1434.
78. Andrews TC, Reimold SC, Berlin JA, et al. Prevention of supraventricular arrhythmias after coronary artery bypass surgery: a meta-analysis of randomized control trials. *Circulation*. 1991;84(5 Suppl):III236–III244.
79. Kowey PR, Taylor JE, Rials SJ, et al. Meta-analysis of the effectiveness of prophylactic drug therapy in preventing supraventricular arrhythmia early after coronary artery bypass grafting. *Am J Cardiol*. 1992;69:963–965.
80. Burgess DC, Kilborn MJ, Keech AC. Interventions for prevention of post-operative atrial fibrillation and its complications after cardiac surgery: a meta-analysis. *Eur Heart J*. 2006;27:2846–2857.
81. Patti G, Chello M, Candura D, et al. Randomized trial of atorvastatin for reduction of post operative atrial fibrillation in patients undergoing cardiac surgery: results of the ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) study. *Circulation*. 2006;114:1455–1461.
82. Gillinov AM, Bagiella E, Moskowitz AJ, et al. Rate control versus rhythm control for atrial fibrillation after cardiac surgery. *N Engl J Med*. 2016;374:1911–1921.
83. Ferraris VA, Ferraris SP, Gilliam HS, et al. Predictors of postoperative ventricular dysrrhythmias: a multivariate study. *J Cardiovasc Surg (Torino)*. 1991;32:12–20.
84. Enriquez AD, Economy KE, Tedrow UB. Contemporary management of arrhythmias during pregnancy. *Circ Arrhythm Electrophysiol*. 2014;7:961–967.
85. Moss AJ. Prolonged QT syndromes. *JAMA*. 1986;256:2985–2987.
86. Johnson JN, Ackerman M. QTc: how long is too long? *Br J Sports Med*. 2009;43:657–662.
87. Moss AJ, Schwartz PJ, Crampton RS, et al. The long QT syndrome: prospective longitudinal study of 328 families. *Circulation*. 1991;84:1136–1144.
88. Moss AJ, Robinson J. Clinical features of the idiopathic long QT syndrome. *Circulation*. 1992;85(suppl 1):140–144.
89. Tzivoni D, Bonai S, Schuger C, et al. Treatment of torsade de pointes with magnesium sulphate. *Circulation*. 1988;77:392–397.
90. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med*. 2001;345:1473–1482.
91. Holmes DR, Davis KB, Mock MB, et al. The effect of medical and surgical treatment on subsequent cardiac death in patients with coronary artery disease: a report from the Coronary Artery Surgery Study. *Circulation*. 1986;73:1254–1263.

92. The Antiarrhythmics Versus Implantable Defibrillators (AVID) investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near fatal ventricular arrhythmias. *N Engl J Med*. 1997;337:1576–1584.
93. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346:877–883.
94. Maron BJ, Shen W-K, Link MS, et al. Efficacy of implantable cardioverter-defibrillators for prevention of sudden death in patients with hypertrophic cardiomyopathy. *N Engl J Med*. 2000;342:365–373.
95. Watanabe Y, Dreifus L. Electrophysiological effects of magnesium and its interactions with potassium. *Cardiovasc Res*. 1972;6:79–88.
96. Ghani MF, Rabah M. Effects of magnesium chloride on electrical stability of the heart. *Am Heart J*. 1977;94:600–602.
97. Mostow ND, Rakita L, Vrobel TR, et al. Amiodarone: intravenous loading for rapid suppression of complex ventricular arrhythmias. *J Am Coll Cardiol*. 1984;4:97–104.
98. Schwartz A, Shen E, Morady F, et al. Hemodynamic effects of intravenous amiodarone in patients with depressed left ventricular function and recurrent ventricular tachycardia. *Am Heart J*. 1983;106:848–855.
99. Côté P, Bourassa MG, Delaye J, et al. Effects of amiodarone on cardiac and coronary hemodynamics and on myocardial metabolism in patients with coronary artery disease. *Circulation*. 1954;67:1347–1355.
100. Dobrev D, Nattel S. New antiarrhythmic drugs for treatment of atrial fibrillation. *Lancet*. 2010;375:1212–1223.
101. Predersen OD, Brendorp B, Elnung H, et al. Does conversion and prevention of atrial fibrillation enhance survival in patients with left ventricular dysfunction? Evidence from the Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) study. *Card Electrophysiol Rev*. 2003;7:220–224.
102. Torp-Pedersen C, Moller M, Bloch-Thomsen PE, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. *N Engl J Med*. 1999;341:857–865.
103. Roukoz H, Saliba W. Dofetilide: a new class III antiarrhythmic agent. *Expert Rev Cardiovasc Ther*. 2007;5:9–19.
104. Duggan ST, Scott LJ. Intravenous vernakalant: a review of its use in the management of recentonst atrial fibrillation. *Drugs*. 2011;71:237–252.
105. The American Heart Association in Collaboration with the International Liasion Committee on Resuscitation (ILCOR). Guidelines 200 or cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2000;102(supplI):I112–I128.
106. Taggart NW, Haglund CM, Tester DJ, et al. Diagnostic miscues in congenital long-QT syndrome. *Circulation*. 2007;115(20):2613–2620.
107. Schwartz PJ, Moss AJ, Vincent GM, et al. Diagnostic criteria for the long QT syndrome. An update. *Circulation*. 1993;88(2):782–784.

23

Cardiac pacing

Aaisha Opel, Oliver R Segal

Cardiac pacing has rapidly evolved since its introduction by Zoll in 1952.[1] The first pacemaker was an external device designed by John Hopps in 1950. This was followed by the insertion of an internal device in 1958 by Elmqvist and Senning. The technological knowledge gained in pacing has assisted in the even more rapidly advancing field of implantable cardioverter defibrillators (ICDs). Although implantation and follow-up of permanent pacemakers and ICDs are in the domain of appropriately trained cardiologists, intensive care physicians should be familiar with such devices, as a significant number of critically ill patients will have cardiac rhythm devices. It is also essential, when urgent pacing is required, that the intensive care physician is skilled in aspects of temporary pacing, including lead insertion and testing.

Cardiac pacing repetitively delivers very low electrical energies to the heart, initiating and maintaining cardiac rhythm. Pacing may be temporary, with an external pulse generator, or permanent, with an implanted pulse generator. More recently, a hybrid approach has been developed using a standard permanent pacemaker generator and lead but externalising the generator outside the body (see temporary-permanent systems). This is useful for patients needing long-term temporary pacing (e.g. those with systemic or device-related infection or those with long-term causes of temporary bradycardia such as Guillain-Barré syndrome or its variant Miller-Fisher syndrome). Pacing is usually used to treat bradycardia, but rapid atrial or ventricular pacing can also be used to terminate both supraventricular (SVT) and ventricular tachycardias (VT).

More recently, the indications for pacing have expanded beyond symptomatic bradycardia and include conditions such as the long QT syndrome, hypertrophic cardiomyopathy (HCM) and congestive cardiac failure.

PACING SITES

TRANSVENOUS ENDOCARDIAL PLACEMENT

Pacing leads are passed via a vein to the endocardial surface of the right atrium (RA), the right ventricle (RV) or both chambers. In patients with heart failure, an additional lead is passed to the left ventricular coronary veins via the coronary sinus (which drains into the right atrium). Balloon-flotation pacing catheters for temporary pacing are less stable and are generally reserved for emergency pacing purposes.

EPICARDIAL PLACEMENT

This is mainly used in conjunction with cardiac surgery, where electrodes are attached directly to the epicardial surface of the atrium and/or ventricle and pass out through the skin in the epigastrium. These are useful after cardiac surgery, particularly after valve surgery, but rapidly deteriorate postoperatively and are typically no longer functional after 5–10 days.

TRANSCUTANEOUS EXTERNAL PACING

Transcutaneous pacing can be instigated rapidly in an emergency by personnel unskilled in transvenous pacing. However, this is a temporary measure. Patches are applied anterolaterally or anteroposteriorly over the heart. Conscious patients can experience significant pain due to pectoral muscle contraction and may require analgesia or sedation.

Other pacing modalities such as the transoesophageal route are used rarely, except in paediatrics.

PERMANENT PACING

INDICATIONS FOR PERMANENT PACING

Guidelines for permanent pacing are published by a joint American taskforce and updated fairly regularly.[2] They recommend the following pacing indications, stratified according to the likely benefit. (Please note that the vast majority of pacing indications have only levels of evidence C [expert consensus] or B [limited non-randomised trials of small numbers of patients], as pacing predated modern randomised controlled trials.)

1. *Class I:* benefit clearly outweighs risks – treatment should be performed:
   a. in second- or third-degree atrioventricular (AV) block with:
      - *symptoms* and bradycardia
      - pauses greater than 3 seconds or rate less than 40 beats per minute whilst awake, even without symptoms

ABSTRACT

Management of pacemakers, both permanent and temporary, can cause anxiety amongst non-cardiac rhythm specialists. More and more patients undergo cardiac device implantation. This chapter provides the intensive care physician with a useful insight into permanent and temporary pacing, indications, method of placement with troubleshooting tips and complications. Pacing modes are described, together with problems that may arise. Tachyarrhythmias and the use of implantable cardioverter defibrillators are described. Management of scenarios encountered in device patients on intensive care is discussed.

KEYWORDS

Pacing
temporary
permanent
temporary-permanent
indications
technique
troubleshooting
ICD

- postoperative or post-AV node ablation
- neuromuscular disease, with or without symptoms

b. in sinus node dysfunction with documented bradycardia *and symptoms*

c. in recurrent syncope due to spontaneous carotid sinus stimulation or carotid sinus pressure and pauses greater than 3 seconds

d. in chronotropic incompetence *with symptoms*

e. in pause-dependent ventricular tachycardia.

2. *Class IIa–IIb:* benefit outweighs risks – reasonable to perform procedure or procedure can be considered:
   a. in asymptomatic complete AV block with average ventricular rate 40 beats/min in an awake patient
   b. in asymptomatic Mobitz type II second-degree AV block with narrow QRS
   c. in asymptomatic sinus bradycardia with heart rate <40 beats/min
   d. in first-degree heart block (>300 ms) in patients with depressed left ventricular function and symptoms of left ventricular failure.
3. *Class III:* risks clearly outweigh the benefits – pacing should not be performed:
   a. in asymptomatic first-degree heart block
   b. in reversible AV block secondary to drug toxicity.
4. Other indications: non-bradycardia indications for pacing include pacing to improve haemodynamics. Evolving indications include the following[2,3]:
   a. *Heart failure*: patients with heart failure, severe left ventricular impairment and left bundle branch block (LBBB) may benefit from restoring synchronous ventricular contraction through pacing the RV and left ventricle (LV) at the same time – known as biventricular pacing. Such cardiac resynchronisation therapy (CRT) improves symptoms of heart failure and survival in about two-thirds of these patients. Patients who benefit most are those in sinus rhythm, have QRS widths greater than 150 ms and New York Heart Association (NYHA) class II–IV heart failure symptoms.[4,5] Some patients with dys-synchronous LV contraction on echocardiography but narrow QRS width can also benefit. The use of CRT via a permanently implantable biventricular pacemaker (the LV lead is usually passed via a tributary of the coronary sinus to the epicardial surface of the LV) has gained widespread acceptance for treatment of heart failure, together with appropriate medications. Temporary biventricular pacing with a temporary transvenous pacemaker lead passed to a coronary vein via the coronary sinus has been used successfully in cardiogenic shock and high-degree AV block.[6] Permanent devices combining CRT and ICDs, known as CRT-D, are used in those who fulfil CRT criteria and have an indication for an ICD.
   b. *HCM*: pacing can be used in symptomatic patients with a high gradient in the left ventricle. Right ventricular apical pacing causes dys-synchronous ventricular activation and can decrease LV gradient and systolic anterior motion (SAM) of the mitral valve. However, the evidence to support this is weak (currently a class IIb indication) and is probably helpful in only a small proportion of suitable patients.

PACEMAKER MODES

The Heart Rhythm Society (HRS), previously known as the North American Society of Pacing and Electrophysiology (NASPE), and British Heart Rhythm Society, previously the British Pacing and Electrophysiology Group (BPEG) and Heart Rhythm UK, developed the North American and British Group (NBG) code[7] for pacing. This is a generic code used to identify modes of pacing (Table 23.1). The code was updated in 2002 to include multisite pacing therapy (position V)[8]:

- *Position I:* refers to the chamber(s) paced: A = atrium, V = ventricle, and D = dual chamber (i.e. both A and V).
- *Position II:* refers to chamber(s) in which sensing occurs: A = atrium, V = ventricle, and D = dual chamber (i.e. both A and V), O = no sensing.
- *Position III:* refers to the pacemaker's response to a sensed event. This may be:
  - I (inhibition) – a pacemaker's discharge is inhibited (switched off) by a sensed signal, for example VVI, where ventricular pacing is inhibited by spontaneous ventricular activity.
  - T (triggered) – a pacemaker's discharge is triggered by a sensed signal.
  - D (dual) – both T and I responses can occur. This designation is reserved for dual-chamber systems. A depolarisation sensed in the atrium inhibits the atrial output but triggers ventricular pacing. There is, however, a delay (the AV interval) between the sensed atrial depolarisation and the triggered ventricular pacing, which mimics the normal P–R interval. If a spontaneous ventricular depolarisation is sensed, ventricular pacing is inhibited.
  - O – no action.
- *Position IV:* refers to *R* or rate response and is only relevant to permanent pacing systems. An *R* indicates that the pacemaker incorporates a sensor(s) to vary the pacing rate independent of intrinsic cardiac activity. The sensor(s)[9] increases or decreases the heart rate according to the body's metabolic needs. They are useful for patients with impaired sinus node function, chronotropic incompetence (when heart rate does not increase appropriately with exercise) and patients with atrial fibrillation (AF) and complete heart block or slow ventricular rates. Two different sensors are widely used:
  1. Activity sensors with vibration detectors (accelerometer or piezoelectric crystal) increase

Table 23.1 The North American and British Group (NBG) pacemaker code

POSITION I	POSITION II	POSITION III	POSITION IV	POSITION V
Chamber(s) paced	Chamber(s) sensed	Response to sensing	Rate modulation	Multisite pacing
O = none	O = none	O = none	O = none	O = none
A = atrium	A = atrium	T = triggered	R = rate modulation	A = atrium
V = ventricle	V = ventricle	I = inhibited		V = ventricle
D = dual	D = dual	D = dual		D = dual

Note: Positions I–III are used exclusively for antibradycardia function.

Reproduced from Bernstein AD, Daubert JC, Fletcher RD, et al. North American Society of Pacing and Electrophysiology/British Pacing and Electrophysiology Group: the revised NASPE/BPEG generic code for antibradycardia, adaptive-rate, and multisite pacing. *Pacing Clin Electrophysiol*. 2002;25:260.

heart rate when movement is detected. They have the disadvantage that they may respond to non-physiological stimuli (e.g. pacing rate increase may occur when the patient is using an electrical drill).

2. Minute ventilation sensors (respiratory rate times tidal volume, which is estimated by measuring impedance differences between the pacing electrode and the pacemaker unit) rely on minute volume changes to alter the pacing rate. This sensor may occasionally inappropriately accelerate the pacing rate (e.g. in a mechanically ventilated patient requiring a large minute volume). Changing the 'upper rate' limit of the pacemaker or switching the rate-adaptive function 'off' will usually solve the problem. Other sensors, such as ventricular paced Q–T interval systems, are also used in clinical practice. Recently, rate-adaptive systems with dual sensors, where one sensor cross-checks the other and only responds if both sensors are receiving consistent data, have become available. All modern permanent pacemakers are programmable and the degree of rate response can be modified to optimise heart rate with exercise.

- *Position V:* is used to indicate whether multisite pacing is present
  O = none of the cardiac chambers
  A = atrium
  V = one or both ventricles
  D = any combination of atria and ventricles.

For example, the code for a patient with dual-chamber rate-responsive pacing (DDDR) and biventricular pacing is DDDRV.

SPECIFIC PACING MODES

The three-position code (Fig. 23.1) is adequate to describe emergency temporary pacing and most forms of permanent pacing in the intensive care unit (ICU) (Table 23.2).

Table 23.2 Examples of pacemaker modes

MODE	
VOO	Paces the ventricle, no sensing, fixed-rate, asynchronous Usually only used for pacemaker testing, during use of diathermy and 'emergency' pacing
VVI	Paces the ventricle, senses ventricular activity, ventricular activity inhibits the pacemaker Ventricular demand
AAI	Paces the atrium, senses atrial activity, atrial activity inhibits the pacemaker Atrial demand Indicated in sinus bradycardia with intact AV conduction
DDD	Paces and senses both atrium and ventricle: atrial activity triggers ventricular pacing
DDI	Paces and senses both atrium and ventricle Atrial activity not tracked; thus atrial tachyarrhythmias do not trigger rapid atrial pacing AV sequential, non-P synchronous Useful for sinus bradycardia with AV block and intermittent atrial tachyarrhythmias

AV, Atrioventricular; *DDD*, dual-chamber.

SINGLE-CHAMBER PACING

1. *AOO and VOO (asynchronous atrial and ventricular) pacing:* in this mode there is no ability to sense cardiac activity (Fig. 23.2) and it is useful during and after cardiac surgery or when a patient is exposed to external sources of noise (e.g. surgical diathermy or MRI scanning).
2. *AAI (atrial demand) pacing:* this is indicated in patients with sinus bradycardia and intact AV conduction. It is reserved for patients in whom the risk of developing AV block is thought to be low.
3. *VVI (ventricular demand) pacing (Fig. 23.3):* this is the most commonly used mode and the mode of choice

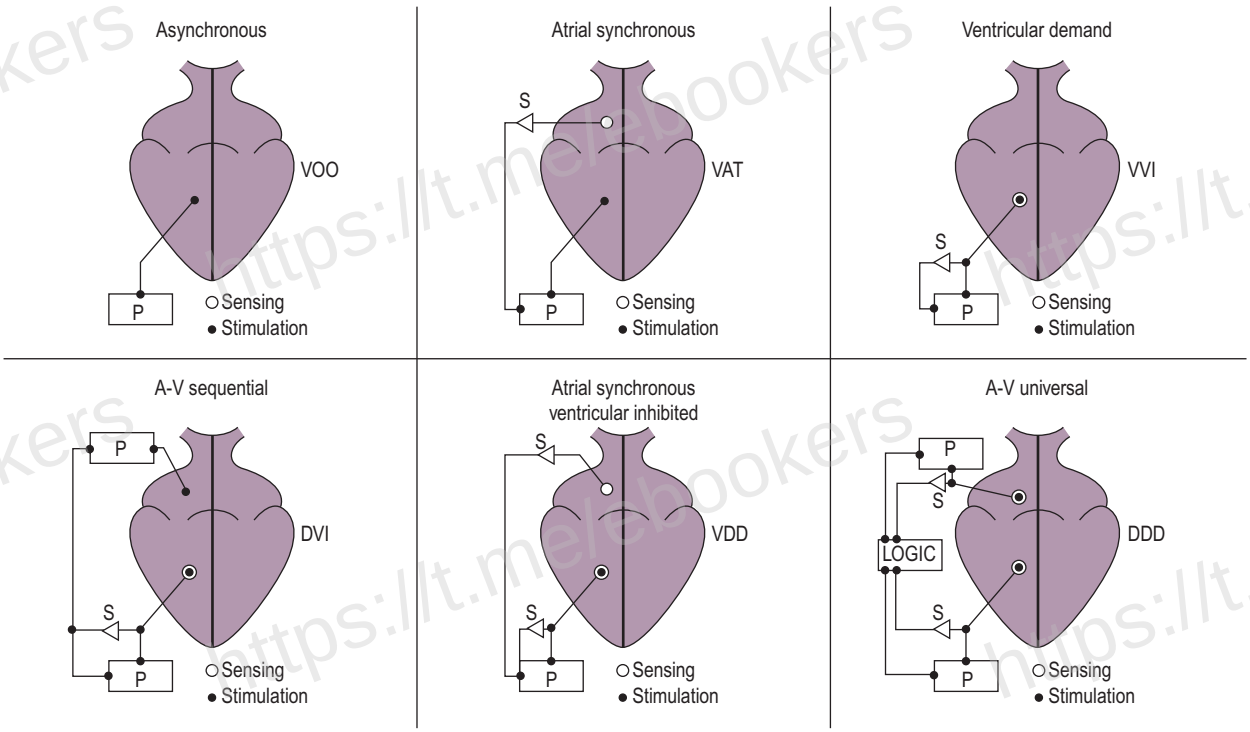


Figure 23.1 Examples of pacemaker modes and their three-position (letter) codes. *DDD*, Dual-chamber; *P*, pacemaker; *S*, sensing.

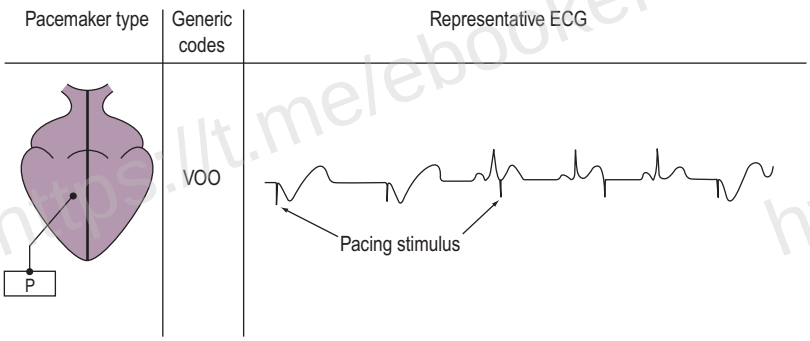


Figure 23.2 Fixed-rate ventricular pacing VOO. *ECG*, Electrocardiography; *P*, pacemaker.

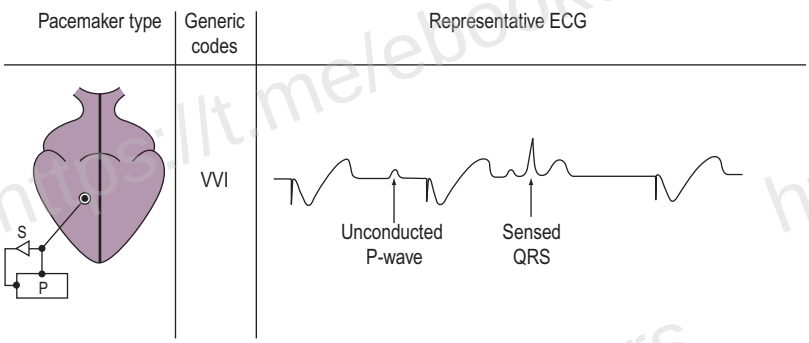


Figure 23.3 Ventricular demand pacing VVI. *ECG*, Electrocardiography; *P*, pacemaker; *S*, sensing.

in life-threatening bradyarrhythmias. Spontaneous cardiac rhythm is sensed and a minimum ventricular rate is programmed to prevent symptoms or in the ICU setting to also optimise cardiac output. There is a low risk of pacemaker-induced ventricular tachyarrhythmia (Fig. 23.4), but AV synchrony is lost, which may depress cardiac output and blood pressure.

DUAL-CHAMBER PACING

Two sets of electrodes are required (atrial and ventricular).

1. *DDD pacing:* there is pacing and sensing in both chambers (Fig. 23.5). An atrial impulse will trigger a ventricular output if none is seen after the programmed AV delay and will simultaneously inhibit an atrial output. If the impulse is conducted normally to the ventricle, ventricular pacing is inhibited. An upper rate limit is programmed to prevent the pacemaker tracking fast atrial rates (e.g. in atrial flutter or tachycardia). The response to DDD pacing depends on the underlying cardiac rhythm:
   - **a.** atrial bradycardia with intact AV conduction – atrial pacing
   - **b.** normal sinus rhythm with high-degree AV block – tracking of P-waves and ventricular pacing
   - **c.** sinus bradycardia with AV block – sequential atrial and ventricular pacing
   - **d.** normal sinus rhythm and AV conduction – inhibition of both atrial and ventricular pacing.

   Pacemaker-mediated tachycardia (PMT), or 'endless-loop' tachycardia,[10] can occur in dual-chamber pacing systems where a ventricular premature beat (Fig. 23.6) conducted retrogradely to the atria is sensed and ventricular pacing is triggered, resulting in an endless loop: the circuit's anterograde limb is the pacemaker, and the retrograde limb is via the AV node. This can be prevented by programming a blanking period after a ventricular-paced beat so that retrograde atrial activity is not sensed. The blanking period is known as the post-ventricular atrial refractory period, or PVARP, and is found on all modern pacemakers. An alternative is to switch to an asynchronous (non-sensing) mode or programming to DDI mode.
2. *DDI pacing (AV sequential, non–P-wave synchronous):* in this mode sensing occurs in both atrium and ventricle, but sensed atrial events do not trigger ventricular pacing. Imagine it as a patient with separate VVI and AAI pacemakers that cannot talk to each other. PMT or endless-loop tachycardia cannot occur in DDI and neither will tracking of rapid atrial rates. For this reason, modern pacemakers programmed DDD will switch to DDI when an atrial tachyarrhythmia is detected (e.g. atrial fibrillation). When this happens the pacemaker will simply pace the ventricle at its back-up rate and not track the tachycardia.

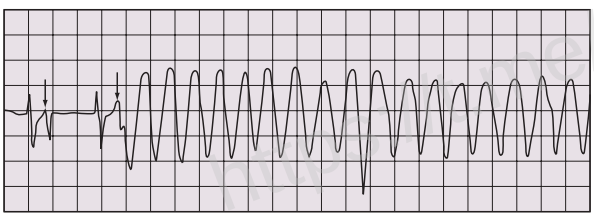


Figure 23.4 Non-sensing of QRS (see first two beats). Pacing spikes *(arrows)* fall on the T-wave with subsequent pacemaker-induced ventricular tachycardia.

HAEMODYNAMICS OF CARDIAC PACING AND THE ATRIOVENTRICULAR INTERVAL

In the normal heart, cardiac output increases three- to fourfold during exercise, mainly due to increased heart rate and stroke volume and the ability of pacemakers to increase heart rate is therefore paramount. Nevertheless, loss of AV synchrony (i.e. the normal activation sequence of atria contracting first and then the

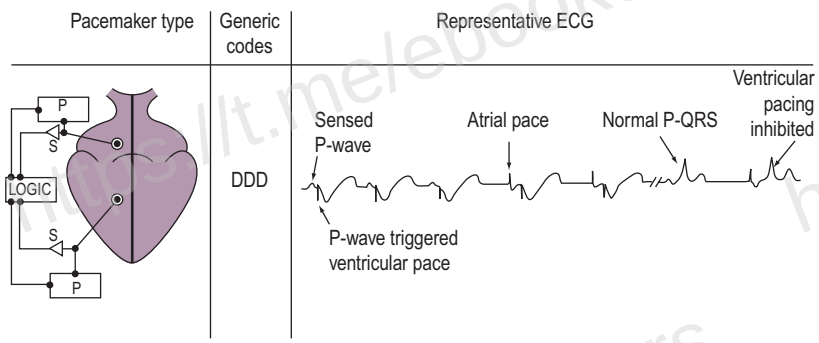


Figure 23.5 Dual-chamber *(DDD)* pacing. *ECG*, Electrocardiography; *P*, pacemaker; *S*, sensing.

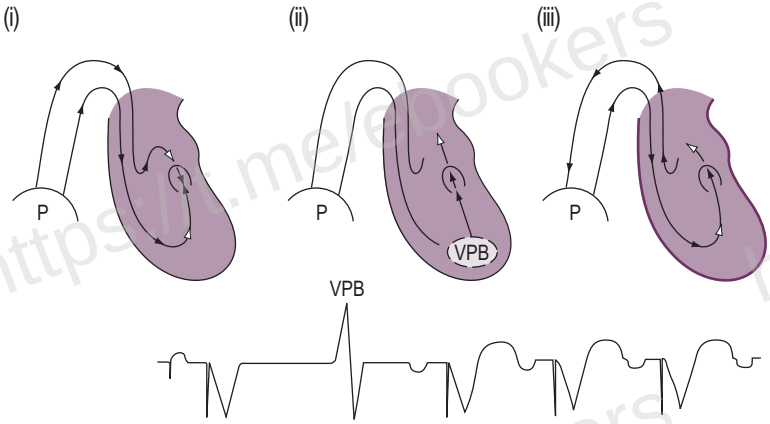


Figure 23.6 Pacemaker-mediated 'endless-loop' tachycardia: (i) under normal conditions (first beat), there is no conduction from the ventricles to the atria because of ventriculo-atrial (VA) block or because the atrial and ventricular impulses collide and extinguish each other in the atrioventricular node; (ii) if a ventricular premature beat *(VPB)* is conducted retrogradely to the atria (second beat), inducing an inverted 'p'-wave, this may be sensed by the pacemaker *(P)* which then triggers a ventricular paced beat (third beat); (iii) if the paced ventricular beat is then retrogradely conducted from the ventricle to the atria and sensed, an 'endless loop' may occur (beats 4, 5); that is, pace ventricle VA conduction 'p' wave (sensed) ventricular pace, and so forth.

ventricles) will decrease cardiac output by up to 25%,[11] most commonly in atrial fibrillation. Many permanent pacemakers are rate-adaptive. When temporary pacing is used, especially in the ICU setting, higher than normal lower rates may be needed if oxygen delivery is inadequate. For life-threatening bradyarrhythmias, increasing heart rate with VVI mode pacing is the treatment of choice and heart rate modulation with exercise is required only for permanent pacemaker patients.

During VVI and VVIR pacing, the atria and ventricles beat independently and AV synchrony is lost. This can have deleterious effects, known collectively as 'pacemaker syndrome.'[12] It can occur with any pacing mode where AV dissociation occurs and blood pressure, stroke volume and cardiac output may fall with the onset of pacing. Another feature is due to the atria contracting against closed tricuspid and mitral valves causing regurgitation of blood into the neck via the jugular veins. This is felt as uncomfortable neck pulsations. The pacemaker syndrome can be eliminated by restoring AV synchrony.

However, and somewhat counterintuitively, dual-chamber pacing has not been shown to improve mortality even though haemodynamics are usually superior to VVI pacing.[13] It does though appear to lower the incidence of AF.[3]

Changing the programmed AV interval of a dual-chamber pacemaker can affect the amount of ventricular pacing that is seen and also the haemodynamics, for the reasons outlined above. If this interval is programmed short (e.g. 80 ms), it will promote ventricular pacing. If it is programmed long (e.g. 250 ms), it will promote intrinsic ventricular activity (if present). The correct AV interval will depend on patients' clinical state and their intrinsic AV conduction and interatrial conduction (the time to conduct between the RA and LA). Promoting ventricular pacing may be a good thing if it improves haemodynamics, but promoting intrinsic conduction is often better, especially if the intrinsic AV delay is not very long. Adjusting the AV interval in the patient with poor cardiac output or low oxygen delivery can be optimised using echocardiography or thermodilution assessment of cardiac output.

TEMPORARY PACING

INDICATIONS FOR TEMPORARY PACING

Temporary cardiac pacing is indicated for:

- any sustained symptomatic bradycardia not promptly responding to medical treatment
- malignant ventricular arrhythmias secondary to bradycardia
- second- or third-degree AV block with haemodynamic compromise
- asystole.

The decision to pace is based on bradycardia causing haemodynamic deterioration, and not on the specific rhythm disturbance. For example, pacing is indicated in a patient with atrial fibrillation and a ventricular rate of 40 beats per minute associated with a blood pressure of 70/40 mm Hg (9.3/5.3 kPa), cardiac failure and oliguria, but not in an asymptomatic,

normotensive patient with the same rhythm or even a patient with an inferior myocardial infarction, complete heart block and a ventricular rate of 45 beats per minute with a narrow QRS complex.

Temporary pacing is indicated for the treatment of heart block or sinus bradycardia after cardiac surgery. In high-risk patients (e.g. aortic or mitral valve replacement), prophylactic epicardial electrodes are attached during surgery. DDD epicardial pacing has been shown to increase cardiac output at any given heart rate compared with VVI pacing.[14] Temporary perioperative cardiac-pacing strategies to increase stroke volume and cardiac output include optimisation of AV delay and rarely multisite pacing.[15] Temporary pacing may be required in patients with inferior myocardial infarction or during coronary angioplasty, particularly of the right coronary, which supplies the SA and AV nodes. Asymptomatic patients with bifascicular block do not require prophylactic pacing prior to general anaesthesia, although transcutaneous pacing should be available, but should be considered for all patients with trifascicular block (bifascicular block and prolonged PR interval). Patients with Mobitz type II or third-degree AV block should be paced prior to general anaesthesia and surgery.

Caution should be exercised in patients with acute myocardial infarction, as many will have received antiplatelet agents. Transcutaneous pacing prevents the need for transvenous pacing, but should only be used as an emergency in high-risk patients.

TEMPORARY LEADS AVAILABLE

VENTRICULAR PACING LEADS

There are different types of temporary pacing leads available with different degrees of rigidity and French size. The most common calibres will be 4–6 F. These leads are relatively stiff and can be shaped before advancing through a sheath, but are still flexible enough to be manipulated under fluoroscopic control to the correct position in the RV. Balloon-flotation leads can, in theory, float into a stable position in the RV and are useful if fluoroscopy is not available in emergent situations, or as back-up when transferring patients to centres for permanent pacing. Alternatively, softer diagnostic electrophysiology catheters can be used with a standard temporary pacing box and have the advantage of being potentially less traumatic than traditional 'temporary pacing wires,' especially if required for longer periods.

ATRIAL PACING LEADS

Leads designed specifically for placement in the right atrium have a preformed J-shaped tip designed to hook into the RA appendage. This site is often best for lead stability, low pacing thresholds and good sensing.

TECHNIQUE OF TEMPORARY TRANSVENOUS PACING

VENTRICULAR PACING

A sterile technique is mandatory in an environment with good fluoroscopic imaging, non-invasive cardiac monitoring and resuscitation facilities. In emergencies, transcutaneous pacing (VVI) can be implemented first while transvenous VVI pacing is being prepared. A bipolar lead introduced under fluoroscopic control is most commonly used.

Vascular access

The Seldinger technique is employed to access a central vein with a 5- or 6-French sheath. The sheath has a haemostatic valve, which prevents blood loss at the time of lead insertion. Percutaneous insertion via the right internal jugular vein probably offers least complications with ease of manipulation and stability of the lead. However, the subclavian vein approach is often used as it allows more freedom for arm and neck movement, but there is a slightly greater risk of pneumothorax. Patients likely to need permanent pacing later in their treatment should have the left subclavian vein saved for this purpose. Antecubital veins are associated with lead instability and thrombophlebitis. The femoral vein can be used. It is usually quick and easy to insert a ventricular pacing wire from this route, but the patient must remain lying flat. Lead stability is probably less good than superior routes and there is higher risk of infection and deep-vein thrombosis. Femoral temporary pacing is useful over a short period of time, for instance to cover a surgical procedure in a patient with trifascicular block or those who have received thrombolytic agents but should not be used for longer-term pacing if possible.

Positioning the pacing lead

The pacing lead is manipulated under fluoroscopic control in the posteroanterior (PA) position close to the apex of the RV (Fig. 23.7). This position offers the greatest stability, but the true apex should be avoided as it is thin and the risk of perforation is higher. As the lead crosses the tricuspid valve to the RV, it is usual to see ventricular ectopy (VE). However, if continuous, the lead should be pulled back to the right atrium. In the absence of VE, the lead position should be confirmed in the left anterior oblique (LAO) position to ensure it is not in the coronary sinus or a posterior vein. Manipulation of the lead is achieved by clockwise and counterclockwise torque in combination with simultaneous advancement and retraction of the lead. Temporary pacing leads are relatively stiff and perforation can occur, especially if leads are seen to buckle whilst advancing, but it is also important to ensure sufficient slack in the lead to avoid the loss of position with subsequent patient movement.

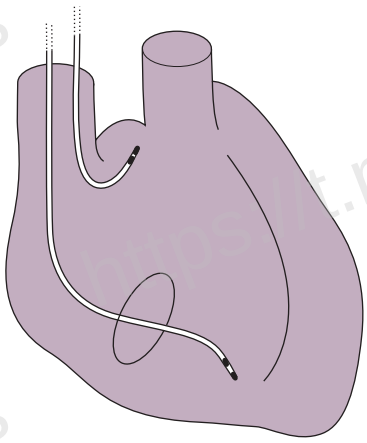


Figure 23.7 Characteristic appearance of temporary transvenous pacing leads ideally positioned in the right atrium (right atrial appendage) and apex of right ventricle.

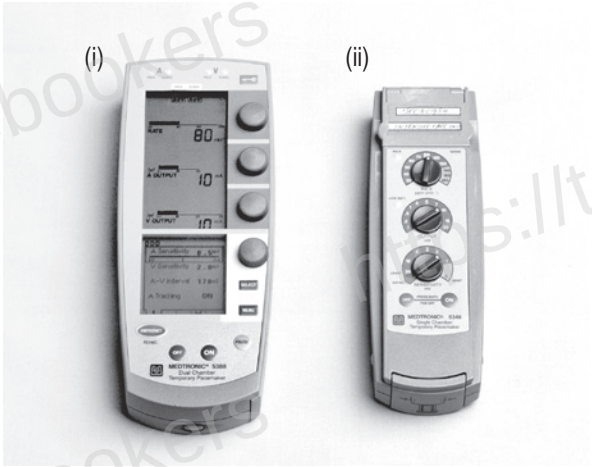


Figure 23.8 External pacemakers. Medtronic, Inc. (i) Model 5388 (dual-chamber); (ii) model 5348 (single-chamber). Both are capable of rapid pacing for certain tachycardias.

Once in a satisfactory position, the lead should be tested electrically for sensing, pacing and diaphragmatic capture (see below). It should be sutured to the skin at two different sites: one where it exits the skin, and a second to a loop formed with the lead. A chest X-ray should be obtained to exclude pneumothorax and to confirm satisfactory positioning.

ATRIAL PACING

J-shaped atrial leads are designed to be advanced and hooked into the right atrial appendage. The appendage is an anterior structure, which is superior to the right atrium. Once the tip is advanced into the appendage orifice, retraction of the lead will hook the tip into the appendage body and a side-to-side motion of the lead tip may be seen if the patient is in sinus rhythm. The correct position is best confirmed by a lateral chest X-ray.

DUAL-CHAMBER PACING

Modern external pacing boxes are available (Fig. 23.8) that will pace in all modes. These units are small, easy to use and can fit into a small pouch suitable for mobile patients.

TEMPORARY-PERMANENT SYSTEMS

Prolonged temporary pacing is commonly associated with complications including systemic and local infection, lead displacement and even right ventricular perforation. Therefore, unless pacing with a temporary wire is extremely shortlived (i.e. for periods of <24 hours), it is no longer recommended. A temporary-permanent system or 'externalised pacemaker' is one where standard permanent pacing leads and a standard implantable generator are used in a temporary, externalised fashion. One area in which they are now very frequently used is in patients with a standard pacing indication but also concurrent infection such that a permanent system should not be implanted immediately. For example, pacing-dependent patients who undergo system extraction for cardiac device infection commonly benefit from this approach before a permanent system is implanted after treatment with antibiotics. Alternatively, patients with potentially reversible causes for bradycardia, for example acute hypothyroidism or Guillain-Barré syndrome, may also benefit from pacing using a so-called 'temporary-permanent' system until the underlying cause has either resolved or been treated.

Typically, an active fixation lead is placed in the right ventricle via an internal jugular vein or subclavian vein approach. A 'peel-away' sheath is used so that just the pacing lead remains externalised at the end of the implant procedure. Permanent pacing leads are typically 'stylet-driven' to provide support and allow positioning of the lead tip. As the proximal end of the lead is externalised, an active fixation lead mechanism is used to reduce the risk of lead displacement within the heart. Such leads can be positioned on the septum (rather than the apex) for more physiological pacing. Once positioned, the stylet is removed and the lead fixed to the skin entry point using sutures around the suture sleeve. The lead is then screwed into the generator in the normal manner, but with the generator remaining outside the body. We recommend using a chlorhexidine-impregnated dressing over the entry site of the lead through the skin to reduce the risk for infection. Any redundant lead is coiled up and this, with the generator, is placed against the patient's skin with an adhesive dressing.

After a short period of observation, the patient with a temporary-permanent system implant can be mobile

and, unlike traditional pacing wires, lead displacement and threshold rise is rare, meaning the need for the lead repositioning is also rare. This also mitigates against complications, which arise in the immobile patient, like venous thrombosis, pressure sores and pneumonia. Similarly, the risk and inconvenience associated with multiple lead repositioning procedures is avoided. In some countries, patients have even been discharged with this type of system, particularly when the reversal of a cause of bradycardia may take a long time, for example in some neurological diseases; however, in the UK, patients remain in hospital. The device can be reprogrammed just like a normal pacemaker if required and the percentage of time that the patient is pacing, or detection of intermittent arrhythmias, can be recorded so where appropriate, a decision to permanently pace or provide other treatment can be made.

Removal of the temporary-permanent system is straightforward and can be performed in a ward-based setting without needing to go to a catheter lab. The sutures are cut, the lead is removed from the generator and the active fixation component of the lead is retracted using the bespoke tool (or just a standard artery forceps). The lead can then be removed with simple traction (fluoroscopy is typically not required). Manual pressure is applied and the area dressed.

Troubleshooting

Lead does not cross the tricuspid valve Looping the lead in the right atrium and then applying counterclockwise torque will help prolapse it into the RV.

Lead cannot be advanced to the right ventricle apex Withdrawing the lead after advancing it to the RV outflow tract (RVOT) may help the tip fall towards the apex. A small amount of torque may aid the process. Alternatively, the lead may need to be shaped with a different degree of curve.

If this manoeuvre does not help, a more basal position on the inferior wall can be used. The RVOT should be used only if the patient is asystolic, as lead stability is poor here with passive leads.

Lead advances only towards the right ventricle outflow tract Ensure that this is not in the coronary sinus by checking that it does not curve posteriorly in the LAO position. If it is not, apply a slightly posteriorly facing curve to the distal tip of the lead and try again.

Testing the pacing leads

Modern temporary pacing boxes are sophisticated devices, which can perform checks of sensing as well as pacing threshold. Checking the sensitivity of a pacing lead electrogram is a very important step. Sensitivity, or sensing, is simply calculation of the amplitude of the sensed electrograms. Large electrograms are easy to sense and small ones are not and undersensing may occur. Undersensing will cause inappropriate delivery of a pacing stimulus. If this occurs on or near a T-wave, this can lead to ventricular fibrillation (VF). On most boxes, sensing is indicated by a flashing light or other digital marker. The sensitivity dial is slowly rotated from a low value to a higher one until sensing stops. This represents the sensitivity of the sensed electrograms. A higher value is better than a lower one. The sensitivity is programmed to allow continuous sensing of all intrinsic signals.

Pacing threshold The rate should be set at least 10 beats per minute faster than the intrinsic heart rate, or at 60 beats per minute if the patient has a profound bradycardia. The pacing output should be set at 5 V and sensitivity at 1 mA. The box is switched on and ventricular capture confirmed by the presence of a pacing spike immediately followed by a broad QRS of LBBB morphology at the same rate as that set on the box.

The output is slowly decreased until consistent capture is lost. It is then increased until capture returns. This is the pacing threshold and ideally should be less than 1 V. However, if another stable position cannot be found, then a higher threshold may be acceptable. In those with no underlying rhythm or profound bradycardia, loss of capture will lead to asystole – in which case the output should be rapidly increased until capture returns. The stability of the wire is checked in its position just above the pacing threshold by asking the patient to take deep breaths, cough and sniff whilst looking for loss of capture and viewing the wire fluoroscopically. Diaphragmatic capture is checked in leads on the inferior RV wall by pacing at the maximum output, usually 10 V, and feeling the abdomen or fluoroscopically screening the diaphragm. If diaphragmatic capture occurs, the lead must be repositioned.

If a threshold of less than 1 V is achieved, the pacing rate is set to the desired rate to achieve adequate cardiac output or 40 beats per minute if intermittent back-up pacing is required. The voltage is usually set to three times the pacing threshold to allow sufficient safety margin, or at least 3 V. Temporary pacing is programmed in VVI mode to allow sensing of spontaneous ventricular activity and to inhibit pacing.

Complications of temporary pacing[16]

Temporary pacing should have a low complication rate. However, it is rare nowadays for operators to gain regular experience at insertion and similarly training may also be inadequate. Several studies from the UK report complications in a third to a half of cases.[17,18] Thus, temporary transvenous pacing is best avoided where possible; rather, insertion of a permanent system at the earliest opportunity is best, and in many centres this now happens out of 'normal' working hours. Complications include:

- pneumothorax, haemothorax, arterial puncture, AV fistula and perforation of the RV or RA leading to cardiac tamponade

- undersensing, leading to inappropriate pacing and pacemaker-induced arrhythmias; oversensing (of extrinsic or intrinsic noise), with pacemaker inhibition and loss of cardiac output; failure to capture due to poor or unstable lead position, increasing pacing threshold with chronicity of lead
- diaphragmatic capture (may be associated with RV perforation)
- thrombus of the central vein and importantly infection, especially with leads older than 7 days.

How to manage abrupt failure to pace

A life-threatening situation may arise if a temporary pacemaker fails suddenly. The following is an ordered approach to such an emergency:

1. Make sure the pacemaker box is switched on and connected to the pacing lead(s).
2. The pacemaker output should be increased to its maximum setting (usually 10 V or 20 mA).
3. Asynchronous DOO/VOO mode(s) should be selected to prevent oversensing.
4. If pacing still fails, connect the pacemaker directly to the pacing lead, bypassing the connecting wire (if present), as occasionally connecting wires may be faulty.
5. Consider replacing the pacemaker box or its batteries.
6. External transcutaneous pacing should be immediately available and commenced while a new pacing system is inserted.
7. Cardiopulmonary resuscitation and positive chronotropic drugs such as atropine, isoproterenol (isoprenaline) or epinephrine (adrenaline) should be available.

PACEMAKER PROGRAMMING

Multiple parameters can be programmed on both modern temporary and permanent pacing systems. All pacing practitioners, and this includes physicians who implant temporary systems, should be familiar with programming the mode, rate, pacing output and sensitivity of a pacing system and should also be able to diagnose and troubleshoot basic pacing problems like undersensing and oversensing. If dual-chamber pacing systems are used, programming the AV delay should be performed to optimise cardiac output and cardiac function (perhaps using echocardiographic guidance). Programming permanent pacing systems is more complicated than for temporary systems and should be performed only by individuals qualified to do so. Internationally recognised pacing qualifications include the IBHRE and EHRA examinations awarded by the Heart Rhythm Society and the European Heart Rhythm Association, respectively.

NOISE AND ELECTROMAGNETIC INTERFERENCE

Any signal sensed by a pacemaker will lead to pacing being inhibited or triggered (e.g. in dual-chamber systems). These signals will include noise or electrical artefact sensed by a pacing system. Noise is characterised as intrinsic (from within the patient) or extrinsic (from outside the patient). Sources of intrinsic noise include lead fracture, fluid in the generator header and diaphragmatic and skeletal myopotentials. Extrinsic noise includes electromagnetic interference (EMI) (e.g. from a nearby electrical device or its trailing wires and surgical diathermy). Other sources include MRI scanners (patients with some modern permanent pacemakers can be safely scanned in MRI scanners) or electronic devices placed over the pacemaker generator (e.g. mobile telephones or MP3 players). Noise can be misinterpreted by ICDs as VT or VF and can result in inappropriate therapy and shocks.

MRI scanning is sometimes necessary in patients with non–MRI-safe pacing systems or ICDs. Recent studies have demonstrated that MRI scanning can be performed safely in selected patients with these types of systems,[19] but this must be performed in collaboration with a pacing expert and the risks presented by MRI must be outweighed by the diagnostic benefit of the scan on a case-by-case basis.

CARDIOVERSION/DEFIBRILLATION IN PATIENTS WITH A PERMANENT PACEMAKER (OR IMPLANTABLE CARDIOVERTER DEFIBRILLATORS)

To avoid damage to the pacemaker device, shocking pads should be placed in the anterior–posterior position and at least 10 cm from the unit. The pacemaker (or ICD) should be checked before and afterwards. In patients with a temporary transvenous pacemaker, the external unit and leads should be kept well away from the pads.

DIATHERMY

Bipolar diathermy should be used whenever possible and the pacemaker programmed to an asynchronous mode in pacing-dependent patients. In an emergency (e.g. asystole in a patient whose pacemaker is inhibited by diathermy), placing a magnet over the pacemaker generator will result in asynchronous pacing at 'magnet' rate (magnet rate varies according to pacemaker manufacturer). ICDs do not have a magnet rate; placing a magnet over an ICD will switch off its therapies (i.e. antitachycardia pacing and shocks), but ICD therapies should be switched off before using diathermy. After surgery the pacemaker or ICD should be tested and reprogrammed appropriately.

Box 23.1 Pacing versus cardioversion for the treatment of tachyarrhythmias

Pacing may assist in rhythm diagnosis
Pacing may be used (cautiously) in digitalis intoxication
Pacing does not require a general anaesthetic
Pacing avoids complications of DC shock, especially myocardial depression
Repeated reversions are easier with pacing
Standby pacing is immediately available if bradycardia or asystole occurs after electrical reversion

Box 23.2 Pacing versus drug therapy for the treatment of tachyarrhythmias

Pacing may aid in arrhythmia diagnosis
Pacing avoids drug-induced cardiac depression and other drug side effects
Pacing can be used when drug therapy has failed
Termination of the tachycardia with pacing is often immediate
Standby pacing is immediately available

Box 23.3 Indications for rapid cardiac pacing in suitable arrhythmias

Failure of drug therapy
Recurrent arrhythmias
Contraindication for cardioversion (e.g. digitalis intoxication)
Aid to arrhythmia diagnosis (e.g. wide-complex tachycardia to differentiate ventricular tachycardia from supraventricular tachycardia)

CARDIAC PACING IN TACHYARRHYTHMIAS

Although pacemakers are not usually inserted for the treatment of atrial arrhythmias, atrio-ventricular nodal reentrant tachycardia (AVNRT) or atrio-ventricular reentrant tachycardia (AVRT), these rhythms may be treated safely and effectively by rapid pacing and/or premature electrical stimulation where a device is already present. They can also be used for treatment of VT, but rapid VT should be managed with DC cardioversion. Rapid cardiac pacing has advantages over DC cardioversion (Box 23.1) and drug therapy (Box 23.2), but is of no value in sinus tachycardia, AF and VF (Box 23.3). Pacing at rates of 80–100 beats per minute can be used to try to suppress ventricular and supraventricular rhythms as well as torsade de pointes in patients with the congenital long QT syndrome.

VENTRICULAR TACHYCARDIA

Ventricular burst pacing is a simple and often effective technique to pace VT. The ventricle is paced at a rate starting at about 120% of the VT rate for 8–10 beats (Fig. 23.9). If this fails (Fig. 23.10), increasing the pacing rate and/or the number of paced beats in the train should be tried cautiously. Slow VTs particularly are very stable and often require very long pacing trains. Potential complications include accelerating the VT rate, which can precipitate VF. Trained personnel, a defibrillator and resuscitation facilities must be available to perform this safely.

Figure 23.9 Wide-complex tachycardia. Ventricular burst pacing with ventricular capture results in normal sinus rhythm on cessation of pacing.

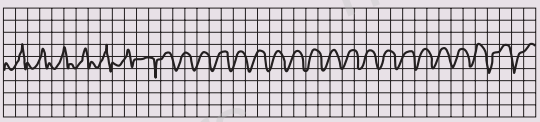


Figure 23.10 Wide-complex tachycardia is followed by ventricular burst pacing. When pacing is discontinued, a wide-complex tachycardia of opposite polarity is precipitated.

IMPLANTABLE CARDIOVERTER DEFIBRILLATORS*

This is an implantable device that recognises and tries to terminate VT and VF through antitachycardia pacing and shocks, respectively. Guidelines are published for ICD implantation.[14] ICDs are of proven survival benefit and a class I indication in patients who have survived VF or haemodynamically unstable VT not due to a transient or reversible cause (e.g. an electrolyte imbalance). ICD implantation is also indicated for patients with structural heart disease and spontaneous sustained VT, whether haemodynamically stable or unstable. ICDs are also now used prophylactically in high-risk patients (i.e. those with severely impaired LV function) and are especially efficacious in patients with previous myocardial infarction.[20]

Most ICD systems are implanted transvenously and can perform antitachycardia pacing as well as normal permanent pacing, if necessary. Single- or dual-chamber ICDs may be implanted. The addition of an atrial lead gives another piece of information for the ICD to use to diagnose a tachycardia as VT rather than an SVT, but has not conclusively been shown to do this better than single-chamber devices. ICDs continuously monitor the patient's heart rate and deliver therapy when the heart rate exceeds the programmed

detection rate. Devices are programmed with different tachycardia zones, stratified according to rate:

1. *VF zone:* for rates usually faster than 200 beats per minute. High-energy shocks are delivered if detection criteria are met, but antitachycardia pacing can be delivered while the device is charging in case it is a very fast VT. Shocks are biphasic, as these are more efficient and require lower energies than monophasic waveforms and can be programmed below the maximum output if the programmer wishes to save device battery life.
2. *Fast VT zone:* for rates between 170 and 200 beats per minute – several attempts of antitachycardia pacing are usually programmed initially, of increasing aggressiveness. This is followed by shocks if unsuccessful.
3. *Slow VT zone:* for rates between 150 and 170 beats per minute. This is similar to the fast VT zone, but even more weighted to antitachycardia pacing.

COMPLICATIONS

Occasionally, ICDs can deliver multiple discharges in short sequence and this is a clinical emergency. Shocks may be appropriate or inappropriate. Frequent malignant ventricular arrhythmias may result in multiple appropriate discharges. If the multiple shocks are successful in defibrillating the patient during an arrhythmia 'storm', the ICD device may be deactivated and antiarrhythmic drugs or even general anaesthesia initiated. This will save device battery longevity and be much more comfortable for the patient. In the absence of a programmer or whilst this is being sought, an ICD can be deactivated in an emergency by a magnet found on resuscitation trolleys. A magnet will disable shock therapy only. If shocks are inappropriate, for example for atrial fibrillation or lead fracture, the ICD needs to be reprogrammed or should be switched off.

KEY REFERENCES

2. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2008;51(21):e1–e62.
4. Cleland JGF, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronisation therapy on morbidity and mortality in heart failure (CARE-HF). *N Engl J Med*. 2005;352:1539–1549.
7. Bernstein AD, Camm AJ, Fletcher RD, et al. The NASPE/BPEG generic pacemaker code for antibradyarrhythmic and adaptive rate pacing and antitachyarrhythmic devices. *Pacing Clin Electrophysiol*. 1987;107:794–799.
8. Bernstein AD, Daubert JC, Fletcher RD, et al. North American Society of Pacing and Electrophysiology/British Pacing and Electrophysiology Group: the revised NASPE/BPEG generic code for antibradycardia, adaptive-rate, and multisite pacing. *Pacing Clin Electrophysiol*. 2002;25:260–264.
11. Donovan KD, Dobb GJ, Lee KY. The haemodynamic importance of maintaining atrioventricular synchrony during cardiac pacing in critically ill patients. *Crit Care Med*. 1991;19:320–326.
13. Toff WD, Skehan JD, De Bono DP, et al. The United Kingdom pacing and cardiovascular events (UKPACE) trial: United Kingdom Pacing and Cardiovascular Events. *Heart*. 1997;78:221–223.
15. Spotnitz HM. Optimizing temporary perioperative cardiac pacing. *J Thorac Cardiovasc Surg*. 2005;129:5–8.
20. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346:877–883.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Zoll PM. Resuscitation of the heart in ventricular standstill by external electric stimulation. *N Engl J Med*. 1952;747:768–771.
2. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2008;51(21):e1–e62.
3. Hayes DL, Zipes DP. Cardiac pacemakers and cardioverter-defibrillators. In: Zipes DP, Libby P, Bonow RO, eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 7th ed. Philadelphia, PA: Elsevier Saunders; 2005:767–802.
4. Cleland JGF, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronisation therapy on morbidity and mortality in heart failure (CARE-HF). *N Eng J of Med*. 2005;352:1539–1549.
5. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac resynchronisation therapy with or without an implantable defibrillator in advanced chronic heart failure (COMPANION). *N Engl J Med*. 2004;350: 2140–2150.
6. Guo H, Hahn D, Olshansky B. Temporary biventricular pacing in a patient with subacute myocardial infarction, cardiogenic shock, and third-degree atrioventricular block. *Heart Rhythm*. 2005;2:112.
7. Bernstein AD, Camm AJ, Fletcher RD, et al. The NASPE/BPEG generic pacemaker code for antibradyarrhythmic and adaptive rate pacing and antitachyarrhythmic devices. *Pacing Clin Electrophysiol*. 1987;107:794–799.
8. Bernstein AD, Daubert JC, Fletcher RD, et al. North American Society of Pacing and Electrophysiology/ British Pacing and Electrophysiology Group: the revised NASPE/BPEG generic code for antibradycardia, adaptive-rate, and multisite pacing. *Pacing Clin Electrophysiol*. 2002;25:260–264.
9. Leung S-K, Lau C-P. Developments in sensor-driven pacing. *Cardiol Clin*. 2000;18:113–155.
10. Furman S, Fisher JD. Endless-loop tachycardia in an AV universal (DDD) pacemaker. *Pacing Clin Electrophysiol*. 1982;5:486–489.
11. Donovan KD, Dobb GJ, Lee KY. The haemodynamic importance of maintaining atrioventricular synchrony during cardiac pacing in critically ill patients. *Crit Care Med*. 1991;19:320–326.
12. Johnson AD, Laiken SL, Engler RL. Hemodynamic compromise associated with ventriculoatrial conduction following transvenous pacemaker placement. *Am J Med*. 1978;65:75–81.
13. Toff WD, Skehan JD, De Bono DP, et al. The United Kingdom pacing and cardiovascular events (UKPACE) trial: United Kingdom Pacing and Cardiovascular Events. *Heart*. 1997;78:221–223.
14. Baller D, Hoeft A, Korb H, et al. Basic physiological studies on cardiac pacing with special reference to the optimal mode and rate after cardiac surgery. *Thorac Cardiovasc Surg*. 1981;29:168–173.
15. Spotnitz HM. Optimizing temporary perioperative cardiac pacing. *J Thorac Cardiovasc Surg*. 2005;129: 5–8.
16. Donovan KD, Lee KY. Indications for and complications of temporary transvenous cardiac pacing. *Anaesth Intensive Care*. 1985;13:63–70.
17. Betts TR. Regional survey of temporary transvenous pacing procedures and complications. *Postgrad Med J*. 2003;79:463–465.
18. Murphy JJ. Problems with temporary cardiac pacing. *Br Med J*. 2001;323:527.
19. Faris OP, Mitchell S. Magnetic resonance imaging of pacemaker and implantable cardioverter-defibrillator patients. *Circulation*. 2006;114:1232–1233.
20. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346:877–883.

24

Acute heart failure and pulmonary hypertension

Andrew Aswani, Nicholas Ioannou

ACUTE HEART FAILURE

Heart failure is a highly prevalent condition affecting 2% of the population worldwide. Most patients with heart failure have underlying coronary artery disease, hypertension, pre-existing cardiomyopathy or valvular disease.[1] Improvements in the treatment of patients with chronic heart failure (CHF) and those presenting with acute coronary syndromes (ACS) mean that the prevalence and resultant societal economic burden of this disease are projected to increase dramatically over the next 20 years.[2]

Patients may present with chest pain, palpitations, shortness of breath, fatigue and peripheral oedema. Management focuses on reducing cardiac work to relieve symptoms and prevent further myocardial damage. Heart failure encompasses a broad range of clinical syndromes and includes stable CHF and acute heart failure (AHF). AHF is estimated to account for 3 million index admissions each year in the United States alone.[1] AHF includes several different phenotypes of varying severity including de novo AHF, acute decompensated heart failure, hypertensive AHF, AHF with pulmonary oedema and cardiogenic shock (CS). It is worth noting that the improved outcomes that have been achieved over the past 30 years in reducing mortality in CHF have not been replicated in AHF, and outcomes remain very poor.[3] Notably, the improvement in outcomes in AHF with CS over this period due to aggressive revascularisation strategies for ACS[4] have lagged behind the improvements seen in septic shock.[5] This comparison points to a poorly researched field with a paucity of randomised trials showing any treatment benefit in AHF. In fact, the treatment armamentarium (comprising diuretics, vasodilators and inotropes) has remained essentially unchanged over the last 30 years.[6]

Patients with AHF may be usefully classified according to their perfusion status *(warm vs. cold)* and the presence or absence of congestion *(wet vs. dry)* (Fig. 24.1). Most patients (>95%) presenting with AHF present with symptoms and signs of congestion. Conversely, only 5% present with symptoms and signs of poor perfusion.[7] First-line management will thus be guided by this initial clinical assessment. Commonly, there is resolution of presenting signs and symptoms in most patients during the index admission. Despite this, the rates of readmission are significant, and 1 year mortality rates remain unacceptably high with figures ranging from 25% for acute decompensated heart failure[8] to as high as 50% for those presenting with CS.[5]

The situation in critical care is further complicated by the involvement of other organ systems. Management in the critical care setting focuses on both improving global and regional oxygen delivery and maintaining perfusion pressure, often with the use of drugs that stimulate rather than rest the myocardium.[9,10] The resolution of this apparent paradox requires that, for each patient, management should attempt to resolve the difficult balance between the best interests of the myocardium and the circulatory requirements of the other vital organs. The intensivist should target the minimum necessary oxygen delivery and arterial pressure to maintain other organ function at maximum cardiac efficiency (e.g. ensuring adequate fluid resuscitation before starting inotropic agents) so that cardiac work and the risk of myocardial ischaemia and necrosis from exuberant beta-agonist use are minimised, and the cardiologist should consider the wider circulation and other organ requirements when instituting strategies to protect the myocardium. Despite the known significant side-effect profile of inotropic agents,[11] they remain part of the recommended treatment for incipient or overt CS in international guidelines.[7,12,13] In practical terms, they should be utilised for hypotensive and hypoperfused patients for the shortest period possible.

The development of the cardio-renal syndrome in AHF also requires a careful balancing act in critical care. Congestion is thought to be the dominant problem causing increased venous pressure in the kidneys, which further compounds the injurious effects of the low cardiac output (CO) state found in AHF.[14] Fluid removal is therefore key to the improvement of both cardiac and renal function – sometimes at the expense of short-term renal deterioration due to diuretic-induced vasoconstriction, nephrotoxicity and other factors.[15] Judging the degree of acceptable renal injury is often challenging[16] and the presence of diuretic resistance and/or requirement for ultrafiltration for fluid removal portend a poor outcome.[17]

ABSTRACT

Acute heart failure is a common clinical condition associated with significant morbidity and mortality. Acute heart failure can present either de novo or following decompensation of chronic heart failure, and precipitating factors should be identified and promptly reversed. The diagnosis and management of the critically ill patient with acute heart failure can be challenging and the intensivist must balance the best interests of the myocardium with the circulatory requirements of the other vital organs. A sound knowledge of cardiovascular physiology and pharmacology is essential to allow safe and effective management of these patients to ensure the best possible outcomes.

Pulmonary hypertension is also frequently encountered in critically ill patients and is associated with high morbidity and mortality. Underlying pathophysiology is diverse, and the key to the management of critically ill patients with pulmonary hypertension is early diagnosis and prompt reversal of precipitating factors.

KEYWORDS

Acute heart failure
cardiogenic shock
echocardiography
ejection fraction
preload
contractility
afterload
vasopressors
inotropes
pulmonary hypertension

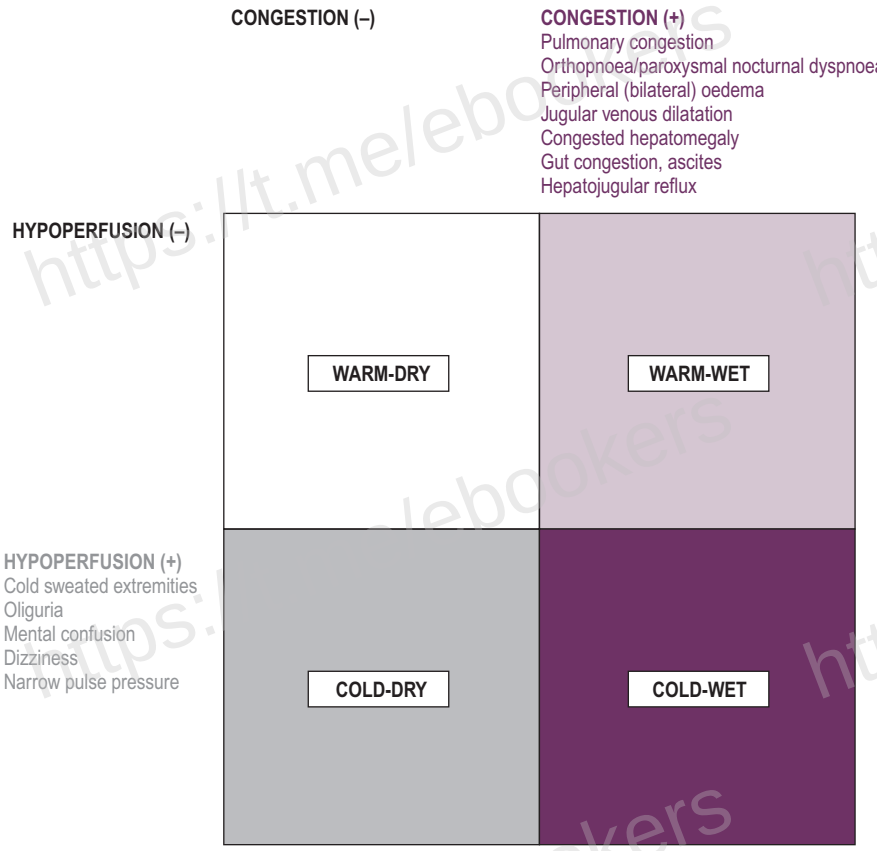


Figure 24.1 Classification of patients with acute heart failure according to their perfusion status and the presence or absence of congestion. *With permission from Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC.* Eur Heart J. *2016;37(27):2129–2200. doi:10.1093/eurheartj/ehw128.*

DIAGNOSIS OF ACUTE HEART FAILURE

The diagnosis of AHF in critically ill patients is more difficult than is commonly recognised. Although the underlying pathology in most patients with AHF in critical care will be a primary cardiac problem, other diagnoses must also be considered (Box 24.1). Early diagnosis and prompt management is paramount in this potentially life-threatening clinical situation. When a patient presents with suspected AHF, the 'CHAMP' acronym is a useful tool that can be used at the initial assessment to identify treatable causes (however, this is by no means an exhaustive list):

C: acute **C**oronary syndrome leading to AHF should prompt rapid consideration for percutaneous coronary revascularisation, irrespective of electrocardiogram (ECG) or biomarker changes.

H: **H**ypertensive emergency, commonly presenting as pulmonary oedema, mandates rapid blood

Box 24.1 Causes of acute heart failure in critical care

- Coronary artery disease/acute coronary syndrome (ACS)
- Cardiac arrhythmias – atrial fibrillation (AF)
- Infection – systemic sepsis, viral myocarditis
- Mechanical – endocarditis, pulmonary emboli, valve problems, septal defects, tamponade, high intrathoracic pressure with inadequate preload
- Drugs – beta-blockers, calcium antagonists, cytotoxic drugs (e.g. doxorubicin), alcohol, cocaine
- Hypoxaemia
- Metabolic – acidaemia, thiamine deficiency, thyrotoxicosis, hypocalcaemia, hypophosphataemia
- Myocardial contusion – blunt thoracic trauma
- Myocardial infiltration – tumour, sarcoidosis, amyloidosis
- Vasculitis
- Neuromuscular conditions – Duchenne muscular dystrophy, Friedrich ataxia, myotonic dystrophy

pressure reduction initially with vasodilators and diuretics.

A: **A**rrhythmias should be rapidly corrected via pharmacological, electrical or pacing device means as appropriate. However, restoration of normal sinus rhythm may be neither necessary nor achievable; the risks and benefits of each approach should be weighed carefully.

M: acute **M**echanical causes, most commonly occurring as a complication of ACS; for example, free wall rupture, ventricular septal defect and acute mitral regurgitation, and due to chest trauma, acute valve incompetence from endocarditis and aortic dissection, necessitate either surgical or percutaneous approaches for repair.

P: acute **P**ulmonary embolism (PE) leading to obstructive shock requires either systemic or localised catheter directed thrombolysis. Surgical options are rarely undertaken. The management of sub-massive PE, with echocardiographic and/or CT evidence of heart strain and elevated biomarkers, is more challenging with no convincing evidence of benefit with systemic thrombolysis[18]; catheter-directed thrombolysis trials are eagerly awaited for this cohort.

It is also important to critically reassess the patient referred with a diagnosis of AHF to decide whether this is indeed the primary problem. The history, examination and initial investigations with routine blood tests, ECG and chest radiograph may be compatible with this diagnosis, but many such patients are elderly with multiple co-morbidities, and deciding whether the patient is suffering from a primary myocardial pathology as opposed to a pulmonary problem or indeed systemic sepsis[19,20] can be difficult. Equally, patients believed to have a primary respiratory problem may fail to wean from ventilatory support because of a failure to realise that they have left ventricular (LV) failure with a high left atrial pressure (LAP) and incipient pulmonary oedema, causing a reduction in pulmonary compliance, an increased work of breathing and respiratory distress when ventilatory support is withdrawn.

Further investigations that can help to confirm or refute an initial diagnosis of AHF are echocardiography and the measurement of biomarkers, such as natriuretic peptides and cardiac troponins.

ECHOCARDIOGRAPHY

Echocardiography (see Chapter 27) is an essential investigation in the management of critically ill patients with AHF[7,21] and the modern intensivist should at least be able to perform a focused examination. Transthoracic echocardiography (TTE) is non-invasive and can be performed rapidly at the bedside. TTE may be technically challenging in mechanically ventilated critically ill patients but experienced operators can often obtain adequate images from at least one imaging window, and considerable improvement in image quality can be achieved using microbubble contrast techniques.[22] If transthoracic views are difficult to obtain or if better resolution is required (e.g. for the detection of small vegetation or intracardiac thrombi) then transoesophageal echocardiography (TOE) should be considered. TOE requires a higher level of expertise but will provide excellent views of the mitral and aortic valves, the left atrial appendage and the ascending aorta (dissection flaps); however, right heart structures and the apex of the LV are less well visualised.

Echocardiography will frequently establish the underlying cardiac pathology and can be used to monitor the response to treatment. It will:

1. Identify increased LV end-systolic and diastolic dimensions, indicating ventricular contractile failure; termed systolic dysfunction or heart failure with reduced ejection fraction (HFrEF).[7] HFrEF is defined as an ejection fraction (EF) less than 40%. However, the use of EF as an index of ventricular contractility can be misleading, especially in critically ill patients on vasopressors and inotropic drugs, as it is dependent on both preload and afterload. Therefore, EF should be interpreted in the context of LV loading conditions and any structural changes that lead to alterations in LV end-diastolic volume.[23] The typical pitfalls with sole reliance on EF are the failure to appreciate the presence of excess afterload (e.g. vasopressor use) and augmented preload (e.g. mitral regurgitation) which leads to an underestimate of true LV systolic function; conversely, the EF can overestimate true LV systolic function in concentric LVH.
2. Identify diastolic dysfunction as a consequence of impaired ventricular relaxation, also termed heart failure with preserved ejection fraction (HFpEF). HFpEF is defined as an EF greater than or equal to 50% often in the context of increased LV wall thickness and/or left atrial enlargement. Preserved EF in this context does not necessarily equate to an adequate CO,[24] and high-pressure preload measurements may fail to reflect the true volume preload and the potential need for extra fluid volume. Up to 50% of AHF patients present with HFpEF or mid-range EF (HFmrEF, with EF of 40% to 49%) and these patients tend to have a history of hypertension and/or present in a hypertensive state.[25] Outcomes for patients with HFpEF and HFmrEF are similarly poor to those with HFrEF, but the reasons for this reflect a combination of the absence of proven therapies for the former groups and the sequelae of their non-cardiovascular co-morbidities.[26] Therefore, the arbitrary cut-offs that define HFpEF, HFmrEF and HFrEF should not deter a thorough clinical assessment of the patient to allow an individualised approach to the

treatment of the particular AHF phenotype and management of other end-organ dysfunction.

3. Identify pericardial effusions and determine whether ventricular filling is impaired (tamponade) and whether drainage is indicated. However, ultimately, tamponade is a clinical diagnosis based on the full haemodynamic picture in the context of pericardial fluid demonstrated on the echocardiogram. Many of the diagnostic features related to alterations with respiration are affected by positive-pressure ventilation, and drainage may be appropriate even if such classic echocardiographic criteria are not present. Even small effusions may cause tamponade since it is the rate of accumulation of fluid rather than the amount of fluid that determines the degree of cardiac compromise.
4. Identify obstruction to cardiac filling from other intrathoracic space-occupying lesions that increase intrathoracic pressure, particularly in ventilated patients (pleural effusions, alveolar gas trapping in asthma).
5. Assess adequacy of volume preload of LV, particularly in the context of raised preload pressures; assess fluid responsiveness and monitor the effects of a fluid challenge.
6. Identify primary valvular heart disease (critical aortic stenosis, acute mitral regurgitation from papillary muscle rupture, acute endocarditis) when urgent surgery is indicated, and distinguish this from functional valvular regurgitation due to primary ventricular disease for which surgery could be lethal.
7. Identify septal defects, regional wall motion abnormalities and aneurysmal dilation from recent or previous myocardial infarction.
8. Identify the presence of intracardiac thrombus.
9. Identify pulmonary hypertension (PH) associated with tricuspid regurgitation when an estimate of pulmonary artery (PA) systolic pressure can be made.
10. Identify right ventricular (RV) size and function and discriminate between pressure and volume overload of the RV. The presence of RV dysfunction also can be used to diagnose and risk stratify patients presenting with suspected acute PE.

MEASUREMENT OF NATRIURETIC PEPTIDES AND CARDIAC TROPONINS

Myocardial injury and the development of AHF are common, but frequently unrecognised complications of critical illness occurring not only in patients with an overt ACS but also in other conditions, such as sepsis and massive PE.[27] Relying on blood tests alone to establish a diagnosis or to plan management is inadvisable but, when interpreted in conjunction with the wider clinical picture, natriuretic peptides and cardiac troponins appear to be sensitive markers of myocardial stress and necrosis.

NATRIURETIC PEPTIDES

B-type natriuretic peptide (BNP) and *N*-terminal pro B-type natriuretic peptide (NT-proBNP) are the most commonly measured natriuretic peptides in clinical practice. BNP was first isolated from porcine brain[28] and was originally termed 'brain natriuretic peptide'; however, the major source was subsequently shown to be from the ventricular myocardium. The main stimulus for natriuretic peptide synthesis and release is myocardial wall stress; cardiac myocytes release the prohormone, proBNP, which is subsequently cleaved into biologically active BNP and the inactive *N*-terminal fragment (NT-proBNP). Although natriuretic peptide release appears to be related to end-diastolic volume and pressure, it does not reliably differentiate between HFrEF and HFpEF or accurately predict EF or filling pressures.[29] Measurement of BNP and NT-proBNP in the emergency department may discriminate patients with heart failure from those with pulmonary or other non-cardiac causes for acute dyspnoea and has been shown to reduce rates of intensive care unit (ICU) admission, length of hospital stay and cost.[30] Routine measurement of natriuretic peptides is now recommended by several international heart failure guidelines.[7,12,13] Studies have demonstrated that, at a cut-off of 100 pg/mL, BNP has a sensitivity of 90% and a specificity greater than 70% as a test for excluding heart failure.[31] Similar data have also been reported for NT-proBNP with a cut-off value of 300 pg/mL.[32] BNP and NT-proBNP have high negative predictive values but lower positive predictive values; therefore their main utility is to rule out the diagnosis of heart failure in both the acute and non-acute setting. There are a number of cardiovascular and non-cardiovascular causes of raised natriuretic peptides including atrial fibrillation (AF), advanced age and renal failure. BNP has also been shown to be a marker of myocardial dysfunction and prognosis in severe sepsis.[33] Therefore, elevated levels of natriuretic peptides should prompt further cardiac investigation, specifically echocardiography. However, the use of natriuretic peptide levels to guide heart failure management has not been shown to improve outcomes.[34]

CARDIAC TROPONINS

Troponins are regulatory proteins that form part of the thin filament of the myocyte contractile apparatus (in addition to actin and tropomyosin); three subunits have been identified: (1) TnI, which binds actin to inhibit actin–myosin interaction; (2) TnT, which binds tropomyosin; and (3) TnC, which binds calcium ions resulting in a conformational change in the troponin–tropomyosin complex thus exposing myosin-binding sites. The cardiac isoforms, cTnI and cTnT, are specific to the heart and can be measured in the blood after myocyte necrosis with 50% release by 4 hours,

peaking at 12–24 hours and remaining elevated for up to 10 days. They are far more sensitive than traditional cardiac enzyme tests, such as creatine kinase, and have substantially changed the definition, diagnosis and management of acute myocardial infarction (AMI). Cardiac troponins may be released in conditions other than acute coronary ischaemia,[35] such as sepsis, and after chemotherapy, and in the absence of evidence of myocardial necrosis, as in AHF or major PE, where it is believed that the acute ventricular dilation causes increased membrane permeability. Raised troponin levels are also associated with increased morbidity and mortality in surgical ICU patients[36–38] and in patients presenting with acute decompensated heart failure.[39,40]

Elevated levels of cardiac troponins, BNP and NT-proBNP, may also be detected in the presence of RV dysfunction following an acute PE.[41] They can be used to risk stratify patients owing to their high negative predictive value for in-hospital death and adverse events. In haemodynamically stable patients, normal values indicate a lower risk of adverse outcome; therefore, less aggressive therapy may be warranted.[42–44]

Raised levels of these markers, indicating early myocardial stress, may have an important role in alerting the clinician to impending myocardial failure and the need to review the use of drugs that stimulate the myocardium, and to consider the introduction of a beta-blocker, particularly in the context of tachycardia.

It should be remembered that, for critically ill patients with AHF not resulting from primary myocardial infarction, if the precipitating cause is successfully treated without significant myocardial necrosis occurring the AHF will resolve, cardiac function will return to its premorbid state and the prognosis will be improved.

The remainder of this chapter addresses the assessment and principles of management of ventricular function in patients admitted to critical care with AHF.

CIRCULATORY FAILURE OR 'SHOCK'

The principal function of the heart is the generation of the energy necessary to perfuse the lungs with venous blood and to propel the oxygenated arterial blood through the systemic circulation at a rate and pressure that ensure that the fluctuating metabolic requirements of the various organs are met at rest and during exercise. This should be performed at maximum efficiency so that the work performed is not at the cost of unnecessarily high myocardial energy expenditure and the risk of myocardial ischaemia is minimised.

Failure to maintain an adequate oxygen supply to the tissues with the consequent development of anaerobic cellular metabolism defines circulatory failure or 'shock', a term that benefits from brevity but little else since it implies neither cause nor prognosis, but its use is now widespread and inescapable. Box 24.2 classifies circulatory 'shock'.

Box 24.2 Major categories of circulatory failure or 'shock'

- Cardiogenic – myocardial infarction, myocarditis, vasculitis, valve dysfunction (e.g. critical aortic stenosis, mitral regurgitation, acute endocarditis), post-cardiac-bypass surgery, drug overdose (beta-blockers, calcium antagonists)
- Hypovolaemic – haemorrhage, burns, gastrointestinal fluid loss
- Obstructive – pulmonary embolus, cardiac tamponade, tension pneumothorax
- Anaphylactic – drugs, blood transfusion, insect sting
- Septic – bacterial infection, non-infective inflammatory conditions (e.g. pancreatitis, burns, trauma)
- Neurogenic – intracranial haemorrhage, brainstem compression, spinal cord injury

In considering these causes of circulatory failure, several points require emphasis:

1. AHF resulting in CS is not a pathological diagnosis but a collective term that embraces all causes of myocardial failure. Treatment must focus on the underlying diagnosis.
2. Patients admitted to critical care may have AHF either as the primary reason for admission (e.g. following AMI), or develop it as part of multiple-organ failure triggered by an extra-cardiac cause, which is frequently the delayed or ineffective treatment of severe sepsis.
3. Pre-existing cardiac disease, usually ischaemic heart disease, is an important factor in determining the physiological response to critical illness. Several studies investigating the effect of manipulating oxygen delivery have demonstrated the poor prognosis associated with the inability of the heart to achieve a hyperdynamic response to critical illness either spontaneously or with volume loading and inotropic support.[9,10] Preoperative assessment with cardiopulmonary exercise testing is probably appropriate for all patients undergoing major surgery as a means of identifying those with poor physiological reserve so that the true risk of surgery can be identified and perioperative management planned accordingly.
4. Although hypotension is often considered to be the cardinal sign of circulatory failure, other global features (persistent tachycardia, confusion, tachypnoea, impaired peripheral perfusion, progressive metabolic acidaemia) occur earlier since the body has powerful homeostatic mechanisms that maintain pressure at the expense of flow.
5. The heart must provide its own blood supply, and if coronary blood flow does not match myocardial oxygen requirements coronary ischaemia develops, and cardiac and global circulatory failure may ensue.[45]

6. The primary problem in hypovolaemic, cardiogenic and obstructive shock is a progressive decline in CO and global oxygen delivery, which, if not corrected, leads to secondary failure of the peripheral circulation and progressive organ dysfunction. In septic, anaphylactic and neurogenic shock, however, the primary problem is the loss of control of the peripheral circulation resulting in systemic hypotension and disordered distribution of blood flow, although CO and global oxygen delivery are usually increased.[46]
7. Although a primary cause for the circulatory failure may be identified, other causes may contribute to the evolution of the final pathology. For example, in septic shock the initial and major derangement is peripheral; it is characterised by microcirculatory chaos triggered by cytokine release, white-cell activation, disruption of the coagulation cascade resulting in microthrombi that occlude the microvasculature and endothelial disruption resulting in interstitial oedema. This same process occurs in the coronary microvasculature impairing myocyte function. There is also widespread loss of fluid from the intravascular to the extravascular space, resulting in hypovolaemia. The primary peripheral circulatory failure may therefore be compounded by both cardiogenic and hypovolaemic shock.
8. '*Early*' and '*late*' shock are terms that reflect the association between the duration and severity of the circulatory derangement and prognosis. Early intervention in circulatory shock has a major impact on survival.[47,48] If treatment is delayed until organ failure is established, the underlying pathological processes are frequently irreversible.
9. Although not a true 'mixed' venous sample, the oxygen saturation of blood ($S_{cv}O_2$) taken from an internal jugular or subclavian central venous catheter has been shown to be valuable in assessing whether global oxygen delivery is adequate for global tissue oxygen consumption. A value less than 70% should prompt consideration of whether a fluid challenge or other strategy to increase global oxygen delivery is indicated. A value greater than 70% is not necessarily reassuring in patients with established hyperdynamic shock as this may reflect an inability of the tissues to extract and utilise oxygen. However, the use of $S_{cv}O_2$ to guide resuscitation in early shock states has more recently been shown not to improve outcomes; thus, assessing the trend of this surrogate marker may be a more sensible approach.[49–51]

ASSESSMENT OF VENTRICULAR FUNCTION

Making the considerable assumption that the circulation can be analysed as a constant-flow fixed-compliance system, six key measurements traditionally define ventricular performance:

- right and left atrial pressures (RAP, LAP) or ventricular preload
- mean systemic and pulmonary arterial pressures (MAP, PAP) or ventricular afterload
- heart rate (HR)
- CO

Table 24.1 illustrates typical values in normal subjects and in the common causes of circulatory failure with the calculation of the associated vascular resistances and oxygen delivery. The values quoted are merely examples that indicate the pattern of circulatory derangement produced by these pathologies: pre-existing cardiopulmonary disease and the severity of the condition will affect the precise figures obtained in individual cases and the response to vasoactive therapy.

Stroke volume (SV) is calculated from CO and HR:

$$SV = CO/HR \quad (24.1)$$

Three factors determine stroke volume: (1) preload, (2) afterload, and (3) myocardial contractility.

VENTRICULAR PRELOAD

Ventricular preload, traditionally assessed from atrial filling pressures, determines the end-diastolic ventricular volume, which, according to Starling's law of the heart, and depending on ventricular contractility, dictates the stroke work generated by each ventricle at the next cardiac contraction. The resulting stroke volume depends on the resistance or afterload that confronts the ventricle.[52]

On the general ward, the jugular venous pressure is measured from the sternal angle; however, in ICU, vascular pressures are measured from the mid-axillary line in the fifth intercostal space. From this reference point, in the supine position, the normal RAP is between 2 and 6 mm Hg, but it has also been shown to approximate to zero,[53] and the LAP is between 4 and 12 mm Hg. Relative changes in either the contractility of the two ventricles or the respective vascular resistances will change the relationship between the atrial pressures, which must then be independently assessed.

The predominant factor determining preload is venous return, which depends on the intravascular volume and venous tone, which is controlled by the autonomic nervous system, circulating catecholamine levels and local factors, particularly PO_2, PCO_2 and pH.

The systemic venous bed is the major intravascular capacitance or reservoir of the circulation with a compliance that can vary from 30 to over 300 mL/mm Hg and which provides a buffer against the effects of intravascular volume loss. It also explains the response observed in major haemorrhage and subsequent transfusion. As volume is lost, venous tone increases, preventing the large falls in atrial filling pressures and

Table 24.1 Measurements in a normal 75 kg adult and in various conditions causing circulatory 'shock'

	RAP (mm Hg)	LAP (mm Hg)	mPAP (mm Hg)	MAP (mm Hg)	HR (beats per minute)	CARDIAC OUTPUT (L/min)	SVR*	PVR*	STROKE WORK (g.m) LV	STROKE WORK (g.m) RV	VENOUS COMPLIANCE (mL/mm Hg)	CaO_2 (mL/100 mL)	DO_2 (mL/min)
Normal	5	10	15	90	70	5.0	17	1.0	78	9.7	300	20	1000
Major haemorrhage	0	3	10	80	100	3.2	25	2.2	34	4.4	40	16	512
Left ventricular failure	7	19	23	90	100	3.6	23	1.1	35	7.8	80	18	648
Cardiac tamponade	14	16	19	65	110	2.3	22	1.3	14	1.4	50	20	460
Major PE	10	6	35	70	110	2.6	23	11.2	21	8.0	40	16	416
Exacerbation of COPD	10	9	35	80	100	6.5	11	4.0	63	22.1	150	13	845
Septic shock:													
(i) pre-volume	2	7	17	49	130	4.2	11	2.4	18	6.6	350	15	630
(ii) post-volume	10	14	25	68	120	8.0	7	1.4	49	13.6	200	14	1120

Typical circulatory measurements in a normal adult and in various cardiorespiratory conditions that may cause shock. The severity of the condition and pre-existing cardiorespiratory disease will affect the precise figures obtained in individual cases.

Pressures referenced to zero at fifth intercostal space, mid-axillary line in supine patient.

SVR*/PVR* × 80 to give SI units: dyn·s·cm^{-5}.

CaO_2, Arterial oxygen content; *COPD*, Chronic obstructive pulmonary disorder; *DO_2*, global oxygen delivery; *HR*, heart rate; *LAP*, left atrial pressure; *LV*, left ventricle; *mPAP/MAP*, mean pulmonary artery/arterial pressure; *PE*, pulmonary embolism; *PVR*, pulmonary vascular resistance; *RAP*, right atrial pressure; *RV*, right ventricle; *SVR*, systemic vascular resistance.

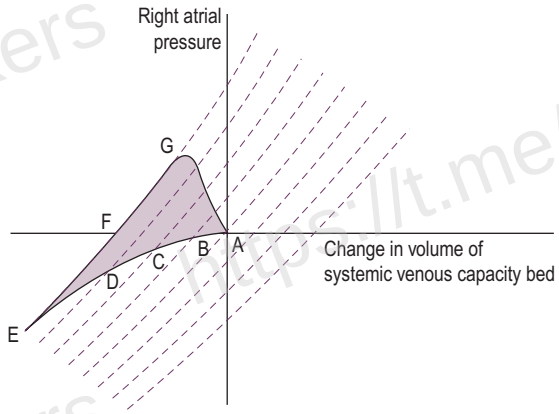


Figure 24.2 Venous compliance curves: each *dotted line* represents a line of constant venous compliance ranging from low compliance (increased tone) on the left to increased compliance (reduced tone) on the right. Line ABCDE shows the effect of progressive haemorrhage with the reduction in venous compliance limiting the fall in atrial pressure. Line EFGA shows the effect of rapid reinfusion of the same volume that was removed, but at a rate that does not allow the sympathetically mediated increase in venous tone to abate. Each dotted line represents a line of constant venous compliance ranging from minimum on the left to diminished venous tone on the right.

CO that would otherwise occur. If the equivalent volume is returned over the subsequent few hours, the RAP gradually returns to normal as the intravascular volume is restored and the reflex increase in sympathetic tone abates. However, rapid re-infusion of the same volume does not allow sufficient time for the venous and arteriolar tone to fall and may result in the LAP rising to a level that precipitates pulmonary oedema, although the intravascular volume has only been returned to the pre-haemorrhage level and LV function is normal (Fig. 24.2).

If the preload is low and either blood pressure or CO is inadequate, the priority is volume loading to restore intravascular volume and venous return.

Raised preload pressures reflect: (1) high intravascular volume, (2) impaired myocardial contractility, or (3) increased afterload.

Preload may be reduced by:

- removing volume from the circulation (diuretics, venesection, haemofiltration[54,55]) or increasing the capacity of the vascular bed with venodilator therapy (e.g. glyceryl trinitrate, morphine[56]). Caution is advised with the use of morphine in this regard as the deleterious effects on respiratory and cognitive function can offset useful vasodilation[57]
- improving contractility
- reducing afterload.[55,58]

In assessing preload, end-diastolic volume rather than pressure is relevant and when interpreting atrial

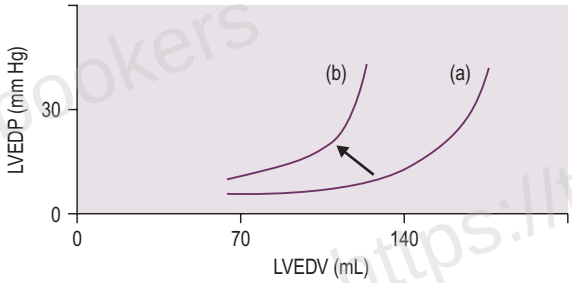


Figure 24.3 End-diastolic pressure-volume relationship (EDPVR) curves: (a) normal heart; (b) diastolic dysfunction. In the context of reduced ventricular compliance the EDPVR curve shifts upward and to the left. *LVEDP*, Left ventricular end-diastolic pressure; *LVEDV*, left ventricular end-diastolic volume. *Modified from Brandis K. The physiology viva.*

pressures as measures of preload, two points must be considered:

1. Intravascular pressure (*P*v) measurements are misleading if the intrathoracic pressure (*P*t) is raised since the true distending pressure that determines ventricular end-diastolic volume is the transmural pressure (*P*v–*P*t). This is particularly relevant if there is significant alveolar gas trapping generating intrinsic positive end-expiratory pressure (PEEP), as seen in asthma; in positive-pressure ventilation with high PEEP levels; and when an inverse inspiratory-to-expiratory time ratio is used.[59,60]
2. When the ventricle is poorly compliant, as in diastolic dysfunction, the end-diastolic pressure–volume relationship ceases to exhibit the approximately linear relationship over the normal physiological range of ventricular filling volumes (Fig. 24.3). Under these conditions, pressure will not necessarily reflect the adequacy of volume preload.

VENTRICULAR AFTERLOAD

The vascular resistance against which each ventricle works is calculated, by analogy with Ohm's law, as the pressure gradient across the vascular bed divided by the CO (Box 24.3).

Circulatory management requires a clear understanding of this relationship between pressure, flow and resistance. If ventricular work is constant, increased vascular resistances produce higher pressures but with a lower CO. A systemic dilator such as sodium nitroprusside will reduce systemic resistance and blood pressure and increase CO. Although such manipulation is attractive in increasing CO for the same cardiac work, it is important to maintain a blood pressure that ensures appropriate distribution of blood flow and a diastolic pressure sufficient to maintain coronary artery perfusion, particularly in patients

Box 24.3 Calculation of ventricular afterload and stroke work

Systemic vascular resistance (SVR) = [(MAP – RAP)/CO] × 80 dyn.s.cm^{-5}
= [(90 – 5)/5] × 80 = 1360 dyn.s.cm^{-5}
SVRI = SVR × BSA = 1360 × 1.65 = 2244 dyn.s.cm^{-5}.m^{-2}
Pulmonary vascular resistance (PVR) = [(mPAP – LAP)/CO] × 80 dyn.s.cm^{-5}
= [(15 – 10)/5] × 80 = 80 dyn.s.cm^{-5}
PVRI = PVR × BSA = 80 × 1.65 = 132 dyn.s.cm^{-5}.m^{-2}
Stroke volume (SV) = CO/HR = 72 mL
Stroke volume index (SVI) = 72/1.65 = 44 mL/m^2
Ventricular stroke work (VSW) = SV × (afterload – preload)
LVSW = SV × (MAP – LAP) × 0.0136 g.m
= 72 × (90 – 10) × 0.0136 = 78 g.m
LVSWI = 78/1.65 = 47 g.m/m^2
RVSW = SV × (mPAP – RAP) × 0.0136 g.m
= 72 × (15 – 5) × 0.0136 = 10 g.m
RVSWI = 10/1.65 = 6 g.m/m^2

Pressures are measured in mm Hg, CO in L/min. Values for resistance and stroke work are frequently indexed using the patient's BSA derived from height and weight. In calculating ventricular stroke work, 0.0136 converts to SI units of g.m. Example calculations assume a normal 75 kg individual with BSA 1.65 m^2.

BSA, Body surface area; *CO*, cardiac output; *HR*, heart rate; *LAP*, left atrial pressure; *LVSW*, left ventricular stroke work; *LVSWI*, left ventricular stroke work index; *MAP*, mean systemic pressure; *mPAP*, mean pulmonary arterial pressure; *PVR*, pulmonary vascular resistance; *PVRI*, pulmonary vascular resistance index; *RAP*, right atrial pressures; *RVSW*, right ventricular stroke work; *RVSWI*, right ventricular stroke work index; *SV*, stroke volume; *SVR*, systemic vascular resistance; *SVRI*, systemic vascular resistance index.

with known ischaemic heart disease or pre-existing hypertension.

The effects of some of the commonly used vasoactive agents are shown in Table 24.2.

VENTRICULAR CONTRACTILITY AND EFFICIENCY

The work that the ventricle performs under given loading conditions defines contractility. For each ventricle it may be expressed mathematically as the gradient and intercept of the relationship between atrial filling pressure and stroke work (Fig. 24.4). The resulting stroke volume varies with the resistance of the vascular bed into which the ventricle is ejecting. Although the RV generates a much smaller stroke work, the afterload (pulmonary vascular resistance, PVR) against which it ejects is correspondingly lower as the RV and LV stroke volumes must necessarily be the same over time.

The work generated by each ventricle with each heart beat is the ventricular stroke work and is calculated as shown in Box 24.3.

Consideration of ventricular work is important since optimum circulatory management requires that the necessary pressures and flows to maintain satisfactory organ perfusion and oxygen delivery are achieved at maximum cardiac efficiency (i.e. for the minimum ventricular work to avoid myocardial ischaemia). Furthermore, LV efficiency is the ratio of work output to energy input and may be less than 20% in patients with AHF, with over 80% of energy lost as heat.

If circulatory failure is due to impaired myocardial contractility, as defined by a 'flattened' stroke work/filling pressure equation (see Fig. 24.4), the atrial pressures will often already be raised. Provided such pressures reflect volume preload, further increases are not helpful since the ventricle becomes increasingly distended with high wall tension, as predicted by Laplace's law:

$$(24.2)\ \text{wall tension} = (\text{intraventricular pressure} \times \text{radius}) \div (\text{wall thickness} \times 2)$$

This increase in wall tension compromises myocardial blood supply, particularly epicardial to endocardial blood flow, resulting in endocardial ischaemia, further impairment of ventricular contractility and the risk of pulmonary oedema developing.

The remaining therapeutic options are:

- *Reduce afterload* using an arteriolar dilator (nitrates, alpha-blockers, phosphodiesterase-3 [PDE-3] inhibitors, angiotensin-converting enzyme [ACE] inhibitors), although this strategy is frequently limited by the resulting fall in systemic pressure.[61]
- *Increase myocardial contractility*, either by removing negatively inotropic influences (acidaemia, hyperkalaemia, drugs; e.g. beta-blockers) or by using a positive inotropic agent, which may be defined as an agent that increases the gradient of the stroke work to filling pressure relationship, resulting in a larger stroke volume for the same preload and afterload pressures. When considering the use of an inotropic agent (see Table 24.2), the adverse effects of vasoactive agents on ventricular efficiency, metabolic rate and regional distribution of flow should be considered.

Table 24.2 Circulatory effects of commonly used vasoactive drug infusions

DRUG	RECEPTORS/ MECHANISM OF ACTION	CARDIAC CONTRACTILITY	HEART RATE	BLOOD PRESSURE	CARDIAC OUTPUT	SPLANCHNIC BLOOD FLOW	SVR	PVR
Dopamine								
(<5 μg/kg/min)	DA, β1	+	0/+	0/+	+	0/+	0/+	0/+
(>5 μg/kg/min)	β1, α1, DA	++	+	+	++	0	+	+
Epinephrine	β1, β2, α1	++	++	++	+++	–	+	+
Norepinephrine	α1, β1	0/+	0	++	0/–	0/–	++	++
Vasopressin	Vasopressin receptors	0	0	++	0/–	0/–	++	–
Isoprenaline	β1, β2	+	++	+/0	0/+	0/+	–	–
Dobutamine	β1, β2, α1	++	+	–/0/+	++	0	–	–
Levosimendan	Sensitises cTnC, ATP-sensitive K^+ channels, ±PDE-3 enzyme inhibitor	++	0/+	0/–	++	0	–	–
Dopexamine	β2, DA, β1	+	+	0/–	+	+	–	–
Glyceryl Trinitrate	Via NO	0	0/+	–	+	+	–	–
Sodium Nitroprusside	Via NO	0	0/+	–	+	+	–	–
Milrinone	PDE-3 enzyme inhibitor	+	+	–	++	0/+	–	–
Nitric Oxide (iNO)	Via NO	0	0	0	0/+	0	0	–
Prostacyclin	Prostacyclin receptors	0	0/+	–	+	+	–	–

+, increase; 0, no change; –, decrease. These effects are guidelines only. The response will depend on the circulatory state of the patient when the drug is started.

ATP, Adenosine triphosphate; *DA*, dopamine; *iNO*, inhaled nitric oxide; *NO*, nitric oxide; *PDE-3*, phosphodiesterase-3; *PVR*, pulmonary vascular resistance; *SVR*, systemic vascular resistance.

HEART RATE AND RHYTHM

In cardiac failure, the stroke volume is usually constant for rates up to 100/min and thereafter falls as restriction of diastolic filling time limits end-diastolic volume. Increasing the HR from 70 to 90/min will increase CO by almost 30%. Achieving this with a chronotrope such as the beta$_1$-agonist isoprenaline increases myocardial work and oxygen consumption and also ventricular irritability. In patients with ischaemic heart disease and particularly after an AMI, atrial or atrioventricular sequential pacing (which maintains coordinated atrial contraction in heart block) improves haemodynamics without stimulating myocardial metabolism and increasing myocardial irritability.[62]

HRs above 110/min, particularly with an irregular rhythm, should be controlled by either drugs or DC cardioversion after ensuring that plasma potassium and magnesium levels have been corrected. If the rhythm is supraventricular and unstable with intermittent periods of sinus rhythm, pharmacological control is indicated using either digoxin or amiodarone. Digoxin is appropriate for AF and has a temporary positive inotropic effect.[63] However, amiodarone is suitable for all supraventricular rhythms and is more likely to restore sinus rhythm. A meta-analysis showed that, used prophylactically, it reduced the rate of arrhythmic episodes and sudden death in patients with recent myocardial infarction or congestive cardiac failure.[64] However, it is a negative inotrope and this can be significant in the patient with severe heart failure.

A fixed rate of 150/min suggests atrial flutter and should prompt careful inspection of the ECG and a trial of adenosine. A persistent sinus tachycardia unexplained by fever may be due to hypovolaemia, pain or anxiety.

ASSESSMENT OF MYOCARDIAL FUNCTION

Of the six key circulatory variables that define ventricular function, three (RAP, MAP and HR) can be assessed clinically and are routinely monitored in ICU patients. However, additional monitoring, traditionally using the PA catheter, is required to measure the

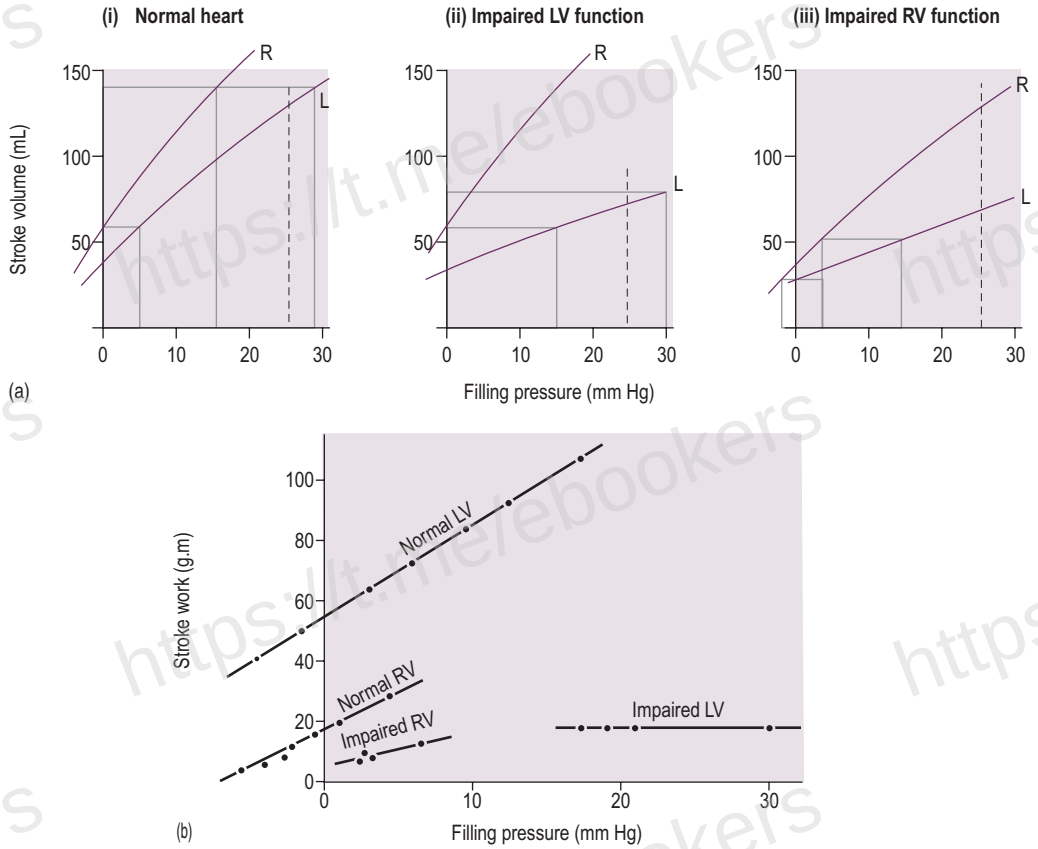


Figure 24.4 Ventricular function curves: (a) relationship between stroke volume (mL) and atrial filling pressure for left (L) and right (R) ventricles in patients with normal and impaired ventricular function; (b) relationship between stroke work (g.m.) and atrial filling pressure (in mm Hg) for the left (L) and right (R) ventricles for a normal subject and a patient with severe left and right ventricular failure.

other three variables (LAP, PAP and CO) in order to answer the following questions:

1. Is further intravascular volume indicated?
2. Is CO too low and compromising global oxygen delivery?
3. Is dilator, constrictor or inotropic therapy appropriate?

It is certainly not always necessary to use invasive monitoring. Initial management can be based on clinical assessment of intravascular volume and CO. The discipline of committing to an estimate of these key variables ensures that both the analysis of the circulation and the approach to treatment are logical. Further monitoring should be instituted if the initial management does not produce clinical improvement. Alternative, less invasive methods are available for assessing CO such as oesophageal Doppler,[65,66] lithium dilution (LiDCO),[67] transpulmonary thermodilution with pulse contour analysis,(PiCCO)[68] arterial pressure waveform analysis[69–71] and echocardiography[21,72] – techniques that can also provide data on the volume rather than pressure preload of the LV, in addition to dynamic measures of CO. Table 24.3 lists some features of the techniques available for measuring CO and whether they provide information on LV preload. Further details of circulatory monitoring and these other techniques are described in the chapter on haemodynamic monitoring (see Chapter 16). A recent international consensus produced guidelines for the diagnosis, treatment and monitoring of patients with shock.[73]

KEY POINTS WHEN ASSESSING CARDIAC FUNCTION

- Pressure is no guarantee of flow.
- Trends and changes are more important than a single observation.
- Dynamic tests (e.g. assessing stroke volume response or a change in pulse pressure or stroke volume variation to a fluid challenge) are more revealing than static tests (e.g. central venous pressure, MAP).
- Monitoring devices may be complex with many potential sources of error (e.g. 'blocked' catheters,

Table 24.3 Comparison of methods for assessing cardiac output

METHOD	INVASION/ RISK	VENTRICULAR PRELOAD ASSESSED	COMPLEXITY	MEASUREMENT ERROR
Indicator dilution				
Pulmonary thermodilution (using PA catheter)	+++	From 'wedge' pressure	++	+
Transpulmonary thermodilution (PiCCO)	++	Yes (ITBV)	+	++
Fick	+++	No	+++	+
Indocyanine green	+++	No	++	+
Lithium (LiDCO)	+	Yes	+	+
Respired gas				
Modified Fick	+	No	++	++
Inert gas rebreathing	+	Yes	+++	++
Oesophageal Doppler	+	Yes	++	++
Echocardiography	0	Yes	++	+++
Impedance cardiography	0	No	++	++
Arterial pressure waveform analysis	+	No	+	++
Clinical assessment	0	Yes	+	++

ITBV, Intrathoracic blood volume; *PA*, pulmonary artery.

failure to re-level the transducer after a change in the patient's position). Readings should always be interpreted with care and in conjunction with clinical assessment.

- Invasive monitoring has its own hazards (infection, trauma, immobility) and should be removed if no longer required.

PULMONARY ARTERY CATHETERISATION

This remains a widely used method for measurement of LAP and PAP, and assessment of CO using a pulmonary thermodilution technique. Although generally viewed as the 'gold standard' for determining CO, the error is at least 10%, even with fastidious attention to technical detail.[74]

Inflation of the balloon at the end of the catheter provides a PA occlusion pressure (or pulmonary capillary wedge pressure), which reflects LAP provided there are no significant pulmonary vascular bed abnormalities, as occur in chronic obstructive pulmonary disease and long-standing mitral valve disease. Despite obtaining a good-quality wedge tracing, the measurement must be interpreted with caution since increased intrathoracic pressure and diastolic dysfunction make this pressure measurement an unreliable index of true LV volume preload.

The focus on 'goal-directed therapy' led to the widespread use of PA catheters, but their indiscriminate use was challenged by a multicentre case-controlled study, which suggested that patients managed with a PA catheter had a poorer outcome than those managed without such intervention.[75,76] This study probably reflected the enthusiasm for inappropriate goal-directed therapy prevalent at that time, poor training in the use of the catheter and an inability of clinicians to respond appropriately to the data obtained.[77] More recent evidence suggests neither harm nor benefit with the use of a PA catheter and a risk–benefit assessment should be made on an individual patient basis prior to its use.[76,78]

Box 24.4 lists the indications for PA catheterisation in heart failure.

ASSESSMENT OF INTRAVASCULAR VOLUME STATUS

CLINICAL

This is conventionally based on measurement of the right atrial filling pressure and the assumption that a normal relationship exists between the atrial filling pressures, which is not necessarily valid in the critically ill patient particularly in CS. Although values less than 12 mm Hg suggest hypovolaemia, higher levels are more difficult to interpret, particularly in the ventilated patient. The RAP should therefore be interpreted carefully and in light of other clinical evidence. However, such static tests for assessing the intravascular volume are less valuable than dynamic tests, such

Box 24.4 Indications for pulmonary arterial catheterisation in patients with heart failure

- Failure to improve with initial circulatory management and uncertainty about adequacy of cardiac output and relationship between atrial filling pressures
- Assessment of left ventricular preload when the relationship between right and left atrial pressures is uncertain owing to recent myocardial infarction, valvular abnormalities or high pulmonary vascular resistance. A low wedge pressure indicates that further volume is indicated, but a high value does not necessarily exclude the need for further volume
- Measurement of cardiac output by thermodilution to direct appropriate choice of vasoactive drug and to manipulate therapy, particularly when high doses are being used
- Need to monitor pulmonary arterial pressures and assess right ventricular function

as the fluid challenge[79,80] and the effect of positive-pressure ventilation,[81–84] which assess the circulatory response to an intervention.

Intravascular volume depletion is suggested if hypotension is precipitated by sedation, analgesia and postural change. In the patient receiving positive-pressure ventilation, respiratory fluctuation in the arterial pressure tracing also suggests relative hypovolaemia. This is confirmed if brief disconnection from the ventilator causes the blood pressure to rise and venous pressure to fall; the measurement off the ventilator more accurately reflects the ventricular end-diastolic transmural pressure. This manoeuvre is relatively contraindicated in patients with severe respiratory failure as loss of PEEP may cause widespread alveolar collapse.

FLUID CHALLENGE

If hypovolaemia is suspected, a fluid challenge should be administered and the impact on blood pressure, flow and preload observed. In the volume-depleted patient, blood pressure and flow will increase with only a small, transient increase in filling pressure. While pulmonary gas exchange and overall fluid balance remain satisfactory, there is less anxiety about giving further fluid. Sufficient volume will have been given when either the target pressures are achieved and the evidence of poor peripheral perfusion and organ dysfunction has resolved, or when there is a sustained rise in filling pressures to a level above which there is a risk of pulmonary oedema developing. An objective assessment of the effect of such a fluid challenge can also be made by looking for a ≥10% rise in stroke volume. Caution is warranted with this approach; higher rates of critical care admission, requirement for organ support and increased mortality have been shown with as little as 1 L fluid administration administered early in the course of hospital admission for AHF, compared to diuretic treatment alone.[85]

Deciding the appropriate fluid volume to give in sepsis can be difficult and frequently represents a balance between giving sufficient volume to prevent the use of excessive doses of constricting inotropes and giving excessive amounts with consequent tissue oedema and deterioration in pulmonary gas exchange.

If there is concern about administering a fluid challenge, an assessment of fluid responsiveness in critically ill patients can be made using a passive leg raising test[86,87]; this results in a 'reversible' fluid challenge, as ~300 mL venous blood from the lower body is diverted towards the right heart.

VALSALVA MANOEUVRE

The effect of changes in intrathoracic pressure can be used to assess intrathoracic blood volume and provide an estimate of true LV preload. Fig. 24.5 shows the classic Valsalva response in a normal subject and in a patient with a high intrathoracic blood volume. If a normal-type trace is observed on the monitor, further volume is indicated, whereas a square-wave response indicates an adequate LV volume preload.[88] This response can be quantified by calculating the ratio of the pulse pressure during phase 2 of the manoeuvre to the baseline value. This correlates with measurements of pulmonary capillary wedge pressure[89] and can be applied at the bedside in sedated, ventilated patients.[90] However, if the patient is breathing spontaneously, this test is difficult both to perform and to interpret.

ECHOCARDIOGRAPHY

Echocardiography is useful in identifying inadequate volume preload and the need for further fluid resuscitation, particularly when the preload pressures are high, as may occur with diastolic dysfunction. Performing serial studies to assess the response to therapy (fluid challenge, starting vasoactive therapy, changing ventilator settings) can be particularly valuable.

MANAGEMENT OF CARDIAC FUNCTION IN THE CRITICALLY ILL

Circulatory management should be regularly reviewed in the critically ill patient. Following initial assessment and with knowledge of the primary diagnosis, the need for extra monitoring should be decided, provisional targets should be set for fluid balance, central venous saturation ($S_{cv}O2$), mean and diastolic arterial pressures and a management plan agreed on how to achieve these goals. Generally, a MAP of 60–65 mm Hg with a diastolic pressure greater than 50 mm Hg is acceptable, but adequate cerebral, coronary, splanchnic and renal perfusion may require higher pressures,

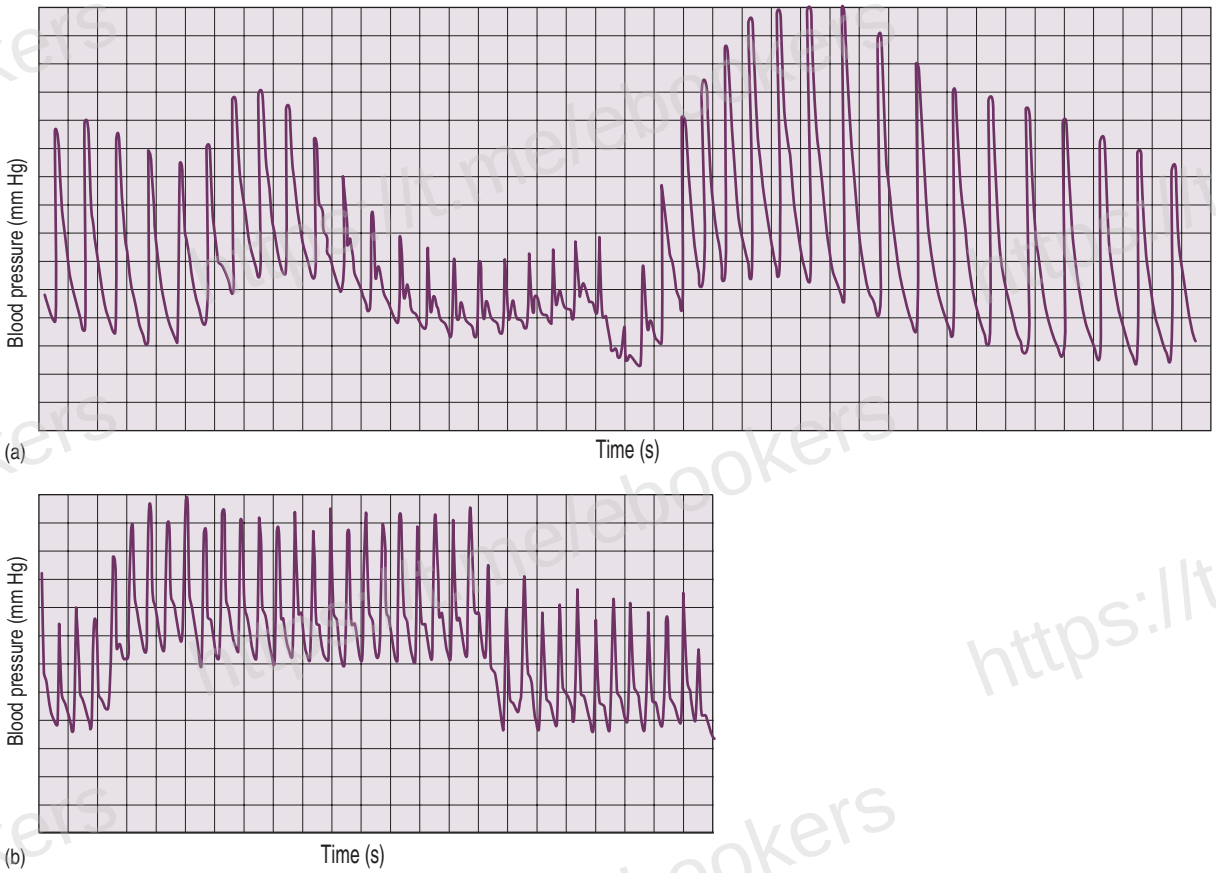


Figure 24.5 Valsalva traces (arterial waveforms): the Valsalva manoeuvre is performed by applying a pressure of at least 30 mm Hg (judged from an RA trace) for 12–15 seconds. (a) Normal pulse pressure response. (b) Square-wave pulse pressure response.

particularly in the elderly patient with pre-existing hypertension or widespread atheromatous disease.

CORRECTION OF METABOLIC FACTORS

The following metabolic factors should be promptly corrected:

- *hypoxaemia:* PO_2 <8 kPa
- *acidaemia:* pH <7.35
- *hyperkalaemia:* K^+ >5.5 mmol/L
- *hypomagnesaemia:* Mg^{2+} <0.9 mmol/L
- *hypocalcaemia:* ionised Ca^{2+} <1.0 mmol/L
- *hypophosphataemia:* PO_4^- <0.8 mmol/L
- *anaemia:* Hb <80 g/L
- *thiamine (vitamin B1) deficiency:* malnutrition, chronic alcohol use, diuretic or digoxin treatment.

A pH <7.35 and a negative base excess should be promptly corrected since myocardial contractility may be significantly reduced in the presence of a metabolic acidaemia. The suggestion that sodium bicarbonate should not be used as it produces a damaging paradoxical intracellular acidosis is misleading since the experiments demonstrating this effect were performed in vitro using non-physiological solutions, within a closed system that allowed no correction for any rise in carbon dioxide concentration and in which the sodium bicarbonate was given by bolus rather than by slow infusion.[91] The case for using bicarbonate to correct a metabolic acidaemia in the clinical setting has been recognised[92] and is supported by studies looking at the use of bicarbonate rather than lactate as the buffer solution in haemofiltration.[93] Fig. 24.6 shows the effect of correcting a severe metabolic acidaemia on CO by changing from lactate to bicarbonate haemofiltration.

Although a prospective, randomised study demonstrated an improved survival for critically patients if haemoglobin concentration was maintained at 70–90 g/L rather than at 100–120 g/L, this did not apply to the elderly and those with co-existing cardiovascular disease in whom the haemoglobin level should probably be maintained greater than 80 g/L.[94,95]

Patients with poor dietary thiamine (vitamin B1) intake, chronic alcohol use and those on chronic

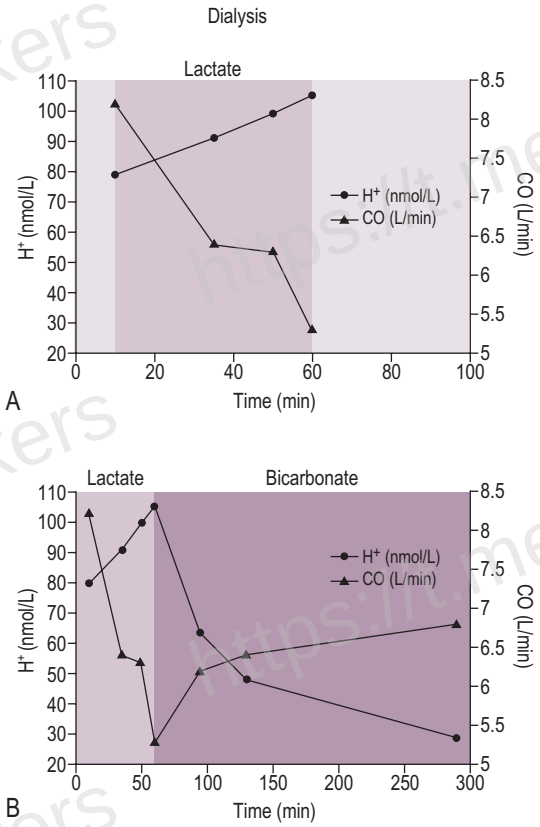


Figure 24.6 Effect of dialysis: (a) rising hydrogen ions and falling CO with lactate buffer dialysis; (b) change to bicarbonate buffer – there is falling hydrogen ion concentration and a rising CO.

furosemide or digoxin therapy are at risk of thiamine deficiency, resulting in impaired myocardial function. Oral thiamine improves LV function in these patients.[96,97]

SELECTION OF APPROPRIATE VASOACTIVE AGENTS

The choice of vasoactive agent when treating AHF represents a balance between the global circulatory requirements and those of a stressed myocardium. The properties of commonly used agents are shown in Table 24.2.

The impact of these drugs in individual patients will be influenced by the baseline state of the circulation; that is, if either intensely constricted or dilated, the same drug will potentially produce different effects on pressure, flow and its distribution. The initial choice of vasoactive agent will depend on the MAP, CO and derived systemic vascular resistance (SVR). For example:

- *CO and MAP are both low with a high SVR:* an inotropic and dilating (inodilator) effect is required and dobutamine or milrinone would be appropriate. Levosimendan would also be a suitable choice in this setting. If CO rises but MAP falls, as may happen with dobutamine, milrinone and levosimendan, and a more powerful inotropic effect is required, epinephrine may be appropriate. However, increasing doses of epinephrine risk myocardial ischaemia, ventricular irritability, splanchnic ischaemia and the development of hyperlactataemia.[98] Consequently, it may be more appropriate to use norepinephrine to maintain MAP when inodilating drugs are being administered.
- *MAP and SVR are low with high CO:* this is frequently seen in sepsis: arteriolar constriction with norepinephrine is indicated after adequate volume resuscitation.
- *MAP is at or above target but CO is low with raised SVR:* a dilating agent (e.g. glyceryl trinitrate) or an inodilator is appropriate.

When PVR and RAP are acutely raised, a pulmonary vasodilator to offload the RV and maintain CO is required but hypotension may result from concomitant systemic arteriolar dilation and hypoxaemia can develop owing to increased ventilation–perfusion mismatch.

Dopamine has been widely used in the erroneous belief that it selectively improves renal blood flow.[99] A recent randomised controlled trial demonstrated a greater number of adverse events with the use of dopamine compared with norepinephrine in patients with shock. Moreover, in a predefined subgroup of patients with CS mortality was higher in patients treated with dopamine.[100]

Dopexamine is used to improve splanchnic blood flow but, despite reported benefits when used with volume loading in perioperative patients,[101,102] there is little evidence of outcome benefit in established shock.

Patients with CHF and those receiving long-term beta-agonist infusion often develop tolerance with reduced catecholamine receptor responsiveness, resulting in less effect in raising intracellular cyclic adenosine monophosphate (cAMP) levels and increasing myocardial contractility. PDE-3 inhibitors (milrinone, enoximone) offer an alternative strategy. Milrinone competitively inhibits the PDE-3 isoenzyme, responsible for the breakdown of cAMP, thereby increasing intracellular cAMP levels and improving myocardial contractility independent of beta-receptor stimulation. There is also improvement in ventricular diastolic relaxation and a reduction in PVR. However, these agents are powerful vasodilators and hypotension frequently limits their use or requires a norepinephrine infusion.

Levosimendan is an intracellular calcium sensitiser and thus bypasses the receptors through which other inotropic agents act. It binds to and sensitises cTnC to calcium without raising intracellular calcium,

thus improving cardiac performance and contractility during systole without impairing ventricular relaxation during diastole. Administered as a continuous infusion (0.1 µg/kg per minute) over 24 hours, it has a long-lasting, pharmacologically active metabolite, which results in any improvement in myocardial contractility being sustained for several days.[103,104] Levosimendan also causes vasodilation of vascular smooth muscle due to its action on adenosine triphosphate (ATP)-sensitive potassium channels found in the myocardium, peripheral blood vessels and coronary arteries. Consequently, dose-dependent hypotension may occur, although the reduction in preload and afterload and improved coronary blood flow will be beneficial to the failing heart. Furthermore, levosimendan may also have inhibitory effects on PDE-3.[105] In the patient with severe heart failure already on inotropic drugs, treatment should start with a low-dose infusion (0.05 µg/kg per minute) and no loading dose should be given. Levosimendan may be used concomitantly with beta-blockers owing to its site of action, which does not involve beta-adrenergic receptors.[106] Its role in severe acute decompensated heart failure and CS following AMI appears promising.[106–109] However, levosimendan remains unlicensed in several countries worldwide, and the available evidence to date does not consistently confirm a significant mortality benefit.[110–113]

BETA-BLOCKADE

Several studies have demonstrated a reduction in mortality and number of hospitalisations in patients with CHF treated with beta-blockers.[114–116] Furthermore, large studies have demonstrated their benefit early after AMI.[117] Conversely, there is conflicting evidence regarding the perioperative role of beta-blockers, and their use should be limited to high-risk patients in order to minimise adverse events.[118]

Although beta-blockers are usually commenced in stable patients with heart failure, there is good evidence that they may be safely initiated in patients recovering from recent decompensation or in fact continued at a reduced dose during an episode of decompensation.[119,120]

If tachycardia develops or persists during an episode of acute decompensated heart failure, it may be appropriate to consider a trial of a beta-blocker but it is advisable to start with a small dose of a short-acting drug, such as metoprolol or a low-dose esmolol infusion. If this beta-blocker 'challenge' is successful then the beneficial effects will include an increased time for ventricular filling, improved coronary perfusion and reduced myocardial oxygen demand.

MECHANICAL SUPPORT FOR THE HEART

Continuous positive airway pressure (CPAP), non-invasive intermittent positive pressure ventilation (NIPPV) and invasive mechanical ventilation are commonly used to provide support for patients with acute cardiogenic pulmonary oedema. A systematic review concluded that non-invasive ventilation reduced hospital mortality, endotracheal intubation and ICU length of stay.[121] However, a large, randomised controlled trial did not show a mortality benefit with the use of non-invasive ventilation, although the study did show an improvement in symptoms and physiological and metabolic parameters.[122] The benefits result from improved oxygenation and reducing or eliminating the work of breathing, which may account for up to 30% of oxygen consumption.[123] This reduction in oxygen consumption reduces LV workload and alleviates myocardial ischaemia. When instituting invasive mechanical ventilation the clinician must be prepared to give volume and even inotropic or vasopressor support as the sedation and other anaesthetic agents given for intubation will reduce endogenous levels of catecholamines, producing arteriolar and venular dilation and potentially catastrophic hypotension.

Intra-aortic balloon pump (IABP) counterpulsation is physiologically attractive as it reduces afterload, improves coronary and peripheral circulatory perfusion and decreases cardiac work. This results in a more efficient cardiac performance with improvement in both CO and myocardial oxygenation.[124] A common indication for IABP insertion is CS complicating AMI; however, a recent randomised controlled trial has questioned the benefit of the IABP in this setting; the study demonstrated that there was no significant difference in 30-day mortality in the IABP and the no IABP groups.[125] Other indications for IABP support include weaning from cardiopulmonary bypass, high-risk percutaneous coronary intervention (PCI), although current evidence does not support the routine insertion of IABP in this setting,[126] and as a 'bridging therapy' to cardiac transplantation. The main absolute contraindications to IABP insertion are moderate-to-severe aortic regurgitation and aortic dissection, and complications include limb and bowel ischaemia, bleeding and infection.

Extracorporeal membrane oxygenation (ECMO) is a technology that has developed from the cardiopulmonary bypass circuit and in a venoarterial (VA) configuration can provide short-term circulatory support in refractory CS. In this circumstance, VA-ECMO will act as bridge to myocardial recovery, to a ventricular assist device (VAD) or to heart transplantation. VA-ECMO is also used peri-operatively in cardiac surgery and during cardiopulmonary arrest.[127]

VADs are mechanical systems that provide circulatory support for patients with severe AHF and CHF. Support can be provided for the LV, the RV or both. VADs can temporarily take over myocardial function and are usually indicated only if all other treatment options have been explored and an improvement in

myocardial function can be anticipated.[128] VADs are currently used as a 'bridge' to myocardial recovery in AHF following cardiac surgery or recent myocardial infarction, or when there is a realistic prospect of heart transplantation. However, with recent advances in VAD technology a role appears to be emerging for these devices as a 'destination therapy' in patients with end-stage CHF who are not eligible for heart transplantation.[129] Complications associated with VADs can be significant and include device failure, bleeding, infection, thromboembolism and stroke.

CARDIOGENIC SHOCK AFTER ACUTE MYOCARDIAL INFARCTION

The incidence of CS has remained relatively unchanged over recent years, occurring in 5%–10% of patients following AMI, and despite aggressive intervention strategies the mortality rate remains significant in patients in whom shock is present (~50%).[4,130–132] In patients admitted to critical care with CS, the following additional points should be noted:

- The effects of management on myocardial oxygenation must be considered as well as global circulatory targets.
- Although the patient may be ventilated on ICU, therapies demonstrated to improve myocardial salvage must not be overlooked or delayed. Emphasis should be placed on early revascularisation therapy, and patients should undergo urgent coronary angiography to allow PCI if appropriate. The benefits of aspirin are significant if given in the early hours after infarction; if necessary the aspirin can be given rectally. A beta-blocker[117] and an ACE inhibitor[133] should be started as soon as clinically possible but bradycardia, heart block, hypotension and impairment of renal function may cause delay. Once stable, patients with LV dysfunction and heart failure should also be started on an aldosterone receptor antagonist, such as spironolactone[134] or eplerenone.[135,136]
- In patients admitted following an out-of-hospital cardiorespiratory arrest, targeted temperature management has been shown to be beneficial,[137–139] but if planned this should not prevent other interventions, such as primary PCI being performed if appropriate.
- It is important to recognise:
  - RV infarction (ST elevation in lead V_3R and/ or V_4R in patients with inferior ST segment elevation MI (STEMI) is highly specific for RV ischaemia due to a proximal right coronary artery occlusion)[140] since further monitoring may be necessary to ensure appropriate volume loading and to direct therapy to offload the RV.[141]
  - the development of either a ventricular septal defect or mitral regurgitation from papillary rupture as urgent surgery may be indicated.[142]

PULMONARY HYPERTENSION

PH is a frequently encountered pathophysiological disorder in ICU and is associated with high mortality.[143] Box 24.5 summarises the most recent clinical classification of PH.[144,145] The classification splits PH into five diagnostic groups according to underlying cause and therefore likely to have similar treatment strategies. An important distinction to note is that group 1 PH or pulmonary arterial hypertension (PAH), previously known as primary PH, includes a set of disorders where PH is the primary problem. In contrast, all other classification groups are due to conditions that lead to PH as a result of cardiac dysfunction, abnormalities in the lung parenchyma, chest wall abnormalities, or mechanical obstruction of the pulmonary vasculature.

PH is defined as a mean pulmonary arterial pressure (mPAP) greater than or equal to 25 mm Hg on right heart catheterisation while the patient is at rest.[146] In the critical care setting, common pathological conditions leading to PH include severe respiratory failure,[147] acute respiratory distress syndrome (ARDS),[148] left-sided heart failure leading to increased LAP,[149] massive PE,[150] mechanical ventilation,[151] and following cardiac and thoracic surgery.[152] The presence of PH in many of these conditions is associated with increased mortality.[148–150,152] In addition, several factors including sepsis, cardiac arrhythmias, and treatment failure can precipitate acute exacerbations of chronic PAH leading to ICU admissions. Sepsis in these patients is associated with poor outcome.[153]

Several disorders lead to PH in ICU, yet there are no consensus or international guidelines that exist to assist with the management of these patients. Detailed reviews addressing PH[154–156] and PAH[156,157] in the critical care setting fail to make authoritative recommendations, mainly as a result of paucity of data. Therefore management of PH relies on extrapolated data from animal studies, surgical patients, local expertise and biological plausibility of interventions.

PATHOPHYSIOLOGY

An understanding of the pathophysiological changes seen in patients with PH is essential to understand the available treatment strategies and the likelihood of their success. Invariably the most crucial manifestation of PH is RV dysfunction. Under normal conditions RV outflow is to a high-compliance, low-pressure and low-resistance system. The thin-walled RV is highly sensitive to small increases in the PVR leading to ventricular dilation, an increase in end-systolic volume, and reduced RV ejection fraction and pulmonary blood flow. This in turn results in a reduction in CO. In the initial stages the RV responds by enhancing contractility in order to maintain CO.[158] Further increases in RV afterload overwhelm these compensatory mechanisms

Box 24.5 Clinical classification of pulmonary hypertension

1. Pulmonary arterial hypertension (PAH)
   - 1.1 Idiopathic
   - 1.2 Familial
     - 1.2.1 BMPR2
     - 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
     - 1.2.3 Unknown
   - 1.3 Drug and toxin induced
   - 1.4 Associated with:
     - 1.4.1 Connective tissue diseases
     - 1.4.2 HIV infection
     - 1.4.3 Portal hypertension
     - 1.4.4 Congenital heart diseases
     - 1.4.5 Schistosomiasis
     - 1.4.6 Chronic haemolytic anaemia
   - 1.5 Persistent pulmonary hypertension of the newborn

1′. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

2. Pulmonary hypertension due to left heart disease
   - 2.1 Systolic dysfunction
   - 2.2 Diastolic dysfunction
   - 2.3 Valvular disease

3. Pulmonary hypertension due to lung diseases and/or hypoxia
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   - 3.4 Sleep-disordered breathing
   - 3.5 Alveolar hypoventilation disorders
   - 3.6 Chronic exposure to high altitude
   - 3.7 Developmental abnormalities

4. Chronic thromboembolic pulmonary hypertension

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
   - 5.1 Haematological disorders: myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK1, Activin receptor-like kinase 1 gene; *BMPR2*, bone morphogenetic protein receptor type 2; *HIV*, human immunodeficiency virus; *PAH*, pulmonary arterial hypertension.

Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D34-D41. Kiely DG, Elliot CA, Sabroe I, Condliffe R. Pulmonary hypertension: diagnosis and management. *BMJ*. 2013;346:f2028.

resulting in reduced CO and systemic circulatory failure. The intimate anatomical relationship of the two ventricles sharing a septum and both being bound by tight pericardial fibres leads to interdependence. In the setting of increased afterload the dilated RV loses its normal shape and pushes the septum towards the LV, thereby compromising LV filling and output.[159,160] RV dilation can also lead to tricuspid regurgitation further lowering CO. In addition to these anatomical considerations, a fall in systemic blood pressure can compromise RV coronary perfusion, thereby leading to ischaemia and further RV dysfunction. Unlike the LV, under normal conditions coronary perfusion to the RV is maintained throughout the cardiac cycle. As RV pressure increases there is a decrease in the perfusion pressure gradient between the aorta and the RV during systole, thereby limiting coronary perfusion mainly to diastole.[161]

ACUTE COR PULMONALE

Acute cor pulmonale (ACP) is caused by acute pressure overload of the RV due to an acute increase in PVR and thus RV afterload. The RV dilates acutely, RV systolic function is impaired and the interventricular septum becomes dyskinetic and displays paradoxical motion.[162,163] ACP is commonly seen in critically ill patients with severe ARDS and following massive PE. The incidence of ACP in severe ARDS was historically reported to be 50%–60%; however this has reduced to 20%–30% following the widespread adoption of lung protective ventilation strategies.[164] The detection of ACP is independently associated with increased mortality in patients with severe ARDS and will ultimately result in acute circulatory failure if it is not managed aggressively.

CLINICAL ASPECTS

Key to the management of patients with PH is diagnosis of the underlying cause and, if feasible, treatment should focus on prompt reversal of precipitating factors. Principles of management include optimising fluid balance (RV preload), reducing RV afterload, maintaining perfusion pressures and improving RV contractility.[154,164] The prone position, as a means to offload the RV, can also be considered.[165] Like most other disorders requiring critical care, the maxim of good ICU care is also applicable to these patients. The discussion that follows looks at treatment strategies specific to PH and the associated RV dysfunction.

MONITORING

The gold standard for diagnosing and monitoring PH in the ICU remains the PA catheter. Invasiveness of the procedure and a lack of evidence supporting a benefit in the general ICU population have meant that the use of the PA catheter has declined in the critical

care setting.[78,166] Furthermore, the use of PA catheters specifically in PH has not been studied. Echocardiography is increasingly being used in ICU and can provide clinicians with much of the information needed to manage such patients. It has the added benefit of being non-invasive and provides information on RV and LV structure and function, pericardial effusions and tricuspid incompetence.[155] However, a recent systematic review found only modest correlation between pulmonary pressures determined by echocardiography and those measured by right heart catheterisation.[167] The virtues of echocardiography in PH in ICU populations have not been studied, and ultimately local expertise is likely to dictate local practice.

MANAGEMENT

The need for adequate oxygenation applies to most critically ill patients but assumes greater importance in PH. RV myocardial oxygen demands are increased in severe PH and hypoxia may increase PVR by precipitating hypoxic pulmonary vasoconstriction. In many cases, mechanical ventilation may be unavoidable; however, it comes at a cost. Positive-pressure ventilation has adverse effects on RV afterload and along with administration of sedatives can further compromise CO. Ventilatory strategies should focus on maintaining adequate oxygenation whilst avoiding high plateau pressures.

Fluid resuscitation of patients with PH is extremely challenging. The RV predominantly relies on adequate filling to maintain CO. Conversely, RV dilation as a consequence of volume overload can lead to impaired RV function and impaired LV filling, due to ventricular interdependence, which results in a reduction in systemic CO.[168] In patients with evidence of RV volume overload and septal bowing, aggressive fluid removal, with diuretics[54] or renal replacement therapy, should be considered as it may improve CO as a consequence of improved LV filling.

The maintenance of sinus rhythm in these patients will improve RV end-diastolic volume and CO. Where possible, cardioversion should be performed in patients with tachyarrhythmias. In those patients where this cannot be achieved, the focus should be on rate control to optimise ventricular filling time.

Vasopressors and inotropes

The goal of using vasoactive drugs in patients with RV dysfunction secondary to PH is to maintain an adequate CO whilst avoiding increases in PVR and cardiac arrhythmias. In the face of systemic hypotension norepinephrine, a powerful systemic vasoconstrictor, should be considered in these patients. Improving systemic blood pressure has the additional benefit of improving coronary perfusion. However, norepinephrine also causes pulmonary vasoconstriction. In an animal model of acute PH, administration of norepinephrine restored systemic blood pressure and increased PAP.[169] Overall, the effect was to improve both RV contractility and CO. In the same study, animals treated with dobutamine showed a greater improvement in RV contractility in comparison with norepinephrine. The dobutamine-treated animals also showed a greater reduction in mPAP. In clinical studies, dobutamine has been shown to improve RV performance in ischaemic failure.[170] Evidence from these studies suggest that low-dose dobutamine may be useful in acute PH complicated by RV failure. Increases in myocardial oxygen demand and tachyarrhythmias may preclude dobutamine use in all patients with PH. Vasopressin can also be considered as an alternative to norepinephrine; in addition to powerful systemic vasoconstriction, it causes pulmonary vasodilation, which may be beneficial in PH.[171]

In another animal study the use of levosimendan and dobutamine in PH was compared. Improvement in RV contractility was similar after administration of both drugs; of the two agents, levosimendan was superior at reducing PVR.[172] Small observational studies in humans have shown a similar trend of improved RV contractility and reduced PVR following the administration of levosimendan in patients with CS.[173] In theory, levosimendan appears to be a promising alternative to dobutamine with the additional benefit of PVR reduction without increasing oxygen consumption.

PDE-3 inhibitors, such as milrinone, have inotropic and vasodilating properties. They can improve CO by reducing PVR and increasing RV contractility. PDE-3 inhibitors have been shown to successfully reduce PVR and improve RV contractility in animal models of PH[174,175] and in patients undergoing cardiac surgery.[176,177] Treatment with milrinone may require additional vasopressor support, given its propensity for systemic vasodilation. Inhaled milrinone has shown promise as a therapy to selectively reduce PVR in heart transplant patients[178] and in an animal model of PH,[179] but its use is currently experimental.[180,181]

Pulmonary vasodilators

Several pulmonary vasodilators are available and the choice of therapy and route of administration usually depend on the side effects of the drug and the condition of the patient. Intravenous agents can lead to systemic haemodynamic instability, and inhaled vasodilators may be more favourable in the ICU setting.[155]

Inhaled nitric oxide (iNO) increases production of cyclic guanosine monophosphate (cGMP) and is a potent pulmonary vasodilator. It results in the reversal of hypoxic pulmonary vasoconstriction, reduction in PVR and improved oxygenation. iNO therapy has been shown to reduce PVR and improve RV stroke work in postoperative cardiothoracic patients with PH.[182,183] When used in the context of severe ARDS and hypoxia refractory to maximal medical treatment, iNO commonly provides 48 hours improvement in

oxygenation, but fails to reduce the length of mechanical ventilation or improve mortality.[184,185] Methaemoglobinaemia and nitrogen dioxide (NO_2) production are recognised adverse effects, and rebound PH may also occur after abrupt cessation of iNO.

Inhaled and intravenous prostacyclins are also used as vasodilators in PH. Inhaled prostacyclin (epoprostenol) use is associated with significant reduction in mPAP and improvement in ICU patients with PH.[186] However, there are considerable associated side effects in this population. Inhaled iloprost, a synthetic prostacyclin analogue, has been shown to reduce mPAP and improve RV function in PH post-cardiopulmonary bypass. There was also a significant reduction in PVR to SVR ratio.[187] In a small single-centre study in post-heart-and-lung-transplant patients, inhaled prostacyclin showed similar efficacy to iNO in managing PH.[188]

Phosphodiesterase-5 (PDE-5) inhibitors stop the degradation of cGMP leading to vasodilation. In patients with chronic PAH, oral sildenafil, a selective PDE-5 inhibitor, has been shown to reduce mPAP[189] and improve CO by reducing PVR.[190] Sildenafil has also been used as a bridge to avoid rebound hypotension following iNO withdrawal in post-cardiac-surgery patients.[191] Following haemodynamic stabilisation, there may be a role for sildenafil in reducing PVR in the critical care setting.

Mechanical devices

In patients where all other treatment options have been exhausted, lung transplantation may be the only viable option. Case studies have reported the use of RV assist devices in patients with PH. Extracorporeal life support has also been described as a bridge to transplantation. VA-ECMO will help to unload the RV, reduce RV afterload and improve perfusion of vital organs and thus may provide temporary support in the acute situation.[154,164]

SUMMARY

PH and consequent RV dysfunction are frequently encountered in the ICU with a high associated mortality rate. Prompt identification of the underlying cause and its treatment should be the main focus of management. There is very little evidence for the use of specific treatments in the ICU setting and a 'one-size fits all' approach is unlikely to work given the varied aetiology. A few general principles, such as optimising fluid status, optimising HR and rhythm, avoiding high-pressure ventilation, maintaining coronary perfusion by optimising systemic pressure, inotropic support for RV dysfunction and inhaled pulmonary vasodilation may be applied where appropriate. The choice of individual therapies should be guided by an understanding of their mechanism of action and the expected physiological response in an individual patient. The response should be monitored closely to avoid adverse events and to optimise therapy.

KEY REFERENCES

1. Writing Group Members, Mozaffarian D, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2016 Update: a report from the american Heart Association. *Circulation*. 2016;133(4):e38–e360.
7. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37(27):2129–2200.
9. Hayes MA, Timmins AC, Yau EH, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med*. 1994;330(24):1717–1722.
10. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. *N Engl J Med*. 1995;333(16):1025–1032.
11. Teerlink JR, Metra M, Zaca V, et al. Agents with inotropic properties for the management of acute heart failure syndromes. Traditional agents and beyond. *Heart Fail Rev*. 2009;14(4):243–253.
29. Omland T. Advances in congestive heart failure management in the intensive care unit: B-type natriuretic peptides in evaluation of acute heart failure. *Crit Care Med*. 2008;36(1 suppl):S17–S27.
37. Writing Committee for the VISION Study Investigators, Devereaux PJ, Biccard BM, et al. Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. *JAMA*. 2017;317(16):1642–1651.
55. Metra M, Teerlink JR. Heart failure. *Lancet*. 2017; 390(10106):1981–1995.
71. Marik PE. Noninvasive cardiac output monitors: a state-of-the-art review. *J Cardiothorac Vasc Anesth*. 2013;27(1):121–134.
73. Cecconi M, De Backer D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med*. 2014;40(12):1795–1815.
100. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362(9):779–789.
126. Perera D, Stables R, Thomas M, et al. Elective intra-aortic balloon counterpulsation during high-risk percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2010;304(8): 867–874.
139. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med*. 2013;369(23):2197–2206.

145. Kiely DG, Elliot CA, Sabroe I, et al. Pulmonary hypertension: diagnosis and management. *BMJ*. 2013;346:f2028.
156. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37(1):67–119.
164. Zochios V, Parhar K, Tunnicliffe W, et al. The Right Ventricle in ARDS. *Chest*. 2017;152(1):181–193.
185. Adhikari NK, Dellinger RP, Lundin S, et al. Inhaled nitric oxide does not reduce mortality in patients with acute respiratory distress syndrome regardless of severity: systematic review and meta-analysis. *Crit Care Med*. 2014;42(2):404–412.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Writing Group Members, Mozaffarian D, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2016 Update: a report from the American Heart Association. *Circulation*. 2016;133(4):e38–e360.
2. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail*. 2013; 6(3):606–619.
3. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics – 2014 update: a report from the American Heart Association. *Circulation*. 2014;129(3):e28–e292.
4. De Luca L, Olivari Z, Farina A, et al. Temporal trends in the epidemiology, management, and outcome of patients with cardiogenic shock complicating acute coronary syndromes. *Eur J Heart Fail*. 2015;17(11):1124–1132.
5. Puymirat E, Fagon JY, Aegerter P, et al. Cardiogenic shock in intensive care units: evolution of prevalence, patient profile, management and outcomes, 1997-2012. *Eur J Heart Fail*. 2017;19(2):192–200.
6. Yancy CW. Acute Heart Failure: searching for a new evident truth. *J Am Coll Cardiol*. 2017;69(11): 1420–1423.
7. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37(27):2129–2200.
8. Teerlink JR, Alburikan K, Metra M, et al. Acute decompensated heart failure update. *Curr Cardiol Rev*. 2015;11(1):53–62.
9. Hayes MA, Timmins AC, Yau EH, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med*. 1994;330(24):1717–1722.
10. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. *N Engl J Med*. 1995;333(16):1025–1032.
11. Teerlink JR, Metra M, Zaca V, et al. Agents with inotropic properties for the management of acute heart failure syndromes. Traditional agents and beyond. *Heart Fail Rev*. 2009;14(4):243–253.
12. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128(16): 1810–1852.
13. Dworzynski K, Roberts E, Ludman A, et al. Diagnosing and managing acute heart failure in adults: summary of NICE guidance. *BMJ*. 2014; 349:g5695.
14. Hanberg JS, Sury K, Wilson FP, et al. Reduced cardiac index is not the dominant driver of renal dysfunction in heart failure. *J Am Coll Cardiol*. 2016;67(19):2199–2208.
15. Mehta RL, Pascual MT, Soroko S, et al. Diuretics, mortality, and nonrecovery of renal function in acute renal failure. *JAMA*. 2002;288(20):2547–2553.
16. Salah K, Kok WE, Eurlings LW, et al. Competing risk of cardiac status and renal function during hospitalization for acute decompensated heart failure. *JACC Heart Fail*. 2015;3(10):751–761.
17. Damman K, Testani JM. The kidney in heart failure: an update. *Eur Heart J*. 2015;36(23):1437–1444.
18. Konstantinides SV, Vicaut E, Danays T, et al. Impact of thrombolytic therapy on the long-term outcome of intermediate-risk pulmonary embolism. *J Am Coll Cardiol*. 2017;69(12):1536–1544.
19. Maisel A, Neath SX, Landsberg J, et al. Use of procalcitonin for the diagnosis of pneumonia in patients presenting with a chief complaint of dyspnoea: results from the BACH (Biomarkers in Acute Heart Failure) trial. *Eur J Heart Fail*. 2012;14(3):278–286.
20. Turner A, Tsamitros M, Bellomo R. Myocardial cell injury in septic shock. *Crit Care Med*. 1999; 27(9):1775–1780.
21. Price S, Nicol E, Gibson DG, et al. Echocardiography in the critically ill: current and potential roles. *Intensive Care Med*. 2006;32(1):48–59.
22. Maurer G. Contrast echocardiography: clinical utility. *Echocardiography*. 2000;17(6 Pt 2):S5–S9.
23. Konstam MA, Abboud FM. Ejection fraction: misunderstood and overrated (changing the paradigm in categorizing heart failure). *Circulation*. 2017;135(8):717–719.
24. Andrew P. Diastolic heart failure demystified. *Chest*. 2003;124(2):744–753.
25. Yancy CW, Lopatin M, Stevenson LW, et al. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol*. 2006;47(1):76–84.
26. Chan MM, Lam CS. How do patients with heart failure with preserved ejection fraction die? *Eur J Heart Fail*. 2013;15(6):604–613.
27. Guest TM, Ramanathan AV, Tuteur PG, et al. Myocardial injury in critically ill patients. A frequently unrecognized complication. *JAMA*. 1995;273(24):1945–1949.
28. Sudoh T, Kangawa K, Minamino N, et al. A new natriuretic peptide in porcine brain. *Nature*. 1988;332(6159):78–81.
29. Omland T. Advances in congestive heart failure management in the intensive care unit: B-type natriuretic peptides in evaluation of acute heart failure. *Crit Care Med*. 2008;36(1 suppl):S17–S27.
30. Mueller C, Scholer A, Laule-Kilian K, et al. Use of B-type natriuretic peptide in the evaluation

and management of acute dyspnea. *N Engl J Med*. 2004;350(7):647–654.
31. McCullough PA, Nowak RM, McCord J, et al. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation*. 2002;106(4):416–422.
32. Januzzi JL Jr, Camargo CA, Anwaruddin S, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol*. 2005;95(8):948–954.
33. Charpentier J, Luyt CE, Fulla Y, et al. Brain natriuretic peptide: a marker of myocardial dysfunction and prognosis during severe sepsis. *Crit Care Med*. 2004;32(3):660–665.
34. Felker GM, Anstrom KJ, Adams KF, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA*. 2017;318(8):713–720.
35. Arlati S, Brenna S, Prencipe L, et al. Myocardial necrosis in ICU patients with acute non-cardiac disease: a prospective study. *Intensive Care Med*. 2000;26(1):31–37.
36. Relos RP, Hasinoff IK, Beilman GJ. Moderately elevated serum troponin concentrations are associated with increased morbidity and mortality rates in surgical intensive care unit patients. *Crit Care Med*. 2003;31(11):2598–2603.
37. Investigators VS, Devereaux PJ, Biccard BM, et al. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. *JAMA*. 2017;317(16):1642–1651.
38. Mauermann E, Bolliger D, Fassl J, et al. Postoperative high-sensitivity troponin and its association with 30-day and 12-month, all-cause mortality in patients undergoing on-pump cardiac surgery. *Anesth Analg*. 2017;125(4):1110–1117.
39. Peacock WF 4th, De Marco T, Fonarow GC, et al. Cardiac troponin and outcome in acute heart failure. *N Engl J Med*. 2008;358(20):2117–2126.
40. Westermann D, Neumann JT, Sorensen NA, et al. High-sensitivity assays for troponin in patients with cardiac disease. *Nat Rev Cardiol*. 2017;14(8):472–483.
41. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;35(43):3033–3069, 69a-69k.
42. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. *Circulation*. 2007;116(4):427–433.
43. Coutance G, Le Page O, Lo T, et al. Prognostic value of brain natriuretic peptide in acute pulmonary embolism. *Crit Care*. 2008;12(4):R109.
44. Cavallazzi R, Nair A, Vasu T, et al. Natriuretic peptides in acute pulmonary embolism: a systematic review. *Intensive Care Med*. 2008;34(12):2147–2156.
45. Corday E, Williams JH, De Vera LB, et al. Effect of systemic blood pressure and vasopressor drugs on coronary blood flow and the electrocardiogram. *Am J Cardiol*. 1959;3(5):626–637.
46. Parrillo JE. Pathogenetic mechanisms of septic shock. *N Engl J Med*. 1993;328(20):1471–1477.
47. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368–1377.
48. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med*. 2017;45(3):486–552.
49. ProCESS Investigators, Yealy DM, Kellum JA, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014;370(18):1683–1693.
50. ARISE Investigators, ANZICS Clinical Trials Group, Peake SL, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med*. 2014;371(16):1496–1506.
51. ProMISe Trial Investigators, Mouncey PR, Osborn TM, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med*. 2015;372(14):1301–1311.
52. Sarnoff SJ, Berglund E. Ventricular function. I. Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in the dog. *Circulation*. 1954;9(5):706–718.
53. Notarius CF, Levy RD, Tully A, et al. Cardiac versus noncardiac limits to exercise after heart transplantation. *Am Heart J*. 1998;135(2 Pt 1):339–348.
54. Heinemann HO. Right-sided heart failure and the use of diuretics. *Am J Med*. 1978;64(3):367–370.
55. Metra M, Teerlink JR. Heart failure. *Lancet*. 2017;390(10106):1981–1995.
56. Vismara LA, Leaman DM, Zelis R. The effects of morphine on venous tone in patients with acute pulmonary edema. *Circulation*. 1976;54(2):335–337.
57. Peacock WF, Hollander JE, Diercks DB, et al. Morphine and outcomes in acute decompensated heart failure: an ADHERE analysis. *Emerg Med J*. 2008;25(4):205–209.
58. Ross J Jr. Afterload mismatch and preload reserve: a conceptual framework for the analysis of ventricular function. *Prog Cardiovasc Dis*. 1976;18(4):255–264.
59. Cournand A, Motley HL, et al. Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. *Am J Physiol*. 1948;152(1):162–174.
60. Buda AJ, Pinsky MR, Ingels NB Jr, et al. Effect of intrathoracic pressure on left ventricular performance. *N Engl J Med*. 1979;301(9):453–459.
61. Francis GS. Vasodilators in the intensive care unit. *Am Heart J*. 1991;121(6 Pt 1):1875–1878.
62. Chamberlain DA, Leinbach RC, Vassaux CE, et al. Sequential atrioventricular pacing in heart block complicating acute myocardial infarction. *N Engl J Med*. 1970;282(11):577–582.

63. Smith TW. Digoxin in heart failure. *N Engl J Med*. 1993;329(1):51–53.
64. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials. Amiodarone Trials Meta-Analysis Investigators. *Lancet*. 1997;350(9089):1417–1424.
65. Singer M. Oesophageal Doppler monitoring: should it be routine for high-risk surgical patients? *Curr Opin Anaesthesiol*. 2011;24(2):171–176.
66. Singer M, Clarke J, Bennett ED. Continuous hemodynamic monitoring by esophageal Doppler. *Crit Care Med*. 1989;17(5):447–452.
67. Linton R, Band D, O'Brien T, et al. Lithium dilution cardiac output measurement: a comparison with thermodilution. *Crit Care Med*. 1997;25(11): 1796–1800.
68. Hadian M, Kim HK, Severyn DA, et al. Cross-comparison of cardiac output trending accuracy of LiDCO, PiCCO, FloTrac and pulmonary artery catheters. *Crit Care*. 2010;14(6): R212.
69. Monnet X, Vaquer S, Anguel N, et al. Comparison of pulse contour analysis by Pulsioflex and Vigileo to measure and track changes of cardiac output in critically ill patients. *Br J Anaesth*. 2015;114(2):235–243.
70. Montenij LJ, de Waal EE, Buhre WF. Arterial waveform analysis in anesthesia and critical care. *Curr Opin Anaesthesiol*. 2011;24(6):651–656.
71. Marik PE. Noninvasive cardiac output monitors: a state-of-the-art review. *J Cardiothorac Vasc Anesth*. 2013;27(1):121–134.
72. Scolletta S, Franchi F, Romagnoli S, et al. Comparison between doppler-echocardiography and uncalibrated pulse contour method for cardiac output measurement: a multicenter observational study. *Crit Care Med*. 2016;44(7):1370–1379.
73. Cecconi M, De Backer D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med*. 2014;40(12):1795–1815.
74. Monnet X, Persichini R, Ktari M, et al. Precision of the transpulmonary thermodilution measurements. *Crit Care*. 2011;15(4):R204.
75. Connors AF Jr, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. *JAMA*. 1996;276(11):889–897.
76. Simini B. Pulmonary artery catheters in intensive care. *Lancet*. 2005;366(9484):435–436.
77. Iberti TJ, Fischer EP, Leibowitz AB, et al. A multicenter study of physicians' knowledge of the pulmonary artery catheter. Pulmonary Artery Catheter Study Group. *JAMA*. 1990;264(22):2928–2932.
78. Rajaram SS, Desai NK, Kalra A, et al. Pulmonary artery catheters for adult patients in intensive care. *Cochrane Database Syst Rev*. 2013;(2):CD003408.
79. Vincent JL, Weil MH. Fluid challenge revisited. *Crit Care Med*. 2006;34(5):1333–1337.
80. Muller L, Toumi M, Bousquet PJ, et al. An increase in aortic blood flow after an infusion of 100 ml colloid over 1 minute can predict fluid responsiveness: the mini-fluid challenge study. *Anesthesiology*. 2011;115(3):541–547.
81. Marik PE, Cavallazzi R, Vasu T, et al. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med*. 2009;37(9):2642–2647.
82. Michard F, Boussat S, Chemla D, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med*. 2000;162(1):134–1348.
83. Mallat J, Meddour M, Durville E, et al. Decrease in pulse pressure and stroke volume variations after mini-fluid challenge accurately predicts fluid responsiveness. *Br J Anaesth*. 2015;115(3): 449–456.
84. Ansari BM, Zochios V, Falter F, et al. Physiological controversies and methods used to determine fluid responsiveness: a qualitative systematic review. *Anaesthesia*. 2016;71(1):94–105.
85. Bikdeli B, Strait KM, Dharmarajan K, et al. Intravenous fluids in acute decompensated heart failure. *JACC Heart Fail*. 2015;3(2):127–133.
86. Monnet X, Rienzo M, Osman D, et al. Passive leg raising predicts fluid responsiveness in the critically ill. *Crit Care Med*. 2006;34(5):1402–1407.
87. Maizel J, Airapetian N, Lorne E, et al. Diagnosis of central hypovolemia by using passive leg raising. *Intensive Care Med*. 2007;33(7):1133–1138.
88. Sharpey-Schafer EP. Effects of Valsalva's manoeuvre on the normal and failing circulation. *Br Med J*. 1955;1(4915):693–695.
89. McIntyre KM, Vita JA, Lambrew CT, et al. A noninvasive method of predicting pulmonary-capillary wedge pressure. *N Engl J Med*. 1992;327(24): 1715–1720.
90. Marik PE. The systolic blood pressure variation as an indicator of pulmonary capillary wedge pressure in ventilated patients. *Anaesth Intensive Care*. 1993;21(4):405–408.
91. Ritter JM, Doktor HS, Benjamin N. Paradoxical effect of bicarbonate on cytoplasmic pH. *Lancet*. 1990;335(8700):1243–1246.
92. Narins RG, Cohen JJ. Bicarbonate therapy for organic acidosis: the case for its continued use. *Ann Intern Med*. 1987;106(4):615–618.
93. Hilton PJ, Taylor J, Forni LG, et al. Bicarbonate-based haemofiltration in the management of acute renal failure with lactic acidosis. *QJM*. 1998;91(4): 279–283.
94. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian

Critical Care Trials Group. *N Engl J Med*. 1999; 340(6):409–417.
95. Docherty AB, Walsh TS. Anemia and blood transfusion in the critically ill patient with cardiovascular disease. *Crit Care*. 2017;21(1):61.
96. Leslie D, Gheorghiade M. Is there a role for thiamine supplementation in the management of heart failure? *Am Heart J*. 1996;131(6):1248–1250.
97. Zenuk C, Healey J, Donnelly J, et al. Thiamine deficiency in congestive heart failure patients receiving long term furosemide therapy. *Can J Clin Pharmacol*. 2003;10(4):184–188.
98. Day NP, Phu NH, Bethell DP, et al. The effects of dopamine and adrenaline infusions on acid-base balance and systemic haemodynamics in severe infection. *Lancet*. 1996;348(9022):219–223.
99. Bellomo R, Chapman M, Finfer S, et al. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet*. 2000;356(9248):2139–2143.
100. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362(9): 779–789.
101. Wilson J, Woods I, Fawcett J, et al. Reducing the risk of major elective surgery: randomised controlled trial of preoperative optimisation of oxygen delivery. *BMJ*. 1999;318(7191):1099–1103.
102. Pearse RM, Belsey JD, Cole JN, et al. Effect of dopexamine infusion on mortality following major surgery: individual patient data meta-regression analysis of published clinical trials. *Crit Care Med*. 2008;36(4):1323–1329.
103. Hasenfuss G, Pieske B, Castell M, et al. Influence of the novel inotropic agent levosimendan on isometric tension and calcium cycling in failing human myocardium. *Circulation*. 1998;98(20): 2141–2147.
104. Antila S, Sundberg S, Lehtonen LA. Clinical pharmacology of levosimendan. *Clin Pharmacokinet*. 2007;46(7):535–552.
105. Orstavik O, Ata SH, Riise J, et al. Inhibition of phosphodiesterase-3 by levosimendan is sufficient to account for its inotropic effect in failing human heart. *Br J Pharmacol*. 2014;171(23):5169–5181.
106. Bergh CH, Andersson B, Dahlstrom U, et al. Intravenous levosimendan vs. dobutamine in acute decompensated heart failure patients on beta-blockers. *Eur J Heart Fail*. 2010;12(4): 404–410.
107. Follath F, Cleland JG, Just H, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet*. 2002;360(9328):196–202.
108. Moiseyev VS, Poder P, Andrejevs N, et al. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN). *Eur Heart J*. 2002;23(18):1422–1432.
109. Mebazaa A, Nieminen MS, Packer M, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. *JAMA*. 2007;297(17):1883–1891.
110. Gordon AC, Perkins GD, Singer M, et al. Levosimendan for the prevention of acute organ dysfunction in sepsis. *N Engl J Med*. 2016;375(17): 1638–1648.
111. Landoni G, Lomivorotov VV, Alvaro G, et al. Levosimendan for hemodynamic support after cardiac surgery. *N Engl J Med*. 2017;376(21): 2021–2031.
112. Mehta RH, Leimberger JD, van Diepen S, et al. Levosimendan in patients with left ventricular dysfunction undergoing cardiac surgery. *N Engl J Med*. 2017;376(21):2032–2042.
113. Cholley B, Caruba T, Grosjean S, et al. Effect of Levosimendan on low cardiac output syndrome in patients with low ejection fraction undergoing coronary artery bypass grafting with cardiopulmonary bypass: the LICORN Randomized Clinical Trial. *JAMA*. 2017;318(6):548–556.
114. Committees C-IIa. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999;353(9146):9–13.
115. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353(9169): 2001–2007.
116. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation*. 2002;106(17):2194–2199.
117. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med*. 1998;339(8):489–497.
118. POISE Study Group, Devereaux PJ, Yang H, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet*. 2008;371(9627):1839–1847.
119. Krum H, Roecker EB, Mohacsi P, et al. Effects of initiating carvedilol in patients with severe chronic heart failure: results from the COPERNICUS Study. *JAMA*. 2003;289(6):712–718.
120. Jondeau G, Neuder Y, Eicher JC, et al. B-CONVINCED: Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode. *Eur Heart J*. 2009;30(18):2186–2192.
121. Vital FM, Saconato H, Ladeira MT, et al. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary edema. *Cochrane Database Syst Rev*. 2008;(3):CD005351.

122. Gray A, Goodacre S, Newby DE, et al. Noninvasive ventilation in acute cardiogenic pulmonary edema. *N Engl J Med*. 2008;359(2):142–151.
123. Aubier M, Trippenbach T, Roussos C. Respiratory muscle fatigue during cardiogenic shock. *J Appl Physiol Respir Environ Exerc Physiol*. 1981;51(2):499–508.
124. Nanas JN, Moulopoulos SD. Counterpulsation: historical background, technical improvements, hemodynamic and metabolic effects. *Cardiology*. 1994;84(3):156–167.
125. Thiele H, Zeymer U, Neumann FJ, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med*. 2012;367(14):1287–1296.
126. Perera D, Stables R, Thomas M, et al. Elective intra-aortic balloon counterpulsation during high-risk percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2010;304(8):867–874.
127. Sidebotham D, McGeorge A, McGuinness S, et al. Extracorporeal membrane oxygenation for treating severe cardiac and respiratory disease in adults: Part 1 – overview of extracorporeal membrane oxygenation. *J Cardiothorac Vasc Anesth*. 2009;23(6):886–892.
128. Westaby S, Katsumata T, Houel R, et al. Jarvik 2000 heart: potential for bridge to myocyte recovery. *Circulation*. 1998;98(15):1568–1574.
129. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med*. 2009;361(23):2241–2251.
130. Babaev A, Frederick PD, Pasta DJ, et al. Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. *JAMA*. 2005;294(4):448–454.
131. Goldberg RJ, Spencer FA, Gore JM, et al. Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction: a population-based perspective. *Circulation*. 2009;119(9):1211–1219.
132. Kolte D, Khera S, Aronow WS, et al. Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. *J Am Heart Assoc*. 2014;3(1):e000590.
133. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med*. 1992;327(10):669–677.
134. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341(10):709–717.
135. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348(14):1309–1321.
136. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364(1):11–21.
137. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346(8):557–563.
138. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346(8):549–556.
139. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med*. 2013;369(23):2197–2206.
140. Isner JM, Roberts WC. Right ventricular infarction complicating left ventricular infarction secondary to coronary heart disease. Frequency, location, associated findings and significance from analysis of 236 necropsy patients with acute or healed myocardial infarction. *Am J Cardiol*. 1978;42(6):885–894.
141. Cohn JN, Guiha NH, Broder MI, et al. Right ventricular infarction. Clinical and hemodynamic features. *Am J Cardiol*. 1974;33(2):209–214.
142. Hasdai D, Topol EJ, Califf RM, et al. Cardiogenic shock complicating acute coronary syndromes. *Lancet*. 2000;356(9231):749–756.
143. Huynh TN, Weigt SS, Sugar CA, et al. Prognostic factors and outcomes of patients with pulmonary hypertension admitted to the intensive care unit. *J Crit Care*. 2012;27(6):739.e7–739.e13.
144. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 suppl):D34–D41.
145. Kiely DG, Elliot CA, Sabroe I, et al. Pulmonary hypertension: diagnosis and management. *BMJ*. 2013;346:f2028.
146. Rubin LJ, American College of Chest Physicians. Diagnosis and management of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest*. 2004;126(1 suppl):7S–10S.
147. Zapol WM, Snider MT. Pulmonary hypertension in severe acute respiratory failure. *N Engl J Med*. 1977;296(9):476–480.
148. Bull TM, Clark B, McFann K, et al. National Institutes of Health/National Heart, Lung, and Blood Institute ARDS Network. Pulmonary vascular dysfunction is associated with poor outcomes in patients with acute lung injury. *Am J Respir Crit Care Med*. 2010;182(9):1123–1128.
149. Guazzi M, Arena R. Pulmonary hypertension with left-sided heart disease. *Nat Rev Cardiol*. 2010;7(11):648–659.
150. Kasper W, Konstantinides S, Geibel A, et al. Prognostic significance of right ventricular

afterload stress detected by echocardiography in patients with clinically suspected pulmonary embolism. *Heart*. 1997;77(4):346–349.
151. Pinsky MR. Cardiovascular issues in respiratory care. *Chest*. 2005;128(5 suppl 2):592S–597S.
152. Denault A, Deschamps A, Tardif JC, et al. Pulmonary hypertension in cardiac surgery. *Curr Cardiol Rev*. 2010;6(1):1–14.
153. Sztrymf B, Souza R, Bertoletti L, et al. Prognostic factors of acute heart failure in patients with pulmonary arterial hypertension. *Eur Respir J*. 2010;35(6):1286–1293.
154. Hoeper MM, Granton J. Intensive care unit management of patients with severe pulmonary hypertension and right heart failure. *Am J Respir Crit Care Med*. 2011;184(10):1114–1124.
155. Price LC, Wort SJ, Finney SJ, et al. Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. *Crit Care*. 2010;14(5):R169.
156. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37(1):67–119.
157. Delcroix M, Naeije R. Optimising the management of pulmonary arterial hypertension patients: emergency treatments. *Eur Respir Rev*. 2010;19(117):204–211.
158. Yerebakan C, Klopsch C, Niefeldt S, et al. Acute and chronic response of the right ventricle to surgically induced pressure and volume overload – an analysis of pressure-volume relations. *Interact Cardiovasc Thorac Surg*. 2010;10(4):519–525.
159. Bemis CE, Serur JR, Borkenhagen D, et al. Influence of right ventricular filling pressure on left ventricular pressure and dimension. *Circ Res*. 1974;34(4):498–504.
160. Louie EK, Lin SS, Reynertson SI, et al. Pressure and volume loading of the right ventricle have opposite effects on left ventricular ejection fraction. *Circulation*. 1995;92(4):819–824.
161. Fixler DE, Archie JP, Ullyot DJ, et al. Effects of acute right ventricular systolic hypertension on regional myocardial blood flow in anesthetized dogs. *Am Heart J*. 1973;85(4):491–500.
162. Lazzeri C, Peris A. The spectrum of changes in the right ventricle in ARDS: dilatation, dysfunction, and acute cor pulmonale. *Chest*. 2017;152(1):214.
163. Repesse X, Charron C, Vieillard-Baron A. Acute cor pulmonale in ARDS: rationale for protecting the right ventricle. *Chest*. 2015;147(1):259–265.
164. Zochios V, Parhar K, Tunnicliffe W, et al. The right ventricle in ARDS. *Chest*. 2017;152(1):181–193.
165. Vieillard-Baron A, Charron C, Caille V, et al. Prone positioning unloads the right ventricle in severe ARDS. *Chest*. 2007;132(5):1440–1446.
166. Wiener RS, Welch HG. Trends in the use of the pulmonary artery catheter in the United States, 1993–2004. *JAMA*. 2007;298(4):423–429.
167. Janda S, Shahidi N, Gin K, et al. Diagnostic accuracy of echocardiography for pulmonary hypertension: a systematic review and meta-analysis. *Heart*. 2011;97(8):612–622.
168. Goldstein JA, Harada A, Yagi Y, et al. Hemodynamic importance of systolic ventricular interaction, augmented right atrial contractility and atrioventricular synchrony in acute right ventricular dysfunction. *J Am Coll Cardiol*. 1990;16(1):181–189.
169. Kerbaul F, Rondelet B, Motte S, et al. Effects of norepinephrine and dobutamine on pressure load-induced right ventricular failure. *Crit Care Med*. 2004;32(4):1035–1040.
170. Ferrario M, Poli A, Previtali M, et al. Hemodynamics of volume loading compared with dobutamine in severe right ventricular infarction. *Am J Cardiol*. 1994;74(4):329–333.
171. Tayama E, Ueda T, Shojima T, et al. Arginine vasopressin is an ideal drug after cardiac surgery for the management of low systemic vascular resistant hypotension concomitant with pulmonary hypertension. *Interact Cardiovasc Thorac Surg*. 2007;6(6):715–719.
172. Kerbaul F, Rondelet B, Demester JP, et al. Effects of levosimendan versus dobutamine on pressure load-induced right ventricular failure. *Crit Care Med*. 2006;34(11):2814–2819.
173. Russ MA, Prondzinsky R, Carter JM, et al. Right ventricular function in myocardial infarction complicated by cardiogenic shock: improvement with levosimendan. *Crit Care Med*. 2009;37(12):3017–3023.
174. Hashiba E, Hirota K, Yoshioka H, et al. Milrinone attenuates serotonin-induced pulmonary hypertension and bronchoconstriction in dogs. *Anesth Analg*. 2000;90(4):790–794.
175. Chen EP, Bittner HB, Davis RD Jr, et al. Milrinone improves pulmonary hemodynamics and right ventricular function in chronic pulmonary hypertension. *Ann Thorac Surg*. 1997;63(3):814–821.
176. Lee JH, Oh YJ, Shim YH, et al. The effect of milrinone on the right ventricular function in patients with reduced right ventricular function undergoing off-pump coronary artery bypass graft surgery. *J Korean Med Sci*. 2006;21(5):854–858.
177. Mishra A, Kumar B, Dutta V, et al. Comparative effect of levosimendan and milrinone in cardiac surgery patients with pulmonary hypertension and left ventricular dysfunction. *J Cardiothorac Vasc Anesth*. 2016;30(3):639–646.
178. Sablotzki A, Starzmann W, Scheubel R, et al. Selective pulmonary vasodilation with inhaled aerosolized milrinone in heart transplant candidates. *Can J Anaesth*. 2005;52(10):1076–1082.

179. Hentschel T, Yin N, Riad A, et al. Inhalation of the phosphodiesterase-3 inhibitor milrinone attenuates pulmonary hypertension in a rat model of congestive heart failure. *Anesthesiology*. 2007;106(1):124–131.
180. Bednarczyk J, Strumpher J, Jacobsohn E. Inhaled milrinone for pulmonary hypertension in high-risk cardiac surgery: silver bullet or just part of a broader management strategy? *Can J Anaesth*. 2016;63(10):1122–1127.
181. Theodoraki K, Thanopoulos A, Rellia P, et al. A retrospective comparison of inhaled milrinone and iloprost in post-bypass pulmonary hypertension. *Heart Vessels*. 2017;32(12):1488–1497.
182. Ardehali A, Hughes K, Sadeghi A, et al. Inhaled nitric oxide for pulmonary hypertension after heart transplantation. *Transplantation*. 2001;72(4): 638–641.
183. George I, Xydas S, Topkara VK, et al. Clinical indication for use and outcomes after inhaled nitric oxide therapy. *Ann Thorac Surg*. 2006;82(6): 2161–2169.
184. Adhikari NK, Burns KE, Friedrich JO, et al. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. *BMJ*. 2007;334(7597):779.
185. Adhikari NK, Dellinger RP, Lundin S, et al. Inhaled nitric oxide does not reduce mortality in patients with acute respiratory distress syndrome regardless of severity: systematic review and meta-analysis. *Crit Care Med*. 2014;42(2):404–412.
186. Hache M, Denault AY, Belisle S, et al. Inhaled prostacyclin (PGI2) is an effective addition to the treatment of pulmonary hypertension and hypoxia in the operating room and intensive care unit. *Can J Anaesth*. 2001;48(9):924–929.
187. Theodoraki K, Rellia P, Thanopoulos A, et al. Inhaled iloprost controls pulmonary hypertension after cardiopulmonary bypass. *Can J Anaesth*. 2002;49(9):963–967.
188. Khan TA, Schnickel G, Ross D, et al. A prospective, randomized, crossover pilot study of inhaled nitric oxide versus inhaled prostacyclin in heart transplant and lung transplant recipients. *J Thorac Cardiovasc Surg*. 2009;138(6):1417–1424.
189. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*. 2005;353(20):2148–2157.
190. Mikhail GW, Prasad SK, Li W, et al. Clinical and haemodynamic effects of sildenafil in pulmonary hypertension: acute and mid-term effects. *Eur Heart J*. 2004;25(5):431–436.
191. Trachte AL, Lobato EB, Urdaneta F, et al. Oral sildenafil reduces pulmonary hypertension after cardiac surgery. *Ann Thorac Surg*. 2005;79(1): 194–197, discussion -7.

25

Valvular and congenital heart disease and infective endocarditis

Steven T Galluccio

VALVULAR HEART DISEASE

Valvular heart disease (VHD) has been described as the next 'cardiac epidemic'.[1] In high-income countries, aortic stenosis (AS) is predicted to significantly increase in incidence.[2] Despite being less common than coronary artery disease, the burden of VHD is significant due to the requirement, not just for treatment, but for ongoing investigation and follow-up. Although the incidence of rheumatic heart disease has dramatically declined in high-income countries, this same reduction has not been seen in low-income countries or within low-income populations living in high-income countries.[3]

For the intensivist, VHD may pose a clinical challenge as the primary cause for haemodynamic decompensation, when manifest with an unrelated concurrent illness, or in the peri-operative period where valve replacement or repair is performed. Haemodynamic support of severe uncorrected VHD in the critical care setting can be difficult since cardiac output may remain largely independent of conventional manipulations. Nonetheless, it is important to conceptualise the underlying lesion and haemodynamic state into a model that can anticipate problems and predict responses to intervention (Table 25.1).

Recent consensus guidelines provide recommendations for the timing of intervention for VHD.[4,5] The principles of decision making involve the assessment of: patient symptoms; echocardiographic evidence of severity by standard criteria[6–8]; associated cardiac disease (e.g. coronary artery disease); co-morbidities and the risk of intervention utilising validated scoring systems. In all forms of valvular surgery, key postoperative clinical syndromes might be anticipated by the preoperative clinical information (Table 25.2).

AORTIC STENOSIS

Left ventricular (LV) hypertrophy is the adaptive response to the pressure-work brought about by AS. The initial pathophysiological hallmark is diastolic failure, but as the disease progresses, dilatation ensues and overt systolic failure becomes evident. Typically, patients remain asymptomatic for a prolonged period, but once symptoms occur the prognosis is poor if left untreated.

MEDICAL MANAGEMENT

For patients presenting with critical symptomatic AS, surgical or percutaneous intervention is required as medical management is limited. A modest heart rate is ideal and inotropic support may have a role if there is LV systolic dysfunction, but stroke volume is otherwise largely fixed. Vasodilators potentially have a temporising role but more critical is the defence of systemic pressure with vasopressors. Hypotension is an ominous sign and restoration of coronary perfusion pressure is paramount. This may require the addition of intra-aortic balloon counterpulsation (IABC).

INTERVENTION FOR AORTIC STENOSIS

Aortic valve replacement (AVR) is recommended as a Class 1 indication for severe AS with symptoms, or when it is associated with decreased left ventricular ejection fraction (LVEF) or the need for other cardiac surgery.[5] A dilemma in selecting patients for surgery occurs with so-called 'low-flow, low-gradient severe AS'.[9] Since transaortic pressure gradients (using spectral Doppler velocities) are dependent upon true valve area as well as flow rate (stroke volume), the key is to differentiate low-flow due to intrinsic poor LV function (pseudo-stenosis) versus that due to truly severe AS. The former group will have a poor outcome from intervention whereas the latter are likely to benefit. Low-flow, low-gradient severe AS can also occur in patients with normal LVEF but concentric LV hypertrophy and small chamber volumes ('paradoxical low-flow, low gradient AS').

The choice between surgical versus transcatheter intervention (transcatheter aortic valve replacement [TAVR]) is likely to evolve over the coming years as more experience and high-quality evidence is incorporated into clinical guidelines and practice.[10] Currently, surgical AVR is recommended in patients with low to intermediate surgical risk, whereas TAVR is recommended for those with prohibitive surgical risk on the condition that the predicted post-TAVR survival is greater than 12 months.[4,5] In patients with an intermediate to high surgical risk, TAVR may be a reasonable option, especially if carried out via a transfemoral approach.[4,5] In difficult cases, multidisciplinary assessment should be utilised. However, it appears that already there is drift towards the use of TAVR in lower-risk cases as well as

ABSTRACT

Seemingly disparate entities, valvular heart disease, adult congenital heart disease and infective endocarditis share several commonalities. These conditions all present challenges to the intensivist and their impact in the broader health care context is increasing. Associated haemodynamic perturbations can be complex; uncorrected structural heart disease will often render inadequate the armamentarium of critical care support. Optimal management requires integration of core clinical skills with appropriate utilisation and interpretation of laboratory, echocardiographic and radiological data. Multidisciplinary engagement is vital in determining the feasibility and timing of surgical or percutaneous interventions.

KEY WORDS

Heart valve diseases
cardiac surgical procedures
heart valve prosthesis implantation
postoperative complications
heart defects, congenital
endocarditis

Table 25.1 Characteristics of valvular lesions

LESION	AETIOLOGY	MURMUR CHARACTERISTICS	CLINICAL FEATURES OF SEVERITY	ECHOCARDIOGRAPHIC FEATURES OF SEVERITY (13–15)	COMMENTS
AS	Degenerative (calcific), congenital (bicuspid valve), rheumatic	Mid-systolic ejection murmur Maximal over aortic area Radiation to carotid arteries Loudest sitting up in full expiration	Plateau pulse, aortic thrill, length and lateness of murmur, pressure-loaded apex beat, soft/absent A2, signs of LVF* (very late sign)	Mean aortic gradient ≥ 40 mm Hg Peak aortic velocity ≥ 4 m/s Aortic valve area ≤ 1 cm^2	Lower HR (50–60 bpm) preferable Often associated with 'post-stenotic' aortic root dilatation
AR (chronic)	Valvular (calcific, congenital bicuspid, rheumatic); Aortic root dilatation (aortitis, Marfan syndrome)	Decrescendo diastolic murmur Loudest at left third and fourth intercostal spaces	Collapsing pulse, wide pulse pressure, long decrescendo murmur, LV S3, Austin Flint murmur, signs of LVF*	Jet width ≥65% LVOT Vena contracta >6 mm Holodiastolic flow reversal in abdominal aorta RVol ≥ 60 mL EROA ≥ 0.3 cm^2 Regurgitant fraction ≥ 50% LV dilatation	IABC contraindicated
AR (acute)	Valvular (IE), aortic root dilatation, aortic dissection	Faint early diastolic murmur (may be absent)	Low-output state, soft and short diastolic murmur, no collapsing pulse (hypotension), narrow pulse pressure	As above	Surgical emergency Often associated with aortic root pathology (dilatation, abscess)
MR (chronic)	Primary (degenerative, MV prolapse); Secondary (annular dilatation, ischaemic)	Pansystolic murmur Maximal at apex Radiates to axilla	Small volume pulse, enlarged LV, loud S3, soft S1, early A2, signs of LVF*, signs of PHT† and RVF‡	Vena contracta ≥ 0.7 cm EROA ≥ 0.2 cm^2 Regurgitant fraction ≥ 50% Systolic flow reversal in pulmonary veins	Higher HR (80–100 bpm) preferable
MR (acute)	Ischaemic, IE, spontaneous chordal rupture (myxomatous degeneration)	Murmur may be absent	Low-output state, pulmonary oedema, soft systolic murmur	As above	Surgical emergency Higher HR (80–100 bpm) preferable Typically high/normal LVEF but low forward SV IABC to ↑ systemic pressure and ↓ afterload
MS	Rheumatic, degenerative	Mid to late diastolic murmur Low pitched	Small pulse pressure, soft S1, early opening snap, long diastolic murmur, diastolic thrill, signs of PHT	MV area ≤ 1.5 cm^2 Diastolic pressure half-time ≥ 220 ms	Normal LVEF Low HR preferred; AV synchrony critical High thromboembolic risk

Table 25.1 Characteristics of valvular lesions—cont'd

LESION	AETIOLOGY	MURMUR CHARACTERISTICS	CLINICAL FEATURES OF SEVERITY	ECHOCARDIOGRAPHIC FEATURES OF SEVERITY (13–15)	COMMENTS
TR	Primary (rheumatic, congenital, IE); secondary/ functional (tricuspid annular dilatation or leaflet tethering)	Pansystolic murmur at left sternal edge Louder with inspiration	Signs of PHT and RVF	Jet area ≥ 10 cm^2 Vena contracta ≥ 0.7 cm CW jet dense, triangular Hepatic vein systolic flow reversal	Mostly commonly secondary/ functional Severity of TR not always proportional to severity of PHT

*Signs of LVF: tachypnoea, Cheyne-Stokes respiration, hypotension, low pulse-pressure, LV S3, basal inspiratory crackles.

†Signs of PHT: loud P2, palpable P2, prominent A wave in JVP, left parasternal heave, RV S4.

‡Clinical features of RVF: TR murmur, PR murmur, elevated JVP, prominent V wave in JVP, RV S3, hepatomegaly, pulsatile liver, peripheral oedema, ascites, pleural effusions.

AR, Aortic regurgitation; *AS*, aortic stenosis; *AV*, aortic valve; *EROA*, effective regurgitant orifice area; *HR*, heart rate; *IABC*, intra-aortic balloon counterpulsation; *IE*, infective endocarditis; *LV*, left ventricle; *LVEF*, left ventricular ejection fraction; *LVF*, left ventricular failure; *LVOT*, left ventricular outflow tract obstruction; *MR*, mitral regurgitation; *MS*, mitral stenosis; *MV*, mitral valve; *PHT*, pulmonary hypertension; *RV*, right ventricle; *RVF*, right ventricular failure; *RVol*, regurgitant volume; *SV*, stroke volume; *TR*, tricuspid regurgitation.

performing valve-in-valve procedures for failing bioprosthetic valves.[10] With limited magnitude and duration of benefit, percutaneous aortic balloon dilatation may be considered as a bridge to surgical AVR or TAVR in patients requiring rescue from severe symptoms or haemodynamic deterioration.

In the majority of cases, the key management concern post-AVR is diastolic LV failure. This can be exacerbated by injury related to inadequate myocardial protection associated with LV hypertrophy. Maintaining AV synchrony is crucial and this may require temporary sequential AV pacing. A particular difficulty following the correction of AS is the rapid reduction in afterload, which can produce a low-output state associated with a hypertrophic, hyperdynamic, small-cavity LV or 'suicide ventricle'. This may mimic systolic dysfunction or even pericardial tamponade, both clinically and by haemodynamic monitoring because despite the chamber size, 'filling pressures' will be elevated with low cardiac output. Inotropic agents, including vasopressors with beta-agonist activity and IABC, can exacerbate the problem, so echocardiography is critical in defining the haemodynamic state. This will confirm small cavity size with preserved systolic function, but with colour and spectral Doppler findings of flow acceleration and high-pressure gradients across the left ventricular outflow tract (LVOT) or LV cavity proper. Transoesophageal echocardiography (TOE) is usually required to ensure that local chamber compression or right-sided dysfunction is not contributing to low LV preload. Combined right ventricular (RV) dysfunction is especially challenging because this can produce a series of competing interests. For example, positive inotropes may be indicated for RV systolic dysfunction, but this may adversely affect the LV. In this situation, selective pulmonary vasodilators and early spontaneous ventilation with minimal positive end-expiratory pressure (PEEP) should be considered as this reduces RV afterload, but increases that of the left ventricle.

AORTIC REGURGITATION

Chronic aortic regurgitation (AR) generally progresses slowly with a protracted interval to development of LV dilatation, dysfunction and symptoms. However, unlike AS, once symptoms develop, LV systolic function is usually evident. The most common causes relate to the valve itself (congenital bicuspid aortic valve, degenerative calcific disease) or due to aortic root dilatation (such as occurs in Marfan syndrome). Rheumatic disease is the predominant aetiology in developing countries. Acute AR places an acute volume load on the LV, which can result in pulmonary oedema and low cardiac output, requiring urgent surgical intervention. Typical causes include infective endocarditis (IE) and aortic dissection.

MEDICAL MANAGEMENT

A generous heart rate will reduce the regurgitant volume, but medical management is essentially limited to inotropic, vasopressor and ventilatory support. Unlike other forms of cardiogenic shock, AR represents a contraindication to IABC. The main conundrum is balancing an adequate perfusion pressure, including to the coronary circulation, without worsening regurgitant volume and further LV dilatation. In acute AR, these goals may be mutually exclusive and hence the need for urgent surgery.

Table 25.2 Typical features of valvular surgery

	CONDITION	LV SIZE	LV SYSTOLIC DYSFUNCTION	LV DIASTOLIC DYSFUNCTION	PHT AND RV DYSFUNCTION	MYOCARDIAL PROTECTION*	RISK AV BLOCK	COMMENTS
AVR	AS	Hypertrophic but non-dilated	+ (usually normal LVEF unless late stage or ischaemic cardiomyopathy)	+++	+ (very late feature)	Cardioplegia less effective if LV hypertrophy is severe	+	Beware LVOT/mid-cavity obstruction ('suicide' ventricle) AVR established choice in patients with low-intermediate surgical risk
TAVR	AS	Hypertrophic but non-dilated	+ (usually normal LVEF unless late stage or ischaemic cardiomyopathy)	+++	+ (very late feature)	Risk myocardial injury due to: rapid ventricular pacing and hypotension; arterial embolisation; coronary obstruction by prosthesis	++	Beware LVOT/mid-cavity obstruction ('suicide' ventricle) TAVR established choice in patients with prohibitive surgical risk
AVR	AR	Dilated	++	++	++	Reliance on retrograde cardioplegia or direct ostial cannulation	+	LV dysfunction can potentially improve after AVR
MVR	MS	Normal	Normal	'Normal' but LV filling dependent upon HR, atrial function and AV synchrony	+++	Risk circumflex artery injury	++	Severity of pulmonary HT/RVF key considerations in postoperative management
MVR	MR	Dilated	+++ (can be underestimated by echocardiography)	++	Variable	Risk circumflex artery injury	++	LV dysfunction unmasked by valve replacement (↑ LV afterload)
MV repair	MR	Dilated	+++ (can be underestimated by echocardiography)	++	Variable	Risk circumflex artery injury	++	SAM/LVOT obstruction in 4%–10% of cases.[11,12] LV dysfunction unmasked by valve repair (↑ LV afterload)
TV replacement or repair	TR	Variable	Variable	Variable	++	Risk right coronary artery injury	+++	May unmask RV systolic dysfunction; caution if RV function severely impaired

*RV protection is worse when retrograde cardioplegia is solely used.

AR, Aortic regurgitation; *AS*, aortic stenosis; *AV*, aortic valve; *AVR*, AV replacement; *HT*, hypertension; *LV*, left ventricle; *LVEF*, left ventricular ejection fraction; *LVOT*, left ventricular outflow tract obstruction; *MR*, mitral regurgitation; *MS*, mitral stenosis; *MV*, mitral valve; *MVR*, MV replacement; *PHT*, pulmonary hypertension; *RV*, right ventricle; *RVF*, right ventricular failure; *SAM*, systolic anterior motion of the mitral valve; *TAVR*, transcatheter aortic valve replacement; *TR*, tricuspid regurgitation; *TV*, tricuspid valve.

INTERVENTION FOR AORTIC REGURGITATION

For chronic AR warranting surgical intervention, the anatomical conditions are generally less favourable towards repair, and AVR is required. Such indications include symptomatic patients with severe AR or those without symptoms, but when associated with LV dysfunction or if undergoing cardiac surgery for other indications. Whether AVR is indicated for AR or AS, it is also important to assess for dilatation of the aorta (aortopathy) as this may also warrant replacement. Due to anatomical differences, transcatheter intervention for AR is more challenging than for AS, although TAVR devices are currently in development.[10]

Survival following AVR is strongly related to preoperative symptoms, with worse outcomes once patients reach New York Heart Association class III symptoms or have reduced exercise capacity. Surgical risk is also increased as LV function deteriorates, as assessed by echocardiography. Nonetheless, even in patients with both symptoms and LV dysfunction, surgery is still recommended over medical therapy.[4,5]

Postoperatively, the course will be largely predicted by the underlying degree of systolic LV dysfunction and, if present, pulmonary hypertension (PHT) and RV failure. Inotropic and vasopressor support will be simplified with the correction of AR, and there is the potential for significant improvements in function even in patients with a poor baseline state.

MITRAL REGURGITATION

Mitral regurgitation (MR) poses a volume load on the LV with progressive left atrial (LA) and LV dilatation. Although this chamber dilatation preserves forward stroke volume, eventually systolic dysfunction occurs and cardiac output deteriorates. When evaluating significant MR, echocardiography will tend to overestimate LV systolic function, since MR represents a low-afterload state. This is often illustrated postoperatively when mitral valve repair or replacement unmasks the degree of LV dysfunction.

Understanding the mechanism of MR is important in detecting associated pathology and determining optimal treatment. MR can be broadly classified as primary, referring to intrinsic pathology of the valve apparatus (leaflets, chordae tendineae, papillary muscles) or secondary (functional) MR, referring to structurally normal leaflets but with abnormal function due to LV dilatation and remodelling. Alternatively, the Carpentier classification is determined upon leaflet motion as being normal, restricted or excessive. In high-income countries, the most common aetiologies of MR are degenerative disease with mitral valve prolapse (a primary cause) and coronary heart disease (a secondary cause).

Acute MR can present dramatically with florid pulmonary oedema and shock. In this scenario, the LA is unable to accommodate the high regurgitant volume under high pressure with subsequent pulmonary venous hypertension, acute pulmonary arterial hypertension and potentially overt RV failure. The non-dilated LV is hyperdynamic with a high ejection fraction but a low forward stroke volume. Causes include spontaneous chordal rupture with degenerative disease, leaflet perforation with IE and papillary muscle rupture due to myocardial infarction. This condition can be difficult to diagnose, sometimes mimicking severe pneumonia or ARDS, and is particularly challenging if only unilateral pulmonary oedema is present due to an eccentrically directed MR jet.

MEDICAL MANAGEMENT

Unlike stenotic lesions with relatively fixed stroke volume, there will be variable recruitment in LV function, and hence stroke volume with inotropic agents. Afterload reduction is key but often a compromise needs to be reached between acceptably low systemic arterial pressure and higher forward flow (as occurs in AR as discussed above).

Acute MR will almost always require urgent surgical intervention. Frequent communication between intensive care and surgical teams is crucial in determining the timing of surgery prior to attempts at stabilisation. Key measures are positive pressure ventilation with sufficient PEEP and the use of IABC to simultaneously reduce afterload as well as increase systemic mean arterial pressure. Further afterload reduction with vasodilators is ideal, but systemic hypotension is often a limiting factor and vasopressors are required.

INTERVENTION FOR MITRAL REGURGITATION

Based largely on observational data, MV surgery is recommended for severe chronic primary MR in symptomatic patients with LVEF greater than 30%, or in asymptomatic patients with LVEF 30%–60%.[4,5] In patients with severely depressed LV function (LVEF <30%), surgery may be reasonable but supportive data are lacking.

The preferred surgical option in all cases of primary MR is repair, especially if disease is limited to the posterior leaflet.[5,8] Repair has advantages over replacement including preservation of LV function and lower operative mortality, and it avoids the thromboembolic risk of mechanical valves and the inevitable deterioration of bioprosthetic valves. The balance swings towards MV replacement (MVR) as the chance of successful and durable repair diminish (e.g. complex anterior and posterior leaflet disease). For those with prohibitive surgical risk, but with an otherwise reasonable life expectancy, transcatheter repair may be considered.[5,8] Based on the principles of an Alfieri repair, the MitraClip tethers together the anterior and posterior leaflets. This is a feasible option if anatomical factors are favourable, but results in greater residual MR than standard open surgical approaches. Additional devices are currently in development, and will perhaps soon provide the capacity for transcatheter mitral valve replacement.

For secondary MR, the benefit of intervention on mortality or morbidity remains uncertain. Surgical

intervention is reasonable in patients undergoing simultaneous aortic valve replacement or coronary artery bypass grafting.[5] Repair or replacement can also be considered in patients with persistent symptoms despite optimal medical management.[5] Secondary MR is currently the most common indication for MitraClip use in Europe.[13]

Postoperatively, key considerations are the state of the pulmonary circulation and RV function, but previously underestimated LV systolic dysfunction can manifest as afterload is now increased. A specific complication of MV repair is LVOT obstruction with systolic anterior motion of the anterior leaflet, especially if there is excessive posterior leaflet length.[11,12] Ideally, this is identified in the operating room following the weaning of cardiopulmonary bypass as re-operation with MVR may be required.

MITRAL STENOSIS

Mitral stenosis (MS) is predominantly due to rheumatic disease. Ironically, being a left-sided valve disease, LV function is usually unaffected. The major clinical issues are left atrial hypertension with resultant PHT, RV failure, atrial arrhythmia and heightened thromboembolic risk.

MEDICAL MANAGEMENT

If severe MS is the main driver for critical care unit admission then percutaneous or surgical intervention will be required. Controlling the ventricular rate is crucial to maximise the diastolic interval with atrial fibrillation being both common (occurring in 30%–40% of patients) and poorly tolerated. Anticoagulation is recommended in the presence of atrial fibrillation (paroxysmal, persistent or permanent), a prior embolic event or LA thrombus.

INTERVENTION FOR MITRAL STENOSIS

Percutaneous mitral balloon commissurotomy (PMBC) is the preferred option in symptomatic patients with severe MS and favourable valve morphology (relatively thin, mobile leaflets and free of calcium).[5,14] Open surgery is recommended in symptomatic patients who are not candidates for PMBC, or if undergoing cardiac surgery for other indications.

Since isolated MS does not cause substantive detriment to LV function, postoperative attention is focused on the pulmonary circulation and RV function. With correction of MS, left atrial and right-sided pressures should immediately improve. However, the insults of cardiopulmonary bypass and aortic cross-clamping can be significant, and RV dysfunction can be a challenge, especially if PHT remains largely fixed and irreversible.

RIGHT-SIDED VALVULAR LESIONS

Isolated valve lesions of the right heart are rarely encountered in adult critical care practice. Occasional cases requiring surgery may relate to infective endocarditis or residual and uncorrected congenital heart disease, such as severe pulmonary regurgitation (PR) following Tetralogy of Fallot (TOF) repair.

Tricuspid regurgitation (TR) is almost ubiquitous in patients with left-sided heart disease. A common dilemma is when to perform simultaneous tricuspid valve repair or replacement in patients undergoing left-sided valvular surgery. Repair, in particular, does not add appreciably to the risks of surgery and should be performed in cases of severe TR or severe tricuspid annular dilatation. However, careful consideration is required in the presence of severe RV dysfunction or significant PHT, as such repair can provoke catastrophic RV failure.

VALVULAR HEART DISEASE IN PREGNANCY

For native VHD in pregnancy, the highest-risk lesions are those that are stenotic rather than regurgitant, and left- rather than right-sided. Pregnancy-associated haemodynamic changes include increased heart rate and decreased systemic vascular resistance (SVR), which are favourable conditions for regurgitant faults, but disadvantageous for those stenotic.[15,16] With severely stenotic lesions, cardiac output may not realise the usual 50% increase that is reached by the end of the second trimester.

Prior to pregnancy, intervention for stenotic lesions is recommended in severe AS with symptoms and for severe MS (with preference for PMBC) regardless of symptoms.[5,17] For severe regurgitant lesions, repair or replacement is indicated for symptomatic women.[5,17] In pregnant patients, severe MS is poorly tolerated. If PMBC is not feasible, surgical MVR may the safest option, but it carries significant risk of both foetal (30%–40%) and maternal (9%) mortality.[5]

ADULT CONGENITAL HEART DISEASE

Congenital heart disease (CHD) is common. Birth prevalence is 7–10 per 1000 live births, but more than 25% of CHD diagnoses are made after infancy. In high-income countries, survival in children to adulthood has improved markedly over recent decades to over 85%, with adult survivors now outnumbering twofold affected children and adolescents.[18,19] However, the same gains have not been realised in low- and middle-income countries with the burden of disease only increasing.[20,21] Although adult CHD (ACHD) is highly variable in complexity and presentation, heart failure (HF) is the leading cause of death.[22,23]

THE INTENSIVIST PERSPECTIVE

The management of ACHD patients requiring critical care presents unique challenges to the intensivist. One must appreciate the anatomical diagnosis, the history of corrective procedures, the anticipated late complications, the

Table 25.3 Considerations for the intensivist managing adult congenital heart disease

QUESTION	COMMENTS
What is the congenital diagnosis and history of corrective procedures?	Appreciate natural history, post-procedural residual abnormalities or anticipated complications (see Table 25.4)
Are there residual shunts?	Consider effect of altering PVR:SVR relationship* on shunt direction, oxygenation and cardiac output Potential paradoxical embolisation risk Cyanosis and hyperviscosity syndrome if significant R → L shunt
Which morphological ventricle is the systemic ventricle?	Look for history of transposition (morphological RV is the systemic ventricle in l-TGA or d-TGA with atrial switch)
Is pulmonary hypertension an expected feature?	May be prominent with residual shunts, but also occurs with congenital or acquired left heart and pulmonary disease RVF may be the predominant haemodynamic issue
Is PVR critically important?	Especially important with single ventricle ('Fontan' circulation) Also, consider influence of PVR on residual shunt lesions
What influence will positive pressure ventilation have on cardiopulmonary interaction?	Possibly beneficial with: left heart dysfunction (↓ LV wall stress) Possibly detrimental with: Fontan circulation, RVF, significant TR and PHT, shunts (↑ RV afterload and ↓ preload)
Is there a preload-dependent state?	Caution with Fontan circulation, Eisenmenger syndrome, LVOT obstruction
Is particular caution required with negative inotropic or vasodilatory drugs?	Beware heart failure syndromes and pulmonary hypertension With shunts, consider effect on changing ratio of SVR:PVR Caution ↓ SVR with left-sided obstructive lesions
Does IV access present any issues?	Potential difficulty if history of multiple interventions. In Fontan circulation, standard CVC approach will enter PA and transvenous ventricular pacing is not possible
Are arrhythmias a feature and is a device (PPM, AICD) in situ?	Consider device interrogation

*Factors ↑ PVR: Hypoxia, hypercarbia, high haematocrit, positive pressure ventilation, hypothermia, metabolic acidosis, alpha-adrenergic stimulation. Factors ↓ SVR: Vasodilators, general anaesthesia, hyperthermia.

AICD, Automatic implantable cardiac defibrillator; *CVC*, central venous catheter; *d-TGA*, dextro-transposition of the great arteries; *IV*, intravenous; *l-TGA*, levo-transposition of the great arteries; *LV*, left ventricle; *LVOT*, left ventricular outflow tract obstruction; *PA*, pulmonary artery; *PHT*, pulmonary hypertension; *PPM*, permanent pacemaker; *PVR*, pulmonary vascular resistance; *RV*, right ventricle; *RVF*, right ventricular failure; *SVR*, systemic vascular resistance; *TR*, tricuspid regurgitation.

associated systemic disease and the holistic consideration of cardiopulmonary interaction (Tables 25.3 and 25.4).

KEY CLINICAL SCENARIOS AND SYNDROMES

HEART FAILURE IN ADULT CONGENITAL HEART DISEASE

Major societies have recently published position statements on the treatment of HF in ACHD but these chiefly relate to the outpatient setting.[23–25] These papers highlight difficulties in diagnosis (e.g. atypical symptoms), treatment (i.e. a paucity of controlled trials with hard end points in ACHD patients) and prognosis (e.g. New York Heart Association scores are not validated for palliated ACHD).[26] Furthermore, there are no scientific trials to guide intensivists on managing ACHD patients in the critical care context. Therefore, an approach based on pathophysiological first principles and the recognition of specific syndromes (below) are paramount. Generic, acquired contributors to ventricular dysfunction (e.g. coronary artery disease) should not be discounted, especially as the incidence of these will increase as the ACHD population ages. The patients at great risk for the development of HF are those with single-ventricles palliated with a Fontan procedure, TOF patients with residual PR, and those with a systemic RV, discussed below.[27]

SHUNTS, PULMONARY VASCULAR DISEASE AND PULMONARY HYPERTENSION

ACDH results in PHT in approximately 5%–10% of patients.[28] Systemic to pulmonary shunting, with

Table 25.4 Glossary of terminology and procedures in adult congenital heart disease

NAME	DIAGNOSIS/ INDICATION	PROCEDURE	RATIONALE	COMPLICATIONS	ADULT PHYSIOLOGY AND CONSIDERATIONS
Simple shunts	Any cause of L → R shunting:		Completely correct defect; prevent long-term sequelae	Arrhythmia, residual shunt	Excellent prognosis if repaired as child
	ASD	Transcatheter repair preferred option	RV volume overload, PHT, paradoxical emboli		If unrepaired, direction and magnitude of shunt is highly variable
	VSD	Surgical patch repair preferred option	LV volume overload, PHT, paradoxical emboli		Prognosis is determined by the degree of shunt, pulmonary HT and RVF/LVF
	PDA	Transcatheter repair preferred option	LV volume overload, PHT		
Left-sided obstructive lesions	Congenital AS (bicuspid aortic valve)	Surgical repair Balloon valvuloplasty has role in selected adolescents and young adults	Relieve ↑ LV afterload and prevent complications (see across)	Residual AS or coarctation	Uncorrected lesions will result in LV hypertrophy and diastolic dysfunction Maintain preload, sinus rhythm and adequate SVR
	Aortic coarctation	Stenting preferred option over open surgery			If untreated, risks include systemic HT, stroke, aortic dissection and LVF
Right-sided obstructive lesions	Valvular PS occurs as isolated defect in ≈ 7%–12% of all CHD	Balloon valvotomy treatment of choice	Relieve ↑ RV afterload	RVOT obstruction with severe RVH when obstruction is relieved; PR (post valvotomy)	Asymptomatic valve stenosis gains more importance in adults (↓ RV compliance, ↑ filling pressures/ venous congestion)
	Subvalvular PS (rare as an isolated defect, usually associated with VSD or post TOF repair)	Surgical myomectomy ± patch repair		Residual RVOT obstruction	Can present de novo in adults as double-chambered RV
	Supravalvular PS and PA stenosis	Transcatheter intervention if anatomically feasible		Residual stenosis	RVF if untreated
Tetralogy of Fallot	Pulmonary outflow obstruction, overriding aorta, VSD, RV hypertrophy	Surgical repair	Complete intra-cardiac repair, prevent complications	Residual VSD, residual RVOT obstruction, RV aneurysm Arrhythmia Severe PR	PR most common complication in adulthood with lesions repaired in childhood

Table 25.4 Glossary of terminology and procedures in adult congenital heart disease—cont'd

NAME	DIAGNOSIS/ INDICATION	PROCEDURE	RATIONALE	COMPLICATIONS	ADULT PHYSIOLOGY AND CONSIDERATIONS
PA banding	Any cause of ACHD with excessive pulmonary blood flow (e.g. single ventricle, multiple VSDs, AVSD, double-outlet ventricle)	Encircling main PA with prosthetic band	Decrease pulmonary blood flow and increase systemic perfusion until definitive repair or as palliation	PA impingement, damage to pulmonary valve	Pulmonary stenosis; proximal main PA dilatation, PR
Blalock-Taussig-Thomas (modified) shunt	Staging procedure prior to complete repair or palliative procedure to augment pulmonary blood flow when definitive repair not possible	Subclavian artery to ipsilateral PA shunt; timing: neonate	Increase pulmonary blood flow as neonatal PA pressures transition from high to normal	Shunt thrombosis; phrenic nerve injury, steal syndrome, chylothorax, seroma	Lower BP in ipsilateral upper limb
Glenn – bidirectional shunt (BDG) or hemi-Fontan	Staging procedure for single-ventricle physiology to augment pulmonary blood flow (prior to Fontan procedure)	Anastomosis SVC to right PA; timing: usually after 2–3 months of age	Increase pulmonary blood flow after neonatal PA pressures have normalised	Permanent Pulmonary AV fistulae	Usually followed at 2–4 years of age by complete Fontan procedure
Fontan procedure (total cavopulmonary connection)	All disease types in which a two-ventricle circulation cannot be restored (e.g. hypoplastic left heart, tricuspid atresia, pulmonary atresia, double inlet ventricle)	BDG + external conduit from IVC to PA	Diversion of all systemic venous blood direct to lungs (cavo-pulmonary bypass) Circuit flow: SV > direct to PA > LV > SV	Pulmonary AVMs, thrombosis right heart chambers	Single ventricle physiology Long term: pump failure (≈40%), SV congestion (cirrhosis, protein losing enteropathy)
Norwood procedure	Hypoplastic left heart	Staged procedures to create new functional systemic circulation: create neo-aorta (from PA), atrial septectomy, PA (BT) shunt; BDG; Fontan.	End-result is modified Fontan circulation with RV as single functioning ventricle	Traditionally associated with high surgical mortality but recent outcomes are improving (≈90% early survival)	RV is the single ventricle Often associated subaortic or aortic obstruction compromising the systemic RV

Continued

Table 25.4 Glossary of terminology and procedures in adult congenital heart disease—cont'd

NAME	DIAGNOSIS/ INDICATION	PROCEDURE	RATIONALE	COMPLICATIONS	ADULT PHYSIOLOGY AND CONSIDERATIONS
Pott's shunt	Palliative procedure in TOF	Anastomosis between left PA and descending aorta	Improve pulmonary blood flow due to RVOT obstruction with L → R shunt Offloads RV with R → L shunt in severe PAH	Abandoned procedure (used prior to availability of complete repair) Also used as palliative procedure in severe PAH	Palliative procedure
d-TGA	Pulmonary and systemic circuits are parallel and independent Aorta arises from RV PA arises from LV	See below	Incompatible with life; requires surgical correction Two circuits as follows: LV > PA > PV > LV and RV > aorta > SV > RV	See below	See below
Mustard, Senning procedures ('atrial switch')	d-TGA	Intra-atrial baffle to redirect systemic venous return to LV (and PA); pulmonary venous flow to RV (and aorta)	Correction of TGA at atrial level; corrects parallel circulation; allows adequate oxygenated systemic blood flow RV is systemic ventricle Circuit flow: SV > LV > PA > RA > aorta > SV	Baffle obstruction, caval obstruction, stenosis, thromboembolism	RV remains systemic ventricle; LV is the pulmonary ventricle Variable incidence RV failure (≈22%) Now superseded by arterial switch Arrhythmia
Rastelli, Jatene procedures ('arterial switch')	d-TGA	Aorta and PA transected, reattached to the opposite AV valves; coronaries reimplanted into neoaorta. Timing as neonate	Correction of TGA at arterial level LV is systemic ventricle Circuit flow is 'normal': SV > RV > neoPA > LV > neoaorta > SV	PA stenosis, PR, neoaortic stenosis	LV becomes the systemic ventricle; near-normal adult physiology Rarely, coronary circulation issues related to reimplantation
l-TGA ('congenitally corrected TGA)	Morphological RV and LV are inverted <1% of all CHD	See below	Circulation is 'physiologically corrected' at birth with circuit flow: SV > LV > PA > RV > SV	See below	RV is the systemic ventricle; progressive RV failure and TR are key issues
Double-switch procedure	l-TGA	Atrial correction (Mustard/ Senning) + arterial switch ± PA band to 'train' LV	Complete anatomic repair; controversial if l-TGA is isolated defect	Mortality up to 7%	Limited data on long-term outcome

Table 25.4 Glossary of terminology and procedures in adult congenital heart disease—cont'd

NAME	DIAGNOSIS/ INDICATION	PROCEDURE	RATIONALE	COMPLICATIONS	ADULT PHYSIOLOGY AND CONSIDERATIONS
Ebstein's anomoly	≈1% of all CHD TV is apically displaced with 'atrialisation' of RV Commonly has an associated ASD	TV repair preferred if possible BDG may be required if RV is too small for correction	Correct TR and small RV cavity with limited stroke volume	Previously high operative mortality; current rate <6%	Arrhythmias, RVF, paradoxical embolism

ACHD, Adult congenital heart disease; *AS*, aortic stenosis; *ASD*, atrial septal defect; *AV*, aortic valve; *AVM*, arteriovenous malformation; *BDG*, bidirectional shunt; *BP*, blood pressure; *BT*, Blalock-Taussig; *CHD*, congenital heart disease; *d-TGA*, dextro-transposition of the great arteries; *HT*, hypertension; *IVC*, inferior vena cava; *l-TGA*, levo-transposition of the great arteries; *LV*, left ventricle; *LVF*, left ventricular failure; *PA*, pulmonary artery; *PAH*, pulmonary arterial hypertension; *PDA*, patent ductus arteriosis; *PHT*, pulmonary hypertension; *PR*, pulmonary regurgitation; *PS*, pulmonary stenosis; *RV*, right ventricle; *RVF*, right ventricular failure; *RVH*, right ventricular hypertrophy; *RVOT*, right ventricular outflow tract; *SV*, systemic veins; *SVC*, superior vena cava; *SVR*, systemic vascular resistance; *TGA*, transposition of the great arteries; *TOF*, Tetralogy of Fallot; *TR*, tricuspid regurgitation; *VSD*, ventricular septal defect.
See references 24, 31, 57–59.

persistent exposure of the pulmonary vasculature to increased blood flow and pressure, may lead to obstructive arteriopathy with increased pulmonary vascular resistance (PVR). At the extreme, when PVR approaches and exceeds SVR, the shunt is reversed (Eisenmenger syndrome).

For adult patients with simple shunts repaired as children, the prognosis is excellent. However, lesions are often only diagnosed once symptoms develop in adulthood. The role of shunt correction in these situations is less well defined. This requires assessment of the defect, the patient age, the PVR:SVR ratio and the ratio of pulmonary to systemic flow (Qp:Qs). Somewhat paradoxically, the left-to-right shunt has to be large enough to warrant surgery, but the risk becomes prohibitive once significant PHT is present. For atrial septal defects (ASDs), closure is recommended for large shunts with signs of RV volume overload, regardless of symptoms.[25] For ventricular septal defects (VSDs), closure is indicated for symptoms attributable to the VSD or when signs of LV volume overload are present.[25] The latter occurs as a compensatory increase in intravascular volume acts to maintain LV diastolic volume and systemic cardiac output. For secundum ASD closure, percutaneous device insertion is the preferred method, whereas for VSD, pericardial patch repair is preferred if the surgical risk is acceptable.[25] For either level of shunt, current guidelines suggest a Qp/Qs >1.5 and PVR ≤4.6 Wood units (368 dynes-sec/cm^5) as upper limits of safety.[29,30] Conversely, patients who develop PHT after shunt closure have a poor prognosis.

In the case of residual shunting, the SVR:PVR balance (see Table 25.3) will determine the magnitude and direction of the shunt, effecting systemic cardiac output, the degree of hypoxaemia and the risk of systemic embolisation. For the most severely affected patients with Eisenmenger syndrome, bosentan is recommended if World Health Organization functional class III symptoms are present.[30,31] Although lacking as strong an evidence-base, other endothelin-receptor antagonists and pulmonary vasodilators (prostanoids and phosphodiesterase type 5 inhibitors) can be considered. Secondary erythrocytosis is generally tolerated unless haematocrit is greater than 65% and is associated with hyperviscosity symptoms. For the intensivist, management can be extremely challenging. Prioritising the pulmonary circulation may warrant subtle but deliberate changes to practice to optimise PVR such as: 'earlier' use of renal replacement therapy to correct metabolic acidosis; preferential use of non-catecholamines (e.g. vasopressin) for defending systemic (coronary perfusion) pressure[32,33]; re-evaluation of haematocrit targets; cautious/selective use of sedative/hypnotic agents; use of intravenous or inhaled selective pulmonary vasodilator therapy; judicious use of non-invasive ventilation; and meticulous attention to carbon dioxide tension when controlled positive pressure ventilation is mandated.

TETRALOGY OF FALLOT

TOF is the most common cyanotic CHD in adults. For patients with lesions repaired in childhood, the prognosis is excellent. Significant PR is the most frequent complication; although well tolerated for years, PR eventually leads to RV dilatation and dysfunction, making optimal timing of valve replacement challenging. Additional long-term complications include residual VSD or right ventricular outflow tract obstruction, aortic root dilatation and

arrhythmia. Left-sided ventricular dysfunction is being increasingly recognised, largely due to interventricular interaction including abnormal septal configuration and electromechanical dyssynchrony.

THE MORPHOLOGICAL RV AS THE SYSTEMIC VENTRICLE

A systemic right ventricle is destined to fail. This group largely includes patients with dextro-transposition of the great arteries (d-TGA; palliated with atrial switch) or levo-transposition of the great arteries (l-TGA). In addition to RV systolic dysfunction, d-TGA patients who have undergone atrial switch (Mustard or Senning procedures) are often limited by fixed stroke volume due to limited flow through stiff atrial baffles. These complications do not occur with the more recent arterial switch procedures, in which normal atrioventricular and ventriculoarterial connections are restored. Patients with l-TGA (where connections are 'congenitally corrected') often develop progressive systemic AV regurgitation.

FONTAN CIRCULATION (SINGLE-VENTRICLE PHYSIOLOGY)

This group includes tricuspid atresia, double-inlet LV and hypoplastic left heart syndrome. Surgical correction bypasses systemic venous return around the subpulmonary ventricle; all systemic venous blood returns directly to the lungs via the pulmonary arteries. These patients are at high risk for HF. The lack of a subpulmonic ventricle requires a central venous pressure higher than mean pulmonary arterial and pulmonary venous pressure to maintain return to the single ventricle. The circulation is thus 'preload' dependent, but PVR is critically important (see above). Although these patients have high afterload and stroke-work, there is no clinical trial evidence to guide the use of specific afterload-reducing therapy. Pulmonary vasodilator therapies have shown mixed results.[29] Long-term complications include cirrhosis, portal hypertension and protein-losing enteropathy.

SYSTOLIC FAILURE OF THE MORPHOLOGICAL LEFT VENTRICLE

Systolic LV dysfunction may result from pressure-overload lesions, such as congenital AS, bicuspid aortic valve and coarctation of the aorta. Bicuspid valves may develop progressive insufficiency as well as aortic root dilatation and dissection. Culprit volume-overload lesions include aortic regurgitation, VSD, patent ductus arteriosis or mitral regurgitation. Although specific trials in ACHD patients with hard end-points are lacking, current treatment guidelines extrapolate data from the general HF population to include recommendations for diuretics, renin-angiotensin-aldosterone system antagonists, beta blockers and mineralocorticoid receptor antagonists.

TRANSPLANTATION

Compared to patients without CHD, adult patients with CHD undergoing heart transplantation have lower early (30-day) survival rates, but higher long-term survival rates with similar 10-year outcomes.[19,34] The timing of assessment for transplant is difficult, and patients with irreversible multisystem dysfunction may require combined multiorgan transplantation (e.g. pulmonary, hepatic or renal).

ROLE OF VENTRICULAR ASSIST DEVICES

The utilisation of ventricular assist devices (VADs) is lower in ACHD awaiting transplantation than those with acquired heart disease.[19,22] ACHD patients are more likely to have right-sided HF, pulmonary HT or residual shunts that may make them less appealing for VADs.

ARRHYTHMIA

A gamut of tachy- and bradyarrhythmias may become manifest in ACHD patients, with arrhythmias now a major cause of morbidity and mortality. Sudden cardiac death (SCD) accounts for 20%–25% of late deaths in ACHD patients with systemic ventricular dysfunction a key risk factor.[35] Selection criteria for implantable cardioverter defibrillator devices, as primary or secondary prevention of SCD are based on data extrapolated from the generalised population.[22] Catheter ablation and device implantation all may be viable options but specific planning may be required with consideration of anatomy and vascular pathways.

INFECTIVE ENDOCARDITIS

ACHD patients have a greater (15–140-fold) incidence of IE than the general population.[36] Echocardiographic diagnosis can be difficult, with disease more often involving the right side, but overall prognosis is better than other patient groups, with mortality less than 10%.

NON-CARDIAC DISEASE AND OTHER CONSIDERATIONS IN ADULT CONGENITAL HEART DISEASE

Non-cardiovascular morbidity may relate to the underlying lesion, surgical repair or medical treatment. Neurological complications include embolic stroke, intracranial haemorrhage and brain abscess. Coarctation and bicuspid aortic valve are associated with an increased risk of intracranial aneurysms.[37,38] Pulmonary abnormalities most commonly manifest as restrictive ventilatory defects, and renal dysfunction is present in ≈50% of ACHD population.[39,40] In addition to associated congenital airway abnormalities, previous prolonged intubation can result in subglottic stenosis or vocal cord paresis. Congestive hepatopathy occurs chiefly in Fontan patients and those

with RV failure. Due to radiation exposure, especially in childhood, patients with ACHD are possibly at increased cancer risk, particularly for haematological and head/neck malignancies.[24,41] Pregnancy in CHD is associated with an increased rate of maternal and neonatal adverse events.[42,43] Groups at highest risk during pregnancy include those with severe pulmonary arterial hypertension, left heart obstruction, poor systemic ventricular function and aortic root dilatation.[25,44]

INFECTIVE ENDOCARDITIS

IE can be a taxing disease for the intensivist. In critically unwell patients managed in the ICU, the short-term mortality approximates 30%–57% in those treated aggressively with surgery; whereas for patients meeting an indication but denied surgery, the prognosis is dismal with a mortality of 85%.[45–49] Common reasons for ICU admission include HF in over 60% of cases, septic shock in 20% and neurological sequelae in 15%.[48] Staphylococci have emerged as the most prevalent culprit organisms, although alternative organisms, such as fungi are proportionately more common in the ICU. Overall, the incidence of IE is static but the epidemiology is transforming: mean age at diagnosis is increasing; an increasing proportion relates to prosthetic valves, cardiac devices and other nosocomial factors; the proportion associated with rheumatic heart disease is decreasing.[50–52]

DIAGNOSIS

The modified Duke criteria, although well accepted, lack accuracy for early diagnosis, and in this context are intended as a guide and must not replace clinical judgment.[36,52,53] Diagnosis in ICU patients can be particularly challenging. This requires holding a high index of suspicion, searching meticulously for clinical features, such as fever, vascular and immunological phenomena, and arranging appropriate microbiological testing. Echocardiography is cornerstone, with major features including vegetation (defined as oscillating intracardiac masses on valve or supporting structures), abscess, new partial dehiscence of prosthetic valve and new valvular regurgitation (Table 25.5). Recent guidelines suggest additional imaging modalities may be of use. In doubtful cases, computed tomography (CT) may detect local paravalvular complications, CT and magnetic resonance imaging may detect distant embolic phenomena and 18F-fluorodeoxyglucose positron emission tomography/CT may detect prosthetic valve infection.[36]

ROLE OF TRANSOESOPHAGEAL ECHOCARDIOGRAPHY

Although transthoracic echocardiography (TTE) is the first-line imaging technique for suspected IE, TOE should be considered if clinical suspicion remains high with a negative TTE or there are concerns for local complications. Even after a negative TOE, if clinical suspicion

Table 25.5 Echocardiographic features of infective endocarditis

FEATURE	DESCRIPTION
Vegetations*	Shape: usually amorphous, shaggy, lobulated, less commonly linear or round Motion: high-frequency flutter, oscillating, chaotic, orbiting Location: typically atrial side of atrioventricular valves, ventricular side of the aortic valve
Valvular disease	New regurgitation*, leaflet perforation or destruction
Abscess*	Echolucent or echogenic-heterogeneous space or tissue thickening Usually paravalvular but may affect any myocardial region Aortic valve most commonly affected
Pseudoaneurysm	Pulsatile perivalvular echo-free space; colour-flow Doppler present
Perforation	Interruption of endocardial continuity
Fistula	Colour-Doppler communication between neighbouring cavities (e.g. aorta-ventricle or aorta-atrium)
Valve aneurysm	Saccular bulging of valvular tissue
Dehiscence of prosthetic valve*	Paravalvular regurgitation; rocking motion of prosthesis
Other findings	Altered left ventricular size or function Elevated left or right ventricular filling and pulmonary artery pressures

*Constitute the Modified Duke major echocardiographic criteria.[53]
See references 36, 60, 61.

remains high, a repeat study should be considered in 3–5 days.[52] Such an interval may allow vegetation to reach a detectable size or abscess cavities or fistulous tracts to be evident. For right-sided lesions, TOE is also more sensitive in diagnosing lead-associated and pulmonary-valve disease.

ANTIMICROBIAL THERAPY

Early antimicrobial therapy is imperative and should reflect major society guidelines in the context of local expertise and protocols. General principles include the use of prolonged, parenteral, bactericidal therapy, recognising the altered pharmacokinetics typically seen in critically ill patients. Initial empirical therapy, whilst awaiting microbiological testing, should cover staphylococci, streptococci and enterococci in native valve endocarditis (NVE). Flucloxacillin is more effective than vancomycin for methicillin-susceptible staphylococci, but the latter should be used empirically in prosthetic valve endocarditis (PVE) and healthcare-associated IE regimens to cover methicillin-resistant strains.[36]

INDICATIONS FOR AND TIMING OF SURGERY

Currently, the proportion of IE patients proceeding to surgery is ≈50%. Although the theoretical indications for surgery are clear, practical application is complex and relies largely on clinical judgement, with consideration of the real-time status of the patient, the perceived natural history and the risks of surgery. Decision making in patients requiring critical care unit admission is challenging, and multidisciplinary involvement is recommended.[36,52] It should be noted that the bulk of the evidence and guidelines relate to left-sided endocarditis.

HEART FAILURE

HF is the most common complication of IE and the most common indication for surgery. The usual mechanism of HF is new or progressive valvular regurgitation although intracardiac fistulae or valve obstruction may occur. In these circumstances, the European Society of Cardiology suggest 'urgent' surgery (within a few days), but with refractory shock or pulmonary oedema, the recommendation is for 'emergency' surgery (within 24 hours).[36] For similar indications, the American Heart Association guidelines only use the time discriminator of 'early', meaning surgery during initial hospitalisation and before completion of the antibiotic course.[52]

UNCONTROLLED INFECTION

Uncontrolled infection is described as persisting infection with ongoing positive blood cultures after an arbitrary 7–10 days of antibiotic treatment. However, recent data suggest that prognosis is worse even with only 3 days of persistently positive blood cultures.[54] Uncontrolled infection may also refer to perivalvular extension with feared complications, such as abscess formation, pseudoaneurysms and fistulae.

Although 'early' or 'urgent' surgery is recommended for patients with uncontrolled infection, surgical outcomes for patients with overt septic shock, as opposed to cardiogenic shock, are much poorer. In practice, it may be difficult to compartmentalise the haemodynamic disturbance as purely 'septic' or 'cardiogenic'. If possible, it may be preferable to attempt a period of stabilisation prior to surgical commitment. Navigating this decision-making process requires careful and repeated clinical examination, appropriate haemodynamic monitoring including serial echocardiography, and close liaison with surgical and other colleagues.

PREVENTION OF EMBOLISATION

Embolisation rates improve significantly with appropriate antibiotics, so prompt initiation is paramount. Only one randomised trial has examined the role of early surgery in this context.[55] The precise role of surgery remains unclear, with guidelines based on the size and mobility of the vegetation, the associated valve dysfunction and the presence of established embolic events. Adjunctive anticoagulation or antiplatelet therapy is not recommended.

NEUROLOGICAL EVENTS AND RISK OF SURGERY

Symptomatic neurological events develop in 15%–30% of all IE patients, and are the most common complications in patients following ICU admission.[45,56] Yet, many of these patients might otherwise warrant urgent valvular surgery, with the attendant risks of systemic heparinisation and other rheological effects of cardiopulmonary bypass. Current recommendations suggest that as long as coma and intracerebral haemorrhage are absent, ischaemic stroke should not be considered a contraindication to surgery, with an estimated neurological risk in the order of 3%–6%.[36,52,56] In the case of intracerebral haemorrhage, surgery should be delayed by at least 1 month, although patients with small lesions have been operated on safely.[36,52,56]

PROSTHETIC VALVE ENDOCARDITIS

PVE represents 10%–30% of all IE cases.[36] Antimicrobial therapy for staphylococcal PVE generally warrants more prolonged treatment often in combination with aminoglycosides and rifamycins. Surgery is more likely to be required but its precise role remains controversial, and current guidelines follow similar principles to NVE.

INFECTIVE ENDOCARDITIS ASSOCIATED WITH CARDIAC IMPLANTED ELECTRONIC DEVICES

IE associated with cardiac implanted electronic devices (CIEDs) is associated with high mortality. Diagnosis is particularly difficult and because of CIED implantation patients may inevitably have severe co-morbidity.

Coagulase-negative Staphylococci are the most common causative organisms. Management requires prolonged antibiotic therapy as well as removal of the device and leads. Transvenous explantation is preferred, but is not risk free, and should only be performed in centres with ready access to cardiac surgical rescue.

RIGHT-SIDED ENDOCARDITIS

Constituting 5%–10% of cases and despite a better prognosis, surgery for right-sided IE is less commonly employed, but can be considered reasonable for patients with right HF due to severe TR with intractable symptoms; sustained infection caused by difficult-to-treat organisms or lack of response to appropriate antimicrobial therapy; and recurrent pulmonary embolism or paradoxical emboli despite antimicrobial therapy. Valve repair may be preferred if possible rather than replacement.[36]

FUNGAL ENDOCARDITIS

Fungal IE is more commonly seen with PVE, immunocompromised patients, and in the setting of intravenous drug use. *Candida* and *Aspergillus* species are the main offenders. Surgery is more frequently required in conjunction with long-term antifungal chemotherapy.

REFERENCES

1. d'Arcy JL, Prendergast BD, Chambers JB, et al. Valvular heart disease: the next cardiac epidemic. *Heart*. 2011;97(2):91–93.
2. Coffey S, Cairns BJ, Iung B. The modern epidemiology of heart valve disease. *Heart*. 2016;102(1):75–85.
3. Colquhoun SM, Condon JR, Steer AC, et al. Disparity in mortality from rheumatic heart disease in indigenous Australians. *J Am Heart Assoc*. 2015; 4(7).
4. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J*. 2012;33(19):2451–2496.
5. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(23):e521–e643.
6. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2013;14(7):611–644.
7. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr*. 2009;22(1):1–23, quiz 101–102.
8. De Bonis M, Al-Attar N, Antunes M, et al. Surgical and interventional management of mitral valve regurgitation: a position statement from the European Society of Cardiology Working Groups on Cardiovascular Surgery and Valvular Heart Disease. *Eur Heart J*. 2016;37(2):133–139.
9. Clavel MA, Magne J, Pibarot P. Low-gradient aortic stenosis. *Eur Heart J*. 2016;37(34):2645–2657.
10. Bonow RO, Leon MB, Doshi D, et al. Management strategies and future challenges for aortic valve disease. *Lancet*. 2016;387(10025):1312–1323.
11. Ibrahim M, Rao C, Ashrafian H, et al. Modern management of systolic anterior motion of the mitral valve. *Eur J Cardiothorac Surg*. 2012;41(6):1260–1270.
12. Varghese R, Anyanwu AC, Itagaki S, et al. Management of systolic anterior motion after mitral valve repair: an algorithm. *J Thorac Cardiovasc Surg*. 2012;143(suppl 4):S2–S7.
13. Nishimura RA, Vahanian A, Eleid MF, et al. Mitral valve disease – current management and future challenges. *Lancet*. 2016;387(10025):1324–1334.
14. Nunes MC, Nascimento BR, Lodi-Junqueira L, et al. Update on percutaneous mitral commissurotomy. *Heart*. 2016;102(7):500–507.
15. Sliwa K, Johnson MR, Zilla P, et al. Management of valvular disease in pregnancy: a global perspective. *Eur Heart J*. 2015;36(18):1078–1089.
16. Thorne S. Pregnancy and native heart valve disease. *Heart*. 2016;102(17):1410–1417.
17. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32(24):3147–3197.
18. Avila P, Mercier LA, Dore A, et al. Adult congenital heart disease: a growing epidemic. *Can J Cardiol*. 2014;30(suppl 12):S410–S419.
19. Budts W, Roos-Hesselink J, Radle-Hurst T, et al. Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology. *Eur Heart J*. 2016;37(18):1419–1427.
20. Penny DJ. Global perspectives on pediatric cardiac critical care. *Pediatr Crit Care Med*. 2016;17(8 suppl 1): S388–S393.
21. Hoffman J. The global burden of congenital heart disease. *Cardiovasc J Afr*. 2013;24(4):141–145.
22. Stout KK, Broberg CS, Book WM, et al. Chronic heart failure in congenital heart disease: a scientific statement from the American Heart Association. *Circulation*. 2016;133(8):770–801.
23. Verheugt CL, Uiterwaal CS, van der Velde ET, et al. Mortality in adult congenital heart disease. *Eur Heart J*. 2010;31(10):1220–1229.
24. Bhatt AB, Foster E, Kuehl K, et al. Congenital heart disease in the older adult: a scientific statement from the American Heart Association. *Circulation*. 2015;131(21):1884–1931.
25. Baumgartner H, Bonhoeffer P, De Groot NM, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J*. 2010;31(23):2915–2957.

26. Krieger EV, Valente AM. Heart failure treatment in adults with congenital heart disease: where do we stand in 2014? *Heart*. 2014;100(17):1329–1334.
27. Dinardo JA. Heart failure associated with adult congenital heart disease. *Semin Cardiothorac Vasc Anesth*. 2013;17(1):44–54.
28. Diller GP, Gatzoulis MA. Pulmonary vascular disease in adults with congenital heart disease. *Circulation*. 2007;115(8):1039–1050.
29. D'Alto M, Diller GP. Pulmonary hypertension in adults with congenital heart disease and Eisenmenger syndrome: current advanced management strategies. *Heart*. 2014;100(17):1322–1328.
30. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37(1):67–119.
31. Galie N, Beghetti M, Gatzoulis MA, et al. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation*. 2006;114(1):48–54.
32. Price LC, Wort SJ, Finney SJ, et al. Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. *Crit Care*. 2010;14(5):R169.
33. Vlahakes GJ, Turley K, Hoffman JI. The pathophysiology of failure in acute right ventricular hypertension: hemodynamic and biochemical correlations. *Circulation*. 1981;63(1):87–95.
34. Doumouras BS, Alba AC, Foroutan F, et al. Outcomes in adult congenital heart disease patients undergoing heart transplantation: a systematic review and meta-analysis. *J Heart Lung Transplant*. 2016;35(11):1337–1347.
35. Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. [corrected]. *Circulation*. 2012;126(14):1784–1800.
36. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J*. 2015;36(44):3075–3128.
37. Schievink WI, Raissi SS, Maya MM, et al. Screening for intracranial aneurysms in patients with bicuspid aortic valve. *Neurology*. 2010;74(18):1430–1433.
38. Connolly HM, Huston J 3rd, Brown RD Jr, et al. Intracranial aneurysms in patients with coarctation of the aorta: a prospective magnetic resonance angiographic study of 100 patients. *Mayo Clin Proc*. 2003;78(12):1491–1499.
39. Dimopoulos K, Diller GP, Koltsida E, et al. Prevalence, predictors, and prognostic value of renal dysfunction in adults with congenital heart disease. *Circulation*. 2008;117(18):2320–2328.
40. Ginde S, Bartz PJ, Hill GD, et al. Restrictive lung disease is an independent predictor of exercise intolerance in the adult with congenital heart disease. *Congenit Heart Dis*. 2013;8(3):246–254.
41. Lee YS, Chen YT, Jeng MJ, et al. The risk of cancer in patients with congenital heart disease: a nationwide population-based cohort study in Taiwan. *PLoS ONE*. 2015;10(2):e0116844.
42. Opotowsky AR, Siddiqi OK, D'Souza B, et al. Maternal cardiovascular events during childbirth among women with congenital heart disease. *Heart*. 2012;98(2):145–151.
43. Thompson JL, Kuklina EV, Bateman BT, et al. Medical and obstetric outcomes among pregnant women with congenital heart disease. *Obstet Gynecol*. 2015;126(2):346–354.
44. Harris IS. Management of pregnancy in patients with congenital heart disease. *Prog Cardiovasc Dis*. 2011;53(4):305–311.
45. Sonneville R, Mirabel M, Hajage D, et al. Neurologic complications and outcomes of infective endocarditis in critically ill patients: the ENDOcardite en REAnimation prospective multicenter study. *Crit Care Med*. 2011;39(6):1474–1481.
46. Mourvillier B, Trouillet JL, Timsit JF, et al. Infective endocarditis in the intensive care unit: clinical spectrum and prognostic factors in 228 consecutive patients. *Intensive Care Med*. 2004;30(11):2046–2052.
47. Samol A, Kaese S, Bloch J, et al. Infective endocarditis on ICU: risk factors, outcome and long-term follow-up. *Infection*. 2015;43(3):287–295.
48. Karth G, Koreny M, Binder T, et al. Complicated infective endocarditis necessitating ICU admission: clinical course and prognosis. *Crit Care*. 2002;6(2):149–154.
49. Mirabel M, Sonneville R, Hajage D, et al. Long-term outcomes and cardiac surgery in critically ill patients with infective endocarditis. *Eur Heart J*. 2014;35(18):1195–1204.
50. Bor DH, Woolhandler S, Nardin R, et al. Infective endocarditis in the U.S., 1998-2009: a nationwide study. *PLoS ONE*. 2013;8(3):e60033.
51. Cahill TJ, Prendergast BD. Infective endocarditis. *Lancet*. 2016;387(10021):882–893.
52. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132(15):1435–1486.
53. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis

of infective endocarditis. *Clin Infect Dis*. 2000;30(4): 633–638.
54. Lopez J, Sevilla T, Vilacosta I, et al. Prognostic role of persistent positive blood cultures after initiation of antibiotic therapy in left-sided infective endocarditis. *Eur Heart J*. 2013;34(23):1749–1754.
55. Kang DH, Kim YJ, Kim SH, et al. Early surgery versus conventional treatment for infective endocarditis. *N Engl J Med*. 2012;366(26):2466–2473.
56. Garcia-Cabrera E, Fernandez-Hidalgo N, Almirante B, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. *Circulation*. 2013;127(23):2272–2284.
57. Gaca AM, Jaggers JJ, Dudley LT, et al. Repair of congenital heart disease: a primer-part 1. *Radiology*. 2008;247(3):617–631.
58. Yuan SM, Jing H. Palliative procedures for congenital heart defects. *Arch Cardiovasc Dis*. 2009;102(6–7):549–557.
59. Rhodes JF, Hijazi ZM, Sommer RJ. Pathophysiology of congenital heart disease in the adult, part II. Simple obstructive lesions. *Circulation*. 2008;117(9): 1228–1237.
60. Saric M, Armour AC, Arnaout MS, et al. Guidelines for the use of echocardiography in the evaluation of a cardiac source of embolism. *J Am Soc Echocardiogr*. 2016;29(1):1–42.
61. Keynan Y, Singal R, Kumar K, et al. Infective endocarditis in the intensive care unit. *Crit Care Clin*. 2013;29(4):923–951.

26

Postoperative cardiac intensive care

Nick Fletcher, Michael Adlam

Coronary artery bypass surgery is one of the most frequently undertaken surgical procedures globally. Because of the prevalence of cardiac disease, cardiac surgery has significant health and economic implications. Intensive care may account for up to 40% of the total hospital costs for these patients and much of the short-term morbidity and mortality is based on perioperative events.

The overall mortality following cardiac surgery is low (approximately 3%). However, this ranges from less than 1% for elective coronary artery bypass grafting to more than 30% for more complex surgery in patients with significant myocardial dysfunction and significant co-morbidities. Intensive care management following cardiac surgery usually involves a short period of recovery before discharge to the ward. For a small percentage of patients, significant complications may require the complete spectrum of high acuity intensive therapy, with a profound impact on the intensive care unit (ICU) capacity, hospital budgets and resources.

ORGANISATION

TYPES OF UNIT

The co-location of large numbers of patients with similar problems in the cardiac ICU provides an ideal environment for the standardisation of care based on protocols and clinical pathways. One of the traps of postoperative cardiac care is that this apparent similarity of the patients tends to obscure their particularity. Individual patient assessment must carefully address the multisystemic manifestations of cardiovascular and other degenerative diseases. In some institutions, cardiac patients may be located with other surgical and medical intensive care patients to centralise critical care resources – staffing in particular. There is no adequate supporting evidence as to whether cardiac surgical patients have better outcomes with any particular model; rather, it is likely that high quality dedicated critical care, constructive relationships with surgeons and a multidisciplinary culture will positively impact on the results. There has been significant research into organisational factors in general ICU; however, there is less supporting information around issues such as open versus closed ICU, and surgeon-led care versus intensivist-led care in the cardiac arena.

SURGEON/INTENSIVIST RELATIONSHIP

Cardiac surgery involves a continuum of care from presentation to post-discharge management and rehabilitation. The intensive care specialist must be involved in this continuum, rather than functioning in isolation from surgeons, anaesthetists, cardiologists and even family practitioners.

The postoperative stage and outcome is largely set by the preoperative and operative phases of management, and it is the fitness of the patient to undergo surgery that is the primary determinant.[1] A component of postoperative management is active participation in patient selection and preparation, as well as in the conduct of anaesthesia and surgery. Relevant aspects include suitability and preparation for surgery, advanced care planning and more technical issues, such as temperature management, invasive monitoring, haemodynamic management and transport. Movement from the operating theatre to the ICU and on to the ward presents a potential hazard and will appear seamless only if the patient journey has been well coordinated in advance.

Joint selection and morbidity and mortality meetings may allow a forum to discuss complex cases and facilitate improvement of the institutional processes. In particular, the human factors, which are so essential to successful cardiac surgery, may be put under the microscope. Regular audit of discharge timeliness, readmission and hospital mortality allows benchmarking against other units, both internal and external, and ensures good practices are maintained and poor practice is eliminated.

OUTCOME AUDIT

In the United States and the United Kingdom, risk-adjusted cardiac surgical results are available in the public domain by individual surgeon and institution. EuroSCORE II is the predominant preoperative cardiac surgical risk score, but this performs less well as an

ABSTRACT

The worldwide volume of cardiac surgery is increasing as a result of a greater disease prevalence, surgical centre development and availability in the developing world; an ageing population in the developed world and an increasing diversity of surgical techniques. In older patients, this greater co-morbidity and increased complexity means they are sicker and are staying longer in postoperative cardiac critical care units. Organ support and rehabilitation have developed in this population in parallel to general critical care. Factors affecting the immediate postoperative care of these patients are better understood, and organisational processes have been developed in response. A good understanding of the anatomy, physiology and pharmacology that underpins this area is essential. The common complications secondary to the surgery and circulatory bypass must be recognised early and treated to minimise organ hypoperfusion and consequent failure.

KEYWORDS

Cardiac surgery
echocardiography
critical care
intensive care
circulation
haemodynamic support
cardiac failure

ICU score. The majority of ICU scoring systems were not designed with cardiac surgery patients in mind; hence, some cardiac ICU-specific scoring systems have been more recently introduced. Currently, these are specific to different health systems.[2,3]

TYPES OF PROCEDURE

Changing patterns of practice are resulting in the management of older patients with more co-morbid pathologies. Procedures are now being offered to patients previously considered unfit for surgery, and there is a continuing growth in the use of minimally invasive forms of surgery. At the same time, patient and family expectations of surgery are increasing. This, together with greater expectation for regular and detailed communication, will increasingly impact on cardiac intensive care practice.

IMMEDIATE POSTOPERATIVE MANAGEMENT PRINCIPLES

STRUCTURED HANDOVER

The first step in the intensive care management involves a simple transfer of ventilation, monitoring and drug administration from transport to ICU systems. This should be structured to minimise disruption and maximise communication. The priorities are:

- Confirm surgical procedure and any complications
- Confirm integrity and position of the endotracheal tube
- Re-establish mechanical ventilation of both lungs
- Re-establish all patient monitoring
- Confirm venous, arterial and central access
- Heart rhythm and presence and mode of any pacing devices
- Document results of any intraoperative echocardiography regarding ventricular function.
- Intraoperative transfusion of blood or factors together with the results of any benchtop or laboratory tests of haemostasis
- An early 12-lead electrocardiograph to exclude or identify acute ischaemia.

Management is conveniently dictated by standardised protocols, which should cover investigations, fluid and electrolyte management, vasoactive and other drug administration, and weaning and withdrawal mechanical ventilation. Standardisation is probably more important than the particulars of the protocol, which might vary considerably among institutions.

HAEMODYNAMIC MONITORING

Continuous invasive blood pressure and central venous pressure monitoring are standard following surgery, and should be monitored during transfer. Patients may commonly become unstable during transfer and rapid assessment is needed to ensure the correct calibration of transducers, continuity of all infusions, evidence of hypovolaemia and haemorrhage. Cardiac output measurement by pulse contour analysis, pulse power analysis and a variety of ultrasound techniques are becoming more commonplace. Cardiac output-guided fluid boluses allow individualised treatment, and unresponsiveness can guide inotropic and vasopressor use. Of note, pulse analysis is invalid in the presence of intra-aortic counterpulsation.

In complex surgical patients, and those in which minimally invasive strategies are invalid, more invasive methods of haemodynamic monitoring are required.

Flotation pulmonary artery (PA) catheterisation has become somewhat controversial. It is now reasonably well established that PA catheterisation is safe but may not alter outcomes.[4]

- Surgery can be safely undertaken at least in low-risk patients without PA catheterisation.
- Collateral evidence supports PA catheter use in more complicated cases.
- It is essential that the known limitations and complications of PA catheters are considered in usage and interpretation.[5]

Transoesophageal echocardiography (TEE) is now almost routine in the operating theatre – at least for more complicated patients. The technique is less suitable for monitoring in the ICU, but is helpful in the diagnosis and management of cardiovascular instability in postoperative patients. Continuous TEE monitoring has been described, but the application is not widely used.[6]

Transthoracic echocardiography is of limited use postoperatively due to the poor cardiac windows. The apical window may allow some assessment of biventricular function and volume status. Inferior vena caval assessment is problematic and should not be used in this context.[7]

FLUIDS

Despite generous intraoperative fluid administration, effective hypovolaemia is common in the early postoperative period, especially as warming with associated vasodilatation occurs.

- Use of isotonic fluid is essential.
- No benefit for any specific resuscitation fluid has been established.
- Larger volumes of crystalloid than colloid solutions are required.
- An excessively positive fluid balance may increase perioperative complications.

Polyuria is frequently observed in the early postoperative period, possibly related to hypothermia,

haemodilution and the after-effects of non-pulsatile cardiopulmonary bypass on stretch and baroreceptors. This usually settles within the first 6 hours, but often necessitates considerable volume replacement in the meantime.

ELECTROLYTES

Hypomagnesaemia and hypokalaemia are frequent in the early postoperative stage and are exacerbated by polyuria. It is generally considered that levels should be maintained in the high normal range (4.5–5.0 mmols/L) although this has recently been challenged.[8]

Late hyperkalaemia may occur, especially in patients with renal impairment or prior angiotensin-converting enzyme (ACE) inhibitor administration. Treatment for hyperkalaemia is rarely required in the absence of significant renal impairment, but discontinuation of potassium-containing fluid may be required.

Calcium homeostasis is generally not disrupted by cardiopulmonary bypass. However, massive transfusion frequently causes hypocalcaemia. Ionised calcium levels are now easily monitored by point-of-care blood gas analysers.

SHIVERING

Shivering is frequent following cardiac surgery. Mechanisms are complex and not entirely related to core temperature. Shivering causes a significant increase in metabolic rate and hence cardiac workload. This is especially important in the patient with impaired cardiac function and limited reserve. Forced air warmers are the most effective treatment, but pharmacological agents may be considered; these include dexamethasone, clonidine, pethidine and high-dose morphine. Short-term neuromuscular blockade is occasionally required.

HAEMODYNAMIC COMPLICATIONS AND MANAGEMENT

HYPERTENSION

Significant postoperative hypertension is more common in patients having a history of hypertension and with cessation of beta blockade, but is reasonably common in the early postoperative period. Both absolute pressure and dp/dt are important factors in vascular injury. Complications associated with hypertension include:

- bleeding
- heart failure
- vascular (especially aortic) injury
- myocardial ischaemia.

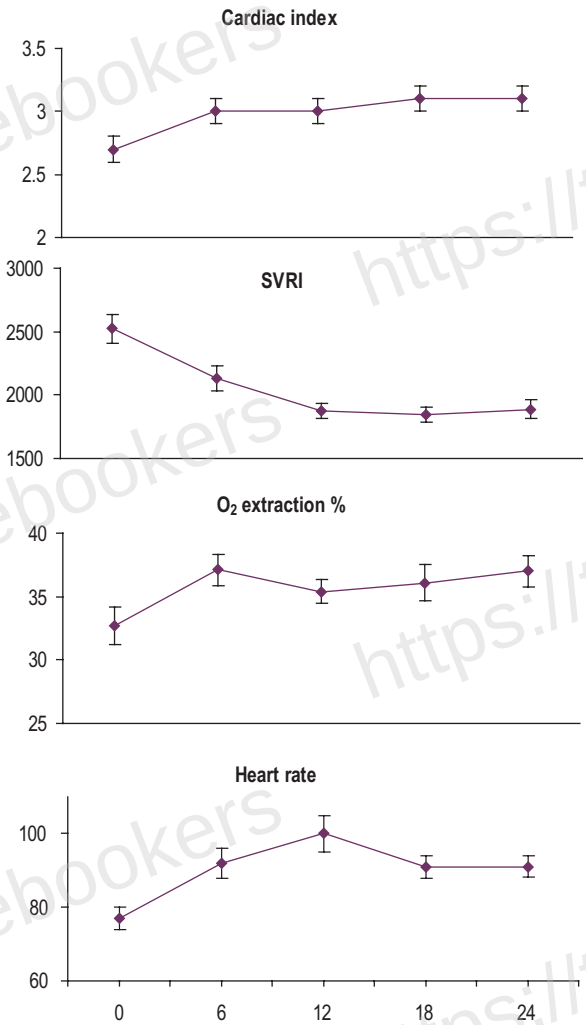


Figure 26.1 Haemodynamic changes following cardiac surgery. *SVRI*, Systemic vascular resistance index.

Vascular resistance declines over the first few hours (Fig. 26.1)[9] so that therapy during this period is best undertaken with agents with a short duration of action. Glyceryl trinitrate infusions are often useful over the first 24 hours, after which regular oral medication can be restarted. Simple measures, such as the provision of adequate analgesia and sedation, also should be considered.

The target blood pressure varies with the indication. Excessive reduction of blood pressure risks reducing myocardial oxygen supply more than demand. Under most circumstances, a mean arterial pressure between 60 and 80 mm Hg seems optimal.

HYPOTENSION

Hypotension is very common and can be a result of vasodilatation and low cardiac output (Box 26.1).

Box 26.1 Causes of postoperative hypotension

Hypovolaemia
- Haemorrhage
- Vasodilation
  - Rewarming
  - Drugs – milrinone
- Vasoplegia secondary to circulatory bypass

Low cardiac output
- Preload
  - Hypovolaemia, including haemorrhage
  - Tamponade, pericardial constriction
  - Left ventricular diastolic dysfunction
  - Right ventricular failure
- Afterload
  - Excessive vasoconstriction
  - Aortic stenosis
  - Functional left ventricular obstruction
- Myocardial function
  - Mechanical (ventricular septal defect, valve pathology)
  - Cardiomyopathy
  - Ischaemia, postischaemic stunning
  - Metabolic, electrolyte abnormalities, pharmacological depression

Whatever the cause, hypotension can cause myocardial ischaemia and consequent heart failure.

In general, all patients should have some form of cardiac output monitoring to guide fluid, vasopressor and inotropic therapy. An initial straight leg raise to assess fluid responsiveness is a safe starting point. If not fluid responsive, vasoconstrictors may be useful in breaking the cycle of hypotension–ischaemia–hypotension, but must be used cautiously in patients with impaired ventricular function, and especially in patients with major vascular or aortic pathology, for whom a hypertensive overshoot may be catastrophic.

- Norepinephrine (noradrenaline) is a potent vasoconstrictor. It is commonly used to manage vasodilation, but it should not be used alone in the presence of a low cardiac output.
- Vasopressin has an increasing role in postoperative cardiac surgery; it reduces the level of norepinephrine (noradrenaline) required, and may thus spare the myocardium from excessive beta stimulation.

Recognition of a low-output state in the absence of invasive monitoring may be difficult. Many of the usual signs of low output are also consequences of anaesthesia and surgery. Tachycardia may be obscured by drugs, hypothermia and heart disease, and even lactic acidosis may be an unreliable marker in this patient group.[9]

In the early postoperative period, a relatively low cardiac output may not warrant intervention, providing tissue oxygen delivery is adequate. Since beta blockade is beneficial in the postoperative cardiac

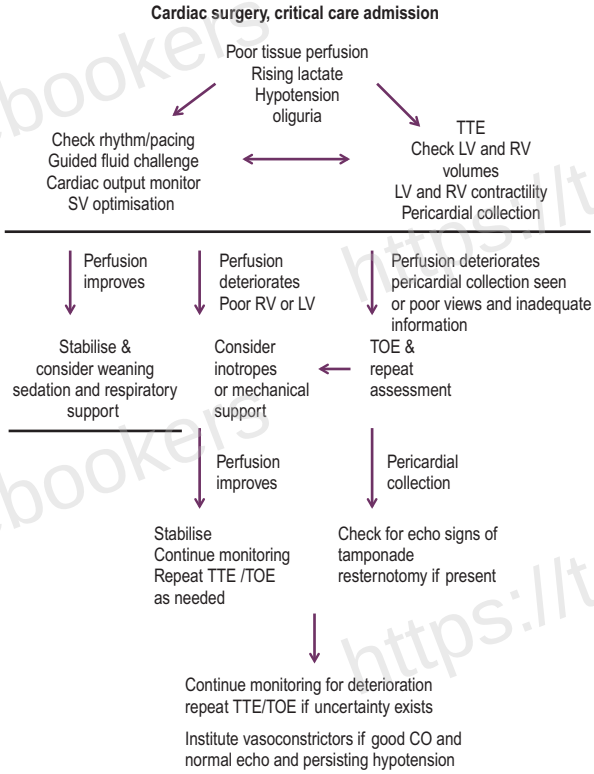


Figure 26.2 Suggested simple practical algorithm for use of echocardiography in postcardiac surgical patients. *LV*, Left ventricular; *RV*, right ventricular; *TOE*, tranoesophageal echocardiography; *TTE*, transthoracic echocardiography.

patient, beta agonists should not be used unquestioningly. Nevertheless, optimisation of cardiac function may confer some benefit[10] and intervention is clearly required when tissue oxygen delivery is inadequate.

On a specialised unit, an integrated algorithm can be used to assess and treat in sequence (Fig. 26.2).[7]

Mechanical ventilation is generally continued, reducing cardiac workload by removing the work of breathing. Positive intrathoracic pressure reduces left ventricular (LV) afterload, which is beneficial to the dilated left ventricle. Positive pressure may be detrimental; however, in the presence of diastolic ventricular dysfunction or hypovolaemia, the reduction in venous return may further reduce ventricular preload.

TAMPONADE

A high index of suspicion for tamponade in postcardiac surgery patients is paramount. Any patient with a rising central venous pressure and low cardiac output should be assumed to have tamponade unless proved otherwise. Of note, hypotension may be absent with the addition of vasopressors; thus haemodynamic monitoring is essential. Clinical assessment is difficult, and early echocardiography is required. Transthoracic

images can miss posterior thrombus, but may be diagnostic and are more readily available.[11] Early discussion with surgical teams and TEE imaging will often be required.

LEFT VENTRICULAR DYSFUNCTION

Postoperative LV dysfunction is common and can be diagnosed by echocardiography or cardiac output monitoring. Inotropic agents are frequently required, alone or in combination. Pre-emptive use of inotropic drugs may be associated with harm, so inotropes should not be used routinely without monitoring their effect.[12] Issues to consider include:

- Dobutamine is an essentially pure β_1-agonist. In the management of acute heart failure, it has been associated with an increase in mortality.[13]
- Epinephrine (adrenaline) is a potent ino-constrictor but its metabolic effects (especially lactic acidosis) and relative tachycardia make usage in cardiac surgical patients problematic.[14]
- Milrinone is a phosphodiesterase inhibitor with a long duration of action and potent vasodilating properties. These make milrinone relatively difficult to introduce and to wean. It has similar haemodynamic effects to dobutamine and is associated with increased atrial fibrillation (AF). Overall benefit is not established.[15] It may be a useful inotropic agent in patients with β-receptor down-regulation.
- Levosimendan is a calcium-sensitising agent. It offers little overall benefit in the treatment of heart failure,[16] but it may be beneficial in the perioperative period.[16,17]

Postoperative myocardial ischaemia predicts a more complicated course.[17] Recognition is enhanced by automated ECG multilead ST segment analysis with confirmatory electrocardiography, although diagnosis may be difficult in the presence of preoperative electrocardiographic abnormalities.[18]

Ischaemia may be due to graft failure. Remedial options include coronary angiography and/or reoperation. Angiography offers the potential for tailored reoperation or non-operative intervention. Management decisions may be influenced by surgical factors, such as the availability of further conduit and the state of the native arteries. Thus, close liaison among ICU personnel, cardiologists and surgeons is essential.

Delayed sternal closure has an established role in improving outcome after cardiac surgery.[19] Cardiac output is increased and inotropic requirement is reduced. Subsequent sternal closure has an acceptably low complication rate. The sternum may be left open following an initial attempt at closure, or reopened with later deterioration. Sternal retraction may be required.

RIGHT VENTRICULAR DYSFUNCTION

Right ventricular (RV) failure following cardiac surgery is reasonably common. Aetiological factors include:

- direct RV ischaemia or infarction
- poor myocardial protection
- anteriorly placed RV
- pre-existing pulmonary hypertension.

Management involves:

- careful volume resuscitation
- maintenance of RV perfusion pressure with vasoconstrictors
- intra-aortic balloon counterpulsation (IABC) as required
- inotrope administration
- RV afterload reduction.

Useful afterload-reducing agents include nitric oxide, prostaglandins and sildenafil. Conventional vasodilators tend to produce excessive systemic vasodilatation. Occasionally, RV balloon counterpulsation or an RV assist device may be required. Delayed sternal closure has an established role.

MECHANICAL SUPPORT

Intra-aortic balloon pumps (IABP) have an established role in support of cardiac surgery. Its two actions are: (1) augmentation of diastolic coronary perfusion pressure and (2) left ventricular afterload reduction. This is achieved by balloon inflation (30–50 mL capacity) within the aorta during diastole and rapid deflation of the balloon immediately before aortic valve opening. The catheter is usually inserted using a Seldinger technique, but can be placed by femoral artery cut down or directly into the descending thoracic aorta. Timing of inflation and deflation is critical to optimal function. This is best achieved using the pressure waveform (Fig. 26.3).

Inflation is timed to coincide with the dicrotic notch. Deflation is timed to occur as late as possible in diastole, ensuring that the IABP end-diastolic pressure is lower than the patient's end-diastolic pressure. IABC increases the cardiac index and coronary perfusion and reduces the left ventricular filling pressure, myocardial lactate production and oxygen extraction percentage.

Indications for IABP are summarised in Box 26.2.

IABP has an established role in the management of reversible myocardial dysfunction especially in the context of myocardial revascularisation (surgical or endovascular). There is a probable benefit in high-risk surgical patients undergoing elective revascularisation.[20] However, IABP is not helpful in the management of cardiogenic shock from irremediable causes except as a bridge to transplant. Complications include:

- limb ischaemia (6%–16%)
- vascular trauma, dissection
- infection (cut down > percutaneous)
- balloon rupture
- bleeding
- thrombocytopenia

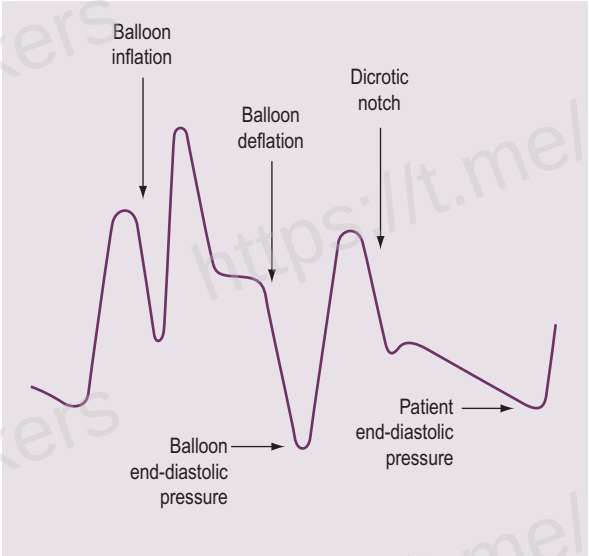


Figure 26.3 Intra-aortic balloon counterpulsation pressure waveform. Inflation is timed to coincide with the dicrotic notch. Deflation is timed to occur as late as possible in diastole, ensuring that the intra-aortic balloon counterpulsation end-diastolic pressure is lower than the patient's end-diastolic pressure.

Box 26.2 Indications for intra-aortic balloon counterpulsation

Prophylactic
- Cardiac surgery, two of:
  Left main >70%, left ventricular ejection fraction <0.4, unstable angina, reoperation
  Failure to wean from cardiopulmonary bypass
- Non-cardiac procedures in the presence of severe left ventricular impairment, unstable angina

Cardiogenic shock
- Reversible myocardial depression
- Support for reperfusion, revascularisation
- Bridge to transplant

- malposition, vascular obstruction
- malfunction, failure to unwrap.

Limb ischaemia is the most frequent complication and optimal management requires early recognition based on routine, systematic observation.

Ventricular assist devices (VAD) are expensive and technically far more demanding than IABP. The refinement of extracorporeal membrane oxygenation (ECMO) circuits has increased their use for short-term cardiac support. When instituted for failure to wean from bypass, the outlook is generally poor.[21,22] Most published VAD data relate to non-surgical patients in whom the role of heart assist devices is increasingly established both as a 'bridge to transplant' and as 'destination therapy'.

DYSRHYTHMIAS AND PACING

Ventricular and supraventricular dysrhythmias are common. Prevention and treatment of electrolyte abnormalities may be prophylactic. New occurrence of complex ventricular dysrhythmias should stimulate a search for causal ischaemia and graft malfunction.

Ventricular fibrillation and pulseless ventricular tachycardia require rapid defibrillation, preferably before external cardiac massage, which may cause mechanical injury post-sternotomy. If haemodynamic stability cannot be rapidly restored, open cardiac massage should be instituted.

Facilities for atrioventricular pacing are essential as transient heart block is common.

All units should have regular training in life support protocols focused on the post-cardiac surgical patient. AF is the most common complication of cardiac surgery.[23] Its incidence varies from 10% to 40% in patients undergoing coronary artery surgery and up to 50% with some valvular procedures. Predisposing factors include a history of AF, valvular heart disease (especially mitral valve pathology), increasing age and prolonged P-wave duration. AF can be effectively treated and its recurrence prevented with intraoperative radiofrequency ablation and left atrial reduction during cardiac surgery[24]; these may also provide a long-term survival benefit.[25] AF is probably less frequently observed following 'off-pump' surgery, and is most frequently encountered around the second and third postoperative days, but may occur weeks after surgery and hospital discharge.

AF is a potentially serious complication. Apart from discomfort, it may provoke or complicate haemodynamic instability. However, the major complication of AF is stroke, with an increased risk of approximately threefold. Based on echocardiography, there is the potential for embolic stroke within 3 days of onset of AF.

AF is also associated with:

- increase in inotrope usage
- increased use of IABP
- increased reoperation for bleeding
- prolonged ICU and hospital stay
- increased costs.

Several strategies are beneficial in preventing AF[26]:

- beta blockade
- amiodarone
- sotalol[27]
- diltiazem
- bi-atrial pacing
- dexamethasone
- colchicine[28]
- statins.[29]

Box 26.3 Management of atrial fibrillation

Rate control
- Beta blockade
- Calcium channel blockers
- Sotalol
- Digitalis

Cardioversion
- Amiodarone
- Magnesium
- Electrical cardioversion

Anticoagulation
- Always for elective cardioversion
- Consider if atrial fibrillation persists beyond 48 hours

Treatment should be tempered with an understanding that spontaneous reversion to sinus rhythm is frequent. A treatment strategy is summarised in Box 26.3.

Whether to rate control or rhythm control is unclear, with both strategies having similar complication and conversion rates.[30] Early cardioversion tends to be ineffective and potentially harmful. Although officially recommended in the presence of instability, this is not based on any empirical evidence.

EMERGENCY REOPERATION

Emergency re-sternotomy is indicated as part of resuscitation when haemodynamic stability cannot be rapidly re-established with conventional means. Advantages compared with closed-chest resuscitation include:

- establishment of the cause of instability
- correction of the cause (e.g. tamponade, kinked graft)
- more effective cardiac massage
- direct establishment of atrial and ventricular pacing.

Re-sternotomy also enables the re-establishment of cardiopulmonary bypass and regrafting or correction of mechanical abnormalities as required. Infectious complications of emergency resternotomy are probably increased, but the incidence is not prohibitive.

A protocol specific to cardiac surgical units and an internationally recognised course are available.[31]

OTHER COMPLICATIONS

COAGULATION

Excessive postoperative bleeding is a major cause of increased morbidity and mortality. Mechanisms are complex and include preoperative anticoagulation, thrombolysis and antiplatelet therapy, as well as activation of haemostatic mechanisms, including fibrinolysis.

A systematic approach to operative and postoperative blood conservation, including point-of-care testing to guide therapy, can significantly reduce bleeding, transfusion and resultant complications.[32] There is increasing evidence that transfusion is associated with excessive complications, including death, and that transfusion rates vary amongst institutions.[33]

Effective postoperative measures include reversal of residual heparin (including 'heparin rebound') and correction of coagulopathy with blood products. Retransfusion of shed blood reduces autologous transfusion requirements without apparent side effects. A restrictive transfusion strategy can reduce exposure to transfusion without increased risk[34]; restrictive transfusion to a Hb of 75 versus 90 g/L found no benefit in mortality or cost.[35]

Most studies of pharmacological strategies to minimise postoperative blood loss have involved preoperative or intraoperative intervention. Extrapolation to the postoperative phase is intuitive rather than established. Tranexamic acid reduces bleeding and exposure to blood and blood products.[36] Aprotinin has been associated with an increased risk of serious end-organ damage and was withdrawn from the market for a period, although it is now available with a license restricted to coronary surgery.[37] Desmopressin is probably less effective and has been associated with an increased risk of myocardial infarction.[38] Activated factor VII may be effective in controlling bleeding, but may result in an increased risk of stroke.[39]

'Off-pump' surgery has been associated with excessive bleeding because of the administration of anticoagulant and antiplatelet therapy out of fear of early graft closure. Controlled tamponade with discontinuation of drain suction and even clamping of drains has been reported.[40] Application of positive end-expiratory pressure (PEEP) has been shown to be effective in some studies, but not others.

RESPIRATORY

Postoperative mechanical ventilation remains routine in cardiac surgical patients. Immediate extubation appears to offer little patient benefit[41]; similarly, neither does routine prolongation of ventilation. Extubation can be safely undertaken with simple protocols. Reintubation is rarely required, but is more likely in older patients with pre-existing lung and vascular disease and impaired ventricular function. Reoperative surgery and bleeding requiring massive transfusion also increase the likelihood of early extubation failure.

Hypoxia is very common in the early postoperative period. It is mostly attributable to atelectasis as a consequence of cardiopulmonary bypass and intraoperative ventilation with high inspired oxygen and repeated disconnection from the ventilator. Treatment involves simple measures, such as appropriate PEEP and lower tidal volume selection, prolonged inspiration and simple recruitment manoeuvres.

Long-term sequelae are rare. Incentive spirometry and chest physiotherapy are commonly utilised in the postoperative period, without good supportive evidence. Early mobilisation and the use of continuous positive airway pressure (CPAP) or high flow nasal oxygen are commonly employed strategies. Adequate analgesia facilitates physiotherapy and mobilisation. Non-steroidal agents may increase the risk of complications and are rarely used.[42]

More sinister causes of hypoxia include severe heart failure and acute respiratory distress syndrome (ARDS). The aetiology of ARDS is diverse, but includes shock, massive blood product administration and cardiopulmonary bypass itself. Management is not particular to this group of patients. Occasionally, profound hypoxia accompanies minor atelectasis with moderate pulmonary hypertension. Patent foramen ovale (which is seen in 10%–15% of the normal population) with right-to-left intracardiac shunt is the likely mechanism.

Clinically detected pulmonary embolism is an uncommon complication of cardiac surgery, probably due to bypass-induced platelet dysfunction, routine postoperative antiplatelet therapy and thromboprophylaxis.[43] However, asymptomatic thromboembolism may be significantly more common.[44,45] Contrary to earlier beliefs, 'off-pump' surgery may not be associated with an increase in prothrombotic tendency or a need for a more aggressive thromboprophylaxis regimen.[46]

Pleural drains are not routinely inserted after valve surgery. When the mammary artery is harvested, the pleura is breached and thus pleural drains are placed. Once coagulation is normalised and drain output is less than 20 mL/h for 4 hours, the drains can be removed.

In patients with poor left ventricular ejection fraction, pleural effusions may accumulate and limit ventilation. This often presents after several days, and if deemed necessary new pleural drains will need to be placed.

Currently, there is much interest in oxygen, and specifically whether hyperoxia or normoxia is most beneficial. Studies in cardiac surgery of intraoperative and postoperative hyperoxia have shown no benefit – and even possible harm.[47]

Diastolic dysfunction can be exposed following surgery when trying to wean a patient from the ventilator. As a result, the heart may fail on changing from positive to negative pressure ventilation, resulting in sudden onset pulmonary oedema. The reasons for this are an increase in venous return, an increase in work of breathing and oxygen demand, and catecholamine discharge during transition. In any patient who fails extubation, an echocardiogram is needed to assess diastolic function. Treatment options include avoiding tachycardia to allow LV filling, treat AF to allow atrial synchrony, fluid removal with diuresis, and medical optimisation with ACE inhibitors.

RENAL

Depending on definition and patient groups, acute renal failure is observed in 1%–5% of patients undergoing cardiac surgery. Risk factors include increasing age, heart failure, prolonged bypass, diabetes, pre-existing renal impairment and postoperative shock. Surgery without cardiopulmonary bypass may be relatively protective and other potentially modifiable factors include anaemia, blood transfusion and re-exploration.[48] Morbidity, mortality and costs are significantly increased. Effective preventive strategies beyond careful haemodynamic management and the minimisation of associated nephrotoxic insults have not been established. Nevertheless, attention to urine output in the presence of known risk factors appears warranted.

The use of renal replacement therapy (RRT) is common to allow the normalisation of biochemistry. However, the decision on when to implement RRT is unclear. Current research shows no benefits of early initiation[49]; however, due to the large fluid load cardiac patients receive, they may benefit from early intervention if the fluid is overloaded.

NEUROLOGICAL

Neurological complications of cardiac surgery include neuropsychiatric deterioration as a consequence of cardiopulmonary bypass, delirium and a range of peripheral neuropathies – the most frequent of which is unilateral phrenic nerve palsy. Paraplegia is a recognised complication of thoracic aortic surgery.

The most devastating neurological complication is cerebral infarction. The incidence varies with patient selection, but ranges from 1% to 5%. The pathophysiology is mostly embolic. Risk factors include carotid artery stenosis, hypertension, AF, aortic atheroma, impaired ventricular function and peripheral vascular disease. 'Off-pump' and especially 'anaortic' surgery (no aortic manipulation) are protective,[50] and other operative techniques may also reduce the incidence.

Postoperative cognitive dysfunction is common, and multifactorial in nature. Standard intensive care measures include regular reorientation, minimising medications and investigating other causes, such as infection. Unless there is focal neurology, early imaging with either computed tomography or magnetic resonance imaging is not indicated.

GASTROINTESTINAL

Gastrointestinal complications after cardiac surgery are rare (<1%). However, morbidity is quite high.[51] The risk factors include increased age, complex surgery and postoperative shock. The incidence of gastrointestinal complications may be reduced with 'off-pump' surgery.

The commonest complication is mesenteric ischemia secondary to atheromatous emboli, hypoperfusion and heparin-induced thrombocytopenia. Early postoperative rises in lactate are common post-bypass; therefore distinguishing early mesenteric ischaemia is difficult, and any sign of abdominal pain should be investigated rapidly. Pseudo-obstruction and constipation are common. Perforation of the bowel or gallbladder, appendicitis and pancreatitis are rare but have been reported following cardiac surgery. Stress ulcer prophylaxis should be routine in this patient population until they are re-established on normal diets, which should happen as soon as possible following extubation.

INFECTION

Deep sternal wound infection is uncommon (0.5%–2.5%). Associated morbidity and mortality are significant. Risk factors have been variously reported but consistently include diabetes, obesity and the use of internal mammary arteries, especially if bilateral. Other contributing factors include prolonged surgery, chronic lung disease, male sex, low postoperative cardiac output, blood transfusion, sternal reopening and dialysis. Close control of blood sugar levels in diabetics[52] and preoperative nasal and oropharyngeal decontamination[53] may help prevent infection. In the last 2 years, mycobacterium chimaera has been identified as a contaminant of extracorporeal heater-cooler units and should be considered in the case of unexplained early and persistent pyrexia.

SPECIFIC PROCEDURES AND PROBLEMS

ENDOCARDITIS VALVULAR SURGERY

These patients may have acute or subacute presentation. They should be managed by a multidisciplinary endocarditis team, including cardiac surgeons, cardiologists and microbiologists. Early organism identification can aid antibiotic selection and duration. Prior undiagnosed end-organ damage may present postoperatively, and a high index of suspicion is required. If expedited surgery occurs, then there may be a massive inflammatory response with bleeding and hypotension. If it persists, a secondary source of infection must be sought through clinical and radiological examination.

AORTIC SURGERY

Aortic surgery involves a period of deep hypothermic circulatory arrest, which can be up to 30 minutes at 18°C. They should be carefully rewarmed in theatre, and the avoidance of pyrexia is a key postoperative precaution. Active cooling may be considered. High arterial pressures are avoided to minimise the risk of extending arterial intimal dissection; however, the maintenance of cerebral circulation must be considered. There is a high vascular complication rate in these patients with mortality 8%–15% and stroke rates 7%–11%.[54] Subtle long-term cognitive dysfunction is common.[55]

MITRAL AND TRICUSPID VALVE SURGERY

In the developed world, surgery for mitral incompetence is more common, whereas mitral stenosis predominates in nations with undeveloped economies. Pulmonary hypertension, right ventricular pressure overload and impairment, and tricuspid valve regurgitation may develop with longstanding disease. These conditions significantly increase the risk of cardiac surgery; therefore expert management is demanded. Tricuspid valve repair with a de Vega suture or an annuplasty ring is increasingly performed at the same time as left-sided surgery. The treatment of pulmonary hypertension with pulmonary vasodilators may be needed in addition to inotropic support of the right ventricle and appropriate ventilator settings. Monitoring with a PA catheter and phosphodiesterase inhibitors have a role here, but dose titration to avoid refractory hypotension is important.

SURGERY FOR HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY

Patients with symptomatic hypertrophic obstructive cardiomyopathy suffer exertion dyspnoea and fatigue. A dynamic outflow obstruction in the left ventricular outflow tract is often the underlying lesion. Surgery involves septal myectomy, which alleviates this obstruction and co-existing mitral regurgitation. Diastolic dysfunction is common in these patients and they do not tolerate AF. In addition, inotropes should be avoided. There is an increased risk of heart block and these patients may need permanent pacemakers.

TRANSCUTANEOUS AORTIC VALVE INSERTION

Transcutaneous aortic valve insertion (TAVI) allows treatment of aortic stenosis in patients felt not to be medically fit for open surgery. This is often due to advanced age, LV dysfunction, and multiple co-morbidities. Compared with medical therapy for those patients unable to have open surgery TAVI reduces mortality. However, there is an increase in stroke and vascular complications.[56] On the ICU, these patients have a high risk of delirium. Due to their premorbid state, the risks of other organ failure is raised and they may benefit from prolonged postoperative monitoring.

END OF LIFE CARE

When severe complications occur following cardiac surgery that may significantly reduce the chances of

patients making the expected postoperative recovery, this may give rise to conflict between teams. As the patient opted for surgery, consideration must be given to allowing ample time for recovery to occur; however, when severe complications, such as stroke, end-stage renal failure and failure to wean, occur, family discussions may arise around treatment limitation and withdrawal of care. It is important that the surgical team are involved in this dialogue and that the family are not given conflicting messages. Advice can be sought from palliative care teams when needed.

REFERENCES

1. Papachristofi O, Sharples L, Mackay J, et al. The contribution of the anaesthetist to risk-adjusted mortality after cardiac surgery. *Anaesthesia*. 2016; 71(2):138–146.
2. Fletcher N. Climate change in cardiothoracic intensive care. *Anaesthesia*. 2016;71(12):1395–1398.
3. Shahin J, Ferrando-Vivas P, Power G, et al. The Assessment of Risk in Cardiothoracic Intensive Care (ARCtIC): prediction of hospital mortality after admission to cardiothoracic critical care. *Anaesthesia*. 2016;71(12):1410–1416.
4. Shah MR, Hasselbad V, Stevenson LW, et al. Impact of the pulmonary artery catheter in critically ill patients. Meta-analysis of randomized clinical trials. *JAMA*. 2005;294:1664–1670.
5. Leibowitz AB, Beilin T. Pulmonary artery catheters and outcome in the perioperative period. *New Horiz*. 1997;5:214–222.
6. Fletcher N, Geisen M, Meeran H, et al. Initial clinical experience with a miniaturized transesophageal echocardiography probe in a cardiac intensive care unit. *J Cardiothorac Vasc Anesth*. 2015;29(3):582–587.
7. Geisen M, Spray D, Nicholas Fletcher S. Echocardiography-based hemodynamic management in the cardiac surgical intensive care unit. *J Cardiothorac Vasc Anesth*. 2013;28(3):733–744.
8. Hoekstra M, Hessels L, Reinstra M, et al. Computer-guided normal-low versus normal-high potassium control after cardiac surgery: no impact on atrial fibrillation or atrial flutter. *Am Heart J*. 2016;172:45–52.
9. Raper RF, Cameron G, Walker D, et al. Type B lactic acidosis following cardiopulmonary bypass. *Crit Care Med*. 1997;25:46–51.
10. Polonen P, Ruokonen E, Hippelainen M, et al. A prospective randomized study of goal-oriented haemodynamic therapy in cardiac surgical patients. *Anesth Analg*. 2000;90:1052–1059.
11. Price S, Prout J, Gibson DG, et al. 'Tamponade' following cardiac surgery: terminology and echocardiography may both mislead. *Eur J Cardiothorac Surg*. 2004;26:1156–1160.
12. Nielsen DV, Hansen MK, Johnsen SP, et al. Health outcomes with and without use of inotropic therapy in cardiac surgery: results of a propensity score-matched analysis. *Anesthesiology*. 2014;120:1098–1108.
13. Tacon CL, McCaffery J, Delaney A. Dobutamine for patients with severe heart failure: a systematic review and meta-analysis of randomised trials. *Intensive Care Med*. 2012;38:359–367.
14. Totaro RJ, Raper RF. Epinephrine-induced lactic acidosis following cardiopulmonary bypass. *Crit Care Med*. 1997;25:1693–1699.
15. Jebelli M, Ghazinoor M, Mandegar MH, et al. Effect of milrinone on short-term outcome of patients with myocardial dysfunction undergoing coronary artery bypass graft: a randomized controlled trial. *Cardiol J*. 2010;17:73–78.
16. Delaney A, Bradford C, McCaffrey J, et al. Levosimendan for the treatment of acute severe heart failure: a meta-analysis of randomised controlled trials. *Int J Cardiol*. 2010;138:281–289.
17. Landoni G, Mizzi A, Biondi-Zoccai G, et al. Reducing mortality in cardiac surgery with levosimendan: a meta-analysis of randomized controlled trials. *J Cardiothorac Vasc Anesth*. 2010;24: 51–57.
18. Yazigi A, Richa F, Gebara S, et al. Prognostic importance of automated ST-segment monitoring after coronary artery bypass graft surgery. *Acta Anaesthesiol Scand*. 1998;42:532–535.
19. Furnary AP, Magovern JA, Simpson KA, et al. Prolonged open sternotomy and delayed sternal closure after cardiac operations. *Ann Thorac Surg*. 1992;54:233–239.
20. Theologou T, Bashir M, Rengarajan A, et al. Preoperative intra aortic balloon pumps in patients undergoing coronary artery bypass grafting. *Cochrane Database Syst Rev*. 2011;(1):CD004472. Online. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004472.pub3/abstract.
21. Elsharkawy HA, Li L, Esa WA, et al. Outcome in patients who require venoarterial extracorporeal membrane oxygenation support after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2010;24: 946–951.
22. Hsu PS, Chen JL, Hong GJ, et al. Extracorporeal membrane oxygenation for refractory cardiogenic shock after cardiac surgery: predictors of early mortality and outcome from 51 adult patients. *Eur J Cardiothorac Surg*. 2010;37:328–333.
23. Bharucha DB, Kowey PR. Management and prevention of atrial fibrillation after cardiovascular surgery. *Am J Cardiol*. 2000;85(10A):20D–24D.
24. Scherer M, Therapidis P, Wittlinger T, et al. Left atrial size reduction improves the sinus rhythm conversion rate after radiofrequency ablation for continuous atrial fibrillation in patients undergoing concomitant cardiac surgery. *Thorac Cardiovasc Surg*. 2006;54:34–38.
25. Attaran S, Saleh HZ, Shaw M, et al. Does the outcome improve after radiofrequency ablation for atrial fibrillation in patients undergoing cardiac surgery? A propensity-matched comparison. *Eur J Cardiothorac Surg*. 2012;41:806–810.
26. Crystal E, Garfinkle MS, Connolly SS, et al. Intervention is favoured in the prevention of

post-operative atrial fibrillation and in the reduction of patient length of stay. *Cochrane Database Syst Rev*. 2004;(4):CD003611. Online. Available at: http://summaries.cochrane.org/CD003611/.
27. Kerin NZ, Jacob S. The efficacy of sotalol in preventing postoperative atrial fibrillation: a meta-analysis. *Am J Med*. 2011;124:875e.1–875e.9.
28. Imazio M, Brucato A, Ferrazzi P, et al. Colchicine reduces postoperative atrial fibrillation: results of the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPS) atrial fibrillation study. *Circulation*. 2011;124:2290–2295.
29. Chopra V, Wesorick D, Sussman J, et al. Effect of perioperative statins on death, myocardial infarction, atrial fibrillation, and length of stay. A systematic review and meta-analysis. *Arch Surg*. 2012;147:181–189.
30. Gillinov A, Bagiella E, Moskowitz A, et al. Rate control versus rhythm control for atrial fibrillation after cardiac surgery. *N Engl J Med*. 2016;374(20): 1911–1921.
31. Dunning J, Nandi J, Ariffin S, et al. The Cardiac Surgery Advanced Life Support Course (CALS): delivering significant improvements in emergency cardiothoracic care. *Ann Thorac Surg*. 2006;81(5): 1767–1772.
32. Moskowitz DM, McCullogh JN, Shander A, et al. The impact of blood conservation on outcomes in cardiac surgery: is it safe and effective? *Ann Thorac Surg*. 2010;90:451–458.
33. Rogers MA, Blumberg N, Saint S, et al. Hospital variation in transfusion and infection after cardiac surgery: a cohort study. *BMC Med*. 2009;7:37.
34. Hajjar L, Vincent J-L, Galas FRBG, et al. Transfusion requirements after cardiac surgery. The TRACS Randomized Controlled Trial. *JAMA*. 2010;304: 1559–1567.
35. Murphy G, Pike K, Rogers C. Liberal or restrictive transfusion after cardiac surgery. *N Engl J Med*. 2015;372(11):998–1008.
36. Mykes P, Smith J, Forbes A. Tranexamic acid in patients undergoing coronary-artery surgery. *N Engl J Med*. 2016;376(19):1893.
37. Fergusson DA, Hebert PC, Mazer CD, et al. A comparison of aprotonin and lysine analogues in high-risk cardiac surgery. *N Engl J Med*. 2008;358: 2319–3123.
38. Levi M, Cromheecke ME, de Jonge E, et al. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. *Lancet*. 1999;354: 1940–1947.
39. Ponschab M, Landoni G, Biondi-Zoccai G, et al. Recombinant activated factor VII increase stroke in cardiac surgery: a meta-analysis. *J Cardiothorac Vasc Anesth*. 2011;25:804–810.
40. Aravot DJ, Barak J, Vidne BA. Induction of controlled tamponade in the management of massive unexplained postcardiotomy bleeding. Case report and review of the literature. *J Cardiovasc Surg (Torino)*. 1986;27:613–617.
41. Montes FR, Sanchez SI, Giraldo JC, et al. The lack of benefit of tracheal extubation in the operating room after coronary artery bypass surgery. *Anesth Analg*. 2000;91:776–780.
42. Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med*. 2005;352:1133–1135.
43. Shammas NW. Pulmonary embolus after coronary artery bypass surgery: a review of the literature. *Clin Cardiol*. 2000;23:637–644.
44. Schwann TA, Kistler L, Engoren MC, et al. Incidence and predictors of postoperative deep vein thrombosis in cardiac surgery in the era of aggressive thromboprophylaxis. *Ann Thorac Surg*. 2010;90:760–766.
45. Lahtinen J, Ahvenjarvi L, Bincari F, et al. Pulmonary embolism after off-pump coronary artery bypass surgery as detected by computed tomography. *Am J Surg*. 2006;192:396–398.
46. Paulitsch FS, Schneider D, Sobel BE, et al. Hemostatic changes and clinical sequelae after on-pump compared with off-pump coronary artery bypass surgery: a prospective randomized study. *Coron Artery Dis*. 2009;20:100–105.
47. Spoelstra-de Man A, Smit B, Oudemans-van Straaten H, et al. Cardiovascular effects of hyperoxia during and after cardiac surgery. *Anaesthesia*. 2015; 70(11):1307–1319.
48. Karkouti K, Duminda N, Wijeysundera MD, et al. Acute kidney injury after cardiac surgery. Focus on modifiable risk factors. *Circulation*. 2009;119:495–502.
49. Wierstra B, Kadri S, Alomar S, et al. The impact of early versus late initiation of renal replacement therapy in critical care patients with acute kidney injury: a systematic review and evidence synthesis. *Crit Care*. 2016;20:122.
50. Misfield M, Potger K, Ross DE, et al. 'Anaortic' off-pump coronary artery bypass grafting significantly reduces neurological complications compared to off-pump and conventional on-pump surgery with aortic manipulation. *Thorac Cardiovasc Surg*. 2010;58:408–414.
51. Mangi A, Christison-Lagay E, Torchiana D, et al. Gastrointestinal complications in patients undergoing heart operation. *Ann Surg*. 2005;241(6): 895–904.
52. Furnary AP, Zerr KJ, Grunkemeier GL, et al. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. *Ann Thorac Surg*. 1999;67:352–360.
53. Segers P, Speekenbrink RGH, Ubbink DT, et al. Prevention of nosocomial infection in cardiac surgery by decontamination of the nasopharynx and oropharynx with chlorhexidine gluconate. A randomized controlled trial. *JAMA*. 2006;296: 2460–2466.
54. Augoustides JG, Floyd TF, McGarvey ML, et al. Major clinical outcomes in adults undergoing

thoracic aortic surgery requiring deep hypothermic circulatory arrest: quantification of organ-based perioperative outcome and detection of opportunities for perioperative intervention. *J Cardiothorac Vasc Anesth*. 2005;19:446–452.

55. Welz A, Pogarell O, Tatsch K, et al. Surgery of the thoracic aorta using deep hypothermic total circulatory arrest. Are there neurological consequences other than frank cerebral defects? *Eur J Cardiothorac Surg*. 1997;11:650–656.
56. Leon M, Smith C, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363(17):1597–1607.

27

Echocardiography in intensive care

Ubbo F Wiersema

Echocardiography is an integral part of modern intensive care practice. A wide range of diagnostic, monitoring and procedural indications are suitable for echocardiographic evaluation in critically ill patients (Table 27.1). Image acquisition, analysis and interpretation are, however, entirely operator dependent. Therefore the clinician needs to have a clear understanding of the purpose and potential limitations each time an echocardiogram is performed.[1–5]

INTENSIVE CARE ECHOCARDIOGRAPHY

Used as an extension of the physical examination in the emergency situation, or used to supplement or replace traditional haemodynamic monitoring tools, echocardiography needs to be immediately available and may be required for repeated studies of the same patient. The information required is often more about function than structure. More robust, but less sophisticated echocardiography machines are often used where image quality may be inferior to that obtained with advanced 'high-end' machines. Furthermore, image acquisition may be challenging because of the patient's position, dressings, positive pressure ventilation and tachycardia. A clinician with expertise in echocardiography may not be readily available. To overcome these limitations and achieve satisfactory information for clinical decision making, the concept of a focused or targeted echocardiogram looking to answer a small number of specific questions in a limited number of defined clinical situations has evolved.[1,2,4,5] At other times, a more detailed study with expert interpretation is required.[6] A suggested terminology for different types of study is shown in Table 27.2.[1,2,4,5,7] Appropriate certification for different levels of expertise should be achieved through a recognised training programme that uses competency-based assessment.[1,4,5,7–9]

ULTRASOUND PHYSICS

Ultrasound consists of waves of alternating compression and rarefaction at frequencies higher than that audible to the human ear. Echocardiography involves transmission of a beam of ultrasound waves and the subsequent detection of the returning waves reflected at interfaces between tissues with differing acoustic impedance. The degree of impedance mismatch determines the amplitude of the reflected wave. The depth of the reflecting interface is determined from the time taken for the pulse of ultrasound waves to return. Ultrasound waves that are not reflected are attenuated by absorption, refraction and scattering. The machine software adjusts the detector amplifier to compensate for the loss of energy with depth penetration. Time gain compensation (TGC) control allows manual adjustment of the relative brightness of structures at different depths. For echocardiography, ultrasound frequencies of 1–5 MHz are used, which is a compromise between the higher spatial resolution achieved with higher frequencies and the greater depth penetration achieved with lower-frequency imaging.

To produce an ultrasound image, repeated pulses of ultrasound waves are transmitted and received. The number of pulses emitted per second is called the pulse repetition frequency. To build a 2D image, the ultrasound beam sweeps across the plane of interrogation, creating the image one line at a time. The frame rate is the frequency with which the 2D image is renewed (temporal resolution), which depends on the pulse repetition frequency and the image width (number of scan lines). M-mode imaging provides high temporal resolution by scanning along a single line.

DOPPLER ECHOCARDIOGRAPHY

The Doppler effect is the change in frequency (Δf) of ultrasound waves that occurs when the reflecting structure is moving relative to the wave transmitter and receiver. The velocity of the structure (v) can be calculated from the measured frequency shift by the Doppler equation: $v = c(\Delta f)/2f_T.\cos\theta$ where c is the velocity of sound in soft tissue (1540 m/s), f_T is the transmitted frequency and θ is the angle between the ultrasound beam and the direction of movement.

The four most commonly used modes of Doppler echocardiography are as follows:

Continuous wave (CW) Doppler involves continuous transmission and reception of a beam of ultrasound waves along the line of interrogation. The frequency

ABSTRACT

Echocardiography is suitable for a wide range of diagnostic, monitoring and procedural indications in intensive care. In most circumstances a focused transthoracic study is sufficient to guide management, but the clinician should be familiar with the indications for a more comprehensive study. Transoesophageal echocardiography is appropriate in intubated patients if transthoracic images are inadequate, or for a limited number of other indications. Image interpretation is operator dependent and thus requires recognition of pitfalls that may lead to misdiagnosis. Quantitative methods may be used, but are often not required.

A guide to the role of echocardiography in the diagnosis and management of different causes of circulatory failure, pericardial effusion, and complications of acute coronary syndrome and cardiac surgery is described. The role of echocardiography in pulmonary embolism, acute respiratory distress syndrome and cardiac arrest with non-shockable rhythm is also provided.

KEYWORDS

Echocardiography
Doppler
fluid responsiveness
pericardial effusion
systolic function
diastolic function
shock
pulmonary embolism
acute cor pulmonale
cardiac arrest

Table 27.1 Indications for echocardiography in intensive care

HYPOTENSION OR HAEMODYNAMIC INSTABILITY
Hypotension or haemodynamic instability of uncertain aetiology
Assessment of fluid responsiveness during controlled mechanical ventilation
Evaluation of left and right ventricular function in sepsis
MYOCARDIAL INFARCTION (MI)
Acute chest pain with suspected MI and non-diagnostic electrocardiograph
No chest pain but laboratory markers indicative of ongoing MI
Suspected complication of myocardial infarction
Evaluation of ventricular function following MI
RESPIRATORY FAILURE
Respiratory failure of uncertain aetiology
Acute respiratory distress syndrome
Failure to wean from mechanical ventilation
Suspected hepatopulmonary syndrome
PULMONARY EMBOLISM (PE)
Known acute PE to guide therapy
Re-evaluation of known PE after thrombolysis or thrombectomy for assessment of change in right ventricular function and/or pulmonary artery pressure
CARDIAC ARREST
Non-shockable cardiac arrest to identify cause
Non-shockable cardiac arrest to distinguish between pulseless electrical activity and pseudo-pulseless electrical activity
Ventricular tachycardia/fibrillation after return of spontaneous circulation to identify regional wall motion abnormalities as a surrogate for acute coronary syndrome
CARDIAC TRAUMA
Blunt trauma with haemodynamic instability (severe deceleration injury or chest trauma with suspected valve injury, pericardial effusion or cardiac injury)
Penetrating chest trauma with or without haemodynamic instability
EVALUATION OF VALVULAR FUNCTION
Suspected valvular heart disease
Re-evaluation of known valvular heart disease after a change in clinical status
Suspected prosthetic valve dysfunction
Initial evaluation of suspected infective endocarditis
Re-evaluation of infective endocarditis after a change in clinical status
EVALUATION OF INTRACARDIAC AND EXTRACARDIAC STRUCTURES AND CHAMBERS
Suspected cardiac mass, source of embolus
Suspected pericardial effusion
PROCEDURAL GUIDANCE
Percutaneous pericardial drainage
Temporary transvenous pacemaker insertion when radiographic imaging is not feasible
Cannulation for extracorporeal membrane oxygenation

See references 1, 3, 6.

shift of the reflected waves is used to calculate velocity at all points along the line. This allows measurement of high velocities, but at the expense of spatial uncertainty. Velocity is displayed against time. High-amplitude, low-velocity signals are filtered out (wall filter) so that only blood flow velocities are displayed.

Pulse wave (PW) Doppler involves alternating transmission and reception of pulses of ultrasound to interrogate the velocity of blood at the specific site (sampling volume) selected by the operator. Velocity is calculated from the phase shift of the reflected PW, thus limiting the highest velocity (Nyquist limit) that can be measured. Velocities greater than the Nyquist limit are displayed as if flow is in the opposite direction (aliasing phenomenon).

Colour Doppler is a pulse-wave Doppler method that determines the velocity at multiple points along multiple lines of interrogation. Each sampling volume is assigned a colour according to the average velocity and direction of blood flow (blue away, red towards), and displayed in a colour box superimposed on the 2D image.

Tissue Doppler imaging is a form of pulse-wave Doppler used to measure myocardial wall motion velocities by filtering out the high-velocity, low-amplitude signals of blood flow.

Measurement of blood velocity by Doppler methods makes it possible to calculate blood flow and pressure gradients. Volumetric flow is calculated from the velocity and the cross sectional area of the structure through

Table 27.2 Terminology for echocardiography in the intensive care setting

TERMINOLOGY DERIVED FROM ECHOCARDIOGRAPHY LITERATURE (see references 4, 5)
FOCUSED CARDIAC ULTRASOUND
Focused transthoracic study used by the clinician at the point of care, as an adjunct to physical examination, to recognise specific ultrasound signs that represent a narrow list of potential diagnoses in specific clinical settings
COMPREHENSIVE ECHOCARDIOGRAM
A complete transthoracic or transoesophageal study including quantitative evaluation, performed by experts in image acquisition with a fully equipped echocardiography platform and interpreted by a specialist in echocardiography
LIMITED ECHOCARDIOGRAM
A definitive study that requires the same level of expertise as a comprehensive study, but where a reduced number of images is obtained in order to address a specific clinical question
TERMINOLOGY DERIVED FROM CRITICAL CARE LITERATURE (see references 1, 2, 7, 9)
FOCUSED CRITICAL CARE ECHOCARDIOGRAM
As for focused cardiac ultrasound, but using either a transthoracic or transoesophageal probe
BASIC CRITICAL CARE ECHOCARDIOGRAM
As for focused critical care echocardiogram, but also including basic colour Doppler to identify severe valvular regurgitation
ADVANCED CRITICAL CARE ECHOCARDIOGRAM
As for comprehensive echocardiogram, but performed by an intensive care clinician, using either a transthoracic or transoesophageal probe

which the blood flows. Accuracy depends on parallel alignment of the Doppler ultrasound beam with the direction of flow, laminar flow with a flat profile, and accurate measurement of the cross sectional area. For pulsatile flow, the stroke volume is calculated from the integral of instantaneous velocity with respect to time during one pulse period (velocity time integral [VTI]), multiplied by the cross-sectional area.

The *continuity principle* states that the net forward stroke volume in one part of the heart equals the net forward flow in another part of the heart, provided that there is no shunt. The continuity principle is used to calculate valve orifice area. The *principle of conservation of energy* allows pressure gradients (ΔP) to be calculated from velocity, using the Bernoulli equation.

Table 27.3 Artefacts

TYPE OF ARTEFACT	EXAMPLES OF ERRONEOUS FINDINGS
REFLECTION AND/OR REFRACTION-RELATED ARTEFACTS	
Reverberation	Thrombus in left atrial appendage Thoracic aortic dissection Pacemaker lead reverberation
Mirror artefact	'Double barrelled' aorta or inferior vena cava Prosthetic valve pseudo-mitral regurgitation on colour Doppler
Acoustic shadowing	Obscuration of structures and colour Doppler deep to prosthetic valves
Refraction	Duplicate mitral valve leaflets or aortic root
ULTRASOUND BEAM PROPERTY-RELATED ARTEFACT	
Side-lobe artefact	Thrombi or vegetations Ascending aortic dissection flap
Beam-width artefact	Thrombi or vegetations Tricuspid regurgitation due to disturbed left ventricular outflow tract flow
Near-field clutter	Left ventricular apical thrombus

In practice, a simplified form of the Bernoulli equation is used, $\Delta P = 4v^2$, where pressure is measured in mm Hg and velocity in m/s. The simplified Bernoulli equation overestimates pressure gradients in the setting of severe anaemia (lower blood density) and if the upstream velocity is greater than 1 m/s.

IMAGE OPTIMISATION

With 2D imaging, spatial resolution is improved by using the highest frequency probe for the required depth of scanning. Temporal resolution is improved by using a higher frame rate, by decreasing imaging depth and narrowing image width. Gain should be set to show a bright myocardium but echo-free blood space.

With colour Doppler, temporal resolution is improved by reducing the width and depth of the colour box. Gain should be set just below the level at which colour speckling occurs.

ARTEFACTS

Imaging artefacts can result in false, missing or distorted structures (Table 27.3).[10] Failure to recognise artefacts may lead to misinterpretation and misdiagnosis. Artefacts may occur with 2D and Doppler imaging.

Prosthetic devices such as catheters, wires and artificial valves are particularly prone to causing artefacts.

Decreasing the gain, adjustment of focal depth and alternative imaging planes can be used to circumvent artefacts. Application of colour Doppler can sometimes help distinguish between true and artefactual structures.

COMPONENTS OF INTENSIVE CARE ECHOCARDIOGRAPHY

For a focused cardiac ultrasound, 2D images are obtained from the parasternal long-axis (PLAX) view, parasternal short-axis (PSAX) mid-papillary view, apical four-chamber view, and subcostal four-chamber and inferior vena cava (IVC) views.[2,4,5] For a more complete study, additional parasternal and apical views, and M-mode and Doppler methods are required.

LEFT VENTRICLE

Echocardiography of the left ventricle (LV) includes evaluation of dimensions, geometry and contractile function. The LV should be imaged in multiple views, even with a focused study, so that an accurate picture of LV size and function is obtained. Subjective estimation of LV cavity size (small, normal or dilated), LV wall thickness (thinned, normal or hypertrophied) and global LV systolic function (normal, mildly impaired or severely impaired) is usually sufficient to guide clinical decision making.[11] LV systolic function is assessed subjectively by observing the degree of inward (radial) movement and wall thickening during systole; this is most easily done by observing movement towards an imaginary centre point in the LV cavity in the PSAX mid-papillary view. However, longitudinal movement should also be evaluated (PLAX and apical views); impaired longitudinal shortening is an early sign of LV systolic dysfunction.

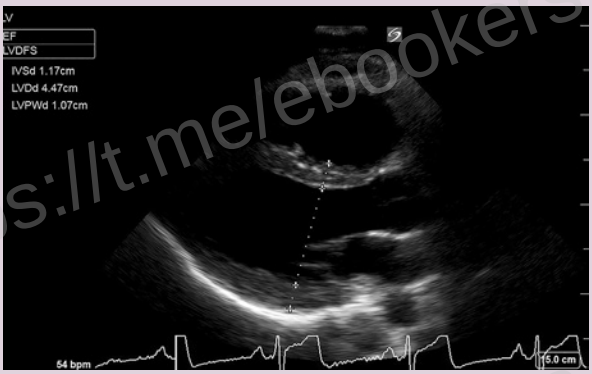
For a more complete evaluation, quantitative measurements can be made (Table 27.4).[12,13]

LV dimensions are measured at end-diastole. LV cavity size can be measured in one, two or three dimensions as follows: *LV diameter* is measured in the PLAX view, with the cursor perpendicular to the long axis of the LV at the level of the mitral valve leaflet tips (see Table 27.4). *LV cross-sectional area* is measured by tracing the endocardial border in the PSAX mid-papillary view. Monitoring of changes in LV area in the transoesophageal trans-gastric mid short-axis view is suited to intraoperative monitoring of preload (see below). *LV volume* can be measured with 3D echocardiography, or calculated from perpendicular 2D views, but is rarely applicable in intensive care.

LV wall thickness is measured at the basal inferolateral (posterior) wall. Severe hypertrophy is defined as a thickness greater than 20 mm. A wall thickness less than 2 mm represents non-viable myocardium at risk of rupture.

LV systolic function is evaluated by measuring changes in LV cavity dimensions, as follows: *Fractional shortening* measures changes in a single LV dimension and is the least accurate. *Fractional area change* measures change in mid-papillary cross-sectional area, calculated as (end-diastolic area – end-systolic area)/end-diastolic area (see Table 27.4). *Ejection fraction* (EF) measures change in LV cavity volume. With the Simpson biplane method (preferred EF method), the LV cavity volume at end-diastole and end-systole is calculated by tracing the endocardial borders of the LV in the apical four-chamber and apical two-chamber views. EF is calculated as (LV end-diastolic volume – LV end-systolic volume)/LV end-diastolic

Table 27.4 Basic quantitative echocardiography methods and expected values: dimensions and systolic function

PARAMETER AND METHOD	IMAGE	CALCULATIONS AND SPECIFIC VALUES
LV linear dimensions 2D PLAX view		Normal values: LVEDD men 4.2–5.9 cm women 3.8–5.3 cm IVSD <10 mm PWD <10 mm

Continued

Table 27.4 Basic quantitative echocardiography methods and expected values: dimensions and systolic function—cont'd

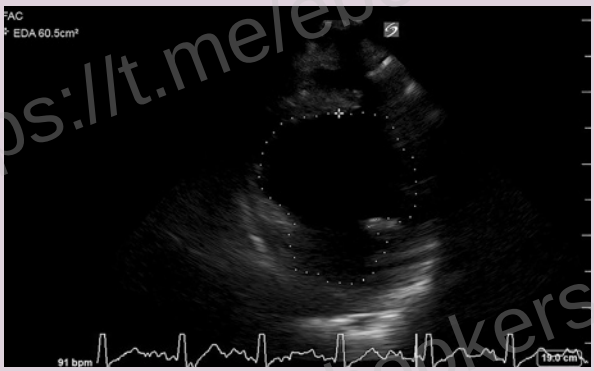
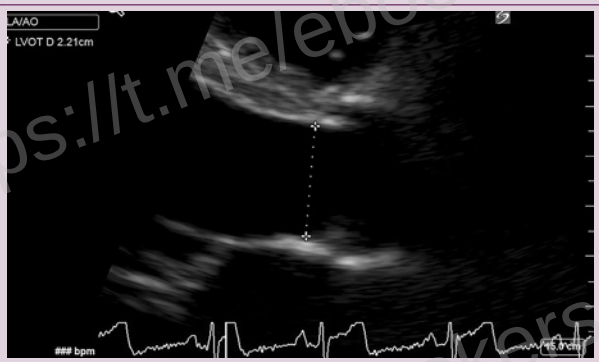
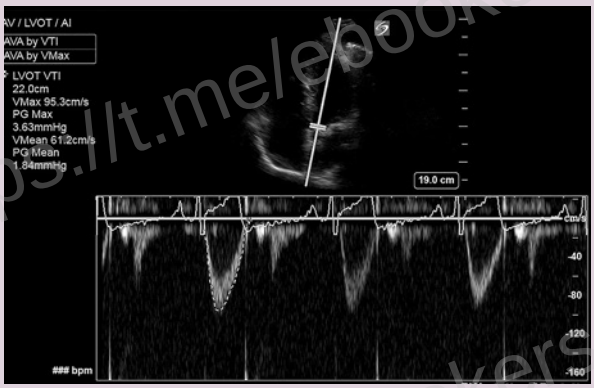
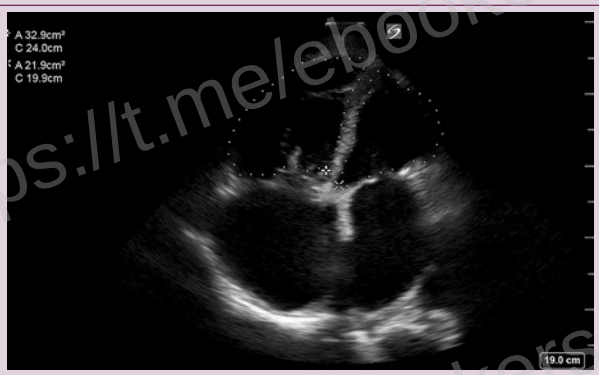
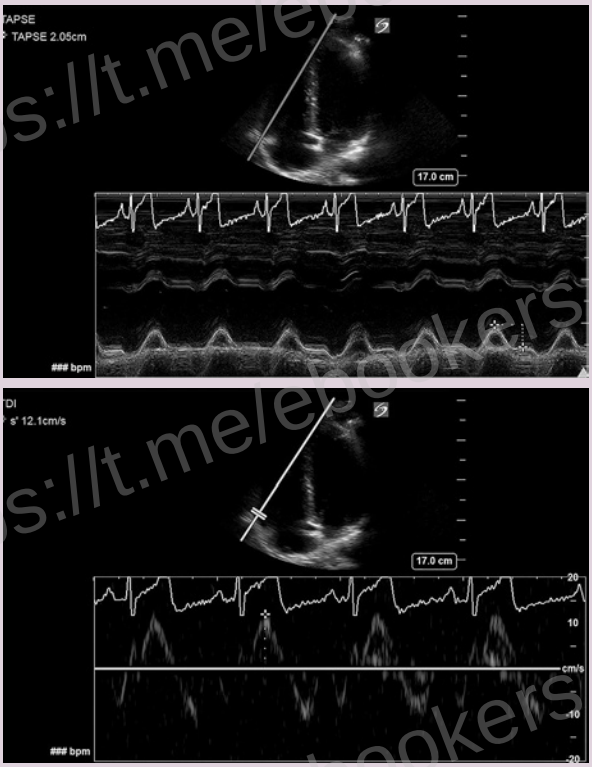
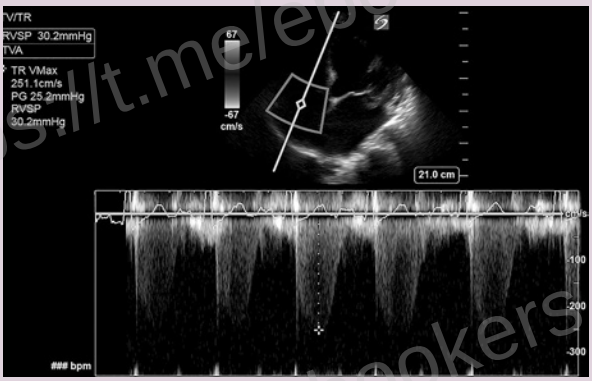
PARAMETER AND METHOD	IMAGE	CALCULATIONS AND SPECIFIC VALUES
LV area 2D PSAX mid-papillary view		Normal values: LVEDA 8–14 cm^2
LVOT diameter Zoom of aortic root from 2D PLAX view **LVOT VTI** PW Doppler from 2D apical 5-chamber view	 	Normal values: LVOT diameter 1.8–2.2 cm LVOT VTI >18 cm
RV area 2D apical 4-chamber view		Normal: RV area <0.6 LV area, RV apex <LV apex RV dilatation: Mild: RV area 0.6–1.0 LV area, RV apex <LV apex Moderate: RV area = LV area, RV apex = LV apex Severe: RV area >LV area, RV apex >LV apex

Table 27.4 Basic quantitative echocardiography methods and expected values: dimensions and systolic function—cont'd

PARAMETER AND METHOD	IMAGE	CALCULATIONS AND SPECIFIC VALUES
TAPSE M-mode from 2D apical 4-chamber view **RV s'** Tissue Doppler from 2D apical 4-chamber view		Normal values: TAPSE ≥ 16 mm RV s' ≥ 10 cm/s
Pulmonary artery systolic pressure CW Doppler across colour Doppler of TR jet from multiple views		Normal values: TRmax <2.8 m/s PASP <35 mm Hg
Notes on timing:	*Mitral valve visible*: End-diastole defined as frame at or immediately prior to mitral valve leaflet coaptation. End-systole defined as frame immediately preceding mitral valve opening. *Mitral valve not visible*: End-diastole defined as frame coinciding with Q wave on ECG. End-systole defined as frame with smallest LV cavity area.	

CW, Continuous wave; *ECG*, electrocardiograph; *IVSD*, interventricular septum diameter; *LV*, left ventricle; *LVEDA*, left ventricular end-diastolic area; *LVEDD*, left ventricular end-diastolic diameter; *LVOT*, left ventricular outflow tract; *PASP*, pulmonary artery systolic pressure; *PLAX*, parasternal long-axis; *PSAX*, parasternal short-axis; *PW*, pulse wave; *PWD*, posterior wall diameter; *RV*, right ventricle; *TAPSE*, tricuspid annular plane systolic excursion; *TR*, tricuspid regurgitation; *VTI*, velocity time integral.

See references 3, 12, 14.

volume. Normal EF is greater than 55%, severe dysfunction is an EF less than 30%. Measurement of EF is highly suited to comprehensive serial evaluation of systolic function in the outpatient setting, but in the intensive care environment is time consuming and prone to inaccuracies from apical foreshortening and poor endocardial definition. A simple method to quantify longitudinal systolic function is the mitral annular plane systolic excursion (MAPSE). Normal MAPSE is greater than 12 mm, severe dysfunction is a MAPSE less than 6 mm.

Caution must be exercised in interpretation of all the methods of evaluating LV systolic function because of the confounding effects of loading conditions (preload and afterload), valvular dysfunction (e.g. mitral regurgitation) and the degree of cardiorespiratory support (inotropes and mechanical ventilation).

Stroke volume is calculated as left ventricular outflow tract (LVOT) VTI (measured in the apical five-chamber view with the PW Doppler sampling volume in the LVOT) × LVOT cross-sectional area (calculated from LVOT diameter assuming a circular cross section, measured in the PLAX zoom view during mid-systole) (see Table 27.4). *Cardiac* output is stroke volume × heart rate.

Regional LV systolic function is described for each wall segment by the extent of wall thickening and inward wall motion during systole (Fig. 27.1). Regional abnormalities are usually due to coronary artery disease and thus distributed according to the pattern of coronary artery perfusion. However, septal dysfunction may also be due to right ventricular (RV) disorders and pulmonary hypertension, conduction abnormalities and pacing, or following cardiopulmonary bypass.

DIASTOLIC FUNCTION AND LEFT ATRIAL PRESSURE

The ability of the LV to fill during diastole depends on active relaxation (in early diastole), LV restoring forces

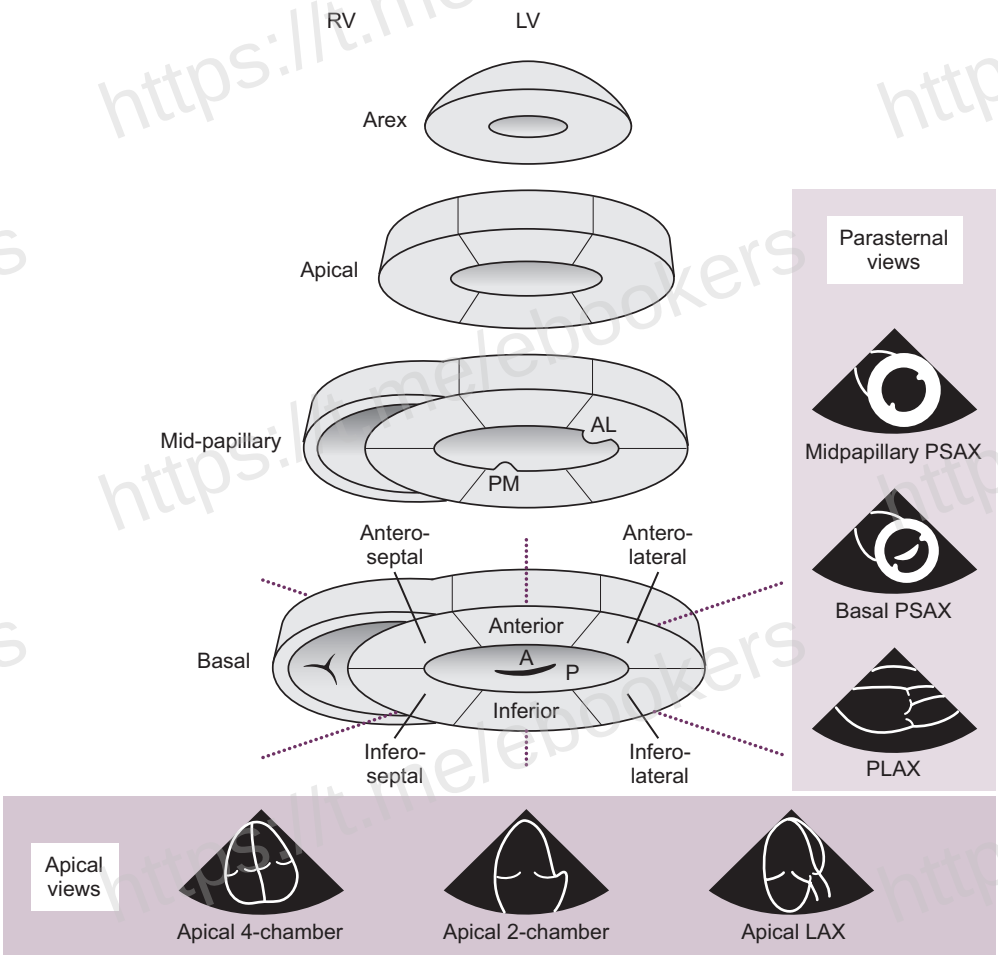
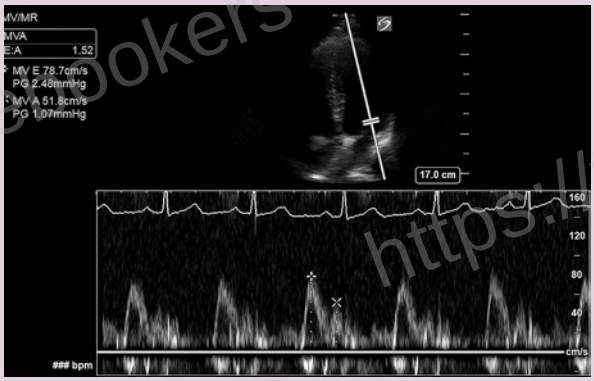
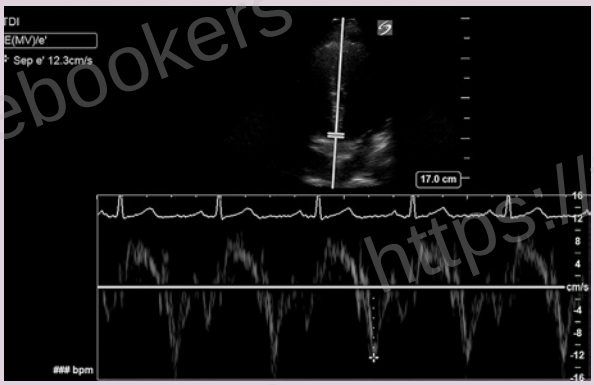
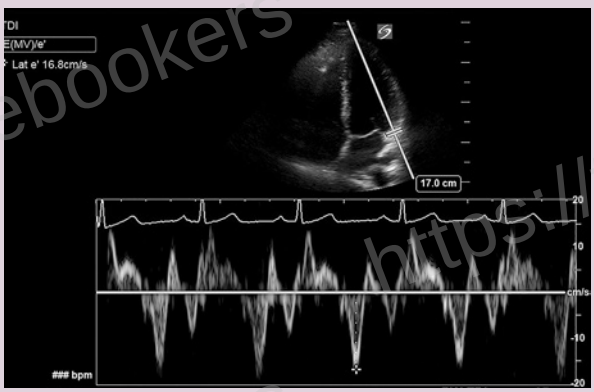


Figure 27.1 Left ventricular (LV) wall segments and standard transthoracic echocardiography views. *A*, Anterior mitral valve leaflet; *AL*, anterolateral papillary muscle; *P*, posterior mitral valve leaflet; *PLAX*, parasternal long-axis; *PM*, posteromedial papillary muscle; *PSAX*, parasternal short-axis.

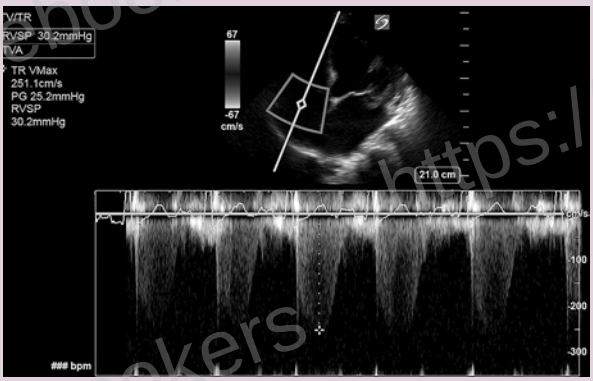
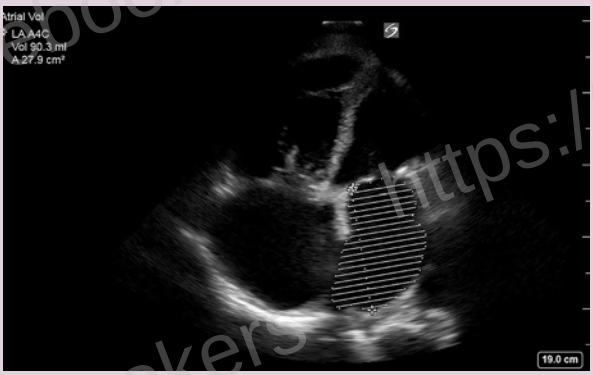
and LV chamber compliance. Impaired diastolic function manifests as increased LV filling pressure, heart failure with normal ejection fraction (HFNEF) and reduced capacity of the LV to increase stroke volume in response to physiological stress. On echocardiography, diastolic dysfunction should be suspected if there is LV hypertrophy or left atrial (LA) enlargement not explained by mitral valve disease or longstanding atrial fibrillation. Further evaluation of diastolic function is largely based on Doppler methods.[13] There is significant overlap between the values of Doppler indices in subjects with and without diastolic dysfunction, and normal aging is associated with slowing of LV relaxation and increased LV chamber stiffness. Doppler indices are also affected by heart rate, rhythm, volume status, mitral valve disease, cardiomyopathy and systolic function. In the presence of systolic dysfunction, severity of diastolic dysfunction is primarily graded according to the PW Doppler mitral inflow E to A wave velocity ratio (Table 27.5). Diagnosis of

Table 27.5 Basic quantitative echocardiography methods and expected values: diastolic function

PARAMETER AND METHOD	IMAGE
Mitral inflow E and A wave 2D apical 4-chamber view – PW Doppler sampling volume at tips of mitral valve leaflets	
Tissue Doppler e' 2D apical 4-chamber view – PW tissue Doppler sampling volume in LV septal and lateral walls at level of mitral annulus	 

Continued

Table 27.5 Basic quantitative echocardiography methods and expected values: diastolic function—cont'd

PARAMETER AND METHOD	IMAGE
Tricuspid regurgitant velocity See pulmonary artery systolic pressure (see Table 27.4)	
Left atrial volume Estimate from 2D PLAX and 4-chamber views	

Diagnostic criteria for diastolic dysfunction in the setting of normal systolic function and mitral valve

CRITERIA	*NUMBER OF CRITERIA MET AND DIAGNOSIS*
$E/e'_{average}$ >14	0–1 Normal diastolic function
e'_{septal} <7 or $e'_{lateral}$ <10 cm/s	2 Uncertain
TR velocity >2.8 m/s	3–4 Diastolic dysfunction and elevated LAP
Enlarged LA volume	

Grading severity of diastolic dysfunction in the setting of impaired systolic function

PARAMETER	*MITRAL INFLOW PATTERN*	*DIAGNOSIS*
E/A ≤0.8 and E ≤50 cm/s	Impaired relaxation	Grade 1 diastolic dysfunction with normal LAP
E/A ≤0.8 and E >50 cm/s, or E/A 0.8–2	Pseudonormal	Grade 2 diastolic dysfunction – LAP uncertain
E/A ≥2	Restrictive	Grade 3 diastolic dysfunction with elevated LAP

LA, Left atrial; *LV*, left ventricle; *LAP*, left atrial pressure; *PLAX*, parasternal long-axis; *PW*, pulse wave; *TR*, tricuspid regurgitation.
See reference 13.

diastolic dysfunction with normal systolic function requires additional measurement of tissue Doppler mitral annular velocities, LA size (volume) and pulmonary artery pressure (see Table 27.5).[13]

Two additional methods, both suited to transoesophageal echocardiography, may be useful for estimating LA pressure[15,16]:

- PW Doppler of pulmonary vein flow normally demonstrates forward systolic (S) and early-diastolic (D) waves, and a smaller reverse atrial (A) wave. Normally the S wave VTI is greater than D wave VTI, but with a high LA pressure this ratio is reversed.[15] This method has limited accuracy in patients with normal systolic function, atrial fibrillation or mitral valve disease.
- The position of the interatrial septum is determined by the relative pressure in the left and right atrium. During positive pressure ventilation, the interatrial septum is normally bowed from left to right for most of the cardiac cycle, except transiently in mid-systole. With high LA pressure, the septum remains fixed bowed left to right.[16] With low atrial pressures, movement of the septum is increased with a buckled appearance during systole.

RIGHT VENTRICLE

The complex 3D shape of the RV makes measurement of RV size from 2D images subject to inaccuracy. RV size is thus usually determined by comparing RV cavity area to LV cavity area, and the relative position of the RV apex to the LV apex, in the apical four-chamber view (see Table 27.4).[14] Care must be taken to ensure optimal imaging planes, and appropriate adjustments made to account for abnormal LV dimensions. RV free wall thickness is measured at end-diastole by M-mode or 2D echocardiography in the subcostal four-chamber view or PLAX view. To avoid overestimation of wall thickness, care must be taken to exclude RV trabeculations, epicardial fat and visceral pericardium.[14]

The shape of the RV also limits 2D assessment of RV systolic function. Longitudinal RV systolic function may be quantified through the tricuspid annular plane systolic excursion (TAPSE) measured using M-mode with the cursor directed through the lateral tricuspid annulus in the apical four-chamber view (see Table 27.4). Alternatively, the lateral tricuspid annulus tissue Doppler systolic wave (s') can be measured from the same view (see Table 27.4). RV radial systolic function is assessed by visualisation of RV free wall thickening and inward wall excursion during systole.

Interventricular septal curvature and kinetics should be examined in the PSAX view for signs of RV volume or pressure overload. RV volume overload (e.g. tricuspid regurgitation) causes flattening (leftward shift) of the interventricular septum, with a characteristic D-shaped LV cavity in cross section, during diastole. LV pressure overload (e.g. pulmonary hypertension) causes septal flattening predominantly during systole. The degree of septal shift can be quantified by the eccentricity index, calculated as the anterior-posterior LV diameter divided by the septal-lateral LV diameter in short axis. A ratio greater than 1.0 signifies RV overload. The precise timing of septal dyskinesia is easier to appreciate with M-mode. Septal dyskinesia is also seen with intraventricular conduction disorders, septal infarction and after cardiac surgery.

Estimation of pulmonary artery pressure is an integral part of right heart evaluation. RV systolic pressure (RVSP) can be estimated from peak tricuspid regurgitant jet velocity (TRmax), using the simplified Bernoulli equation, plus the right atrial pressure (RAP): $RVSP = 4(TRmax)^2 + RAP$. In the absence of pulmonary stenosis, systolic pulmonary artery pressure is equal to RV systolic pressure. The tricuspid regurgitant jet velocity is measured using CW Doppler at a sweep speed of 100 mm/s, with the cursor aligned through the vena contracta on colour Doppler. The tricuspid regurgitant signal from multiple views should be examined and the highest velocity used in calculations. Pulmonary hypertension is likely to be present if the tricuspid regurgitant jet velocity is greater than 2.8 m/s. Underestimation of systolic pulmonary artery pressure occurs if there is poor alignment of the Doppler cursor with the tricuspid regurgitant jet, or severe tricuspid regurgitation (which causes early RV to RA pressure equalisation).[17] Advanced techniques may be used to estimate mean and diastolic pulmonary artery pressures.[14]

VALVULAR ASSESSMENT

Valvular stenosis or regurgitation can be identified with 2D imaging and simple application of colour Doppler.[1,2] Two-dimensional images are examined for abnormal chamber dimensions and geometry (the cause or consequence of valvular dysfunction), valve leaflet thickening or calcification, and excessive or restricted valve leaflet motion. Colour Doppler imaging is used to identify valvular regurgitation.

Aortic stenosis should be suspected on 2D imaging if the aortic valve leaflets appear thickened or calcified, with restricted leaflet motion, and the LV is hypertrophied.

Aortic regurgitation can be detected with colour Doppler in the PLAX, apical long-axis view or apical five-chamber view. Two-dimensional imaging may demonstrate aortic root dilatation, excessive leaflet motion (flail) or LV dilatation.

Mitral stenosis should be suspected if the mitral valve leaflets are thickened or calcified, with restricted leaflet motion. With rheumatic mitral stenosis, fusion

of the commissures causes a characteristic ice-hockey stick appearance of the valve leaflets in cross section in diastole.

Mitral regurgitation can be detected with colour Doppler in multiple echocardiography views. Two-dimensional images are examined for valve leaflet prolapse or flail, and for distorted LV geometry causing dilatation of the mitral annulus or restriction of mitral leaflet coaptation.

Tricuspid regurgitation can be detected with colour Doppler in the PSAX, right tilted PLAX and apical four-chamber views. Two-dimensional images are examined for RV or tricuspid annular dilatation.

Structurally normal valve leaflets and ventricular geometry, with a central narrow jet, is consistent with only trivial or mild regurgitation. This is a common normal finding with the mitral and tricuspid valves. A broader or eccentric jet, or involvement of the aortic valve, is abnormal.

If signs of valvular stenosis or abnormal regurgitation are identified, comprehensive evaluation is indicated to quantify the severity and determine the mechanism of dysfunction (Table 27.6). Comprehensive echocardiography is also indicated for evaluation of prosthetic valve function, or if endocarditis is suspected.

Methods of quantifying valvular stenosis are[18]:

- Peak transvalvular jet velocity, or mean transvalvular pressure gradient derived from tracing the VTI, using CW Doppler. Multiple acoustic windows should be sampled to obtain the highest velocity signal. Recordings are made with the time scale set at 100 mm/s. Velocity and pressure gradient methods are affected by the haemodynamic loading conditions.
- Effective orifice area calculated with the continuity equation.

Table 27.6 Echocardiographic signs of severe valvular heart disease

	AORTIC STENOSIS	MITRAL STENOSIS
Peak velocity (m/s)	>4	
Mean pressure gradient (mm Hg)	>40	>10
Valve area by planimetry (cm^2)		>1
Effective orifice area (cm^2)	<1	<1
Pressure half time (ms)		>220
Velocity ratio	<0.25	
Systolic pulmonary artery pressure (mm Hg)		>50
Low flow, low pressure severe aortic stenosis	Mean pressure gradient <40 mm Hg, Effective orifice area <1 cm^2, LVEF <40%	
Additional features	LV hypertrophy	LA dilatation

	AORTIC REGURGITATION	MITRAL REGURGITATION	TRICUSPID REGURGITATION
Vena contracta width (mm)	>6	>7	>7
Jet width/LVOT width (%)	>65		
Effective regurgitant orifice area (cm^2)	>0.3	>0.4	
Pressure half time (ms)	<200		
Colour Doppler regurgitant jet	Large central, or eccentric jet	Large central, or eccentric jet	Large central jet
Additional features	Dilated LV Holodiastolic flow reversal in descending aorta	Dilated LV and LA Systolic flow reversal in pulmonary veins. Flail leaflet Ruptured papillary muscle	Dilated RV, RA and IVC Systolic flow reversal in hepatic veins

IVC, Inferior vena cava; *LA*, left atrial; *LV*, left ventricle; *LVOT*, left ventricular outflow tract; *RA*, right atrial; *RV*, right ventricle.
See references 18, 19.

- Anatomical orifice area traced from a 2D image (planimetry).
- Pressure half time for mitral stenosis. Severe mitral stenosis is characterised by slow diastolic pressure equalisation between the LA and LV and thus a long pressure half time.

Aortic stenosis is quantified most easily by the peak jet velocity; care must be taken to avoid misdiagnosis due to LVOT obstruction or eccentric mitral regurgitation. Additional measures include mean pressure gradient and aortic valve effective orifice area by the continuity equation. Mitral stenosis is quantified by a combination of mean pressure gradient, planimetry and pressure half time.

Methods for quantifying valvular regurgitation are[19]:

- Width of the colour Doppler jet at its narrowest point through the valve (vena contracta). Zoom mode and a small colour Doppler box are used to optimise spatial and temporal resolution. Accuracy is improved if the jet origin, width of vena contracta and spatial orientation in the receiving chamber are all visualised.
- The colour Doppler jet area in the receiving chamber. The Nyquist limit is set at 50–60 cm/s. This method underestimates severity with eccentric jets as they are constrained against the wall of the receiving chamber, and is particularly unreliable with acute regurgitation because of tachycardia, rapid pressure equalisation and small size of the receiving chamber.
- Effective regurgitant orifice area, regurgitant fraction and regurgitant volume calculated with the continuity equation.
- Proximal isovelocity surface area (PISA) method, which is a form of the continuity equation using a combination of measurements from 2D, colour Doppler and CW Doppler. This is often technically challenging in the critically ill patient.
- Pressure half time for aortic regurgitation. Severe or acute aortic regurgitation results in rapid pressure equalisation between the proximal aorta and LV during diastole, and thus a short pressure half time.
- Detection of flow reversal upstream of the receiving chamber, using PW or colour Doppler.

Aortic regurgitation is quantified by the width of the colour Doppler regurgitant jet within 1 cm of the aortic valve or the vena contracta, and the pressure half time method. Mitral and tricuspid regurgitation are quantified most easily by the width of the vena contracta. Continuity equation methods should be used for a comprehensive assessment of mitral regurgitation when there is uncertainty.

Prosthetic valves are inherently stenotic compared to native valves. Thus, it may be difficult to distinguish mild obstruction due to valve design from that due to pathological changes or prosthesis-patient mismatch. Most prosthetic valves are associated with trivial or mild regurgitation. Imaging of prosthetic valves may be difficult due to shadowing artefacts; transoesophageal echocardiography may be required, particularly for a mitral prosthesis.

PRELOAD AND VOLUME RESPONSIVENESS

In the appropriate clinical context, several echocardiographic indices may be used to predict fluid responsiveness.

Static indices measure preload rather than fluid responsiveness. Direct measures of preload include LV end-diastolic area or volume. Indirect measures include estimates of LV end-diastolic pressure based on Doppler mitral and pulmonary vein inflow, or the pattern of interatrial septal movement. An LV end-diastolic area of less than 8 cm^2 likely represents hypovolaemia. Monitoring of LV end-diastolic area (with transoesophageal echocardiography in the transgastric mid-papillary view) is sometimes used to guide fluid therapy intraoperatively when large fluid shifts are anticipated (e.g. cardiopulmonary bypass, liver transplantation).

Dynamic indices apply the Frank-Starling law of the heart to examine the effect of a change in preload on stroke volume or systemic venous return. If the LV is operating on the steep ascending part of the ventricular function curve, then changes in preload induced by mechanical ventilation will be associated with variation in stroke volume or diameter of the vena cavae, and predict fluid responsiveness.[20–22] These methods are only valid in the mechanically ventilated patient with no spontaneous respiratory effort, no arrhythmia, no impairment of right or left systolic function, and no intra-abdominal hypertension. IVC distensibility with inspiration can be measured using 2D or M-mode imaging of the proximal IVC in the subcostal view. Care must be taken to ensure that the cursor remains over the widest part of the IVC throughout the respiratory cycle (Fig. 27.2). With transoesophageal echocardiography, superior vena cava collapsibility can be measured in the upper oesophageal short-axis view. The vena cava methods can be used with arrhythmia, but otherwise have the same limitations as the stroke volume variability method.[20–22] In the spontaneously breathing patient, the stroke volume response to a passive leg raise test may be used.[23]

PERICARDIAL EFFUSION AND TAMPONADE

Echocardiography is the initial imaging modality of choice to detect a pericardial effusion and is the best method for assessing the physiological effects of pericardial effusion on cardiac function.[24] In the normal subject, the pericardial space contains a minimal amount of fluid and separation of the parietal pericardial and the epicardial layers is visible only in systole. Accumulation of more than 50 mL of fluid in

Figure 27.2 Dilated inferior vena cava demonstrated in a subcostal long-axis view.

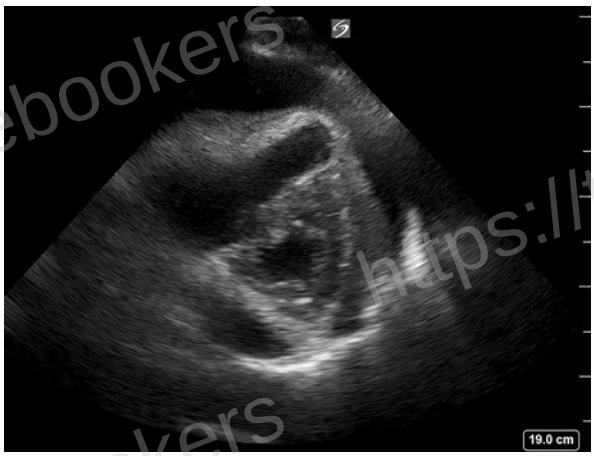


Figure 27.3 A large pericardial effusion with right ventricular free wall compression demonstrated in a parasternal short-axis view.

the pericardial space is abnormal, resulting in pericardial effusion formation with separation of the layers throughout both systole and diastole. A simple pericardial effusion manifests as an echolucent space surrounding the cardiac chambers. The size of an effusion may be quantified by measuring the maximum separation of the pericardial layers at end-diastole. A small effusion is defined as less than 0.5 cm, moderate effusion 0.5–2.0 cm and large effusion greater than 2.0 cm. In the PLAX view, pericardial effusion is distinguished from pleural effusion by its anatomical relationship to the descending aorta. Complex pericardial effusions may contain echogenic fibrinous strands with tethering to adjacent structures. Pericardial haematoma often has a heterogeneous echodensity and variable thickness around the heart, or may be localised.

Pericardial tamponade occurs when intrapericardial pressure exceeds intracardiac pressures causing cardiac chamber compression, increased ventricular interdependence, venous obstruction and ultimately haemodynamic compromise. Both the rate of accumulation and volume of a pericardial effusion determine the degree of physiological compromise. In the structurally normal heart, the lowest intracardiac pressure occurs in the right atrium during ventricular systole and then the RV during diastole. Thus, with increasing pericardial pressure, chamber compression manifests at first as systolic right atrial free wall collapse, and later also with RV free wall collapse (Fig. 27.3). Chamber collapse is best appreciated in the subcostal four-chamber view, where the right heart lies close to the probe. In the apical four-chamber view, the right atrium lies deep to other structures and the right atrial free wall may be poorly visualised if imaging conditions are difficult. In the presence of pulmonary hypertension and RV hypertrophy, right-sided free wall collapse occurs at higher pericardial pressure and left-sided compression may occur first.

In the spontaneously breathing patient, increased ventricular interdependence manifests as increased respiratory variation in mitral and tricuspid blood flow. This can be measured with CW Doppler echocardiography in the apical four-chamber view at an imaging sweep speed of 25 cm/s. An inspiratory decrease in mitral E wave velocity greater than 25% and decrease in tricuspid E wave velocity greater than 40% is consistent with tamponade physiology. However, marked respiratory variation in blood flow can also occur with acute respiratory disease, RV disease, or hypovolaemia. In the mechanically ventilated patient, respiratory variation in blood flow is decreased rather than increased. Fixed IVC dilatation is present whether the patient is spontaneously breathing or mechanically ventilated (see Fig. 27.2).

In practice, the combination of clinical features of tamponade (shock with hypotension and tachycardia) and the presence of a pericardial effusion on echocardiography confirms a diagnosis of tamponade. LV contractility may be hyperdynamic or hypodynamic.

When performing pericardiocentesis, echocardiography is used to guide the best approach (apical versus subxiphoid), confirm pericardial entry of the needle, and confirm guidewire and catheter placement.[3]

TRANSOESOPHAGEAL ECHOCARDIOGRAPHY

Transoesophageal echocardiography provides better image quality compared to transthoracic imaging because of reduced imaging depth, use of higher

Table 27.7 Indications for transoesophageal echocardiography

Inadequate visualisation of relevant structures on transthoracic echocardiography (e.g. haemodynamic assessment after cardiac surgery)
Suspected aortic dissection where computed tomography is not immediately available
Suspected native valve infective endocarditis, where transthoracic echocardiography is inconclusive
Suspected prosthetic valve endocarditis
Evaluation of left atrium (appendage) to guide decisions regarding cardioversion and anticoagulation for atrial fibrillation
Evaluation for cardiovascular source of embolus

See references 1, 3, 6.

frequency transducers and lack of intervening chest wall and lung. Posterior cardiac structures such as the left atrium, mitral valve, pulmonary veins and aorta are particularly well imaged. In mechanically ventilated patients, transthoracic views are often limited, and transoesophageal echocardiography may be required (Table 27.7). However, transoesophageal echocardiography is an invasive procedure that is contraindicated in the setting of oropharygneal or oesophageal disease and severe bleeding diathesis. Risks also include dislodgement of endotracheal and enteral tubes, and oesophageal burn from prolonged imaging in hyperthermic patients. Transoesophageal echocardiography should generally be avoided in the unintubated critically ill patient because of the risk of worsening hypoxaemia and aspiration. Limitations of transoesophageal echocardiography include inability to obtain true anatomical measurements due to oblique imaging planes, difficulty obtaining Doppler beam alignment resulting in underestimation of velocities, and inability to visualise the distal ascending aorta and proximal aortic arch.

CLINICAL SITUATIONS

Indications for echocardiography in intensive care are listed in Table 27.1.[1,6] The type of study (basic versus comprehensive and transthoracic versus transoesophageal) will depend on the clinical situation, availability of equipment and the echocardiography expertise of the attending clinician. Most often, a focused study, with basic assessment of valvular function, will suffice to address the clinical problem.[4,5,25]

Repeated studies may be indicated in patients with haemodynamic instability or acute cor pulmonale to guide fluid and vasoactive drug therapy, and monitor the haemodynamic effects of changes in ventilator settings.[11,26,27] Usually a subjective impression is sufficient to gauge the response to intervention, but quantitative parameters may also be followed, as long as meticulous care is taken with measurement technique (see Table 27.4).[3]

HAEMODYNAMIC INSTABILITY

Echocardiography may be used to augment clinical findings to characterise the basic haemodynamic state as follows[11,20–22,25–27]:

Hypovolaemia is characterised by positive indices of fluid responsiveness and reduced LV diastolic dimensions. Systolic function may appear normal or reduced.

Vasodilatation is characterised by reduced LV systolic dimensions. Systolic function appears normal or hyperdynamic. With severe hypovolaemia or vasodilatation, there is obliteration of the LV cavity during systole, so called 'kissing papillary muscles'. Obliteration is more likely to occur if the LV is hypertrophied.

LV systolic dysfunction can usually be identified by subjective assessment, but account must be taken of the loading conditions, co-existent valvular heart disease and the amount of circulatory support (inotropes, vasopressors and mechanical ventilation). The cause of LV dysfunction should be sought. A dilated, thinned LV is consistent with pre-existing dilated cardiomopathy. Regional wall motion abnormalities are consistent with coronary artery disease. LV structure appears normal in sepsis-induced LV dysfunction.[11,26] Takotsubo (stress) cardiomyopathy causes circumferential mid-wall or apical akinesia, with hyperdynamic basal function.[28]

LV diastolic dysfunction is likely if the LV wall is thickened, or LV systolic function is impaired, but requires Doppler interrogation to confirm the diagnosis.[13]

RV dysfunction is characterised by RV dilatation, with interventricular septal flattening in diastole with RV volume overload, and with interventricular septal flattening in systole with RV pressure overload.[14,26] The features of acute cor pulmonale and RV infarction are described below.

ACUTE CORONARY SYNDROME

Regional wall motion abnormalities visible on echocardiography develop within 30 minutes of an acute coronary syndrome. Wall motion abnormalities should be described in terms of the segments affected and severity of hypokinesia or akinesia; normal myocardial radial thickening is greater than 30%. The location of segments involved should be correlated with the distribution of coronary artery perfusion.

A change in clinical status following an acute coronary syndrome should prompt echocardiography to detect complications as follows:

Complete or partial papillary muscle rupture usually causes severe *mitral regurgitation*. Posterior leaflet restriction due to inferior or posterior myocardial infarction causes less severe functional mitral regurgitation, which may be dynamic, presenting as failure to wean from mechanical ventilation.

Ventricular septal rupture causes cardiogenic shock; on echocardiography one or more septal defects can be detected with colour Doppler. LV function may appear deceptively good due to offloading to the RV. *LV free wall rupture* causes very rapid accumulation of pericardial blood with severe tamponade.

RV infarction is differentiated from acute cor pulmonale by the absence of pulmonary hypertension and coexistence of LV inferior wall hypokinesia.

SEPTIC SHOCK

Basic echocardiography is well suited to provide rapid and repeated evaluation of the haemodynamic state in septic shock.[11,26] Fluid administration may be guided by indices of fluid responsiveness in the sedated, mechanically ventilated patients. Alternatively, the development of B lines on lung ultrasound after fluid loading can be used as a stopping criteria to discontinue further fluid administration (see Chapter 40). Treatment of persistent hypotension after adequate fluid loading, with either vasopressors or inotropes, is then guided by echocardiographic assessment of LV function. Impaired LV systolic function is a common finding in septic shock, but may not be evident until at least 24 hours after presentation, or is only 'unmasked' after vasopressor therapy is commenced, increasing LV afterload.[26,28] Impaired RV function may also occur, either as a part of global ventricular dysfunction, or due to acute cor pulmonale.[27-29]

INFECTIVE ENDOCARDITIS

Diagnosis of infective endocarditis by major Duke criteria requires a combination of positive microbiological culture and evidence of endocardial involvement on echocardiography: vegetations (mobile echodense masses visible on a valve or prosthetic material, e.g. pacemaker lead), abscess, or dehiscence of a prosthetic valve. Transoesophageal echocardiography may be required if transthoracic imaging is inconclusive, and is warranted if prosthetic valve involvement is suspected.

RESPIRATORY FAILURE

Echocardiography is useful for evaluating the cause and haemodynamic consequences of respiratory failure. Firstly, in patients with pulmonary infiltrates on chest radiograph, examination of the left heart is focused on findings that may predispose to cardiogenic pulmonary oedema such as LV systolic dysfunction, diastolic dysfunction or left-sided valvular heart disease.

Secondly, examination of the right heart is focused on identifying signs of acute cor pulmonale and quantifying the severity of pulmonary hypertension.[17,27] Acute cor pulmonale is the result of a sudden increase in RV afterload, caused by acute respiratory distress syndrome or pulmonary embolism. On echocardiography acute cor pulmonale is characterised by RV dilatation, and interventricular septal dyskinesia with septal flattening in late systole (D-shaped LV in short axis). Chronic pulmonary hypertension is distinguished from acute cor pulmonale by the presence of RV hypertrophy; however, hypertrophy can develop within several days of having a sustained increase in RV afterload.[27]

Thirdly, in patients with hypoxaemia disproportionate to the severity of underlying illness, a bubble study during echocardiography can be used to identify a right-to-left shunt through a patent foramen ovale, or intrapulmonary shunt (e.g. with hepatopulmonary syndrome).

PULMONARY EMBOLISM

The echocardiographic signs of high-risk pulmonary embolism are those of acute cor pulmonale.[30] In addition, the combination of RV free wall hypokinesis and relative sparing of apical systolic function (McConnell sign) has a high specificity for pulmonary embolism. Rarely, thrombus may be directly visible in transit through the right heart. Thrombus may also be visible in the main pulmonary artery on transoesophageal echocardiography.

Echocardiography is indicated in the hypotensive or shocked patient with suspected pulmonary embolism where computed tomography pulmonary angiography to confirm the diagnosis is considered too risky or impractical.[30] In this setting, echocardiography can be used to exclude other causes of haemodynamic instability. Absence of echocardiographic signs of acute cor pulmonale effectively excludes pulmonary embolism as the cause for haemodynamic compromise. Conversely, the presence of acute cor pulmonale in this setting has been used to justify thrombolysis therapy.[30]

In the patient with known pulmonary embolism, but haemodynamic instability, a normal echocardiogram can be used to justify withholding thrombolysis.

ACUTE RESPIRATORY DISTRESS SYNDROME

A quarter of patients with acute respiratory distress syndrome develop acute cor pulmonale due to a combination of pulmonary vascular dysfunction and mechanical ventilation.[27] Acute cor pulmonale usually develops over a few days, but may become severe, particularly in the setting of high ventilator driving pressures (>18 cm H_2O), severe hypoxaemia (P/F <150 mm Hg) and hypercapnia. Thus, repeated

echocardiography may be required to detect the development of acute cor pulmonale and guide optimal ventilatory strategy to protect the right heart.[27]

FAILURE TO WEAN FROM MECHANICAL VENTILATION

During the transition from mechanical ventilation to spontaneous breathing, the change in ventricular loading conditions may unmask occult systolic or diastolic dysfunction (with increased LA pressure). Echocardiography should be combined with lung ultrasound to detect signs of acute pulmonary oedema (B lines) and assess diaphragmatic function (see Chapter 40).

POSTCARDIAC SURGERY

The early postoperative period after cardiac surgery presents unique challenges to image optimisation due to mechanical ventilation, surgical dressings and drains, and to image interpretation because of diagnostic findings unusual in other clinical settings:

Pericardial haematoma can cause focal cardiac chamber compression; thus, every cardiac chamber must be clearly visualised. Rarely, massive haemothorax can cause tamponade.

Dynamic LVOT obstruction should be suspected in the patient with mitral valve repair, hypertrophic LV, or aortic valve replacement for aortic stenosis, who develops shock that fails to respond to catecholamines or intra-aortic balloon counterpulsation. Echocardiography demonstrates a high LVOT flow velocity and mitral regurgitation.

RV dysfunction may occur in isolation due to inadequate intraoperative cardioplegia.

Increased intrathoracic pressure may present with haemodynamic features similar to pericardial tamponade, but should be recognised from assessment of ventilation. On echocardiography there are features of acute cor pulmonale.

Patient prosthesis mismatch results in a high transvalvular pressure gradient and difficultly weaning from mechanical ventilation. Other causes of prosthetic valve dysfunction (e.g. leaflet entrapment or paravalvular leak) warrant expert evaluation.

CARDIAC ARREST

Echocardiography may be used during cardiac arrest with non-shockable rhythm to assess myocardial contractility and help identify potentially reversible causes such as pericardial tamponade, pulmonary embolism, hypovolaemia, or tension pneumothorax.[31] Echocardiography should not disrupt good quality chest compressions. A clearly defined approach such as the focused echocardiographic evaluation in life support (FEEL) should be followed.[31] Subxiphoid placement of the probe just before chest compressions are paused for a planned rhythm assessment allows image acquisition within 5 seconds during the pause.[31] Echocardiography findings should be clearly communicated to the resuscitation team.

With asystole, echocardiography may demonstrate myocardial activity when the electrocardiogram monitoring falsely shows no electrical activity. The absence of cardiac activity with asystole is highly predictive of death.[32] With pulseless electrical activity (PEA), the presence of myocardial activity (pseudo-PEA) confers a better prognosis.

Transoesophageal echocardiography can provide better imaging quality than transthoracic echocardiography, without interruption of chest compressions. The transoesophageal probe should not be inserted until after the airway has been secured with an endotracheal tube and satisfactory ventilation has been achieved.

REFERENCES

1. Levitov A, Frankel HL, Blavias M, et al. Guidelines for the appropriate use of bedside general and cardiac ultrasonography in the evaluation of critically ill patients-part II: cardiac ultrasonography. *Crit Care Med*. 2016;44:1206–1227.
2. Oren-Grinsberg A, Talmor D, Brown SM. Focused critical care echocardiography. *Crit Care Med*. 2013;41:2618–2626.
3. Porter TR, Shillcutt SK, Adams MS, et al. Guidelines for the use of echocardiography as a monitor for therapeutic intervention in adults: a report from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2015;28:40–56.
4. Spencer KT, Kinmura BJ, Korcarz CF, et al. Focused cardiac ultrasound: recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2013;26:567–581.
5. Vie G, Hussain A, Wells M, et al. International evidence-based recommendations for focused cardiac ultrasound. *J Am Soc Echocardiogr*. 2014;27:683–698.
6. Douglas PS, Garcia MJ, Haines DE, et al. CCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 appropriate use criteria for echocardiography. *J Am Soc Echocardiogr*. 2011;24:229–267.
7. Mayo PH, Beaulieu Y, Doelken P, et al. American College of Chest Physicians/La Société de Réanimation de Langue Française statement on competence in critical care ultrasonography. *Chest*. 2009;135:1050–1060.
8. Expert Round Table on Ultrasound in ICU. International expert statement on training standards for critical care ultrasonography. *Intensive Care Med*. 2011;37:1077–1083.
9. Price S, Via G, Sloth E, et al. Echocardiography practice, training and accreditation in the intensive care: document for the World Interactive Network

Focused on Critical Ultrasound (WINFOCUS). *Cardiovasc Ultrasound*. 2008;6:49.
10. Bertrand PB, Levine RA, Isselbacher EM, et al. Fact or artefact in two-dimensional echocardiography: avoiding misdiagnosis and missed diagnosis. *J Am Soc Echocardiogr*. 2016;29:381–391.
11. Vieillard-Baron A, Charron C, Chergui K, et al. Bedside echocardiographic evaluation of hemodynamics in sepsis: is qualitative evaluation sufficient? *Intensive Care Med*. 2006;32:1547–1552.
12. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.
13. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29:277–314.
14. Kuecherer HF, Muhiudeen IA, Kusumoto FM, et al. Estimation of mean atrial pressure from transesophageal pulse Doppler echocardiography of pulmonary venous flow. *Circulation*. 1990;82: 1127–1139.
15. Kusumoto FM, Muhiudeen IA, Kuecherer HF, et al. Response of interatrial septum to transatrial pressure gradients and its potential for predicting pulmonary capillary wedge pressure: an intraoperative study using transesophageal echocardiography in patients during mechanical ventilation. *J Am Coll Cardiol*. 1993;21:721–728.
16. Rudski LG, Lai WW, Afilado J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:687–713.
17. Fisher MR, Forfia PR, Chamera E, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med*. 2009;179:615–621.
18. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr*. 2009;22:1–23.
19. Zogbi WA, Enriquez-Srano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr*. 2003;16:777–802.
20. Feissel M, Michard F, Faller JP, et al. The respiratory variation in inferior vena cava diameter as a guide to fluid therapy. *Intensive Care Med*. 2004;30:1834–1837.
21. Barbier C, Loubieres Y, Schmit C, et al. Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients. *Intensive Care Med*. 2004;30:1740–1746.
22. Vieillard-Baron A, Chergui K, Rabiller A, et al. Superior vena caval collapsibility as a gauge of volume status in ventilated septic patients. *Intensive Care Med*. 2004;30:1734–1739.
23. Monnet X, Teboul JL. Passive leg raising. *Intensive Care Med*. 2008;34:659–663.
24. Klein AL, Abbara S, Agler DA, et al. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease. *J Am Soc Echocardiogr*. 2013;26:965–1012.
25. Shokoohi H, Boniface KS, Pourmand A, et al. Bedside ultrasound reduces diagnostic uncertainty and guides resuscitation in patients with undifferentiated hypotension. *Crit Care Med*. 2015;43:2562–2569.
26. Vieillard-Baron A, Prin S, Chergui K, et al. Hemodynamic instability in sepsis: bedside assessment by Doppler echocardiography. *Am J Respir Crit Care Med*. 2003;168:1270–1276.
27. Vieillard Baron A, Prin S, Chergui K, et al. Echo Doppler demonstration of acute cor pulmonale at the bedside in the medical intensive care unit. *Am J Respir Crit Care*. 2002;166:1310–1319.
28. Citro R, Lyon AR, Meimoun P, et al. Standard and advanced echocardiography in takotsubo (stress) cardiomyopathy: clinical and prognostic implications. *J Am Soc Echocardiogr*. 2015;28:57–74.
29. Etchecopar-Chevreuil C, Francois B, Clavel M. Cardiac morphological and functional changes during early septic shock: a transesophageal echocardiographic study. *Intensive Care Med*. 2008;34:250–256.
30. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;35:3033–3069.
31. Breitkreutz R, Walcher F, Seeger FH. Focused echocardiographic evaluation in resuscitation management: concept of an advanced life support-conformed algorithm. *Crit Care Med*. 2007;35:S150–S161.
32. Blyth L, Atkinson P, Gadd K, et al. Bedside focused echocardiography as predictor of survival in cardiac arrest patients: a systematic review. *Acad Emerg Med*. 2012;19:1119–1126.

Part Four
Respiratory Failure

This page intentionally left blank

28

Oxygen therapy

Brett Sampson, Shailesh Bihari

In humans, uptake of environmental oxygen via the lungs provides necessary substrates for energy production. This is a key ingredient to survival. Aerobic respiration is the most efficient mechanism for adenosine triphosphate (ATP) production by oxidative phosphorylation and serves as the fuel to maintain cellular homeostasis and metabolism. Absence or lack of ATP leads to loss of cellular integrity initially, followed by cellular and later organism death. Under hypoxic conditions, ATP production is inefficient (through glycolysis) and leads to production of lactic acid. A substantial part of critical care is targeted at treating and/or preventing hypoxia, yet in recent years the risks of hyperoxia leading to organ damage have become better understood. Thus an understanding of the common pathways and significance of cellular hypoxia is vital to providing appropriate and safe support and treatment to the acutely unwell patient.

PHYSIOLOGY OF OXYGEN DELIVERY

The transfer of a gas across a membrane relies on physical principles and is summarised by Fick's first law of diffusion[1]:

$$(28.1) \qquad O_2 \text{ diffusion} = K \times A/T \times \Delta P$$

where K is the diffusion constant for a particular gas, A is the surface area of a membrane; T is the membrane's thickness and ΔP the difference in partial pressure across the membrane. Because oxygen is poorly soluble in water, diffusion alone is insufficient to deliver oxygen to the cells, and novel methods of delivery have evolved, most notably the cardiovascular system.[2] This provided the means to deliver oxygen around the body.

OXYGEN DELIVERY

Transport of oxygen to the cells can thus be divided into six simple steps reliant only on the laws of physics: (1) convection of oxygen from the environment into the body via the lungs (ventilation); (2) diffusion of oxygen into the blood through the alveolar–capillary membrane (oxygen uptake); (3) reversible chemical bonding with haemoglobin; (4) convective transport of oxygen to the tissues (cardiac output [CO]); (5) diffusion into the cells and organelles; and (6) the redox state of the cell. This chain of events is oxygen delivery or more correctly oxygen flux ($\dot{D}_{O_2}$).

Step 1: convection – ventilation The first step occurs in the lung in the form of pulmonary ventilation. At sea level the partial pressure of oxygen in environmental air is approximately 160 mm Hg (21.3 kPa). On inspiration the air is humidified and mixed with exhaled carbon dioxide (CO_2) such that the partial pressure of oxygen at the alveolus (P_{AO_2}) is 100 mm Hg (13.3 kPa). P_{AO_2} varies in different environments and different conditions (Table 28.1) and can be calculated from the alveolar gas equation:

$$(28.2) \qquad P_{AO_2} = Fi_{O_2} \times (P_{atm} - P_{H_2O}) - PaCO_2/R$$

where P_{AO_2} is partial pressure of O_2 in the 'ideal' alveolus, Fi_{O_2} is the fraction of O_2 in inspired gas, P_{atm} is atmospheric pressure, P_{H_2O} is saturated vapour pressure of water (47 mm Hg), $PaCO_2$ is partial pressure of CO_2 in arterial blood, and R is the respiratory quotient (ratio of CO_2 production to O_2 consumption), which is 0.8 for a modern diet (see Chapter 18).

Much of oxygen therapy is based on increasing Fi_{O_2} during spontaneous or mechanical ventilation. However, it is important to note that the delivery of oxygen to the alveolus can still be achieved without lung ventilation. During apnoea, ongoing oxygen consumption results in a fall in P_{AO_2}, creating a pressure gradient for the mass movement (bulk flow) of oxygen into the alveoli. Clinically, this can be used to maintain oxygenation during the apnoeic period following induction of anaesthesia (apnoeic oxygenation) and during brain death testing, discussed later.

Step 2: diffusion – alveolus to blood Oxygen within the alveolus diffuses across the alveolar–capillary membrane. The average thickness of the alveolar capillary membrane is 0.3 µm, and the surface area of the respiratory membrane between 50 and 100 m^2. This leads to a partial pressure of oxygen in the pulmonary capillaries (Pa_{O_2}) of approximately 90 mm Hg (12 kPa). Herein lies many of the problems seen in the critically ill, where two mechanisms predominate: (1) the thickness and barrier effect of the space between alveolus

ABSTRACT

Although oxygen is essential for human survival and is a life-saving therapy, its injudicious use must be avoided to prevent inadvertent harm. Careful titration of oxygen therapy is essential to ensure hypoxia is safely treated and hyperoxia avoided. This requires a sound understanding of the pathophysiological perturbations in oxygen delivery and utilisation seen in the critically ill. Choosing the appropriate oxygen therapy device in the conscious self-ventilating patient can be challenging and may require a trial of different devices before a balance between patient tolerability and satisfactory oxygenation is achieved. Humidified high-flow oxygen and non-invasive ventilation have become the mainstay treatment for conscious hypoxaemic patients; however, close monitoring is required to ensure invasive ventilation is not delayed when indicated. Oxygen toxicity is to be avoided, but this may not always be possible. Hyperbaric oxygen therapy has few indications in the critically ill, including severe carbon monoxide poisoning and necrotising soft-tissue infections.

KEYWORDS

Oxygen
aerobic metabolism
hypoxia
hyperoxia
arterial oxygen saturation
mixed venous oxygen saturations
central venous oxygen saturations
high-flow oxygen therapy
preoxygenation
apnoeic oxygenation

Table 28.1 Clinical significance of some Pa_{O_2} and Sa_{O_2} values

Pa_{O_2} mm Hg	Pa_{O_2} kPa	Sa_{O_2} (%)	CLINICAL SIGNIFICANCE
160	20.0	99	Inspired air at sea level
97	12.9	97	Young normal man
80	10.6	95	Young normal man asleep Old normal man awake Inspired air at 19,000 ft (5800 m)
70	9.3	93	Lower limit of normal
60	8.0	90	Respiratory failure (mild); shoulder of O_2 dissociation curve
50	6.7	85	Respiratory failure (significant); admit to hospital
40	5.3	75	Venous blood – normal Arterial blood – respiratory failure (severe) Acclimatised man at rest at 9000 ft (2750 m)
30	4.0	60	Unconscious if not acclimatised
26	3.5	50	P50 of haemoglobin
20	2.7	36	Acclimatised mountaineer exercising at 19,000 ft (5800 m); hypoxic death

P50, The partial pressure of oxygen when haemoglobin is 50% saturated with oxygen.

and capillary – usually a minor issue, and (2) the relationship between perfusion and ventilation at alveolar level (V/Q ratio). Thus any pathophysiological state that causes a diffusion defect and/or V/Q mismatch will result in an increased gradient between P_{AO_2} and Pa_{O_2}, known as the A-a gradient. The A-a gradient also increases with advancing age and right-to-left shunt and is discussed further in Chapter 18.

Step 3: haemoglobin binding Oxygen is poorly soluble in water, having a solubility of 0.003082 g/100 g H_2O. Having diffused across the alveolar capillary membrane, the oxygen binds rapidly to the respiratory pigment haemoglobin. The saturation of haemoglobin with oxygen (Sa_{O_2}): Pa_{O_2} relationship is not linear and forms a sigmoidal shape (Fig. 28.1). The P50 is the Pa_{O_2} at which 50% of the haemoglobin is saturated. Various factors are known to alter the affinity of haemoglobin for oxygen (Table 28.2). These have teleological advantages because, for example, a low pH or high CO_2 at tissue level could imply tissue hypoxia, and the reduction in oxygen-binding affinity increases oxygen availability. Similarly, hyperthermia (fever), hypercarbia and an increase in the concentration of 2,3-diphosphoglycerate (2,3 DPG) all move the curve to the right and increase oxygen availability.

Table 28.2 Factors influencing the position of the oxygen dissociation curve

FACTORS INCREASING P50 (CURVE SHIFTS TO THE RIGHT)	FACTORS DECREASING P50 (CURVE SHIFTS TO THE LEFT)
Hyperthermia	Hypothermia
Decreased pH (acidaemia)	Increased pH (alkalaemia)
Increased P_{CO_2} (Bohr effect)	Decreased P_{CO_2}
Increased 2,3 DPG	Decreased 2,3 DPG Foetal haemoglobin Carbon monoxide Methaemoglobin

DPG, Diphosphoglycerate; *P50*, the partial pressure of oxygen when haemoglobin is 50% saturated with oxygen.

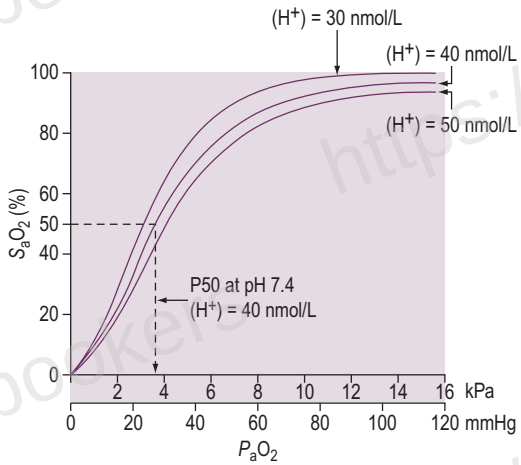


Figure 28.1 Haemoglobin oxygen dissociation curve. Normal curve at 40 nmol/L and shifts to left and right. H^+, Hydrogen ion concentration; *P50*, the partial pressure of oxygen when haemoglobin is 50% saturated with oxygen; PaO_2, arterial partial pressure of oxygen; SaO_2, arterial oxygen saturation.

2,3-DPG is a by-product of glycolysis and therefore binds haemoglobin in predominantly hypoxic tissues, facilitating a release of oxygen. Conversely, hypocarbia, alkalosis and low concentrations of 2,3-DPG result in a leftward shift of the curve and a higher affinity for binding for any given P_{O_2}. Systemic interventions such as alteration in P_{CO_2} or pH will influence the curve and therefore oxygen dissociation and availability. Exposure to carbon monoxide causes a conformational change in haemoglobin causing an increased affinity for oxygen and a left shift of the oxygen dissociation curve.

Step 4: convection – cardiovascular In humans the cardiovascular system is the solitary delivery system of oxygen to the cells. This is achieved by the convection (bulk flow) of oxygen, predominantly bound to

haemoglobin from the lungs via the heart and out into the systemic circulation by way of the arteries. These branch down to form the capillaries, where the oxygen is offloaded to the tissues. Convection of oxygen by the cardiovascular system is influenced centrally by the CO and peripherally by local control of the regional perfusion of the tissues.

Oxygen delivery also relies on its concentration in the blood (Ca_{O_2}). This is calculated by the following formula 28.3 and is approximately 20 mL O_2/dL in health[3]:

(28.3)
$$Ca_{O_2} = (\text{Hb(g/dL)} \times 1.39 \times Sa_{O_2}(\%)) + (0.003 \times Pa_{O_2})$$

Each gram of haemoglobin binds 1.39 mL of oxygen. Thus changes in Sa_{O_2} and haemoglobin concentration are important in determining the oxygen concentration. Delivery of oxygen is therefore summarised by the formula:

(28.4)
$$\text{delivery of oxygen } (\dot{D}_{O_2})\ \text{mL/min} = 10 \times \text{CO(L/min)} \times Ca_{O_2}$$

Normal resting $\dot{D}_{O_2}$ is approximately 1000 mL/min. Oxygen consumption ($\dot{V}_{O_2}$) at rest is approximately 250 mL/min:

(28.5)
$$\text{oxygen consumption } (\dot{V}_{O_2})\ \text{mL/min} = 10 \times \text{CO(L/min)} \times (Ca_{O_2} - C\bar{v}_{O_2})$$

where $C\bar{v}_{O_2}$ is calculated as $(1.39 \times [\text{Hb}] \times S\bar{v}_{O_2}) + (0.003 \times P\bar{v}_{O_2})$. It can be seen that the amount of oxygen extracted is approximately 25% of that delivered at rest and that there is a large reserve. This obviously varies between organs. This ratio is referred to as the oxygen extraction ratio (OER): $\text{OER} = \dot{V}_{O_2}/\dot{D}_{O_2}$.

During exercise this can increase by up to 70%–80% at maximum. Oxygen that is not removed by the tissues returns to the heart and lungs. Globally the difference between that delivered and that returning is the consumption. This model can also be used to look at regional consumption. Hence the saturation of mixed venous blood ($S\bar{v}_{O_2}$) which is all the returning blood, or central venous blood (most of the returning blood), can be used as an indicator of global $\dot{V}_{O_2}$ and indirectly the adequacy of $\dot{D}_{O_2}$. If oxygen delivery by the microcirculation and cellular oxygen uptake are adequate, then a $S\bar{v}_{O_2}$ value of 65% usually indicates that global $\dot{D}_{O_2}$ is appropriate. Lower values may indicate increased uptake but more often reduced or inadequate delivery. Mixed venous blood is useful for measurement of global $\dot{D}_{O_2}$, but it usually requires the presence of a pulmonary artery catheter. The use of central venous saturations has become an alternative surrogate that is usually adequate and considerably more practical. The body cannot store large amounts of oxygen (although the lungs and myoglobin can act as short-term reservoirs) so is dependent on a continuous supply. The excess ability to increase $\dot{D}_{O_2}$ to match changes in $\dot{V}_{O_2}$ is an adaptation that permits sudden changes in demand, such as exercise where $\dot{V}_{O_2}$ can sometimes exceed 1500 mL/min.

Step 5: diffusion – blood to mitochondrion Ninety per cent of cellular aerobic metabolism takes place in the mitochondria. The rate of diffusion of oxygen from bound oxyhaemoglobin to the mitochondria follows similar principles to the diffusion of oxygen into the blood from the alveoli: (1) Fick's law of diffusion, where ΔP depends on $\dot{D}_{O_2}$ and the rate of cellular uptake and utilisation; and (2) the position of the oxygen haemoglobin dissociation curve. Once delivered to the cell, oxygen generates ATP by the electron transport chain, using the reducing power of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) generated from the citric acid cycle.[4] The movement of electrons through the chain requires a terminal electron acceptor. This is molecular oxygen, which combines with the electrons and protons to form water. Without oxygen, the proton motive force generated by the electron chain would not exist and phosphorylation of adenosine diphosphate (ADP) to ATP would cease (Fig. 28.2).[4]

Starting at approximately 160 mm Hg (21.3 kPa), the partial pressure of oxygen (P_{O_2}) at the mouth can fall to as low as 1 mm Hg (0.133 kPa) (Pasteur point) in some mitochondria. Below this value, cellular demands for oxygen outweigh its delivery, and ATP production may be reduced.

Step 6: the redox state of the cell Oxygen delivery from atmosphere to cell is conventionally considered a cascade, implying that a high concentration at one end cascades down and increases oxygen in the cell. Although this will increase oxygen potentially available to the cell, the driving force for it to enter the cell and mitochondrion is the gradient between the partial pressures of oxygen within and outside the cell. Increased oxygen utilization reduces that tension and increases that gradient; conversely, adequate oxygen in the cell will reduce the gradient until oxygen will not diffuse. Hence the cell itself determines how much oxygen it uses by creating the gradient that 'sucks in' oxygen – and not a cascade. Similarly, it is the ATP/ADP ratio and probably hydrogen ion concentration that drives ATP production and modifies oxygen requirement (i.e. the cell is largely autonomous and uses what it needs).[5] Although adequate oxygen delivery is important, excess oxygen is at least theoretically of no benefit.

PATHOLOGY OF OXYGEN DELIVERY ($\dot{D}_{O_2}$)

Failure of oxygen delivery to the cells leads rapidly to cellular dysfunction and can lead to cellular death and organ dysfunction culminating in the organism's death. $\dot{V}_{O_2}$ drives the $\dot{D}_{O_2}$ requirement, and failure of $\dot{D}_{O_2}$ to match $\dot{V}_{O_2}$ results in reduction in aerobic metabolism and energy production, necessitating ATP production

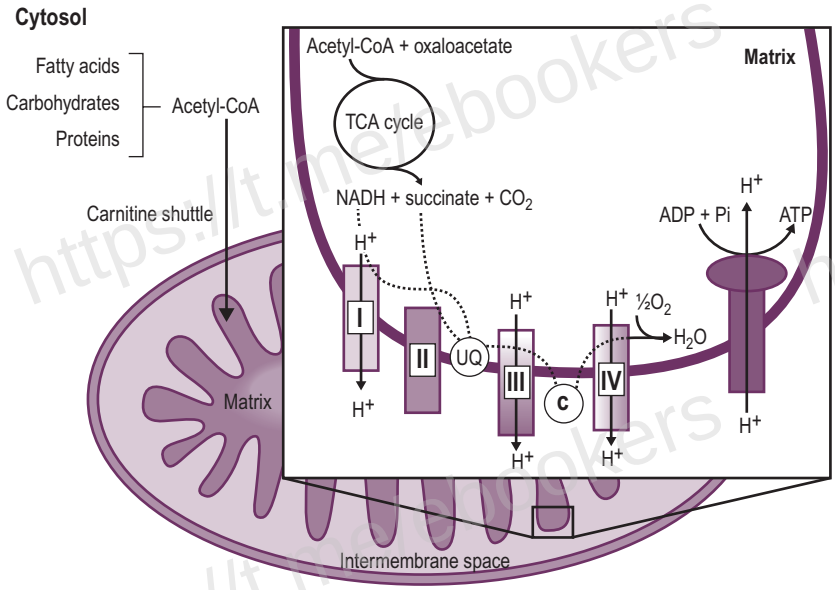


Figure 28.2 Schematic representation of the mitochondrion. Detail of the electron transport chain within the inner mitochondrial membrane is shown. *ADP*, Adenosine diphosphate; *ATP*, adenosine triphosphate; *C*, cytochrome C; CO_2, carbon dioxide; *NADH*, nicotinamide adenine dinucleotide; *Pi*, inorganic phosphate; *TCA*, tricarboxylic acid; *UQ*, ubiquinone. *van Boxel G, Doherty WL, Parmar M. Cellular oxygen utilization in health and sepsis.* CEACCP. *2012;12(4):207–212.*

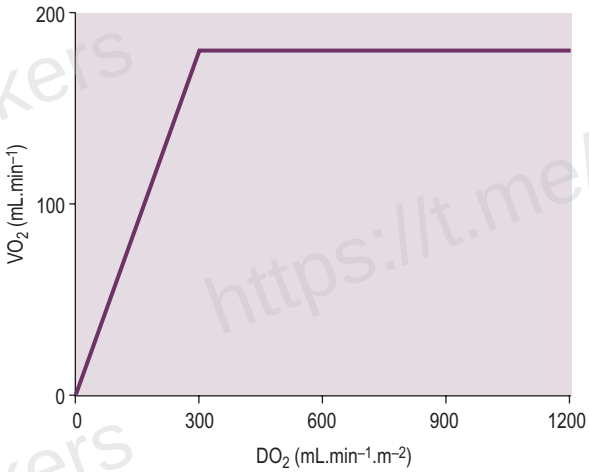


Figure 28.3 The normal relationship between $\dot{V}_{O_2}$ and $\dot{D}_{O_2}$. Greater than the value of 'critical $\dot{D}_{O_2}$' $\dot{V}_{O_2}$ is independent of oxygen delivery. Less than this value and $\dot{V}_{O_2}$ becomes supply dependent and may be amenable to therapeutic interventions.

by the less-efficient glycolytic pathway. The level of $\dot{D}_{O_2}$ at which $\dot{V}_{O_2}$ begins to decline has been termed the 'critical $\dot{D}_{O_2}$' and is approximately 300 mL/min in an adult (Fig. 28.3).[6] 'Shock' is the usual term used in this situation, defined loosely as failure of oxygen delivery to match tissue demand. Commonly this refers to failure of the circulation, but low $\dot{D}_{O_2}$ can result from several pathological mechanisms that can occur singly or in combination (Table 28.3).

The impact of a low $\dot{D}_{O_2}$ can be worsened by increased oxygen demand. The metabolic rate increases with exercise, inflammation, sepsis, pyrexia, thyrotoxicosis, shivering, seizures, agitation, anxiety and pain.[7] Therapeutic interventions such as adrenergic drugs (e.g. epinephrine)[8] and certain feeding strategies can also lead to an increased $\dot{V}_{O_2}$. In critical illness, in which oxygen delivery is considered to be in jeopardy, there has been considerable interest in the relationship between $\dot{D}_{O_2}$ and $\dot{V}_{O_2}$ (see Fig. 28.3). The presence of signs or markers of tissue hypoxia such as acidosis implies inadequate tissue oxygenation. This could be from either inadequate delivery failing to meet consumption requirements or reduced ability of the tissues to extract oxygen. The former could be corrected by increasing delivery; the latter is more difficult. Historically this has led to the strategy for delivering 'supranormal' $\dot{D}_{O_2}$ to ensure adequate supply.[9,10] It is irrefutable that if delivery is inadequate it should be corrected to meet consumption; however, increasing delivery can increase consumption through mathematical linkage.[11,12] Furthermore, the inotropes used to increase delivery also increase consumption. As discussed later, hyperoxia also has directly detrimental effects.

Clinical studies clearly show that adequate resuscitation to meet oxygen requirements is sensible. In the critically ill going beyond this is not helpful.[13,14] Early reports in sepsis suggested the combined use of tissue hypoxia markers (acidosis and lactate) and surrogates of oxygen delivery (Scv_{O_2}) were beneficial when used in conjunction with standard haemodynamic

Table 28.3 Types of hypoxia

TYPE OF HYPOXIA	PATHOPHYSIOLOGY	EXAMPLES
Hypoxic hypoxia	Reduced supply of oxygen to the body leading to a low arterial oxygen tension	1. Low environmental oxygen (e.g. altitude) 2. Ventilatory failure (respiratory arrest, drug overdose, neuromuscular disease) 3. Pulmonary shunt: (a) anatomical – VSD with R–L flow (b) physiological – pneumonia, pneumothorax, pulmonary oedema, asthma
Anaemic hypoxia	The arterial oxygen tension is normal, but the circulating haemoglobin is reduced or functionally impaired	Massive haemorrhage, severe anaemia, carbon monoxide poisoning, methaemaglobinaemia
Stagnant hypoxia	Failure of transport of sufficient oxygen due to inadequate circulation	Left ventricular failure, pulmonary embolism, hypovolaemia, hypothermia
Histotoxic hypoxia	Impairment of cellular metabolism of oxygen despite adequate delivery	Cyanide poisoning, arsenic poisoning, alcohol intoxication

monitoring.[15] Although this saw the widespread adoption of 'early goal-directed therapy' in sepsis,[16] current evidence now suggests it is not superior to usual care in patients with septic shock.[17]

Oxygen delivery can be improved in a variety of ways from the ambient inspired oxygen through the lungs and cardiovascular system to the cell itself, but once at the cell, the ability to manipulate delivery ceases.

CELLULAR HYPOXIA

In environments where the $\dot{D}_{O_2}$ is reduced, human cells can tolerate hypoxia to a certain extent by adapting 'hibernation' strategies to reduce metabolic rate, increased oxygen extraction from surrounding tissues and enzyme adaptations that allow continuing metabolism at low P_{O_2}.[18] Anaerobic metabolism is actively used by some tissues. In low oxygen concentrations, both myocardial and vascular endothelium upregulate glycolytic enzymes and glucose transport proteins.[19] Experiments in humans at altitude, to mimic hypoxic stress, suggest that, although $\dot{D}_{O_2}$ is preserved, $\dot{V}_{O_2}$ is reduced.[20] This may be due to reduced oxygen uptake at a microcirculatory level, reduced cellular oxygen consumption or an improvement in the efficiency of ATP production. These theories may be evidenced by the recovery of critical illness multiorgan failure, in which function may be compromised in the short term without long-term structural damage,[21] and in vitro studies of mitochondria, which demonstrate more efficient ATP production when exposed to hypoxic environments.[22] The ability of humans to tolerate and then acclimatise to altitude mainly by a reduction in $\dot{V}_{O_2}$ may explain why many critical care strategies to increase Pa_{O_2} (e.g. inhaled nitric oxide) fail to convey any survival benefit. Indeed, accepting a Pa_{O_2}/Sa_{O_2} less than 'normal' levels does not appear to significantly reduce survival and may reduce the risk of oxygen toxicity.[22]

REGIONAL HYPOXIA

Much of what has been discussed describes effects of oxygen delivery and uptake for the body as a whole. The reality is far more complex because not only can the $\dot{D}_{O_2}$ of each organ system be manipulated to meet demand, but also, within each organ, regional demands may vary and can be varied. Few of the clinical methods commonly used for assessing $\dot{D}_{O_2}$ can identify changes in either organ or regional $\dot{D}_{O_2}$. Thus it is possible in critical illness for tissue hypoxia to exist with associated organ dysfunction despite normal global $\dot{D}_{O_2}$ and $S\bar{v}_{O_2}$ values.[23]

The effects of disordered or diverted regional blood flow can be important. For example, splanchnic blood flow is often reduced in shock, with the potential for ischaemia. Clearly, detection of gut ischaemia could be used to influence management of oxygen delivery and hopefully reduce the likelihood of multiorgan failure.[24] The control of regional blood flow is itself complex. Methods of increasing global $\dot{D}_{O_2}$ in the hope that this will optimise all tissues often necessitate the use of vasoactive drugs (vasopressors, inotropes and vasodilators). Paradoxically, although such therapy can influence regional flow, it may not necessarily be in the direction sought in individual regions.

DIAGNOSIS AND MONITORING OF $\dot{D}_{O_2}$

Early recognition and treatment of oxygen delivery failure is important for preserving organ function. Clinical assessment of $\dot{D}_{O_2}$ and $\dot{V}_{O_2}$ (e.g. heart rate, blood pressure or urine output) can be misleading. Particularly in the young patient, the ability of the OER to increase to as high as 70%–80% can mean that

such variables can change only late in the evolution of diminished $\dot{D}_{O_2}$. However, the assessment of an effective cardiac output – normal heart rate, blood pressure and peripheral perfusion with signs of organ function and normal oxygen saturation – must not be excluded in favour of more technical quantitative methods. Rather, the technical values must be considered in the clinical context. All assessments of $\dot{D}_{O_2}$, clinical or technical, require continuous reevaluation to ensure that treatments being planned or administered are appropriate for the patient's current condition.

Sa_{O_2} AND Pa_{O_2}

Both these measures are included in the Ca_{O_2} (Eq. 28.3), and their importance is clear. However, what is a 'safe' Sa_{O_2} and/or Pa_{O_2} can be difficult to define. Measured systemically, they do not alone reflect tissue oxygenation, and oxygen extraction mechanisms vary between organs. However, supplementary oxygen is generally required when Pa_{O_2} falls to less than 60 mm Hg (8 kPa) or the Sa_{O_2} is less than 88%. Table 28.1 lists the clinical significance of common Pa_{O_2} and Sa_{O_2} values.

ACID–BASE BALANCE

Many intensive care units (ICUs) use acid–base balance as a simple bedside indicator of global $\dot{D}_{O_2}$. The presence of acidosis and a base deficit of less than –2 may be used to detect evidence of inadequate $\dot{D}_{O_2}$, presuming this reflects lactate accumulation. However, plasma lactate concentration is an unreliable indicator of tissue hypoxia; it represents the balance between production and consumption so, if used in isolation or as a single value to assess $\dot{D}_{O_2}$, can easily mislead.[25] The use of lactate as a marker of $\dot{D}_{O_2}/\dot{V}_{O_2}$ balance is best used as a trend using serial measurements.

$S\bar{v}_{O_2}/Scv_{O_2}$

In critical illness, a falling $\dot{D}_{O_2}$ can be compensated for by an increase in oxygen extraction. This leads to a lower oxygen saturation of haemoglobin returning to the right side of the heart. Analysis of this saturation either in vivo (fibreoptic oximetry) or in vitro (oximetry) allows assessment of the OER. Classically, a low $S\bar{v}_{O_2}$ (<70%) in the face of a normal Sa_{O_2} implies tissue hypoperfusion secondary to a low CO, either hypovolaemia or pump failure. However, it could indicate very high $\dot{V}_{O_2}$, as may occur with hyperthermia. Conversely, a raised $S\bar{v}_{O_2}$ (>75%) will imply low demand (e.g. hypothermia, or a cellular use problem), easily explained in cyanide poisoning when the oxidative phosphorylation mechanism is inhibited but much more difficult to rationalise when seen (commonly) in sepsis. In a very low output state, it could indicate total failure of peripheral perfusion and therefore no oxygen usage. Scv_{O_2} is a reasonable surrogate for $S\bar{v}_{O_2}$ and reduces the need for the more complex pulmonary artery catheter.[26] Whichever method of venous oxygen saturation is used, it must be in conjunction with other markers of adequacy of oxygen delivery and clinical context.

MEASUREMENT OF REGIONAL $\dot{D}_{O_2}$

Most assessments of $\dot{D}_{O_2}$ are global and do not reflect regional differences between organs or even different tissues within an organ. Current methods of non-invasively assessing individual organ or tissue oxygenation are limited; measurements are difficult, require specialised techniques and are not widely available. Currently, only gastric tonometry and near-infrared spectroscopy have clinical applications in the detection of organ hypoxia.[24] Novel techniques such as palladium porphyrin phosphorescence–based techniques are being evaluated in animals but require improvement as palladium is itself cytotoxic.[27] Cellular oxygenation measurement methods are also in development.[28]

OXYGEN THERAPY APPARATUS AND DEVICES

In the hypoxic self-ventilating patient, delivery of oxygen to the alveoli is usually achieved by increasing the Fi_{O_2}. Most commonly this involves the application of one of the many varieties of oxygen mask to the face, such that it covers the nose and mouth. There are other methods (e.g. nasal cannulae), but each needs to fulfil the same basic requirements.

Most of the simpler devices (e.g. plastic masks, nasal cannulae) deliver oxygen at relatively low oxygen flow rates relative to peak inspiratory flows (25–100+ L/min). The final Fi_{O_2} delivered is heavily influenced by the entrainment of environmental air, which dilutes the set Fi_{O_2}. From a physical principle perspective, the actual concentration of oxygen delivered is determined by the interaction between the delivery system and the patient's breathing pattern. The Fi_{O_2} that reaches the alveolus is therefore unpredictable. Factors that influence this can broadly be divided up into patient factors and device factors (Box 28.1).[29,30]

Box 28.1 Factors that influence the Fi_{O_2} delivered to a patient by oxygen delivery devices

Patient factors	Device factors
Inspiratory flow rate	Oxygen flow rate
Presence of a respiratory pause	Volume of mask
Tidal volume	Air vent size
	Tightness of fit

Leigh J. Variation in performance of oxygen therapy devices. *Anaesthesia*. 1970;25(2):210–222.

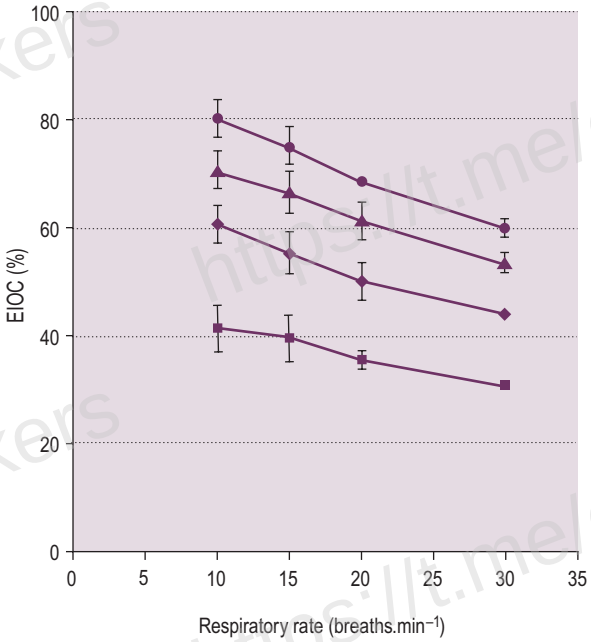


Figure 28.4 The performance of a Hudson mask on a model of human ventilation at a tidal volume of 500 mL and four oxygen flow rates (2 L/min [□], 6 L/min [◇], 10 L/min [△] and 15 L/min [○]). As the respiratory rate increases, the effective inspired oxygen concentration (EIOC) deteriorates. *From Wagstaff TAJ, Soni N. Performance of six types of oxygen delivery devices at varying respiratory rates.* Anaesthesia. *2007;62(5): 492–503.*

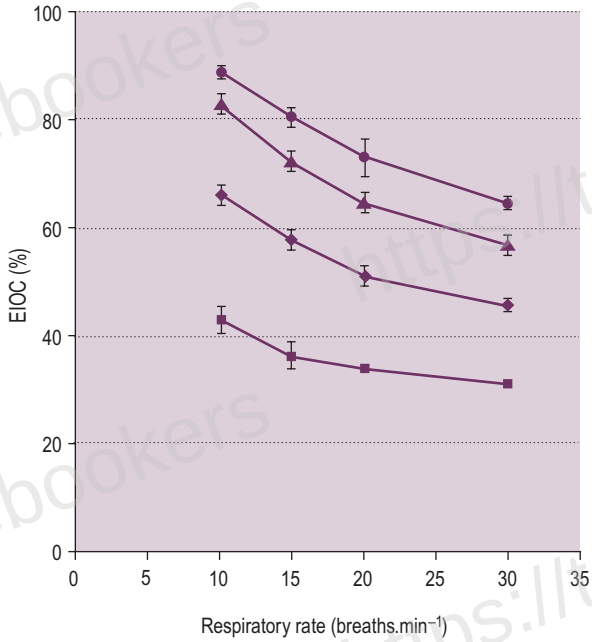


Figure 28.5 The performance of a Hudson non-rebreather mask on a model of human ventilation at a tidal volume of 500 mL and four oxygen flow rates (2 L/min [□], 6 L/min [◇], 10 L/min [△] and 15 L/min [○]). As the respiratory rate increases, the effective inspired oxygen concentration (EIOC) deteriorates. Note also how the curves of the graph are similar to the Hudson mask without the reservoir bag, implying no superiority with its addition. *From Wagstaff TAJ, Soni N. Performance of six types of oxygen delivery devices at varying respiratory rates.* Anaesthesia. *2007;62(5):492–503.*

In the hypoxic patient, it is common to find significant increases of inspiratory flow rates, as well as an absence of the respiratory pause. This can result in the actual Fi_{O_2} at the alveolus being significantly less than that thought to be delivered. This is due to a greater proportion of the inhaled gas being entrained air when the patient's inspiratory flow rate increases. The normal peak inspiratory flow rate (PIFR) is 25–35 L/min; in critical illness this can increase eightfold, greater than 200 L/min.[31] The greater the inspiratory flow rate, the lower is the alveolar Fi_{O_2}. This is particularly true for the variable performance-type masks but is seen even in the more 'reliable' Venturi-type masks, particularly when higher Fi_{O_2} inserts are used. The presence of a valve-controlled reservoir bag on a 'non-rebreather' semi-rigid plastic mask should compensate for high inspiratory flows – hence the belief that such masks can deliver 100% oxygen. However, this is not the case, and in models of human ventilation, such masks do not seem to confer significant extra oxygen delivery ability greater than that of semi-rigid plastic masks without a reservoir bag (Figs 28.4 and 28.5).[32] The failure of oxygen masks to deliver the desired Fi_{O_2} can be improved either by having a high enough oxygen flow rate and reservoir to compensate for the high inspiratory flow rate (e.g. high-flow nasal cannulae [HFNC] such as the Vapotherm) or by sealing the upper airway (nose and mouth) from the environment (e.g. the continuous positive airway pressure [CPAP] mask). Indeed, there is evidence supporting the hypothesis that some of the improvement in oxygenation seen with CPAP ventilation may be due to the eradication of entrainment of environmental air rather than the positive airway pressure exerted by the CPAP valve.[32]

In summary, the use of non-sealing oxygen masks and cannulae should be guided by the patient's requirements and response to therapy, rather than a belief that the concentration being delivered is that reaching the alveolus. This can be particularly important in the treatment of patients whose ventilatory drive is sensitive to P_{O_2} levels.

OXYGEN DELIVERY DEVICES

Methods of delivering oxygen to conscious patients with no instrumentation to their airway can broadly be divided into four categories: (1) variable performance

systems, (2) fixed performance systems, (3) high-flow systems, and (4) others. With the exception of the intravascular devices, all comprise similar component parts:

1. *Oxygen supply:* oxygen can be delivered from pressurised cylinders, hospital supply from cylinder banks or a vacuum-insulated evaporator, or an oxygen concentrator.
2. *Oxygen flow control:* oxygen supplied to the device is controlled by some sort of valve, often with an associated flow meter.
3. *Connecting tubing:* both from the supply to the flow control and from the flow control to the device, the type and size of the tubing are important. Small-bore tubing can limit oxygen flow when high flow is intended. In some systems the connecting tubing can also act as a reservoir (e.g. Ayre's T-piece). Some devices require specialised tubing with appropriate end attachments, such as the Schräeder valves required for connecting to the wall oxygen supply.
4. *Reservoir:* all oxygen delivery devices have some sort of reservoir. In a simple oxygen mask, it is the mask itself. Some low-flow CPAP circuits have a balloon reservoir. Nasal cannulae use the nasopharynx as a reservoir. An oxygen tent uses the volume of the tent as a large reservoir. The effectiveness of the reservoir in 'storing' oxygen ready for the next inspiratory effort is one of the important factors in governing its ability to deliver the desired oxygen concentration. The oxygen tent is a good example of the effectiveness of a large reservoir because it eliminates air entrainment, whatever the patient's PIFR. Thus the oxygen flow rate does not have to be high, but just enough to ensure that CO_2 re-breathing is abolished. Indeed, it is the retention of CO_2 that can be the major problem if gas is expired into the reservoir.
5. *Patient attachment:* the patient is connected to the oxygen supply and reservoir such that the device delivers oxygen to the airway – either by directly covering the upper airway (e.g. plastic mask/head box), intranasally or by increasing the oxygen concentration in the wider environment as in an oxygen tent.
6. *Expired gas facility:* expired gas from the patient needs to be allowed to dissipate into the environment and not be retained in the system to be inspired at the next inspiratory effort. Most masks achieve this by having a small reservoir capacity and holes in the plastic to allow the gas to exit. One-way valves, as in the non-rebreather type reservoir mask, aid in unidirectional flow of gas away from the patient. High-flow T-piece systems like those used in a CPAP system use the high flow to remove the gas down an expiratory limb and into the environment.
7. *Humidification:* most systems use the physiological humidification properties of the nasopharynx and trachea. However, high-flow systems may overcome this, leading to drying of the airway and secretions, which can be uncomfortable and undesirable. Artificial humidification (and warming) should be employed, using devices such as a water bath or heat and moisture exchanger (HME).
8. *Oxygen monitor:* some systems have an oxygen monitor incorporated in the apparatus (e.g. a fuel cell). This allows the much more accurate monitoring of Fi_{O_2}, but this is dependent on where in the system it is placed and also adds bulk and expense to the oxygen delivery method.

VARIABLE PERFORMANCE SYSTEMS

Typically these are non-sealed mask or nasal cannulae systems, which deliver oxygen at low gas flows (2–15 L/min). The reservoir is usually small, consisting of the volume of the mask in the case of the semi-rigid type, or the nasopharynx as in the nasal cannulae. The entrainment of environmental air is important in their delivery capability and has to be considered when being used.

Nasal cannulae The proximity of the reservoir – the nasopharynx – means that these systems are particularly sensitive to changes in inspiratory flow rate and particularly the loss of the respiratory pause. However, for mild hypoxia, they are tolerated well by patients who can eat and drink with them in situ. They can cause drying of the nasal mucosa when used at higher flow rates, and newer systems are available that can humidify and warm the inspired oxygen. They are cheap and easy to use, with no risk of CO_2 retention.

Simple semi-rigid plastic masks (e.g. Hudson) The most commonly used type of oxygen mask, these are cheap and easy to administer. The reservoir comprises the mask, and rebreathing of CO_2 can therefore occur if used at oxygen flow rates less than 4 L/min. A maximum Fi_{O_2} of only 0.6–0.7 can be achieved, which will be lower in the presence of respiratory distress.

Tracheostomy masks These semi-rigid plastic masks act in the same way as their facial counterparts. However, the delivery they achieve is very dependent on the presence of an endotracheal tube and the inflation status of its cuff. If absent, or if the cuff is deflated, then air from the nasopharynx will mix with that being delivered to the tracheostomy and further dilute the Fi_{O_2}.

T-piece system These simple systems, consisting of an inspiratory limb and expiratory limb forming the bar of the 'T', can be used with endotracheal tubes (oral, nasal or tracheostomy) or with a sealed CPAP-type mask. The oxygen flow rate needs to be high enough to match the patient's PIFR so as to prevent rebreathing of expired gas and thus potential entrainment of air from the expiratory limb. The seal of the mask or tube cuff is important also to prevent entrainment of air.

FIXED PERFORMANCE SYSTEMS

These systems are so called because their delivery of oxygen is independent of the patient factors outlined previously.

Venturi-type masks Oxygen concentration is determined by the Venturi principle: oxygen passing through a small orifice entrains air to a predictable dilution. The Fi_{O_2} is adjusted by changing the Venturi 'valve' and setting the appropriate oxygen flow rate. Although the Venturi effect can deliver 40–60 L/min, this is possible only at the lower Fi_{O_2} valves (e.g. at Fi_{O_2} of 0.24 the flow rate is approximately 53 L/min at an inflow of 2 L/min), and oxygen flow rate falls as the Fi_{O_2} increases. Thus, in respiratory distress associated with hypoxia, the reduction in oxygen flow rate can lead to failure despite a higher Fi_{O_2} setting. The larger orifice leads to the system behaving more like a simple mask.

Anaesthetic breathing circuits Non-rebreathing systems (e.g. Mapleson A, B, C, D and E) depend on the gas flows to ensure no re-breathing. No air entrainment is possible, but re-breathing occurs readily at low flows (most require flows >150 mL/kg). Delivery of oxygen to the patient with a Mapleson circuit via face mask takes considerable skill and training. Bag inflation is reliant on continuous fresh gas flow and a tight mask seal, without which the bag will not maintain adequate inflation (or will empty completely) rendering ventilation ineffective (or impossible). However, use of the Mapleson circuit is a skill worth acquiring because there is no inspiratory valve to overcome (unlike the bag valve mask [BVM] discussed later), minimising the inspiratory effort required during spontaneous breathing.

Self-inflating bag valve mask Despite the BVM being easier to use than Mapleson circuits by the non-expert, it has disadvantages. By design, self-inflating BVMs are not reliant on fresh gas flow or mask seal to deliver a hand-ventilated inspiratory volume. Therefore vigilance is required to establish a tight mask seal and to ensure the oxygen source is connected, turned on and filling the reservoir bag. In addition, a self-ventilating patient in respiratory failure may not be able to open the one-way valve to achieve effective ventilation; hence inspiratory effort often needs to be assisted by hand, which can be challenging, especially when two hands are required for a mask seal. There is also no direct feedback from the self-inflating bag itself to alert the operator to a loss of mask seal or inform them of ventilation adequacy. A blow-off valve, usually set at 60 cm H_2O, is the only means of detecting high airway pressure.

HIGH-FLOW SYSTEMS

High-flow oxygen therapy, originally developed in the neonatal and paediatric settings, is a relatively recent innovation in the critically ill adult patient.[33] It delivers warm humidified high-flow oxygen at flow rates between 15 and 60 L/min through a small nasal or face mask interface. Humidification of this high gas flow rate contributes to a remarkably high degree of tolerance, and, rather than cyclically increasing the upper airway inspired oxygen concentration which is then diluted by entrained air (standard oxygen therapy), it offers (1) a gas flow rate closer to the subjects inspiratory flow rate, (2) flow-dependent continuous positive airway pressure (CPAP) with increased end-expiratory lung volume, and (3) washout of upper airway CO_2 leading to decreased physiological dead space, with both latter mechanisms possibly contributing to reduce the work of breathing.[34–36] A number of investigators have shown that HFNC is comfortable and effective at improving oxygenation.[37] The current evidence suggests that in patients with hypoxaemic respiratory failure, high-flow oxygen therapy prevents reintubation after extubation when compared with standard oxygen therapy.[38] However, a high proportion of patients with de novo acute hypoxaemic respiratory failure require intubation when initially managed with high-flow oxygen therapy[39]; and when intubation is delayed in these patients, it is associated with increased ICU mortality.[40] This reinforces the need for an appropriate high-acuity clinical environment and appropriately trained team to manage patients with acute hypoxaemic respiratory failure with high-flow oxygen therapy.

Positive-pressure devices Non-invasive ventilation (NIV) delivers oxygen with some element of positive pressure exerted during the respiratory cycle. It does not require instrumentation of the airway and is delivered either by a tight-fitting mask to the face or nose or as a helmet. The simplest CPAP system is a T-piece with a positive-pressure valve attached to the expiratory limb, as with a Mapleson E system. Other methods are also available; some use a balloon reservoir rather than a high-flow oxygen generator (Mapleson A). CPAP helps to improve functional residual capacity (FRC) and compliance.[41] There is no air entrainment, which contributes to the initial rapid improvement. Theoretically the positive pressure aids alveolar recruitment. A potential problem with the T-piece CPAP systems is that the oxygen flow rate has to be adjusted to the patient's PIFR so as to prevent closure of the valve, increasing the inspiratory work of breathing. Other methods of NIV such as bilevel positive airway pressure (BPAP) deliver oxygen at flows that should match the patient's demand.

OTHER METHODS OF OXYGEN DELIVERY

Intravascular oxygenation has been used but not extensively – particularly in the self-ventilating patient population. Extracorporeal membrane oxygenation (ECMO) supporting the lung has recently grown in use, secondary to a landmark study and recent influenza pandemics.[42,43]

MANAGEMENT OF OXYGEN THERAPY

In the correct situations, oxygen is a life-saving drug/therapy. It remains part of the initial resuscitation and ongoing management of the critically unwell. In the United Kingdom at any one time, 15%–17% of all hospital inpatients will be receiving oxygen.[44] However, oxygen can have detrimental effects in certain patient groups and/or situations, and this may result in significant morbidity or mortality.

RESPIRATORY FAILURE

Identifying patients that require oxygen therapy is vital. Supplemental oxygen is required to treat most causes of hypoxia, yet different patient groups may have different resting oxygen concentrations. For example, patients with cyanotic heart disease or chronic neuromuscular disorders may have a Sa_{O_2} of 80%, yet have adapted to tolerate these oxygen tensions. The normal values of Pa_{O_2} and Sa_{O_2} in healthy volunteers are summarised in Table 28.4.[45] In many cases of critical illness, low oxygen tensions are due to hypoxic hypoxia. This may be as a result of reduced environmental oxygen such as that seen at altitude, pulmonary oedema or pneumonia resulting in ventilation–perfusion mismatch and intrapulmonary shunt. This is so-called type I respiratory failure where ventilation is intact, but gas transfer or haemoglobin saturation is impaired. It is defined as a $Pa_{O_2} < 8$ kPa (60 mm Hg) with a normal or low $PaCO_2$.[45] Broadly speaking, hypoxia in any of these situations will be improved by increasing inhaled oxygen concentrations. However, caution must be taken when dealing with ventilatory or type II respiratory failure. The differentiation of the two types of respiratory failure is made using the $PaCO_2$. The normal value is 4.6–6.1 kPa (34–46 mm Hg) and hypoxic patients with $PaCO_2$ concentrations above this range should be considered as being in type II respiratory failure. Many causes of ventilatory failure are not affected by the oxygen tension in the blood (e.g. Guillain–Barré, opioid overdose). However, with commoner causes, such as acute exacerbations of chronic obstructive pulmonary disease and acute severe asthma, the patient's ventilation can be sensitive to oxygen therapy.

TARGETED OXYGEN THERAPY

The need for oxygen to prevent tissue hypoxia and cellular dysfunction is clear. However, it is not possible to define a single level of hypoxaemia that is dangerous to all patients. Some patients with chronic lung disease may be accustomed to living with an Sa_{O_2} of 80%, whereas others with acute organ failure may be harmed by short-term exposure to an Sa_{O_2} of less than 90%. So the level of hypoxaemia has to be given context not just in severity but also in time and evidence of negative physiological effect. There is no evidence that saturations above normal result in benefit. Rather, hyperoxia can have adverse effects. As a rule of thumb, maintaining Sa_{O_2} greater than 90% in critically ill patients is considered best practice and permits a margin of error.[46,47] Those patients at risk of hypercarbic type II respiratory failure should be managed with a little more caution and their Sa_{O_2} target should be set between 88% and 92%.

Table 28.4 Mean (SD) Pa_{O_2} and Sa_{O_2} values (with range) in kPa and mm Hg

AGE (years)	MEAN Pa_{O_2} (kPa and mm Hg)	RANGE ± 2 SD Pa_{O_2} (kPa and mm Hg)	MEAN Sa_{O_2} (%)	Sa_{O_2} ± 2 SD
18–24	13.4 (0.71) 99.9 (5.3)	11.98–14.82 89.3–110.5	96.9 (0.4)	96.1–97.7
25–34	13.4 (0.66) 99.8 (4.9)	12.08–14.72 90–109.6	96.7 (0.7)	95.3–98.1
35–44	13.18 (1.02) 98.3 (7.6)	11.14–15.22 83.1–113.5	96.7 (0.6)	95.5–97.9
45–54	13.0 (1.07) 97 (8)	10.86–15.14 81–113	96.5 (1)	94.4–98.5
55–64	12.09 (0.6) 90.2 (4.5)	10.89–13.29 81.2–99.2	95.1 (0.7)	94.5–97.3
>64	11.89 (1.43) 88.7 (10.7)	9.02–14.76 67.3–110.1	95.5 (1.4)	92.7–98.3

Values shown for seated healthy men and women, non-smoking volunteers at sea level.

From Crapo RO, Jensen RL, Hegewald M, et al. Arterial blood gas reference values for sea level and an altitude of 1,400 meters. *Am J Respir Crit Care Med*. 1999;160(5 Pt 1):1525–1531.

MONITORING

All patients demonstrating hypoxia and the need for oxygen therapy should have a full medical history and physical examination. Focus should be placed on pre-existing respiratory or cardiac disease to ensure correct interpretation of the technical data, as well as appropriate oxygen targets being set. Pulse oximetry is extremely valuable as a non-invasive measure of arterial oxygenation. Calibrated on normal subjects, their readings must be treated with caution when less than 80% but are accurate when greater than 88%. They may have decreased accuracy in the critically ill, but the mean difference is within 1.3%.[48] Although pulse oximetry is an excellent tool for assessing Sa_{O_2}, it gives no data regarding pH and/or $PaCO_2$ as a marker of ventilatory function or the haemoglobin concentration. Thus it cannot be used as a monitor of ventilation or an absolute assessment of Ca_{CO_2}. In addition, in scenarios in which hypoxaemia is suspected, an arterial blood gas should be performed and interpreted (Chapters 18 and 94). Arterial blood gas analysis is the gold standard for assessing respiratory failure. Usually assessed from aspirating blood from a systemic artery, ear lobe specimens also have utility in assessing $PaCO_2$ and pH, at less discomfort to the patient. However, they are less accurate and less precise at lower oxygen tensions.[49,50]

PREOXYGENATION AND APNOEIC OXYGENATION

Preoxygenation prior to induction of anaesthesia aims to delay desaturation to provide a safe apnoeic period for endotracheal intubation. In patients with normal lungs and ventilatory drive, preoxygenation with 100% oxygen for 3 minutes of tidal breathing, or eight vital capacity breaths over 60 seconds, maximally denitrogenates the FRC to allow maximal oxygen storage in the lung.[51,52] Many methods of preoxygenation are in common practice. Although the simple method of delivering greater than or equal to 15 L/min O_2 via a tight-fitting semi-rigid face mask with reservoir bag is described, it can achieve only a Fi_{O_2} between 0.6 and 0.7, as described above, which may be inadequate in the critically ill. Methods of preoxygenation with a Fi_{O_2} of 1.0 include: BVM (with or without positive end expiratory pressure [PEEP] valve), HFNC, Mapleson circuit and NIV.[51,53–55] NIV may improve preoxygenation when the other methods are (or are likely to be) ineffective, such as occurs with severe acute and/or chronic hypoxic respiratory failure.[51,53,56] A head up position of 20 degrees or more has been shown to improve the efficacy of preoxygenation, by maximising FRC (and therefore oxygen stores),[51,53,57,58] especially in morbid obesity.[59]

Preoxygenation ends after the patient becomes apnoeic and the oxygen source is removed to allow laryngoscopy and intubation. Continuation of oxygen delivery throughout the apnoeic period (apnoeic oxygenation) has been shown to safely prolong the period of adequate oxygenation, delay the onset of critical desaturation and improve first-pass intubation success.[51,60–62] Apnoeic oxygenation is likely to provide maximal benefit during prolonged or repeated intubation attempts in an adequately preoxygenated patient with a difficult airway (anticipated or unanticipated). Likewise, it may provide a longer safe apnoea period for the inexperienced intubator to either secure the airway or have a more skilled intubator takeover. However, apnoeic oxygenation is unlikely to benefit the maximally preoxygenated patient who is intubated rapidly by an experienced intubator and may unnecessarily complicate the intubation. In ideal conditions, apnoeic oxygenation can achieve a long delay to desaturation by continually replenishing the denitrogenated FRC with oxygen from the nasopharynx reservoir, limited only by the consequential hypercarbia.[63] Ideal conditions (uncommon in the critically ill) include normal lungs, normal pulmonary circulation, normal DO_2 and an open airway (to allow oxygen flow below the vocal cords during apnoea). The most commonly reported technique for apnoeic oxygenation is the delivery of 15 L/min O_2 via nasal cannulae, commenced on induction (or during preoxygenation).[51,60–62] The use of HFNC for both preoxygenation and apnoeic oxygenation may offer some advantages due to the ease of use, patient tolerability, improved maintenance of upper airway patency during apnoea and CO_2 washout delaying hypercarbia.[54,55,64] Despite a rapid uptake of apnoeic oxygenation practice in the emergency department and pre-hospital settings, its role in the ICU setting is yet to be established due to conflicting studies.[64–67] Indeed, the most recent randomised control trial in the emergency department setting was negative, causing further uncertainty as to when, how and in whom to use apnoeic oxygenation.[68] In addition, studies in all settings are limited by a lack of blinding, no control of preoxygenation techniques or patient position, different methods of apnoeic oxygenation (HFNC vs nasal cannulae) and variable experience of the intubator.

Apnoeic oxygenation is also used in clinical brain death testing to demonstrate absence of a brainstem response to severe hypercarbia (see Chapter 53).

HAZARDS OF OXYGEN THERAPY

SUPPLY

Medical oxygen supply is a compressed gas. Pipeline supply to the 'wall' is usually at 4 bars of pressure (3040 mm Hg). The cylinder supply pressure, when full, is 137 bars (104-120 mm Hg). As such, oxygen as explosion is a risk. Direct administration of oxygen at delivery pressures also carries a real risk of barotrauma

to the airway and alveoli, if not governed by an appropriate pressure-limiting valve.

Oxygen also supports combustion. The possibility of sparks in an oxygen-rich environment must be avoided. Patients must not smoke cigarettes when receiving oxygen therapy, even via nasal cannula. Another example is to ensure that oxygen supplies are removed or turned off when defibrillating because a spark can occur in such situations. An ICU fire secondary to an oxygen cylinder explosion has been reported in the literature.[69]

OXYGEN TOXICITY

Despite being a naturally occurring substance, the use of oxygen in a medical environment should be considered pharmacotherapy. As with all drugs, it has side effects in overdose. There has been a great interest in the potential toxic effects of oxygen in recent years. As is evident from the previous management of oxygen therapy, there needs to be a limit to the concentrations of oxygen used. There is no apparent benefit in hyperoxia, except in one or two specific settings. Indeed, in the critical care environment, studies have shown that a high Pa_{O_2} level within the first 24 hours is an independent risk factor for hospital mortality.[70] However, this finding remains contentious, with further studies demonstrating the effect of hypoxia as a predictor of mortality, but no strong effect seen with hyperoxia.[71] Adverse outcomes have also been reported following treatment of postcardiac arrest patients with hyperoxia.[72] These findings also have not been reproduced by further studies, but there is still evidence of a U-shaped mortality curve for Pa_{O_2} in this group of patients.[73] More recently, among critically ill patients with an ICU length of stay of 72 hours or longer, a conservative protocol for oxygen therapy (Pa_{O_2} between 70 and 100 mm Hg or SpO_2 between 94% and 98%) versus conventional therapy (Pa_{O_2} values up to 150 mm Hg or SpO_2 between 97% and 100%) resulted in lower ICU mortality.[74] What is more certain is the effect of resuscitation with 100% oxygen in neonates. This has been shown to lead to an excess mortality, and air is now the recommended gas to be used in the resuscitation of infants.[75]

VASOCONSTRICTION

Oxygen is known to cause constriction of the coronary, cerebral and renal vasculature, which could lead to hypoperfusion of key organ systems – potentially reducing $\dot{D}_{O_2}$ when an increase is desired. This hazard would be played off only against a very moderate increase in Ca_{O_2} assuming all the haemoglobin is saturated. In healthy subjects, hyperoxia reduces cerebral blood flow by 11%–33%.[76,77] This may be associated with a worse outcome following a mild to moderate cerebrovascular accident.[77] Similarly, coronary blood flow is reduced in the presence of hyperoxaemia (8%–29% in healthy subjects).[78] This may promote myocardial ischaemia during acute coronary syndromes, possibly increasing myocardial infarction size.[79] This has led international guidelines for the management of acute coronary syndromes to stipulate that supplementary oxygen should *not* be given to patients with acute chest pain unless there is evidence of hypoxaemia.[80,81] Pulmonary vasculature is a notable exception, whereby alveolar hypoxia induces vasoconstriction of small pulmonary arteries (Euler-Liljestrand mechanism), improving ventilation perfusion matching.[82]

CENTRAL NERVOUS SYSTEM (CNS) TOXICITY (PAUL BERT EFFECT)

Seen in diving, oxygen delivered at high pressure (>3 atmospheres, ≈300 kPa) can lead to acute central nervous system signs and seizures.

LUNG TOXICITY (LORRAINE SMITH EFFECT)

Exposure to a high Fi_{O_2} results in pulmonary injury with a progressive reduction in compliance occurs, and associated interstitial oedema, leading to fibrosis. The mechanism remains unclear but is believed to involve direct cellular damage to the lung tissue by highly reactive oxygen species (ROS). High concentrations of oxygen produce a higher concentration of ROS that overwhelm the normal scavenging mechanism lining the respiratory tract. This is possibly associated with loss of surfactant, increase in sympathetic activity and alveolar collapse due to both the increase in surface tension and the lack of other non-respiratory gases. Evidence for this mechanism is supported by the worsening of lung damage seen in paraquat poisoning. Paraquat produces large amounts of ROS, and the administration of supplemental oxygen worsens its effects. Identifying this as the sole aetiology for pulmonary pathology can be difficult, especially as the usual indications for oxygen therapy usually imply some form of pulmonary pathology. However, the presence of endotoxin has been shown to protect against oxygen-induced lung toxicity.[83,84]

It is reasonable that the risk of oxygen-induced pulmonary toxicity is dependent on concentration and duration of exposure. However, the concentration/duration that 'likely causes toxicity' is not clear. In some subjects, long exposure times and high concentrations do not lead to problems. In general, patients should remain below an Fi_{O_2} of 0.5 where possible, and periods greater than this should be kept to the minimum required.

BRONCHOPULMONARY DYSPLASIA

First described in 1967, this is a form of chronic lung disease associated with neonatal ventilation; its pathophysiology includes the same factors as the adult, but with the additional effect of immaturity.[85] The advent of surfactant in the treatment of respiratory distress of the newborn and the addition of maternal steroid therapy

to promote pulmonary development have lowered the incidence and reduced the severity of the disease.

OTHER PULMONARY EFFECTS

Supplemental oxygen also has other more predictable physiological effects within the lungs that may not been seen as truly toxicological, but cause problems in themselves. The greatest is the effect of oxygen on ventilation, especially in those at risk of type II respiratory failure.

I. *V/Q mismatch:* high concentrations of inspired oxygen will reduce the physiological effects of hypoxic pulmonary vasoconstriction, thus diverting blood through poorly ventilated lung, increasing shunt and reducing Pa_{O_2}. In lungs without chronic disease, this can be compensated for by an increase in ventilation. However, in patients with borderline ventilation, this can lead to increasing $PaCO_2$ and worsening acidaemia.
II. *Ventilatory drive:* hypoxia less than 8 kPa (60 mm Hg) leads to an increase in ventilation. Values greater than this level have little impact on ventilation. It remains contentious whether this mechanism is important when rises in $PaCO_2$ are seen in patients with COPD.[86,87]
III. *Haldane effect:* increasing Fi_{O_2} decreases the CO_2 buffering capacity of haemoglobin, thus potentially leading to an increase in $PaCO_2$ and acidaemia.
IV. *Absorption atelectasis:* in the presence of small-airway obstruction, high alveolar oxygen concentrations result in rapid absorption of gas, causing collapse of the alveoli and reduction in the diffusion surface area. This has been demonstrated even at an Fi_{O_2} of 0.5.[88]
V. *Higher density of oxygen compared with air:* oxygen is more dense than air and thus breathing high concentrations at increased viscosity increases the work of breathing. This effect is probably negligible in patients with normal underlying lungs and neuromuscular function but can be significant in those with chronic disease.

RETINOPATHY OF PREMATURITY

Previously referred to as retrolental fibroplasia, retinopathy of prematurity (ROP) was first described in 1942. It is a vasoproliferative disorder of the eye affecting premature neonates. Similar to the lungs, the completion of development of the retinal vasculature is late in gestation (32–34 weeks).[89] In the 1950s an epidemic of ROP was described and a causal link to uncontrolled oxygen therapy was made.[90] Improved monitoring of oxygen therapy reduced the incidence of ROP but was associated with an increase in perinatal mortality secondary to respiratory failure.[91] Subsequently, and despite good oxygen control, ROP continues to occur. This is now most likely due to the increased survival of increasingly premature low-birth-weight infants[92] rather than high Pa_{O_2} alone. This suggests both oxygen- and non–oxygen-related factors. ROP is a biphasic disease in which the relatively hyperoxic environment following delivery initially leads to a slowing or even cessation of retinal vascular development of the premature infant. Additional oxygen may further contribute to this problem by affecting the expression of vascular growth factors. The second phase of the disease is a hypoxic-induced neovascularisation, similar to that seen in diabetic retinopathy. This leads to fibrous scarring with risk of retinal detachment. How much oxygen is too much remains contentious and further research is required.[93]

HYPEROXIC AND HYPERBARIC OXYGEN THERAPY

As stated previously, there are very few indications for increasing the Pa_{O_2} above 'normal', approximately 13 kPa (100 mm Hg). Indeed, it is likely to be harmful. However, there exist some data to support its use in certain conditions, the majority of which do not involve the critical care physician. These include the treatment of cluster headache, reduction in oxidative stress in colonic surgery and prevention of desaturation during endoscopy.[94–97] The use of hyperoxia to treat postoperative nausea and vomiting and prevent postoperative wound infections lacks high-quality evidence.[95]

ACUTE CARBON MONOXIDE POISONING

Carbon monoxide poisoning as a condition necessitating hyperoxic therapy attracts particular attention. A common consequence of house fires, it binds to haemoglobin with an affinity 210 times that of oxygen. Its half-life in air is 320 minutes, but this can be reduced to 90 minutes by giving the patient 100% oxygen, or 23 minutes with the addition of 3 atmospheres (≈300 kPa) of hyperbaric therapy. Competitive dissociation of carbon monoxide from the haem-binding site and provision of dissolved oxygen to the tissues are believed to combine to reduce the sequelae of carbon monoxide poisoning, but the mechanisms are likely to be more complex.[98] Some studies have suggested both acute and longer-term benefit,[99,100] but others have been unable to conclude significant improvement.[101,102] Investigations have attempted to distinguish those patients more likely to benefit from hyperbaric oxygen therapy. Factors such as increasing age (>35 years), an exposure time of greater than 24 hours, an associated loss of consciousness and carboxyhaemoglobin levels greater than 25% appear to result in an increased incidence of neurological sequelae and probably benefit from hyperbaric oxygen.[103] Geographical distance to an appropriate centre often has a significant influence on hyperbaric use in the acute setting, but mobile units

Box 28.2 Recognised indications for hyperbaric oxygen therapy

Primary therapy	Adjunctive therapy
Carbon monoxide poisoning	Radiation tissue damage
Air or gas embolism	Crush injuries
Decompression sickness (the 'bends')	Compromised skin flaps or grafts
Osteoradionecrosis	Refractory osteomyelitis
Clostridial myositis and myonecrosis	Intracranial abscess
	Chronic wound healing

Bennett M. Randomised controlled trials in diving and hyperbaric medicine. In: Weaver LK, ed. *Hyperbaric Oxygen Indications*. 6th ed. The Hyperbaric Oxygen Therapy Committee Report. Durham, NC: Undersea and Hyperbaric Medicine Society; 2014:259–283.

and some evidence that late therapy may be of benefit should not necessarily preclude its usage.[104,105]

HYPERBARIC OXYGEN

As alluded to in the treatment of carbon monoxide poisoning, oxygen can be delivered to patients at higher than atmospheric pressure (2–3 atmospheres). This serves to increase the amount of oxygen carried in the plasma, rather than bound to haemoglobin. This follows Henry's law, which states: 'At a constant temperature, the amount of a given gas dissolved in a given type and volume of liquid is proportional to the partial pressure of that gas in equilibrium with that liquid.' As the partial pressure of oxygen in the environment rises, so too does the amount of oxygen dissolved in the plasma. Consequently, the contribution of the Pa_{O_2} in the Ca_{O_2} formula (28.3) increases. At rest, the metabolic demands of an average person can be met by dissolved oxygen alone when breathing 100% at 3 atmospheres.

Hyperbaric oxygen therapy can be delivered either in a monoplace chamber designed for one individual, or in multiplace chambers for 2–10 people. The chambers encompass the whole body, and gas is piped from source, heated and humidified. The common indications and complications of hyperbaric oxygen therapy are listed in Boxes 28.2 and 28.3, respectively.[106,107]

Box 28.3 Complications of hyperbaric oxygen therapy

- *barotrauma:* middle ear and sinuses, rupture of the oval or round window, gastrointestinal distension, tooth displacement and pain, gas embolism on decompression
- *oxygen toxicity (as above):* especially a problem in the critically ill who may be on high concentrations for longer periods[78]
- *generalised seizures*: Paul Bert effect
- *visual problems:* acute myopia, cataract formation.

Acknowledgement

We acknowledge the significant contribution of Adrian J. Wagstaff for the previous version of this chapter, much of which has remained unchanged in this current version.

KEY REFERENCES

4. van Boxel G, Doherty WL, Parmar M. Cellular oxygen utilization in health and sepsis. *CEACCP*. 2012; 12(4):207–212.
20. Grocott MP, Martin DS, Levett DZ, et al. Caudwell Xtreme Everest Research Group. Arterial blood gases and oxygen content in climbers on Mount Everest. *N Engl J Med*. 2009;360(2):140–149.
31. Wagstaff TAJ, Soni N. Performance of six types of oxygen delivery devices at varying respiratory rates. *Anaesthesia*. 2007;62(5):492–503.
33. Bihari S, Bersten AD. High-flow nasal cannula oxygen therapy in acute hypoxemic respiratory failure: proceed with caution. *CMAJ*. 2017;189(7): E258–E259.
51. Weingart SD, Levitan RM. Preoxygenation and prevention of desaturation during emergency airway management. *Ann Emerg Med*. 2012;59(3): 165–175.
74. Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the oxygen-ICU randomized clinical trial. *JAMA*. 2016;316(15):1583–1589.
98. Weaver LK. Clinical practice. Carbon monoxide poisoning. *N Engl J Med*. 2009;360(12):1217–1225.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. West JB. *Respiratory Physiology, The Essentials*. 6th ed. Philadelphia, PA: Lippincott: Williams & Wilkins; 2000.
2. Hameed SM, Aird WC, Cohn SM. Oxygen delivery. *Crit Care Med*. 2003;31(suppl 12):S658–S667.
3. Guyton AC, ed. *Textbook of Medical Physiology*. 10th ed. Philadelphia, PA: Saunders; 2000.
4. van Boxel G, Doherty WL, Parmar M. Cellular oxygen utilization in health and sepsis. *CEACCP*. 2012;12(4):207–212.
5. Kuper M, Soni N. The oxygen whirlpool. In: Vincent JL, ed. *Yearbook of Intensive Care and Emergency Medicine*. New York, NY: Springer; 2004: 656–674.
6. Ronco JJ, Fenwick JC, Tweeddale MG, et al. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *JAMA*. 1993;270(14): 1724–1730.
7. Walsh T. Recent advances in gas exchange measurements in intensive care patients. *Br J Anaesth*. 2003; 91(1):120–131.
8. Fellows IW, Bennett T, MacDonald IA. The effects of adrenaline upon cardiovascular and metabolic functions in man. *Clin Sci*. 1985;69: 215–222.
9. Shoemaker WC, Appel PL, Kram HB, et al. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest*. 1988;94(6):1176–1186.
10. Boyd O. Optimisation of oxygenation and tissue perfusion in surgical patients. *Intensive Crit Care Nurs*. 2003;19(3):171–181.
11. Walsh TS, Lee A. Mathematical coupling in medical research: lessons from studies of oxygen kinetics. *Br J Anaesth*. 1998;81(2):118–120.
12. Vermeij CG, Feenstra BW, Adrichem WJ, et al. Independent oxygen uptake and oxygen delivery in septic and postoperative patients. *Chest*. 1991;99(6): 1438–1443.
13. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. *N Engl J Med*. 1995;333(16):1025–1032.
14. Hayes MA, Timmins AC, Yau EH, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med*. 1994;330(24): 1717–1722.
15. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19): 1368–1377.
16. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign guidelines committee including the pediatric subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41(2):580–637.
17. PRISM Investigators, Rowan KM, Angus DC, et al. Early, goal-directed therapy for septic shock – a patient-level meta-analysis. *N Engl J Med*. 2017; 376(23):2223–2234.
18. Hochachka PW, Buck LT, Doll CJ, et al. Unifying theory of hypoxia tolerance: molecular/metabolic defense and rescue mechanisms for surviving oxygen lack. *Proc Natl Acad Sci USA*. 1996;93(18): 9493–9498.
19. Cartee GD, Douen AG, Ramlal T, et al. Stimulation of glucose transport in skeletal muscle by hypoxia. *J Appl Physiol*. 1991;70(4):1593–1600.
20. Grocott MP, Martin DS, Levett DZ, et al. Caudwell Xtreme Everest Research Group. Arterial blood gases and oxygen content in climbers on Mount Everest. *N Engl J Med*. 2009;360(2):140–149.
21. Protti A, Singer M. Bench-to-bedside review: potential strategies to protect or reverse mitochondrial dysfunction in sepsis-induced organ failure. *Crit Care*. 2006;10(5):228.
22. Martin D, Windsor J. From mountain to bedside: understanding the clinical relevance of human acclimatisation to high-altitude hypoxia. *Postgrad Med J*. 2008;84(998):622–627, quiz 626.
23. Curtis SE, Cain SM. Regional and systemic oxygen delivery/uptake relations and lactate flux in hyperdynamic, endotoxin-treated dogs. *Am Rev Respir Dis*. 1992;145(2 Pt 1):348–354.
24. Gutierrez G, Palizas F, Doglio G, et al. Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. *Lancet*. 1992; 339(8787):195–199.
25. Leach RM, Treacher DF. The pulmonary physician in critical care 2: oxygen delivery and consumption in the critically ill. *Thorax*. 2002;57(2):170–177.
26. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wheeler AP, Bernard GR, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med*. 2006;354(21):2213–2224.
27. Schober P, Schwarte LA. From system to organ to cell: oxygenation and perfusion measurement in anesthesia and critical care. *J Clin Monit Comput*. 2012;26(4):255–265.
28. Mik EG, Ince C, Eerbeek O, et al. Mitochondrial oxygen tension within the heart. *J Mol Cell Cardiol*. 2009;46(6):943–951.
29. Wagstaff TAJ, Soni N. Arterial oxygenation in respiratory failure: the importance of the CPAP valve. *Br J Anaesth*. 2006;97(3):435P.
30. Leigh J. Variation in performance of oxygen therapy devices. *Anaesthesia*. 1970;25(2):210–222.
31. Wagstaff TAJ, Soni N. Performance of six types of oxygen delivery devices at varying respiratory rates. *Anaesthesia*. 2007;62(5):492–503.
32. Wagstaff T, Glover C, Soni N. Continuous positive airway pressure in acute respiratory failure: the importance of the valve. *JICS*. 2012;13(1):17–24.
33. Bihari S, Bersten AD. High-flow nasal cannula oxygen therapy in acute hypoxemic respiratory failure: proceed with caution. *CMAJ*. 2017;189(7): E258–E259.

34. Parke RL, Eccleston ML, McGuinness SP. The effects of flow on airway pressure during nasal high-flow oxygen therapy. *Respir Care*. 2011;56: 1151–1155.
35. Riera J, Perez P, Cortes J, et al. Effect of high-flow nasal cannula and body position on end-expiratory lung volume: a cohort study using electrical impedance tomography. *Respir Care*. 2013;58:589–596.
36. Goligher EC, Slutsky AS. Not just oxygen? Mechanisms of benefit from high-flow nasal cannula in hypoxemic respiratory failure. *Am J Respir Crit Care Med*. 2017;195(9):1128–1131.
37. Del Sorbo L, Ferguson ND. High-flow nasal cannulae or noninvasive ventilation for management of postoperative respiratory failure. *JAMA*. 2015; 313(23):2325–2326.
38. Ou X, Hua Y, Liu J, et al. Effect of high-flow nasal cannula oxygen therapy in adults with acute hypoxemic respiratory failure: a meta-analysis of randomized controlled trials. *CMAJ*. 2017;189(7): E260–E267. http://doi.org/10.1503/cmaj.160570.
39. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med*. 2015;372: 2185–2196.
40. Kang BJ, Koh Y, Lim CM, et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. *Intensive Care Med*. 2015;41: 623–632.
41. Lenique F, Habis M, Lofaso F, et al. Ventilatory and hemodynamic effects of continuous positive airway pressure in left heart failure. *Am J Respir Crit Care Med*. 1997;155(2):500–505.
42. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009;374(9698):1351–1363.
43. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators, Davies A, Jones D, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA*. 2009;302(17):1888–1895.
44. O'Driscoll BR, Howard LS, Bucknall C, et al. British thoracic society emergency oxygen audits. *Thorax*. 2011;66(8):734–735.
45. Crapo RO, Jensen RL, Hegewald M, et al. Arterial blood gas reference values for sea level and an altitude of 1,400 meters. *Am J Respir Crit Care Med*. 1999;160(5 Pt 1):1525–1531.
46. Bowton DL, Scuderi PE, Haponik EF. The incidence and effect on outcome of hypoxemia in hospitalized medical patients. *Am J Med*. 1994; 97(1):38–46.
47. Slutsky AS. Consensus conference on mechanical ventilation – January 28–30, 1993 at Northbrook, Illinois, USA. Part 2. *Intensive Care Med*. 1994;20(2): 150–162.
48. Perkins GD, McAuley DF, Giles S, et al. Do changes in pulse oximeter oxygen saturation predict equivalent changes in arterial oxygen saturation? *Crit Care*. 2003;7(4):R67.
49. Murphy R, Thethy S, Raby S, et al. Capillary blood gases in acute exacerbations of COPD. *Respir Med*. 2006;100(4):682–686.
50. Zavorsky GS, Cao J, Mayo NE, et al. Arterial versus capillary blood gases: a meta-analysis. *Respir Physiol Neurobiol*. 2007;155(3):268–279.
51. Weingart SD, Levitan RM. Preoxygenation and prevention of desaturation during emergency airway management. *Ann Emerg Med*. 2012;59(3): 165–175.
52. Baraka AS, Taha SK, Aouad MT, et al. Preoxygenation: comparison of maximal breathing and tidal volume breathing techniques. *Anesthesiology*. 1999;91(3):612–616.
53. Pourmand A, Robinson C, Dorwart K, et al. Pre-oxygenation: implications in emergency airway management. *Am J Emerg Med*. 2017;35(8): 1177–1183.
54. Simon M, Wachs C, Braune S, et al. High-flow nasal cannula versus bag-valve-mask for preoxygenation before intubation in subjects with hypoxemic respiratory failure. *Respir Care*. 2016;61(9): 1160–1167.
55. Mir F, Patel A, Iqbal R, et al. A randomised controlled trial comparing transnasal humidified rapid insufflation ventilatory exchange (THRIVE) pre-oxygenation with facemask pre-oxygenation in patients undergoing rapid sequence induction of anaesthesia. *Anaesthesia*. 2017;72(4):439–443.
56. Baillard C, Fosse JP, Sebbane M, et al. Noninvasive ventilation improves preoxygenation before intubation of hypoxic patients. *Am J Respir Crit Care Med*. 2006;174(2):171–177.
57. Lane S, Saunders D, Schofield A, et al. A prospective, randomised controlled trial comparing the efficacy of pre-oxygenation in the 20 degrees head-up vs supine position. *Anaesthesia*. 2005;60(11):1064–1067.
58. Ramkumar V, Umesh G, Philip FA. Preoxygenation with 20° head-up tilt provides longer duration of non-hypoxic apnea than conventional preoxygenation in non-obese healthy adults. *J Anesth*. 2011; 25(2):189–194.
59. Altermatt FR, Muñoz HR, Delfino AE, et al. Preoxygenation in the obese patient: effects of position on tolerance to apnoea. *Br J Anaesth*. 2005;95(5): 706–709.
60. Oliveira JE, Silva L, Cabrera D, et al. Effectiveness of apneic oxygenation during intubation: a systematic review and meta-analysis. *Ann Emerg Med*. 2017;70(4):483–494.e11. pii: S0196-0644(17)30582-6.
61. Pavlov I, Medrano S, Weingart S. Apneic oxygenation reduces the incidence of hypoxemia during emergency intubation: a systematic review and meta-analysis. *Am J Emerg Med*. 2017;35(8): 1184–1189.

62. Binks MJ, Holyoak RS, Melhuish TM, et al. Apneic oxygenation during intubation in the emergency department and during retrieval: a systematic review and meta-analysis. *Am J Emerg Med*. 2017; 35(10):1542–1546.
63. Frumin MJ, Epstein RM, Cohen G. Apneic oxygenation in man. *Anesthesiology*. 1959;20:789–798.
64. Miguel-Montanes R, Hajage D, et al. Use of high-flow nasal cannula oxygen therapy to prevent desaturation during tracheal intubation of intensive care patients with mild-to-moderate hypoxemia. *Crit Care Med*. 2015;43(3):574–583.
65. Semler MW, Janz DR, Lentz RJ, et al. Pragmatic Critical Care Research Group. Randomized trial of apneic oxygenation during endotracheal intubation of the critically ill. *Am J Respir Crit Care Med*. 2016;193(3):273–280.
66. Jaber S, Monnin M, Girard M, et al. Apnoeic oxygenation via high-flow nasal cannula oxygen combined with non-invasive ventilation preoxygenation for intubation in hypoxaemic patients in the intensive care unit: the single-centre, blinded, randomised controlled OPTINIV trial. *Intensive Care Med*. 2016;42(12):1877–1887.
67. De Jong A, Jaber S. Apneic oxygenation for intubation in the critically ill. Let's not give up! *Am J Respir Crit Care Med*. 2016;193(3):230–232.
68. Caputo N, Azan B, Domingues R, et al. Lincoln Airway Group. EmergeNcy Department use of Apneic Oxygenation versus usual care during rapid sequence intubation: a randomized controlled trial (The ENDAO Trial). *Acad Emerg Med*. 2017;24(11):1387–1394.
69. Kelly FE, Hardy R, Hall EA, et al. Fire on an intensive care unit caused by an oxygen cylinder. *Anaesthesia*. 2013;68(1):102–104.
70. de Jonge E, Peelen L, Keijzers PJ, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care*. 2008;12(6):R156.
71. Eastwood G, Bellomo R, Bailey M, et al. Arterial oxygen tension and mortality in mechanically ventilated patients. *Intensive Care Med*. 2012;38(1): 91–98.
72. Kilgannon JH, Jones AE, Shapiro NI, et al. Emergency medicine shock research network (EMShockNet) investigators. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA*. 2010;303(21):2165–2171.
73. Bellomo R, Bailey M, Eastwood GM, et al. Study of Oxygen in Critical Care (SOCC) Group. Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest. *Crit Care*. 2011; 15(2):R90.
74. Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the oxygen-ICU randomized clinical trial. *JAMA*. 2016;316(15):1583–1589.
75. Saugstad OD. Resuscitation of newborn infants: from oxygen to room air. *Lancet*. 2010;376(9757): 1970–1971.
76. Singhal AB, Benner T, Roccatagliata L, et al. A pilot study of normobaric oxygen therapy in acute ischemic stroke. *Stroke*. 2005;36(4):797–802.
77. Ronning OM, Guldvog B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. *Stroke*. 1999;30(10): 2033–2037.
78. Farquhar H, Weatherall M, Wijesinghe M, et al. Systematic review of studies of the effect of hyperoxia on coronary blood flow. *Am Heart J*. 2009; 158(3):371–377.
79. Rawles JM, Kenmure AC. Controlled trial of oxygen in uncomplicated myocardial infarction. *Br Med J*. 1976;1(6018):1121–1123.
80. Chew DP, Scott IA, Cullen L, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the management of acute coronary syndromes 2016. *Med J Aust*. 2016;205(3): 128–133.
81. O'Connor RE, Al Ali AS, Brady WJ, et al. Part 9: acute coronary syndromes: 2015 American Heart Association Guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132(18 suppl 2): S483–S500.
82. Sylvester JT, Shimoda LA, Aaronson PI, et al. Hypoxic pulmonary vasoconstriction. *Physiolo Rev*. 2012;92(1):367–520.
83. Frank L, Roberts RJ. Endotoxin protection against oxygen-induced acute and chronic lung injury. *J Appl Physiol Respir Environ Exerc Physiol*. 1979; 47(3):577–581.
84. Frank L, Yam J, Roberts RJ. The role of endotoxin in protection of adult rats from oxygen-induced lung toxicity. *J Clin Invest*. 1978;61(2):269–275.
85. Saugstad OD. Bronchopulmonary dysplasia-oxidative stress and antioxidants. *Semin Neonatol*. 2003;8(1):39–49.
86. Dick CR, Liu Z, Sassoon CS, et al. O_2-induced change in ventilation and ventilatory drive in COPD. *Am J Respir Crit Care Med*. 1997;155(2): 609–614.
87. Feller-Kopman D, Schwartzstein R. The role of hypoventilation and ventilation-perfusion redistribution in oxygen-induced hypercapnia during acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2001; 163(7):1755.
88. Downs JB. Has oxygen administration delayed appropriate respiratory care? Fallacies regarding oxygen therapy. *Respir Care*. 2003;48(6):611–620.
89. Roth AM. Retinal vascular development in premature infants. *Am J Ophthalmol*. 1977;84(5): 636–640.
90. Campbell K. Intensive oxygen therapy as a possible cause of retrolental fibroplasia; a clinical approach. *Med J Aust*. 1951;2(2):48–50.

91. Avery ME. Recent increase in mortality from hyaline membrane disease. *J Pediatr*. 1960;57:553–559.
92. Flynn JT. Acute proliferative retrolental fibroplasia: multivariate risk analysis. *Trans Am Ophthalmol Soc*. 1983;81:549–591.
93. Tin W, Gupta S. Optimum oxygen therapy in preterm babies. *Arch Dis Child Fetal Neonatal Ed*. 2007;92(2):F143–F147.
94. Garcia de la Asuncion J, Belda FJ, Greif R, et al. Inspired supplemental oxygen reduces markers of oxidative stress during elective colon surgery. *Br J Surg*. 2007;94(4):475–477.
95. Iscoe S, Beasley R, Fisher JA. Supplementary oxygen for nonhypoxemic patients: O_2 much of a good thing? *Crit Care*. 2011;15(3):305.
96. Bennett MH, French C, Schnabel A, et al. Normobaric and hyperbaric oxygen therapy for migraine and cluster headache. *Cochrane Database Syst Rev*. 2008;(3):CD005219.
97. Crantock L, Cowen AE, Ward M, et al. Supplemental low flow oxygen prevents hypoxia during endoscopic cholangiopancreatography. *Gastrointest Endosc*. 1992;38(4):418–420.
98. Weaver LK. Clinical practice. Carbon monoxide poisoning. *N Engl J Med*. 2009;360(12):1217–1225.
99. Weaver LK, Hopkins RO, Chan KJ, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. *N Engl J Med*. 2002;347(14):1057–1067.
100. Hawkins M, Harrison J, Charters P. Severe carbon monoxide poisoning: outcome after hyperbaric oxygen therapy. *Br J Anaesth*. 2000;84(5):584–586.
101. Scheinkestel CD, Bailey M, Myles PS, et al. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial. *Med J Aust*. 1999;170(5):203–210.
102. Juurlink DN, Buckley NA, Stanbrook MB, et al. Hyperbaric oxygen for carbon monoxide poisoning. *Cochrane Database Syst Rev*. 2005;(1):CD002041.
103. Weaver LK, Valentine KJ, Hopkins RO. Carbon monoxide poisoning: risk factors for cognitive sequelae and the role of hyperbaric oxygen. *Am J Respir Crit Care Med*. 2007;176(5):491–497.
104. Lueken RJ, Heffner AC, Parks PD. Treatment of severe carbon monoxide poisoning using a portable hyperbaric oxygen chamber. *Ann Emerg Med*. 2006;48(3):319–322.
105. Stoller KP. Hyperbaric oxygen and carbon monoxide poisoning: a critical review. *Neurol Res*. 2007;29(2):146–155.
106. Tibbles PM, Edelsberg JS. Hyperbaric-oxygen therapy. *N Engl J Med*. 1996;334(25):1642–1648.
107. Bennett M. Randomised controlled trials in diving and hyperbaric medicine. In: Weaver LK, ed. *Hyperbaric Oxygen Indications*, 6th ed. The Hyperbaric Oxygen Therapy Committee Report. Durham NC: Undersea and Hyperbaric Medicine Society; 2014:259–283.

29

Airway management and acute airway obstruction

Gordon YS Choi, Gavin M Joynt

The primary objective of airway management is to clear or bypass the obstructed airway and protect the lungs from soiling. Acute upper airway obstruction is a life-threatening emergency, resulting from a wide range of pathophysiological processes. Rapid assessment and establishment of a patent airway are vital, often in the absence of a specific diagnosis. As no single airway management modality is universally applicable, the intensive care unit (ICU) physician must be capable of performing a variety of airway management techniques (Fig. 29.1).

AIRWAY MANAGEMENT TECHNIQUES

Airway management techniques can be considered non-invasive or invasive, depending on whether instrumentation occurs above or below the glottis, and is surgical or non-surgical (Table 29.1). Definitive techniques secure the trachea and provide some protection from macroscopic aspiration and soiling. Although most airway management in ICU is still achieved by bag-and-mask ventilation and direct laryngoscopic tracheal intubation, the use of fibreoptic bronchoscopy and video laryngoscopy is increasingly common, especially in special circumstances. Management of failed intubation and ventilation by various alternative techniques (e.g. laryngeal mask airway [LMA] and cricothyroidotomy) is now well described.[1,2]

The technique of choice will depend on each situation and is a consequence of the interaction of patient factors and the clinician's experience (Table 29.2). Other factors include availability of help, levels of training and supervision and accessibility of equipment. A portable storage unit with a wide choice of equipment appropriate for difficult airway management is necessary in the ICU (Box 29.1).

NON-INVASIVE TECHNIQUES

BAG-MASK VENTILATION

As with most airway management techniques, mask ventilation is a basic skill that requires time and experience to master. It should be learned using manikins, simulators and practiced in the controlled environment of the operating theatre so that when used in the emergency setting in the ICU the skill is well established. The bag may be a self-inflating resuscitator or one attached to an anaesthetic circuit. Most resuscitators require a reservoir bag in series with the self-inflating bag that ensures a high oxygen concentration can be delivered. The addition of positive end-expiratory pressure (PEEP) may improve arterial oxygenation and overcome airway obstruction due to laryngospasm.

Some considerations when performing mask ventilation include the following:

- *Inadequate ventilation:* the seal of the mask against the face may be inadequate and good hand positioning is essential. Ventilation of edentulous patients may be aided by improving hand position or special masks. Two operators are recommended if a mask face leak is excessive: one to hold the mask and the other to manipulate the bag-mask resuscitator.
- *Hyperventilation:* unnecessary hyperventilation may occasionally cause dynamic pulmonary hyperinflation and cardiovascular compromise.
- *Gastric insufflation:* this increases the risk of vomiting and aspiration. Carefully applied cricoid pressure may prevent gastric gas insufflation.
- *Pulmonary aspiration:* in the emergency situation with a full stomach, mask ventilation with cricoid pressure may be necessary until the airway can be secured. Passage of a nasogastric tube to aspirate gastric contents may be successful, but emptying cannot be guaranteed and vomiting may be induced.

ORO- AND NASOPHARYNGEAL AIRWAYS

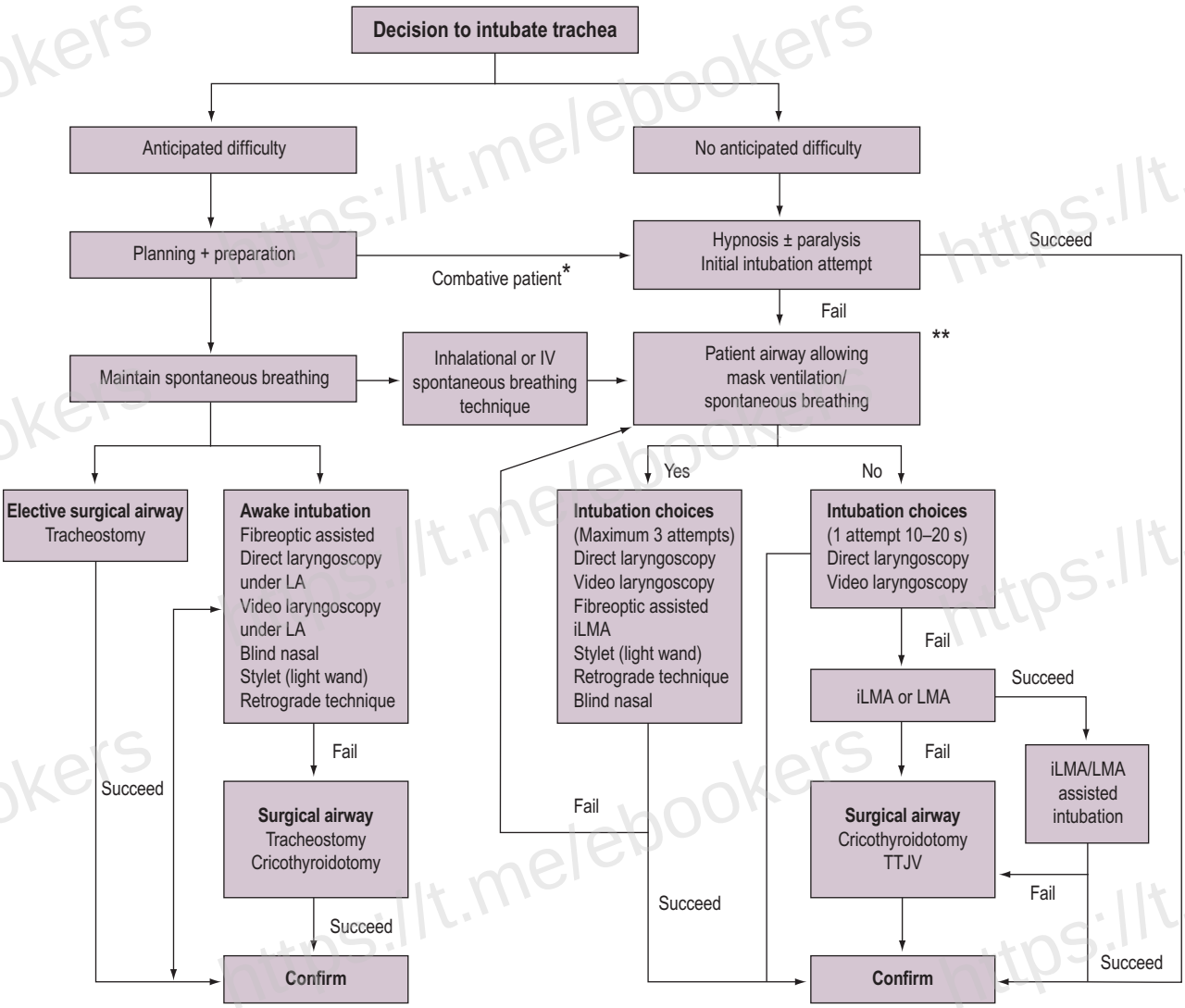
In the unconscious patient, functional obstruction may occur because of loss of muscular tone and inspiratory airway narrowing at the soft palate, epiglottis and tongue base. An oropharyngeal airway device may establish an adequate airway for spontaneous or bag-mask ventilation when proper head positioning is insufficient. It is inserted with the concavity facing the palate and then rotated 180 degrees into the proper position as it is advanced. Complications include mucosal trauma, worsening the obstruction by pressing the epiglottis against the laryngeal outlet if the

ABSTRACT

Obstruction to the airway is a life-threatening emergency. Causes of obstruction are many and varied. Rapid assessment followed by immediate establishment of a patent airway is vital. No single management modality is universally applicable, and therefore the intensivist must be capable of performing a variety of airway management techniques. Non-invasive techniques appear simple, but require manual dexterity and regular practice to guarantee competence. While traditional rigid laryngoscopy remains a gold standard for tracheal intubation, video laryngoscopic techniques are increasingly available and may offer advantages in specific patients and situations. Alternative methods of securing an airway include flexible fibreoptic tracheal intubation, the use of a laryngeal mask, and the execution of a surgical airway, such as cricothyroidotomy or tracheostomy. Upper airway obstruction is uncommon, but immediately life threatening. Participation in airway courses and simulations to improve and maintain diagnostic and interventional skills in this setting is recommended.

KEYWORDS

Laryngoscopy
flexible fibreoptic intubation
video laryngoscope
cricothyroidotomy
tracheostomy
laryngeal mask
end-tidal carbon dioxide
laryngeal oedema



* Consider maintaining spontaneous breathing.

** Call for help and consider allowing patient to wake up if immediate intubation is not essential.

Figure 29.1 Difficult airway algorithm (see text). *iLMA*, Intubating laryngeal mask airway; *IV*, intravenous; *LA*, local anaesthetic; *LMA*, laryngeal mask airway; *TTJV*, transtracheal jet ventilation.

tongue displaces posteriorly, and occasionally laryngospasm. The following sizes (length from flange to tip) are recommended: large adult: 100 mm (Guedel size 5), medium adult: 90 mm (Guedel size 4), and small adult: 80 mm (Guedel size 3).

A nasopharyngeal airway is a soft rubber or plastic tube inserted into the nostril and advanced along the floor of the nose (in the direction of the occiput). It is better tolerated by semiconscious patients than the oropharyngeal airway. Complications include epistaxis, aspiration and, rarely, laryngospasm and oesophageal placement.

SUPRAGLOTTIC AIRWAYS

The original LMA is a reusable device that consists of a silicone rubber tube connected to a distal elliptical spoon-shaped mask with an inflatable rim, which is positioned blindly into the pharynx to form a low-pressure seal against the laryngeal inlet.[3] There are a variety of sizes for use in children and adults. LMAs are useful to achieve non-definitive airway patency in many emergency situations (see Fig. 29.1), and can be used to provide limited positive-pressure ventilation.

Once positioned, the LMA can be used to guide the passage of stylets, bougies, the bronchoscope or

even an endotracheal tube into the trachea. The intubating LMA (FasTrach) is a modification of the LMA with several features to facilitate intubation once the LMA is placed. There is a guiding ramp and epiglottic elevating bar at the aperture to direct the endotracheal tube to the glottis. It also has an anatomically curved, rigid shaft and handle to allow easy and firm manipulation during placement and when the endotracheal tube is passed.

Table 29.1 Characteristics of airway management techniques

TECHNIQUE	EXPERIENCE REQUIRED	TIME REQUIRED	DEFINITIVE
NON-INVASIVE			
Bag-and-mask	+	Seconds	–
LMA and iLMA	+	1 min	–
Combitube	–	1 min	+
INVASIVE (NON-SURGICAL)			
Endotracheal intubation			
Direct laryngoscopy	+	Variable	+
Bronchoscopic	+	Several minutes	+
Video laryngoscopy	+	Variable	+
Retrograde	–	Minutes	+
INVASIVE (SURGICAL)			
Jet ventilation Cricothyroidotomy	–	Minutes	–
Percutaneous	–	Minutes	±
Surgical	+	1 min	+
Tracheostomy			
Percutaneous	+	Minutes	+
Surgical	+	Minutes	+

iLMA, Intubating laryngeal mask airway; *LMA*, laryngeal mask airway.

The LMA is prepared for insertion by deflating and smoothing out the cuffed rim to be wrinkle-free, and the posterior surface is lubricated with water-soluble jelly. The patient is positioned as for endotracheal intubation, with slight flexion of the neck and extension of the atlanto-occipital joint (sniffing-the-morning-air position). The LMA is inserted with the tip of the cuff continuously applied to the hard palate, and with the right index finger guiding the tube to the back of the tongue until a firm resistance is encountered. The cuff is then inflated with 20–40 mL of air (adult sizes) before attachment of the breathing circuit. The successful use of LMA requires some familiarity with the equipment and technique, and at least simulated exposure is strongly recommended.

Second-generation LMAs are inserted in essentially the same way, although cuff inflation with air may not be required. They have additional advantageous features such as higher seal pressure, facilitate easy passage of a tube for gastric decompression, and allow improved conditions for fibre-optically guided tracheal intubation.[4] Examples include the i-gel (Intersurgical, Wokingham, United Kingdom), the Proseal LMA (PLMA; Teleflex Medical Europe Ltd, Athlone, Ireland), and the LMA Supreme (SLMA; Teleflex Medical Ltd). Differences in clinical performance between the second-generation devices are generally small.[5,6]

Contraindications for using the LMA include inability to open the mouth, pharyngeal pathology, airway obstruction at or below the larynx, low pulmonary compliance or high airway resistance. Complications

Table 29.2 Application of airway management techniques

	DIFFICULT DIRECT LARYNGOSCOPIC INTUBATION	DIFFICULT SPONTANEOUS/MASK VENTILATION
Awake	Fibreoptic bronchoscopic intubation Blind nasal intubation Retrograde intubation	Percutaneous cricothyroidotomy* Surgical tracheostomy*
Anaesthetised or comatose (empty stomach)	Bag-and-mask ventilation Direct laryngoscopic intubation Different blade choices Video laryngoscopy Fibreoptic bronchoscopic intubation Intubating LMA/LMA Lighted stylet Blind nasal intubation	Laryngeal mask airway Transtracheal jet ventilation Rigid ventilating bronchoscope Percutaneous cricothyroidotomy Surgical tracheostomy
(full stomach)	Consider cricoid pressure Consider ProSeal LMA Combitube	Percutaneous cricothyroidotomy Surgical tracheostomy Combitube

*Under local anaesthesia.

LMA, Laryngeal mask airway.

Examples of common alternatives are given. The technique chosen will depend on clinician preference.

Box 29.1 Suggested contents of a portable storage facility for difficult airway management

- Masks
  - Face and nasal masks of differing make and size variety
- Airways
  - Oropharyngeal airways
  - Nasopharyngeal airways
  - Airway intubator guide for oral endoscopic intubation
  - Laryngeal mask airway (LMA) and intubating LMA with appropriate endotracheal tubes
- Rigid laryngoscope with a variety of designs and sizes
  - Short handle or variable angle (Patil–Syracuse) laryngoscope
  - Curved blades: Macintosh, Bizzarri–Giuffrida
  - Straight blades: Miller
  - Bent blades: Belscope
  - Articulating tip blades: McCoy
- Video laryngoscope
  - Disposable
  - Non-disposable
- Endotracheal tubes of assorted size
  - Murphy tubes
  - Microlaryngoscopy tubes
- Endotracheal tube stylets
  - Gum elastic bougie (Eschmann stylet)
  - Malleable stylet
  - Tube changer, hollow tube changer (jet stylet)
  - Lighted stylet (light wand)
- Fibreoptic intubation equipment
  - Patil endoscopic mask for oral endoscopic intubation
  - Fibreoptic endoscopes with light source, adult and paediatric-sized
  - Device for emergency non-surgical airway ventilation
- Combitube
- Emergency surgical airway access
  - Percutaneous cricothyroidotomy set
  - Transtracheal jet ventilation – cannula and high-pressure O_2 source connectors
  - Regulated central wall O_2 pressure (Sanders-type injector)
  - Unregulated central wall O_2 pressure
- Exhaled carbon dioxide monitor
  - Capnometer/capnograph
  - Chemical indicators

include aspiration, gastric insufflation, partial airway obstruction, coughing, laryngospasm, postextubation stridor and kinking of the shaft of the LMA.

COMBITUBE (OESOPHAGEAL–TRACHEAL DOUBLE-LUMEN AIRWAY)

The oesophageal–tracheal Combitube is a double-lumen tube that is blindly inserted into the oropharynx up to the indicated markings.[7] The oesophageal lumen has a stopper at the distal end and side perforations at the pharyngeal level, whereas the tracheal lumen has a hole at the distal end. It has two cuffs, a distal one and a proximal pharyngeal balloon. The patient is ventilated through the oesophageal lumen initially as the Combitube usually enters the oesophagus,[7] with the distal cuff sealing the oesophagus and the proximal balloon sealing the pharynx. Gas exits the perforations and enters the pharynx and larynx. In the event of failure of ventilation, the tracheal lumen is ventilated and the distal cuff seals the trachea.

Although demonstrated to be useful in the prehospital setting, its role in resuscitation and management of the difficult airway in the ICU environment is yet to be established. Barotrauma, especially oesophageal rupture, has been reported.

INVASIVE TECHNIQUES

ENDOTRACHEAL INTUBATION

Endotracheal intubation remains the gold standard airway management technique, allowing for spontaneous and positive-pressure ventilation, with good macroscopic protection from aspiration. Indications include acute airway obstruction, facilitation of tracheal suctioning, protection of the airway in those without protective reflexes and respiratory failure requiring ventilatory support with high inspired concentrations of oxygen and PEEP.

Prior to proceeding with an intubation attempt, regardless of the technique chosen, pre-oxygenation, as well as preparation and checking of all relevant equipment, is essential. Difficult airway management equipment (see Box 29.1) should also be accessible within a few minutes. Food, vomitus, blood or sputum may obstruct the airway and suction should always be available. Suction apparatus should generate at least 300 mm Hg (40 kPa) and 30 L/min. Excessively vigorous suctioning should be avoided, as it can cause laryngospasm, vagal stimulation, mucosal injury and bleeding.

Direct laryngoscopy

Although essential for all intensivists, direct laryngoscopy is a difficult skill to master.[8] If multiple intubation attempts are required, the maximum interruption to ventilation should be about 30 seconds. Adequate ventilation and oxygenation must be provided between attempts. Minimum monitoring should consist of continuous-pulse oximetry, electrocardiogram (ECG) and blood pressure. The BURP (backward, upward, rightward pressure) technique may be helpful to bring the vocal cords into the field of vision. Endotracheal tube size describes the internal diameter and, where possible, 8.0–9.0 mm in adult males and 7.5–8.0 mm in adult females are generally used to facilitate sputum clearance, minimise airway resistance and allow access for fibreoptic bronchoscopy. Special-purpose tubes include double-lumen tubes to facilitate lung isolation, spiral embedded tubes, and laser-resistant tubes.

The route of intubation may be orotracheal or nasotracheal. The orotracheal route is generally recommended because it may be associated with fewer complications.[9] However, nasotracheal intubation allows easier tube fixation and avoids the risk of tube occlusion from biting. It is contraindicated in the presence of fracture of the base of the skull. Other complications include epistaxis, turbinate cartilage and nasal septal damage during insertion.

Stylet guide (introducer)

The 'anterior larynx' can often be more easily intubated if a gum elastic bougie is advanced in the midline and directed anteriorly into the trachea. The endotracheal tube is then advanced over the guide. Clinical signs of correct tracheal placement of the guide include coughing, resistance felt before the guide is fully advanced (usually at 45 cm or less from the lips because of resistance at the carina or bronchus) and a sensation of clicks from the tracheal rings. A number of alternative intubating guides are available, including the hollow endotracheal tube changer, which can be attached to a side-stream capnometer, or to an oxygen source. The lighted stylet is less commonly used and has a light at the distal end that results in a characteristic midline transillumination appearance when the light enters the larynx.

Rigid indirect fibreoptic instruments

The video-laryngoscope (VL) is a relatively new device that generates a view of the glottis from near the laryngoscope tip. When used for difficult airway management, VLs produce similar or better intubation success rates compared with direct laryngoscopy, and reduce cervical spine movement during laryngoscopy.[10] Comparisons between VLs and the traditional laryngoscope for routine use for intubation in ICU have not demonstrated consistent superiority. Glottic visualisation appears better with VL techniques; however, placement of the endotracheal tube may be more challenging. While a recent meta-analysis suggested some superiority for VL, a sensitivity analysis including only randomised controlled trials (RCTs) showed no significant clinical superiority,[11] and a recent RCT showed no improvement in first-pass intubation rate.[12] Limitations do exist for each particular device, and both training and operator experience contribute to successful use. Although increasingly available, there remains insufficient evidence supporting the routine use of video-laryngoscopy as a replacement for traditional direct laryngoscopy.

Fibreoptic bronchoscopic technique

This technique offers advantages of direct visualisation, immediate diagnosis of upper airway lesions and immobility of the neck during the procedure. It also allows reasonably comfortable intubation of a cooperative, awake patient under local anaesthesia, and use of the sitting position. Experience and skill are necessary, especially for dealing with emergent situations, but success rates greater than 96% are expected.[13] Fibreoptic intubation may also be performed in anaesthetised patients, using a modified facemask with diaphragm for oral intubation. Nasal intubation is usually performed through an endotracheal tube placed in the nasopharynx, with the tip just above the glottis. The fibreoptic bronchoscope tip is guided into the trachea and the tube is advanced over the bronchoscope. Correct placement is visually checked before the scope is removed. In ICU, the fibreoptic bronchoscope can be used to improve the safety of airway procedures such as endotracheal tube changes and percutaneous tracheostomy.[14] A number of specially designed oral airways are available to assist oral fibreoptic intubation (e.g. the Ovassapian, Williams or Berman airway). The most common cause of failure is obstructed vision from blood or secretions.

Blind nasal intubation

Blind nasal intubation is sometimes considered in spontaneously breathing patients. Possible indications include inability to open the mouth (e.g. mandibular fracture or temporomandibular joint pathology), and cervical spine and faciomaxillary injury. Contraindications include bleeding disorders, nasal airway obstruction, skull base fracture and pre-existing sinusitis. Operator proficiency is required.

Retrograde intubation technique

A J-tip guidewire (length required in adults approximately 70 cm) is introduced percutaneously through the cricothyroid membrane, and advanced into the retropharynx. The tip is retrieved from the oral cavity, and the wire is used to guide an oral endotracheal tube past the obstruction and into the trachea.[15] The procedure is a relatively simple and safe alternative if other techniques fail or are not possible. Commercial kits are available.

Confirmation of tracheal tube placement

Confirmation of correct intratracheal tube placement is essential. Direct visualisation and measurement of expired CO_2 by capnography are the most reliable methods.[16] Capnography may produce false-positive results with the first few breaths after oesophageal intubation (i.e. detectable PE_{CO_2}), if gastric insufflation from mask ventilation has occurred. A false-negative (decreased PE_{CO_2}, despite correct position) may occur with cardiac arrest and low-cardiac-output states. Position can also be reliably confirmed by the use of self-inflating oesophageal detectors. Other clinical signs, such as auscultation of breath sounds over both sides of the chest and epigastrium, visualisation of condensed water vapour in the tube and chest wall movement are less reliable. The use of capnography is further discussed in Chapter 38.

Complications of endotracheal intubation

These may be classified into those occurring during intubation (e.g. incorrect tube placement, laryngeal trauma, deleterious cardiovascular response to laryngoscopy and intubation, increase in intracranial pressure, hypoxaemia and aspiration), while the tube is in place (e.g. blockage, dislodgement, tube deformation, damage to larynx and complications of mechanical ventilation), and following extubation (e.g. aspiration and postextubation airway obstruction, laryngeal and tracheal stenosis). As few ICU patients can be adequately starved prior to intubation, the use of cricoid pressure, provided it does not obscure the glottic view, is usually required to reduce the risk of aspiration. Hypotension in ICU patients is common immediately following intubation because of drug-induced myocardial depression, decrease in peripheral vascular resistance and sympathetic stimulation, and reduced venous return after positive-pressure ventilation. Fluid administration and the use of vasopressor drugs may be required. Special techniques should be used to minimise side effects such as cardiovascular responses and increases in intracranial pressure when appropriate.

TRANSTRACHEAL JET VENTILATION

Percutaneous transtracheal jet ventilation (TTJV), using a large-bore intravenous (IV) catheter inserted through the cricothyroid membrane, can be used to provide temporary ventilation when other techniques have failed.[17] Ventilation through the cannula with a standard manual resuscitator bag is inadequate, and a jet injector system is necessary. A high-pressure (up to 50 psi or 344 kPa) oxygen source is required for adequate ventilation through a 14 FG IV cannula. Expiratory gases must be able to escape via the glottis. Appropriate chest movements during expiration must be noted. The consequence of expiratory obstruction is severe and potentially fatal barotrauma.

Complications may be caused by insertion of the IV cannula (e.g. bleeding and oesophageal perforation), use of high-pressure gases (e.g. hyperinflation, barotrauma), catheter kinking or displacement (the latter causing potentially catastrophic subcutaneous emphysema) and failure to protect the airway (i.e. aspiration).

CRICOTHYROIDOTOMY

Cricothyroidotomy, by surgery or percutaneously, is a reliable, relatively easy way of providing an emergency airway.[18] It is the method of choice if severe or complete upper airway obstruction exists. The simplest, fastest and most proven method uses a horizontal incision through the cricothyroid membrane (with the space held wide open by the scalpel handle or forceps), followed by insertion of a small tracheostomy or endotracheal tube (Fig. 29.2). Commercial cricothyroidotomy sets, using the Seldinger technique, are available. A tube with internal diameter of 3.0 mm will allow adequate gas flow for self-inflating bag ventilation provided supplemental oxygen is used. Since the diameter of the cricothyroid space is 9 by 30 mm, tubes of 8.5 mm outer diameter or less should avoid laryngeal and vocal cord damage. Complications such as subglottic stenosis (1.6%), thyroid fracture, haemorrhage and pneumothorax are acceptably low. Cricothyroidotomy is generally contraindicated in complete laryngotracheal disruption and age less than 12 years.

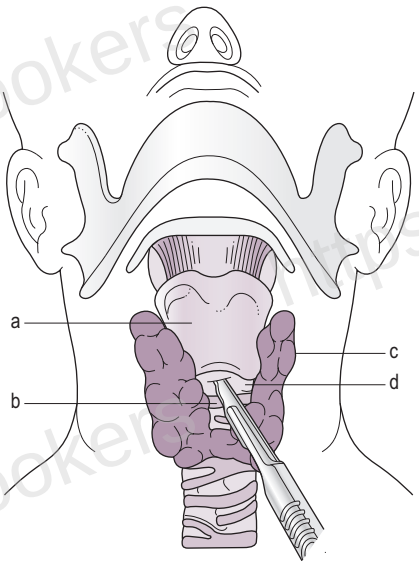


Figure 29.2 Cricothyroidotomy performed with a scalpel: *(a)* thyroid cartilage; *(b)* cricoid cartilage; *(c)* thyroid gland; *(d)* cricoid membrane, usually easily palpable subcutaneously.

TRACHEOSTOMY

There is little agreement on the indications, best technique or optimal timing of tracheostomy in ICU patients. Suggested indications for tracheostomy include[19]:

- bypass of glottic and supraglottic obstruction
- access for tracheal toilet
- provision of a more comfortable airway for prolonged ventilatory support
- protection of the airways from aspiration.

In uncomplicated patients, percutaneous tracheostomy performed by an intensivist at the bedside is at least as safe as surgical tracheostomy performed in the operating room, and is probably associated with a lower incidence of infectious complications.[20,21] Convenience and cost savings have made percutaneous tracheostomy the procedure of choice in many institutions. Ciaglia's percutaneous technique was described in 1985.[22] After making an adequate skin incision and using blunt dissection with forceps, the endotracheal tube is first withdrawn so that its cuff lies just above the vocal cords. The operator confirms tube position

to be above the stoma site by palpation of the trachea. A J-wire is placed in the trachea through a needle inserted through the membrane above or below the second tracheal ring.

Curved dilators can be used to enlarge the stoma. A tracheostomy tube is then inserted into the trachea and the endotracheal tube removed. A modified tapered dilator to avoid the use of multiple dilators is quicker to use, but may cause more tracheal wall injuries and ring fractures. The Griggs technique utilises a Kelly forceps, modified to allow it to be guided by the J-wire, to dilate the tract before insertion of the tracheostomy tube.[23] The speed and safety of the two techniques are similar, although the Griggs technique may cause marginally more bleeding and cannula insertion may be more difficult.[24] Fibreoptic bronchoscopy during percutaneous tracheostomy may help to prevent incorrect guidewire placement and tracheal ring rupture or herniation, but definitive evidence supporting its routine use is lacking.[25]

Minitracheostomy describes the percutaneous insertion of a small 4 mm non-cuffed tracheostomy tube through the cricothyroid membrane or trachea, mainly to facilitate suctioning in patients with poor cough ability. Complications of tracheostomy are listed in Box 29.2.

LOCAL ANAESTHESIA

Instrumentation of the upper airway in awake patients requires good local anaesthesia to increase comfort, improve cooperation, attenuate cardiovascular responses and reduce the risk of laryngospasm. Rapid transcricoid injection, 'spray as you go' with a fibreoptic bronchoscope, or nebulised lidocaine to the nares, posterior pharynx and tongue is effective (Table 29.3).[26] Nerve block techniques may improve analgesia but are not essential. Systemic absorption of topically applied lidocaine (maximum dose 4 mg/kg) is variable, and the clinician should be alert for signs and symptoms of toxicity.

Box 29.2 Complications of tracheostomy

Immediate
- Procedural complications
  - Haemorrhage
  - Surgical emphysema, pneumothorax, air embolism
  - Cricoid cartilage damage
- Misplacement in pretracheal tissues or right main bronchus
- Compression of tube lumen by cuff herniation
- Occlusion of the tip against the carina or tracheal wall

Delayed
- Blockage with secretions
- Infection of the tracheostomy site, tracheobronchial tree, and larynx
- Pressure on tracheal wall from the tracheostomy tube or cuff
  - Mucosal ulceration and perforation
  - Deep erosion into the innominate artery
  - Tracheo-oesophageal fistula

Late
- Granulomata of the trachea
- Tracheal and laryngeal stenosis
- Persistent sinus at tracheostomy site
- Tracheomalacia and tracheal dilatation

Table 29.3 Local anaesthesia of the upper airway in adults

TECHNIQUE	DRUG DOSAGE
NERVE BLOCK	
Internal branch of superior laryngeal nerve	Lidocaine 1%–2% (2 mL/side)
Glossopharyngeal nerve	Lidocaine 1%–2% (3 mL/side)
TOPICAL ANAESTHESIA OF THE TONGUE AND OROPHARYNX	
Gargle	Lidocaine viscous 4% (5 mL)
Commercial lidocaine spray	Lidocaine 10% (5–10 sprays = 50–100 mg)
Nebulised	Lidocaine 4%
Spray as you go	Lidocaine 1%–2%
TOPICAL ANAESTHESIA OF THE NASAL MUCOSA	
Cocaine spray or paste	Cocaine 4%–5% (0.5–2 mL)
Gel	Lidocaine 2% gel (5 mL)
Commercial lidocaine spray	Lidocaine 10% (10 sprays = 100 mg)
Lidocaine laryngeal mask airway + phenylephrine spray	Lidocaine 3% + phenylephrine 0.25% (0.5 mL)
TOPICAL ANAESTHESIA OF GLOTTIS AND TRACHEA	
Spray-as-you-go through bronchoscope	Lidocaine 1%–4% (3 mg/kg)
Cricothyroid membrane puncture	Lidocaine 2% (5 mL)
Nebulised	Lidocaine 4% (4 mL) ± phenylephrine 1% (1 mL)

THE DIFFICULT AIRWAY

The difficult airway has been described as one in which a conventionally trained anaesthesiologist experiences difficulty with mask ventilation, tracheal intubation or both. Difficult intubations may be expected in 1%–3% of patients presenting for general anaesthesia, and the incidence is likely to be considerably higher in ICU patients.

More than 85% of difficult intubations can be managed successfully by experienced clinicians without resorting to a surgical solution. The experience of the operator is probably the most important factor determining success or failure. Experience implies greater manual skills, better anticipation of problems, use of preprepared strategies, and familiarity with multiple techniques. Thus, training of intensivists must specifically include a variety of airway management strategies and skills.

ASSISTANCE AND ENVIRONMENT

The patient's condition may rapidly deteriorate as a consequence of a poorly managed airway emergency. The most senior help available should be immediately summoned. If the situation allows, the patient should be moved to the best location for emergency airway interventions, usually the operating theatre or ICU, and difficult airway equipment requested (see Box 29.1). A senior assistant can help in gaining IV access, administering drugs, setting up equipment and managing the airway. A skilled intensivist or ear, nose and throat surgeon (gowned and standing by) can help to provide a surgical airway or perform rigid bronchoscopy to remove foreign bodies.

ANTICIPATING AND GRADING A DIFFICULT AIRWAY

Intubation difficulty can be anticipated or predicted by the following (although the sensitivity and specificity of individual features and classifications tend to be low):

1. Anatomical or pathological features of difficult intubation in subjects who otherwise appear normal:
   - **a.** short neck, especially if obese or muscular (a thyromental distance <6 cm)
   - **b.** limited neck and jaw movements (e.g. as a result of trismus, osteoarthritis, ankylosing spondylitis, rheumatoid arthritis or perioral scarring)
   - **c.** protruding teeth, small mouth, long high curved palate or receding lower jaw
   - **d.** space-occupying lesions of the oropharynx and larynx
   - **e.** congenital conditions with any of the above features (e.g. Marfan syndrome).
2. Mallampati classification[27] of visualising the oropharyngeal structures (a cooperative sitting patient is required for this assessment, and class >2 predicts possible difficulty):
   - **a.** class 1: visible soft palate, uvula, fauces and pillars
   - **b.** class 2: visible soft palate, uvula and fauces
   - **c.** class 3: visible soft palate and base of uvula
   - **d.** class 4: soft palate is not visible.
3. The degree of difficulty experienced visualising the larynx by direct laryngoscopy should be recorded and is commonly graded by the classification of Cormack and Lehane, and modified by Yentis[28,29]:
   - **a.** grade I: complete glottis is visible
   - **b.** grade IIa: partial view of glottis, and grade IIb: only the posterior part of the cords/arytenoids visible
   - **c.** grade III: epiglottis but not glottis is visible
   - **d.** grade IV: epiglottis is not visible.

FAILED INTUBATION AND VENTILATION ALGORITHMS

A preformulated plan in the event of failed intubation and/or ventilation is essential and a number have been described. The algorithm shown in Fig. 29.1 is an example. Effective implementation depends on the appropriate use of the algorithm and airway techniques described above.

If the initial attempt at intubation fails, call for help immediately. Repeated attempts at direct laryngoscopy should be avoided unless a more experienced operator intervenes, or a potentially helpful manoeuvre has been carried out (e.g. significant repositioning, externally applied laryngeal pressure or change of laryngoscope blade). Hypoxia will quickly result if the patient is inadequately ventilated between attempts. In addition, oedema and bleeding caused by repeated attempts may impair both mask ventilation and the use of alternative techniques such as fibreoptic intubation. When indicated to prevent hypoxia, a surgical airway should not be delayed (see Figs 29.1 and 29.2).

UPPER AIRWAY OBSTRUCTION

ANATOMY AND PATHOPHYSIOLOGY

The upper airway begins at the nose and mouth, and ends at the carina. Obstruction is likely to occur at sites of anatomical narrowing, such as the hypopharynx at the base of the tongue, and the false and true vocal cords at the laryngeal opening. Sites of airway obstruction are classified as supraglottic (above the true cords), glottic (involving the true vocal cords) or infraglottic (below the true cords and above the carina).

The upper airway can also be divided into intrathoracic and extrathoracic portions, which behave differently during inspiration and expiration. The intrathoracic airway dilates during inspiration because it is 'pulled outwards' by negative intrapleural pressure.

Positive intrapleural pressure during expiration causes compression and narrowing. Conversely, the compliant extrathoracic airway, unexposed to intrapleural pressure, collapses during inspiration and expands during expiration. Recalling this phenomenon helps the understanding of typical clinical signs, imaging and flow-volume loops.

AETIOLOGY

Acute upper airway obstruction may result from functional or mechanical causes (Box 29.3). Functional causes include central nervous system and neuromuscular dysfunction. Mechanical causes may occur within the lumen, in the wall or extrinsic to the airway.

Box 29.3 Clinical conditions associated with acute upper airway obstruction

Functional causes
Central nervous system depression
- Head injury, cerebrovascular accident, cardiorespiratory arrest, shock, hypoxia, drug overdose, metabolic encephalopathies

Peripheral nervous system and neuromuscular abnormalities
- Recurrent laryngeal nerve palsy (postoperative, inflammatory or tumour infiltration), obstructive sleep apnoea, laryngospasm, myasthenia gravis, Guillain–Barré polyneuritis, hypocalcaemic vocal cord spasm

Mechanical causes
Foreign-body aspiration
Infections
- Epiglottitis, retropharyngeal cellulitis or abscess, Ludwig angina, diphtheria and tetanus, bacterial tracheitis, laryngotracheobronchitis

Laryngeal oedema
- Allergic laryngeal oedema, angiotensin-converting enzyme inhibitor associated, hereditary angioedema, acquired C1 esterase deficiency

Haemorrhage and haematoma
- Postoperative, anticoagulation therapy, inherited or acquired coagulation factor deficiency

Trauma
Burns
- Inhalational thermal injury, ingestion of toxic chemical and caustic agents

Neoplasm
- Pharyngeal, laryngeal and tracheobronchial carcinoma, vocal cord polyposis

Congenital
- Vascular rings, laryngeal webs, laryngocele

Miscellaneous
- Cricoarytenoid arthritis, achalasia of the oesophagus, hysterical stridor, myxoedema

CLINICAL PRESENTATION

The signs of sudden complete upper airway obstruction are characteristic and progress rapidly. The victim cannot breathe, speak or cough, and may hold the throat between the thumb and index finger – the universal choking sign.[30] Agitation, panic and vigorous breathing efforts are rapidly followed by cyanosis. Respiratory efforts diminish as consciousness is lost, and death results within 2–5 minutes if obstruction is not relieved. Lethargy, diminishing respiratory efforts and loss of consciousness are late signs of hypoxaemia and hypercarbia. Bradycardia and hypotension herald impending cardiac arrest.

Signs of partial airway obstruction include voice changes and coughing, progressing to drooling, gagging, choking, noisy respiration and inspiratory stridor. Paradoxical chest wall movements and intercostal and supraclavicular retractions may be marked in severe obstruction. Powerful respiratory efforts may produce dermal ecchymoses and subcutaneous emphysema. Respiratory decompensation may be of rapid onset, and progress to complete obstruction.

SPECIAL EVALUATION OR INVESTIGATIONS

If the patient remains stable, specific diagnostic evaluation may be undertaken, provided advanced airway management facilities and skilled personnel are immediately available.

LARYNGOSCOPY AND BRONCHOSCOPY

Indirect laryngoscopy in a stable, cooperative patient is useful to diagnose foreign bodies, retropharyngeal or laryngeal masses and other glottic pathology.

Assessment with a flexible fibreoptic bronchoscope or laryngoscope is the evaluation method of choice in ICU patients and enables direct visualisation of upper airway anatomy and function. The procedure can be performed without transporting the patient and risking complete obstruction. It can be applied to an awake, spontaneously breathing patient and, with care, should not worsen the obstruction. Definitive airway control by intubation can usually be achieved. Disadvantages are the need for a skilled operator and a cooperative patient, and a reduced visual field limits effectiveness if blood and secretions are copious.

Direct laryngoscopy enables forceps removal of foreign bodies and high-volume suctioning of blood, vomitus and secretions. Endotracheal intubation can rapidly be achieved under direct vision. A disadvantage is the need for general anaesthesia or good local analgesia (often difficult in the emergency setting). Direct laryngoscopy can be traumatic, and may worsen soft-tissue bleeding and oedema.

RADIOGRAPHIC IMAGING

Patients with potentially unstable airways should not be transported from a ‘safe’ environment like

the emergency room, operating theatre or ICU for radiological investigation until the airway is secure. Anteroposterior and lateral plain neck X-rays may be useful to detect radiopaque foreign bodies. Computed tomography (CT), preferably with three-dimensional postprocessing, may provide detailed diagnostic information and prognostic at initial evaluation in stable patients, or in those in whom the airway has been secured.[31] Although magnetic resonance imaging (MRI) has been used to image the upper airway, its use in acute airway obstruction is unproven.

GAS FLOW MEASUREMENT

Flow-volume loop measurement reveals characteristic patterns corresponding to different types and position of pathological lesions (Fig. 29.3).[32]

MANAGEMENT

Simplified algorithms to assist the management of partial and complete upper airway obstruction are shown in Figs 29.4 and 29.5, respectively. Improvisation may be required for certain difficult problems.

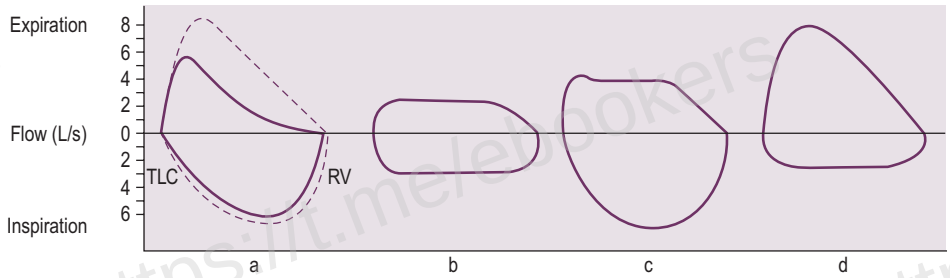


Figure 29.3 Flow-volume loops. Patterns resulting from different pathological lesions: *(a)* lower airway obstruction (e.g. chronic obstructive pulmonary disease or asthma); *(b)* fixed, non-variable upper airway obstruction (e.g. fibrous ring in trachea); *(c)* variable upper airway obstruction, intrathoracic (e.g. tumour in the lower trachea); *(d)* variable upper airway obstruction, extrathoracic (e.g. vocal cord tumour or paralysis). *L/s*, Litres per second; *RV*, residual volume; *TLC*, total lung capacity.

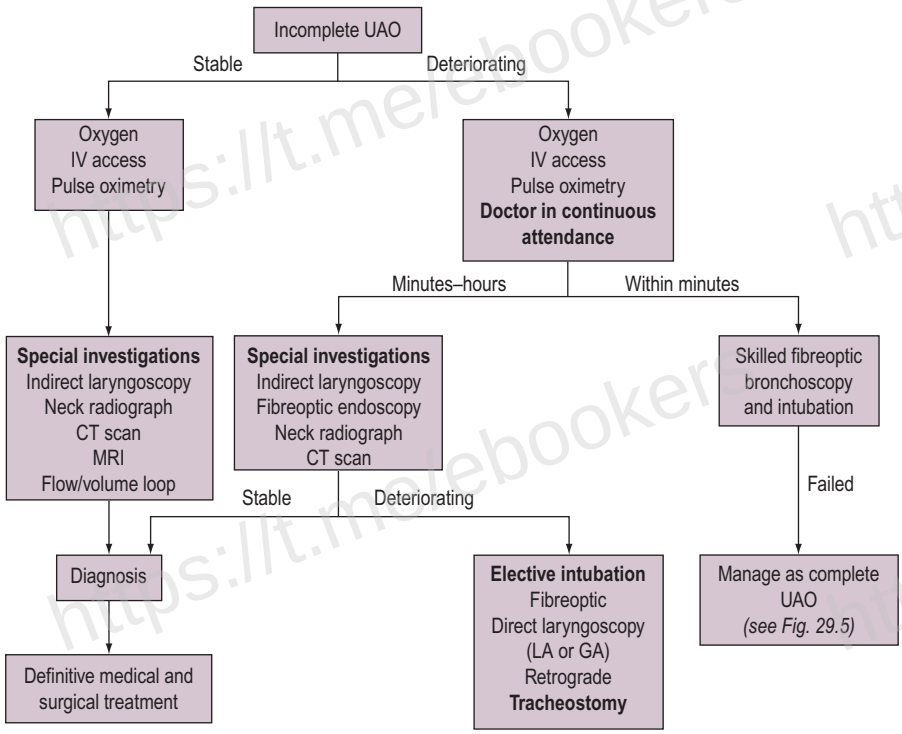


Figure 29.4 Management of partial upper airway obstruction (UAO). *CT*, Computerised tomography; *GA*, general anaesthesia; *IV*, intravenous; *LA*, local anaesthesia; *MRI*, magnetic resonance imaging.

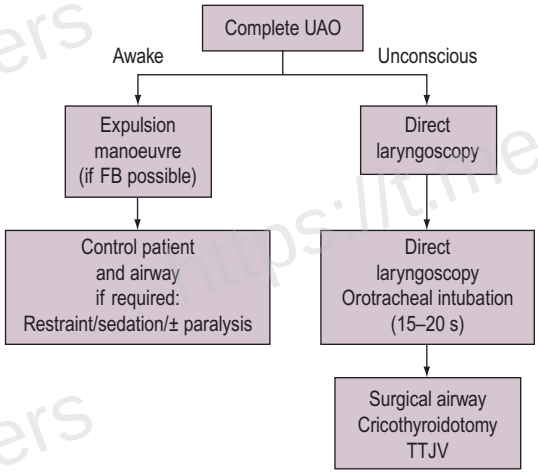


Figure 29.5 Management of complete upper airway obstruction (UAO). Attempts at orotracheal intubation should not take longer than 10–20 seconds. *FB*, Foreign body; *TTJV*, transtracheal jet ventilation.

The chosen technique should be an appropriate one in which the clinician has reasonable skill and experience. Special techniques in patients with suspected cervical spine instability are discussed in Chapter 80.

1. Supplemental oxygen (100%) is immediately administered and adequate help summoned.
2. A choice of equipment for definitive airway control must be available and ready for use (see Box 29.1).
3. In adults IV access should be secured.
4. Initiate continuous monitoring of vital signs and pulse oximetry.
5. The risk and benefit of patient transport before securing the airway must be carefully considered.

AIRWAY MANAGEMENT TECHNIQUES IN AIRWAY OBSTRUCTION

THE UNCONSCIOUS PATIENT

If the upper airway is obstructed by the tongue and retropharyngeal tissues in an unconscious patient, airway patency is initially achieved by using standard airway manoeuvres[33] and oropharyngeal and nasopharyngeal airways. Definitive airway control should follow if consciousness does not immediately return.

ENDOTRACHEAL INTUBATION

1. *Direct laryngoscopic intubation* is the method of choice for the unconscious, apnoeic patient, as it allows rapid evaluation of any supraglottic problem and immediate airway security. *Video laryngoscopy* is an alternative in experienced hands. Both can also be attempted in an awake patient after careful application of local anaesthesia. Although there is some risk of loss of the airway after local anaesthesia, complete loss of the airway under general anaesthesia is common and may be catastrophic.
2. *Awake fibreoptic intubation* in a spontaneously breathing patient is usually safe, but requires a skilled operator. The procedure will take 2–10 minutes or longer,[34] and urgency of the case must be assessed beforehand with this timeframe in mind. Alternatives should be initiated if the obstruction progresses or if intubation fails after a reasonable time. The following points may assist visualisation in acute upper airway obstruction:
   a. The procedure should be clearly explained to the patient.
   b. Good local anaesthesia and mucosal vasoconstrictors are important (see Table 29.3).
   c. If desired, the suction port of the fibrescope can be used to insufflate 100% oxygen or apply local anaesthetic. This also clears the fibrescope tip of secretions. Additional large-bore suction catheters may help. Failure is most commonly due to excessive secretions and bleeding.
3. *Blind nasotracheal intubation* may be considered by experienced operators. Once endotracheal intubation is safely accomplished and confirmed, secure fixation of the endotracheal tube is mandatory. The patient's upper limbs may need to be restrained to avoid self-extubation.

SURGICAL AIRWAYS

A surgical airway is indicated when endotracheal intubation is not possible, or when an unstable cervical spine is threatened by available airway techniques. It is the last line of defence against hypoxia. In airway obstruction, options include the following:

1. *Cricothyroidotomy:* this is the method of choice if severe or complete upper airway obstruction exists.
2. *Percutaneous transtracheal jet ventilation:* the technique must not be used in complete upper airway obstruction because expiratory obstruction can cause severe and potentially fatal barotrauma.
3. *Tracheostomy:* in the emergency setting this is rarely required, although surgical tracheostomy under local anaesthesia may be reasonable under some controlled conditions (see Fig. 29.4).

COMMON CLINICAL CONDITIONS AND THEIR MANAGEMENT

FOREIGN-BODY OBSTRUCTION

Foreign-body obstruction is the most common cause of acute airway obstruction. The elderly, especially those in institutions, are at risk. The use of dentures, alcohol and depressant drugs increases risk. Fatal food asphyxiation or 'café coronary' should be considered in any acute respiratory arrest where the victim cannot be ventilated.[35]

Those still able to cough or speak clearly should be given the opportunity to expel the foreign body spontaneously. Expulsion of the foreign body can be attempted with up to five back blows, followed by the Heimlich manoeuvre.[30,33] Unwanted effects, such as vomiting, aspiration, fractured ribs, barotrauma and ruptured organs, have been reported. If these manoeuvres fail, management immediately proceeds as shown in Figs 29.4 and 29.5.

EXTRINSIC AIRWAY COMPRESSION

Extrinsic space-occupying lesions can cause upper airway obstruction. Compression from haematomas may be associated with trauma, neck surgery, central venous catheterisation, anticoagulants and congenital or acquired coagulopathies. Haematomas following surgery should immediately be evacuated by removing skin and tissue sutures. If this fails, an artificial airway must be secured immediately. In patients with coagulation abnormalities, intubation is preferred over a surgical airway. Most haematomas secondary to coagulopathy do not require surgical intervention, and resolve with conservative therapy (i.e. vitamin K and blood component therapy).

Partial airway obstruction caused by retropharyngeal abscess is best managed by drainage under local anaesthesia. Gentle fibreoptic examination and intubation or direct laryngoscopy and intubation may be considered. Risks are related to inadvertent rupture of the abscess, with subsequent flooding of the airway. Ludwig's angina is a mixed infection of the floor of the mouth resulting in an inflammatory mass in the space between the tongue and the muscles and anterior neck fascia. The supraglottic airway is compressed and becomes narrowed.[36] Direct laryngoscopy is difficult, as the tongue cannot be anteriorly displaced. Awake fibreoptic-guided intubation and a surgical airway, along with antibiotic therapy, are management options.

INTRINSIC AIRWAY COMPRESSION

Burn inhalation and ingestion injury

Patients with large burn area (more than 40%), or with severe facial burns or inhalation injury (soot in the nostrils, burns of the tongue and pharynx, stridor or hoarseness) are at risk of developing progressive supraglottic oedema, usually within 24–48 hours. Such patients may require early prophylactic tracheal intubation. Assessment of injury and need for tracheal intubation can best be decided by frequently repeated awake fibreoptic laryngoscopy, together with close clinical observation.[37] Ingestion of hot fluids or corrosive agents can also cause delayed oedema and airway swelling and should be managed similarly.[38]

Adult epiglottitis

Epiglottitis is an uncommon but increasingly recognised infectious disease in adults.[39] It involves the epiglottis and supraglottic larynx, causing swelling with consequent airway obstruction. *Haemophilus influenzae* and *H. parainfluenzae*, *Streptococcus pneumoniae*, haemolytic streptococci and *Staphylococcus aureus* are common causative organisms. Clinical features are sudden onset of sore throat (pain often greater than suggested by clinical findings), muffled voice, dysphagia, stridor, dyspnoea and respiratory distress. Systemic toxaemia is common. Gentle indirect laryngoscopy, fibreoptic laryngoscopy or lateral neck X-ray confirms the diagnosis. Reported mortality in adults ranges from 0% to 7%.[40]

Airway management is controversial.[40,41] Some experts recommend securing a definitive airway on presentation, whereas others suggest close observation in the ICU. There are, however, reports of sudden obstruction and death with the latter approach.[40] Onset of dyspnoea, dysphonia, stridor, a rapid clinical course and diabetes may predict the need for intubation.[42] Tracheal intubation and tracheostomy are acceptable, but tracheal intubation may result in better long-term outcome.

Prior to securing the airway, patient positioning is important, and changing from a sitting to supine position may induce complete obstruction. In more stable patients, awake fibreoptic intubation is preferable if a skilled operator is available. Endotracheal intubation under general anaesthesia following gaseous induction is often recommended. Obstruction can occur, even when this procedure is undertaken by a skilled anaesthetist in the operating room.[41] A skilled assistant, scrubbed and ready to secure a surgical airway, may prevent disaster. Rapid-sequence induction using muscle relaxants is dangerous and should be avoided. Tracheostomy under local anaesthesia is a safe alternative.

Airway management is followed by antibiotics and supportive care. Cefotaxime 2 g IV 6-hourly or ampicillin 1–2 g IV 6-hourly *plus* chloramphenicol 50 mg/kg per day are empirical regimens. Patient factors, local bacterial sensitivities and cultures of blood and epiglottal swabs may influence the antibiotic choice. Supportive care includes adequate sedation and tracheobronchial toilet. Abscesses should be surgically drained. There is no good evidence supporting the use of steroids.

Angioedema

Allergic responses involving the upper airway may be localised or part of a systemic anaphylactic reaction. Angioedema is characterised by subepithelial swelling. Angioedema of the lips, supraglottis, glottis and infraglottis may result in airway obstruction. The systemic reaction consists of variable combinations of urticaria, bronchospasm, shock, cardiovascular collapse and abdominal pain. Common causative agents are Hymenoptera stings, shellfish ingestion and drugs.

Treatment consists of immediately ensuring an adequate airway (see Figs 29.4 and 29.5), and

administration of oxygen, epinephrine (adrenaline), histamine antagonists and steroids. Close observation in case of relapse for at least 24 hours after severe reactions is necessary. As it is likely to recur, the patient should be followed-up and fully investigated.

Hereditary angioedema is a rare, inherited disorder of the complement system, caused by functionless or low levels of C1 esterase inhibitor.[43] Non-pruritic, usually non-painful angioedema involving skin and subcutaneous tissue occurs in various locations, including the upper airway.[44] Precipitating causes include stress, physical exertion and localised trauma (including dental or maxillofacial surgery and laryngoscopy). Acute attacks do not respond to epinephrine, antihistamines or corticosteroids. Management consists of establishing a secure airway and infusion of C1 esterase inhibitor concentrate (25 U/kg) which has an onset of action of 30–120 minutes.[44,45] If not available, fresh frozen plasma (2–4 units) may be considered.

Stanozolol 2 mg daily or danazol 200 mg/day has been shown to be effective in decreasing frequency and severity of attacks with reduced side effects.[46] Antifibrinolytic agents (e.g. tranexamic acid) are less effective. Guidelines recommend use of C1-inhibitor concentrate for preoperative prophylaxis or, if this is unavailable, the dose of attenuated androgen should be doubled for 5 days before and 2 days after the procedure. Icatibant acetate, a subcutaneous synthetic peptide blocker of the bradykinin-2 receptor, and ecallantide, a subcutaneous recombinant protein kallikrein antagonist, have both recently become available for the symptomatic treatment of hereditary angioedema.[46] Angiotensin-converting enzyme inhibitor-related angioedema is increasingly seen and is possibly the result of reduced bradykinin metabolism.[47] Treatment focuses on airway support.

Postextubation laryngeal oedema

Laryngeal oedema following extubation occurs in about 20% of adults, but is severe enough to precipitate reintubation in only 1%–5%. The risk of postextubation oedema may be increased by excessive airway manipulation, traumatic intubation, high cuff pressures and duration of tracheal intubation greater than 36 hours (however, after 1 week the risk appears to decline again). Prophylactic use of corticosteroids (e.g. methylprednisolone initiated 12 hours before planned extubation at 20 mg IV 4-hourly with the last dose immediately prior to tube removal) has been shown to reduce the incidence of postextubation laryngeal oedema and subsequent reintubation.[48] Treatment in adults is conservative, with close observation and humidified oxygen therapy. Nebulised plain epinephrine (1–2 mL 1:1000 solution diluted with 2 mL saline or undiluted 1:1000 solution 4–5 mL) or racemic epinephrine (0.25–0.5 mL 2.25% solution in 2–4 mL saline) have been used. Nebulisation may need to be repeated every 30–60 minutes.

Postobstruction pulmonary oedema

Postobstruction pulmonary oedema, also known as negative-pressure pulmonary oedema, may occur after general anaesthesia (incidence 0.05%–0.1%) or after relief of acute upper airway obstruction (incidence 11%).[49] This appears to be related to the markedly decreased intrathoracic pressure caused by forced inspiration against a closed upper airway, resulting in transudation of fluid from pulmonary capillaries to the interstitium. In addition, increased venous return may increase pulmonary blood flow and pressure, further worsening oedema. Hypoxia, the hyperadrenergic stress state, and increased ventricular afterload may also affect capillary hydrostatic pressure, although pulmonary capillary occlusion pressure is often normal. The oedema usually occurs within minutes after the relief of the obstruction, but may be delayed several hours.[50] Management includes the application of continuous positive-airways pressure or positive-pressure ventilation with PEEP, maintenance of airway patency, oxygen therapy, diuretics, morphine and fluid restriction.

REFERENCES

1. Practice guidelines for management of the difficult airway. An updated report by the American Society of Anesthesiologists Task Force on management of the difficult airway. *Anesthesiology*. 2003;98:1269–1277.
2. Henderson JJ, Popat MT, Latto IP, et al. Difficult Airway Society guidelines for management of the unanticipated difficult intubation. *Anaesthesia*. 2004;59:675–694.
3. Brain AIJ. The laryngeal mask: a new concept in airway management. *Br J Anaesth*. 1983;55:801–805.
4. De Montblanc J, Ruscio L, Mazoit JX, et al. A systematic review and meta-analysis of the i-gel vs laryngeal mask airway in adults. *Anaesthesia*. 2014;69:1151–1162.
5. Maitra S, Khanna P, Baidya DK. Comparison of laryngeal mask airway Supreme and laryngeal mask airway Pro-Seal for controlled ventilation during general anaesthesia in adult patients: systematic review with meta-analysis. *Eur J Anaesthesiol*. 2014;31:266–273.
6. Park SK, Choi GJ, Choi YS, et al. Comparison of the i-gel and the laryngeal mask airway proseal during general anesthesia: a systematic review and meta-analysis. *PLoS ONE*. 2015;10:e0119469.
7. Frass M, Frenzer R, Rauscha F, et al. Evaluation of esophageal tracheal combitube in cardiopulmonary resuscitation. *Crit Care Med*. 1986;15:609–611.
8. Konrad C, Schupfer G, Witlisbach M, et al. Learning manual skills in anesthesiology: is there a recommended number of cases for anesthetic procedures? *Anesth Analg*. 1998;86:635–639.
9. Dodek P, Keenan S, Cook D, et al. Evidence-based clinical practice guideline for the prevention of

ventilator-associated pneumonia. *Ann Intern Med*. 2004;141:305–313.
10. Niforopoulou P, Pantazopoulos I, Demestiha T, et al. Video-laryngoscopes in the adult airway management: a topical review of the literature. *Acta Anaesthesiol Scand*. 2010;54:1050–1061.
11. De Jong A, Clavieras N, Conseil M, et al. Implementation of a combo videolaryngoscope for intubation in critically ill patients: a before-after comparative study. *Intensive Care Med*. 2013;39: 2144–2152.
12. Lascarrou JB, Boisrame-Helms J, Bailly A, et al. Video laryngoscopy vs direct laryngoscopy on successful first-pass orotracheal intubation among ICU patients: a randomized clinical trial. *JAMA*. 2017;317: 483–493.
13. Ovassapian A. Fibreoptic assisted airway management. *Acta Anaesthesiol Scand*. 1997;110(suppl): 46–47.
14. Reilly PM, Schapiro MB, Malcynski JT. Percutaneous dilation tracheostomy under the microscope: justification for intra-procedural bronchoscopy? *Intensive Care Med*. 1999;25:3–4.
15. Dhara SS. Retrograde tracheal intubation. *Anaesthesia*. 2009;64:1094–1104.
16. Tinker JH, Dull DL, Caplan RA. Role of monitoring devices in prevention of anesthetic mishaps: a closed claim analysis. *Anesthesiology*. 1989;71:541.
17. Benumof JL, Scheller MS. The importance of transtracheal jet ventilation in the management of the difficult airway. *Anesthesiology*. 1989;71: 769–778.
18. Kress TD, Balasubramaniam S. Cricothyroidotomy. *Ann Emerg Med*. 1982;11:197–201.
19. Pryor JP, Reilly PM, Schapiro MB. Surgical airway management in the intensive care unit. *Crit Care Clin*. 2000;16:473–488.
20. Delaney A, Bagshaw SM, Nalos M. Percutaneous dilatational tracheostomy versus surgical tracheostomy in critically ill patients: a systematic review and meta-analysis. *Crit Care*. 2006;10:R55.
21. Silvester W, Goldsmith D, Uchino S, et al. Percutaneous versus surgical tracheostomy: a randomized controlled study with long-term follow-up. *Crit Care Med*. 2006;34:2145–2152.
22. Ciaglia P, Firsching R, Syniec C. Elective percutaneous dilatational tracheostomy. *Chest*. 1985; 87:715–719.
23. Griggs WM, Worthley LIG, Gilligan JE, et al. A simple percutaneous tracheostomy technique. *Surg Gynecol Obstet*. 1990;170:543–545.
24. Nates JL, Cooper DJ, Myles PS, et al. Percutaneous tracheostomy in critically ill patients: a prospective, randomized comparison of two techniques. *Crit Care Med*. 2000;28:3734–3739.
25. Jackson LS, Davis JW, Kaups KL, et al. Percutaneous tracheostomy: to bronch or not to bronch – that is the question. *J Trauma*. 2011;71:1553–1556.
26. Koerner IP, Brambrink AM. Fiberoptic techniques. *Best Pract Res Clin Anaesthesiol*. 2005;19:611–621.
27. Mallampatti SR, Gugino LD, Desai SP, et al. A clinical sign to predict difficult tracheal intubation: a prospective study. *Can J Anaesth*. 1985;32: 429–434.
28. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia*. 1984;39:1105–1111.
29. Yentis SM, Lee DJ. Evaluation of an improved scoring system for the grading of direct laryngoscopy. *Anaesthesia*. 1998;53:1041–1044.
30. Heimlich HJ. A life saving maneuver to prevent food-choking. *JAMA*. 1975;234:398–401.
31. Angood PB, Attia EL, Brown RA, et al. Extrinsic civilian trauma to the larynx and cervical trachea – important predictors of long term morbidity. *J Trauma*. 1986;26:869–873.
32. Miller RD, Hyatt RE. Evaluation of obstructing lesions of the trachea and larynx by flow volume loops. *Am Rev Respir Dis*. 1973;108:475–481.
33. Perkins GD, Handleyc AJ, Kosterd RW, et al. European Resuscitation Council Guidelines for Resuscitation 2015 Section 2. Adult basic life support and automated external defibrillation. *Resuscitation*. 2015;95:81–99.
34. Afilalo M, Guttman A, Stern E, et al. Fibreoptic intubation in the emergency department: a case series. *J Emerg Med*. 1993;11:387–391.
35. Mittleman RE, Wetli CV. The fatal café coronary: foreign body airway obstruction. *JAMA*. 1982;247: 1285–1288.
36. Barakate MS, Jensen MJ, Hemli JM, et al. Ludwig's angina: report of a case and review of management issues. *Ann Otol Rhinol Laryngol*. 2001;110:453–456.
37. Muehlberger T, Kunar D, Munster A, et al. Efficacy of fibreoptic laryngoscopy in the diagnosis of inhalation injuries. *Arch Otolaryngol Head Neck Surg*. 1998;124:1003–1007.
38. Joynt GM, Ho KM, Gomersall CD. Delayed upper airway obstruction. A life-threatening complication of Dettol poisoning. *Anaesthesia*. 1997;52:261–263.
39. Syed I, Odutoye T, Lee MS, et al. Management of acute epiglottitis in adults. *Br J Hosp Med*. 2011;72: M74–M76.
40. Mathoera RB, Wever PC, van Dorsten FR, et al. Epiglottitis in the adult patient. *Neth J Med*. 2008;66: 373–377.
41. Ames WA, Ward VM, Tranter RM, et al. Adult epiglottitis: an under-recognized, life-threatening condition. *Br J Anaesth*. 2000;85:795–797.
42. Katori H, Tsukuda M. Acute epiglottitis: analysis of factors associated with airway intervention. *J Laryngol Otol*. 2005;119:967–972.
43. Donaldson VH, Evans RR. A biochemical abnormality in hereditary angioneurotic edema: absence of serum inhibitor of C'1-esterase. *Am J Med*. 1963;35:37–44.
44. Joynt GM, Abdullah V, Wormald PJ. Hereditary angioedema: report of a case. *Ear Nose Throat J*. 2001;80: 321–324.
45. Bork K, Barnstedt SE. Treatment of 193 episodes of laryngeal edema with C1 inhibitor concentrate in

patients with hereditary angioedema. *Arch Intern Med*. 2001;161:714–718.
46. Longhurst H, Cicardi M. Hereditary angio-oedema. *Lancet*. 2012;379(9814):474–481.
47. Agostoni A, Cicardi M, Cugno M, et al. Angioedema due to angiotensin-converting enzyme inhibitors. *Immunopharmacology*. 1999;44:21–25.
48. François B, Bellissant E, Gissot V, et al. 12-h pretreatment with methylprednisolone versus placebo for prevention of postextubation laryngeal oedema: a randomised double-blind trial. *Lancet*. 2007;369(9567):1083–1089.
49. Tami TA, Chu F, Wildes TO, et al. Pulmonary edema and acute upper airway obstruction. *Laryngoscope*. 1986;96:506–509.
50. Udeshi A, Cantie SM, Pierre E. Postobstructive pulmonary edema. *J Crit Care*. 2010;25:508.e1–508.e5.

30

Acute respiratory failure in chronic obstructive pulmonary disease

Matthew T Naughton, David V Tuxen

The term chronic obstructive pulmonary disease (COPD) is applied to patients with chronic bronchitis and/or emphysema. COPD affects up to 10% of the adult population aged greater than 40 years and is the fourth most common cause of death worldwide.[1] COPD is increasing in prevalence, particularly in women.[2] COPD is commonly associated with cardiovascular disease, depression, gastro-oesophageal reflux, osteoporosis and cancer.[3,4] Severity of COPD can be easily assessed objectively by spirometry[5] (Table 30.1) and functionally based upon dyspnoea and exercise capacity (Table 30.2).[6]

An acute exacerbation of COPD (AECOPD) is defined as 'an event in the natural course of the disease characterised by change in dyspnoea, cough or sputum'.[4] AECOPD is the most common admission diagnosis in UK general hospitals (~16% of admissions).[4] Patients with an AECOPD have an in-hospital mortality of 3%–8%, and a 30-day readmission rate of 23%, and a 30-day mortality of 14%–26% (compared with 8% for myocardial infarction).[4,7–9] Targeted oxygen therapy and non-invasive ventilatory (NIV) support have been the major advances in therapy in the past decade which have resulted in a reduced need for invasive mechanical ventilation (IMV) and improved survival. The need for either IMV or NIV ventilatory support in AECOPD varies considerably across continents; for example, in the United Kingdom, NIV and IMV are used in 11% and 1% of admissions, respectively,[8] whereas in the United States they are used in 5% and 3% of admissions, respectively.[9]

AETIOLOGY

The causes of COPD can be divided into environmental and host factors. Environmental factors include tobacco smoke, air pollution, indoor fumes (e.g. indoor cooking with solid biomass fuel) and poor socioeconomic status. The biggest single factor in over 95% of patients with COPD is tobacco smoking. However, only approximately 15% of smokers develop COPD. Marijuana smoking may cause premature and quite advanced bullous emphysema compared with tobacco smokers due to extremely hot and toxic inhaled smoke held at peak inspiration for prolonged periods of time.[3] Host factors are the balance between circulating proteases and antiproteases (e.g. alpha-1 antitrypsin deficiency) and the intake of antioxidant vitamins (A, C, E) (Fig. 30.1).[10]

PATHOPHYSIOLOGY

Reduced expiratory airflow in COPD is due to both increased airway resistance and reduced lung elastic recoil. Airway resistance is increased by mucosal oedema and hypertrophy, secretions, bronchospasm, airway tortuosity and airflow turbulence and loss of lung parenchymal elastic tissues that normally support the small airways. Loss of lung elastic recoil pressure is due both to loss of lung elastin and loss of alveolar surface tension from alveolar wall destruction.

Reduced lung elastic recoil decreases expiratory airflow by reducing the alveolar pressure driving expiratory airflow and by reducing the intraluminal airway pressure, which normally distends small airways during expiration. Forced expiration increases alveolar driving pressure but also causes dynamic airway compression, resulting in no improvement or sometimes reduction in expiratory airflow. These factors are present in varying proportions, depending on the degree of chronic bronchitis and emphysema and the individual patient.

Airflow limitation results in prolonged expiration, pulmonary hyperinflation, inspiratory muscle disadvantage, increased work of breathing and the sensation of dyspnoea. All these factors are worsened during an exacerbation of COPD.

Pulmonary hyperinflation has both static and dynamic components. The static component remains at the end of an expiratory period long enough for all expiratory airflow to cease (30–120 seconds), enabling the lungs and chest wall to reach their static functional residual capacity (FRC). This component of hyperinflation is due to loss of parenchymal elastic recoil, chest wall adaptation and airway closure that occurs throughout expiration.[12] Dynamic pulmonary hyperinflation is the further increase in hyperinflation due to slow expiratory airflow not allowing completion of

ABSTRACT

Although acute exacerbations of chronic obstructive pulmonary disease (COPD) are most commonly due to bacterial or viral chest infections and underlying cardiac disease (arrhythmias and heart failure), a thorough history and examination should be undertaken to confirm a precise precipitant (e.g. social, nutritional, gastroreflux). Early assessment with blood gases will help identify the third who will develop hypercapnic respiratory failure. In addition to glucocorticoids, bronchodilators and antibiotics (if infective), targeted oxygen therapy to a desired SpO_2 range should be instigated. Note uncontrolled oxygen therapy often causes severe hypercapnic respiratory failure. Attention to underlying cardiac factors (arrhythmia or pump failure) should also be considered. In those with hypercapnic acidosis, non-invasive ventilatory (NIV) support should be considered; if used correctly, it should negate the need for invasive ventilatory support. Nasal high flow (NHF) cannula, which provides a heated humidified air-oxygen mixture with a small amount of positive end-expiratory pressure via comfortable wide-bore nasal pillows, may help those COPD patients with high oxygen needs (>3 lpm), yet normal CO_2 values. Pre-discharge assessment should include confirmation of COPD with spirometry, smoking cessation, vaccination, rehabilitation and need for domiciliary oxygen and/or NIV. The 30-day mortality (14%–26%) and readmission rate (23%) are useful metrics of successful treatment.

KEYWORDS

Chronic obstructive lung disease
acute respiratory failure
non-invasive ventilation
airways disease

Table 30.1 Global initiative for obstructive lung disease criteria for chronic obstructive pulmonary disease severity based upon spirometry[5]

	FEV1/FVC (%)	FEV1 (% PREDICTED)
1	<70	>80
2	<70	50–80
3	<70	30–50
4	<70	<30

FEV_1, Forced expiratory volume in 1 second; *FVC*, forced vital capacity.

Table 30.2 The body mass index, airflow obstruction, dyspnoea and exercise capacity index (maximum is 10)

SCORE	0	1	2	3
FEV_1 (% predicted)	>65	50–64	36–49	<35
Six-minute walk distance (meters)	>350	250–350	150–250	<150
Modified MRC dyspnoea score	0–1	2	3	4
Body mass index (kg/m^2)	>21	<21		

The 4-year survival rates are 80% for a score of 2, 70% for 3–4, 60% for 5–6 and 20% for scores 7–10. Modified Medical Research Council (MRC) score is from zero (no dyspnoea) to 4 (extreme dyspnoea upon getting dressed or leaving the house).

FEV_1, Forced expiratory volume in 1 second.

From Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350(10):1005-1012.

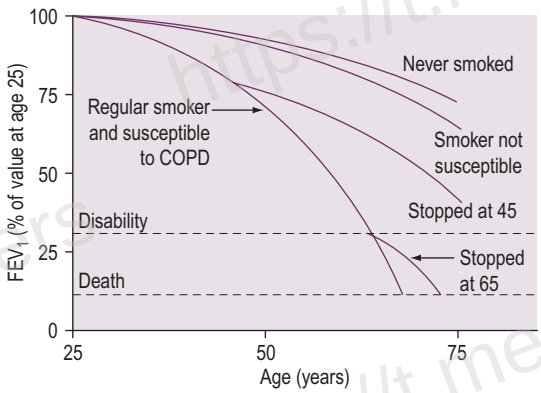


Figure 30.1 Decline in lung function with age in different smoking categories. *COPD*, Chronic obstructive pulmonary disease[11]; *FEV1*, forced expiratory volume in 1 second.

expiration before the arrival of the next breath. The extent of dynamic hyperinflation depends on the severity of airflow obstruction, the amount inspired (tidal volume) and the expiratory time.[13] Chest wall hyperinflation leads to suboptimal muscle length-tension relationships and mechanical disadvantage, thereby predisposing patients to respiratory muscle fatigue, as the work of breathing increases, particularly if associated with myopathic situations (steroids, electrolyte disturbances).[14,15] Minor reductions in lung function due to infection, mild cardiac failure or atelectasis increase the work of breathing due to both increases in respiratory impedance and increases in dead space. With acute changes in workload, rapid decompensation with ventilatory failure and acute hypercapnia may occur.

Although chronic hypercapnia, as a consequence of reducing minute ventilation, is a fatigue-sparing mechanism that occurs in some patients, this is usually accompanied by renal compensation with retention of bicarbonate ions to correct the low pH. This has the additional effect of reducing the respiratory distress caused by hypercapnic acidosis. Central respiratory drive may also be impaired, or poorly responsive to physiological triggers – hypoxaemia or hypercapnia – and lead to chronic hypercapnia. This may occur in the setting of sleep (i.e. obstructive sleep apnoea),[12] obesity or drugs (sedatives, antiepileptics, alcohol).

Hypoxia and vascular wall changes lead to pulmonary vasoconstriction, pulmonary hypertension, cor pulmonale, V/Q mismatching, and the development of shunts.

CHRONIC BRONCHITIS OR EMPHYSEMA?

The value of labelling patients as chronic bronchitis or emphysema is uncertain as the two disease processes usually coexist and the principles of management are similar. Five pathophysiological processes may be present to varying degrees in each patient with COPD: (1) inflammatory airway narrowing (bronchiolitis); (2) loss of connective tissues tethering airways; (3) loss of alveoli and capillaries; (4) hyperinflation; and (5) increased pulmonary vascular resistance. Early/mild COPD tends to be dominated by bronchiolitis with a minimal component of emphysema, whereas when COPD becomes severe, the reverse is true. However, recognition that COPD is dominated by one of these patterns is helpful with regard to clinical pattern and prognosis.

PRECIPITANTS OF ACUTE RESPIRATORY FAILURE

In approximately 50% of patients, there is an infective cause, in 25% heart failure and in the remaining 25% retained secretions, air pollution, co-existent medical problems (e.g. aspiration, pulmonary embolus, medication compliance or side effects), social issues or no cause can be identified (Box 30.1).[15,16]

INFECTION

The most common bacterial isolates are *Streptococcus pneumoniae* and *Haemophilus influenzae* in 80% of

Box 30.1 Precipitants of acute respiratory failure in chronic obstructive pulmonary disease

- Infective (including aspiration)
- Left ventricular failure (systolic and diastolic failure)
- Sputum retention (postoperative, traumatic)
- Pulmonary embolism
- Pneumothoraces and bullae
- Uncontrolled oxygen
- Sedation
- Medication – non-compliance or side effects
- Nutritional (K, PO_4, Mg deficiency, CHO excess)
- Sleep apnoea

exacerbations. *Streptococcus viridans*, *Moraxella* (previously *Branhamella*) *catarrhalis*, *Mycoplasma pneumoniae* and *Pseudomonas aeruginosa* may also be found. Viruses can be isolated in 20%–30% of exacerbations and include rhinovirus, influenza and parainfluenza viruses, coronaviruses and occasionally adenovirus, and respiratory syncytial virus. Whether these organisms are pathogens or colonisers is often unclear. Background microbiological agents are identified in 48% of stable COPD compared with 70% during an AECOPD.[17,18] Pneumonia has been estimated to account for 20% of presentations requiring mechanical ventilation.[4]

HEART FAILURE

Left ventricular (LV) systolic failure may result from co-existing ischaemic heart disease, fluid overload, tachyarrhythmias (e.g. atrial fibrillation) or biventricular failure secondary to cor pulmonale. LV diastolic failure occurs commonly and is precipitated by hypoxaemia, tachycardia, pericardial constraint due to intrinsic positive end-expiratory pressure (PEEPi) or right ventricular (RV) dilation.[12,19,20] Increased work of breathing related to COPD will also increase by up to 10-fold the amount of blood flow to the respiratory pump muscles,[21] thereby causing an increased demand upon the overall cardiac output. In patients with borderline cardiac status, this may precipitate heart failure. The components of RV and LV failure can be accurately distinguished by Doppler echocardiography. Pulmonary congestion can be difficult to diagnose because of the abnormal breath sounds and chest X-ray appearance which are commonly present in COPD. In a recent publication, 51% of patients with AECOPD had echocardiographic evidence of left heart failure (systolic 11%, diastolic 32%, systolic and diastolic 7%).[12] A further study of computed tomography (CT) and magnetic resonance (MR) scanning and echocardiography in a large community population (15% of whom had COPD) identified that severity of emphysema on CT scanning indirectly correlated with LV end diastolic volume, stroke volume and cardiac output.[19] These authors concluded that increasing severity of COPD was associated with worsening cardiac function.

UNCONTROLLED OXYGEN

This may precipitate acute hypercapnia in patients with more severe COPD due to: (1) shunting blood to low-V/Q lung units and increasing dead space; (2) loss of hypoxic drive; (3) dissociation of CO_2 from Hb molecule (Haldane effect); and (4) anxiolysis and reduction in tachypnoea.[22] Major randomised controlled trials have indicated significant reductions in need for IMV, hospital length of stay and mortality with targeted oxygen therapy (i.e. a specific SpO_2 range – e.g. 88%–92%) compared with uncontrolled oxygen therapy in ambulance,[22] emergency rooms[23] and hospital wards.[8]

DIAGNOSIS AND ASSESSMENT

The clinical examination findings of COPD should be confirmed and severity quantified by spirometry (see Tables 30.1 and 30.2). In mild stable disease (e.g. forced expiratory volume in 1 second [FEV1] >50% predicted normal), an expiratory wheeze on forced expiration and mild exertional dyspnoea may be the only symptoms.

In moderate-severity COPD (e.g. FEV1 30%–50% predicted normal), modest to severe exertional dyspnoea is associated with clinical signs of hyperinflation (ptosed upper border of liver beyond the fourth intercostal space anteriorly and loss of cardiac percussion) and signs of increased work of breathing (use of accessory muscles and tracheal tug).

In severe stable COPD (e.g. FEV1 <30% predicted normal), marked accessory muscle use is associated with tachypnoea at rest, pursed-lip breathing, hypoxaemia and signs of pulmonary hypertension (RV heave, loud and palpable pulmonary second sound and elevated a-wave in jugular venous pressure [JVP]) and cor pulmonale (elevated JVP, hepatomegaly, ankle swelling).

In severe unstable COPD, there is marked tachypnoea at rest, hypoxaemia and tachycardia, and, in some, signs of hypercapnia (dilated cutaneous veins, blurred vision, headaches, obtunded mentation, confusion).

Clinical examination may also identify associated medical conditions that might have precipitated the exacerbation such as crackles and bronchial breathing due to infection, crackles and cardiomegaly related to heart failure or mediastinal shift related to a pneumothorax. Acute respiratory failure (ARF) in COPD can present with two distinct clinical patterns (Table 30.3),[16] namely, relatively thin and normocapnic or obese and hypercapnic.

Table 30.3 Clinical differences between normocapnic and hypercapnic chronic obstructive pulmonary disease

NORMOCAPNIC ($PaCO_2$ 35–45 mm Hg)	HYPERCAPNIC ($PaCO_2$ >45 mm Hg)
Emphysema > chronic bronchitis	Chronic bronchitis > emphysema
Thin	Obese
Pursed-lip breathing	Central nervous system depression: consider the role of oxygen therapy
Accessory muscle use	Alcohol, sedatives, analgesics
Hyperinflated	Sleep-related hypoventilation
Right heart failure late	Right heart failure early

Basic investigations such as spirometry are very useful in confirming a clinical diagnosis and determining severity of disease. An FEV1/VC ratio less than 70% with an FEV1 of 50%–80% predicted normal without a bronchodilator response usually indicates mild COPD. A significant bronchodilator response, which implies asthma, is regarded as a 12% or greater increase and 200 mL increase in either FEV1 or vital capacity (VC). An FEV1 30%–50% predicted normal indicates moderately severe COPD and FEV1 less than 30% predicted normal indicates severe COPD.[5]

Flow-volume curves usually demonstrate reduced expiratory flow rates at various lung volumes and the characteristic concave expiratory flow pattern. Lung volumes measured by either helium dilution or plethysmography show elevated total lung capacity, FRC and residual volume. Characteristically, the residual volume/total lung capacity ratio is greater than 40% in COPD and represents intrathoracic gas trapping. The total lung carbon monoxide (TLCO) uptake is a measurement of alveolar surface area and its reduction approximates the amount of emphysema present (usually <80% predicted normal).

A chest X-ray will commonly show hyperinflated lung fields, as suggested by 10 ribs visible posteriorly, six ribs visible anteriorly or large airspace anterior to heart (> ⅓ of the length of the sternum), flattened diaphragms (best seen on lateral chest X-ray) and a paucity of lung markings. Pulmonary hypertension is manifest by enlarged proximal and attenuated distal vascular markings and by RV and atrial enlargement. Lung bullae may be evident.

A high-resolution CT scan of the chest (1–2-mm slices) can demonstrate characteristic appearance and regional distribution of emphysema. It can also assess any co-existent bronchiectasis, LV failure and pulmonary fibrosis. Such scans are less sensitive than standard chest CT scans (1-cm slice) for detecting pulmonary lesions (e.g. neoplasms). Nuclear ventilation perfusion scans can also provide a characteristic appearance of COPD.

An electrocardiogram (ECG) is commonly normal but may show features of right atrial or RV hypertrophy and RV strain, including P pulmonale, right-axis deviation, dominant R-waves in V1–2, right bundle-branch block, ST depression and T-wave flattening or inversion in V1–3. These changes may be chronic or may develop acutely if there is significant increase in pulmonary vascular resistance during the illness. The ECG may also show co-existent ischaemic heart disease, tachycardia and atrial fibrillation. Occasionally, continuous ECG monitoring is required to identify transient arrhythmias, which may also precipitate acute deterioration. Plasma brain natriuretic peptide (BNP) levels may also assist in the diagnosis of heart failure (elevated BNP) from pulmonary causes (low BNP) in patients under 70 years free of renal impairment.[24]

DIFFERENTIAL DIAGNOSIS

The history of chronic asthma is one of long-term dyspnoea, wheeze and cough, usually at night or upon exercise, beginning in childhood with clear-cut precipitating agents (e.g. weather, dust, pets, drugs) and a favourable response to either steroids or inhaled β2-agonists. Late-onset asthma (>40 years of age) is not uncommon and is often associated with recurrent gastro-oesophageal reflux. In both forms of asthma, TLCO is normal. There is usually a bronchodilator response in the FEV1 if the patient has unstable asthma. In patients in whom asthma is considered but lung function tests are normal, the FEV1 response to an inhalational challenge (e.g. methacholine or hypertonic saline) may assist in discriminating asthma from other causes of dyspnoea.

Bronchiolitis obliterans is a condition which presents as a fixed airflow obstruction following a viral illness, inhalation of toxic fumes, following bone marrow or heart/lung transplantation, or related to drugs (e.g. penicillamine). It generally begins as a cough some weeks after insult and insidious onset of dyspnoea. There is a broad spectrum of radiological appearances from normal to reticulonodular to diffuse nodular. Lung tissue via bronchoscopy or by thoracoscopy is required for diagnosis. Histologically, there is a characteristic chronic bronchiolar inflammation appearance, and if granulation tissue extends into the alveoli, it is referred to as bronchiolitis obliterans or organising pneumonia. Removal of the offending agent and instigation of steroids are generally associated with a favourable prognosis.

Bronchiectasis is often associated with fixed mild-to-moderate airflow obstruction. A chronic productive cough (daily for 2 consecutive years) is characteristic. Clinical features such as clubbing, localised pulmonary crackles and a characteristic appearance on

high-resolution CT, with dilated or plugged small airways at least twice the size of accompanying blood vessel, assist in the diagnosis.

Congestive heart failure (CHF) may be a differential diagnosis of COPD, or simply co-exist, as both disorders are common in smokers.[12] Orthopnoea and paroxysmal nocturnal dyspnoea are features which correlate with heart failure severity. A past history of myocardial ischaemia or atrial fibrillation should alert one to the possibility of heart failure. An echocardiogram and high-resolution CT (looking for shift in interstitial oedema with changes in posture from supine to prone)[25] are sensitive markers of CHF.

ASSESSMENT OF RESPIRATORY FAILURE

An AECOPD is defined as 'an event in the natural course of the disease characterised by change in dyspnoea, cough or sputum'.[4]

Arterial blood gases are mandatory to assess hypoxia, hypercapnia and acid-base status. Chronic hypercapnia may be recognised by a bicarbonate level greater than 30 mmol/L and a base excess greater than 4 mmol/L indicating renal compensation. However, other causes of a high serum bicarbonate need to be excluded (e.g. diuretic therapy, high-dose steroids or high-volume gastric fluid loss) or chronic hypercapnia may be incorrectly assumed and the severity of COPD overestimated. Renal compensation for chronic hypercapnia will increase the serum bicarbonate by approximately 4 mmol/L for each 10 mm Hg (1.33 kPa) of chronic $PaCO_2$ rise above 40 mm Hg (5.3 kPa), in order to return pH to the low-normal range. Irrespective of the COPD patient's usual $PaCO_2$ level, an acute increase in $PaCO_2$ leads to a decreased arterial pH. This indicates that compensatory mechanisms are exhausted and there is an increased risk of respiratory collapse. The agreement between arterial and peripheral venous blood gases in terms of pH or $PaCO_2$ is extremely poor (±0.1 and ±25 mm Hg, respectively).[26] Thus, the use of peripheral venous blood gases to assess respiratory failure should be used with great caution.

MANAGEMENT OF RESPIRATORY FAILURE

NON-VENTILATORY MANAGEMENT

TARGETED OXYGEN THERAPY

Oxygen given by low-flow intranasal cannulae or 24%–35% Venturi mask should be titrated to achieve a targeted saturation using pulse oximetry (SpO_2) of 88%–92%, as these levels will avoid significant increases in $PaCO_2$ in the majority of COPD patients with ARF. Increases in $PaCO_2$ are most common in patients with initial $PaCO_2$ greater than 50 mm Hg and pH less than 7.35.[27] Excessive oxygen therapy is the cause of increased hypercapnia in a third of acidaemic AECOPD patients.[8] For this reason, ABGs should be repeated 1 hour following initiation of oxygen therapy, as with NIV, to ensure an optimal direction of improvement in the underlying AECOPD. If the rise in $PaCO_2$ is excessive (>10 mm Hg or 1.33 kPa), then FiO_2 should be reduced, titrating SpO_2 to 2%–3% below the previous value, and arterial blood gases should be repeated. If no $PaCO_2$ rise occurs with oxygen therapy, then a higher SpO_2 may be targeted with repeat ABG.

Inadequate reversal of hypoxia (e.g. SpO_2 <85%) is suggestive of an additional problem such as pneumonia, pulmonary oedema or embolus, or a pneumothorax. Investigation of this should commence and a higher O_2 delivery system [e.g. nasal high flow (NHF)] should be used (see Chapter 28). Although high levels of O_2 should be avoided, reversal of hypoxia is important and O_2 should not be withheld in the presence of hypercapnia, or withdrawn if it worsens.

BRONCHODILATORS

Bronchodilators are routinely given in all acute exacerbations of COPD because a small reversible component of airflow obstruction is common, and bronchodilators improve mucociliary clearance of secretions. A large meta-analysis of 22 large randomised controlled long-term trials of ambulatory COPD patients involving either anticholinergics and/or β2 agonists (short- and long-acting) over 3–60 months indicated that anticholinergics are more favourable than placebo in terms of acute exacerbations and hospitalisations.[3,28] There were no favourable advantages with β2-agonists compared with placebo for acute exacerbations or hospitalisations, and placebo was better than β2-agonists in terms of respiratory death.[28] There is a cardiovascular risk if given in excessive doses.[29]

Anticholinergic agents, such as ipratropium bromide, have been shown to have a similar or greater bronchodilator action than β-agonists in COPD, and also to have fewer side effects and no tachyphylaxis. Anticholinergic agents should be used routinely in AECOPD. An ipratropium bromide nebule of 0.5 mg in 2 mL should be nebulised initially 2-hourly, then every 4–6 hours. Long-term use of ipratropium bromide has been shown to reduce the incidence of exacerbations[30] and is therefore recommended for chronic use in ambulatory COPD. Long-acting anticholinergics (e.g. tiotropium) offer potential of once-daily dosing.

Nebulised β-agonists are also effective bronchodilators in COPD, although they may cause tachycardia, tremor, mild reductions in potassium and $PaCO_2$ (due to pulmonary vasodilatation) and tachyphylaxis. As in asthma, lactic acidosis may also occur with excessive β-agonists, either nebulised or intravenous. Nebulised β-agonists (e.g. salbutamol, terbutaline or fenoterol) given 2–4-hourly should be used routinely in combination with ipratropium. This combination has been shown to be more effective than either agent alone.

Parenteral sympathomimetic agents are not recommended for routine use. In stable patients, long-term use of β-agonists may improve symptoms of dyspnoea, particularly in the subgroup of COPD with an objective bronchodilator response.

STEROIDS

In acute exacerbations of COPD, short-term steroids have been shown to improve airflow obstruction including those patients requiring mechanical ventilation for COPD.[31] Doses similar to those for acute asthma should be used. Methylprednisolone 0.5 mg/kg, given 6-hourly for 72 hours, was used in the study by Albert et al., demonstrating benefit in patients with an exacerbation of COPD.[32] Current guidelines recommend the equivalent to oral prednisolone at 0.5 mg/kg body weight for 5 days,[33] then ceasing; however, this will depend upon the response to treatment, and their premorbid use. Steroids should be avoided if the deterioration is clearly due to bacterial pneumonia without bronchospasm.

Longer-term oral steroids in COPD are associated with a substantial increased risk of side effects (osteoporosis, diabetes, peptic ulcer, myopathy, systemic hypertension, fluid retention, weight gain), and are therefore not recommended.[5] A small group of patients (15%) may demonstrate a significant bronchodilator response; co-existent asthma is likely in these patients and longer-term high-dose (oral or inhaled) steroids may be necessary. In the majority of patients, long-term inhaled steroids do not improve lung function or survival and may contribute to recurrent pulmonary infections; however, they may improve quality of life and reduce admissions in a small select population.[5]

ANTIBIOTICS

Antibiotics have an accepted role in the treatment of infection-induced exacerbations of COPD. Amoxicillin is a suitable first-line agent against *H. influenzae* and *Streptococcus pneumoniae* for outpatient exacerbations.[4] Serious exacerbations requiring hospital admission require newer agents such as ciprofloxacin or a third-generation cephalosporin. Antibiotics for pneumonia are discussed in Chapter 36.

AMINOPHYLLINE

Aminophylline is a weak bronchodilator in COPD. It improves diaphragm contractility, stimulates respiratory drive, improves mucociliary transport and right heart function, is anti-inflammatory and is a weak diuretic.[34,35] Some studies have shown no benefit and significant side effects, whereas others have shown small benefit[36] in stable COPD. For an exacerbation, a trial of aminophylline can be considered (loading dose 5–6 mg/kg IV over 30 min, followed by an infusion of 0.5 mg/kg per hour). Serum theophylline levels must be monitored regularly to reduce risk of toxicity.

ANTICOAGULANTS

Subcutaneous heparin (e.g. 5000 units b.d.) is recommended as a prophylactic measure against venous thromboembolism. There is no evidence for warfarinisation in COPD patients with pulmonary hypertension.

ELECTROLYTE CORRECTION

Electrolyte correction is important. Hypophosphataemia,[14] hypomagnesaemia,[37] hypocalcaemia[15] and hypokalaemia may impair respiratory muscle function. Hyponatraemia may occur with inappropriate antidiuretic hormone release or with excess use of diuretics and inappropriate intravenous fluids.

NUTRITION

Nutrition is important, as patients with severe COPD are often undernourished – a subnormal body mass index (BMI) is a risk factor for mortality in COPD.[6] Excessive carbohydrate calories should be avoided, as this increases CO_2 production (by >15%) and may worsen respiratory failure. Low-carbohydrate/high-fat combinations are preferred in ARF during spontaneous ventilation.

CHEST PHYSIOTHERAPY

Chest physiotherapy should be initiated and regularly repeated as both a curative and preventive measure. Encouragement of coughing and deep breathing are the two most important factors. 'Bubble positive expiratory pressure (PEP)' is an inexpensive method of assisting sputum clearance in patients with retained secretions or those having difficulty expectorating.

NEBULISED MUCOLYTIC AGENTS

Nebulised mucolytic agents, such as N acetylcysteine, continue to be proposed, although their benefit has never been established in acute exacerbations of COPD. Oral mucolytics have been shown to reduce cough frequency and severity in stable COPD.[38]

NON-INVASIVE VENTILATION

NIV, a technique in which ventilatory support is provided via a nasal or facial mask without endotracheal intubation, is now a routine standard of care for AECOPD. When applied well, NIV has the same physiological effect as IMV.[39] Two landmark randomised controlled trials in intensive care wards in 1995[40] and in general medical wards in 2001[41] clearly indicated a role for NIV in hypercapnic AECOPD. Since then, there have been several randomised controlled trials and meta-analyses of NIV in hypercapnic AECOPD which have demonstrated improved respiratory physiology, reduced mortality (up to 12 months), reduced iatrogenic complications, reduced need for intubation and mechanical ventilation and reduced length of stay in hospital.[8,9,42,43] All studies have shown good tolerance of the technique (>80% of patients),

with few side effects, and improvements in both oxygenation and $PaCO_2$ compared with medically treated control patients.

Two important reviews of acute NIV use in AECOPD from the United States and the United Kingdom have been recently been published. In the United States between 1998 and 2008, the use of NIV increased (from 1.0 to 4.5% of all admissions) and IMV decreased (from 6.0 to 3.5%), with NIV eclipsing IMV in 2008.[9] Associated with this significant change in pattern of ventilatory support was an overall reduction in mortality in those started on NIV or IMV early.[9] In the United Kingdom, during a 3-month snapshot of 232 hospitals during 2008, 11% of all admissions with AECOPD received NIV.[8] Oxygen toxicity was found to occur in a third of hypercapnic AECOPD.[8] In both US and UK studies, NIV failure with transfer to IMV was associated with greatest mortality (estimated to be ~30% [US]–40% [UK]) compared with successfully used NIV (6% [US]–11% [UK]) and non-hypercapnic COPD (~3% [US], 5% [UK]).

The goal of NIV is: (1) to unload respiratory muscles and augment ventilation and oxygenation, reduce CO_2 and correct acidosis until the underlying problem can be reversed; (2) when applied intermittently, to offset the adverse effects of sleep or position-induced adverse changes to ventilation, increased upper airway resistance and lung volume.

Indications for NIV are a deterioration of COPD with: (1) acute dyspnoea; (2) respiratory rate greater than 28 breaths/min; (3) $PaCO_2$ greater than 45 mm Hg with a pH less than 7.35, despite optimal medical treatment and not related to excessive supplemental oxygen.[8,42,43] Although these indications are for mild exacerbations, most randomised studies have used these as entry guidelines. Initial guidelines recommended NIV use to be limited to patients with pH in the range 7.25–7.35; however, recent evidence suggests that NIV is useful even in those patients with lower pH values (to as low as 7.0) and associated more severe hypercapnia (as high as 140 mm Hg).[44]

Included in the indications are recently extubated patients in whom NIV has been shown to reduce reintubation rates significantly.[45,46] Recently, NIV has been advocated for use in patients with hypoxic respiratory failure,[47] but success is significantly less in the setting of hypoxaemia and either normocapnia or hypocapnia. NIV may also have a role in some patients where mechanical ventilation is considered inappropriate.

Side effects of NIV include discomfort, intolerance, skin necrosis, gastric distension and aspiration. Pressure support has been reported as better tolerated than assist/control.[48] End-of-life plans should be considered in all patients with AECOPD, particularly those undergoing NIV, as ~20% of patients will fail to respond or deteriorate. This period of time on NIV can be used to assess resuscitation status.

INVASIVE MECHANICAL VENTILATION

When respiratory failure progresses despite aggressive conservative management, including NIV, IMV support may be necessary. The decision to ventilate requires careful consideration in some patients who may have near-end-stage lung disease and whose quality of life may not justify aggressive treatment. This decision requires consideration of the outcome of ARF.

An episode of ARF further decreases survival (Fig. 30.2). ARF precipitated only by bronchitis has a better outcome, whereas ARF due to more serious causes, such as pneumonia, LV failure and pulmonary embolus, has a worse outcome and studies including all such outcomes have lower survival rates.

If ARF requires IMV, survival decreases further still (see Fig. 30.2). Although only 1%[8]–3.5%[9] of patients with AECOPD require IMV, and 4.5%[9]–11%[8] need NIV, the short-term survival in this more severe subset is still good, with a hospital survival rate in some series as high as 90%, but 2- and 3-year survival is significantly lower. The severity of ARF and the severity of underlying COPD based on FEV1, lifestyle score and dyspnoea score are also predictors of outcome. Lifestyle and dyspnoea categories may be the most useful factors in the decision to withhold IMV. Lifestyle categories 3 (house-bound and at least partly dependent) and 4 (bed- or chair-bound) indicate both a poor outcome[49] and quality of life that may not justify aggressive treatment.

Thus IMV may be withheld in end-stage lung disease when low survival, poor quality of life or permanent ventilator dependence are likely. If end-stage lung disease is suspected but there is insufficient information, then a brief trial of aggressive therapy, including IMV, should be undertaken and subsequently withdrawn if unsuccessful. Despite this, most patients with COPD who present with ARF do not have end-stage disease and, although their immediate problems may be life threatening, their short-term outcome is sufficiently good to justify full active treatment.

Many studies have indicated that hospitals with high NIV use have a very low need for IMV to treat AECOPD. In the largest study to date, NIV use for AECOPD varied from 9% to 94% in the United States, and was independent of severity of COPD.[50] Moreover, the greater the NIV use, the less IMV was needed, with downstream benefits in terms of hospital length of stay, reduced costs and reduced mortality. Thus, familiarity with NIV is hugely important to the successful caring of patients with AECOPD.

INVASIVE MECHANICAL VENTILATION TECHNIQUE

The goals of IMV in COPD are to support ventilation while reversible components improve, to allow respiratory muscle to rest and recover whilst preventing

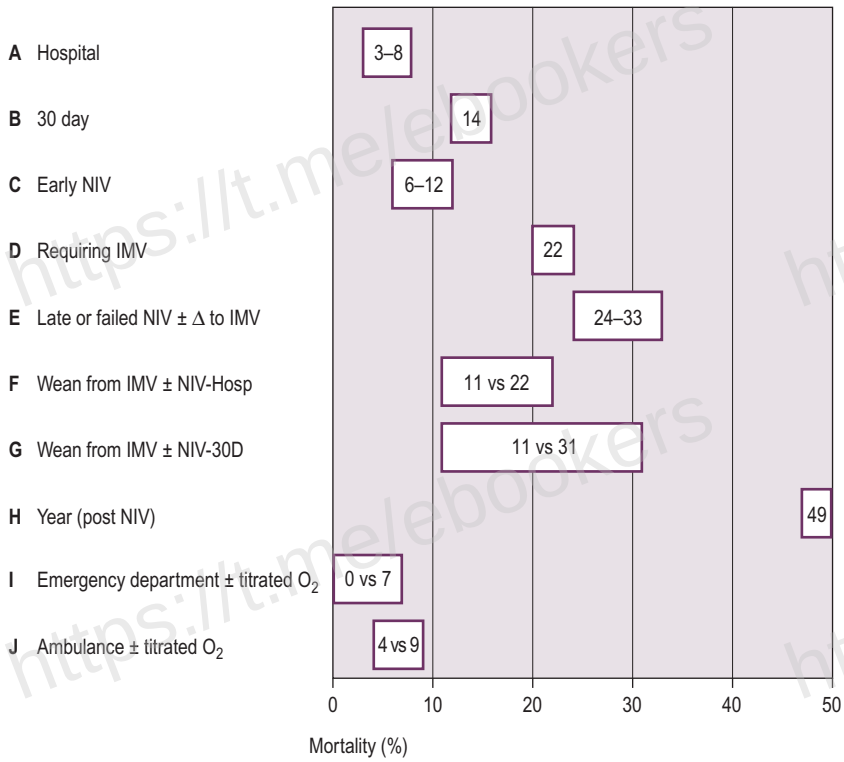


Figure 30.2 Estimated mortality for groups of patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD). A and B groups: refer to in-hospital and 30-day mortality[8,9]; C group: refers to early institution of non-invasive ventilatory (NIV)[8,9]; D group: refers to patients requiring invasive mechanical ventilation (IMV)[9]; E group: refers to hypercapnic AECOPD patients either failing NIV and needing IMV, or those identified late as requiring NIV[8,9]; F and G groups: weaned from IMV and randomised to either immediate NIV or not (i.e. randomised controlled trial) with in-hospital and 30-day mortality[45]; H group: 1-year mortality post NIV[7]; I and J groups: effect of titrated versus untitrated oxygen at emergency department[23] and ambulance.[22]

wasting from total inactivity and to minimise dynamic hyperinflation. This is usually best accomplished with low-level ventilatory support. Patients requiring low-level support may be commenced on 8–15 cm H_2O pressure support, with 3–8 cm H_2O PEEP. Patients who are completely exhausted, post-arrest, comatose or not tolerating pressure support alone, should be commenced or transferred to synchronised intermittent mandatory ventilation mode.

Excessive dynamic hyperinflation must be avoided by using a low-minute ventilation – 115/mL per kg is a guideline and allowing adequate time for expiration. This should be achieved by the use of a small tidal volume (8 mL/kg) and a ventilator rate less than 14 breaths/min. Dynamic hyperinflation can be assessed clinically by visualising the expiratory flow-curve, and by measuring plateau airway pressure (Pplat) or PEEPi. Pplat should be measured by applying an end-inspiratory pause of 0.5 seconds. This should only be applied following a single breath as it shortens expiratory time and, if it is applied to a series of breaths, it increases dynamic hyperinflation, resulting in an increased Pplat level and increased risk to the patient. If Pplat is greater than 25 cm H_2O, there is likely to be excessive dynamic hyperinflation, and the ventilator rate should be reduced. However, Pplat may be high without dynamic hyperinflation if chest wall compliance is low. Intrinsic PEEP measured as a prolonged end-expiratory pause more directly assesses dynamic hyperinflation. Provided PEEPi is accurately measured, it is a useful tool to follow dynamic hyperinflation. In severe airflow limitation it may be necessary to accept low levels of PEEPi, but as PEEPi rises above 8–10 cm H_2O, further prolongation of expiratory time must be considered. Although still controversial, the use of a high inspiratory flow rate is recommended as it results in a shorter inspiratory time and hence a longer expiratory time for a given ventilatory rate.[12,51] It has been shown to reduce dynamic hyperinflation and alveolar pressure[13] further and to improve gas exchange.[51]

If dynamic hyperinflation is excessive and causing circulatory compromise or risk of barotrauma, then minute ventilation should be decreased, hypercapnic acidosis accepted and spontaneous ventilation, which will only increase dynamic hyperinflation, should be

discouraged by sedation. Muscle relaxants should be avoided unless essential. When dynamic hyperinflation is critical during controlled mechanical ventilation, PEEPi increases pulmonary hyperinflation and should not be applied.[52]

If dynamic hyperinflation is not excessive, then spontaneous ventilation should be encouraged to promote ongoing respiratory muscle activity and to minimise wasting. Flow-by, pressure support and low-level continuous positive airway pressure (CPAP) may all reduce the work of spontaneous breathing and promote a better ventilatory pattern. CPAP approximately equal to the level of PEEPi is most commonly recommended.[53] Care must be taken with all of these supports, as each can increase dynamic hyperinflation by a different mechanism, leading to circulatory compromise or risk of barotrauma. Flow-by increases resistance through the expiratory valve, pressure support increases tidal volume and may increase inspiratory time and CPAP reduces threshold load and makes ventilator triggering easier in patients with PEEPi.

WEANING FROM INVASIVE MECHANICAL VENTILATION

Approximately 6%–20% of patients on IMV support fail weaning and place themselves in a high mortality and morbidity group (see Chapter 31).[45,46] Numerous criteria have been proposed to assess the capacity of the patient to wean[54]; however, the predictive value of any of these individual criteria is limited. The simple criterion of patient respiration rate/tidal volume less than 100 breaths/min per litre had the best predictive value for weaning success, but the advantage of this overly simple clinical assessment during weaning is uncertain. Other indications to safely extubate COPD patients include FiO_2 less than 40%; PaO_2/FiO_2 greater than 200, PEEP 5 cm H_2O, cardiovascular stability, afebrile, pH greater than 7.35, $PaCO_2$ less than 50 mm Hg, Glascow Coma Score greater than 10 and if available to be measured static compliance greater than 25 mL/cm H_2O.[45] Some patients unable to achieve these criteria may require weaning with $PaCO_2$ 50–65 mm Hg with a bicarbonate level of greater than 30 mmol/L allowed or encouraged to reduce the work of breathing and achieve a less abnormal pH. Following extubation, weaning can be continued with immediate placement upon NIV or NHF which is associated with reduced reintubation rates, lower intensive care unit and hospital length of stay and mortality and morbidity.[45,46] Synchronisation of NIV, especially during sleep, is crucial and may require polysomnography.[55]

TRACHEOSTOMY

Tracheostomy may be beneficial in a small group of patients who have failed extubation despite NIV, or who have successfully weaned but are unable to adequately clear secretions, or who have required long-term ventilatory support. After 10 days of endotracheal intubation, the risk of laryngeal trauma and sepsis increases.

A tracheostomy allows long-term ventilatory support, sputum clearance, protection of the upper airway from oral secretions and, off mechanical ventilation, reduced dead space and upper-airway resistance. Compared with naso/orotracheal intubation, tracheostomy is much less intrusive and therefore less sedation is required. Also, it allows direct access to the large airways for the purpose of suctioning and bronchoscopy. However, patients are unable to generate sufficient upper-airway seal to cough, and as such may have ongoing atelectasis until tracheostomy removal and the development of an effective cough. Usually a nasoenteric feeding tube is required. Consider percutaneous endoscopic gastrostomy (PEG) tube feeding if long-term tracheostomy is being considered to avoid nasal trauma and infection and to reduce oesophagitis. Minimal occlusion tracheostomy cuff pressures (usually <20 cm H_2O) should be checked 8-hourly. Temporary tracheostomies require specific attention to adequate humidification. In addition, tracheostomies should have an inner and outer cannula; the inner cannula needs to be changed 1–3 times per day.

Consider removing the tracheostomy when:

1. the oxygenation requirement is low (e.g. FiO_2 <40%)
2. the patient does not require ventilatory support or requires only intermittent low-level ventilatory support and NIV support is available.
3. the patient is cooperative and has a good capacity to cough and can, for example, clear secretions via the tracheostomy tube
4. the patient has a low suction frequency requirement (<2–4-hourly)

Before tracheostomy removal, always ensure the patient is able to protect the upper airway from aspiration and can swallow safely and there is an absence of upper-airway obstruction (e.g. no granulation tissue or tracheal stenosis).

NASAL HIGH FLOW CANNULA

Nasal high flow cannula has emerged to be a novel therapy in patients with acute hypoxic respiratory failure[56] or when weaning from IMV in patients with a high risk of reintubation.[57] This therapy is characterised by the delivery of heated and humidified room air with entrained oxygen via large-bore cannula to the nares. The nasal high flow devices are electrically driven CPAP flow generators with built-in humidifiers and supplemental oxygen inlets plus oxygen and temperature analysers which are displayed within the device. Nasal high flow has distinct physiological advantages over standard oxygen prongs and NIV. It provides warm humidified room air-oxygen blend,

at an accurate FiO_2 (determined by the inflow rate of oxygen) and temperature (31–37°C) and overall flow rate of 30–60 L/min. The 'high flow' has been shown to provide low-level positive airway pressure (about 35 lpm flow equates to 3 cm H_2O PEEP)[58] and greater patient comfort due to the warm air-oxygen mix. The PEEP has two actions: first, to reduce work of breathing, estimated in stable COPD patients by about 40% during sleep[59] and improve lung mechanics[60]; second, to reduce physiological airway dead space by flushing out CO_2.[61]

Clinically, nasal high flow is useful in ARF without hypercapnia[56] and post extubation from IMV.[57]

POST INTENSIVE UNIT CARE

CARE BUNDLES

A systematic approach to the management of acute exacerbations of COPD, summarised in so-called 'care bundles', used at the time of admission and discharge, are associated with improved survival, greater NIV use, shorter length of stay and reduced readmission rates.[62] Care bundles are a method of ensuring optimal care is provided uniformly across large organisations. Using 'care bundles' during the time of admission, attention is given to (1) obtaining a correct diagnosis, (2) targeted oxygen therapy, (3) recognition and management of respiratory acidosis (i.e. NIV), (4) correct treatment and (5) respiratory specialist review within 24 hours. At the time of discharge, 'care bundles' are directed towards ensuring (1) inhaler technique, (2) self-care management plans, (3) smoking, (4) pulmonary rehabilitation and (5) telephone contact within 72 hours post discharge.

REASSESSMENT OF POTENTIAL PRECIPITATING CAUSES

COPD is commonly associated with cardiovascular disease, depression (and social isolation) and occult malignancy, all of which may need further management following an admission. Lung function assessment is crucial post admission and during regular follow-up.

Assessment for long-term oxygen therapy should be undertaken (PaO_2 <55 mm Hg or <60 mm Hg with cor pulmonale), as there are two trials indicating a survival benefit. Current smoking is a contraindication to domiciliary oxygen therapy due to the risk of fire. This can be checked by assessing carboxyhaemoglobin values on ABG (>2% suggests smoking) or urinary cotinine levels.

Assessment of underlying obstructive sleep apnoea (COPD & OSA = overlap syndrome) should be considered. Treatment of this combination with CPAP is associated with an improved survival and exacerbation-free survival over a 9.5 year period according to a large, although uncontrolled, Spanish trial.[63] Habitual snoring, witnessed apnoeas, obesity (BMI >30), large neck size (>45 cm) and crowded oropharynx (Mallampati grade 3–4) provide clues of the possibility of underlying obstructive sleep apnoea.

DOMICILIARY NOCTURNAL NON-INVASIVE VENTILATORY SUPPORT

In COPD patients with chronic hypercapnia, avoidance of excessive domiciliary oxygen therapy is advised. Whether long-term domiciliary nocturnal NIV is required in this group is less clear. Four large and long-term studies have been conducted in which most,[64–66] but not all,[67] have indicated improved physiology (sleep quality and ABG) with an improvement in survival and readmission rate without changes in FEV1. Long-term NIV has also been associated with improved ventilation perfusion matching.[29] Patients may benefit from domiciliary NIV if they have the following: (1) confirmed COPD diagnosis with optimal medical treatment and reversal of co-existent medical problems, (2) chronic hypercapnia extending at least 2 weeks following an acute hypercapnic admission with COPD, (3) at least two admissions with acute acidotic hypercapnia which responded to NIV, (4) demonstration of sleep-related hypoventilation (e.g. total sleep time hypoxic [SpO_2 <90%] >30% plus a rise in $PaCO_2$ of >5 mm Hg) and (5) one-month trial of domiciliary NIV with objective adherence and improved quality of life and (6) an improvement in physiological markers (e.g. awake $PaCO_2$ or 6-minute walk distance).

REHABILITATION

Rehabilitation should be considered for all patients with COPD, particularly those following ARF. There are numerous randomised controlled trials showing improvements in exercise physiology, lung function, quality of life and reduced hospitalisation rates.[68] The change in 6-minute walk distance with rehabilitation is a powerful predictor of improved survival and significant patient motivator.[69]

VACCINATION AND ANTIBIOTICS

Two large trials have recently advocated the use of macrolide antibiotics (Erythromycin[16] or Azithromycin[17]) for stable COPD. Both studies, conducted over a 12-month period, indicated a significant reduction in exacerbations, probably via anti-inflammatory and antibacterial effects. However, this benefit needed to be offset against potential for greater long-term microbiological resistance and side effects such as hearing loss. Vaccination should be considered in all patients with COPD when stable. Annual influenza and 5-yearly pneumococcal vaccination is recommended.[4]

DOMICILIARY OXYGEN

Based upon two studies[70,71] conducted in the 1970s–1980s indicating a mortality benefit, supplemental oxygen should be provided to patients with advanced COPD who (1) are optimally controlled medically, (2) do not smoke, (3) and have PaO_2 less than 55 mm Hg or PaO_2 less than 60 mm Hg with cor pulmonale. Great caution should be undertaken to avoid excessive oxygen at home when stable (aim for overnight oximetry of 88%–92%) and during acute exacerbations.[8,22,23]

LUNG TRANSPLANTATION

Lung transplantation is another palliative surgical procedure for patients with advanced disabling COPD who are aged less than 65 years, are not ventilator-dependent, are on less than 10 mg prednisolone/day and are free of significant coexistent disease.[72] The current 1-, 2- and 5-year international survival figures are 75%, 66% and 50%, respectively. Common complications are systemic hypertension, bronchiolitis obliterans, acute rejection, viral infection with cytomegalovirus and neoplasms.

PROGNOSIS

Patients with sufficiently severe COPD to warrant hospital admission incur an inpatient mortality of 8%, and 90-day mortality of 15% in the United Kindom.[8,9] Predictors of mortality were performance status, age and admission urea, albumin, pH, $PaCO_2$ and SpO_2 plus the presence of respiratory physicians involved in the care.[73] Although in-hospital mortality for hypercapnic COPD patients may reach 62%,[74] in an Australian report, in-hospital mortality for hypercapnic COPD patients treated with NIV was 11% and all deaths were with palliative intent, which followed time to allow for patient and family discussions.[44] In Hong Kong, acute hypercapnic COPD patients have a 12-month readmission rate of 80% and a 49% 1-year mortality.[7] The BMI, airflow obstruction, dyspnoea and exercise capacity (BODE) index is a 10-point scale made up from the following four variables: (1) BMI; (2) airflow obstruction; (3) severity of dyspnoea; and (4) exercise capacity, and has been found to be very useful in predicting survival in ambulatory patients with COPD (see Table 30.2).[6]

REFERENCES

1. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet*. 2007;370(9589):741–750.
2. Devereux G. ABC of chronic obstructive pulmonary disease. Definition, epidemiology, and risk factors. *BMJ*. 2006;332(7550):1142–1144.
3. Niewoehner DE. Clinical practice. Outpatient management of severe COPD. *N Engl J Med*. 2010; 362(15):1407–1416.
4. Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. *Lancet*. 2007;370(9589):786–796.
5. Pauwels RA, Buist AS, Calverley PM, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med*. 2001;163(5): 1256–1276.
6. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350(10):1005–1012.
7. Chu CM, Chan VL, Lin AW, et al. Readmission rates and life threatening events in COPD survivors treated with non-invasive ventilation for acute hypercapnic respiratory failure. *Thorax*. 2004; 59(12):1020–1105.
8. Roberts CM, Stone RA, Buckingham RJ, et al. Acidosis, non-invasive ventilation and mortality in hospitalised COPD exacerbations. *Thorax*. 2011; 66(1):43–48.
9. Chandra D, Stamm JA, Taylor B, et al. Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998-2008. *Am J Respir Crit Care Med*. 2012;185(2):152–159.
10. Britton JR, Pavord ID, Richards KA, et al. Dietary antioxidant vitamin intake and lung function in the general population. *Am J Respir Crit Care Med*. 1995;151(5):1383–1387.
11. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J*. 1977;1(6077): 1645–1648.
12. Abroug F, Ouanes-Besbes L, Nciri N, et al. Association of left-heart dysfunction with severe exacerbation of chronic obstructive pulmonary disease: diagnostic performance of cardiac biomarkers. *Am J Respir Crit Care Med*. 2006;174(9): 990–996.
13. Tuxen DV, Lane S. The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe air-flow obstruction. *Am Rev Respir Dis*. 1987;136(4):872–879.
14. Aubier M, Murciano D, Lecocguic Y, et al. Effect of hypophosphatemia on diaphragmatic contractility in patients with acute respiratory failure. *N Engl J Med*. 1985;313(7):420–424.
15. Aubier M, Viires N, Piquet J, et al. Effects of hypocalcemia on diaphragmatic strength generation. *J Appl Physiol*. 1985;58(6):2054–2061.
16. Seemungal TA, Wilkinson TM, Hurst JR, et al. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. *Am J Respir Crit Care Med*. 2008; 178(11):1139–1147.

17. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med*. 2011;365(8):689–698.
18. Barr RG, Bluemke DA, Ahmed FS, et al. Percent emphysema, airflow obstruction, and impaired left ventricular filling. *N Engl J Med*. 2010;362(3): 217–227.
19. Baum GL, Schwartz A, Llamas R, et al. Left ventricular function in chronic obstructive lung disease. *N Engl J Med*. 1971;285(7):361–365.
20. Robertson CH Jr, Pagel MA, Johnson RL Jr. The distribution of blood flow, oxygen consumption, and work output among the respiratory muscles during unobstructed hyperventilation. *J Clin Invest*. 1977;59(1):43–50.
21. Malhotra A, Schwartz DR, Ayas N, et al. Treatment of oxygen-induced hypercapnia. *Lancet*. 2001;357(9259):884–885.
22. Austin MA, Wills KE, Blizzard L, et al. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. *BMJ*. 2010;341:c5462.
23. Joosten SA, Koh MS, Bu X, et al. The effects of oxygen therapy in patients presenting to an emergency department with exacerbation of chronic obstructive pulmonary disease. *Med J Aust*. 2007;186(5):235–238.
24. Schneider HG, Lam L, Lokuge A, et al. B-type natriuretic peptide testing, clinical outcomes, and health services use in emergency department patients with dyspnea: a randomized trial. *Ann Intern Med*. 2009;150(6):365–371.
25. Kato S, Nakamoto T, Iizuka M. Early diagnosis and estimation of pulmonary congestion and edema in patients with left-sided heart diseases from histogram of pulmonary CT number. *Chest*. 1996;109(6):1439–1445.
26. Lim BL, Kelly AM. A meta-analysis on the utility of peripheral venous blood gas analyses in exacerbations of chronic obstructive pulmonary disease in the emergency department. *Eur J Emerg Med*. 2010;17(5):246–248.
27. Bone RC, Pierce AK, Johnson RL Jr. Controlled oxygen administration in acute respiratory failure in chronic obstructive pulmonary disease: a reappraisal. *Am J Med*. 1978;65(6):896–902.
28. Salpeter SR, Buckley NS, Salpeter EE. Meta-analysis: anticholinergics, but not beta-agonists, reduce severe exacerbations and respiratory mortality in COPD. *J Gen Intern Med*. 2006;21(10):1011–1019.
29. De Backer L, Vos W, Dieriks B, et al. The effects of long-term noninvasive ventilation in hypercapnic COPD patients: a randomized controlled pilot study. *Int J Chron Obstruct Pulmon Dis*. 2011;6: 615–624.
30. Fahey PJ, Hyde RW. 'Won't breathe' vs 'can't breathe'. Detection of depressed ventilatory drive in patients with obstructive pulmonary disease. *Chest*. 1983;84(1):19–25.
31. Rubini F, Rampulla C, Nava S. Acute effect of corticosteroids on respiratory mechanics in mechanically ventilated patients with chronic airflow obstruction and acute respiratory failure. *Am J Respir Crit Care Med*. 1994;149(2 Pt 1):306–310.
32. Albert RK, Martin TR, Lewis SW. Controlled clinical trial of methylprednisolone in patients with chronic bronchitis and acute respiratory insufficiency. *Ann Intern Med*. 1980;92(6):753–758.
33. Leuppi JD, Schuetz P, Bingisser R, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. *JAMA*. 2013;309(21):2223–2231.
34. Aubier M, De Troyer A, Sampson M, et al. Aminophylline improves diaphragmatic contractility. *N Engl J Med*. 1981;305(5):249–252.
35. Berry RB, Desa MM, Branum JP, et al. Effect of theophylline on sleep and sleep-disordered breathing in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1991;143(2): 245–250.
36. Guyatt GH, Townsend M, Pugsley SO, et al. Bronchodilators in chronic air-flow limitation. Effects on airway function, exercise capacity, and quality of life. *Am Rev Respir Dis*. 1987;135(5): 1069–1074.
37. Dhingra S, Solven F, Wilson A, et al. Hypomagnesemia and respiratory muscle power. *Am Rev Respir Dis*. 1984;129(3):497–498.
38. Petty TL. The National Mucolytic Study. Results of a randomized, double-blind, placebo-controlled study of iodinated glycerol in chronic obstructive bronchitis. *Chest*. 1990;97(1):75–83.
39. Elliott MW, Nava S. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease: 'Don't think twice, it's alright!'. *Am J Respir Crit Care Med*. 2012;185(2):121–123.
40. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*. 1995;333(13):817–822.
41. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet*. 2000;355(9219):1931–1935.
42. Lightowler JV, Wedzicha JA, Elliott MW, et al. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. *BMJ*. 2003; 326(7382):185.
43. Keenan SP, Sinuff T, Cook DJ, et al. Which patients with acute exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive-pressure ventilation? A systematic review of the literature. *Ann Intern Med*. 2003;138(11):861–870.
44. Crummy F, Buchan C, Miller B, et al. The use of noninvasive mechanical ventilation in COPD with severe hypercapnic acidosis. *Respir Med*. 2007;101(1):53–61.

45. Ferrer M, Sellares J, Valencia M, et al. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. *Lancet*. 2009;374(9695):1082–1088.
46. Burns KE, Adhikari NK, Keenan SP, et al. Use of non-invasive ventilation to wean critically ill adults off invasive ventilation: meta-analysis and systematic review. *BMJ*. 2009;338:b1574.
47. Antonelli M, Conti G, Rocco M, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *N Engl J Med*. 1998; 339(7):429–435.
48. Mehta S, Hill NS. Noninvasive ventilation. *Am J Respir Crit Care Med*. 2001;163(2):540–577.
49. Menzies R, Gibbons W, Goldberg P. Determinants of weaning and survival among patients with COPD who require mechanical ventilation for acute respiratory failure. *Chest*. 1989;95(2): 398–405.
50. Lindenauer PK, Stefan MS, Shieh MS, et al. Hospital patterns of mechanical ventilation for patients with exacerbations of COPD. *Ann Am Thorac Soc*. 2015;12(3):402–409.
51. Connors AF Jr, McCaffree DR, Gray BA. Effect of inspiratory flow rate on gas exchange during mechanical ventilation. *Am Rev Respir Dis*. 1981; 124(5):537–543.
52. Tuxen DV. Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. *Am Rev Respir Dis*. 1989;140(1):5–9.
53. Baigorri F, de Monte A, Blanch L, et al. Hemodynamic responses to external counterbalancing of auto-positive end-expiratory pressure in mechanically ventilated patients with chronic obstructive pulmonary disease. *Crit Care Med*. 1994;22(11): 1782–1791.
54. Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. *N Engl J Med*. 1995;332(6):345–350.
55. Vignaux L, Vargas F, Roeseler J, et al. Patient-ventilator asynchrony during non-invasive ventilation for acute respiratory failure: a multicenter study. *Intensive Care Med*. 2009;35(5):840–846.
56. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med*. 2015;372(23): 2185–2196.
57. Maggiore SM, Idone FA, Vaschetto R, et al. Nasal high-flow versus Venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. *Am J Respir Crit Care Med*. 2014;190(3):282–288.
58. Parke R, McGuinness S, Eccleston M. Nasal high-flow therapy delivers low level positive airway pressure. *Br J Anaesth*. 2009;103(6):886–890.
59. Biselli PJ, Kirkness JP, Grote L, et al. Nasal high-flow therapy reduces work of breathing compared with oxygen during sleep in COPD and smoking controls: a prospective observational study. *J Appl Physiol*. 2017;122(1):82–88.
60. Mauri T, Turrini C, Eronia N, et al. Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. *Am J Respir Crit Care Med*. 2017;195(9):1207–1215.
61. Moller W, Celik G, Feng S, et al. Nasal high flow clears anatomical dead space in upper airway models. *J Appl Physiol*. 2015;118(12):1525–1532.
62. Turner AM, Lim WS, Rodrigo C, et al. A care-bundles approach to improving standard of care in AECOPD admissions: results of a national project. *Thorax*. 2015;70(10):992–994.
63. Marin JM, Soriano JB, Carrizo SJ, et al. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. *Am J Respir Crit Care Med*. 2010;182(3): 325–331.
64. Murphy PB, Rehal S, Arbane G, et al. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. *JAMA*. 2017;317(21): 2177–2186.
65. McEvoy RD, Pierce RJ, Hillman D, et al. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. *Thorax*. 2009;64(7):561–566.
66. Kohnlein T, Windisch W, Kohler D, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med*. 2014;2(9):698–705.
67. Struik FM, Sprooten RT, Kerstjens HA, et al. Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. *Thorax*. 2014;69(9):826–834.
68. Goldstein RS, Gort EH, Stubbing D, et al. Randomised controlled trial of respiratory rehabilitation. *Lancet*. 1994;344(8934):1394–1397.
69. Rasekaba T, Lee AL, Naughton MT, et al. The six-minute walk test: a useful metric for the cardiopulmonary patient. *Intern Med J*. 2009;39(8):495–501.
70. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med*. 1980;93(3):391–398.
71. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet*. 1981;1(8222):681–686.
72. Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update—a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2006;25(7):745–755.

73. Price LC, Lowe D, Hosker HS, et al. UK National COPD Audit 2003: impact of hospital resources and organisation of care on patient outcome following admission for acute COPD exacerbation. *Thorax*. 2006;61(10):837–842.

74. Squadrone E, Frigerio P, Fogliati C, et al. Noninvasive vs invasive ventilation in COPD patients with severe acute respiratory failure deemed to require ventilatory assistance. *Intensive Care Med*. 2004;30(7):1303–1310.

31

Mechanical ventilator support

Andrew D Bersten

Mechanical ventilation for acute respiratory failure (ARF) is now routine in the intensive care unit (ICU). The 1952 Copenhagen polio epidemic introduced the notion of organised areas (ICU) for the provision of positive-pressure ventilation,[1] which was usually applied through a tracheostomy that had been inserted to allow suction of secretions. However, methods of ventilatory assistance without intubation had proliferated prior to the polio epidemic (both negative-pressure chest wall devices and positive-pressure face-mask devices), and current trends are to an increased use of non-invasive ventilation (NIV) in patients with respiratory failure.[2]

Almost all of the ventilatory modes that are conventionally applied during *intubated* ventilation (IV) can be applied *non-invasively*; however, IV remains the primary mode of respiratory assistance in critically ill patients. There is also an increasing number of patients receiving chronic ventilatory assistance, but, since the majority of these use chronic NIV, this chapter is primarily directed at intubated mechanical ventilation for both ARF and acute-on-chronic respiratory failure.

A PHYSIOLOGICAL APPROACH

During normal spontaneous breathing, contraction of the respiratory muscles overcomes both the elastic recoil and resistance of the respiratory system (lung and chest wall). A fall in regional pleural pressure results in alveolar inflation due to the resultant pressure gradient. Expiration is usually passive, but the expiratory muscles may assist the elastic recoil of the respiratory system.

The work (W) performed by the respiratory muscles (W_{mus}) can be measured from the relationship between pressure (P) and volume (V), and partitioned into elastic (W_{el}) and resistive (W_{res}) work:

$$W_{mus} = W_{el} + W_{res} \quad (31.1)$$

Inertial work is negligible, and usually ignored; furthermore, Eq. 31.1 does not explicitly describe the elastic work required to initiate inspiration when intrinsic PEEP ($PEEP_i$) is present.

Because volume is constant in Eq. 31.1, it can be simplified to:

$$P_{mus} = P_{el} + P_{res} \quad (31.2)$$

It follows that during positive-pressure ventilatory assistance, where P_{ao} is the ventilatory pressure applied at the airway:

$$P_{ao} + P_{mus} = P_{el} + P_{res} \quad (31.3)$$

and that when the work is solely applied by the ventilator with no respiratory muscle contraction (controlled mechanical ventilation [CMV]):

$$P_{ao} = P_{el} + P_{res} \quad (31.4)$$

This nomenclature allows physiological discussion of the different ventilatory modes from controlled ventilation to spontaneous, unassisted ventilation, and introduces the equation of motion that is used in the estimation of respiratory mechanics (see Chapter 38):

$$P_{ao} = E_{rs} \bullet V + R_{rs} \bullet \dot{V} + P_o \quad (31.5)$$

where E_{rs} is the respiratory system (lung and chest wall) elastance (the inverse of compliance), R_{rs} is the respiratory system resistance, $\dot{V}$ is the gas flow rate, and P_o is the total PEEP (the sum of extrinsic PEEP [$PEEP_e$] and $PEEP_i$). $PEEP_i$ imposes a threshold load – additional elastic work, as inspiratory muscle contraction must occur without $\dot{V}$ until P_{ao} falls below atmospheric pressure (see below, patient-ventilator interaction).

MODES OF VENTILATION

CONTROLLED MECHANICAL VENTILATION

The simplest form of positive-pressure breath occurs in a relaxed subject, and the ventilator provides a constant gas flow during inspiration.

$$P_{ao} = E_{rs} \bullet V + R_{rs} \bullet \dot{V} + P_o$$

The volume delivered will depend upon the inspiratory time (T_i), and P_{ao} during inspiration will reflect E_{rs} and R_{rs} (Fig. 31.1). Expiration is a passive, and usually exponential, decline in volume to the relaxation volume

ABSTRACT

Mechanical ventilator assistance is routine in the intensive care unit; while the most basic form is controlled mechanical ventilation where the ventilator performs all the work of the respiratory muscles, a variety of modes of partial-ventilatory assistance are available and commonly used. The benefits of mechanical ventilation include improved oxygenation through recruitment of poorly aerated lung, control of alveolar ventilation and $PaCO_2$, reduced work of breathing, and airway access and security when the patient is intubated or has a tracheostomy. Protective ventilation aims to minimise lung injury from excessive lung stretch and repeated recruitment-derecruitment of air sacs; while this has been termed ventilator-induced lung injury, similar processes may occur during partial-ventilatory support, non-invasive ventilator support and spontaneous breathing. Consequently, the concept of protective ventilation may have broader application than initially thought.

KEYWORDS

Mechanical ventilation
pressure support
tidal volume
positive end-expiratory pressure (PEEP)
weaning
patient-ventilator asynchrony

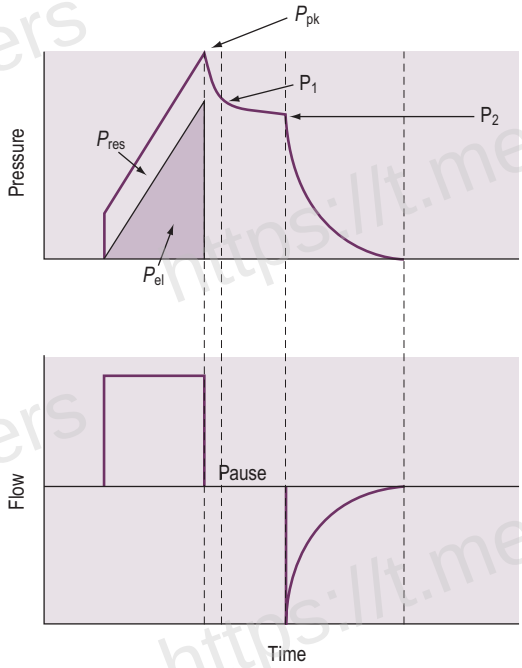


Figure 31.1 Schematic diagram of a volume-controlled breath with constant inspiratory flow. A period of no inspiratory gas flow has been interposed before expiration (pause) to illustrate dissipation of lung resistance as airways resistance (fall from P_{pk} to P_1) and tissue resistance (fall from P_1 to P_2). The inspiratory pressure due to the elastic properties of the respiratory system is illustrated in the top panel as the filled area (P_{el}), and the lung resistive pressure is labelled as P_{res}. (See text for more detail.)

of the respiratory system, also termed the functional residual capacity (FRC).

CMV is the most basic form of mechanical ventilation; however, it is extremely useful, and still commonly used. Preset minute ventilation is made up from a fixed respiratory rate (f) and tidal volume (V_T). Provided that there are not large variations in alveolar dead space, this maintains a preset alveolar ventilation (V_A) and CO_2 clearance. Consequently, CMV is useful in conditions where there is alveolar hypoventilation (e.g. respiratory muscle weakness), when $PaCO_2$ needs to be maintained in a fixed range (e.g. raised intracranial pressure) or when the work of breathing must be minimised (e.g. severe cardiorespiratory failure). Because CMV may not match respiratory drive, and spontaneous, supported or assisted breaths are not possible during CMV, sedation and sometimes muscle paralysis may be needed. CMV is usually combined with $PEEP_e$, which can recruit collapsed lung and reduce intrapulmonary shunt. The components are discussed below.

TIDAL VOLUME

Larger V_T, typically 12–15 mL/kg, or intermittent recruitment manoeuvres (sighs) prevent progressive atelectasis and intrapulmonary shunt during general anaesthesia.[3] However, this may result in excessive lung stretch, leading to ventilator-induced lung injury (VILI). For example, in acute respiratory distress syndrome (ARDS), V_T of 6 mL/kg versus 12 mL/kg predicted body weight (i.e. often 4–5 mL/kg vs. 9–10 mL/kg true weight) reduced mortality from 40% to 31%.[4] Consequently, lower V_T should be strongly considered during CMV, and other forms of ventilatory assistance, in patients with ARDS; however, greater levels of PEEP are usually required. Whereas the reduction in V_T is particularly applicable to ARDS where a smaller proportion of the lung is ventilated (see Chapter 33) clinical outcomes are improved with protective lung ventilation in both critically ill patients without ARDS, and following general anaesthesia.[5,6] Intermediate V_T offers more efficient V_A when ventilator support is required for obstructive lung disease, as the anatomical dead space fraction is lower.

RESPIRATORY RATE (f)

The desired minute ventilation is determined by the product of V_T and f. Common CMV rates are 10–20 breaths/min in adults. Sufficient expiratory time (T_e) must be allowed to minimise dynamic hyperinflation and $PEEP_i$. Although high f (up to 35 breaths per minute) was allowed in the ARDS Network protocol, and the low V_T, low mortality group had a mean f of ~30 breaths per minute,[4] laboratory data suggest a possible additive role of high f in VILI.[7]

INSPIRATORY FLOW PATTERN

The simplest form of CMV uses a constant inspiratory $\dot{V}$ ($\dot{V}_I$) and, in combination with T_i, a preset volume is delivered. This is also called volume-controlled ventilation (VCV); some ventilators use V_T and T_i to set $\dot{V}_I$. Alternative $\dot{V}_I$ patterns that are commonly available with VCV include a ramped descending flow pattern and a sine pattern. When a time preset inspiratory pressure is delivered, this is termed pressure-controlled ventilation (PCV).

Although there are no convincing physiological or outcome data differentiating these different modes of CMV,[8] PCV is increasingly used when the peak airway pressure (P_{pk}) is high with VCV. However, the alveolar distending pressure, which is usually inferred from the plateau pressure (P_{plat}), is no different provided that T_i and V_T are the same.[9] During PCV, P_{res} is dissipated during inspiration so P_{pk} and P_{plat} are equal, and during VCV P_{res} accounts for the difference between P_{pk} and P_{plat} (Fig. 31.2). Similarly, different CMV $\dot{V}_I$ patterns will alter P_{pk} without changing P_{plat} or mean airway pressure (P_{mean}) when T_i and V_T are constant. In ARDS patients, comparing VCV and PCV there was no difference in haemodynamics, oxygenation, recruited lung volume or distribution of regional ventilation.[10] Although PCV may dissipate viscoelastic strain earlier,[10] high $\dot{V}_I$ may cause or exacerbate VILI,[11]

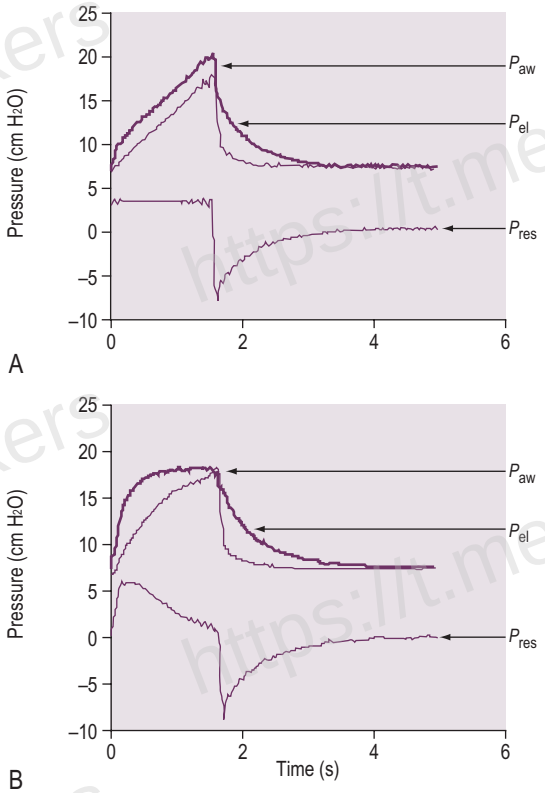


Figure 31.2 Actual pressure-time data from a patient with acute respiratory distress syndrome ventilated with volume-controlled ventilation *(panel a)*, and then with pressure-controlled ventilation *(panel b)*; tidal volume, I:E ratio and respiratory rate are constant. The airway pressure (P_{aw}, *bold line*) has been broken down to its components, P_{el} and P_{res} (see Fig. 31.1). Although there is no inspiratory pause, there is marked similarity between *panel a* and Fig. 31.1, with the inspiratory difference between P_{aw} and P_{el} due to a constant P_{res}. In *panel b*, the decelerating inspiratory flow pattern seen with pressure-controlled ventilation results in dissipation of P_{res} by end inspiration. Consequently, during pressure-controlled ventilation $P_{aw} \approx P_{plat}$ obtained during volume-controlled ventilation. In other words, for the same ventilator settings there is no difference in the elastic distending pressure.

which may explain why some animal models have found PCV, which inherently has a high early $\dot{V}_I$, to be injurious compared with VCV.

Pressure-regulated volume control (PRVC) is a form of CMV where the V_T is preset, and achieved at a minimum pressure using a decelerating flow pattern.

INSPIRATORY PAUSE

An end-inspiratory pause allows examination of the decay in P_{pk}, and measurement of P_{plat} (see Chapter 38), and may alter the distribution of ventilation. If T_i and V_T are maintained constant, there is no improvement in oxygenation, and a more rapid $\dot{V}_I$ will be needed. Theoretically, during an end-inspiratory pause, 32% of the total energy loss within the respiratory system will be dissipated,[12] which may significantly reduce the forces driving expiration, potentially exacerbating gas trapping in patients with severe air-flow limitation.

INSPIRATORY TIME, EXPIRATORY TIME, I:E RATIO

The combination of V_T and inspiratory $\dot{V}$ will determine T_i, which in combination with f sets T_e. A typical T_i is 0.8–1.2 seconds; with a V_T of 500 mL and inspiratory $\dot{V}$ of 0.5 L/s, the T_i is 1.0 second. During spontaneous ventilation, the distribution of ventilation at low $\dot{V}$ is determined by regional E, and at high inspiratory $\dot{V}$ by regional R, leading to greater ventilation of non-dependent lung. In patients with severe air-flow limitation, high inspiratory flow rates may be used in order to prolong T_e and minimise dynamic hyperinflation.[13]

The I:E ratio is usually set at or below 1:2 to allow an adequate T_e for passive expiration. During inverse ratio ventilation (IRV), the I:E ratio is greater than 1:1. The putative benefits of a prolonged T_i include higher expiratory $\dot{V}$ and improved mucus clearance,[14] and recruitment of long time-constant alveoli, and a short T_e results in gas trapping and $PEEP_i$. Early reports of clinical benefit did not control for $PEEP_i$, and, when total PEEP, f and V_T are constant,[9,10] pressure controlled inverse ratio ventilation (PCIRV) tends to reduce $PaCO_2$ but does not improve oxygenation, and may have deleterious haemodynamic effects and exaggerate regional overinflation.[10]

POSITIVE END-EXPIRATORY PRESSURE

Positive end-expiratory pressure (PEEP) is an elevation in the end-expiratory pressure upon which all forms of mechanical ventilation are to be imposed. When PEEP is maintained throughout the respiratory cycle in a spontaneously breathing subject, the term constant positive airway pressure (CPAP) is used. The primary role of PEEP is to maintain recruitment of collapsed lung, increase FRC and minimise intrapulmonary shunt. PEEP may also improve oxygenation by redistributing lung water from the alveolus to the interstitium and, although there is no direct effect of PEEP to reduce extravascular lung water, this may occur in patients with left ventricular failure due to a reduction in venous return and left ventricular afterload. Furthermore, inadequate PEEP may contribute to VILI by promoting tidal opening and closing of alveoli. PEEP levels of 5–15 cm H_2O are commonly used, and levels up to 25 cm H_2O may be required in patients with severe ARDS. Although meta-analysis of three large multicentre trials[15] found no benefit of higher PEEP levels in ARDS, mortality was lower in more hypoxaemic patients and there were fewer rescue therapies required, suggesting individual titration may need to be considered.

PEEP titration in ARDS is complex (see Chapter 33), and should aim to improve oxygenation and minimise VILI. Since PEEP reduces venous return, cardiac output and O_2 delivery may fall despite an improvement in Pa_{O_2}; indeed, this concept has been used to optimise PEEP in ARF.[16] However, in addition to recruitment, increasing PEEP may lead to overinflation of non-dependent alveoli that are already aerated at end expiration.[17,18] Patients with focal ARDS are a particular risk group as recruitment is limited; VILI can be minimised when PEEP is reduced below standard levels.[19] In general, overinflation and VILI are less likely if alveolar distending pressure is kept less than 30–35 cm H_2O, or the change in driving pressure is less than 2 cm H_2O when V_T is constant.[20]

$PEEP_e$ is applied by placing a resistance in the expiratory circuit (Fig. 31.3), with most ventilators using a solenoid valve. Independent of the technique, a threshold resistor is preferred since it offers minimal resistance to flow once its opening P is reached. This will minimise expiratory work, and avoid barotrauma during coughing or straining.

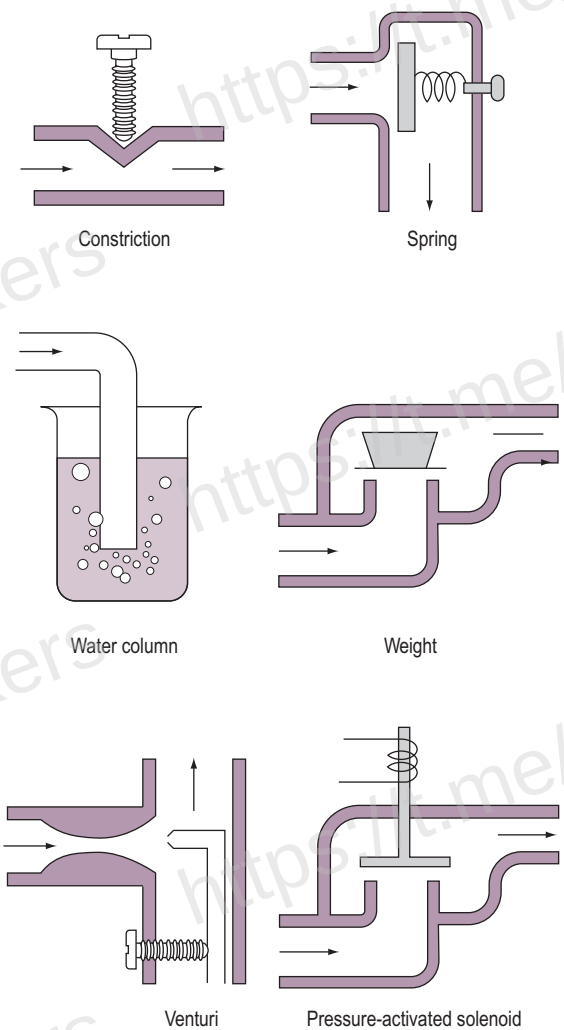


Figure 31.3 Positive end-expiratory pressure values.

$PEEP_i$ is an elevation in the static recoil pressure of the respiratory system above $PEEP_e$ at end expiration. $PEEP_i$ arises due to an inadequate T_e, usually in the setting of severe air-flow obstruction. However, it may be a desired end-point during IRV. The sum of $PEEP_e$ and $PEEP_i$ is the total PEEP ($PEEP_{tot}$). The distribution of $PEEP_i$ is likely to be less uniform than an equivalent $PEEP_e$; this may not have the same physiological effects. When patients with severe air-flow obstruction are triggering ventilation, $PEEP_e$ less than $PEEP_i$ may be applied to reduce elastic work (see later in the chapter, Patient-Ventilator Interaction).

FRACTIONAL INSPIRED OXYGEN CONCENTRATION (Fi_{O_2})

Adequate arterial oxygen saturation is achieved through a combination of minute ventilation, PEEP and Fi_{O_2} adjustment. Even patients with normal respiratory systems usually need an $Fi_{O_2} > 0.21$ due to ventilation-perfusion mismatch secondary to positive-pressure ventilation. In patients with ARF, it is common to start with an Fi_{O_2} of 1 and titrate down as PEEP and minute ventilation are adjusted. Because high Fi_{O_2}s are damaging to the lung, and nitrogen washout may exacerbate atelectasis, it is reasonable to aim at an $Fi_{O_2} \leq 0.6$. The target PaO_2 or SpO_2 remains controversial; as both hypoxaemia and hyperoxia increase the risk of adverse clinical outcomes,[21] normoxia should be targeted until further evidence is available.

SIGH

Many ventilators have the ability to intermittently deliver a breath at least twice V_T. Sighs may reduce atelectasis, in part, through release of pulmonary surfactant,[22] resulting in recruitment and improved oxygenation in ARDS.[23] However, if sighs or recruitment manoeuvres are used, care must be taken to avoid recurrent excessive lung stretch.

ASSIST-CONTROL VENTILATION

During assist-control ventilation (ACV), in addition to the set f, patient effort can trigger a standard CMV breath (Fig. 31.4). This allows greater patient comfort, and V_T is controlled at a safe level; however, there may be little reduction in respiratory work compared to an unassisted breath at low $\dot{V}_I$ because the respiratory muscles continue to contract through much of the breath.[24] The equivalent PCV breath is termed pressure assist-control ventilation (PACV). Differences between triggering modes will be discussed later in the chapter (Patient-Ventilator Interaction).

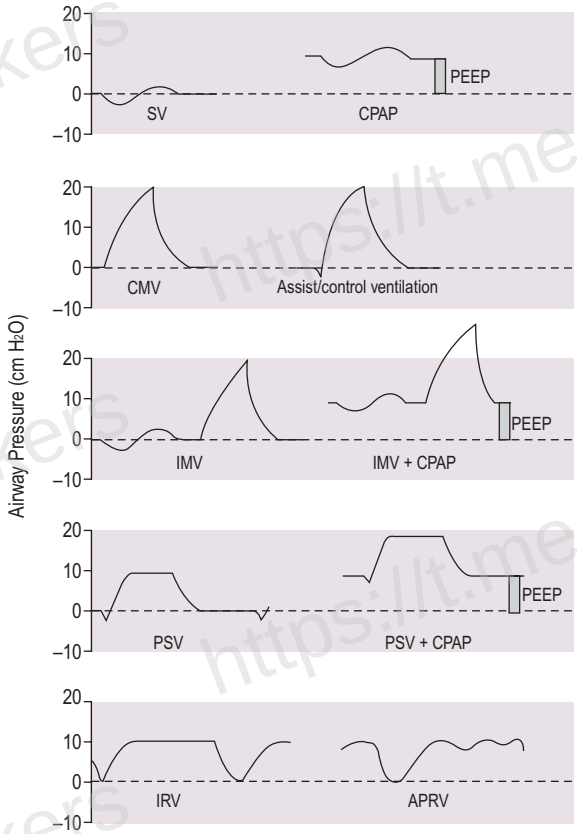


Figure 31.4 Schematic representation of airway pressure versus time for a variety of forms of ventilatory assistance. *APRV*, Airway pressure release ventilation; *CMV*, controlled mechanical ventilation; *CPAP*, continuous positive airway pressure; *IMV*, intermittent mandatory ventilation; *IRV*, inverse-ratio ventilation; *PEEP*, positive end-expiratory pressure; *PSV*, pressure support ventilation; *SV*, spontaneous ventilation.

INTERMITTENT MANDATORY VENTILATION, SYNCHRONISED INTERMITTENT MANDATORY VENTILATION

Intermittent mandatory ventilation (IMV) was introduced over 20 years ago to aid weaning from CMV by allowing the patient to take 'unimpeded' breaths while still receiving a background of controlled breaths. Proposed advantages include a reduction in sedation, lower mean intrathoracic pressure with less barotrauma and adverse haemodynamic consequences, improved intrapulmonary gas distribution, continued use of respiratory muscles and faster weaning. During synchronised intermittent mandatory ventilation (SIMV) T_i is partitioned into patient-initiated and true spontaneous breaths to avoid breath stacking. However, during spontaneous breaths the work of breathing imposed by the endotracheal tube, circuit and ventilator must be overcome.[25] In weaning studies comparing SIMV with T-piece trials and pressure support ventilation (PSV), SIMV is the slowest.[26] Many clinicians add PSV during gradual reduction in respiratory rate with SIMV to overcome the added respiratory work imposed by the circuit and endotracheal tube; however, this approach has not been formally compared with other weaning techniques, and upper airway oedema following extubation increases extubated W_{res} similar to that imposed by the endotracheal tube prior to extubation.[27]

PRESSURE SUPPORT VENTILATION

During PSV, each patient-triggered breath is supported by gas flow to achieve a preset pressure, usually designated to be above the $PEEP_e$. This can be explained by referring to the equation of motion where:

$$P_{mus} + P_{ao} = E_{rs} \bullet V + R_{rs} \bullet \dot{V} + P_o \quad (31.6)$$

During PSV, P_{ao} is the targeted variable by the ventilator, which leads to a significant and important reduction in P_{mus} and work of breathing.[28] The detection of neural expiration varies between ventilators, but commonly relies upon a fall in the inspiratory $\dot{V}$ to either 25% of the initial flow rate or to less than 5 L/min; some ventilators allow titration of the percentage reduction in initial flow to allow improved patient-ventilator synchrony. PSV may also be titrated to offset the work imposed by the circuit and endotracheal tube. The absolute level required to offset this will vary with endotracheal tube size and inspiratory $\dot{V}$,[29] but is commonly 5–10 cm H_2O.[30] PSV can be used during weaning, or as a form of variable ventilatory support with pressures of 15–20 cm H_2O commonly used. Disadvantages include variable V_T, and hence minute ventilation, the potential to deliver an excessive V_T (common in patients recovering from ARDS) and patient-ventilator asynchrony, which is common with high levels of PSV (see later).

Volume-assured pressure support (VAPS) is a mode of adaptive PSV where breath-to-breath logic achieves a preset V_T.

PROPORTIONAL ASSIST VENTILATION

Proportional assist ventilation (PAV) is a form of partial ventilatory support where inspiratory P is applied in proportion to patient effort. Because this allows the breathing pattern and minute ventilation to be matched to patient effort, it is only suitable if respiratory drive is normal or elevated. In concept, this should optimise the patient-ventilator interaction; however, the prescription of PAV requires a greater level of physiological understanding than similar forms of partial ventilatory support such as PSV, since there is no target P, V or $\dot{V}$. PAV is usually prescribed using volume assist (VA) and flow assist (FA), with V

and $\dot{V}$ measured continuously. VA generates greater P as V increases, leading to elastic unloading, and FA generates greater P as $\dot{V}$ increases, leading to resistive unloading. Not surprisingly, the units of VA are cm H_2O/L (i.e. an elastance term) and those for FA are cm H_2O/L/s (i.e. a resistance term). This can be illustrated by referring to Eq. 31.6:

$$P_{mus} + P_{ao} = E_{rs} \bullet V + R_{rs} \bullet \dot{V} + P_o$$

where P_{ao} is determined by PAV, where PAV = VA +FA, so:

$$P_{mus} + VA \bullet V + FA \bullet \dot{V} = E_{rs} \bullet V + R_{rs} \bullet \dot{V} + P_o \quad (31.7)$$

$$\text{consequently } P_{mus} = (E_{rs} - VA) \bullet V + (R_{rs} - FA) \bullet \dot{V} + P_o \quad (31.8)$$

If E_{rs} and R_{rs} are known, PAV can, at least in principle, be targeted to reduce a specified proportion of either, or both, elastic and resistive respiratory work. For example, when VA and FA are adjusted to counterbalance E_{rs} and R_{rs} so as to achieve normal values, minute ventilation increases, and respiratory drive and work decrease; if $PEEP_i$ is present, work can be further reduced by applying $PEEP_e$.[31] Respiratory mechanics are relatively hard to estimate in spontaneously breathing patients, and although they are now offered on some ventilators, their accuracy has been questioned,[32] which may reduce the validity of adjusting PAV according to estimated load (PAV+). Consequently, PAV is often titrated to patient comfort. Despite a growing body of data demonstrating reduced work of breathing, and improved patient-ventilator synchrony with PAV, it is a more difficult technique to use, and definitive studies showing a clinically important outcome difference are awaited.

NEURALLY ADJUSTED VENTILATORY ASSISTANCE

During neurally adjusted ventilatory assistance (NAVA), a modified nasogastric tube is used to record diaphragmatic electrical activity, which is used to control the assisting level of inspiratory pressure. This short-circuits trigger and feedback functions with improved patient-ventilator interaction, less asynchrony and less overassistance compared with PSV[33] in small physiological trials. However, in a multicentre trial[34] of 128 patients, although NAVA was well tolerated and reduced asynchrony overall, autocycling and double triggering were more common, there was no clinically significant benefit compared to PSV, and a pneumothorax resulted from misplacement of the NAVA catheter. NAVA may also improve oxygenation, perhaps by allowing more variable V_T consistent with the concept of biological variability. Although NAVA is available on some commercial ventilators, its use is limited, and there are no data showing a clinically important benefit.

BILEVEL VENTILATION

Also described as biphasic positive airway pressure (BIPAP), this is a ventilatory mode where two levels of airway pressure are provided. Cycling between these two levels of airway pressure may be time cycled or triggered by ventilatory effort, in which case inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) are set; however, this is no different to equivalent support with PSV and PEEP. Patient-triggered bilevel ventilation is most commonly used during NIV.

AIRWAY PRESSURE RELEASE VENTILATION

During airway pressure release ventilation (APRV), spontaneous breathing is possible in addition to time-triggered and time-cycled biphasic pressure levels (high and low CPAP). Usually the time cycling provides a prolonged T_i aimed at recruiting slow time-constant air spaces. Minute ventilation and CO_2 excretion are augmented by brief (1–1.5 seconds) periodic cycling to the lower level of CPAP. A 'personalised' form of APRV has been described where the expiratory time is set using the end-expiratory flow as a fraction of the peak expiratory flow, typically a ratio of 75% with a Te of 0.3–0.6 seconds.[35] As the augmented V_T is dependent upon elastance of the respiratory system, it will be smaller in patients with 'stiff' respiratory systems. APRV without spontaneous breathing has a similar pressure profile to PCIRV.

APRV offers a number of benefits and is usually applied during IV. The prolonged T_i is usually associated with improved oxygenation at a similar or lower P_{aw} to conventional ventilation. Spontaneous respiratory efforts may: (1) improve matching of ventilation and perfusion due to increased dependent aeration, (2) increase venous return and hence cardiac output or pulmonary blood flow in infants following cardiac surgery[36] and (3) promote reduced sedation. However, while there are encouraging case series and physiological studies,[36,37] randomised clinical trials have not shown improved outcomes,[38,39] unsupported spontaneous breaths may increase left ventricular afterload and promote ventilator-patient asynchrony and, as slow time-constant air spaces are also slow to empty, APRV is contraindicated in COPD and asthma.

HIGH-FREQUENCY VENTILATION

High-frequency ventilation (HFV) encompasses techniques where small V_T (1–3 mL/kg) are delivered at high f (100–600/min). This offers reduced tidal lung stretch and reduced VILI. Hazards include inadequate humidification and gas trapping in patients with severe air-flow limitation. High-frequency jet ventilation (HFJV) utilises dry gas from a high-pressure source delivered into an intratracheal catheter or specifically

manufactured endotracheal tube. Although HFJV has been used with improvement in gas exchange in adults with ARDS,[40] high-frequency oscillation (HFO) has received more interest including neonatal, paediatric and adult use.

HFO uses oscillatory flow within the airway to provide active inspiration and expiration at rates of 3–10 Hz. There are a number of putative mechanisms of gas exchange in addition to the more usual bulk flow seen during CMV and SV.[41] Ventilation and V_T are determined by the driving pressure, which controls the reciprocating flow, and by $1/f$. Oxygenation is determined by the mean P_{aw} sometimes in combination with recruitment manoeuvres which influence the volume of recruited lung. Typically, the mean P_{aw} is set 5 cm H_2O above the CMV value.[42] Although the mean P_{aw} during HFO is theoretically dissipated with lower alveolar pressures, and this appears to be the case in homogeneous lung injury, damaged regions of the lung with low compliance, and hence short time constants, may be exposed to alveolar pressures approaching mean P_{aw},[43] resulting in regional VILI.

Although oxygenation is improved in both infants and patients with ARDS, definitive outcome data are lacking. HFO appears to be equivalent to CMV in preterm infants with similar mortality and chronic lung disease.[44] In ARDS, two large randomised trials have reported either no improvement (OSCAR trial),[45] or an increase (OSCILLATE trial)[46] in mortality (47% vs. 35% at hospital discharge). Contributing factors include greater vasopressor use, and greater use of sedation and neuromuscular blockade, with a tendency to greater positive balance, consistent with higher mean airway pressure leading to reduced venous return and greater right ventricular strain.[47] These data refute a meta-analysis that suggested reduced mortality with HFO[48]; however, the largest trial included in this analysis administered a V_T of around 10.6 mL/kg predicted body weight in the control CMV group[37] as compared with protective ventilation in the OSCAR and OSCILLATE studies. Unless new clinical trial data become available, HFO cannot be recommended for routine care in ARDS.

LIQUID VENTILATION

Perfluorocarbons have a high solubility for both O_2 and CO_2, and reduce surface tension, somewhat analogous to pulmonary surfactant. Partial liquid ventilation is now the most common method of administration, with perfluorocarbon equal to the FRC administered via the endotracheal tube. The non-dependent lung is still ventilated, and may have increased blood flow due to compression of the pulmonary circulation in the dependent lung by the perfluorocarbon. Together with the perfluorocarbon-mediated reduction in surface tension, alveoli are recruited and oxygenation improved. However, when PEEP is applied, the perfluorocarbon may be pushed distally and overdistend dependent alveoli.

Small clinical studies have reported improved gas exchange and respiratory mechanics after administration of perfluorocarbons[49]; however, a moderately large clinical study (n = 311) found that patients receiving conventional ventilation compared with both low- and high-dose perflourocarbons had more ventilator-free days and tended to reduced mortality.[50] Consequently, liquid ventilation cannot be recommended.

INDICATIONS AND OBJECTIVES OF MECHANICAL VENTILATION[51]

Institution of mechanical ventilation is a clinical decision; it can only be supported by parameters such as blood gases or measures of respiratory muscle function. Even then, the decision to choose IV over NIV will be influenced by numerous factors including the indication and its likely course. Often there will be an indication for intubation (Box 31.1) and mechanical ventilation; however, if intubation is required to overcome upper airway obstruction, no ventilatory assistance may be needed despite the increase in respiratory work imposed by the endotracheal or tracheostomy tube.[25] Once the decision has been made to proceed to ventilatory support, the choice of mode should be based on a physiological approach, local expertise and simplicity.

Patients who are likely to need ventilatory assistance (e.g. acute severe asthma) should be considered for early ICU admission, since this will allow faster responses and avoid cardiorespiratory arrest. Specific issues and methods of ventilatory assistance are

Box 31.1 Indications and objectives of intubated mechanical ventilation

Endotracheal intubation or tracheostomy
- For airway protection (e.g. coma)
- For suction of secretions
- To assist sedation and neuromuscular paralysis (e.g. to $\downarrow\dot{V}_{O_2}$ $\downarrow$ *respiratory distress*)
- To overcome upper-airway obstruction

Mechanical ventilation
- To manipulate alveolar ventilation (V_A) and $PaCO_2$ (e.g. reverse respiratory acidosis, $\downarrow$ cerebral blood flow and intracranial pressure)
- To $\uparrow Sa_{O_2}$ and Pa_{O_2} (by $\uparrow$ FRC, $\uparrow$end-inspiratory lung volume, $\uparrow V_A$, $\uparrow Fi_{CO_2}$)
- To $\downarrow$ work of breathing (e.g. to overcome respiratory muscle fatigue)
- To $\uparrow$ FRC (e.g. $\uparrow Pa_{O_2}$, $\downarrow$ ventilator-induced injury)
- To control lung stretch during spontaneous breathing, non-invasive ventilation or partially assisted ventilation
- To stabilise the chest wall in severe chest injury

dealt with in the chapters on ARDS, asthma, COPD and NIV. In patients with traumatic brain injury, IV is commonly required to protect the airway and to assist control of ICP; similarly, patients with severe pancreatitis or serious abdominal infection may need prolonged IV to maintain an adequate FRC, reduce work of breathing, protect their airway and allow suctioning of secretions.

MINIMISATION OF LUNG INJURY

Protective ventilation aims to minimise excessive regional lung stretch and cyclic recruitment and collapse, and reduce VILI. Typical protective ventilation combines V_T of 6 mL/kg pbw[4] combined with moderate PEEP[15] and plateau pressures less than 30 cm H_2O (see Chapter 33, ARDS for further discussion). Although the focus has been on protective ventilation during CMV, these processes can occur during spontaneous breathing without ventilator assistance, and during both NIV and partial ventilator support. High respiratory drive due to lung injury or metabolic acidosis may result in relatively large V_T; despite reducing ventilator support, regional differences in aeration can lead to pendelluft and lung injury compared to a controlled breath at the same V_T and transpulmonary pressure, and falls in alveolar pressure may result in greater transmural vascular pressure and pulmonary oedema.[52] The corollaries of this include great care when providing partial ventilator support, and VILI prophylaxis as a possible indication for mechanical ventilation (see Box 31.1).

INITIATION OF INTUBATED MECHANICAL VENTILATION

A manual resuscitation circuit, mechanical ventilator and equipment for safe endotracheal intubation (see Chapter 29) should be available. Initial ventilator settings are commonly set to achieve adequate oxygenation and V_A; however, this will depend upon the patient's condition. Common settings are: V_T 6–8 mL/kg, f 10–20 breaths/min, PEEP 5 cm H_2O, and Fi_{O_2} 1.0, and these will need to be adjusted according to the specific pathophysiology and response.

MANUAL RESUSCITATION CIRCUITS

Manual resuscitation circuits are primarily used to provide emergency ventilation when spontaneous effort is absent or inadequate. They may be used with a face or laryngeal mask, or an endotracheal tube. Occasionally they are used to provide a high inspired O_2 concentration during spontaneous breathing; however, this may impose significant additional respiratory work.[53] In the ICU they are commonly used for preoxygenation and manual lung inflation.

Their basic design includes a fresh gas flow of O_2, a reservoir bag and valves to allow spontaneous or positive-pressure breathing. Most manual resuscitation circuits use a self-inflating reservoir bag since this allows the circuit to be used by unskilled personnel and does not require a fresh gas flow. However, circuits using reservoir bags that are not self-inflating are still used in some institutions since they allow a better manual assessment of the respiratory mechanics, the 'educated hand', and it is clear when there is an inadequate seal with a mask. Oxygen-powered manually triggered devices have been used for many years; however, their use has declined markedly since high $\dot{V}$ and P may lead to barotrauma or gastric inflation.

Self-inflating reservoir bags use a series of one-way valves to allow fresh gas flow oxygen and entrained air to fill the bag. Inspired oxygen fractions as high as 0.8 may be achieved with neonatal or paediatric bags when an additional reservoir bag is used to allow fresh gas flow filling during expiration, after the bag has refilled.[54] However, lower Fi_{O_2}s (~0.6) will be obtained with both conventional O_2 flow rates of 8–15 L/min, and usual V_T and f, with an adult bag. Generally, the valves are simple flap or duckbill in nature, and both positive pressure and spontaneous ventilation are possible. The reservoir bag volume in adults is typically 1600 mL, and V_T can be judged from chest wall movement. It is essential these devices use standard 15/22 mm connectors to allow rapid connection to standard endotracheal tubes and ventilator circuits.

COMPLICATIONS OF MECHANICAL VENTILATION

Although mechanical ventilation may be vital, it also introduces numerous potential complications (Box 31.2).[51] Monitoring includes a high nurse:patient ratio (usually 1:1), ventilator alarms, and pulse oximetry. Capnography is required to confirm endotracheal tube placement, both at the time of intubation and during ventilatory support, and may be used to monitor the adequacy of V_A; however, expired CO_2 is strongly influenced by factors that alter alveolar dead space such as cardiac output. Intermittent blood gases, $PEEP_i$, airway pressures in volume-preset modes and V_T in pressure-preset modes should be recorded. Individual patients may benefit from more extensive monitoring of their respiratory mechanics or tissue oxygenation.

The patient's airway (i.e. patency, presence of leaks and nature and amount of secretions), breathing (i.e. rate, volume, oxygenation), and circulation (i.e. pulse, blood pressure and urine output) must be monitored. Ventilatory and circuit alarms should be adjusted to monitor an appropriate range of V, P and temperature. This should alert adjacent staff to changes in P and/or V that may be caused by an occluded endotracheal tube, tension pneumothorax or circuit disconnection. These alarms may be temporarily disabled while the cause is detected, but never permanently disabled.

Box 31.2 Complications of intubation and mechanical ventilation[51]

Equipment
- Malfunction or disconnection
- Incorrectly set or prescribed
- Contamination

Pulmonary
- Airway intubation (e.g. damage to teeth, vocal cords, trachea; see Chapter 29)
- Ventilator-associated pneumonia (reduced lung defence; see Chapter 36)
- Ventilator-associated lung injury (e.g. diffuse lung injury due to regional overdistension or tidal recruitment of alveoli)
- Overt barotrauma (e.g. pneumothorax)
- O_2 toxicity
- Patient-ventilator asynchrony

Circulation
- ↓ Right ventricular preload →↓ cardiac output
- ↑ Right ventricular afterload (if the lung is overdistended)
- ↓ Splanchnic blood flow with high levels of positive end-expiratory pressure (PEEP) or mean P_{aw}
- ↑ Intracranial pressure with high levels of PEEP or mean P_{aw}
- Fluid retention due to ↓ cardiac output →↓ renal blood flow

Other
- Gut distension (air swallowing, hypomotility)
- Mucosal ulceration and bleeding
- Peripheral and respiratory muscle weakness (see Chapter 57)
- Sleep disturbance, agitation and fear (which may be prolonged after recovery)
- Neurocognitive complications

Sudden difficulties with either high P during volume-preset ventilation or oxygenation must initiate an immediate search for the cause. This should start with the patency of the airway, followed by a structured approach both to the circuit and ventilator, and to factors altering the E and R of the lung and chest wall such as bronchospasm, secretions, pneumothorax and asynchronous breathing. In addition to careful clinical examination, an urgent chest radiograph and bronchoscopy may be required.

Mechanical ventilation is also associated with a marked increase in the incidence of nosocomial pneumonia due to a reduction in the natural defences of the respiratory tract, and this represents an important advantage offered by NIV. In patients successfully managed with NIV, Girou and colleagues reported a reduction in the incidence of nosocomial pneumonia, associated with improved survival, compared to IV.[55] Erect versus semirecumbent posture[56] also reduces the incidence of ventilator-associated pneumonia.

Whereas lung overdistension may result in alveolar rupture leading to pulmonary interstitial air, pneumomediastinum or pneumothorax, it may also lead to diffuse alveolar damage similar to that found in ARDS. Both are termed VILI, and V_T reduction leads to a marked decrease in ARDS mortality due to a reduction in multiple organ dysfunction (see Chapter 33).[4] Laboratory data suggest that inadequate PEEP with tidal recruitment and derecruitment of alveoli also leads to VILI; however, this has not been proven in a clinical trial. Finally, patient-ventilator asynchrony may result in wasted respiratory work, impaired gas exchange and respiratory distress.

Positive-pressure ventilation elevates intrathoracic pressure, which reduces venous return, right ventricular preload and cardiac output. The impact is reduced by hypervolaemia, and partial ventilatory support where patient effort and a reduction in pleural pressure augments venous return. Secondary effects include a reduction in regional organ blood flow leading to fluid retention by the kidney, and possibly impaired hepatic function. This latter effect is seen only at high levels of PEEP where an increase in resistance to venous return and a reduction in cardiac output may combine to reduce hepatic blood flow.

Sleep disturbance, delirium and discomfort are common in mechanically ventilated patients. These effects may be reduced with analgesia and sedation until weaning is planned; however, it is also important not to prolong mechanical ventilation due to excessive use of sedatives, which may also depress blood pressure and spontaneous respiratory effort. A recent large clinical trial found no advantage of daily interruption of sedation over continuous infusion of sedation targeted to the lowest effective dose.[57] Both methods offer early mobilisation in ventilated subjects, shorter duration of ventilation, reduced delirium, ICU and hospital length of stay, and improved mortality and functional outcomes.[58,59] However, this direction must be balanced with strategies such as use of neuromuscular blockers in the first 48 hours of mechanical ventilation in ARDS, which reduced mortality,[60] which prevent or reduce asynchronous ventilatory effort.

Although pulmonary function has generally recovered by 12 months, complex neurocognitive and physical sequelae persist to at least 5 years in surviving ARDS patients.[61] Cognitive impairment has been associated with hypotension, hypoxaemia and hyperglycaemia. In addition, anxiety, depression and post-traumatic stress disorder are common and appear to be associated with the severity of illness, duration of mechanical ventilation and premorbid factors including depression. All of these issues are increasingly important as improvements in care and greater numbers of patients treated result in more survivors from critical illness. Of particular note, it appears that early interventions can be effective, but that late interventions fail to improve outcomes. For example,

physical therapy commenced a median of 7 days after initiation of mechanically ventilation for ARF failed to improve long-term physical function,[62] while much earlier intervention in post-surgical patients resulted in improved functional outcomes and reduced length of ICU and hospital stay.[63]

WITHDRAWAL (WEANING) FROM MECHANICAL VENTILATION

Once the underlying process necessitating mechanical ventilation has started to resolve, withdrawal of ventilatory support should be considered; increased duration of ventilation leads to a progressive rise in complications such as ventilator-associated pneumonia. However, other important parameters that must be considered include the neuromuscular state of the patient (ability to initiate a spontaneous breath), adequacy of oxygenation (typically low requirements for PEEP [5–8 cm H_2O] and Fi_{O_2} [<0.4–0.5]), and cardiovascular stability.[64] Once a patient is considered suitable to wean, a secondary question is whether an artificial airway is still required for airway protection or suction of secretions. Many patients can rapidly make the transition from mechanical ventilation to extubation, but ~20% of patients fail weaning despite meeting clinical criteria.[26] Advanced age, prolonged mechanical ventilation and chronic obstructive pulmonary disease all increase the likelihood that weaning will be difficult.[26]

Weaning failure is usually associated with an increase in respiratory drive, and respiratory rate and a fall in V_T, which contributes to hypercapnea[65]; about 10% of patients fail due to central respiratory depression. Various indices such as maximal inspiratory pressure (MIP), minute ventilation (V_E), f, V_T, f/V_T ratio and the dynamic compliance, respiratory rate, oxygenation, maximum inspiratory pressure (CROP) index have been investigated as predictors of weaning failure (Table 31.1). They are rarely used alone and careful clinical assessment is often adequate, yielding a re-intubation rate as low as 3%,[66] and none of these indices assess airway function following extubation. Although the typical threshold value for the rapid shallow breathing index (f/V_T ratio) is greater than 105, a large multicentre study reported progressive increase in risk as this increased with a threshold of 57; in addition, a positive fluid balance immediately prior to extubation was a significant risk factor for re-intubation.[67] Consequently, weaning indices should not necessarily delay extubation or a weaning trial. However, they may quantitate important issues in the general clinical assessment, and may be directly relevant for a given patient. For example, frequent small V_T, an inadequate vital capacity (less than 8–12 mL/kg), large minute ventilation (≥15 L/min), depressed respiratory drive, and reduced respiratory muscle strength (MIP ≤ –15 cm H_2O) or drive should be strongly factored into deciding whether a patient is ready to safely undergo a trial of weaning.

Table 31.1 Sample of measurements that have been used to predict successful outcome from weaning in critically ill patients

PARAMETER	TYPICAL THRESHOLD VALUE*	COMMENT
V_E	≤15 L/min	Moderate to high sensitivity, low specificity
MIP	≤–15 cm H_2O	High sensitivity, low specificity
CROP index†	≥13	Moderate to high sensitivity, modest specificity
DURING A SPONTANEOUS BREATHING TRIAL		
f	≤38 breaths/min	High sensitivity, low specificity
V_T	≥325 mL (4 mL/kg)	High sensitivity, low specificity
f/V_T	≤105	High sensitivity, moderate specificity

*Although threshold values are often used, the data are not dichotomous. For example, as the f/V_T ratio increases, so does the rate of re-intubation.[53]

†CROP index = $(C_{dyn} \times \text{MIP} \times [Pa_{O_2}/PA_{O_2}]/f)$.[22]

See reference 64 for further detail.

CROP, Compliance, respiratory rate, oxygenation, maximal inspiratory pressure; *MIP*, maximal inspiratory pressure.

Direct comparisons between T-piece trials, PSV and SIMV as weaning techniques have been performed in patients previously failing a 2-hour trial of spontaneous breathing. In the study by Brochard and colleagues,[68] PSV led to fewer failures and a shorter weaning period. In contrast, Esteban and coworkers[69] found that a once-daily trial of spontaneous breathing resulted in the shortest duration of mechanical ventilation; however, a relatively high proportion of patients required re-intubation (22.6%). Viewed together, these studies suggest that weaning was slower with SIMV,[26] although SIMV with PSV was not studied, and that either PSV or a T-piece trial are the preferred methods for weaning. Since low levels of PSV can help compensate for the additional work of breathing attributable to the endotracheal tube and circuit, some clinicians use low levels of PSV (5–7 cm H_2O) during weaning or during a spontaneous breathing trial. However, the work of breathing following extubation is usually higher than expected, probably due to upper airway oedema and dysfunction, so that work is similar to that during a T-piece trial.[26]

Re-intubation is relatively common, with reported rates of 15%, and is associated with a 7–11-fold increased risk of hospital death.[26] Although this may reflect extubation of sicker patients, there does appear to be a specific effect of extubation failure on outcome, perhaps due to the risks of re-intubation itself along with its haemodynamic consequences, and an increased risk of infection. Thille and co-workers[70] reported that 27% of patients developed pneumonia, and that 50% of patients died following re-intubation. They identified age greater than 65 years and underlying cardiorespiratory disease as risk factors for extubation failure. Unplanned extubations were associated with higher endotracheal tube position on chest radiograph. Hence, an important goal during mechanical ventilation will be to proceed to early and expeditious extubation with a low re-intubation rate.

PATIENT-VENTILATOR INTERACTION

During partial ventilatory support or spontaneous breathing, the ventilator should match neural drive; however, suboptimal patient-ventilator interaction, also termed asynchrony, is common, frequently not diagnosed and is associated with prolonged mechanical ventilation, increased length of stay both in hospital and in the ICU, and with increased mortality when more than 30% of breaths are asynchronous.[71] Clinical signs of asynchrony include agitation, diaphoresis, tachycardia, hypertension and failure of weaning or NIV. Once this pattern is identified, it is crucial that airway complications (partial obstruction, displacement) or a major change in the clinical state (e.g. pneumothorax, acute pulmonary oedema) are excluded before considering problems with patient-ventilator interaction.

Although both PAV and NAVA reduce asynchrony, they are complex and less commonly used. Recognition and management of asynchrony are assisted by a physiological approach to the respiratory cycle: (1) triggering of inspiration, (2) inspiration and (3) cessation of inspiration. Difficulties at each of these phases will lead to changes in respiratory drive and effort that may be expressed throughout the respiratory cycle. Careful bedside observation of the patient-ventilator interaction is essential, as isolated observation of P, V and $\dot{V}$ waveforms displayed by the ventilator leads to under-recognition of asynchrony. In one series[72] ineffective triggering accounted for most of the asynchronous episodes with autocycling the next most common cause. Prevalence of asynchrony increased with PSV ≥12 cm H_2O, large V_T and low respiratory rates in part reflecting dynamic hyperinflation and $PEEP_i$.

TRIGGERING OF INSPIRATION

1. $PEEP_i$ is an important hindrance to the triggering of inspiration in patients with severe air-flow limitation, since their inspiratory muscles must first reduce P_{ao} below ambient pressure.[73] Consequently, P_{mus} must exceed $PEEP_i$ prior to triggering an assisted breath, usually by either reducing airway pressure (pressure trigger) or reducing circuit flow (flow trigger). This inspiratory threshold load may be up to 40% of the total inspiratory work in ARF when dynamic hyperinflation is present, and commonly results in ineffective triggering. Triggering can be markedly improved and respiratory work reduced by low levels of $PEEP_e$,[73,74] commonly 80%–90% of dynamic $PEEP_i$[75] if this is measured.
2. Patient effort may be sensed, and the ventilator cycled (triggered) to inspiratory assistance, by changes in any of P_{ao}, flow, volume, shape-signal and detection of neural drive (NAVA). During pressure triggering a fall in P_{ao} is usually sensed at the expiratory block of the ventilator. Sensing at the Y-piece may not be superior since there can be a similar delay in sensing, as the transducer is usually sited in the ventilator (the usual position) and this demands a similar or greater length of gas tubing. Flow triggering senses a fall in continuous circuit flow, and was introduced as a method of reducing inspiratory work. However, there has been a marked improvement of both pressure and flow triggering in modern ventilators with the trigger time delay falling from ~400 ms to <60 ms in most modern ventilators,[76] and a similar improvement in the maximum fall in airway pressure[77]; consequently, ventilator triggering contributes about 5% of respiratory effort. Attempts to improve the trigger function by oversetting the pressure sensitivity (<–0.5 cm H_2O) may lead to autocycling, which may also occur with overset flow triggering. This is due to the P and $\dot{V}$ effects of cardiac oscillations, hiccups, circuit rainout or mask leak with NIV, and has been reported as a cause of apparent respiratory effort in brain-dead patients.[78] Flow triggering reduces the risk of autocycling at a given trigger sensitivity, and reduces respiratory effort a small amount compared with pressure triggering; however, it does not alter the frequency of ineffective efforts, or patient effort following triggering.[76] A combination of shape-signal and volume triggering is used on the Vision (Philips Respironics) ventilator; the increased sensitivity of shape-signal triggering reduces effort but increases autocycling.[76]

INSPIRATION

Once inspiration is triggered or sensed by the ventilator, $\dot{V}$ is determined by P, Ti or $\dot{V}$. For example, during PSV ventilation a target P is held until expiration is sensed, and during ACV $\dot{V}$ is held for a set T_i. During ACV there may be continued inspiratory effort, and since inspiratory $\dot{V}$ is fixed, this will be reflected by a scalloping of the P_{ao}–T graph if $\dot{V}$ is inadequate. Again this may be illustrated using the equation of motion:

$$P_{mus} + P_{ao} = E_{rs} \bullet V + R_{rs} \bullet \dot{V} + P_o \quad (31.9)$$

P_{mus} will reflect the difference between P_{ao} due to E, R and P_o and the observed P_{ao}. In contrast, during P-cycled ventilation (PACV) greater patient effort is rewarded and inspiratory work is lower than during equivalent ACV.[79]

Modern ventilators allow adjustment of inspiratory $\dot{V}$ and $\dot{V}$ pattern, and the rate of rise of P_{ao}. Low inspiratory $\dot{V}$ rates during ACV results in significant inspiratory work, but this may be markedly reduced by increasing inspiratory $\dot{V}$ to 65 L/min.[80] However, these issues are quite complex, and f increases (probably due to a lower respiratory tract reflex) as $\dot{V}_I$ increases,[81] reducing Te, which may contribute to dynamic hyperinflation in patients with severe air-flow obstruction. During PSV and PACV, many ventilators allow adjustment of the rate of rise of P to its target. Although an excessively steep P ramp leads to earlier attainment of the P target and greater early $\dot{V}$ rates, this is associated with increased dyspnoea and effort, as is too flat a P ramp.[76]

CESSATION OF INSPIRATION

During PSV, an increase in airway resistance will result in a longer expiratory time constant and a delayed fall in $\dot{V}_I$. Since this is the usual trigger for cycling to expiration, the ventilator may continue to provide $\dot{V}_I$ while the patient desires to exhale. This commonly leads to recruitment of expiratory muscles, detected both clinically and as a transient rise in the end-inspiratory P_{aO}.[82] Some modern ventilators allow control of the fall in $\dot{V}_I$ that is sensed as end inspiration; the default is usually a reduction of $\dot{V}_I$ to 25% of the peak $\dot{V}_I$ rate. When airway resistance is high, a higher cycling threshold (e.g. 45%) can reduce T_i, V_T and $PEEP_i$ with reduced trigger effort. However, this may result in premature termination of inspiration in ARDS where the time constant is short. High levels of PSV (≥20 cm H_2O), weak respiratory muscles and mask leak with NIV are other common causes of asynchrony at the termination of inspiration. In this last group, PACV, which is time cycled, allows improved patient-ventilator synchrony at end-inspiration compared with PSV.[83]

High V_T, commonly associated with high levels of PSV, often precedes wasted efforts due to shortened T_e and $PEEP_i$. As asynchrony is reduced with less PSV, the optimum level of PSV will occur when there is minimal increase in f and P_{mus}. This typically occurs at a PSV of 13 cm H_2O with V_T 6 mL/kg and T_i 0.8 seconds.[84]

KEY REFERENCES

4. [No authors listed].Ventilation with lower tidal volumes as compared with traditional volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000;342:1301–1308.
15. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA*. 2010;303:865–873.
19. Grasso S, Stripoli T, De Michele M, et al. ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. *Am J Respir Crit Care Med*. 2007;176:761–767.
52. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med*. 2017;195(4):438–442.
70. Thille AW, Harrois A, Schortgen F, et al. Outcomes of extubation failure in medical intensive care unit patients. *Crit Care Med*. 2011;39:2612–2618.
74. Petrof BJ, Legare M, Goldberg P, et al. Continuous positive airway pressure reduces work of breathing and dyspnea during weaning from mechanical ventilation in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1990;141:281–289.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Lassen HC. A preliminary report on the 1952 epidemic of poliomyelitis in Copenhagen with special reference to the treatment of acute respiratory insufficiency. *Lancet*. 1953;1(6749): 37–41.
2. Mehta S, Hill NS. Noninvasive ventilation. *Am J Respir Crit Care Med*. 2001;163:540–547.
3. Bendixen HH, Hedley-White J, Laver MB. Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation: a concept of atelectasis. *N Engl J Med*. 1963;269:991–996.
4. [No authors listed].Ventilation with lower tidal volumes as compared with traditional volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000;342: 1301–1308.
5. Neto AS, Simonis FD, Barbas CS, et al. Lung-protective ventilation with low tidal volumes and the occurrence of pulmonary complications in patients without acute respiratory distress syndrome: a systematic review and individual patient data analysis. *Crit Care Med*. 2015;43: 2155–2163.
6. Futier E, Constantin J-M, Paugam-Burtz C, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med*. 2013;369: 428–437.
7. Hotchkiss JR, Blanch L, Murias G, et al. Effects of decreased respiratory frequency on ventilator-induced lung injury. *Am J Respir Crit Care Med*. 2000;161:463–468.
8. Rittayamai N, Katsios CM, Beloncle F, et al. Pressure-controlled vs volume-controlled ventilation in acute respiratory failure: a physiology-based narrative and systematic review. *Chest*. 2015;148: 340–355.
9. Lessard MR, Guerot E, Lorino H, et al. Effects of pressure-controlled with different I:E ratios versus volume-controlled ventilation on respiratory mechanics, gas exchange, and hemodynamics in patients with adult respiratory distress syndrome. *Anesthesiology*. 1994;80:983–991.
10. Edibam C, Rutten AJ, Collins DV, et al. Effect of inspiratory flow pattern and inspiratory to expiratory ratio on nonlinear elastic behavior in patients with acute lung injury. *Am J Respir Crit Care Med*. 2003;167:702–707.
11. Bersten AD, Bryan DL. Ventilator-induced lung injury: do dynamic factors also play a role? *Crit Care Med*. 2005;33:907–909.
12. Jonson B, Beydon L, Brauer K, et al. Mechanics of respiratory system in healthy anesthetized humans with emphasis on viscoelastic properties. *J Appl Physiol*. 1993;75:132–140.
13. Tuxen DV, Lane S. The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe airflow obstruction. *Am Rev Respir Dis*. 1987;136:872–879.
14. Li Bassi G, Saucedo L, Marti J-D, et al. Effects of duty cycle and positive end-expiratory pressure on mucus clearance during mechanical ventilation. *Crit Care Med*. 2012;40:895–902.
15. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA*. 2010;303:865–873.
16. Suter PM, Fairley B, Isenberg MD. Optimum end-expiratory airway pressure in patients with acute pulmonary failure. *N Engl J Med*. 1975;292: 284–289.
17. Gattinoni L, Pelosi P, Crotti S, et al. Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. *Am J Respir Crit Care Med*. 1995;151:1807–1814.
18. Vieira SRR, Puybasset L, Richecoeur J, et al. A lung computed tomographic assessment of positive end-expiratory pressure-induced lung overdistension. *Am J Respir Crit Care Med*. 1998;158:1571–1577.
19. Grasso S, Stripoli T, De Michele M, et al. ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. *Am J Respir Crit Care Med*. 2007;176:761–767.
20. Bersten AD. Measurement of overinflation by multiple linear regression analysis in patients with acute lung injury. *Eur Respir J*. 1998;12:526–532.
21. Fergusson ND. Oxygen in ICU: too much of a good thing? *JAMA*. 2016;316(15):1553–1554.
22. Nicholas TE, Power JHT, Barr HA. The pulmonary consequences of a deep breath. *Respir Physiol*. 1982; 49:315–324.
23. Pelosi P, Cardringher P, Bottino N, et al. Sigh in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 1999;159:872–880.
24. Marini JJ, Rodriguez M, Lamb V. The inspiratory workload of patient-initiated mechanical ventilation. *Am Rev Respir Dis*. 1986;134:902–909.
25. Bersten AD, Rutten AJ, Vedig AE, et al. Additional work of breathing imposed by endotracheal tubes, breathing circuits and intensive care ventilators. *Crit Care Med*. 1989;17:671–680.
26. Esteban A, Alia I. Clinical management of weaning from mechanical ventilation. *Intensive Care Med*. 1998;24:999–1008.
27. Strauss C, Louis B, Isabey D, et al. Contribution of the endotracheal tube and the upper airway to breathing workload. *Am J Respir Crit Care Med*. 1998; 119:794–798.
28. Brochard L, Harf A, Lorino H, et al. Inspiratory pressure support prevents diaphragmatic fatigue during weaning from mechanical ventilation. *Am Rev Respir Dis*. 1989;139:513–521.
29. Bersten AD, Rutten AJ, Vedig AE. Efficacy of presure support ventilation in compensating for apparatus work. *Anaesth Intensive Care*. 1993;21: 67–71.
30. Brochard L, Rua F, Lorino H, et al. Inspiratory pressure support compensates for the additional

work of breathing caused by the endotracheal tube. *Anesthesiology*. 1991;75:739–745.
31. Appendini L, Purro A, Gudjonsdottir M, et al. Physiologic response of ventilator-dependent patients with chronic obstructive pulmonary disease to proportional assist ventilation and continuous positive airway pressure. *Am J Respir Crit Care Med*. 1999;159:1510–1517.
32. Patel AR, Taylor S, Bersten AD. Comparison of automated pulse respiratory mechanics during supported ventilation with static mechanics. *Crit Care Resusc*. 2012;14:130–134.
33. Piquilloud L, Vignaux L, Bialais E, et al. Neurally adjusted ventilatory assist improves patient-ventilator interaction. *Intensive Care Med*. 2011;37: 263–271.
34. Demoule A, Clavel M, Rolland-Debord C, et al. Neurally adjusted ventilator assist as an alternative to pressure support ventilation in adults: a French multicentre randomized trial. *Intensive Care Med*. 2016;42(11):1723–1732.
35. Jain SV, Kollisch-Singule M, Sadowitz B, et al. The 30-year evolution of airway pressure release ventilation. *Intensive Care Med Exp*. 2016;4:11.
36. Walsh MA, Merat M, Rotta GL, et al. Airway pressure release ventilation improves pulmonary blood flow in infants after cardiac surgery. *Crit Care Med*. 2011;39:2599–2604.
37. Lim J, Litton E, Robinson H, et al. Characteristics and outcomes of patients treated with airway pressure release ventilation for acute respiratory distress syndrome: a retrospective observational study. *J Crit Care*. 2016;34:154–159.
38. MacIntyre N. Airway pressure release ventilation: hope or hype? *Crit Care Med*. 2011;39:2376–2377.
39. Maxwell RA, Green JM, Waldrop J, et al. A randomized prospective trial of airway release ventilation and low tidal volume ventilation in adult trauma patients with acute respiratory failure. *J Trauma*. 2010;69:501–511.
40. Gluck E, Heard S, Patel C, et al. Use of ultrahigh frequency ventilation in patients with ARDS: a preliminary report. *Chest*. 1993;103:1413–1420.
41. Ip T, Mehta S. The role of high-frequency oscillatory ventilation in the treatment of acute respiratory failure in adults. *Curr Opin Crit Care*. 2012;18: 70–79.
42. Sud S, Sud M, Friedrich JO, et al. High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): systematic review and meta-analysis. *BMJ*. 2010; 340:c2327. doi:10.1136/bmj.c2327.
43. Pillow JJ, Sly PD, Hantos Z, et al. Dependence of intrapulmonary pressure amplitudes on respiratory mechanics during high-frequency oscillatory ventilation in preterm lambs. *Pediatr Res*. 2002;52: 538–544.
44. Cools F, Askie LM, Offringa M, et al. Elective high-frequency oscillatory versus conventional ventilation in preterm infants: a systematic review and meta-analysis of individual patients' data. *Lancet*. 2010;375(9731):2082–2091.
45. Young D, Lamb SE, Shah S, et al. High-frequency oscillation for acute respiratory distress syndrome. *N Engl J Med*. 2013;368:806–813.
46. Ferguson ND, Cook DJ, Guyatt GH, et al. High-frequency oscillation in early acute respiratory distress syndriome. *N Engl J Med*. 2013;368: 795–805.
47. Malhotra A, Drazen JM. High-frequency oscillatory ventilation on shaky ground. *N Engl J Med*. 2013; 368:863–865.
48. Derdak S, Mehta S, Stewart TE, et al. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. *Am J Respir Crit Care Med*. 2002;166:801–808.
49. Hirschl RB, Pranikoff T, Wise C, et al. Initial experience with partial liquid ventilation in adult patients with the acute respiratory distress syndrome. *JAMA*. 1996;275:383–389.
50. Kacmarek RM, Wiedemann HP, Lavin PT, et al. Partial liquid ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2006;173:882–889.
51. Slutsky AS. Mechanical ventilation. *Chest*. 1993;104: 1833–1859.
52. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med*. 2017;195(4):438–442.
53. Hess D, Hirsch C, Marquis-D'Amico C, et al. Imposed work and oxygen delivery during spontaneous breathing with adult disposable manual ventilators. *Anesthesiology*. 1994;81:1256–1263.
54. Agarwal KS, Puliyel JM. A simple strategy to improve first breath oxygen delivery by self inflating bag. *Resuscitation*. 2000;45:221–224.
55. Girou E, Schortgen F, Delclaux C, et al. Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. *JAMA*. 2000;284:2361–2367.
56. Drakulovic MB, Torres A, Bauer TT, et al. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet*. 1999;354:1851–1858.
57. Mehta S, Burry L, Cook DJ, et al. Sleap: a multicenter randomized trial of daily awakening in critically ill patients being managed with a sedation protocol. *Am J Respir Crit Care Med*. 2012;185: A3882.
58. Patel SB, Kress JP. Sedation and analgesia in the mechanically ventilated patient. *Am J Respir Crit Care Med*. 2012;185:486–497.
59. Schweickert WD, Kress JP. Implementing early mobilization interventions in mechanically ventilated patients in the ICU. *Chest*. 2011;140: 1612–1617.
60. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363: 1107–1116.
61. Hough CL, Herridge MS. Long-term outcome after acute lung injury. *Curr Opin Crit Care*. 2012;18: 8–15.

62. Moss M, Nordon-Craft A, Malone D, et al. A randomized trial of an intensive physical therapy program for patients with acute respiratory failure. *Am J Respir Crit Care Med*. 2016;193:1101–1110.
63. Schaller SJ, Anstey M, Blobner M, et al. Early, goal-directed mobilization in the surgical intensive care unit: a randomized controlled trial. *Lancet*. 2016;388:1377–1388.
64. MacIntyre NR. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. *Chest*. 2001;120:375S–396S.
65. Tobin MJ, Perez W, Guenther SM, et al. The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation. *Am Rev Respir Dis*. 1986;134:1111–1118.
66. Leitch EA, Moran JL, Grealy B. Weaning and extubation in the intensive care unit. Clinical or index-driven approach? *Intensive Care Med*. 1996;22:752–759.
67. Frutos-Vivar F, Ferguson ND, Esteban A, et al. Risk factors for extubation failure in patients following a successful spontaneous breathing trial. *Chest*. 2006;130:1664–1671.
68. Brochard L, Rauss A, Benito S, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. *Am J Respir Crit Care Med*. 1994;150: 896–903.
69. Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. *N Engl J Med*. 1995;332: 345–350.
70. Thille AW, Harrois A, Schortgen F, et al. Outcomes of extubation failure in medical intensive care unit patients. *Crit Care Med*. 2011;39:2612–2618.
71. Appendini L. Ventilator waveforms-based patient-ventilator asynchrony detection: valuable tool or a pipe dream in the clinical setting? *Crit Care Med*. 2011;39:2566–2568.
72. Colombo D, Cammarota G, Alemani M, et al. Efficacy of ventilator waveform observation in detecting patient-ventilator asynchrony. *Crit Care Med*. 2011;39:2452–2457.
73. Smith TC, Marini JJ. Impact of PEEP on lung mechanics and work of breathing in severe airflow obstruction. *J Appl Physiol*. 1988;65:1488–1499.
74. Petrof BJ, Legare M, Goldberg P, et al. Continuous positive airway pressure reduces work of breathing and dyspnea during weaning from mechanical ventilation in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1990;141:281–289.
75. Ranieri VM, Giuliiani R, Cinnella G, et al. Physiologic effects of positive end-expiratory pressure in patients with chronic obstructive pulmonary disease during acute ventilatory failure and controlled mechanical ventilation. *Am Rev Respir Dis*. 1993;147:5–13.
76. Sassoon CSH. Triggering of the ventilator in patient-ventilator interaction. *Respir Care*. 2011;56:39–51.
77. Alsanian P, El Atrous S, Isabey D, et al. Effects of flow triggering on breathing effort during partial ventilatory support. *Am J Respir Crit Care Med*. 1998;157:135–143.
78. Willatts SM, Drummond G. Brainstem death and ventilator trigger settings. *Anaesthesia*. 2000;55:676–677.
79. Cinnella G, Conti G, Lofaso F, et al. Effects of assisted ventilation on the work of breathing: volume controlled versus pressure-controlled ventilation. *Am J Respir Crit Care Med*. 1996;153:1025–1033.
80. Ward ME, Corbeil C, Gibbons W, et al. Optimization of respiratory muscle relaxation during mechanical ventilation. *Anesthesiology*. 1988;69:29–35.
81. Corne S, Gillespie D, Roberts D, et al. Effect of inspiratory flow rate on respiratory rate in intubated ventilated patients. *Am J Respir Crit Care Med*. 1997;156:304–308.
82. Parthasarathy S, Jubran A, Tobin MJ. Cycling of inspiratory and expiratory muscle groups with the ventilator in airflow limitation. *Am J Respir Crit Care Med*. 1998;158:1471–1478.
83. Calderinin E, Confalonieri M, Puccio PG, et al. Patient-ventilator asynchrony during noninvasive ventilation: the role of expiratory trigger. *Intensive Care Med*. 1999;25:662–667.
84. Thille AW, Cabello B, Galia F, et al. Reduction of patient-ventilator asynchrony by reducing tidal volume during pressure support ventilation. *Intensive Care Med*. 2008;34:1477–1486.

32

Humidifiers and inhalation therapy

Steven T Galluccio, Andrew D Bersten

The upper airway normally warms, moistens and filters inspired gas. When these functions are impaired by disease or when the nasopharynx is bypassed by endotracheal intubation, artificial humidification of inspired gases must be provided.

PHYSICAL PRINCIPLES

Humidity, the amount of water vapour in a gas, may be expressed as:

- *absolute humidity (AH):* the total mass of water vapour in a given volume of gas at a given temperature (g/m^3)
- *relative humidity (RH):* the actual mass of water vapour (per volume of gas) as a percentage of the mass of saturated water vapour, at a given temperature. Saturated water vapour exerts a saturated vapour pressure (SVP). Because the SVP has an exponential relation with temperature (Table 32.1), addition of further water vapour to the gas can occur only with a rise in temperature
- *partial pressure.*

PHYSIOLOGY

Clearance of surface liquids and particles from the lung depends on beating cilia, airway mucus and transepithelial water flux. Airway mucus is derived from secretions from goblet cells, submucosal glands and Clara cells and from capillary transudate. Conducting airways are lined with pseudostratified, ciliated columnar epithelium and numerous fluid-secreting glands. As the airway descends, the epithelium becomes stratified, and then cuboidal and partially ciliated, with very few secretory glands at the terminal airways. The cilia beat in a watery layer (sol) over which is a viscous mucus layer (gel), and move a superficial layer of mucus from deep within the lung towards the glottis (at a rate of 10 mm/min at 37°C and 100% RH). Both cilia function and mucus composition are influenced by temperature and adequate humidification.

The nasal mucosa has a large surface area with an extensive vascular network that humidifies and warms inhaled gas more effectively than during mouth breathing. Heating and humidification of dry gas are progressive down the airway, with an isothermic saturation boundary (i.e. 100% RH at 37°C or AH of 43 g/m^3) just below the carina.[1] Under resting conditions, approximately 250 mL of water and 1.5 kJ (350 kcal) of energy are lost from the respiratory tract in a day. A proportion (10%–25%) is returned to the mucosa during expiration due to condensation.

The minimal moisture level to maintain ciliary function and mucus clearance is uncertain. Although reproducing an isothermic saturation boundary at the carina may be ideal, it does not seem essential in all situations. Mucus flow is markedly reduced when RH at 37°C falls to less than 75% (AH of 32 g/m^3), and ceases when RH is 50% (AH of 22 g/m^3).[2] This suggests that an AH exceeding 33 g/m^3 is needed to maintain normal function. Mucociliary function is also impaired by upper respiratory tract infection, chronic bronchitis, cystic fibrosis, bronchiectasis, immotile cilia syndrome, dehydration, hyperventilation, general anaesthetics, opioids, atropine and exposure to noxious gases. High fractional inspired oxygen concentrations (Fi_{O_2}) may lead to acute tracheobronchitis, with depressed tracheal mucus velocity within 3 hours.[3] Inhaled β_2-adrenergic agonists increase mucociliary clearance by augmenting ciliary beat frequency, and mucus and water secretion.[4]

CLINICAL APPLICATIONS OF HUMIDIFICATION

TRACHEAL INTUBATION

The need for humidification during endotracheal intubation and tracheostomy is unquestioned. As the upper airway is bypassed, RH of inspired gas falls to less than 50% with adverse effects, including[5]:

- increased mucus viscosity
- depressed ciliary function
- cytological damage to the tracheobronchial epithelium, including mucosal ulceration, tracheal inflammation and necrotising tracheobronchitis[6]
- microatelectasis from obstruction of small airways, and reduced surfactant leading to reduced lung compliance

ABSTRACT

The adequate conditioning of inhaled gases and the effective delivery of therapeutic aerosols are both routine but vitally important aspects of managing critically ill patients. These issues can be tackled from a variety of approaches, with different types of humidifiers and aerosol generators and differing indications and modes of implementation. Surprisingly, there is often a lack of high-quality data to guide practice. Furthermore, despite being core business, knowledge of these facets amongst critical care physicians appears to be lacking, and guidelines when available and supported by evidence are not commonly implemented. Ongoing research is needed to further clarify how to best to apply these components of critical care medicine.

KEYWORDS

Humidifiers
nebulisers and vaporisers
bronchodilator agents
administration
inhalational
aerosols

Table 32.1 Relationship of temperature and saturated vapour pressure

TEMPERATURE (°C)	SATURATED VAPOUR PRESSURE (mm Hg)	(kPa)	ABSOLUTE HUMIDITY (g/m^3)
0	4.6	0.6	4.8
10	9.2	1.2	9.3
20	17.5	2.3	17.1
30	31.3	4.2	30.4
34	39.9	5.3	37.5
37	47.1	6.3	43.4
40	55.3	7.4	51.7
46	78.0	10.4	68.7

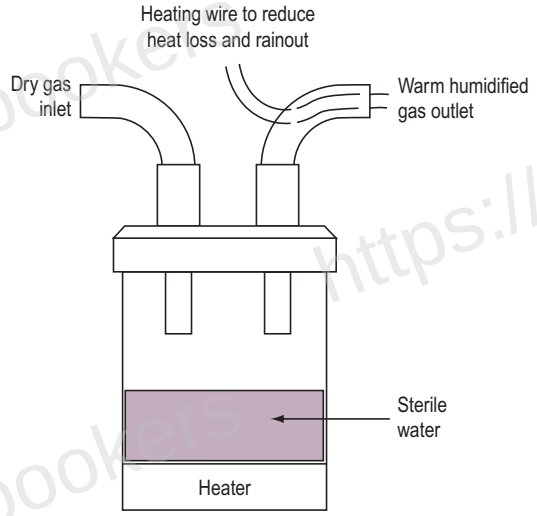


Figure 32.1 Hot-water 'blow-by' humidifier.

- airway obstruction due to tenacious or inspissated sputum with increased airway resistance.

Metaplasia of the tracheal epithelium occurs over weeks to months in patients with a permanent tracheostomy. These patients do not usually require humidified gas, suggesting that humidification occurs lower down the respiratory tree. Nevertheless, humidification of inspired gas may be needed during an acute respiratory tract infection.

HEAT EXCHANGE

The respiratory tract is an important avenue to adjust body temperature by heat exchange. Humidification of gases reduces the fall in body temperature associated with anaesthesia and surgery.[5] Excessive heat from humidification may produce mucosal damage, hyperthermia and overhumidification.[7] However, if water content is not excessive, mucociliary clearance is unaffected up to temperatures of 42°C. Overhumidification may increase secretions and impair mucociliary clearance and surfactant activity, resulting in atelectasis.[6]

IDEAL HUMIDIFICATION

The basic requirements of a humidifier should include the following features[8]:

- the inspired gas is delivered into the trachea at 32°C–36°C with a water content of 30–43 g/m^3
- the set temperature remains constant and does not fluctuate
- humidification and temperature remain unaffected by a large range of fresh gas flows, especially high flows
- the device is simple to use and to service
- humidification can be provided for air, oxygen or any mixture of inspired gas, including anaesthetic agents
- the humidifier can be used with spontaneous or controlled ventilation
- there are safety mechanisms, with alarms, against overheating, overhydration and electrocution
- the resistance, compliance and dead space characteristics do not adversely affect spontaneous breathing modes
- the sterility of the inspired gas is not compromised.

METHODS AND DEVICES

WATER-BATH HUMIDIFIERS

Inspired gas is passed over or through a water reservoir to achieve humidification. Their efficiency is dependent on ambient temperature and the surface area available for gas vaporisation.

Cold-water humidifiers

These units are simple and inexpensive but are inefficient, with a water content of approximately 9 g/m^3 (i.e. approximately 50% RH at ambient temperatures). They are also a potential source of microbiological contamination. Routine use of cold-water humidifiers to deliver oxygen with simple face masks is both unnecessary and at risk of suggesting the gas is adequately humidified.

Hot-water humidifiers (Figs 32.1 and 32.2)

Inspired gas is passed over (blow-by humidifier) or through (bubble or cascade humidifier) a heated-water reservoir. Gas leaving the reservoir theoretically contains high water content. The water-bath temperature is thermostatically controlled (e.g. at 45°C–60°C) to

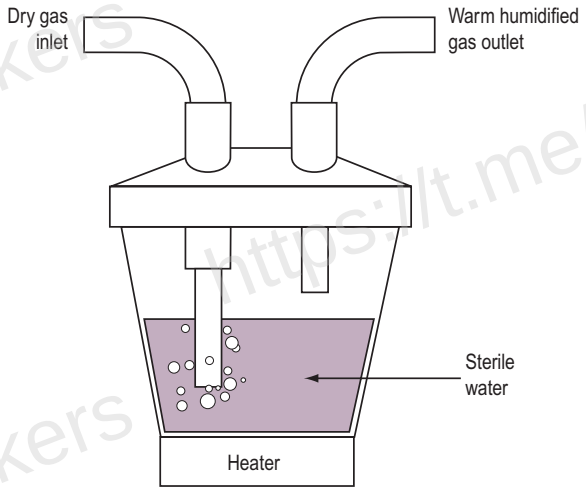


Figure 32.2 Hot-water 'cascade' or 'bubble' humidifier.

compensate for cooling along the inspiratory tubing targeting an inspired RH of 100% at 37°C. A heated wire may be sited in the inspiratory tubing to maintain preset gas temperature and humidity. It is commonly believed that hot-water humidifiers do not produce aerosols, but microdroplets (mostly less than 5 µm diameter) have been reported with bubble humidifiers,[9] and this may be a potential source of infection.

Fisher–Paykel humidifier This is a commonly used blow-by humidifier. The delivery hose is heated by an insulated heating wire to achieve a manual preset inspired temperature. Audible alarms indicate disconnection and variations greater than 2°C from the set delivery temperature. The heater base is protected from overheating by a thermostat set at 47°C. If this fails, another safety thermostat operates at 70°C. A disposable humidification chamber is filled manually with water or by a gravity-feed set. To minimise rainout, the chamber outlet can be set at a temperature less than the delivery hose outlet temperature; 2°C–3°C is usually adequate and does not compromise RH. Temperature alarms are fixed at 41°C and 29.5°C, with a back-up safety set at 66°C for the delivery chamber.

Although these humidifiers are often regarded as providing optimal humidification in ventilated patients, their performance is lower than expected both in practice and under optimal conditions in bench studies.[10] Under conditions of high ambient and/or high ventilator output temperature, the inlet temperature to the humidification chamber can be high enough that the heater base operates at a low enough temperature that humidification is impaired, with reduction in inspired water content.[10] The automatic compensation now available on this humidifier helps to compensate for poor performance, which can also be prevented by setting the chamber outlet and hose to 40°C. High minute ventilation is well tolerated, but a small decrease in water content output has also been found with higher respiratory rates.[11]

HEAT AND MOISTURE EXCHANGERS

Heat and moisture exchangers (HMEs) are popular intensive care unit (ICU) humidifiers due to their simplicity and increased efficiency. Modern HMEs are light with a small dead space (30–95 mL) but show great heterogeneity in humidity output, often not matching manufacturer-claimed performance.[12]

Hygroscopic HMEs adsorb moisture on to a foam or paperlike material that is chemically coated (often calcium chloride or lithium chloride), and this tends to increase their efficiency (i.e. AH approximately 30 g/m^3) compared with hydrophobic HMEs (i.e. AH 20–25 g/m^3).[13-18] Such hydrophobic HMEs possess antimicrobial properties and may act as a microbial filter (HME filter or 'HMEF'). These filters can have efficiencies greater than 99.9977%[19] (i.e. less than 23 out of 1 million bacteria will pass through; filters that can exclude all virus particles are not currently available). Modern HMEs include both hydroscopic and hydrophobic properties (Fig. 32.3). However, because nosocomial pneumonia is primarily due to aspiration of oropharyngeal secretions followed by secondary ventilator tubing colonisation, HMEs have not been shown to reduce the frequency of nosocomial pneumonia more than hot-water humidifiers when compared during prolonged ventilation.[19-21]

The efficiency of older HMEs decreases with time[11]; however, modern HMEs may retain their ability to humidify for prolonged periods with minimal change in resistance (a measure of tube patency and thus adequacy of humidification).[22,23] In patients undergoing invasive ventilation for a mean duration greater than 1 week, there was no difference in endotracheal tube resistance between HME and active humidification.[23] However, allocation of humidification device was not randomised but based on perceived clinical need. Consequently, HMEs that achieve relatively high AH may be suitable for long-term mechanical ventilation in selected patients, particularly because the majority of reported HME complications (e.g. thick secretions and endotracheal tube occlusion) occur with units of lower humidification levels.[24-26] Nevertheless, HMEs increase dead space and imposed work of breathing and cannot match the humidification offered by hot-water humidifiers, which remain the gold standard, particularly if secretions are thick or bloody or minute ventilation is high[16,19,27] or in children and neonates.

COMPLICATIONS OF HUMIDIFICATION

INADEQUATE HUMIDIFICATION

An AH exceeding 30 g/m^3 is recommended in respiratory care.[27] Inadequate humidification is usually a problem only with HMEs. However, with hot-water

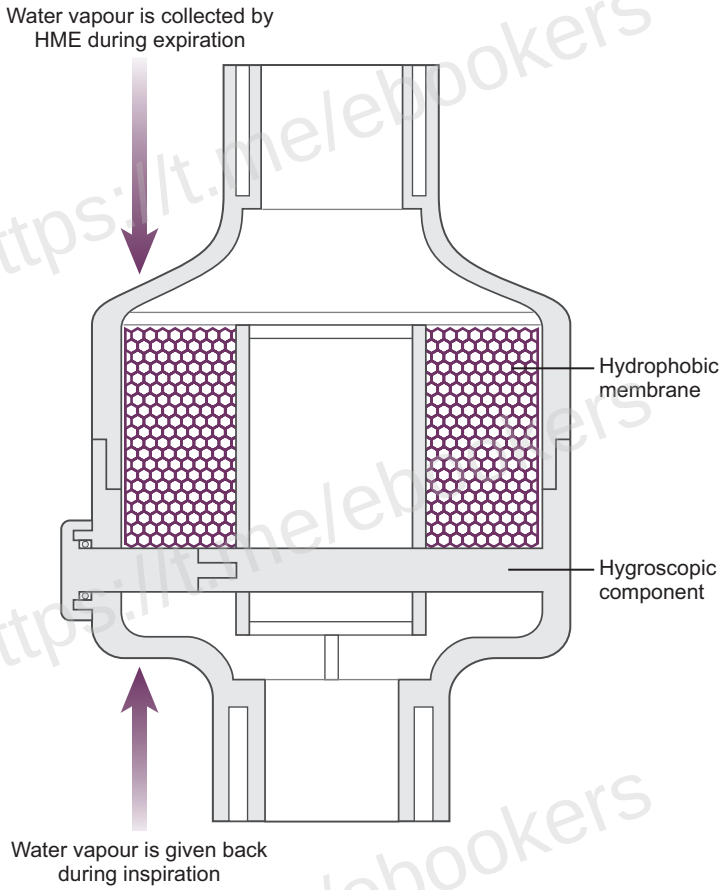


Figure 32.3 Schematic representation of a heat and moisture exchanger (HME). *Adapted from Al Ashry HS, Modrykamien AM. Humidification during mechanical ventilation in the adult patient.* Biomed Res Int. *2014;2014:715434.*

humidifiers, efficiency is reduced by increasing gas flow rates and rainout. A decrease of approximately 1°C occurs for each 10 cm of tubing beyond the end of the delivery hose (i.e. the Y-connector and right-angled connector) and should be catered for. Inadequate humidification in high-frequency ventilation can be overcome by using superheated humidification of the entrained gas with a temperature thermistor built into the endotracheal tube.[24,28]

OVERHUMIDIFICATION

Overheating malfunction of hot-water humidifiers may cause a rise in core temperature, water intoxication, impaired mucociliary clearance and airway burns.[7]

IMPOSED WORK OF BREATHING

The work of breathing imposed by a humidifier is primarily resistive work and increases with inspiratory flow rate; the progressive increase in water content of HMEs is also associated with increased resistance.[29] The Fisher–Paykel humidifier imposes relatively low work compared with a bubble humidifier,[30] and HMEs typically have a resistance of 2.5 cm H_2O/L per second.[16]

INFECTION

Humidifiers do not appear to be an important factor in nosocomial respiratory tract infection. Although water reservoirs represent a good culture medium for bacteria such as *Pseudomonas* species, it is rare to culture bacteria from humidifiers and is usually preceded by colonisation of the circuit by the patient's own flora within the first 24 hours of use.[31,32] Indeed the incidence of nosocomial pneumonia is reported to be higher (due to outside contamination) if the circuit is changed frequently (every 24 or 48 hours).[32,33]

HUMIDIFICATION DURING NON-INVASIVE VENTILATION

The hygrometric effects of non-invasive ventilation (NIV) depend upon several factors, including the type

of ventilator (conventional versus turbine), patient–ventilator interface, V_T, peak inspiratory flow rates, Fi_{O_2}, degree of mask leak and even ambient room temperature.[34-36] NIV applied without artificial humidification has been associated with accumulation of dried secretions in the oropharynx with subsequent aspiration, difficult intubation or frank airway obstruction.[37] In healthy volunteers a delivered AH of at least 15 mg H_2O/L was necessary to ensure comfort during NIV.[38] This level is achievable with either passive or active humidification, but in patients with acute respiratory failure, a higher humidity output may be required. Furthermore, the increased dead space and work of breathing associated with HMEs may be undesirable in these situations.[36] Acknowledging the lack of robust data, current guidelines suggest the use of heated humidification over HMEs.[27]

HUMIDIFICATION FOR OXYGEN THERAPY DURING SPONTANEOUS BREATHING

Despite the ubiquity of oxygen therapy, there is no evidence to guide the addition of humidification for spontaneously breathing patients. No discrete oxygen flow rate or duration of exposure mandates artificial humidification. However, even with flow rates of ≤15 L/min, patient discomfort during oxygen therapy is ameliorated with the use of heated humidification compared with bubble humidifiers or no artificial humidification at all.[39,40] Yet, it is unknown to what extent patient discomfort signals inadequate humidification and the potential for complications such as deranged mucociliary transport or increased airway resistance. An emerging relevant trend is the use of 'high-flow nasal cannula (HFNC) therapy', whereby significantly higher rates of gas flow, typically at 30–60 L/min, are delivered via nasal cannulae.[41,42] In this context, heated humidification is always recommended.

INHALATION THERAPY

Therapeutic aerosols are particles suspended in gas that are inhaled and deposited within the respiratory tract. Numerous factors, including particle size, inertia and physical nature, gravity, volume and pattern of ventilation, temperature and humidity, airway geometry, lung disease and the delivery system, alter aerosol deposition. In general, particles of diameter 40 µm deposit in the upper airway, those of 8–15 µm deposit in bronchi and bronchioles, those of 3–5 µm deposit in peripheral conducting airways and those of 0.8–3.0 µm settle in lung parenchyma. Optimal particle size will depend on the clinical indication and agent used. Obviously, if an HME with filtration characteristics is being used, the aerosol needs to be delivered proximal to the filter. Clinical efficacy of newer HME designs incorporating the facility for aerosol delivery remains to be quantified.[43]

AEROSOL DELIVERY

Therapeutic aerosols may be delivered by nebuliser (jet, ultrasonic or vibrating mesh), pressurised metered-dose inhaler (pMDI) or dry-powdered inhaler (DPI). Although each of these methods tends to be less efficient in ventilated patients, provided that care is taken to optimise their performance, each can provide equivalent clinical effect. Despite being commonly used in the ICU, literacy around aerosol therapy appears low amongst intensive care physicians.

NEBULISERS

The most common jet nebulisers are sidestream nebulisers. These use an extrinsic gas flow through a narrow orifice, to create a pressure gradient that draws the drug mixture from a liquid reservoir (i.e. Bernoulli principle; Fig. 32.4). The gas is then directed at a baffle to reduce the mean particle size. This extrinsic gas flow (usually 3–10 L/min) adds to the inspiratory flow and may increase patient tidal volume unless the ventilator automatically compensates or the preset tidal volume is adjusted. Furthermore, this additional gas flow may impair ventilator triggering because it may prevent the development of a negative pressure or necessary reduction in continuous flow needed. Mainstream nebulisers use inspiratory gas flow to actuate nebulisation. These are commonly large-volume water nebulisers that entrain air to achieve fresh gas flow rates of 20–30 L/min.

Ultrasonic nebulisers use high-frequency sound waves (typically 1 MHz) to create an aerosol above a liquid reservoir, to produce small uniform droplets (<5 µm) and a high mist density (i.e. 100–200 g/m^3). Tidal volume is not altered; however, ultrasonic nebulisers may cause overhydration and increased airway resistance. Further drawbacks in the critical care setting include size, poor battery life and the potential for drug inactivation by ultrasonic waves and heating.[44,45]

More recent nebuliser designs have used a vibrating mesh or plate. Medication in solution or suspension is forced through multiple apertures in the mesh or plate to produce an aerosol. A variety of vibrating mesh nebulisers are commercially available; common features include aerosol generation with high fine-particle fraction and overall higher drug output with minimal residual volume compared with jet nebulisers; additional benefits over ultrasonic types are the lack of heating effect or potential for drug degradation.[44] A comparison of the features of aerosol generators is shown in Table 32.2.

Nebuliser aerosol deposition is highly variable, with significant rainout in the ventilatory circuit, endotracheal tube and large conducting airways. In a bench study, delivery ranged from 6% of nebuliser charge to 37% depending upon humidification and breath activation; parallel in vivo data were similar but found a 20-fold difference in drug delivery.[47] Numerous factors

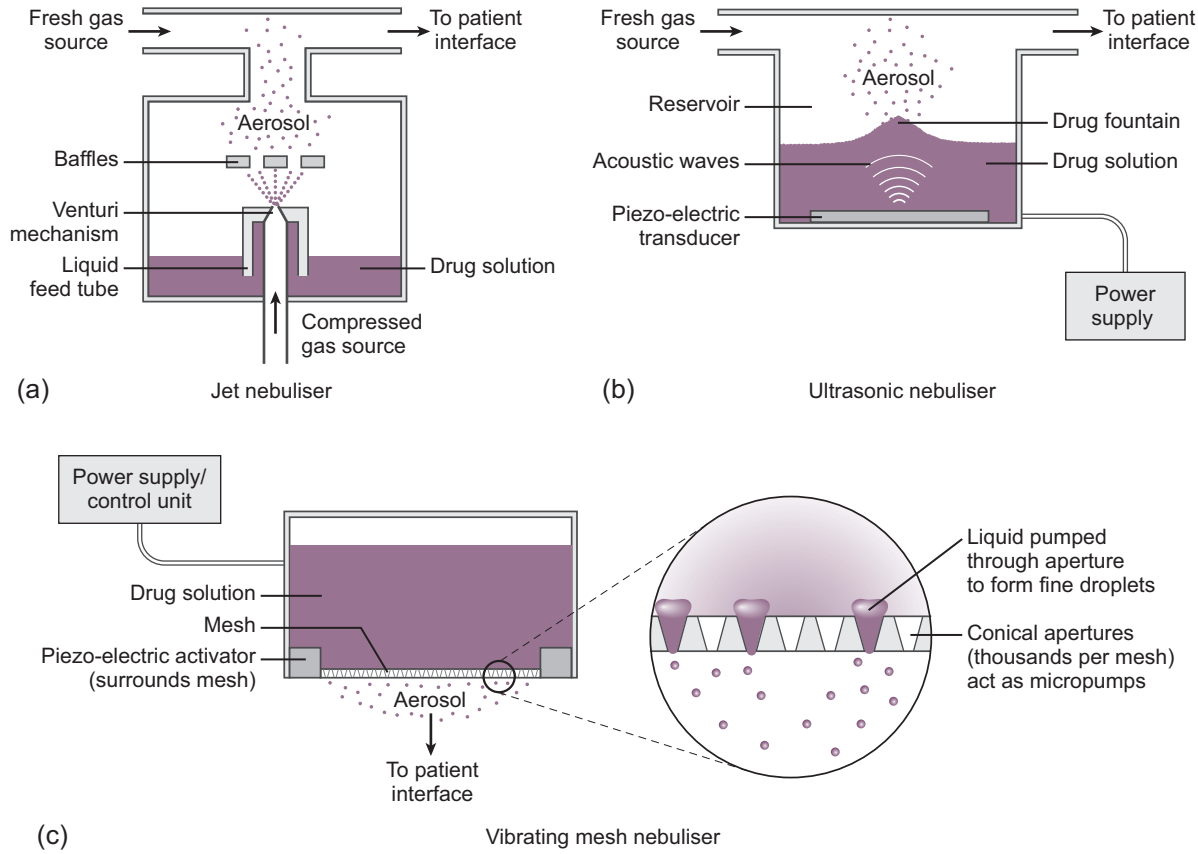


Figure 32.4 Schematic representation of nebuliser design (a) jet nebuliser, (b) ultrasonic nebuliser and (c) vibrating mesh nebuliser. *Yeo LY, Friend JR, McIntosh MP, et al. Ultrasonic nebulization platforms for pulmonary drug delivery.* Expert Opin Drug Deliv. *2010;7(6):663–679.*

have been shown to improve aerosol deposition, but only some of these are commonly practiced (Table 32.3). For example, although heating and humidification reduce aerosol deposition approximately 50% due to increase in both droplet size and rainout, regular circuit disconnection and exclusion of humidification prior to nebulisation are not practical. The position of the aerosol generator within the ventilator circuit also effects aerosol delivery. Vibrating mesh and ultrasonic nebulisers, as well as pMDIs, are most efficient when placed in the inspiratory limb of the circuit approximately 15 cm from the Y-piece.[50] Jet nebulisers function more efficiently when placed closer to the inspiratory port of the ventilator (further from the Y-connector), allowing the tubing to act as a spacer or aerosol-holding chamber. Inspiratory activation of the nebuliser increases deposition by twofold and threefold under dry and humidified conditions, respectively[45]; use of a large chamber fill, tidal volume of 500 mL or more and minimisation of turbulent inspiratory flow (low flow rate, prolonged inspiratory time) also augment aerosol delivery.[40]

METERED-DOSE INHALERS

pMDIs contain drug in ethanolic solution with a hydrofluoroalkane (HFA) propellant, allowing a relatively fixed volume (i.e. dose) to be delivered with each actuation (e.g. 100 µg for salbutamol and 20 µg for ipratropium).[44,51] Aerosol delivery is approximately 4%–6% in ventilated adults but increases to 11% when a spacer chamber is used, which is similar to optimal no-spacer values reported in the ambulant population.[52] Similar to nebulisers, absence of humidification, inspiratory limb position, inspiratory activation and minimisation of turbulence by lowering inspiratory flow rate and prolonging inspiratory time will increase aerosol delivery. It is important to avoid use of an elbow adapter because this has been associated with dramatic reductions in aerosol delivery and efficacy.

DRY-POWDERED INHALERS

DPIs are commonly used in ambulant practice. Their use is not recommended in patients undergoing mechanical ventilation because they are breath actuated (requiring inspiratory flow rates close to 60 L/

Table 32.2 Aerosol generator characteristics

NEBULISER TYPE	JET	ULTRASONIC	VIBRATING MESH	pMDI
Power source	Compressed medical gas	Electrical mains	Electrical mains or batteries	Liquefied compressed gas propellant
Subtypes	Breath enhanced, breath actuated	Small volume, large volume	Active, passive	N/A
Treatment time	Long	Intermediate	Short	Short
Output rate	+	++	+++	++
Ease of use	++	++	+++	+/–
Efficiency	+	++	+++	++
Performance variability	+++	++	+	+
Residual volume	0.8–2 mL	Variable	<0.2 mL	N/A
Effects on aerosol:				
Temperature	Decreases	Increases	Nil effect	Nil effect
Suspensions	Low efficiency	Poor efficiency	Variable	N/A
Denaturation	+	++	–	N/A
Noise level	+++	–	–	–
Device Cost	+	+++	+++	++
Risk of contamination	++	++	+	–

pMDI, Pressurised metered-dose inhaler; *N/A,* not applicable.
See references 43, 46.

min) and, moreover, circuit humidification can cause powder clumping with impeded aerosol formation.[53]

CLINICAL APPLICATIONS OF INHALATION THERAPY

HUMIDIFICATION

Humidifiers produce gas with a water content dictated by temperature and water vapour pressure, whereas nebulisers produce gas with a water content determined by the aerosol content. The latter can provide water to the respiratory tract, particularly if the water reservoir is heated to increase mist density. However, the risk of infection is increased because droplets can carry bacteria to the alveoli. Consequently, only sterile water should be used to fill the reservoir, and all units should be regularly changed and sterilised.

MUCOLYTICS

N-acetylcysteine and other thiol derivatives such as carbocysteine and erdosteine have the ability to liquefy mucus by directly severing disulfide bridges in mucoproteins and DNA. In outpatients with chronic obstructive pulmonary disease (COPD), particularly in those not receiving inhaled corticosteroids, these mucolytic agents result in a very modest reduction in COPD exacerbations and improved quality of life.[54,55] Notably, these clinical trials have used oral formulations of these agents because inhalational administration can induce bronchospasm. Underway currently is a multicentre trial of nebulised *N*-acetylcysteine (in conjunction with salbutamol) in invasively ventilated ICU patients.[56] Case reports of recombinant human DNase (dornase alfa) appear promising when standard regimens fail to clear thick secretions,[52] but the main evidence base for DNase utility is limited to bronchiectasis specifically due to cystic fibrosis.[57,58]

BRONCHODILATOR THERAPY

Optimal aerosol delivery and bronchodilator response are extremely important in critically ill patients with severe airflow limitation; this can be achieved using either a nebuliser or pMDI technique, provided that care is taken to optimise performance. For mechanically ventilated patients, there is currently no evidence to recommend one device type over another.[59] Efficacy of pMDI administration is improved by use of a spacer with actuation synchronised with the onset of inspiration.[44] The response can be judged clinically, and in ventilated patients monitored by changes in peak-to-plateau airway pressure gradient, calculated airways resistance and intrinsic positive end-expiratory pressure (PEEP). Numerous studies show effective bronchodilatation with β_2-agonists and anticholinergic

Table 32.3 Factors favouring effective aerosol delivery

Ventilator settings	Lower flow rate (30–50 L/min ideal) Long inspiratory time Higher PEEP Larger tidal volume (≥500 mL) Lower bias-flow Breath-actuated mechanism
Circuit factors	Larger endotracheal or tracheostomy tube better Delivery *without* humidification better (i.e. remove HME; turn off heated humidification 10 min prior to therapy) Preferred positioning of aerosol generator (during invasive mechanical ventilation): VMN, USN, pMDI: inspiratory limb, 15 cm from Y-piece Jet nebuliser: inspiratory limb, 15 cm from ventilator outlet Preferred positioning of aerosol generator (during NIV): Close to patient interface Driving gas: potentially increased peripheral deposition with heliox
Drug factors	Particle size 2–5 μm more likely to deposit further in respiratory tract
Patient factors	Ensure clear and patent airway
Type of aerosol generator	See Table 32.2 Nebulisers allow for continuous and potentially greater cumulative aerosol delivery For pMDIs, shake and warm to hand temperature prior to use

HME, Heat and moisture exchanger; *NIV*, non-invasive ventilation; *PEEP*, positive end-expiratory pressure; *pMDI*, pressurised metered-dose inhaler; *USN*, ultrasonic nebuliser; *VMN*, vibrating mesh nebuliser.
See references 42, 46, 48, 49.

agents such as ipratropium in ventilated patients, and their combination is more effective than a single agent alone.[52] For non-obstructive pulmonary conditions, including acute respiratory distress syndrome (ARDS), routine use of inhaled bronchodilators is not beneficial and has been associated with increased harm.[60,61]

Bronchodilator dosing

Standard doses of salbutamol for acute asthma are 2.5–5 mg administered by a nebuliser or 4–6 puffs of a pMDI (400–600 μg), but the bronchodilator response can be shorter lasting than in ambulatory subjects. Consequently, dosing should be 3–4 hourly. Ipatropium is usually administered as 0.5 mg by a nebuliser or four puffs (80 μg) of a pMDI. Higher or more frequent drug dosing is often effective when there is severe, reversible airflow obstruction, and continuous nebulisation of a β_2-agonist may be used in acute severe asthma until there has been a clinical response. If the patient is moribund with minimal ventilation or is unable to tolerate nebulisation, parenteral administration should be considered; however, under most circumstances, there is no particular benefit with this route.[62]

NON-INVASIVE VENTILATION

There is no requirement to interrupt NIV to administer inhaled bronchodilator therapy. Both nebulisers and pMDIs appear effective during NIV, although in this context, ultrasonic nebulisers are associated with greatest drug loss.[52,63-65] In contradistinction to invasive mechanical ventilation, optimal positioning of the aerosol generating device in a single-limb NIV circuit appears to be closer to the patient interface and distanced from the ventilator (i.e. between the mask and the leak port).[64]

HIGH-FLOW NASAL CANNULAE

There is very little evidence to guide aerosol delivery during HFNC. It is likely that at high gas flows, significant amounts of drug are lost both through impaction in the circuit and directly to the atmosphere,[64] but a successful approach has been described in a bench study.[66]

INHALED CORTICOSTEROIDS

Inhaled corticosteroids are recommended in moderate persistent asthma[67] and in COPD when associated with frequent exacerbations or persistent symptoms despite use of long-acting inhaled bronchodilators.[68] However, in acute episodes of these conditions, inhalational delivery does not preclude the need for systemic corticosteroid therapy.[69] Small-particle inhaled corticosteroids offer the theoretical benefit of improved total and peripheral lung distribution.[70] HFA-propelled ciclesonide, flunisolide and beclomethasone dipropionate all have mass median aerodynamic diameters (particle size) of less than 2 μm.[70,71] Emerging data would suggest that clinical efficacy is at least equivalent to larger-particle formulations with potential benefits of lower dosing and less adverse effects. Data in mechanically ventilated patients remain to be demonstrated.

DELIVERY OF ANTIBIOTICS AND ANTIVIRAL AGENTS

With clinical experience spanning many decades, aerosolised antibiotics have entered a renaissance. International surveys suggest that inhaled antibiotic use is common in ICU patients undergoing mechanical ventilation,[72] and several reviews of the topic have recently been published.[73-79] The main driver of this renewed interest has been the emergence of multidrug-resistant (MDR) pathogens. Albeit contentious, pulmonary delivery of antibiotics has theoretical benefits of achieving high tissue concentration at the site of infection while minimising systemic adverse effects. A further consideration is that in patients with

purulent secretions, antibiotic concentrations may need to exceed 10–25 times the minimum inhibitory concentration to be effective.[80]

The argument for inhaled antibiotics is most appealing for aminoglycosides and polymixins. These antibiotic classes exhibit concentration-dependent bactericidal effect and have significant systemic toxicities and are perhaps the best studied agents in this context. In humans, gentamicin by conventional intravenous dosing has been shown to reach only subinhibitory concentrations in the alveolar lining fluid.[81] In animal models of bronchopneumonia, inhaled amikacin achieved 3- to 30-time increases in lung tissue concentrations and better sterilisation of lung compared with intravenous administration.[82]

Inhaled tobramycin is strongly recommended in patients with cystic fibrosis and chronic *Pseudomonas aeruginosa* infection, due to its association with improvement in several clinically relevant end points, such as improved lung function per spirometry, improved quality of life and decreased exacerbation frequency and hospitalisation rates.[83-85] Similar benefit has been demonstrated with aztreonam, with lesser evidence for colistin.[76]

For the intensivist, a broader question goes to the role of inhaled antibiotics in treating ventilator-associated pneumonia (VAP) and ventilator-associated tracheitis (VAT). Improved clinical cure rates have been found with nebulised gentamicin[86] and colistin.[78,87] The presumption of emerging bacterial resistance with increased aerosolised antibiotic use, akin to the known risk with systemic delivery, is not confirmed by the available data. Paradoxically, emergence of resistance may be reduced via higher pathogen eradication rates, earlier intervention in treating VAT and reduced exposure to systemic therapy.[88]

However, overall the data suffer from methodological heterogeneity and small patient numbers. The described dosing in VAP (total daily amount) varies widely amongst studies: gentamcin (240–320 mg), colistin (75–300 mg) and amikacin (200–1200 mg). Moreover, there is little consistency in factors known to affect aerosol delivery, such as aerosol generator type or set ventilator parameters. Two systematic reviews of inhaled antibiotics in VAP (with or without combined parenteral antibiotics) have not shown definitive benefit.[75,77] A pragmatic approach is taken by the Infectious Diseases Society of America and American Thoracic Society Guidelines, which state that for patients with VAP due to MDR Gram-negative bacilli (susceptible only to aminoglycosides or polymyxins) both inhaled and systemic antibiotics are recommended, rather than systemic antibiotics alone.[89] It is also considered reasonable to add inhaled antibiotics for patients deteriorating despite appropriate parenteral therapy, even if the organism in not identified as MDR.[89] This rationale places preferential weighting of the potential benefits in these high-risk patient populations against any potential adverse effects. The same guidelines do not extend this recommendation to the treatment of VAT.[89] It should be noted that rarely, and ironically, even systemic adverse effects may result from inhaled administration.[79]

Other antimicrobials that have been safely nebulised include vancomycin, ceftazdime, fluoroquinolones and pentamidine. Inhaled amphotericin B may have a role in treating and preventing invasive fungal disease in select immunosuppressed patients (such as those with haematological malignancy or lung transplantation) but may result in bronchospasm. Aerosolised ribavirin has limited evidence of benefit for respiratory syncytial virus infection[90,91] but may have a significant role specifically in adult hematopoietic stem cell transplant recipients.[92] Ribavirin deposition in the circuit may cause valve malfunction, and concerns of teratogenicity in health care personnel have dictated its use with care.[91] Inhaled zanamivir is associated with reduced duration of illness with influenza infections but can also cause bronchospasm.[93] However, the inhalational powder is not recommended for nebulisation or use in mechanically ventilated patients due to potential for obstruction of the ventilator expiratory filter.[94]

SPUTUM INDUCTION

Hypertonic nebulised saline (typically as 3% solution) is effective in sputum induction for diagnosing *Pneumocystis jiroveci* pneumonia in patients with the acquired immunodeficiency syndrome. The need for bronchoscopy can be obviated,[95] with specificity of sputum induction approaching 100% and sensitivity of at least 55%.[96] Similar benefits are noted for diagnosis of pulmonary tuberculosis.[97] Sputum induction has been used to diagnose a number of other infections and appears to be safe in patients with severe airflow limitation.[98] In any case the procedure should be performed by trained personnel with appropriate personal and environmental protection.

SURFACTANT THERAPY

Surfactant preparations have been delivered by instillation and as an aerosol in neonates with respiratory distress syndrome and in adults with ARDS. Aerosolised surfactant can theoretically achieve more uniform distribution and avoid problems of instilling liquid into injured lungs. However, large amounts are needed for lung deposition, and preferential distribution occurs to less-damaged lung areas that receive better ventilation.[99] Unfortunately, clinical studies of exogenous surfactant in adult ARDS have not shown any mortality benefit and may be associated with excess harm.[100]

INHALED NITRIC OXIDE

The therapeutic potential of inhaled nitric oxide (iNO) lies as a selective pulmonary vasodilator with minimal systemic side effects. iNO improves outcomes in newborns with persistent pulmonary hypertension and

severe hypoxaemia, reducing the need for extracorporeal membrane oxygenation.[101] In adult patients with ARDS, iNO results in an improvement in oxygenation in approximately 60%–80% of patients, with a 10% reduction in pulmonary arterial pressure.[102] However, these physiological gains have not translated into benefits on mortality or duration of mechanical ventilation.[103] iNO is effective in assessment of pulmonary vasoreactivity, but practical difficulties and a lack of long-term safety data limit its application in the ongoing treatment of pulmonary arterial hypertension. Despite a lack of high-level evidence, iNO can be effective in salvaging a failing right ventricle in the setting of pulmonary hypertension. Potential adverse effects, in high doses, include methemoglobinemia, renal injury, direct pulmonary toxicity and, if stopped abruptly, rebound pulmonary hypertension.[103] Rapid deterioration following initiation of iNO might imply venoocclusive disease as the aetiology for the underlying pulmonary hypertension.

PROSTANOIDS

Inhaled prostanoids follow a similar pharmacological rationale to iNO. By selective pulmonary vasodilatation to well-aerated areas, similar improvements in oxygenation as iNO are achieved in patients with the ARDS.[104,105] Iloprost (a synthetic epoprostenol/prostacyclin analogue) has a longer half-life (approximately 20–30 minutes compared with 3 minutes for prostacyclin) and is approved for use in chronic pulmonary hypertension (2.5–5 mg 6–9 times/day).[106] Treprostinil has a longer half-life still, allowing 4 times daily dosing. With an established role in chronic pulmonary arterial hypertension, particular caution is required when delivering these agents systemically in critically ill patients with acute right ventricular failure because any benefit of reducing pulmonary vascular resistance can be offset by the potential for worsening oxygenation and inducing systemic hypotension due to non-selective pulmonary and systemic vasodilatation, respectively.

INHALED HELIUM MIXTURES

Helium is 7.2 and 8 times less dense than air and oxygen, respectively. This property is useful in the setting of increased airways resistance because less turbulent and more efficient laminar flow is encouraged. Therefore, albeit an inert gas without any direct anatomical effect, helium can improve dynamic respiratory mechanics and reduce work of breathing. Effect size relates to the relative helium concentration; in practice at least 60%–70% helium is required, limiting applicability to patients able to tolerate Fi_{O_2} of 30%–40%. Helium–oxygen mixtures (heliox) potentially have a role in managing obstructive disease of both the upper and lower airways.[102] However, clinical use of heliox remains controversial and without evidence-based guidelines. In patients with COPD exacerbations requiring NIV, heliox has not been proven to reduce the NIV failure or the duration of NIV.[107,108] Similarly, there is no definitive evidence that heliox improves outcomes in asthma exacerbations, but its use can be considered in mechanically ventilated patients with severe asthma.[42] It should be noted that heliox, as a driving gas, will influence delivery of other inhaled agents in a ventilator circuit and also aerosols via nebulisers. Heliox may improve particle distribution to the peripheral small airways, perhaps as a function of reduced turbulence.[109] There is some evidence that bronchodilators driven by heliox (vs oxygen) result in improved clinical outcomes.[110]

REFERENCES

1. Hedley RM, Allt-Graham J. Heat and moisture exchangers and breathing filters. *Br J Anaesth*. 1994; 73(2):227–236.
2. Forbes AR. Humidification and mucus flow in the intubated trachea. *Br J Anaesth*. 1973;45(8): 874–878.
3. Sackner MA, Landa J, Hirsch J, et al. Pulmonary effects of oxygen breathing. A 6-hour study in normal men. *Ann Intern Med*. 1975;82(1):40–43.
4. Lafortuna CL, Fazio F. Acute effect of inhaled salbutamol on mucociliary clearance in health and chronic bronchitis. *Respiration*. 1984;45(2): 111–123.
5. Chalon J, Patel C, Ali M, et al. Humidity and the anesthetized patient. *Anesthesiology*. 1979;50(3): 195–198.
6. Circeo LE, Heard SO, Griffiths E, et al. Overwhelming necrotizing tracheobronchitis due to inadequate humidification during high-frequency jet ventilation. *Chest*. 1991;100(1):268–269.
7. Shelly MP, Lloyd GM, Park GR. A review of the mechanisms and methods of humidification of inspired gases. *Intensive Care Med*. 1988;14(1):1–9.
8. Chamney AR. Humidification requirements and techniques. Including a review of the performance of equipment in current use. *Anaesthesia*. 1969; 24(4):602–617.
9. Rhame FS, Streifel A, McComb C, et al. Bubbling humidifiers produce microaerosols which can carry bacteria. *Infect Control*. 1986;7(8):403–407.
10. Lellouche F, Taille S, Maggiore SM, et al. Influence of ambient and ventilator output temperatures on performance of heated-wire humidifiers. *Am J Respir Crit Care Med*. 2004;170(10):1073–1079.
11. Schumann S, Stahl CA, Moller K, et al. Moisturizing and mechanical characteristics of a new counter-flow type heated humidifier. *Br J Anaesth*. 2007;98(4):531–538.
12. Lellouche F, Taille S, Lefrancois F, et al. Humidification performance of 48 passive airway humidifiers: comparison with manufacturer data. *Chest*. 2009;135(2):276–286.
13. Jackson C, Webb AR. An evaluation of the heat and moisture exchange performance of four

ventilator circuit filters. *Intensive Care Med*. 1992;18(5):264–268.
14. Mebius C. Heat and moisture exchangers with bacterial filters: a laboratory evaluation. *Acta Anaesthesiol Scand*. 1992;36(6):572–576.
15. Martin C, Papazian L, Perrin G, et al. Performance evaluation of three vaporizing humidifiers and two heat and moisture exchangers in patients with minute ventilation > 10 L/min. *Chest*. 1992; 102(5):1347–1350.
16. Shelly M, Bethune DW, Latimer RD. A comparison of five heat and moisture exchangers. *Anaesthesia*. 1986;41(5):527–532.
17. Sottiaux T, Mignolet G, Damas P, et al. Comparative evaluation of three heat and moisture exchangers during short-term postoperative mechanical ventilation. *Chest*. 1993;104(1): 220–224.
18. Unal N, Kanhai JK, Buijk SL, et al. A novel method of evaluation of three heat-moisture exchangers in six different ventilator settings. *Intensive Care Med*. 1998;24(2):138–146.
19. Kollef MH, Shapiro SD, Boyd V, et al. A randomized clinical trial comparing an extended-use hygroscopic condenser humidifier with heated-water humidification in mechanically ventilated patients. *Chest*. 1998;113(3):759–767.
20. Kelly M, Gillies D, Todd DA, et al. Heated humidification versus heat and moisture exchangers for ventilated adults and children. *Cochrane Database Syst Rev*. 2010;(4):CD004711.
21. Dreyfuss D, Djedaini K, Gros I, et al. Mechanical ventilation with heated humidifiers or heat and moisture exchangers: effects on patient colonization and incidence of nosocomial pneumonia. *Am J Respir Crit Care Med*. 1995;151(4):986–992.
22. Thomachot L, Boisson C, Arnaud S, et al. Changing heat and moisture exchangers after 96 hours rather than after 24 hours: a clinical and microbiological evaluation. *Crit Care Med*. 2000; 28(3):714–720.
23. Moran I, Cabello B, Manero E, et al. Comparison of the effects of two humidifier systems on endotracheal tube resistance. *Intensive Care Med*. 2011;37(11):1773–1779.
24. Misset B, Escudier B, Rivara D, et al. Heat and moisture exchanger vs heated humidifier during long-term mechanical ventilation. A prospective randomized study. *Chest*. 1991;100(1):160–163.
25. Martin C, Perrin G, Gevaudan MJ, et al. Heat and moisture exchangers and vaporizing humidifiers in the intensive care unit. *Chest*. 1990;97(1): 144–149.
26. Cohen IL, Weinberg PF, Fein IA, et al. Endotracheal tube occlusion associated with the use of heat and moisture exchangers in the intensive care unit. *Crit Care Med*. 1988;16(3): 277–279.
27. Restrepo RD, Walsh BK. Humidification during invasive and noninvasive mechanical ventilation: 2012. *Respir Care*. 2012;57(5):782–788.
28. Gluck E, Heard S, Patel C, et al. Use of ultrahigh frequency ventilation in patients with ARDS. A preliminary report. *Chest*. 1993;103(5):1413–1420.
29. Ploysongsang Y, Branson R, Rashkin MC, et al. Pressure flow characteristics of commonly used heat-moisture exchangers. *Am Rev Respir Dis*. 1988;138(3):675–678.
30. Oh TE, Lin ES, Bhatt S. Resistance of humidifiers, and inspiratory work imposed by a ventilator-humidifier circuit. *Br J Anaesth*. 1991;66(2):258–263.
31. Craven DE, Goularte TA, Make BJ. Contaminated condensate in mechanical ventilator circuits. A risk factor for nosocomial pneumonia? *Am Rev Respir Dis*. 1984;129(4):625–628.
32. Dreyfuss D, Djedaini K, Weber P, et al. Prospective study of nosocomial pneumonia and of patient and circuit colonization during mechanical ventilation with circuit changes every 48 hours versus no change. *Am Rev Respir Dis*. 1991;143(4 Pt 1): 738–743.
33. Craven DE, Connolly MG Jr, Lichtenberg DA, et al. Contamination of mechanical ventilators with tubing changes every 24 or 48 hours. *N Engl J Med*. 1982;306(25):1505–1509.
34. Oto J, Imanaka H, Nishimura M. Clinical factors affecting inspired gas humidification and oral dryness during noninvasive ventilation. *J Crit Care*. 2011;26(5):535.e9–535.e15.
35. Chiumello D, Chierichetti M, Tallarini F, et al. Effect of a heated humidifier during continuous positive airway pressure delivered by a helmet. *Crit Care*. 2008;12(2):R55.
36. Esquinas Rodriguez AM, Scala R, Soroksky A, et al. Clinical review: humidifiers during non-invasive ventilation – key topics and practical implications. *Crit Care*. 2012;16(1):203.
37. Schreiber A, Nava S, Ceriana P, et al. Lack of humidification may harm the patient during continuous positive airway pressure. *Br J Anaesth*. 2012;108(5):884–885.
38. Lellouche F, Maggiore SM, Lyazidi A, et al. Water content of delivered gases during non-invasive ventilation in healthy subjects. *Intensive Care Med*. 2009;35(6):987–995.
39. Chanques G, Constantin JM, Sauter M, et al. Discomfort associated with underhumidified high-flow oxygen therapy in critically ill patients. *Intensive Care Med*. 2009;35(6):996–1003.
40. Cuquemelle E, Pham T, Papon JF, et al. Heated and humidified high-flow oxygen therapy reduces discomfort during hypoxemic respiratory failure. *Respir Care*. 2012;57(10):1571–1577.
41. Roca O, Hernandez G, Diaz-Lobato S, et al. Current evidence for the effectiveness of heated and humidified high flow nasal cannula supportive therapy in adult patients with respiratory failure. *Crit Care*. 2016;20(1):109.
42. Levy SD, Alladina JW, Hibbert KA, et al. High-flow oxygen therapy and other inhaled therapies in intensive care units. *Lancet*. 2016;387(10030): 1867–1878.

43. Ari A. Aerosol therapy in pulmonary critical care. *Respir Care*. 2015;60(6):858–874, discussion 74–79.
44. Dhand R, Guntur VP. How best to deliver aerosol medications to mechanically ventilated patients. *Clin Chest Med*. 2008;29(2):277–296, vi.
45. Dolovich MB, Dhand R. Aerosol drug delivery: developments in device design and clinical use. *Lancet*. 2011;377(9770):1032–1045.
46. Dhanani J, Fraser JF, Chan HK, et al. Fundamentals of aerosol therapy in critical care. *Crit Care*. 2016; 20(1):269.
47. Miller DD, Amin MM, Palmer LB, et al. Aerosol delivery and modern mechanical ventilation: in vitro/in vivo evaluation. *Am J Respir Crit Care Med*. 2003;168(10):1205–1209.
48. Maccari JG, Teixeira C, Gazzana MB, et al. Inhalation therapy in mechanical ventilation. *J Bras Pneumol*. 2015;41(5):467–472.
49. Kallet RH. Adjunct therapies during mechanical ventilation: airway clearance techniques, therapeutic aerosols, and gases. *Respir Care*. 2013;58(6): 1053–1073.
50. Ari A, Areabi H, Fink JB. Evaluation of aerosol generator devices at 3 locations in humidified and non-humidified circuits during adult mechanical ventilation. *Respir Care*. 2010;55(7):837–844.
51. Manthous CA, Hall JB. Administration of therapeutic aerosols to mechanically ventilated patients. *Chest*. 1994;106(2):560–571.
52. Dhand R. Inhalation therapy in invasive and noninvasive mechanical ventilation. *Curr Opin Crit Care*. 2007;13(1):27–38.
53. Dhand R. Aerosol therapy in patients receiving noninvasive positive pressure ventilation. *J Aerosol Med Pulm Drug Deliv*. 2012;25(2):63–78.
54. Cazzola M, Calzetta L, Page C, et al. Influence of N-acetylcysteine on chronic bronchitis or COPD exacerbations: a meta-analysis. *Eur Respir Rev*. 2015;24(137):451–461.
55. Poole PJ, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2006;(3): CD001287.
56. van der Hoeven SM, Binnekade JM, de Borgie CA, et al. Preventive nebulization of mucolytic agents and bronchodilating drugs in invasively ventilated intensive care unit patients (NEBULAE): study protocol for a randomized controlled trial. *Trials*. 2015;16:389.
57. Fuchs HJ, Borowitz DS, Christiansen DH, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *N Engl J Med*. 1994;331(10):637–642.
58. Yang C, Chilvers M, Montgomery M, et al. Dornase alfa for cystic fibrosis. *Cochrane Database Syst Rev*. 2016;(4):CD001127.
59. Holland A, Smith F, Penny K, et al. Metered dose inhalers versus nebulizers for aerosol bronchodilator delivery for adult patients receiving mechanical ventilation in critical care units. *Cochrane Database Syst Rev*. 2013;(6):CD008863.
60. Singh B, Tiwari AK, Singh K, et al. beta2 agonist for the treatment of acute lung injury: a systematic review and meta-analysis. *Respir Care*. 2014; 59(2):288–296.
61. Boyle AJ, Mac Sweeney R, McAuley DF. Pharmacological treatments in ARDS; a state-of-the-art update. *BMC Med*. 2013;11:166.
62. McFadden ER Jr. Acute severe asthma. *Am J Respir Crit Care Med*. 2003;168(7):740–759.
63. Michotte JB, Jossen E, Roeseler J, et al. In vitro comparison of five nebulizers during noninvasive ventilation: analysis of inhaled and lost doses. *J Aerosol Med Pulm Drug Deliv*. 2014;27(6): 430–440.
64. Hess DR. Aerosol therapy during noninvasive ventilation or high-flow nasal cannula. *Respir Care*. 2015;60(6):880–891, discussion 91–93.
65. Parkes SN, Bersten AD. Aerosol kinetics and bronchodilator efficacy during continuous positive airway pressure delivered by face mask. *Thorax*. 1997;52(2):171–175.
66. Reminiac F, Vecellio L, Heuze-Vourc'h N, et al. Aerosol therapy in adults receiving high flow nasal cannula oxygen therapy. *J Aerosol Med Pulm Drug Deliv*. 2016;29(2):134–141.
67. National Asthma Education and Prevention Program. *Expert Panet REport III*. Bethesda, 2007.
68. (GOLD) GIfCOLD. Global initiative for chronic obstructive lung disease (GOLD). *Global strategy for the diagnosis, management, and prevention of COPD 2017*. www.goldcopd.org.
69. Quon BS, Fitzgerald JM, Lemiere C, et al. Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children. *Cochrane Database Syst Rev*. 2010;(12):CD007524.
70. Gentile DA, Skoner DP. New asthma drugs: small molecule inhaled corticosteroids. *Curr Opin Pharmacol*. 2010;10(3):260–265.
71. Lavorini F, Pedersen S, Usmani OS. Dilemmas, confusion, and misconceptions related to small airways directed therapy. *Chest*. 2017;151(6):1345–1355.
72. Sole-Lleonart C, Roberts JA, Chastre J, et al. Global survey on nebulization of antimicrobial agents in mechanically ventilated patients: a call for international guidelines. *Clin Microbiol Infect*. 2016;22(4):359–364.
73. Poulakou G, Siakallis G, Tsiodras S, et al. Nebulized antibiotics in mechanically ventilated patients: roadmap and challenges. *Expert Rev Anti Infect Ther*. 2017;1-19.
74. Falagas ME, Trigkidis KK, Vardakas KZ. Inhaled antibiotics beyond aminoglycosides, polymyxins and aztreonam: a systematic review. *Int J Antimicrob Agents*. 2015;45(3):221–233.
75. Zampieri FG, Nassar AP Jr, Gusmao-Flores D, et al. Nebulized antibiotics for ventilator-associated pneumonia: a systematic review and meta-analysis. *Crit Care*. 2015;19:150.

76. Restrepo MI, Keyt H, Reyes LF. Aerosolized antibiotics. *Respir Care*. 2015;60(6):762-771, discussion 771–73.
77. Russell CJ, Shiroishi MS, Siantz E, et al. The use of inhaled antibiotic therapy in the treatment of ventilator-associated pneumonia and tracheobronchitis: a systematic review. *BMC Pulm Med*. 2016;16:40.
78. Valachis A, Samonis G, Kofteridis DP. The role of aerosolized colistin in the treatment of ventilator-associated pneumonia: a systematic review and metaanalysis. *Crit Care Med*. 2015;43(3):527–533.
79. Quon BS, Goss CH, Ramsey BW. Inhaled antibiotics for lower airway infections. *Ann Am Thorac Soc*. 2014;11(3):425–434.
80. Mendelman PM, Smith AL, Levy J, et al. Aminoglycoside penetration, inactivation, and efficacy in cystic fibrosis sputum. *Am Rev Respir Dis*. 1985;132(4):761–765.
81. Panidis D, Markantonis SL, Boutzouka E, et al. Penetration of gentamicin into the alveolar lining fluid of critically ill patients with ventilator-associated pneumonia. *Chest*. 2005;128(2): 545–552.
82. Goldstein I, Wallet F, Nicolas-Robin A, et al. Lung deposition and efficiency of nebulized amikacin during Escherichia coli pneumonia in ventilated piglets. *Am J Respir Crit Care Med*. 2002;166(10):1375–1381.
83. Ramsey BW, Dorkin HL, Eisenberg JD, et al. Efficacy of aerosolized tobramycin in patients with cystic fibrosis. *N Engl J Med*. 1993;328(24): 1740–1746.
84. Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med*. 1999;340(1):23–30.
85. Mogayzel PJ Jr, Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2013;187(7):680–689.
86. Palmer LB, Smaldone GC, Chen JJ, et al. Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit. *Crit Care Med*. 2008;36(7):2008–2013.
87. Lu Q, Luo R, Bodin L, et al. Efficacy of high-dose nebulized colistin in ventilator-associated pneumonia caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. *Anesthesiology*. 2012;117(6):1335–1347.
88. Palmer LB. Aerosolized antibiotics in the intensive care unit. *Clin Chest Med*. 2011;32(3):559–574.
89. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63(5):e61–e111.
90. American Academy of Pediatrics Committee on Infectious Diseases. Use of ribavirin in the treatment of respiratory syncytial virus infection. *Pediatrics*. 1993;92(3):501–504.
91. Empey KM, Peebles RS Jr, Kolls JK. Pharmacologic advances in the treatment and prevention of respiratory syncytial virus. *Clin Infect Dis*. 2010; 50(9):1258–1267.
92. Shah DP, Ghantoji SS, Shah JN, et al. Impact of aerosolized ribavirin on mortality in 280 allogeneic haematopoietic stem cell transplant recipients with respiratory syncytial virus infections. *J Antimicrob Chemother*. 2013;68(8):1872–1880.
93. Hsu J, Santesso N, Mustafa R, et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. *Ann Intern Med*. 2012;156(7):512–524.
94. Kiatboonsri S, Kiatboonsri C, Theerawit P. Fatal respiratory events caused by zanamivir nebulization. *Clin Infect Dis*. 2010;50(4):620.
95. Bigby TD, Margolskee D, Curtis JL, et al. The usefulness of induced sputum in the diagnosis of *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome. *Am Rev Respir Dis*. 1986;133(4):515–518.
96. Cruciani M, Marcati P, Malena M, et al. Meta-analysis of diagnostic procedures for *Pneumocystis carinii* pneumonia in HIV-1-infected patients. *Eur Respir J*. 2002;20(4):982–989.
97. Hepple P, Ford N, McNerney R. Microscopy compared to culture for the diagnosis of tuberculosis in induced sputum samples: a systematic review. *Int J Tuberc Lung Dis*. 2012;16(5):579–588.
98. Vlachos-Mayer H, Leigh R, Sharon RF, et al. Success and safety of sputum induction in the clinical setting. *Eur Respir J*. 2000;16(5):997–1000.
99. Lewis JF, Jobe AH. Surfactant and the adult respiratory distress syndrome. *Am Rev Respir Dis*. 1993;147(1):218–233.
100. Zhang LN, Sun JP, Xue XY, et al. Exogenous pulmonary surfactant for acute respiratory distress syndrome in adults: a systematic review and meta-analysis. *Exp Ther Med*. 2013;5(1): 237–242.
101. Barrington KJ, Finer N, Pennaforte T, et al. Nitric oxide for respiratory failure in infants born at or near term. *Cochrane Database Syst Rev*. 2017;(1):CD000399.
102. Gentile MA. Inhaled medical gases: more to breathe than oxygen. *Respir Care*. 2011;56(9):1341–1357, discussion 57–59.
103. Gebistorf F, Karam O, Wetterslev J, et al. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. *Cochrane Database Syst Rev*. 2016;(6):CD002787.
104. Ammar MA, Bauer SR, Bass SN, et al. Noninferiority of inhaled epoprostenol to inhaled nitric oxide for the treatment of ARDS. *Ann Pharmacother*. 2015;49(10):1105–1112.
105. Fuller BM, Mohr NM, Skrupky L, et al. The use of inhaled prostaglandins in patients with ARDS: a systematic review and meta-analysis. *Chest*. 2015;147(6):1510–1522.

106. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016; 37(1):67–119.
107. Maggiore SM, Richard JC, Abroug F, et al. A multicenter, randomized trial of noninvasive ventilation with helium-oxygen mixture in exacerbations of chronic obstructive lung disease. *Crit Care Med*. 2010;38(1):145–151.
108. Jolliet P, Ouanes-Besbes L, Abroug F, et al. A multicenter randomized trial assessing the efficacy of helium/oxygen in severe exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2017;195(7):871–880.
109. Anderson M, Svartengren M, Bylin G, et al. Deposition in asthmatics of particles inhaled in air or in helium-oxygen. *Am Rev Respir Dis*. 1993; 147(3):524–528.
110. Rodrigo GJ, Castro-Rodriguez JA. Heliox-driven beta2-agonists nebulization for children and adults with acute asthma: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol*. 2014;112(1):29–34.

33

Acute respiratory distress syndrome

Andrew D Bersten, Shailesh Bihari

The acute respiratory distress syndrome (ARDS), also known by many pseudonyms such as 'DaNang lung', was first described in 1967 by Ashbaugh and colleagues as the 'acute onset of tachypnea, hypoxemia and loss of compliance after a variety of stimuli'.[1] Continued research examining the underlying mechanisms and management strategies is now translating into improved outcome.

DEFINITIONS

The ARDS Definition Task Force (the Berlin definition[2]) has recently revised the long-standing 1994 American-European Consensus Conference (AECC) definition (Table 33.1).[3] ARDS is now classified as mild, moderate and severe based on the Pa_{O_2}/Fi_{O_2} ratio (see Table 33.1). The broad term 'acute lung injury' (ALI), which referred to cases with a Pa_{O_2}/Fi_{O_2} ratio less than 300, has been replaced and many concerns addressed. A minimum positive end-expiratory pressure (PEEP) of 5 cm H_2O is specified, and chest radiograph criteria and exclusion of hydrostatic oedema clarified, including examples. The lung injury score (LIS),[4] which uses a four-point score attributed to ranges of Pa_{O_2}/Fi_{O_2} ratio, PEEP, respiratory system compliance and the number of quadrants involved on chest radiograph, has also been used to quantify severity of ARDS; however, as neither lung compliance nor dead space improved the predictive ability of the Berlin definition, the LIS may become less pertinent.

CHEST RADIOGRAPH AND CHEST COMPUTED TOMOGRAPHY IN ACUTE RESPIRATORY DISTRESS SYNDROME

The intent of chest imaging is to exclude opacities due to pleural effusion, nodules, masses, collapse and pleural thickening; the infiltrate must be bilateral and consistent with pulmonary oedema.[2] Autopsy and chest radiographs of ARDS show a uniform process affecting both lungs. However, chest computed tomography (CT)[5] has demonstrated marked heterogeneity of lung inflation in ARDS with a dorsal, dependent increase in lung density, and relatively normal inflation of ventral lung. In addition, CT frequently reveals previously undiagnosed pneumothorax, pneumomediastinum and pleural effusion. After the second week of mechanical ventilation, CT scans may demonstrate altered lung architecture and emphysematous cysts or pneumatoceles.

CT numbers or Hounsfield units can be assigned to each voxel (~2000 alveoli in a standard 10-mm slice).[5] These data can then be used to assess what proportion of a region of interest is non-aerated, poorly aerated, normally aerated, or hyperinflated. Whole-lung CT allows (a) reconstruction of the upper and lower lobes (the middle lobe is difficult to separate), (b) the same section of lung to be studied at different levels of inflation or PEEP (the lung also moves in a cepahalocaudad direction with respiration), and (c) a broader picture of the lung to be obtained (lung damage is heterogeneous in ARDS). However, whole-lung CT demands considerable exposure to ionising radiation, and different information, perhaps more pertinent to mechanical ventilation, is obtained from dynamic CT.

Clinical assessment of chest CT is discussed in Chapter 39, and CT findings in ARDS as discussed under Clinical management.

EPIDEMIOLOGY

Estimates of the incidence and outcome from ARDS vary widely due to differences in the definitions used, case-mix and local factors. Using the AECC definition, the Australian incidence was 34 per 100,000 for ALI and 28 per 100,000 for ARDS[6]; while US estimates were 79 and 59 per 100,000, respectively[7] – both much greater than many previous estimates. Recent data from 50 countries reports period prevalence of mild ARDS as 30.0%, moderate ARDS as 46.6%, and severe ARDS as 23.4%, respectively. ARDS represented 10.4% of intensive care unit (ICU) admissions and 23.4% of patients requiring mechanical ventilation. Clinical recognition of ARDS ranged from 51.3% in mild to 78.5% in severe ARDS.[8] However, the incidence of ARDS appears to be decreasing likely due to improvements in health care such as use of protective ventilation strategies, reduced transfusion-related acute lung injury ALI (TRALI) and better management of sepsis.[9]

For many years the mortality for ARDS was reported to be ~60%; data from 459 ICUs from 50 countries reports hospital mortality as 34.9% for those

ABSTRACT

Acute respiratory distress syndrome (ARDS) is an acute diffuse, inflammatory lung injury leading to increased pulmonary permeability, increased lung weight, loss of aerated lung tissue, hypoxaemia and bilateral radiographic opacities, associated with increased physiological dead space and decreased lung compliance which is not fully explained by cardiac failure or fluid overload. Patients with ARDS have a high rate of morbidity and mortality. Lung protective invasive mechanical ventilation with adequate positive end-expiratory pressure remains the cornerstone of management, although new therapies are being developed as underlying mechanisms and pathophysiology are better understood.

KEYWORDS

Acute respiratory distress syndrome
mechanical ventilation
positive end-expiratory pressure
fluid balance
ventilation-induced lung injury

Table 33.1 Criteria and classification of acute respiratory distress syndrome

	AECC DEFINITION*	BERLIN DEFINITION†
Onset	Acute (not defined) onset No risk factor formally defined	Within 7 days of a known risk factor (See Box 33.1)
Chest imaging	Bilateral opacities on chest radiograph	Bilateral opacities consistent with pulmonary oedema on either chest radiograph or CT
Pulmonary oedema	PAOP ≤18 mm Hg when measured or no clinical evidence of raised left atrial pressure	Non-hydrostatic oedema; not fully explained by heart failure or fluid overload Echocardiography or another objective measure may be required
Classification	ALI $Pa_{O_2}/Fi_{O_2} \leq -300$ ARDS $Pa_{O_2}/Fi_{O_2} \leq -200$	Mild $200 < Pa_{O_2}/Fi_{O_2} \leq 300$ Moderate $100 < Pa_{O_2}/Fi_{O_2} \leq 200$ Severe $Pa_{O_2}/Fi_{O_2} \leq 100$

*No minimum ventilatory setting defined for Pa_{O_2}/Fi_{O_2} data.

†Based on oxygenation measured on a minimum of 5 cm H_2O PEEP. For the mild classification only, oxygenation can also be assessed during non-invasive ventilation. For the moderate and severe classification, the patient must be receiving intubated ventilatory assistance.

with mild, 40.3% for moderate, and 46.1% for severe ARDS.[8] Particular diagnostic groups such as multiple trauma have a lower mortality rate than other causes of ARDS, and patients with ARDS who have chronic liver disease, non-pulmonary organ dysfunction, sepsis or age greater than 70 years (hazard ratio, 2.5) have a higher risk of death. Clinical trial outcomes report low mortality rates in the control arm in part due to the exclusion of patients with limited life expectancy; consequently, many factors need to be considered when assessing outcome prediction.

PULMONARY FUNCTION IN SURVIVORS

Respiratory function continues to improve after discontinuation of mechanical ventilation, and usually returns towards normal by 6–12 months.[10,11] Although a variety of abnormal pulmonary function tests may be found, impaired diffusing capacity is the most common. This is rarely symptomatic, but occasional patients have severe restrictive disease, and this is correlated with their cumulative LIS.[11]

QUALITY OF LIFE IN SURVIVORS

Compared with disease-matched ICU patients who do not develop ARDS, patients with ARDS have a more severe reduction in both pulmonary and general health-related quality of life.[12] Many patients have reduction in exercise tolerance that may be attributable to associated critical illness neuropathy and myopathy; nerve entrapment syndromes, contractures, postural hypotension, and heterotopic calcification may play a role in a minority.[10] When followed for 5 years in a young and severe cohort (median age 45 years) with relatively few prior co-morbidities, there was persistent functional impairment with little improvement after 12 months.[13] Depression, anxiety and post-traumatic stress disorder are also common (20%–50% of survivors). Finally, most survivors have cognitive impairments such as slowed mental processing, or impaired memory or concentration, and these correlate with the duration of ventilation, hyperglycaemia and variability in blood glucose, and the period and severity of desaturation less than 90%.[14,15] In an analysis of survivors of the ARDS Network Fluid and Catheter Trial (FACTT),[16] Mikkelsen and co-workers[17] found that over half the subjects suffered from cognitive dysfunction and from psychological disability, and that these parameters were associated with lower Pa_{O_2}, enrolment in the restrictive fluid arm, and hypoglycaemia. Taken together these data caution against permissive hypoxaemia as a strategy to reduce ventilator-induced lung injury (VILI), and suggest that quality of survival is an important additional outcome for clinical trials.

PATIENTS AT RISK FOR ACUTE RESPIRATORY DISTRESS SYNDROME

About one-third of critically ill patients exposed to either a direct or indirect risk factor (Box 33.1) develop ARDS, most within 6–48 hours. Multiple risk factors such as low pH, chronic alcohol abuse or chronic lung disease substantially increase the incidence of ARDS in at-risk patients. Diabetes reduces the risk of developing ARDS.[18]

FAT EMBOLISM SYNDROME

Fat embolism syndrome (FES) is most commonly associated with long bone and pelvic fractures, and is more frequent in closed fractures than open fractures. Patients with a single long bone fracture have a 1%–3% chance of developing FES, which increases with the number of fractures. Fat emboli usually result from fat

Box 33.1 Clinical risk factors for acute respiratory distress syndrome

DIRECT	INDIRECT
Pneumonia	Non-pulmonary sepsis
Aspiration of gastric contents	Multiple trauma
Lung contusion	Massive transfusion
Fat embolism	Pancreatitis
Near drowning	Cardiopulmonary bypass
Inhalational injury	
Reperfusion injury	

globules entering the bloodstream or via production of the toxic intermediaries of plasma-derived fat.

FES typically manifests 24–72 hours after the initial insult.[19] Affected patients develop a classic triad – hypoxaemia, neurological abnormalities and a petechial rash. Neurological abnormalities such as confusional state followed by an altered level of consciousness develop in the majority of patients. The characteristic petechial rash may be the last component of the triad to develop. It occurs in only 20%–50% of cases and is found most often on the head, neck, anterior thorax, axillae, and subconjunctiva.[20] The rash resolves in 5–7 days

Early immobilization of fractures reduces the incidence of FES, otherwise treatment is the same as for ARDS.

PATHOGENESIS

Although it is well accepted that diffuse alveolar damage with: (a) pulmonary oedema due to damage of the alveolocapillary barrier, (b) a complex inflammatory infiltrate and (c) surfactant dysfunction,[21] are essential components of ARDS, the sequence of events is uncertain and probably depends upon the precipitating insult and host response. For example, in endotoxin-induced lung injury, hypoxaemia and reduced lung compliance occur well before recruitment of neutrophils or an increase in lung weight due to an increase in permeability.[22] In addition, typical of early ARDS, surfactant turnover is dramatically increased prior to these changes. Furthermore, epithelial lining fluid sampled immediately following intubation in patients with ARDS has markedly increased concentrations of type III procollagen peptide,[23] suggestive of fibrosing alveolitis extremely early in the course of lung damage.

THE ALVEOLOCAPILLARY BARRIER

The normal lung consists of 300 million alveoli with alveolar gas separated from the pulmonary microcirculation by the extremely thin alveolocapillary barrier (0.1–0.2 μm thick). Since the endothelial pore size is 6.5–7.5 nm, and the epithelial pore size is almost one-tenth that at 0.5–0.9 nm, the epithelium is the major barrier to protein flux.[24] The surface area of the alveoli is estimated to be 50–100 m^2, which is made up predominantly of alveolar type I cells, with the metabolically active type II cells accounting for ~10% of the surface area. In turn, these cells are covered by the epithelial lining fluid with an estimated volume of 20 mL, ~10% of which is surfactant, the rest being filtered plasma water and low-molecular-weight proteins and a small number of cells, mainly alveolar macrophages and lymphocytes.

In ARDS the alveolocapillary barrier is damaged with bidirectional leakage of fluid and protein into the alveolus and leakage of surfactant proteins (SP) and alveolar cytokines into the plasma. Total protein content in bronchoalveolar lavage (BAL) fluid is 20–100 times that found in both healthy subjects and ventilated subjects without cardiorespiratory disease.[25,26] There is also disruption of the epithelial barrier, surfactant dysfunction and proliferation of alveolar type II cells as the progenitor of type I cells. Indirect causes of ARDS result in pulmonary endothelial injury, followed by recruitment of inflammatory cells and then epithelial damage, whereas direct causes of ARDS result in epithelial injury and secondary recruitment of inflammatory cells. The outcome of these processes must reflect a balance between repair and fibrosing alveolitis.

CELL TYPES INVOLVED

The large surface area of pulmonary epithelium and endothelium including the associated microcirculation, myofibroblasts, and both alveolar macrophages and recruited neutrophils are all important components of ALI. BAL fluid has a marked increase in cell count; alveolar macrophage numbers are increased about twofold, but as a fraction of the cell count falls from around 90% to 20%–40% of the cell count due to a greater increase in neutrophils from around 1% to 50%–80% of the cell count. In addition, microparticles, tiny vesicles potentially derived from most of these cell types, are found in both BAL fluid and blood and may play an important role in both lung damage and repair.[27] A temporal trend towards more normal neutrophil and alveolar macrophage ratios in BAL fluid is associated with survival.

NEUTROPHILS

Neutrophils are the most abundant cell type found in both the epithelial lining fluid (e.g. BAL fluid), and alveoli in histological specimens from early in the course of ARDS. Although neutrophil migration across the endothelium and then the epithelium does not cause injury, when activated, neutrophils are pro-inflammatory and pro-apoptotic, and release reactive oxygen species, cytokines, eicosanoids and a variety of proteases that may make an important contribution to basement membrane damage, increased permeability and direct cell damage. Following bone marrow

demargination, activated neutrophils adhere to the endothelium on their passage to the alveolus, and this may be accompanied by an early, transient leucopenia. Although neutrophils have an important role in host defence due to their bactericidal activity, there is a marked (50–1000-fold) increase in the release of cytotoxic compounds when they are activated by adherence to the endothelium, epithelium or contact with interstitial extracellular matrix proteins.[28] The factors involved in adhesion of neutrophils are complex and involve the integrin family of proteins, selectins and a number of adhesion molecules.

In models of ARDS, antibodies to adhesion molecules (e.g. CD11b/CD18 antibodies) ameliorate lung injury, suggesting a crucial and central role of this cell type. However, ARDS occurs in neutropenic patients, and was not more common when granulocyte colony-stimulating factor was administered to patients with pneumonia.[29] Clearly, other cell types play an important role, and neutrophil chemoattractants such as interleukin (IL)-8 must be present in the lung prior to neutrophil accumulation.

ALVEOLAR MACROPHAGES

Alveolar macrophages are the most common cell type normally found in BAL fluid, and together with interstitial macrophages play an important role in host defence and modulation of fibrosis. They are capable of releasing IL-6 and a host of mediators similar to the activated neutrophil, including tumor necrosis factor (TNF)-α and IL-8 in response to stretch,[30] and may amplify lung injury. Macrophages also release factors such as transforming growth factor (TGF)-α and platelet-derived growth factor (PDGF) that stimulate fibroblast proliferation, deposition of collagen and glycosaminoglycans, angiogenesis and lung fibrosis.

A study using different cell markers found that there appear to be different pools of alveolar macrophages termed the M1 and M2 phenotype.[31] The M1 phenotype is characterised as a resident alveolar macrophage that is pro-inflammatory, and the M2 phenotype appears to represent recruited monocytes and be central to lung repair and fibrosis depending upon timing, local milieu and cross talk with other cell types. This may account for the observation that ARDS survivors progressively increase alveolar macrophage number; however, any conclusion awaits further work examining alveolar macrophage phenotypes and clinical outcomes.

EPITHELIUM

Alveolar epithelial type II cells are extremely metabolically active; they manufacture and release surfactant, along with type I cells control alveolar water clearance through epithelial Na channels and Na^+/K^+ ATP-ase, express cytokines, which in turn interact with surfactant production, and are the progenitor of type I cells following injury. In response to both stretch and endotoxin, type II cells express IL-8 and TNF-α, with the latter cytokine augmenting Na^+, and hence water, egress from the alveolus.[32] Damage to the epithelium leads to dysfunctional surfactant release and impaired resolution of alveolar oedema which both reduces vectorial transport of Na^+ in part through down-regulation of ion transport genes, and up-regulates gene expression of Il-8, TNF-α, and IL-β.[33] Similarly, TGF-β acutely reduces transepithelial sodium transport by inducing endocytosis of epithelial sodium channel (ENaC) and plays a central role in lung fluid balance.[34]

Epithelial biomarkers include surfactant protein B (SP-B), which is predictive of ARDS,[35] and SP-D, and the receptor for advanced glycation end-products (RAGE), both of which have been associated with severity and outcome of ARDS.

ENDOTHELIUM

Pulmonary endothelial cells express a variety of adhesion molecules and cyclooxygenase (COX)-2, secrete endothelin and cytokines including IL-8,[36] stimulate procoagulant activity and 'cross talk' with the alveolar macrophages and type II cells. In addition to generalised endothelial activation, the endothelium is subject to mechanical stress both secondary to vascular pressure, and its association with the alveolus. Plasma levels of von Willebrand factor antigen are both predictive of and associated with outcomes from ARDS[37]; however, as it is synthesised by all vascular endothelial cells it is a non-specific biomarker. Similarly, plasma Angiopoietin-2 both predicts the onset of ALI in critically ill patients and has prognostic and pathogenetic significance.[38,39]

Microvascular thrombosis is common in ARDS, associated with inflammation, and contributes to pulmonary hypertension and wasted ventilation. Platelet aggregation contributes through release of thromboxane A_2, serotonin, lysosomal enzymes, and platelet-activating factor. Impaired fibrinolysis also contributes to these changes, and abnormal plasma levels of protein C and plasminogen activator inhibitor-1 are associated with outcome and organ failure in ARDS. Lung injury also leads to expression of the coagulation factor X on pulmonary epithelium, which appears to be a direct link between coagulation and pulmonary fibrosis.[40]

CHEMOKINES IN ACUTE RESPIRATORY DISTRESS SYNDROME

The expression and secretion of chemokines (chemoattractant cytokines) at sites of inflammation is a key proximal step in initiating the inflammatory cascade. IL-8-induced chemotaxis and activation of neutrophils are elevated in ARDS BAL fluid both within hours of the initiating insult and before recruitment of neutrophils, and in a manner that reflects subsequent morbidity and mortality. IL-8 antibodies prevent recruitment of neutrophils and protect the lung. Indeed, the recruitment and retention of neutrophils requires the

generation and maintenance of a localised chemotactic/haptotactic gradient.[41]

ION CHANNELS IN ACUTE RESPIRATORY DISTRESS SYNDROME

The transient receptor potential (TRP) ion channel superfamily is involved in sensing and transmission of a broad variety of external or internal stimuli, including mechanical stress.[42] TRP vanilloid (TRPV) 4 is expressed on the pulmonary endothelium, epithelium and macrophages. Activation of TRPV4 channels by shear forces,[43] stretch,[44] overinflation,[45] hypothermia,[44] increased hydrostatic pressure,[46] sudden increases in circulatory forces,[47,48] high intracapillary pressure,[44,46] and hypotonicity[49] leads to the rapid intracellular influx of calcium ions and leads to increased permeability of the alveolocapillary barrier through perturbations in cell morphology and disruption to the alveolar septal barrier[50] possibly via activation of matrix metalloproteinases[51] and calcium-activated K channels,[52] manifesting as lung injury.

MEDIATORS IN ACUTE RESPIRATORY DISTRESS SYNDROME[53]

Inflammation is usually a redundant process so that numerous mediators, including cytokines, chemokines, complement, reactive oxygen species, eicosanoids, platelet-activating factor, nitric oxide, proteases, growth factors and lysosomal enzymes, derived from a number of different cell types, play important roles in the pathophysiology of ARDS. As the alveolocapillary barrier becomes injured, these are no longer compartmentalised in the alveolus, and many of these proteins have been measured in blood as well as in the epithelial lining fluid. Care must be taken when interpreting these data, as immunological levels may not reflect biological activity, inhibitors or binding proteins may complex with the active protein or epitope and interfere with immunological detection, and the ultimate biological effect will depend upon a balance of pro-inflammatory and anti-inflammatory effects.

Of the pro-inflammatory mediators, TNF-α, IL-1β, IL–6, and IL-8 are the most important. However, even greater increases are found in their cognate receptors or antagonists such as the counter-regulatory cytokine IL-10, so that their biological impact is markedly reduced.[54] Blood or epithelial lining fluid levels are associated with mortality, but are rarely used clinically.

RESOLUTION OF ACUTE RESPIRATORY DISTRESS SYNDROME AND THE DEVELOPMENT OF FIBROSING ALVEOLITIS

Although histological evidence of fibrosing alveolitis (mesenchymal cells and new vessels in alveoli) is not usually found until at least 5 days following the onset of ARDS, elevated levels of type III procollagen peptide are found in the epithelial lining fluid soon after diagnosis[21]; both oedema fluid and plasma levels are associated with mortality.

Clinical resolution of ARDS usually occurs provided that both the underlying cause is promptly and effectively treated, and that appropriate supportive care is provided. Alveolar oedema resolves with active transport of Na^+ by the type II cells followed by passive clearance of water through transcellular aquaporin channels; repair of the alveolocapillary barrier is associated with improved outcome. Type II cells proliferate and cover the denuded epithelium before differentiating into type I cells.

Both host response and the clinical course of ARDS influence lung remodelling in ARDS. Cross-talk between type II cells and alveolar macrophages, probably the M2 phenotype, along with epithelial mesenchymal transition – a process where reactive oxygen species, hypoxia, TGF-β and mechanical stress lead to altered epithelial transcription – are central to interstitial responses. Epithelial cells assume characteristics of mesenchymal cells with loss of polarity, increased resistance to apoptosis, and increased migration (into the interstitium) where they lay down a fibrotic matrix.[55]

CLINICAL MANAGEMENT OF ACUTE RESPIRATORY DISTRESS SYNDROME

The factors leading to ARDS must be promptly and appropriately treated. This includes diagnosis and treatment of infection with drainage of collections and appropriate antimicrobial agents, recognition and rapid resuscitation from shock, splinting of fractures, and careful supportive care. Prevention of deep venous thrombosis, stress ulceration, nosocomial infection, and malnutrition, often with enteral nutrition, must all be considered.

Early mobilisation of mechanically ventilated patients accompanied by appropriate levels of analgesia and sedation is feasible and safe, and offers shorter duration of ventilation, reduced delirium, ICU and hospital length of stay, and improved mortality and functional outcomes.[56–58] However, two other randomised controlled trials[59,60] have not shown benefit, and care must be taken not to exacerbate lung injury with premature spontaneous effort which may result in unintended increases in both transpulmonary airway and transmural hydrostatic pressure,[61] and asynchrony. For example, use of neuromuscular blockers in the first 48 hours of mechanical ventilation in ARDS reduced mortality,[62] possibly through prevention or reduction of these factors.

MECHANICAL VENTILATION

Acute hypoxaemic respiratory failure,[63] and an increase in the work of breathing, usually mandates mechanical

Table 33.2 Pathophysiology of acute lung injury and adult respiratory distress syndrome

FEATURE	CAUSE(S)
Hypoxaemia	True shunt (perfusion of non-ventilated airspaces) Impaired hypoxic pulmonary vasoconstriction *V/Q* mismatch is a minor component
↑Dependent densities (CT)	Surfactant dysfunction alveolar instability
(Collapse/consolidation)	Exaggeration of normal compression of dependent lung due to ↑weight (↑lung water, inflammation)
↑Elastance (↓compliance)	Surfactant dysfunction (↑specific elastance) ↓Lung volume ('baby lung') ↑Chest wall elastance Fibrosing alveolitis (late)
↑Minute volume requirement	↑Alveolar dead space (VD_{phys} V_t often 0.4–0.7) ↑ V_{CO_2}
↑Work of breathing	↑Elastance ↑Minute volume requirement
Pulmonary hypertension	Pulmonary vasoconstriction (thromboxane A_2, endothelin) Pulmonary microvascular thrombosis Fibrosing alveolitis Positive end-expiratory pressure

CT, Computed tomography.

ventilation (Table 33.2). The role of non-invasive ventilation in ARDS is contentious; there are no large definitive studies, and although some groups report encouraging results, these are usually in patients with mild ARDS.[64] Failure of non invasive ventilation (NIV) is common, associated with greater complication rates and mortality, perhaps due to delayed intubation.[65–67] If non-invasive ventilation is considered in ARDS, it requires particular care (see Chapter 37).

The method and delivery of ventilatory support must take into account both the pathophysiology of ARDS and VILI. The ARDS Network randomised 861 ALI patients from 75 ICUs to receive either a tidal volume (V_T) of 12 or 6 mL/kg predicted body weight.[68] Mortality was reduced by 22%, from 40% to 31%, in the lower V_T group. There was a strict PEEP and Fi_{O_2} protocol, and patients were ventilated with assist-control ventilation to avoid excessive spontaneous V_T. Similar data with improved long-term survival are found in routine clinical practice[69]; however, it is the concept of lung protection rather than an exact V_T formula that is important.[70] As Hager and colleagues[71] found that lower V_T ventilation was protective across all quartiles of plateau pressure (P_{plat}) in the ARDS Network trial, with no safe upper limit of P_{plat}, it appears that the key variable is lower V_T rather than control of static airway pressure.

AVOIDANCE OF OVERSTRETCH AND INADEQUATE RECRUITMENT

The increase in dependent lung density found on chest CT, due to non-aerated and poorly aerated lung, reduces the volume of aerated lung available for tidal inflation (baby lung). Both PEEP and tidal recruitment will increase aeration of some of these air spaces, but a V_T that is not reduced in proportion to the reduction in aerated lung may lead to overstretch of aerated lung parenchyma and further diffuse alveolar damage. This is termed volutrauma, as increased airway pressure (P_{aw}) despite low V_T, due to decreased chest wall compliance, causes minimal damage compared with high V_T, high P_{aw} ventilation.[72] Atelectrauma refers to injury due to repeated opening and closing of air spaces during tidal inflation. Both volutrauma and atelectrauma result in alveolar inflammation and elevated alveolar cytokines (biotrauma), which may 'spill' into the systemic circulation.[73] However, as CT scans performed during ARDS Network protective ventilation show that tidal inflation occurs primarily in either normally aerated or overinflated compartments, with little tidal recruitment,[74] and PET-CT scans suggest that overinflation but not tidal recruitment is inflammatory,[75] overstretch appears to be the dominant mechanism causing VILI.

OVERSTRETCH

The normal lung is fully inflated at a transpulmonary pressure of ~25–30 cm H_2O. Consequently, a maximum P_{plat}, an estimate of the elastic distending pressure, of 30 cm H_2O has been recommended.[68] However, overinflation may occur at much lower elastic distending pressures (18–26 cm H_2O).[72,76]

The transpulmonary pressure may be lower than expected for a given P_{plat} in patients with a high chest

wall elastance (e.g. obesity, abdominal compartment syndrome, after abdominal or thoracic surgery). While placement of an oesophageal balloon (see Chapter 38) allows measurement of the transpulmonary pressure and may allow better titration of PEEP,[77] it must be correctly placed, have an adequate occlusion pressure ratio, and measurements are preferably performed in a semi-sitting position in order to lift the mediastinum off the oesophagus.

Finally, inspiratory muscle contraction through reduction of intrapleural pressure lowers P_{plat}, potentially avoiding simple detection of an excessive transpulmonary pressure. This is particularly common when pressure support ventilation is used as a primary mode of ventilatory support; V_T that would produce an unacceptably high P_{plat} during mechanical ventilation will produce the same volutrauma during a spontaneous or supported mode of ventilation, and should be avoided. Provided the same V_T is generated, spontaneous ventilation does not reduce VILI compared to controlled ventilation,[78] and may exacerbate it.[61]

Static or dynamic volume-pressure curves or quantitative chest CT can be used to infer overinflation, though chest CT cannot determine overstretch.[5] Consequently, unless particular expertise is available, V_T limitation is currently the most practical approach.

ADEQUATE PEEP

PEEP improves Pa_{O_2} by recruiting alveoli and increasing end-expiratory lung volume. Because PEEP may reduce cardiac output by impairing venous return, Suter and co-workers suggested that at best PEEP the oxygen delivery (oxygen content × flow) was highest, and that this coincided with greatest compliance.[79] PEEP is commonly titrated to a particular Pa_{O_2}/Fi_{O_2} ratio such as the ARDS Network protocol.[68] However, the amount of lung available for recruitment is extremely variable,[80] and does not differ comparing pulmonary with extrapulmonary ARDS.[81] Factors such as the duration, late ARDS being less recruitable, and phenotype influence whether PEEP leads to alveolar recruitment, overinflation or a balance of both. Based on chest imaging, ARDS can be subdivided into focal, intermediate and diffuse phenotypes, with progressive increase in the amount of recruitable lung.[82,83] Applying ARDS Network ventilation to focal ARDS (about ⅓ of most cohorts) leads to high lung stress, with increased cytokine release, which can be ameliorated by using lower levels of PEEP.[84]

The lower inflection point of a volume-pressure curve has been used to set PEEP; early studies suggested that this reflected recruitment of collapsed alveoli. However, in patients with ARDS, recruitment occurs well above the lower inflection point, often along the entire volume-pressure curve and above the upper inflection point.[85,86] Concurrently, there is frequently evidence of overstretching and hyperinflation on CT scans[41,87] or dynamic volume-pressure analysis.[76]

Meta-analysis of major clinical trials using protective V_T and comparing higher and lower PEEP scales[88] did not find an overall improvement in outcome with higher PEEP, although rescue therapies were required less often. However, patients with mild ARDS tended to have worse outcomes with higher PEEP, and those with moderate to severe ARDS had better outcomes.

These data suggest individual patients may benefit from a tailored approach. Although routine CT analysis has been advocated by some, it is cumbersome and has not been shown to influence outcome; non-invasive bedside alternatives are under investigation. Consequently, PEEP titration is often a compromise aiming to minimise both atelectrauma and volutrauma.[89] Reasonable approaches to PEEP titration include: (a) the use of a scale similar to the ARDS Network protocol, (b) titration of PEEP to Pa_{O_2} aiming for a PEEP of ~15 cm H_2O, or (c) measuring elastic mechanics at the bedside. Consistent with Suter's early observation,[79] both nadir elastance after a recruitment manoeuvre,[90] or minimal change in driving pressure[76] (see also Chapter 38), offer bedside methods to individualise PEEP.

In patients at risk for ARDS, prophylactic PEEP (8 cm H_2O) was not protective.[91]

Driving pressure

This is defined as the difference between the end-inspiratory plateau pressure and the total PEEP. In a meta-analysis of nine randomised controlled trials of protective ventilation strategies (lower V_T, lower Pplat, and higher PEEP), Amato and colleagues identified the driving pressure as the variable most robustly associated with improved outcome.[92] Although the driving pressure is an appealing and intuitive way of thinking about minimising lung stress, protocols examining this method need to be prospectively tested using patient-centred outcomes to exclude indirect association as the basis for these findings.

Recruitment manoeuvres and open lung ventilation

Open lung ventilation refers to an approach where the lung is maximally recruited, usually through application of higher PEEP, recruitment manoeuvres, and efforts to minimise derecruitment. In theory, increased lung volume will result in less tidal overinflation and improved outcome. However, despite alveolar recruitment with open lung ventilation, overinflation may occur in previously normally aerated lung.[93] The recruitment manoeuvre may be followed by a marked improvement in oxygenation; however, this is not a consistent finding, and hypotension may occur due to reduced venous return if there is inadequate fluid loading.

During a typical recruitment manoeuvre, a high level of continuous positive airway pressure (CPAP) (30–40 cm H_2O) is applied for 30–40 seconds in an apnoeic patient, followed by return to a lower level of PEEP and controlled ventilation. This may be

suboptimal; an alternative, for example, is a staircase recruitment manoeuvre where airway pressure is sequentially increased every 2 minutes, and then decreased until oxygenation deteriorates.[94] A number of small trials have shown improvement in oxygenation following recruitment manoeuvres; however, the largest clinical trial[95] failed to show an effect. Grasso and colleagues[96] found that recruitment manoeuvres were effective only early in ARDS and with lower levels of baseline PEEP, which probably explains the variable responses reported.

In addition to physical recruitment of alveoli, lung stretch above resting V_T is the most powerful physiological stimulus for release of pulmonary surfactant from type II cells. This is associated with a decrease in lung elastance and improved Pa_{O_2} in the isolated perfused lung,[97] and is a possible explanation for the improvement in oxygenation, recruited lung volume and elastance reported with addition of three sigh breaths in patients with ARDS.[98] Similarly, in models of lung injury, biologically variable or fractal V_T is associated with less lung damage with lower alveolar levels of IL-8,[99] improved oxygenation and lung elastance, and greater surfactant release.[100] These data caution against monotonous low V_T ventilation, and suggest that intermittent or variable lung stretch may reduce lung injury.

MODE OF VENTILATION

Non-invasive ventilation should not be routinely used in ARDS (see Chapter 37) and most patients require intubated mechanical ventilation. Following intubation, controlled ventilation allows immediate reduction in the work of breathing, and application of PEEP and a controlled Fi_{O_2}. Later in the clinical course, assisted or supported modes of ventilation may allow better patient-ventilator interaction (see Chapter 31), and possibly improved oxygenation through better $\dot{V}/\dot{Q}$ mismatch as a result of diaphragmatic contraction.[101] Withdrawal or weaning from mechanical ventilation is discussed in Chapter 31.

An advantage of assist-control ventilation (as used in the ARDS Network study) is that spontaneous effort generates a controlled V_T. However, the fall in airway pressure during triggered ventilation (e.g. assist control or supported ventilation) can result in worse lung injury than controlled ventilation in early ARDS, although a beneficial effect can be seen when the underlying lung injury is less severe.[102] This may be due to greater transpulmonary and transmural pressure changes, and heterogeneity of lung inflation. Care should also be taken with synchronised intermittent mandatory ventilation (SIMV), particularly if pressure support is added to SIMV, as excessive V_T may occur during supported breaths.

There is an increasing tendency to use pressure-controlled ventilation (PC) or pressure-regulated volume control (PRVC), as P_{pk} is lower than volume-controlled (VC) ventilation with a constant inspiratory flow pattern. However, the decelerating flow pattern of PC or PRVC means that most of the resistive pressure (P_{res}) during inspiration is dissipated by end inspiration, which is in contrast to VC with a constant inspiratory flow pattern where P_{res} is dissipated at end inspiration (see Fig. 31.2). Consequently, with PC and PRVC $P_{pk} \approx P_{plat}$ which is the same as P_{plat} during VC.[103] Both oxygenation, haemodynamic stability and mean airway pressure are no different between PC and VC, and a moderate-sized randomised study found no difference in outcome.[104] However, there may be differences in lung stress due to greater viscoelastic build-up with VC.[105]

Inverse ratio ventilation, often together with PC, has been used in ARDS. However, when $PEEP_i$ and total PEEP are taken into account, apart from a small decrease in $PaCO_2$, there are no advantages with inverse ratio ventilation. Mean airway pressure is higher with a greater risk of both haemodynamic consequences, and regional hyperinflation.[103] Consequently, an inspiratory to expiratory ratio greater than 1:1 is recommended.

A number of other modes of ventilation (see Chapter 31) including airway pressure release ventilation (APRV) and high-frequency oscillation (HFO) have been proposed for use in ARDS. Randomised clinical trials have not shown improved outcomes with APRV,[106] despite potential physiological benefits. The small V_T used with HFO, although appealing, may increase hospital mortality when compared with a ventilation strategy of low tidal volume and high PEEP.[107]

Use of venovenous extracorporeal membrane oxygenation (ECMO) has been investigated in patients with ARDS and shown to both increase survival and minimise severe disability, and to be cost effective.[108] However, caution must be taken in extrapolating these results, as almost a quarter of those considered for ECMO group did not receive it, and control patients were not transferred to the trial hospital. Further trials are underway and vv-ECMO is sometimes used as a rescue therapy (see Chapter 41).

TARGET BLOOD GASES

As discussed earlier, there are many variables that need to be considered when choosing target blood gases in ARDS. For example, if a patient also has a traumatic brain injury, it may be inappropriate to accept hypercapnia.

Oxygenation targets and Fi_{O_2}

There must be a compromise between the major determinants of oxygenation, including the extent of poorly or non-aerated lung, hypoxic pulmonary vasoconstriction and mixed venous oxygen saturation, and the target Pa_{O_2}. The association between cognitive impairment and arterial saturation (Sa_{O_2}) less than 90%[14] suggests that a $Sa_{O_2} \geq 90\%$, usually a $Pa_{O_2} > 60$ mm Hg, is a reasonable target. A recent trial reported lower ICU

mortality with target Pa_{O_2} values of 70–100 mm Hg versus values up to 150 mm Hg.[109] Because positive-pressure ventilation may reduce cardiac output, it is also important to consider tissue oxygenation.

In addition to PEEP, increased Fi_{O_2} is used to improve Sa_{O_2}. However, high Fi_{O_2} may also cause tissue injury, including diffuse alveolar damage. The balance between increased airway pressure and Fi_{O_2} is unknown, but high Fi_{O_2} is generally regarded as being less damaging.[110] In part this is because diffuse alveolar damage itself protects the lung against hyperoxia, perhaps through prior induction of scavengers for reactive oxygen species.[111] A reasonable compromise is to start ventilation at a Fi_{O_2} of 1 and to titrate down, aiming for a $Fi_{O_2} \leq 0.6$. In patients with extreme hypoxaemia, additional measures such as inhaled nitric oxide (iNO) and prone positioning may be tried, along with a lower Sa_{O_2} target.

Carbon dioxide target

Low V_T strategies will result in elevations in $PaCO_2$ unless minute ventilation is augmented by an increase in respiratory rate. The ARDS Network protocol aimed at normocapnia, with a maximum respiratory rate of 35, to minimise respiratory acidosis.[68] This exposes the lung to more repeated tidal stretch, and may result in dynamic hyperinflation due to a shortened expiratory time.[112] In addition, allowing the $PaCO_2$ to rise above normal may not be harmful in many patients.

If hypercapnic acidosis occurs slowly, intracellular acidosis is well compensated, and the associated increase in sympathetic tone may augment cardiac output and blood pressure. Although the respiratory acidosis may worsen pulmonary hypertension and induce myocardial arrhythmias, these effects are often small, particularly if there has been time for metabolic compensation. In addition, in an ischaemia-reperfusion model of ARDS, therapeutic hypercapnia reduced lung injury and apoptosis,[113] but was harmful in prolonged untreated pneumonia.[114]

Extracorporeal CO_2 removal technologies may facilitate further lowering of ventilator stretch, allowing dissection of the contribution of CO_2 and tidal stretch to lung injury or protection in ARDS. However, clinical studies of permissive hypercapnia and extracorporeal CO_2 removal technologies must be undertaken before they can be considered. Hypercapnia should be avoided in patients with or at risk from raised intracranial pressure.

NON-VENTILATOR MANAGEMENT

PRONE POSTURE

In patients with severe ARDS, early application of prolonged prone-positioning sessions significantly decreased 28- and 90-day mortality.[115] Notably, the study entry Pa_{O_2}/Fi_{O_2} ratio was less than 150, enrolment was within 36 hours of commencing mechanical ventilation, and the ICUs had more than 5 years of experience in managing ARDS patients with prone positioning. The mechanisms involved include recruitment of dorsal lung, with concurrent ventral collapse; however, perfusion is more evenly distributed leading to better $\dot{V}/\dot{Q}$ matching. While this study is supported by a meta-analysis,[116] a number of prior studies did not find clear evidence of benefit.[117,118] Moreover, the study did not control for lung heterogeneity (ARDS phenotype), or co-interventions (did not control or report fluid balance, or cumulative dose of catecholamines), and had baseline imbalances of neuromuscular blockers and a high rate of cardiac arrest. Consequently, the uptake of prone positioning remains sporadic; more studies are needed.

MANIPULATION OF THE PULMONARY CIRCULATION

iNO and aerosolised prostacyclin (PGI_2) may be used to reduce pulmonary shunt and right ventricular afterload by reducing pulmonary artery impedance. When hypoxic pulmonary vasoconstriction is active, there is redistribution of pulmonary blood flow away from the poorly ventilated dependent areas to more normally ventilated lung leading to an increase in Pa_{O_2}. Both iNO and PGI_2 are delivered to well-ventilated lung; both vasodilate the local pulmonary circulation and augment the effects of hypoxic pulmonary vasoconstriction. Intravenous almitrine is a selective pulmonary vasoconstrictor that reinforces hypoxic pulmonary vasoconstriction and, although this may improve oxygenation alone, there is a synergistic effect with iNO.

Inhaled NO or PGI_2 may also be used to reduce right ventricular afterload; however, a consequent increase in cardiac output is rare in ARDS. Intravenous PGI_2 will improve cardiac output in ARDS, though there is non-specific pulmonary vasodilation with increased blood flow through poorly ventilated lung zones, resulting in deterioration in oxygenation.

Inhaled nitric oxide

Nitric oxide is an endothelium-derived smooth muscle relaxant. It also has other important physiological roles including neurotransmission, host defence, platelet aggregation leucocyte adhesion and bronchodilation. Doses as low as 60 parts per billion iNO may improve oxygenation; however, commonly used doses in ARDS are 1–60 parts per million, with the higher doses required for reduction in pulmonary artery pressure. A rise in Pa_{O_2} exceeding 20% is generally regarded as a positive response; iNO should be continued at the minimum effective dose.

Inhaled NO may be delivered continuously or using intermittent inspiratory injection. Delivery is usually in the form of medical grade NO/N_2, and this should be adequately mixed to avoid delivery of variable NO concentrations. It is recommended that inspiratory NO

and NO_2 concentrations are measured, either by an electrochemical method or by chemiluminescence. The electrochemical method is accurate to 1 ppm, which is adequate for clinical use, and is less expensive. Local environmental levels of NO and NO_2 are low and predominantly influenced by atmospheric concentrations; however, it is still common practice to scavenge expired gas. Binding to haemoglobin in the pulmonary circulation rapidly inactivates NO, and systemic effects are reported only following high concentrations of iNO. Systemic methaemoglobin levels may be monitored, and are generally less than 5% during clinical use of iNO, but they should be compared with a baseline level. Nitric oxide may cause lung toxicity through combination with oxygen free radicals, and through metabolism of NO to NO_2; however, these do not appear to be major clinical problems. However, there are concerns about delayed resolution of pulmonary oedema with its usage.[119]

Only 40%–70% of patients with ARDS have improved oxygenation with iNO (responders), and this is likely due to active hypoxic pulmonary vasoconstriction in the remainder. Addition of IV almitrine can have an additive effect on oxygenation, and may improve the number of responders. Clinical trials[120] have shown no improvement in mortality or reversal of ARDS, and an increased risk of renal impairment. However, iNO transiently improves oxygenation (as compared with placebo or no iNO), which has been sustained beyond 12–24 hours in some trials. As constant dosing of iNO leads to both increased sensitivity and apparent tachyphylaxis,[121] subsequent investigation needs to consider different dose regimens. Currently iNO cannot be recommended for routine use in ARDS; however, in some patients with severe hypoxaemia, perhaps in combination with almitrine, iNO will provide temporary rescue.

Inhaled prostacyclin

PGI_2 (up to 50 ng/kg per minute) improves oxygenation as effectively as iNO in ARDS patients,[122] and may reduce pulmonary hypertension. It is continuously jet nebulised due to its short half-life (2–3 minutes). Potential advantages include increased surfactant release from stretched type II cells, avoidance of the potential complications of iNO, and minimal toxicity. However, PGI_2 is dissolved in an alkaline glycine buffer, which alone can result in airway inflammation, and the sticky nature of the aerosol can result in expiratory valve obstruction. Iloprost is a derivative of PGI_2 with similar activity, a longer duration of action, without an alkaline buffer. Neither agent has been shown to improve outcome in ARDS patients.

CONSERVATIVE FLUID BALANCE

Conservative fluid balance has been shown to decrease the length of mechanical ventilation when compared with liberal fluid balance in patients with ARDS,[16] although in a small number of patients who were followed up (30% of eligible survivors) it was associated with adverse neurocognitive outcome.[17] An intermittent approach between conservative and liberal fluid balance offers[123] solutions but has to be examined in larger prospective trials. A positive sodium balance is associated with respiratory dysfunction independent of fluid balance,[124] and future trials need to control for sodium balance in addition to fluid balance in patients with ARDS.

HIGH FLOW OXYGEN

Use of high flow humidified oxygen through nasal cannula (HFNC) has become common in patients with acute hypoxaemic respiratory failure. As the gas flow rate (15–60 L/min) is close to the subject's inspiratory flow rate, there is little dilution of the inspired oxygen fraction. Additional mechanisms include flow dependent continuous positive airway pressure with increased end-expiratory lung volume, and washout of upper airway carbon dioxide leading to decreased physiological dead space, with both contributing to reduce the work of breathing. Compared to standard oxygen or NIV, HFNC reduced intubation in patients with hypoxic respiratory failure.[125] However, as the rate of intubation was high (38%), caution should be used. The role in of HFNC in ARDS is uncertain and endotracheal intubation and lung protective ventilation should not be delayed.[126]

NEUROMUSCULAR BLOCKER

The ACURASYS trial in 2010 examined neuromuscular blockade in patients with severe, early ARDS and found that both the adjusted 90-day survival rate and time off the ventilator were greater in the cisatracurium group as compared with the placebo group.[62] This was despite the fact that variables commonly used to assess the propensity for VILI (e.g. plateau pressures and tidal volumes) did not differ significantly between the cisatracurium group and the placebo group, although reduced asynchrony and adverse effects attributable to triggering ventilation cannot be excluded.[61,127] These results have to be repeated, the possible mechanisms understood,[128] and concerns about long-term muscle weakness and the optimal duration of neuromuscular blocker also need to be addressed before it becomes a routine in the care of ARDS patients.

SURFACTANT REPLACEMENT THERAPY

Surfactant dysfunction is an important and early abnormality contributing to lung damage in ARDS.[21,129] Pulmonary surfactant reduces surface tension promoting alveolar stability, reducing work of breathing and lung water. In addition, surfactant has important roles in lung host defence. Reactive oxygen species, phospholipases and increased protein permeability lead to inhibition of surfactant function. In addition, composition is abnormal, and turnover markedly increased.

VILI is difficult to demonstrate without surfactant dysfunction.[129] Consequently, there has been considerable interest in exogenous surfactant replacement therapy.

Exogenous surfactant therapy has an established role in neonatal respiratory distress syndrome. In paediatric ARDS, particularly that due to direct lung injury, clinical trials have been promising. However, in adults results have been disappointing; subgroup analysis of recombinant SP-C-based surfactant administered intratracheally improved oxygenation in direct ARDS without an improvement in mortality.[130] However, subsequent research in this cohort failed to confirm these data, perhaps owing to inactivation of the surfactant during administration.[131]

GLUCOCORTICOIDS

Glucocorticoids may have a role in ARDS through their reduction of the intense inflammatory response and their potential to reduce fibroproliferation and collagen deposition, by faster degradation of fibroblast procollagen mRNA. Preventative steroids increase the incidence of ARDS and, although there may be a greater number of ventilator-free days and the possibility of a reduction in mortality,[132,133] neuromuscular complications, immunosuppression, superadded infection and higher blood glucose levels and increased mortality when steroids are administered more than 13 days after the onset of ARDS,[134] argue against their routine use.

OTHER PHARMACOLOGICAL THERAPIES

Numerous other therapies including cytokine antagonism, non-steroidal anti-inflammatory drugs, scavengers of reactive oxygen species, and lisofylline[135] have been trialled without success. The complex balance of inflammation and repair in ARDS, and the critical additional damage secondary to VILI, may explain these results. However, studies in less heterogeneous groups with minimisation of VILI using standardised ventilation protocols, together with a growing understanding of ARDS, offer potential pharmacological therapies. Many promising therapeutic options such as TRPV4 antagonism, hyperosmolar therapy recombinant human angiotensin converting enzyme 2 and stem cell therapy are under trials.

KEY REFERENCES

2. The ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307:2526–2533.
13. Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364:1293–1304.
25. Steinberg KP, Milberg JA, Martin TR, et al. Evolution of bronchoalveolar cell populations in the adult respiratory distress syndrome. *Am J Respir Crit Care Med*. 1994;150:113–122.
61. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med*. 2017;195(4):438–442.
72. Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med*. 1998;157:294–323.

Access the complete references list online at http://www.expertconsult.com.

REFERENCES

1. Ashbaugh DG, Bigelow DB, Petty TL, et al. Acute respiratory distress in adults. *Lancet*. 1967;ii:319–323.
2. The ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307:2526–2533.
3. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med*. 1994;149:818–824.
4. Murray JF, Matthay MA, Luce JM, et al. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis*. 1988;138: 720–723. [Erratum, *Am Rev Respir Dis* 1989;139: 1065].
5. Gattinoni L, Caironi P, Pelosi P, et al. What has computed tomography taught us about the acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2001;164:1701–1711.
6. Bersten AD, Edibam C, Hunt T, et al. Incidence and mortality from acute lung injury and the acute respiratory distress syndrome in three Australian States. *Am J Respir Crit Care Med*. 2002;165: 443–448.
7. Rubenfeld GD, Herridge MS. Epidemiology and outcomes of acute lung injury. *Chest*. 2007;131: 554–562.
8. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*. 2016;315: 788–800.
9. Guangxi L, Malinchoc M, Cartin-Ceba R, et al. Eight year trend of acute respiratory distress syndrome: a population-based study in Olmsted County, Minnesota. *Am J Respir Crit Care Med*. 2011; 183:59–66.
10. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med*. 2003;348: 683–693.
11. McHugh LG, Milberg JA, Whitcomb ME, et al. Recovery of function in survivors of the acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 1994;250:90–94.
12. Davidson TA, Caldwell ES, Curtis SR, et al. Reduced quality of life in survivors of acute respiratory distress syndrome compared with other critically ill control patients. *JAMA*. 1999;281: 354–360.
13. Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364: 1293–1304.
14. Hopkins RO, Weaver LK, Pope D. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 1999;160:50–56.
15. Hopkins RO, Weaver LK, Collingridge D, et al. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2005;171:340–347.
16. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid management strategies in acute lung injury. *N Engl J Med*. 2006;354:2564–2575.
17. Mikkelsen ME, Christie JD, Lanken PN, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. *Am J Respir Crit Care Med*. 2012;185:1307–1315.
18. Honiden S, Gong MN. Diabetes, insulin, and development of acute lung injury. *Crit Care Med*. 2009;37:2455–2464.
19. Carr JB, Hansen ST. Fulminant fat embolism. *Orthopedics*. 1990;13:258.
20. King MB, Harmon KR. Unusual forms of pulmonary embolism. *Clin Chest Med*. 1994;15:561.
21. Albert RK. The role of ventilation-induced surfactant dysfunction and atelectasis in causing acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2012;185:702–708.
22. Davidson KG, Bersten AD, Barr HA, et al. Endotoxin induces respiratory failure and increases surfactant composition and respiration independent of alveolocapillary injury in rats. *Am J Respir Crit Care Med*. 2002;165(11):1516–1525.
23. Chesnutt AN, Matthay MA, Tibayan FA, et al. Early detection of type III procollagen peptide in acute lung injury. Pathogenetic and prognostic significance. *Am J Respir Crit Care Med*. 1997;156: 840–845.
24. Doyle IR, Nicholas TE, Bersten AD. Partitioning lung and plasma proteins: circulating surfactant proteins as biomarkers of alveolocapillary permeability. *Clin Exp Pharmacol Physiol*. 1999;26: 185–197.
25. Steinberg KP, Milberg JA, Martin TR, et al. Evolution of bronchoalveolar cell populations in the adult respiratory distress syndrome. *Am J Respir Crit Care Med*. 1994;150:113–122.
26. Nakos G, Kitsiouli EI, Tsangaris I, et al. Bronchoalveolar lavage fluid characteristics of early, intermediate and late phases of ARDS. Alterations in leukocytes, proteins, PAF and surfactant components. *Intensive Care Med*. 1998;24:296–303.
27. McVey MJ, Tabuchi A, Kuebler WM. Microparticles and acute lung injury. *Am J Physiol Lung Cell Mol Physiol*. 2012;303(5):L364–L381.
28. Downey GP, Dong Q, Kruger J, et al. Regulation of neutrophil activation in acute lung injury. *Chest*. 1999;116:46S–54S.
29. Nelson S, Belknap SM, Carlson RW, et al. A randomized controlled trial of filgrastim as an adjunct to antibiotics for treatment of hospitalized patients with community-acquired pneumonia. *J Infect Dis*. 1998;178:1075–1080.
30. Pugin J, Dunn I, Jolliet P, et al. Activation of human macrophages by mechanical ventilation in vitro. *Am J Physiol*. 1998;275:L1040–L1050.

31. Janssen WJ, Barthel L, Muldrow A, et al. Fas determines differential fates of resident and recruited macrophages during resolution of acute lung injury. *Am J Respir Crit Care Med*. 2011;184: 547–560.
32. Rezaiguia S, Garat C, Declauc C, et al. Acute bacterial pneumonia in rats increases alveolar epithelial fluid clearance by a tumor necrosis-factor-alpha dependent mechanism. *J Clin Invest*. 1997; 99:325–335.
33. Johnson ER, Matthay MA. Acute lung injury: epidemiology, pathogenesis and treatment. *J Aerosol Med Pulm Drug Deliv*. 2010;23:243–252.
34. Peters DM, Vadász I, Wujak L, et al. TGF-β directs trafficking of the epithelial sodium channel ENaC which has implications for ion and fluid transport in acute lung injury. *Proc Natl Acad Sci USA*. 2014;111(3):E374–E383.
35. Bersten AD, Hunt T, Nicholas TE, et al. Elevated plasma surfactant protein-B predicts development of acute respiratory distress syndrome in patients with acute respiratory failure. *Am J Respir Crit Care Med*. 2001;164:648–652.
36. Zimmerman GA, Albertine KH, Carveth HJ, et al. Endothelial activation in ARDS. *Chest*. 1999;116: 18S–24S.
37. Pittet JF, Mackersie RC, Martin TR, et al. Biological markers of acute lung injury: prognostic and pathogenetic significance. *Am J Respir Crit Care Med*. 1997;155:1187–1205.
38. Agrawal A, Matthay MA, Kangelaris KN, et al. Plasma angiopoietin-2 predicts the onset of acute lung injury in critically ill patients. *Am J Respir Crit Care Med*. 2013;187:736–742.
39. Calfee CS, Gallagher D, Abbott J, et al; NHLBI ARDS Network. Plasma angiopoietin-2 in clinical acute lung injury: prognostic and pathogenetic significance. *Crit Care Med*. 2012;40(6):1731–1737.
40. Scotton CJ, Krupiczojc MA, Konigshoff M, et al. Increased local expression of coagulation factor X contributes to the fibrotic response in human and murine lung injury. *J Clin Invest*. 2009;119: 2550–2563.
41. Modelska K, Pittet JF, Folkesson HG, et al. Acid-induced lung injury. Protective effect of anti-interleukin-8 pretreatment on alveolar epithelial barrier function in rabbits. *Am J Respir Crit Care Med*. 1999;160:1450–1456.
42. Yin J, Kuebler WM. Mechanotransduction by TRP channels: general concepts and specific role in the vasculature. *Cell Biochem Biophys*. 2010;56: 1–18.
43. Mochizuki T, Sokabe T, Araki I, et al. The TRPV4 cation channel mediates stretch-evoked Ca2+ influx and ATP release in primary urothelial cell cultures. *J Biol Chem*. 2009;284:21257–21264.
44. Hamanaka K, Jian MY, Weber DS, et al. TRPV4 initiates the acute calcium-dependent permeability increase during ventilator-induced lung injury in isolated mouse lungs. *Am J Physiol Lung Cell Mol Physiol*. 2007;293:L923–L932.
45. Jurek SC, Hirano-Kobayashi M, Chiang H, et al. Prevention of ventilator-induced lung edema by inhalation of nanoparticles releasing ruthenium red. *Am J Respir Cell Mol Biol*. 2014;50:1107–1117.
46. Yin J, Hoffmann J, Kaestle SM, et al. Negative-feedback loop attenuates hydrostatic lung edema via a cGMP-dependent regulation of transient receptor potential vanilloid 4. *Circ Res*. 2008;102: 966–974.
47. Hartmannsgruber V, Heyken WT, Kacik M, et al. Arterial response to shear stress critically depends on endothelial TRPV4 expression. *PLoS ONE*. 2007;2:e827.
48. Kohler R, Heyken WT, Heinau P, et al. Evidence for a functional role of endothelial transient receptor potential V4 in shear stress-induced vasodilatation. *Arterioscler Thromb Vasc Biol*. 2006; 26:1495–1502.
49. Liedtke W, Friedman JM. Abnormal osmotic regulation in trpv4-/- mice. *Proc Natl Acad Sci USA*. 2003;100:13698–13703.
50. Villalta PC, Townsley MI. Transient receptor potential channels and regulation of lung endothelial permeability. *Pulm Circ*. 2013;3:802–815.
51. Villalta PC, Rocic P, Townsley MI. Role of MMP2 and MMP9 in TRPV4-induced lung injury. *Am J Physiol Lung Cell Mol Physiol*. 2014;307:L652–L659.
52. Simonsen U, Wandall-Frostholm C, Olivan-Viguera A, et al. Emerging roles of calcium-activated K channels and TRPV4 channels in lung oedema and pulmonary circulatory collapse. *Acta Physiol (Oxf)*. 2017;219(1):176–187.
53. LeVitt JE, Gould MK, Ware LB, et al. The pathogenetic and prognostic value of biologic markers in acute lung injury. *J Intensive Care Med*. 2009;24:151–167.
54. Park WY, Goodman RB, Steinberg KP, et al. Cytokine balance in the lungs of patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2001;164:1896–1903.
55. Cabrera-Benitez NE, Parotto M, Post M, et al. Mechanical stress induces lung fibrosis by epithelial–mesenchymal transition. *Crit Care Med*. 2012;40:510–517.
56. Patel SB, Kress JP. Sedation and analgesia in the mechanically ventilated patient. *Am J Respir Crit Care Med*. 2012;185:486–497.
57. Schweickert WD, Kress JP. Implementing early mobilization interventions in mechanically ventilated patients in the ICU. *Chest*. 2011;140: 1612–1617.
58. Schaller SJ, Anstery M, Blobner M, et al. Early goal-directed mobilization in the surgical intensive care unit: a randomized controlled trial. *Lancet*. 2016;388:1377–1388.
59. Moss M, Nordon-Craft A, Malone D, et al. A randomized trial of an intensive physical therapy program for patients with acute respiratory failure. *Am J Respir Crit Care Med*. 2016;193: 1101–1110.

60. Morris PE, Barry MJ, Files C, et al. Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure: a randomized controlled study. *JAMA*. 2016;315:2694–2702.
61. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med*. 2017;195(4):438–442.
62. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363:1107–1116.
63. Dantzker DR, Brook CJ, Demart P, et al. Ventilation-perfusion distributions in the adult respiratory distress syndrome. *Am Rev Respir Dis*. 1979;120:1039–1052.
64. Zhan Q, Sun B, Liang L, et al. Early use of noninvasive positive pressure ventilation for acute lung injury: a multicenter randomized controlled trial. *Crit Care Med*. 2012;40:455–460.
65. Delclaux C, L'Her E, Alberti C, et al. Treatment of acute hypoxemic non hypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask. A randomized controlled trial. *JAMA*. 2000;284:2352–2360.
66. Ferrer M, Esquinas A, Leon M, et al. Noninvasive ventilation in severe hypoxemic respiratory failure. A randomized clinical trial. *Am J Respir Crit Care Med*. 2003;168:1439–1444.
67. Gristina GR, Antonelli M, Conti G, et al. Noninvasive versus invasive ventilation for acute respiratory failure in patients with hematologic malignancies: a 5-year multicenter observational study. *Crit Care Med*. 2011;39:2232–2239.
68. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301–1308.
69. Needham DM, Colantouni E, Mendez-Tellez PA, et al, for the ARDS Clinical Trials Network. Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study. *BMJ*. 2012;344:e2124. doi:10.1136/bmj.e2124.
70. Moran JL, Bersten AD, Solomon PJ. Meta-analysis of controlled trials of ventilator therapy in acute lung injury and acute respiratory distress syndrome: an alternative perspective. *Intensive Care Med*. 2005; 31:227–235.
71. Hager DN, Krishnan JA, Hayden DL, et al; for the ARDS Clinical Trials Network. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med*. 2005;172:1241–1245.
72. Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med*. 1998;157:294–323.
73. Chiumello D, Pristine G, Slutsky AS. Mechanical ventilation affects local and systemic cytokines in an animal model of acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 1999;160: 109–116.
74. Terragni PP, Rosboch G, Tealdi A, et al. Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2007;175:160–166.
75. Bellani G, Guerra L, Musch G, et al. Lung regional metabolic activity and gas volume changes induced by tidal ventilation in patients with acute lung injury. *Am J Respir Crit Care Med*. 2011;183:1193–1199.
76. Bersten AD. Measurement of overinflation by multiple linear regression analysis in patients with acute lung injury. *Eur Respir J*. 1998;12:526–532.
77. Talmor D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med*. 2008;359:2095–2104.
78. Engelberts D, Malhotra A, Butler JP, et al. Relative effects of negative versus positive pressure ventilation depend upon applied conditions. *Intensive Care Med*. 2012;38:879–885.
79. Suter PM, Fairley B, Isenberg MD. Optimum end-expiratory airway pressure in patients with acute pulmonary failure. *N Engl J Med*. 1975;292: 284–289.
80. Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med*. 2006;354:1775–1786.
81. Thille AW, Richard J-CM, Maggiore SM, et al. Alveolar recruitment in pulmonary and extrapulmonary acute respiratory distress syndrome. Comparison using pressure-volume curve or static compliance. *Anesthesiology*. 2007;106:212–217.
82. Puybasset L, Gusman P, Muller J-C, et al.; The CT scan ARDS study group. Regional distribution of gas and tissue in acute respiratory distress syndrome. III. Consequences for the effects of positive end-expiratory pressure. *Intensive Care Med*. 2000;26:1215–1227.
83. Caironi P, Cressoni M, Chiumello D, et al. Lung opening and closing during ventilation of acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2010;181:578–586.
84. Grasso S, Stripoli T, De Michele M, et al. ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. *Am J Respir Crit Care Med*. 2007;176: 761–767.
85. Jonson B, Richard JC, Straus R, et al. Pressure-volume curves and compliance in acute lung injury: evidence for recruitment above the lower inflection point. *Am J Respir Crit Care Med*. 1999;159:1172–1178.
86. Crotti S, Mascheroni D, Caironi P, et al. Recruitment and derecruitment during acute respiratory failure: a clinical study. *Am J Respir Crit Care Med*. 2001;164:131–140.
87. Malbouisson LM, Muller JC, Constantin JM, et al. Computed tomography assessment of positive end-expiratory pressure-induced alveolar recruitment in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2001;163: 1444–1450.

88. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA*. 2010;309:865–873.
89. Rouby JJ, Lu Q, Goldstein I. Selecting the right level of positive end-expiratory pressure in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2002;165:1182–1186.
90. Carvalho AR, Spieth PM, Pelosi P, et al. Ability of dynamic airway pressure curve profile and elastance for positive end-expiratory pressure titration. *Intensive Care Med*. 2008;34:2291–2299.
91. Pepe PE, Hudson LD, Carrico CJ. Early application of positive end-expiratory pressure in patients at-risk for adult respiratory distress syndrome. *N Engl J Med*. 1984;311:281–286.
92. Amato MBP, Meade O, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med*. 2015;372: 747–755.
93. Grasso S, Stripoli T, Sacchi M, et al. Inhomogeneity of lung parenchyma during the open lung strategy. A computed tomography study. *Am J Respir Crit Care Med*. 2009;180:415–423.
94. Hodgson CL, Tuxen DV, Davies AR, et al. A randomised controlled trial of an open lung strategy with staircase recruitment, titrated PEEP and low airway pressures in patients with acute respiratory distress syndrome. *Crit Care*. 2011; 15:R133.
95. Brower RG, Morris A, Macintyre N, et al. Effects of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end-expiratory pressure. *Crit Care Med*. 2003;31: 2592–2597.
96. Grasso S, Mascia L, Del Turco M, et al. Effects of recruiting maneuvers in patients with acute respiratory distress syndrome ventilated with protective ventilatory strategy. *Anesthesiology*. 2002;96:795–802.
97. Nicholas TE, Power JHT, Barr HA. The pulmonary consequences of a deep breath. *Respir Physiol*. 1982;49:315–324.
98. Pelosi P, Cadringher P, Bottino N, et al. Sigh in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 1999;159:872–880.
99. Boker A, Ruth Graham M, Walley KR, et al. Improved arterial oxygenation with biologically variable or fractal ventilation using low tidal volumes in a porcine model of acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2002;165:456–462.
100. Arold S, Suki B, Alenkar AM, et al. Variable ventilation induces surfactant release in normal guinea pigs. *Am J Physiol Lung Cell Mol Physiol*. 2003;285:L370–L375.
101. Wrigge H, Zinserling J, Neumann P, et al. Spontaneous breathing improves lung aeration in oleic acid-induced lung injury. *Anesthesiology*. 2003;99:376–384.
102. Yoshida T, Uchiyama A, Matsuura N, et al. The comparison of spontaneous breathing and muscle paralysis in two different severities of experimental lung injury. *Crit Care Med*. 2013;41: 536–545.
103. Lessard MR, Guerot E, Lorino H, et al. Effects of pressure-controlled with different I:E ratios versus volume-controlled ventilation on respiratory mechanics, gas exchange, and hemodynamics in patients with adult respiratory distress syndrome. *Anesthesiology*. 1994;80:983–991.
104. Esteban A, Alia I, Gordo F, et al. Prospective randomized trial comparing pressure-controlled ventilation and volume-controlled ventilation in ARDS. For the Spanish Lung Failure Collaborative Group. *Chest*. 2000;117:1690–1696.
105. Edibam C, Rutten AJ, Collins DV, et al. Effect of inspiratory flow pattern and inspiratory to expiratory ratio on nonlinear elastic behavior in patients with acute lung injury. *Am J Respir Crit Care Med*. 2003;167:702–707.
106. MacIntyre N. Airway pressure release ventilation: Hope or hype? *Crit Care Med*. 2011;39:2376–2377.
107. Ferguson ND, Cook DJ, Guyatt GH, et al; OSCILLATE Trial Investigators. Canadian Critical Care Trials Group. High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med*. 2013;368:795–805.
108. Peek GJ, Mugford M, Tiruvoipati R, et al; CESAR trial collaboration. Efficacy and economic assessment of conventional ventilator support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009;374:1351–1363.
109. Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the Oxygen-ICU Randomized Clinical Trial. *JAMA*. 2016;316:1583–1589.
110. Slutsky AS. Mechanical ventilation. *Chest*. 1993;104:1833–1859.
111. Frank L, Yam J, Roberts RJ. The role of endotoxin in protection of adult rats from oxygen-induced lung injury. *J Clin Invest*. 1978;61:269–275.
112. Richard JC, Brochard L, Breton L, et al. Influence of respiratory rate on gas trapping during low volume ventilation of patients with acute lung injury. *Intensive Care Med*. 2002;28:1078–1083.
113. Laffey JG, Tanaka M, Engelberts D, et al. Therapeutic hypercapnia reduces pulmonary and systemic injury following in vivo lung reperfusion. *Am J Respir Crit Care Med*. 2000;162: 2287–2294.
114. O'Croinin DF, Nichol AD, Hopkins N, et al. Sustained hypercapnic acidosis during pulmonary infection increases bacterial load and worsens lung injury. *Crit Care Med*. 2008;36:2128–2135.

115. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368:2159–2168.
116. Sud S, Friedrich JO, Taccone P, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. *Intensive Care Med*. 2010;36:585–599.
117. Gattinoni L, Tognoni G, Pesenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med*. 2001;345: 568–573.
118. Taccone P, Pesenti A, Latini R, et al. Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 2009;302: 1977–1984.
119. Kaestle SM, Reich CA, Yin N, et al. Nitric oxide-dependent inhibition of alveolar fluid clearance in hydrostatic lung edema. *Am J Physiol Lung Cell Mol Physiol*. 2007;293:L859–L869.
120. Afshari A, Brok J, Moller AM, et al. Inhaled nitric oxide for acute respiratory distress syndrome and acute lung injury in adults and children: a systematic review with meta-analysis and trial sequential analysis. *Anesth Analg*. 2011;112: 1411–1421.
121. Gerlach H, Keh D, Semmerow A, et al. Dose-response characteristics during long-term inhalation of nitric oxide in patients with severe acute respiratory distress syndrome. A prospective, randomized, controlled study. *Am J Respir Crit Care Med*. 2003;167:1008–1015.
122. Van Heerden PV, Barden A, Michalopoulos N, et al. Dose-response to inhaled aerosolized prostacyclin for hypoxemia due to ARDS. *Chest*. 2000;117:819–827.
123. Grissom CK, Hirshberg EL, Dickerson JB, et al. National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network. Fluid management with a simplified conservative protocol for the acute respiratory distress syndrome. *Crit Care Med*. 2015;43:288–295.
124. Bihari S, Peake SL, Prakash S, et al. Sodium balance, not fluid balance, is associated with respiratory dysfunction in mechanically ventilated patients: a prospective, multicentre study. *Crit Care Resusc*. 2015;17:23–28.
125. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med*. 2015;372: 2185–2196.
126. Bihari S, Bersten AD. Hose up the nose in acute hypoxemic respiratory failure: proceed with caution. *CMAJ*. 2017;189:E258–E259.
127. Yoshida T, Fujino Y, Amato MB, et al. Spontaneous breathing during mechanical ventilation – risks, mechanisms & management. *Am J Respir Crit Care Med*. 2017;195:985–992.
128. Slutsky AS. Neuromuscular blocking agents in ARDS. *N Engl J Med*. 2010;363:1176–1180.
129. Bersten AD, Davidson K, Nicholas TE, et al. Respiratory mechanics and surfactant in the acute respiratory distress syndrome. *Clin Exp Pharmacol Physiol*. 1998;25:955–963.
130. Spragg RG, Lewis JF, Walmrath HD, et al. Effect of recombinant surfactant protein C-based surfactant on the acute respiratory distress syndrome. *N Engl J Med*. 2004;351:884–892.
131. Spragg RG, Tatut FJ, Lewis JF, et al. Recombinant surfactant protein C-based surfactant for patients with severe direct lung injury. *Am J Respir Crit Care Med*. 2011;183:1055–1061.
132. Meduri GU, Headley AS, Golden E, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 1998;280: 159–165.
133. Peter JV, John P, Graham PL, et al. Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis. *BMJ*. 2008;336:1006–1009.
134. Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med*. 2006;354:1671–1684.
135. Randomized placebo-controlled trial of lisofylline for early treatment of acute lung injury and acute respiratory distress syndrome. *Crit Care Med*. 2002; 30:1–6.

34

Pulmonary embolism

Sachin Gupta, Andrew R Davies

INTRODUCTION

Pulmonary embolism (PE) is a commonly considered but relatively uncommonly diagnosed condition in hospitalised patients. It is important to have an adequate understanding of the pathophysiology as well as a rapid and reliable strategy for investigation and management. This is particularly important in intensive care unit (ICU) patients where diagnosis can be difficult and PE may be life threatening. While admission rates for PE are rising, outcomes are improving overall.[1] However, mortality amongst haemodynamically unstable patients remains high.[1]

Early deaths in PE are usually the result of acute right ventricular (RV) failure and cardiogenic shock. After the first few days, mortality is less common and mostly determined by recurrent thromboembolic events and the underlying disease state.

AETIOLOGY

Deep venous thrombosis (DVT) and PE are components of a single disease termed venous thromboembolism (VTE). Embolisation of DVT to the pulmonary arteries leads to PE. The incidence of VTE in the population is about 1 in 1000 per year and is more common both with advancing age and in males.

Predisposing risk factors for VTE involve one or more components of Virchow triad: (1) venous stasis, (2) vein wall injury, and (3) hypercoagulability of blood. In addition to the main factors such as immobility (from any cause), surgery, trauma, malignancy, pregnancy, thrombophilia (see Box 34.1) and autoimmune disorders have also been associated with increased risk of PE.[2]

The term thrombophilia refers to any abnormality of blood coagulation that increases the risk of thrombosis, and can be heritable or acquired. Heritable thrombophilias are present in 5% of the population.[3] The most common of the heritable thrombophilias is activated protein C resistance, which is mediated by the factor V Leiden mutation. As most people with thrombophilia do not develop DVT or PE, and diagnosis of thrombophilia does not affect immediate and in most cases long-term management of these patients, investigation for thrombophilia should not be prioritised unless it changes management.[3] Autoimmune disorders are associated with high risk of PE and should be considered hypercoagulable disorders.[2]

Factor V Leiden mutation, oral contraceptive use, pregnancy, pueperium, obesity and minor leg injuries pose a higher risk of DVT as compared to PE, whereas pulmonary conditions like chronic obstructive pulmonary disease, sickle cell disease and pneumonia raise the risk of PE with little effect on risk of DVT.[4]

Most PE results from DVT in the lower limbs, pelvic veins or inferior vena cava (IVC), although thrombi can develop in the right atrium, right ventricle and upper limbs. Up to 40% of patients with DVT develop PE, although if the DVT is isolated to below the knee, then clinically obvious PE is rare. Between 2% and 4% of patients with VTE develop chronic pulmonary hypertension.[5]

PATHOPHYSIOLOGY

The effects of PE range from being incidental and clinically irrelevant to causing severe obstruction to the pulmonary circulation and sudden death. Pulmonary arterial obstruction and the subsequent release of vasoactive substances such as serotonin and thromboxane A_2 from platelets lead to elevated pulmonary vascular resistance and acute pulmonary hypertension.

Acute pulmonary hypertension increases RV afterload and RV wall tension which leads to RV dilatation and dysfunction with coronary ischaemia being a major contributing mechanism.[6] In massive PE, the combination of coronary ischaemia, RV systolic failure, paradoxical interventricular septal shift and pericardial constraint leads to left ventricular (LV) dysfunction and obstructive shock. In patients with underlying cardiorespiratory disease, a small PE can have profound consequences.

Pulmonary arterial obstruction causes a mismatch between lung ventilation and perfusion which leads to hypoxaemia. The ventilation of lung units that have reduced or no perfusion causes increased dead-space ventilation and an increase in the end-tidal to arterial

ABSTRACT

Pulmonary embolism is a commonly considered, uncommonly confirmed yet sometimes overlooked condition. Both clinical and objective parameters can be used to estimate pretest probability which improves detection. Computed tomography pulmonary angiogram (CTPA) scanning remains the mainstay of diagnosis. Echocardiography and biomarkers are important tools to stratify the risk of complications, while presence of haemodynamic compromise puts patients in the highest risk category. Even though treatment carries significant risk of bleeding, undertreatment may lead to death or significant long-term disability. Newer oral anticoagulants have simplified longer-term management and treatment monitoring. Catheter-directed thrombolysis and lower dose fibrinolysis have the potential to reduce bleeding without compromising patient outcomes in carefully chosen patients. Other supportive therapies include haemodynamic support focused on right ventricular function.

KEYWORDS

Pulmonary embolism
deep venous thrombosis
venous thromboembolism
critically ill
thrombolysis
anticoagulation
newer oral anticoagulants
outcome
biomarkers
haemodynamic support

Box 34.1 Risk factors for venous thromboembolism

Primary hypercoagulable states (thrombophilia)
Antithrombin III deficiency
Protein C deficiency
Protein S deficiency
Resistance to activated protein C (inherited factor V Leiden mutation)
Hyperhomocysteinaemia
Lupus anticoagulant (antiphospholipid antibody)
Secondary hypercoagulable states
Immobility
Surgery
Trauma
Malignancy
Pregnancy and puerperium
Obesity
Smoking
Oestrogen-containing oral contraception or hormone replacement therapy
Indwelling catheters in great veins and the right heart
Burns
Patients with limb paralysis (e.g. spinal injuries)
Heart failure
Increasing age
Autoimmune and chronic inflammatory diseases such as inflammatory bowel disease

Box 34.2 Differential diagnosis of pulmonary embolism

Acute myocardial infarction
Acute coronary syndrome
Acute pulmonary oedema
Pneumonia
Asthma or exacerbation of chronic obstructive pulmonary disease
Pericardial tamponade
Pleural effusion
Fat or amniotic fluid embolism
Pneumothorax
Aortic dissection
Rib fracture
Musculoskeletal pain
Anxiety

CO_2 gradient. Alveolar hyperventilation also occurs leading to hypocapnia. Increased right atrial pressure can open a patent foramen ovale, which may result in right-to-left shunting manifested as either refractory hypoxaemia or paradoxical (arterial) embolisation commonly to the brain leading to cerebral infarction.

CLINICAL PRESENTATION

PE is relatively uncommon in critically ill patients despite the frequent presence of risk factors for VTE. However, when PE does occur the diagnosis is frequently overlooked or is difficult to confirm because several more prevalent cardiopulmonary diseases, including heart failure, pneumonia and chronic lung diseases, have similar clinical features. Up to one in six patients have the diagnosis made more than 10 days after symptom onset.[7]

Clinical assessment should raise the suspicion of PE but is neither sensitive nor specific enough to reliably confirm or exclude the diagnosis on its own. Clinical decision rules (CDRs) have been developed, some based entirely on objective parameters such as the combination of symptoms, signs and risk factors (Geneva, Pisa, Charlotte, and Pulmonary Embolism Rule-out Criteria [PERC]) and others still requiring clinician's judgement regarding whether PE is more likely than alternative diagnoses (Wells score) in addition to the objective criteria. The most widely reported of these are the Wells score and the Geneva score.[8] Even though CDRs provide accurate and reproducible determinations of probability for use in a diagnostic strategy, empirical clinical assessment may carry similar sensitivity and specificity, especially when prevalence of PE is higher.[9] However, CDRs may modestly increase the yield of computed tomographic pulmonary angiogram (CTPA).[10] With either strategy, patients can have their probability determined as unlikely (in whom PE can be safely ruled out with a negative D-dimer result) or likely (in whom an imaging test is required and in whom prompt anticoagulant therapy should be considered). The differential diagnoses are listed in Box 34.2.

SYMPTOMS

Dyspnoea, pleuritic chest pain, and haemoptysis are the classic symptoms of PE. Most patients will have at least one of these symptoms, with dyspnoea being the most common. The combination of pleuritic chest pain and haemoptysis reflects a late presentation where pulmonary infarction has occurred. If syncope occurs, and there is no other obvious cause, it is likely that this is a massive PE. A family history of venous thrombosis is itself a risk factor regardless of the presence of an inherited thrombophilia.

PHYSICAL SIGNS

Physical signs can be absent, but the most frequent sign is tachypnoea. Others include tachycardia, fever and signs of RV dysfunction (raised jugular venous pressure, parasternal heave and loud pulmonary component of the second heart sound). In massive PE, signs may include hypotension, pale mottled skin and peripheral or even central cyanosis. It is important to examine for signs of DVT particularly in the legs.

INVESTIGATIONS

The diagnosis of PE requires a high level of clinical suspicion and the appropriate use of investigations. The aim of these investigations is to confirm or exclude the presence of PE but also to stratify treatment to aid planning management. The optimal investigation strategy depends upon the individual patient and institution; however, multidetector CTPA scanning is now the imaging test of first choice. A suggested investigation algorithm is shown in Fig. 34.1.

D-DIMER

The serum D-dimer level, which becomes elevated when acute thrombus formation occurs, is useful for exclusion of VTE, particularly when it is normal and combined with a low-risk clinical assessment.[11] Because of its sensitivity, negative D-dimer tests, particularly using enzyme-linked immunosorbent assays (ELISA), enzyme-linked immunofluorescence assays (ELFAs) and latex quantitative assays, are highly predictive of the absence of both DVT and PE.

A high D-dimer concentration is also an independent predictive factor associated with mortality.[12] Age adjusted D-dimer cut off (defined as age in years × 10 in patients above 50 years of age) increases the number of low-to-intermediate probability patients (revised Geneva score <5 or Wells Score </= 4) in whom PE can be safely ruled out.[13] Unfortunately, D-dimer levels are often elevated in ICU patients for reasons including infection, inflammation, cancer, surgery and trauma, acute coronary syndrome, stroke, peripheral artery disease or ruptured aneurysm. D-dimer tests should be used with caution in patients who are elderly (as the upper limit of normal increases with age), who have prolonged symptoms and who are already receiving therapeutic anticoagulant therapy. In addition, reporting units and performance of the assay used by the laboratory need to be considered when using D-dimer cut offs to rule out PE.[14]

BIOMARKERS

Although of little use for confirming or excluding the diagnosis, biomarkers can assist in risk stratification of patients with diagnosed PE.[15] Below cut-off levels of established biomarkers such as troponin, brain natriuretic peptide (BNP) and N-terminal pro BNP (NT-pro-BNP) can help stratify patients into a low-risk category.

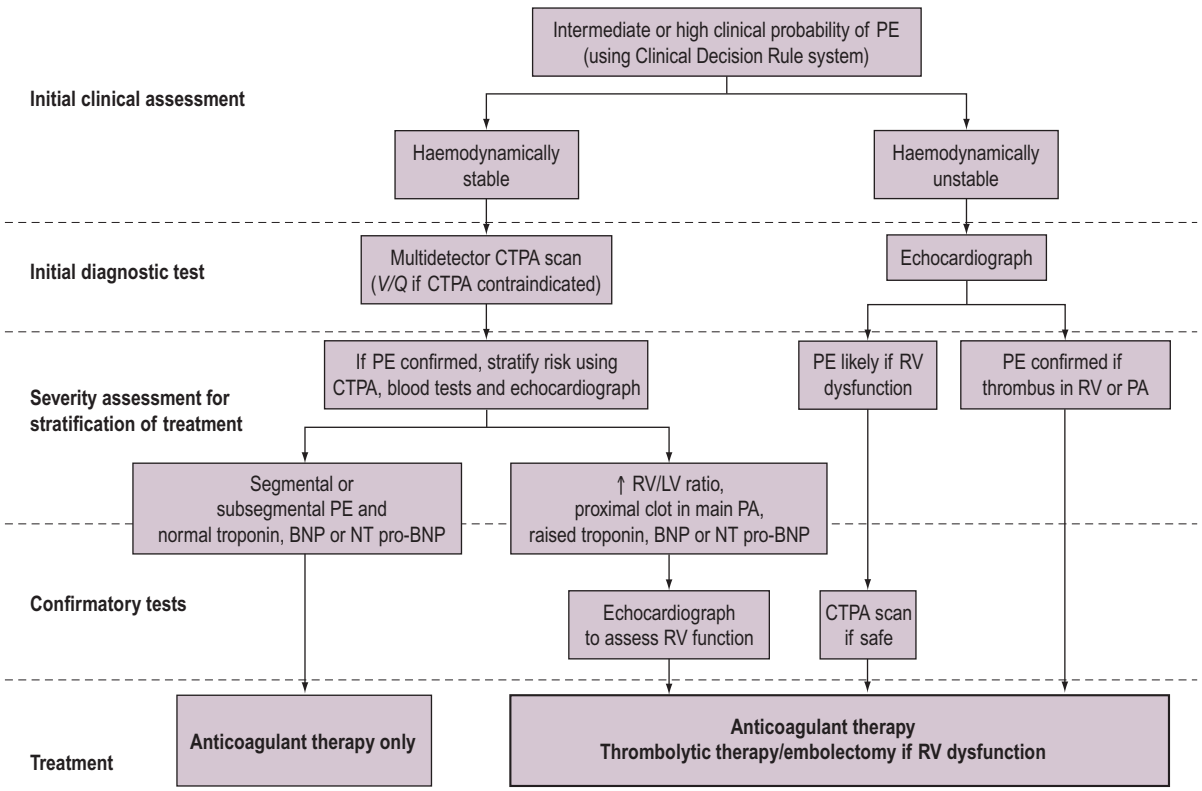


Figure 34.1 Suggested investigation and treatment algorithm for pulmonary embolism (PE). *BNP*, Brain natriuretic peptide; *CTPA*, computed tomographic pulmonary angiography; *IVC*, inferior vena cava; *NT pro-BNP*, N-terminal pro BNP; *PA*, pulmonary artery; *RV*, right ventricular; *RV/LV*, right ventricle/left ventricle; *V/Q*, ventilation/perfusion scan.

Admission troponin levels may be falsely low in some patients who present early, so the troponin level at 8 hours is a better marker for risk stratification for these patients.[16] Heart fatty acid binding protein (H-FABP) is a cytoplasmic protein which appears in the circulation as early as 90 minutes after myocardial injury and is an emerging biomarker for predicting adverse outcomes after PE.[17] These biomarkers should be used in conjunction with other tests investigating for the presence of RV dysfunction (echocardiography or CTPA) to stratify these patients, as none of these biomarkers alone can separate patients with low risk from those with higher risk of death or PE-related complications with an acceptable degree of certainty.[18]

ARTERIAL BLOOD GASES

A normal arterial blood gas profile does not exclude the diagnosis of PE; however, hypoxaemia (with a widened alveolar-arterial oxygen gradient), hypocapnia and an increased end-tidal CO_2 gradient should raise the suspicion of PE, even if these are common findings in critically ill patients for other reasons. Metabolic acidosis may be present if shock from a large PE occurs. Capnography may evolve into a useful tool to rule out PE in patients with positive D-dimer tests but at present the method and optimal cut offs are unclear.[19]

ELECTROCARDIOGRAPH

A normal electrocardiograph (ECG) is found in about one-third of patients. Apart from sinus tachycardia (which is non-specific), the most frequent ECG abnormalities are non-specific S–T depression and T-wave inversion in leads V1–V4, right bundle branch block, S1Q3T3 pattern (deep S-wave in lead I and a Q-wave and inverted T-wave in lead III) and S-T segment elevation in lead AVR, reflecting right heart strain. These ECG abnormalities and the presence of atrial fibrillation are associated with a higher risk of adverse outcomes.[20] The ECG is also useful in excluding acute myocardial infarction and pericarditis. Presence of T-wave inversion in both lead III and V1 increases the likelihood of PE as compared to acute coronary syndrome.[21]

CHEST X-RAY

The chest X-ray is often normal or only slightly abnormal with non-specific signs such as cardiac enlargement, pleural effusion, elevated hemidiaphragm, atelectasis and localised infiltrates. More specific findings, including focal oligaemia, a peripheral wedge-shaped density above the diaphragm (Hampton hump) and an enlarged right descending pulmonary artery (Palla sign), are uncommon and may be difficult for non-radiologists to identify.[22] The chest X-ray is also useful in identifying an alternative diagnosis such as pneumothorax, pneumonia, acute pulmonary oedema, rib fracture and pleural effusion.

CONFIRMATORY IMAGING TESTS INCLUDING CTPA SCAN

Imaging is required in any patient with a high or likely clinical probability. As the technology has improved, CTPA scanning, especially the multidetector scanner (MD-CTPA),[23] has now largely replaced lung ventilation-perfusion (V/Q) scanning as the cost-effective and clinically reliable imaging procedure of choice in patients with suspected PE.[24] This is because the CTPA scan has the advantages of greater diagnostic accuracy, ready availability at most hospitals, more rapid image acquisition time, and the possibility of making an alternative diagnosis. High-resolution images to the level of segmental and in some cases subsegmental pulmonary arteries can be obtained in a short time period (often a single breath-hold). When compared with conventional angiography it appears reliable, with excellent sensitivity, specificity and accuracy.[25] It is therefore recommended that the CTPA scan should be the principal imaging test for patients with high and moderate probability of PE.

Although inconclusive CTPA scans occur in around 10%, a negative CTPA result means that withholding anticoagulant therapy is safe.[26] An emerging problem of CTPA scanning, however, is the increased detection (around 10%) of small peripheral emboli in subsegmental pulmonary arteries due to increased visualisation of these arteries. The clinical significance of these findings in critically ill patients is unknown; however, these are usually unlikely to lead to a poor outcome if left untreated, unless the patient has co-existing DVT, cancer or is symptomatic.

The CTPA scan can also be used to assess the severity of PE. An increased RV/LV ratio, high thrombus load and central location of the clot are associated with worse clinical outcomes. Increased RV/LV ratio is the most significant marker of severity of PE.[27] Severity stratification is further increased by combining CTPA scanning with other tests such as troponin,[10] BNP or NT-Pro-BNP.[15] CTPA scanning may also identify the causative DVT in the veins of the legs, pelvis and abdomen or detect alternative or additional diagnoses such as a pulmonary mass, pneumonia, emphysema, pneumothorax, pleural effusion or mediastinal adenopathy (Fig. 34.2).

Despite the increased use of the CTPA scan, the planar and SPECT V/Q scan retain a role when CTPA is either unavailable or contraindicated (e.g. significant renal impairment, anaphylaxis to intravenous contrast or pregnancy).[28] SPECT V/Q has equivalent diagnostic yield to CTPA, with lower radiation dose, despite improvements in technology progressively reducing the radiation dose of CTPA. Planar V/Q scanning is

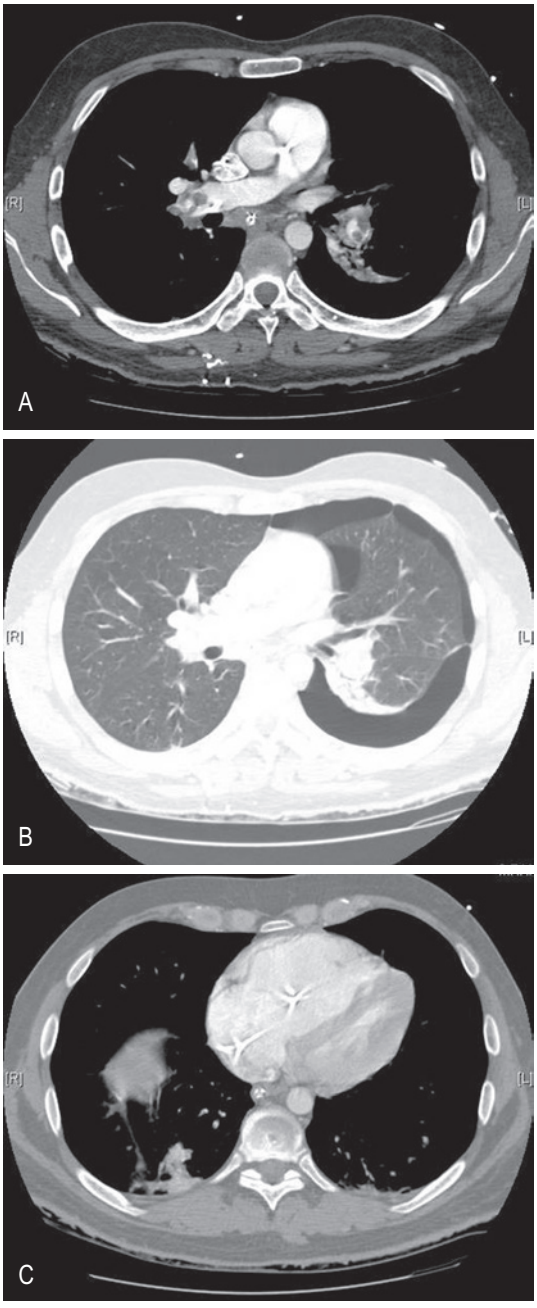


Figure 34.2 Computed tomography (CT) scanning and pulmonary embolism. Three CT images from the same patient demonstrating the ability of CT to detect pulmonary emboli, assess severity and confirm additional diagnoses. (a) (mediastinal window): filling defects in the right pulmonary artery and inferior branch of the left pulmonary artery. A pulmonary artery catheter is also in situ. (b) (lung window): a left pneumothorax with pleural adhesions, and a small area of left-sided posterior consolidation. (c) (mediastinal window): dilatation of the right ventricle relative to the left ventricle.

inferior to both SPECT V/Q and CTPA in diagnostic yield.[29] V/Q scanning also allows quantification of regional blood flow within the lungs which may be required in the assessment of chronic thromboembolic pulmonary hypertension.

PE may also be diagnosed by using a combination of real time magnetic resonance angiography (MRA) and contrast enhanced MRA, which seems to have highest diagnostic yield amongst MRI techniques. While lack of radiation and nephrotoxic intravenous contrast are obvious advantages, significant numbers of low quality images and poor sensitivity for subsegmental PE remain a problem, restricting wider use of this modality.[30]

ECHOCARDIOGRAPHY

Because of its portability, echocardiography has the greatest usefulness in critically ill patients with probable PE. Many patients with PE have an echocardiographic abnormality, the most common being RV dilatation, RV hypokinesis, paradoxical interventricular septal motion towards the LV, tricuspid regurgitation and pulmonary hypertension. The pattern of RV hypokinesis with apical sparing (McConnell sign) reflects tethering of the RV apex to the hyperdynamic LV and was considered pathognomonic for PE, although it can occur in other conditions such as RV infarction.[31] Pulmonary acceleration time less than 60 ms with maximum tricuspid regurgitate pressure of less than 60 mmHg (60/60 sign) may be more sensitive for diagnosing PE in patients without underlying cardiorespiratory comorbidities but needs a more detailed echocardiography assessment.[32] The presence of RV dysfunction correlates with mortality.[33] However, it must be noted that a negative echocardiography does not exclude PE.

Transthoracic echocardiography will also allow estimation of pulmonary arterial pressure, identification of intracardiac thrombi (which usually requires surgical embolectomy) and aids in differential diagnosis by raising suspicion of aortic dissection and excluding pericardial tamponade. Transoesophageal echocardiography has the additional benefit of directly identifying embolus in the proximal pulmonary arteries which is common in patients with haemodynamically significant PE.

Echocardiography has its best application in haemodynamically unstable patients where it can be rapidly brought to the patient. If the patient has RV dilatation and hypokinesis in the right clinical setting, PE is extremely likely.

DIAGNOSIS OF DEEP VENOUS THROMBOSIS USING ULTRASOUND

Doppler ultrasound has been recommended to search for DVT in the leg veins from where over 90% of

emboli originate. If a leg DVT is confirmed, anticoagulation is required unless the DVT is entirely below the knee where the associated morbidity is low. Ultrasound is highly accurate in symptomatic or proximal DVT, although in asymptomatic patients ultrasound is much less likely to find DVT, meaning the absence of DVT does not exclude PE. The best use of ultrasound is when a CTPA scan is contraindicated.[34] Proximal compression ultrasound (CUS) with four-point compression (bilateral femoral vein at the saphenofemoral junction and bilateral popliteal veins) has excellent specificity for diagnosis of PE in the right clinical setting and hence is useful for ruling in the diagnosis in patients in whom CTPA is contraindicated or carries a significant risk of harm (e.g. pregnancy, allergy to intravenous contrast or renal dysfunction).[35]

INVESTIGATION STRATEGY IN HAEMODYNAMICALLY STABLE PATIENTS

- A CTPA scan is the preferred initial test. If positive, the patient should be stratified into high or moderate risk. The presence of clot within pulmonary arteries confirms the diagnosis of PE.
- An echocardiograph should then be considered to assess RV dysfunction for high-risk patients who have:
  - Clot within proximal pulmonary arteries
  - Raised RV/LV ratio (i.e. >0.9–1.0)
  - Raised troponin (repeated at 8 hours if not elevated on admission), BNP or NT-pro-BNP.
- If a CTPA scan is not possible (contraindicated or unavailable), an alternative investigation such as a *V*/*Q* scan, MRA or ultrasound should be considered.
- None of these tests excludes PE but a negative result in a haemodynamically stable patient means that the outcome without anticoagulation is unlikely to be poor.

INVESTIGATION STRATEGY IN HAEMODYNAMICALLY UNSTABLE PATIENTS

- An echocardiograph (transoesophageal if patient is intubated in absence of contraindications) should be the first test performed.
- If the patient has acute RV dilatation with systolic dysfunction and visible embolus, PE is confirmed.
- If there is RV dilatation with or without systolic dysfunction but no visible embolus, then a CTPA scan is required depending on how unstable the patient is.
- If there is no RV dilatation, the haemodynamic instability is unlikely to be due to PE (although this cannot be excluded completely). Finding an alternative diagnosis is the priority.
- If echocardiography is not readily available, a CTPA scan should be performed unless a proximal CUS can expediently confirm a DVT. Absence of a DVT on proximal CUS is insufficient to rule out PE.

MANAGEMENT

MANAGEMENT PRINCIPLES

Once PE has been confirmed, patients at all levels of severity should receive anticoagulation with either unfractionated or low-molecular-weight heparin (LMWH), or newer oral anticoagulants (NOACs), to prevent further embolisation. In more severe cases of PE, however, the key principle is embolus destruction to maximise a more rapid effect on relief of RV dysfunction. To assist in planning management it is important to grade the severity of PE. Prediction models based on clinical findings at diagnosis may be useful for the prognostic assessment of patients with acute PE. The PE severity index is the most extensively validated prognostic clinical score[36] and a simplified version of this has been developed.[37] The place of these indices in critical illness is yet to be determined and it may be that a combination of a predictive scoring system with a combination of imaging for RV dysfunction and cardiac laboratory biomarkers is the most useful.[38]

MASSIVE PULMONARY EMBOLISM (HAEMODYNAMICALLY UNSTABLE)

Patients with PE and hypotension have a high risk of death despite treatment. If cardiopulmonary resuscitation is required the risk is even higher. These patients have the most to benefit from a strategy that includes attempts at urgent embolus destruction (with thrombolytic therapy or embolectomy), concurrent haemodynamic support and prevention of further embolisation.

SUBMASSIVE PULMONARY EMBOLISM (HAEMODYNAMICALLY UNSTABLE WITH EVIDENCE OF RIGHT VENTRICULAR DYSFUNCTION)

Patients with PE and evidence of RV dysfunction have higher mortality (around 15%) and recurrence rates than those with normal RV function.[33] They also develop shock and RV thrombi more frequently. These patients require prevention of further embolisation but also warrant strong consideration of embolus destruction using thrombolytic therapy. Thrombolytic therapy in these patients has been shown to reduce haemodynamic decompensation and mortality at the cost of increased risk of intracranial haemorrhage and major extracranial bleeding, especially in elderly patients.[39,40] Consideration should be given to low-dose thrombolysis or catheter-based techniques.[41–43]

MILD PULMONARY EMBOLISM (HAEMODYNAMICALLY STABLE WITH NO RIGHT VENTRICULAR DYSFUNCTION)

Patients with PE who have normal blood pressure, normal RV function (determined by echocardiography or CTPA scan) and non-elevated cardiac biomarkers

have a low risk of death or recurrence. The predominant management goal is prevention of further embolisation using anticoagulant therapy, as treatment focused on embolus destruction is unlikely to confer additional benefits.

In summary, the major principles of management are therefore

- Prevention of further embolisation (for massive, submassive and mild PE)
- Embolus destruction (for massive and submassive PE)
- Concurrent haemodynamic support (for massive PE).

A suggested management strategy is outlined in Fig. 34.1.

PREVENTION OF FURTHER EMBOLISATION

ANTICOAGULANT THERAPY

Heparin has been known to prevent recurrence and reduce the mortality from PE for over 45 years. LMWHs are as effective and safe as unfractionated heparin (UFH)[44] and may even be better.[45] LMWHs offer several advantages over UFH, including a longer half-life, increased bioavailability, a more predictable dose-response and fewer requirements for monitoring and dose adjustments. They should be readily used in the stable patient with PE.

UFH should be used in patients with renal impairment and following thrombolytic therapy or embolectomy as it can be easily and rapidly reversed. Intravenous UFH should be administered after a bolus and initial monitoring should be with 6-hourly activated partial thromboplastin time (APTT) testing. Since subtherapeutic levels of anticoagulant therapy increase the risk of recurrence, it is important to achieve therapeutic heparinisation rapidly. Weight-based dosing of heparin should be used, as target anticoagulation levels are reached sooner.[46] It is noteworthy that in the context of thrombolysis UFH infusion should be withheld for 12 hours if twice-daily LMWH was being used prior to thrombolysis; or for 24 hours if using once-daily LMWH. If a patient is on UFH infusion prior to thrombolysis, UFH should be stopped during streptokinase or urokinase infusion but can continue during rtPA infusion.[38]

The predominant complications of both UFH and LMWHs are bleeding related. These include bleeding peptic ulcer, stroke, retroperitoneal haematoma and postsurgical wound haemorrhage. Heparin-induced thrombotic thrombocytopenia syndrome (HITTS) can also occur. Bleeding complications and HITTS appear to be less common when LMWHs are being used. A number of conditions are considered to be relative contraindications to anticoagulant therapy. These include active peptic ulceration, recent surgery, recent trauma and recent cerebral haemorrhage. In each individual patient the risk-to-benefit ratio (taking into account the severity of the PE) should be considered before anticoagulation is withheld from the patient.

Oral anticoagulants should be started as soon as possible so that LMWH or UFH can eventually be ceased. For warfarin, this is generally when the international normalised ratio is greater than 2.0. Although warfarin (a vitamin K antagonist [VKA]) has been commonly used as the long-standing anticoagulant of choice, adverse events leading to hospitalisation remain common.[47] NOACs, namely factor Xa antagonists (rivaroxaban, apixaban, edoxaban) and direct thrombin inhibitors (dabigatran), are increasingly being used for treatment of PE. These have advantage of more rapid onset of action, predictable anticoagulant effects and no need for routine laboratory monitoring. Both direct thrombin inhibitors and factor Xa antagonists have been shown to be as efficacious as LMWH-VKA combination in patients with non-massive PE with a lower risk of bleeding.[48] In addition, rivaroxaban and apixaban do not require a heparin lead-in period as opposed to edoxaban and dabigatran, which need at least 5 days of heparin lead-in. While there is no proven advantage of one NOAC over another, pharmacokinetics, severity of disease, individual patient characteristics and preferences should be considered carefully when choosing between these agents. Amongst NOACs, higher severity of disease may favour agents with overlap with heparin while mild to moderate renal impairment may favour factor Xa antagonists over dabigatran. However, severe renal impairment or doubts about compliance favours VKAs, as treatment can be monitored. Recent approval of a reversal agent for dabigatran (idarucizumab) and emerging reversal agents for factor Xa antagonists (andexanet alfa) may help in management of bleeding complications in patients on NOACs.[49,50]

INFERIOR VENA CAVA FILTER

IVC filters are another method used to prevent further embolisation. These can be permanent, temporary (needing removal in a few days) or retrievable (can be left in situ for longer). IVC filters are indicated for patients in whom anticoagulation is contraindicated and those who experience recurrent PE despite adequate anticoagulation.[38] They do not have a role in patients with massive or submassive PE who have undergone open surgical embolectomy or thrombolysis[38] and they do not offer any further benefit if added to therapeutic anticoagulation.[51] Insertion is usually performed percutaneously in a radiology department but it can be done at the bedside. They lower early recurrence rates but increase long-term DVT recurrence rates.[52] Newer retrievable designs may be more efficacious and safe if removed at the appropriate time. If not removed, complications related to these filters may nullify their immediate benefits in the longer term.[53]

Absolute indications include:

- New or recurrent PE despite anticoagulation
- Contraindications to anticoagulation
- Complications resulting from anticoagulation.

EMBOLUS DESTRUCTION

THROMBOLYTIC THERAPY

Intravenous thrombolytic drugs result in dramatic and immediate haemodynamic improvement in some patients by dissolving the embolus and rapidly reducing pulmonary arterial obstruction. Experimental studies, clinical observations and randomised trials have consistently demonstrated the favourable effects of thrombolytic therapy on angiographic, haemodynamic and scintigraphic parameters of patients with acute PE, although comparisons with patients who received heparin have essentially revealed similar degrees of embolus resolution after a few days to a week.

The only randomised trial to date that enrolled patients with massive PE with shock was terminated early, as all the four patients in the anticoagulation arm died while all four patients in the thrombolysis arm survived.[54] A recent meta-analysis concluded that thrombolysis reduced mortality in patients with intermediate-to-high risk PE at the cost of increased risk of major bleeding and intracranial bleeding especially in patients aged greater than 65 years.[40]

It is therefore recommended that once the diagnosis of massive PE has been confirmed, thrombolytic therapy should be given without delay unless there is a clear contraindication.[38] Around 90% of patients should respond to thrombolytic therapy.[55] The clinical benefits and relative underuse of this therapy have been recently highlighted using observational data.[56]

For patients with submassive PE, the benefits of thrombolysis in terms of improvement in haemodynamics and possible lower risk of adverse events like poor functional capacity at 90 days post thrombolysis should be carefully balanced with the increased risk of bleeding.[57] Consideration should be given to low-dose thrombolysis or catheter-based techniques.[41–43] The decision to use thrombolysis for patients with intracardiac thrombi needs to be similarly individualised. Even though thrombolysis has been recommended in recent guidelines, propensity score-matched analysis of data from a large PE specific registry did not support use of reperfusion treatment over anticoagulation with a higher risk of recurrence in the reperfusion treatment arm.[58]

There is a large array of thrombolytic drugs with few comparative studies. Although there may be slight differences between thrombolytic drugs, the choice of drug is less important than the choice to give thrombolytic therapy at all. Suggested doses are recommended in Table 34.1 and can be administered through either a peripheral or a central venous catheter. In contrast to acute myocardial infarction and stroke, thrombolytic therapy may be useful in PE when given up to 14 days after symptoms begin.[59] Once the thrombolytic therapy has been administered, heparin should be commenced.

Table 34.1 Recommended doses of thrombolytic drugs for pulmonary embolism

Urokinase	4400 units/kg bolus (over 10 minutes) followed by 4400 units/kg per hour for 12 hours
Streptokinase	250,000 unit bolus (over 15 minutes) followed by 100,000 units/hour for 24 hours
Alteplase	10 mg bolus followed by 90 mg over 2 hours
Reteplase	10 unit boluses 30 minutes apart

Haemorrhagic complications are not uncommon and can significantly affect patient morbidity; however, it is difficult to predict those patients who are at the highest risk for bleeding. Major clinically significant bleeding can occur in up to 10% of patients, although cerebral haemorrhage is fortunately uncommon (0.9%).[60] Recent surgery is not an absolute contraindication and patients should have their individualised risks and the benefits weighed up; in shocked patients with massive PE, the balance appears to be in favour of thrombolytic therapy for almost all patients.

If bleeding occurs the thrombolytic therapy should be ceased and fresh frozen plasma and cryoprecipitate can be given to replace coagulation factors.

SURGICAL EMBOLECTOMY

The merit of surgical pulmonary embolectomy, which has traditionally been seen as a life-saving option for moribund patients with massive PE, has been questioned since the advent of reliable thrombolytic therapy. Embolectomy surgery results vary widely and there has traditionally been an associated perioperative mortality of 25%–50%. There is little reliable evidence comparing embolectomy and thrombolytic therapy. Mortality rates have been found to be lower when using a surgical approach combining rapid diagnosis, prompt surgical intervention and a high frequency of concurrent IVC filter placement.[61]

Surgical embolectomy should therefore be strongly considered in patients with PE and hypotension who have absolute contraindications to thrombolytic therapy or if thrombolytic therapy has failed.[38] Embolectomy may also be useful when patients have free-floating intracardiac thrombus and a large patent foramen ovale.[62]

PERCUTANEOUS EMBOLECTOMY

Percutaneous pulmonary embolectomy methods include either embolus fragmentation and aspiration

techniques or catheter-directed fibrinolysis techniques, including ultrasound-accelerated fibrinolysis, wherein high frequency, low power ultrasound is used to loosen the fibrin strands, increasing penetration of fibrinolytic agent.[63] Amongst catheter-based techniques ultrasound-assisted thrombolysis has been shown to improve RV function without increased risk of bleeding in patients with intermediate risk PE.[43] As the safety profile of catheter-based techniques improves they should be considered more commonly in patients with intermediate risk to high-risk PE who can be safely transferred to the radiology department in centres where requisite expertise is available.[42]

CONCURRENT HAEMODYNAMIC SUPPORT

Shocked patients with PE (massive PE) need urgent haemodynamic support in addition to attempts at embolus destruction and prevention of further embolisation.

INTRAVENOUS FLUIDS

Volume loading can improve haemodynamic status in patients with massive PE, although if excessive then fluid therapy may worsen RV function which can in turn affect LV function and become detrimental.[64] Cautious administration of small amounts of intravenous fluid should occur.

VASOPRESSORS

Ischaemia in the coronary circulation is an important factor in the haemodynamic instability of massive PE.[6] Embolus destruction (with thrombolytic therapy or embolectomy) should have the greatest effect on ischaemia reduction. However, elevation of the blood pressure and reduction in pulmonary and RV pressures may also be helpful, based on the rationale that the RV coronary perfusion pressure (RVCPP) can be severely impaired in massive PE.

RVCPP is estimated by the formula:

$$\text{RVCPP} = \text{MAP} - \text{RVPm} \quad (34.1)$$

where MAP is the mean arterial pressure and RVPm is the mean RV pressure, all in mmHg.

RVPm can then be estimated by the formula:

$$\text{RVPm} = \text{CVP} + 1/3\,(\text{PAPs} - \text{CVP}) \quad (34.2)$$

where CVP is the central venous pressure and PAPs is the systolic pulmonary arterial pressure, all in mmHg.

When RVCPP falls as low as 30 mm Hg (4 kPa) (normal being around 70–80 mm Hg [9.31–10.64 kPa]), RV myocardial blood flow falls substantially and this contributes significantly to severe RV failure and shock. Efforts to elevate the MAP or reduce the PAPs should increase the RVCPP and therefore improve coronary blood flow to relieve ischaemia. Haemodynamic support for the shock state due to massive PE should therefore predominantly involve vasopressor drugs, as these will predominantly increase MAP and therefore RVCPP.

Norepinephrine (noradrenaline) is preferred to a pure alpha agonist such as phenylephrine as cardiac output and RV myocardial blood flow effects are greater owing to the added beta-adrenoceptor agonist action. Dopamine, epinephrine (adrenaline) and vasopressin are reasonable alternatives to norepinephrine.

Although systemic vasodilators might improve the measured cardiac output in massive PE, they may be harmful overall as the MAP will either fall or remain constant at best and therefore the RVCPP will not increase. Isoprenaline, dobutamine, nitroglycerin, nitroprusside or milrinone should be considered only if the MAP is adequate and treatment is focused on cardiac output or pulmonary artery pressure.

Extracorporeal membrane oxygenation (ECMO) is an alternative form of haemodynamic support that may be available in more specialised institutions.[65] It should be considered for patients with PE who have had cardiopulmonary arrest or have very severe shock.

SELECTIVE PULMONARY VASODILATORS

Inhaled nitric oxide may be useful in patients with massive PE by selectively decreasing pulmonary arterial pressure with minimal effect on systemic haemodynamics. It may also assist in the severely hypoxaemic patient. Inhaled prostacyclin is an alternative.[66]

OTHER SUPPORTIVE MANAGEMENT

Oxygen should be supplemented to target adequate oxygen saturation. High flows may be required because of hyperventilation and the increased dead space. Intubation and mechanical ventilation are often necessary in patients with massive PE.

If chest pain is prominent, morphine should be administered. To guide resuscitation, it is useful to have at least a central venous catheter particularly before thrombolytic therapy is given. Although there is increased risk of bleeding owing to the concurrent administration of thrombolytic therapy and/or anticoagulant therapy in these patients, this is probably outweighed by the importance of secure venous access and monitoring of the circulation in patients with haemodynamic compromise due to PE.

PREVENTION

Prophylaxis is probably the most important management aspect of VTE. All ICU patients should have an adequate assessment as to whether prophylaxis is warranted, although most should receive it using pharmacological thromboprophylaxis.[67] Careful attention to the intervention and dose is required as omission of prophylaxis[68] and failure of prophylaxis[69] are common.

LMWHs have challenged traditional prophylaxis with fixed low-dose subcutaneous UFH such that both

are suggested alternatives for the prevention of VTE in critically ill patients.[67] Both therapies seem comparable for prophylaxis of DVT; however, rates of PE and HITTS were lower in a recent large study.[70]

Mechanical approaches (including graduated-compression stockings and intermittent pneumatic compression devices)[71] seem best utilised in patients who are bleeding or at major risk of bleeding. When bleeding risk decreases, pharmacological thromboprophylaxis should be commenced.

KEY REFERENCES

38. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;35(43):3033–3069, 69a–69k.
39. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med*. 2014;370(15):1402–1411.
40. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA*. 2014;311(23):2414–2421.
60. Stein PD, Matta F, Steinberger DS, et al. Intracerebral hemorrhage with thrombolytic therapy for acute pulmonary embolism. *Am J Med*. 2012;125(1):50–56.
67. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in Nonsurgical Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e195S–e226S.


Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Smith SB, Geske JB, Kathuria P, et al. Analysis of national trends in admissions for pulmonary embolism. *Chest*. 2016;150(1):35–45.
2. Zoller B, Li X, Sundquist J, et al. Risk of pulmonary embolism in patients with autoimmune disorders: a nationwide follow-up study from Sweden. *Lancet*. 2012;379(9812):244–249.
3. MacCallum P, Bowles L, Keeling D. Diagnosis and management of heritable thrombophilias. *BMJ*. 2014;349:g4387.
4. van Langevelde K, Flinterman LE, van Hylckama Vlieg A, et al. Broadening the factor V Leiden paradox: pulmonary embolism and deep-vein thrombosis as 2 sides of the spectrum. *Blood*. 2012; 120(5):933–946.
5. Piazza G, Goldhaber SZ. Chronic thromboembolic pulmonary hypertension. *N Engl J Med*. 2011;364(4): 351–360.
6. Kreit JW. The impact of right ventricular dysfunction on the prognosis and therapy of normotensive patients with pulmonary embolism. *Chest*. 2004;125(4):1539–1545.
7. Ageno W, Agnelli G, Imberti D, et al. Factors associated with the timing of diagnosis of venous thromboembolism: results from the MASTER registry. *Thromb Res*. 2008;121(6):751–756.
8. Ceriani E, Combescure C, Le Gal G, et al. Clinical prediction rules for pulmonary embolism: a systematic review and meta-analysis. *J Thromb Haemost*. 2010;8(5):957–970.
9. Lucassen W, Geersing GJ, Erkens PM, et al. Clinical decision rules for excluding pulmonary embolism: a meta-analysis. *Ann Intern Med*. 2011;155(7): 448–460.
10. Wang RC, Bent S, Weber E, et al. The impact of clinical decision rules on computed tomography use and yield for pulmonary embolism: a systematic review and meta-analysis. *Ann Emerg Med*. 2016;67(6):693–701 e3.
11. Pasha SM, Klok FA, Snoep JD, et al. Safety of excluding acute pulmonary embolism based on an unlikely clinical probability by the Wells rule and normal D-dimer concentration: a meta-analysis. *Thromb Res*. 2010;125(4):e123–e127.
12. Grau E, Tenias JM, Soto MJ, et al. D-dimer levels correlate with mortality in patients with acute pulmonary embolism: findings from the RIETE registry. *Crit Care Med*. 2007;35(8):1937–1941.
13. Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. *JAMA*. 2014;311(11):1117–1124.
14. Goodwin AJ, Higgins RA, Moser KA, et al. Issues surrounding age-adjusted d-dimer cutoffs that practicing physicians need to know when evaluating patients with suspected pulmonary embolism. *Ann Intern Med*. 2017;166(5):361–363.
15. Kucher N, Goldhaber SZ. Risk stratification of acute pulmonary embolism. *Semin Thromb Hemost*. 2006;32(8):838–847.
16. Ferrari E, Moceri P, Crouzet C, et al. Timing of troponin I measurement in pulmonary embolism. *Heart*. 2012;98:732–735.
17. Ruan LB, He L, Zhao S, et al. Prognostic value of plasma heart-type fatty acid-binding protein in patients with acute pulmonary embolism: a meta-analysis. *Chest*. 2014;146(6):1462–1467.
18. Bajaj A, Rathor P, Sehgal V, et al. Prognostic value of biomarkers in acute non-massive pulmonary embolism: a systematic review and meta-analysis. *Lung*. 2015;193(5):639–651.
19. Manara A, D'Hoore W, Thys F. Capnography as a diagnostic tool for pulmonary embolism: a meta-analysis. *Ann Emerg Med*. 2013;62(6):584–591.
20. Shopp JD, Stewart LK, Emmett TW, et al. Findings from 12-lead electrocardiography that predict circulatory shock from pulmonary embolism: systematic review and meta-analysis. *Acad Emerg Med*. 2015;22(10):1127–1137.
21. Kosuge M, Kimura K, Ishikawa T, et al. Electrocardiographic differentiation between acute pulmonary embolism and acute coronary syndromes on the basis of negative T waves. *Am J Cardiol*. 2007;99(6):817–821.
22. Ladeiras-Lopes R, Neto A, Costa C, et al. Hampton's hump and Palla's sign in pulmonary embolism. *Circulation*. 2013;127(18):1914–1915.
23. D.Stein P, Fowler SE, Goodman LR, et al. Multidetector computed tomography for acute pulmonary embolism. *N Engl J Med*. 2006;354(22): 2317–2327.
24. Anderson DR, Kahn SR, Rodger MA, et al. Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. *JAMA*. 2007;298(23):2743–2753.
25. Winer-Muram HT, Rydberg J, Johnson MS, et al. Suspected acute pulmonary embolism: evaluation with multi–detector row CT versus digital subtraction pulmonary arteriography. *Radiology*. 2004;233(3):806–815.
26. Writing Group for the Christopher Study I. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, d-dimer testing, and computed tomography. *JAMA*. 2006;295(2):172–179.
27. Meinel FG, Nance JW Jr, Schoepf UJ, et al. Predictive value of computed tomography in acute pulmonary embolism: systematic review and meta-analysis. *Am J Med*. 2015;128(7):747–759.e2.
28. Piazza G, Goldhaber SZ. Acute pulmonary embolism. *Circulation*. 2006;114:e28–e32.
29. Phillips JJ, Straiton J, Staff RT. Planar and SPECT ventilation/perfusion imaging and computed tomography for the diagnosis of pulmonary embolism: a systematic review and meta-analysis of the literature, and cost and dose comparison. *Eur J Radiol*. 2015;84(7):1392–1400.
30. Zhou M, Hu Y, Long X, et al. Diagnostic performance of magnetic resonance imaging for acute pulmonary embolism: a systematic review and

meta-analysis. *J Thromb Haemost*. 2015;13(9): 1623–1634.
31. Lopez-Candales A, Edelman K, Candales MD. Right ventricular apical contractility in acute pulmonary embolism: the McConnell sign revisited. *Echocardiography*. 2010;27(6):614–620.
32. Lau G, Ther G, Swanevelder J. Echo rounds: McConnell's sign in acute pulmonary embolism. *Anesth Analg*. 2013;116(5):982–985.
33. Konstantinides S, Goldhaber SZ. Pulmonary embolism: risk assessment and management. *Eur Heart J*. 2012;33(24):3014–3022.
34. Righini M, Le Gal G, Aujesky D, et al. Diagnosis of pulmonary embolism by multidetector CT alone or combined with venous ultrasonography of the leg: a randomised non-inferiority trial. *Lancet*. 2008;371(9621):1343–1352.
35. Da Costa Rodrigues J, Alzuphar S, Combescure C, et al. Diagnostic characteristics of lower limb venous compression ultrasonography in suspected pulmonary embolism: a meta-analysis. *J Thromb Haemost*. 2016;14(9):1765–1772.
36. Vanni S, Nazerian P, Pepe G, et al. Comparison of two prognostic models for acute pulmonary embolism: clinical vs. right ventricular dysfunction-guided approach. *J Thromb Haemost*. 2011;9(10): 1916–1923.
37. Lankeit M, Gomez V, Wagner C, et al. A strategy combining imaging and laboratory biomarkers in comparison with a simplified clinical score for risk stratification of patients with acute pulmonary embolism. *Chest*. 2012;141(4):916–922.
38. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;35(43):3033–3069, 69a–69k.
39. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med*. 2014;370(15):1402–1411.
40. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA*. 2014;311(23): 2414–2421.
41. Sharifi M, Bay C, Skrocki L, et al. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). *Am J Cardiol*. 2013; 111(2):273–277.
42. Piazza G, Hohlfelder B, Jaff MR, et al. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II study. *JACC Cardiovasc Interv*. 2015;8(10):1382–1392.
43. Kucher N, Boekstegers P, Muller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation*. 2014;129(4):479–486.
44. Segal JB, Streiff MB, Hofmann LV, et al. Management of venous thromboembolism: a systematic review for a practice guideline. *Ann Intern Med*. 2007;146(3):211–222.
45. Hull RD, Raskob GE, Brant RF, et al. Low-molecular-weight heparin vs heparin in the treatment of patients with pulmonary embolism. *Arch Intern Med*. 2000;160(2):229–236.
46. Raschke RA, Reilly BM, Guidry JR, et al. The weight-based heparin dosing nomogram compared with a standard care nomogram: a randomized controlled trial. *Ann Intern Med*. 1993;119(9):874–881.
47. Budnitz DS, Lovegrove MC, Shehab N, et al. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med*. 2011;365(21): 2002–2012.
48. van Es N, Coppens M, Schulman S, et al. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. *Blood*. 2014;124:1968–1975.
49. Pollack CVJ, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373(6):511–520.
50. Connolly SJ, Milling TJJ, Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2016;375(12): 1131–1141.
51. Mismetti P, Laporte S, Pellerin O, et al. Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial. *JAMA*. 2015;313(16):1627–1635.
52. Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. *N Engl J Med*. 1998;338(7): 409–416.
53. Sarosiek S, Rybin D, Weinberg J, et al. Association between inferior vena cava filter insertion in trauma patients and in-hospital and overall mortality. *JAMA Surg*. 2017;152(1):75–81.
54. Jerjes-Sanchez C, Ramírez-Rivera A, de Lourdes García M, et al. Streptokinase and heparin versus heparin alone in massive pulmonary embolism: a randomized controlled trial. *J Thromb Thrombolysis*. 1995;2(3):227–229.
55. Meneveau N, Seronde M-F, Blonde M-C, et al. Management of unsuccessful thrombolysis in acute massive pulmonary embolism. *Chest*. 2006;129(4): 1043–1050.
56. Stein PD, Matta F. Thrombolytic therapy in unstable patients with acute pulmonary embolism: saves lives but underused. *Am J Med*. 2012;125(5): 465–470.
57. Kline JA, Nordenholz KE, Courtney DM, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. *J Thromb Haemost*. 2014;12(4):459–468.
58. Barrios D, Chavant J, Jimenez D, et al. Treatment of right heart thrombi associated with acute pulmonary embolism. *Am J Med*. 2016;130(5):588–595.

59. Daniels LB, Parker JA, Patel SR, et al. Relation of duration of symptoms with response to thrombolytic therapy in pulmonary embolism. *Am J Cardiol*. 1997;80(2):184–188.
60. Stein PD, Matta F, Steinberger DS, et al. Intracerebral hemorrhage with thrombolytic therapy for acute pulmonary embolism. *Am J Med*. 2012;125(1):50–56.
61. Leacche M, Unic D, Goldhaber SZ, et al. Modern surgical treatment of massive pulmonary embolism: results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. *J Thorac Cardiovasc Surg*. 2005;129(5):1018–1023.
62. Poterucha TJ, Bergmark B, Aranki S, et al. Surgical pulmonary embolectomy. *Circulation*. 2015;132(12): 1146–1151.
63. Jaber WA, Fong PP, Weisz G, et al. Acute pulmonary embolism: with an emphasis on an interventional approach. *J Am Coll Cardiol*. 2016;67(8):991–1002.
64. Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. *Chest*. 2002;121(3):877–905.
65. Yusuff HO, Zochios V, Vuylsteke A. Extracorporeal membrane oxygenation in acute massive pulmonary embolism: a systematic review. *Perfusion*. 2015; 30(8):611–616.
66. Webb SAR, Stott S, van Heerden PV. The use of inhaled aerosolized prostacyclin (IAP) in the treatment of pulmonary hypertension secondary to pulmonary embolism. *Intensive Care Med*. 1996;22(4):353–355.
67. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in Nonsurgical Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(suppl 2): e195S–e226S.
68. Kahn SR, Panju A, Geerts W, et al. Multicenter evaluation of the use of venous thromboembolism prophylaxis in acutely ill medical patients in Canada. *Thromb Res*. 2007;119(2):145–155.
69. Goldhaber SZ, Dunn K, Mac Dougall RC. New onset of venous thromboembolism among hospitalized patients at Brigham and Women's Hospital is caused more often by prophylaxis failure than by withholding treatment. *Chest*. 2000;118(6): 1680–1684.
70. The PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group, Cook D, Meade M, et al. Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med*. 2011;364(14):1305–1314.
71. Urbankova J, Quiroz R, Kucher N, et al. Intermittent pneumatic compression and deep vein thrombosis prevention. A meta-analysis in postoperative patients. *Thromb Haemost*. 2005;94(6):1181–1185.

35

Acute severe asthma

David V Tuxen, Mark Hew

Acute severe asthma is a medical emergency associated with a significant morbidity and mortality. Many of the adverse outcomes are attributed to underestimation of severity with delayed and/or inadequate treatment[1-3] and are potentially preventable.

The worldwide prevalence of asthma varies widely and continues to change. Between 1993 and 2003, the prevalence of asthma increased in low-to-middle income countries but stabilised in high-prevalence countries.[4] Australia, New Zealand and the United Kingdom continue to have amongst the highest incidences.[4] In Australia, 10% have asthma as a long-term condition. In previous decades, many countries, including Australia, have achieved reductions in hospital presentations and admissions,[5,6] reduced intensive care admissions and reduced overall asthma mortality.[5,6] Improved intensive care asthma management has resulted in fewer requirements for mechanical ventilation and decreasing mechanical ventilation mortality (Fig. 35.1).[5,6] These changes have resulted in the group of asthma patients who require mechanical ventilation having more severe asthma, that is, more refractory to treatment and more difficult to manage.[7,8] Despite reducing admissions, significant and potentially preventable mortality continues to occur in those patients who do require intensive care or mechanical ventilation.[7,9,10]

The previous reduction in asthma mortality has been attributed to widespread guideline dissemination, better community management of asthma,[1,2] increasing use of inhaled corticosteroids[3] and other preventative measures, such as action plans. However, in 2015, almost half of the asthma patients in Australia still had uncontrolled asthma, forming a cohort at risk of exacerbations. Gains from improved community management appear to have stalled.[11] At the same time, mortality rates in Australia due to asthma have not fallen further in the last 10 years. An audit of asthma deaths[12] reported to the coroner suggests that social and behavioural determinants may have contributed to these deaths as much as severe asthma biology. Fundamental systemic changes[13] may need to be applied to asthma care in order to address these patient factors and deliver further improvements in asthma control, severe exacerbation risk and mortality rates. Similar conclusions have been reached following a national enquiry[14] into asthma deaths in the United Kingdom.

CLINICAL DEFINITION

Asthma is now defined by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.[15] Asthma is usually characterised by airway inflammation. It is now recognised that asthma is a heterogeneous disease, and distinct inflammatory phenotypes[16] have been described. Exacerbations of asthma are characterised by increasing dyspnoea, cough, wheeze, chest tightness and decreased expiratory air flow. Status asthmaticus has had varying definitions. However, for practical purposes, any patient not responding to initial doses of nebulised bronchodilators should be considered to have status asthmaticus.[17]

'Difficult' (as opposed to 'severe') asthma is another term in which patients can present with mild, moderate or severe asthmatic symptoms. Characteristics include: (a) discordance between symptoms and objective markers of asthma, such as lung function or arterial blood gases, (b) severe asthma despite treatment that should be effective, and (c) a disconnection between patient expectations and effective outcomes.[18] Commonly, there is poor compliance, psychosocial adversity and secondary gain with continued symptoms. Significant anxiety and social and adverse family circumstances frequently co-exist. Differential diagnoses include hyperventilation syndromes, vocal cord dysfunction, chronic obstructive pulmonary disease (COPD) or lack of adherence to treatments (estimated to occur in two-thirds of patients presenting). An alternative description includes poor perceivers or over-reactors. These patients are difficult because sometimes they present with severe life-threatening asthma, yet experience would suggest this to be preventable if the usual medication were taken.

ABSTRACT

Intensive care admissions for asthma are decreasing but admitted patients have more severe asthma that is refractory to treatment and more difficult to ventilate. Acute severe asthma is a life-threatening medical emergency. Underestimation of severity and undertreatment remain the biggest contributors to asthma mortality.

The treatment of life-threatening asthma has many pitfalls that can increase the morbidity and mortality if not well managed. Intravenous and continuous nebulised salbutamol can cause significant lactic acidosis, which can increase dyspnoea and fatigue. Mechanical ventilation can easily cause excessive dynamic hyperinflation leading to hypotension and pneumothorax. Mechanical ventilation needs low initial Ve, minute ventilation less than 115 mL/kg per minute (8 L/min) and Pplat less than 25 mm Hg. In very severe asthma, excessive dynamic hyperinflation can lead to cardio-respiratory collapse. Neuromuscular blocking agents and heavy sedation can lead to severe necrotising myopathy. Mortality risk is increased following a requirement for intensive care and patients require treatment including inhaled steroids, a management plan and careful follow-up.

KEY WORDS

Asthma
mechanical ventilation
dynamic hyperinflation
lactic acidosis
myopathy
pneumothorax

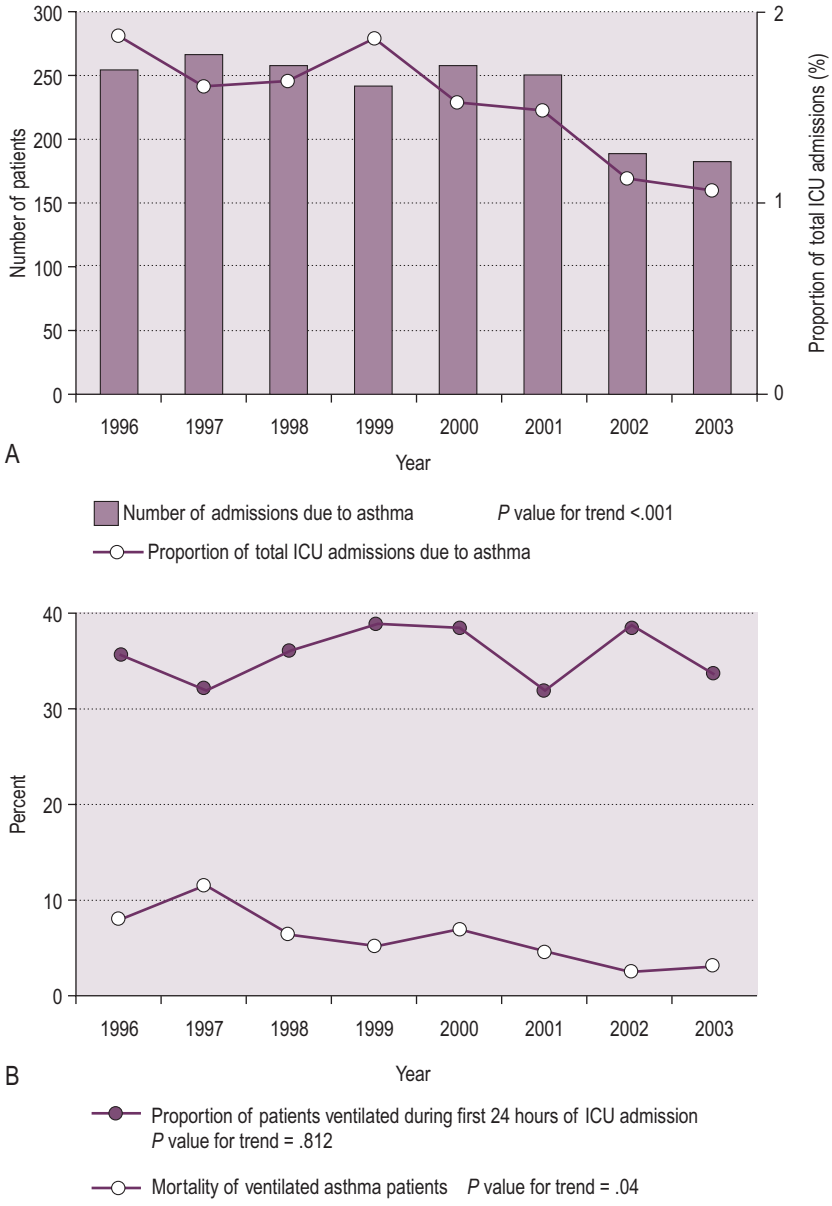


Figure 35.1 Intensive care unit (ICU) admissions (A), mechanical ventilation and mortality (B) due to asthma in Australia from 1996 to 2003. *(Modified from Stow P, Pilcher D, Wilson J, et al. Improved outcomes from acute severe asthma in Australian intensive care units (1996–2003).* Thorax. *2007;62(10):842–847.)*

AETIOLOGY

The pathogenesis of asthma reflects a complex interaction between environmental and genetic influences. In developed nations, a reduced exposure to childhood infections and changes in dietary patterns may alter gut, respiratory and skin bacterial composition and diversity (the microbiome), which then increases risk for developing allergic diseases including asthma.[19] This may be mediated through effects on T cell inflammatory gene transcription, which promote activation towards a T helper 2 phenotype, driving the allergic inflammatory response.[20] Such epigenetic changes have been found in asthma patients, and impair their responsiveness to corticosteroid therapy.[21] These persistent changes also may be passed on to subsequent generations, thus explaining the continuing rise in allergic disease prevalence.[20]

Immunoglobulin-E-dependent mechanisms appear to be important in generating the characteristic state

of airway inflammation and bronchial hyperreactivity with the allergens in the local environment dictating the specificity of the antibody response.[22] In addition to atopic asthma, an asthma phenotype that increases the risk of exacerbations is eosinophilic asthma, which is defined either by blood or sputum eosinophilia, and elevated exhaled nitric oxide.[16] Asthma co-morbidities,[23] such as obesity and chronic rhinosinusitis, also predispose to exacerbations. Triggers of acute asthma can be non-specific (cold air, exercise, atmospheric pollutants), specific allergens (housemite, pollen, animal danders), modifiers of airway control (aspirin, beta blockers), or stress or emotion. No precipitant can be identified in over 30% of patients.

A wide range of risk factors for life-threatening asthmatic episodes and/or the need for mechanical ventilation are now recognised. First is *underestimation of severity*, with delayed and/or inadequate treatment by managing doctors and/or the patient.[1-3] Second is *patient behaviour factors*, which are associated with the requirement for intensive care[24] and mechanical ventilation are smoking (and illicit drugs),[24] poor treatment compliance and prior treatment with beta agonists without inhaled steroids.[7,25] Low socioeconomic status has also been recognised as a risk factor, as has ethnic minority status.[26] Third is *genetic polymorphism* (the IL4RA*576R allele), which is now recognised as a significant factor related to fatal or near-fatal asthma attacks.[8,27] Other functional factors linked to severe asthma attacks include airway remodelling, down-regulation of β-receptors, and lack of steroid responsiveness.[8] Diminished perception of dyspnoea in some patients with acute severe asthma leads to delayed interventions.[8,28]

PATHOPHYSIOLOGY

The postmortem airway pathology of patients who die from acute asthma includes bronchial wall thickening from oedema and inflammatory cell infiltrate, hypertrophy and hyperplasia of bronchial smooth muscle and submucosal glands, deposition of collagen beneath the epithelial basement membrane and prominent intraluminal secretions. These secretions may narrow or occlude the small airways, and postmortem studies frequently report extensive plugging and atelectasis.[29,30] When interpreting the latter findings it is important to remember that during life in very severe asthma the lungs are hyperinflated close to total lung capacity (TLC) by maximal inspiratory effort, and to beyond TLC during mechanical ventilation. At this time, radiological atelectasis is rare, suggesting that most airways are communicating at these high lung volumes, even if airways are very narrowed. Only at death does the prolonged apnoea allow lung deflation, widespread airway closure and alveolar gas absorption to give the postmortem appearance of extensive complete occlusion that was not present to the same degree during life.

In some deaths bronchial mucus is absent; in these cases airway obstruction may be mainly due to intense smooth bronchoconstriction. This observation may account for two patterns of progression of asthma:

1. Acute severe asthma is the more common group (80%–90%), with progression of symptoms over many hours or days, often with a background of poor control and recurrent presentations. Most patients in this group are female, with upper respiratory infections frequent triggers; it responds more slowly to treatment, which may reflect greater contribution from mucous inspissation and chronic bronchial wall inflammation with eosinophilia.[28,31]
2. 'Hyperacute', 'fulminating', 'asphyxic' or 'sudden onset' severe asthma is where the interval between onset of symptoms and intubation is less than 3 hours.[28,31-33] This presentation is less common (approximately 10%–20% of life threatening presentations), tends to occur in younger patients with relatively normal lung function but high bronchial reactivity, and the majority of patients are male. Massive respiratory allergen exposure, cold air or exercise and psychosocial stress are the most frequent triggers.[28] Although patients in this group are less common, 'thunderstorm asthma', due to massive production and distribution of rye-grass micro particles triggered during a thunderstorm, can occasionally result in overwhelming numbers of patients exclusively in this group presenting within a 24-hour period.[34] This group characteristically has neutrophilic inflammation, typically responds quickly to bronchodilators and is thought to be mainly due to bronchial smooth muscle contraction.

The characteristic pathology of asthma leads to increased airway resistance and dynamic pulmonary hyperinflation. This has a number of consequences:

- *Increased work of breathing* results from increased airway resistance and reduced pulmonary compliance as a result of high lung volumes. When asthma is severe, dynamic hyperinflation (DHI) may bring the lung volume close to TLC.[34] This causes a severe mechanical disadvantage of inspiratory muscles with diaphragm flattening and results in a large inspiratory muscle effort affecting a small change in inspiratory pressure. The final outcome can be respiratory muscle failure with insufficient alveolar ventilation and consequent hypercapnia.[35]
- *Ventilation–perfusion mismatch* is the result of airway narrowing and closure. This leads to impaired gas exchange and increases the minute ventilation requirement, further adding to the work of breathing.[35]
- *Adverse cardiopulmonary interactions* are seen when the marked changes in lung volume and pleural pressure impact on the function of both left and

right ventricles.[36,37] Spontaneous breathing during acute asthma can generate inspiratory pressures as low as –35 cm H_2O.[36,37] This increases venous return to the right ventricle (RV) and increases RV volume during inspiration. However, increased RV afterload as a result of hypoxic pulmonary vasoconstriction, acidosis and increased lung volume,[36,37] and increased pulmonary capacitance decrease return to the left ventricle (LV). These negative intrapleural pressures also cause increased LV afterload,[36,37] and increased RV afterload with septal shift reduces LV volume[36,37] further reducing LV output during inspiration. Pulsus paradoxus is the most direct result of these cardiopulmonary interactions in severe asthma. This is a decrease in systolic blood pressure during inspiration of greater than 10 mm Hg (1.33 kPa), typically 15–25 mm Hg (2–3.33 kPa), normal ≤5 mm Hg (0.66 kPa). The degree of pulsus paradoxus may not correlate with the severity of asthma as it may be reduced by inspiratory muscle weakness or fatigue.

CLINICAL FEATURES AND ASSESSMENT OF SEVERITY

The symptoms of asthma are well known and include wheeze, cough, dyspnoea and chest discomfort or tightness. Triage and assessment of severity of the acute asthma attack are crucial. Underestimation or non-measurement of asthma severity is associated with increased mortality.[38] Assessment has two key features: assessment of initial severity (Box 35.1) and ongoing assessment of response to treatment.

HISTORY

Any history of prior intubation and mechanical ventilation for asthma is a predictor for life-threatening asthma.[38] A history of poor asthma control, multiple recent medical presentations for asthma and poor response to prior treatments are recognised risk factors. Other risk factors are listed above (see section 'Aetiology').

PHYSICAL EXAMINATION

The general appearance and level of distress can be an important indicator of severity (Table 35.1). The use of accessory muscles, suprasternal retraction, markedly diminished breath sounds or a silent chest, central cyanosis, the inability to speak, a disturbance in the level of consciousness, upright posture and diaphoresis all suggest a severe attack. A respiratory rate greater than 30/min, pulse rate greater than 120/min and pulsus paradoxus of greater than 15 mm Hg (2 kPa) are associated with severe asthma, though their absence does not preclude life-threatening asthma. Patients with

Box 35.1 Key points

1. Asthma prevalence in the community is increasing but admissions to hospital and intensive care are decreasing.
2. Acute severe asthma is a lifethreatening medical emergency both on presentation and during mechanical ventilation.
3. Underestimation of severity and undertreatment are the biggest contributors to asthma mortality.
4. Patients who do require mechanical ventilation have more severe asthma refractory to treatment and are more difficult to ventilate.
5. Intravenous and continuous nebulised salbutamol can cause significant lactic acidosis.
6. Mechanical ventilation can easily cause excessive dynamic hyperinflation leading to hypotension and pneumothorax.
7. Mechanical ventilation needs careful regulation with initial V_e <115 mL/kg per minute (8 L/min) and P_{plat} <25 mm Hg (3.32 kPa).
8. Very severe dynamic hyperinflation can lead to cardiorespiratory collapse diagnosed by an apnoea test.
9. Neuromuscular-blocking agents and heavy sedation can lead to severe necrotising myopathy.
10. Following intensive care, asthma requires full treatment including inhaled steroids, a management plan and careful follow-up.

Table 35.1 Assessment of asthma severity

	MILD	MODERATE	SEVERE
Conscious state	Alert, relaxed	Anxious, difficulty sleeping	Agitated, delirious
Speech	Sentences	Phrases	Words
Accessory muscles	Nil	Mild	Significant sitting upright
Wheeze	Moderate	Loud	Loud or silent
Pulse rate (BPM)	<100	100–120	>120
Peak expiratory flow (% predicted)	>80%	60%–80%	<60%
$PaCO_2$ (mm Hg) (kPa)	<45 (5.98)	<45 (5.98)	>45 (5.98)

Pulsus paradoxus when present indicates severe asthma; however, it is an unreliable test.

BPM, Beats per minute.

diminished perception of dyspnoea may mask severe asthma and lead to underestimation of severity.[28]

VENTILATORY FUNCTION TESTS

The patient may not be able to perform these due to breathlessness. However, FEV_1 and peak expiratory flow rate (PEFR) are useful indicators of severity and response to treatment when done serially. An FEV_1 less than 1.0 L or PEFR less than 100 L/min indicates very severe asthma at significant risk of requiring mechanical ventilation. In some patients forced expiration may worsen symptoms; these measurements should cease if this occurs.

PULSE OXIMETRY

Pulse oximetry is usually readily available and provides a rapid assessment of oxygenation. It is also very valuable in regulation oxygen therapy, both for avoiding hypoxia (SpO2 >90%)[39] and for avoiding potential side effects of hyperoxia (SpO2 <95%).[40] Of course, pulse oximetry cannot assess arterial $PaCO_2$ or acid-base state, therefore it does not replace the need for blood gases.

ARTERIAL BLOOD GASES

Arterial hypoxaemia is almost invariably present in a patient with severe asthma breathing room air though it usually responds well to low-level oxygen supplementation (28%–35%).[39] Blood gases should not delay initiation of treatment, and are not required in mild asthma or moderate asthma that is responding well to treatment. They are very important in severe asthma, or moderate asthma with inadequate treatment response. The $PaCO_2$ is an important measure of severity and, if hypercapnia is present, an important guide to treatment response. Venous blood gases have had increasing use in place of arterial blood gases. Such blood gases will usually determine the upper limit of $PaCO_2$ and the lower limit of pH; however, there is insufficient agreement between venous and arterial PCO2 measurements to determine the degree of hypercapnia in obstructive airways disease.[41] We therefore recommend arterial blood gas measurement in the assessment of acute severe asthma, where initial and follow-up PCO2 levels inform critical treatment decisions.

Ventilation is initially increased in an acute attack leading to hypocapnia and a respiratory alkalosis.[39] As the asthmatic attack worsens, the work of breathing, V/Q mismatch and adverse cardiopulmonary interactions all increase, and the minute ventilation required to maintain the same alveolar ventilation and $PaCO_2$ increases. Eventually the patient is incapable of meeting this demand and the $PaCO_2$ rises. The presence of hypercarbic acidosis is associated with a FEV_1 of less than 20% predicted and reliably indicates that asthma is severe. A metabolic acidosis may also be present, and this is most commonly due to lactic acidosis associated with intravenous or continuous nebulised beta agonists.[42,43]

CHEST X-RAY

Chest X-rays are not generally helpful in assessing severity and are not routinely indicated. A chest X-ray should be performed when asthma is severe or refractory to treatment, when barotrauma or lower respiratory tract infection is suspected or when the diagnosis is in doubt. It is not required in milder attacks that respond well to treatment.

ASSESSMENT OF TREATMENT RESPONSE

Repeated evaluation of the patient's response to treatment is a valuable tool in assessing severity of acute asthma. The response to the first 2 hours of treatment is an important predictor of outcome.[44] Adverse events are associated with underestimation of severity, inadequate observation after initial assessment and under treatment. Ongoing evaluation of response to therapy is critical. This evaluation should include repeated assessments of: (1) appearance and physical indicators of severity (see Table 35.1); (2) objective measurements – FEV1 or PEFR, heart rate, respiratory rate, pulsus paradoxus; (3) SpO2 and oxygen requirements; and (4) progress of $PaCO_2$ or metabolic acidosis if present on blood gases.

Admission to intensive care is preferred if the above criteria suggest severe asthma. Indications for immediate admission to intensive care include respiratory arrest, altered mental status, dysrhythmias or associated myocardial ischaemia.

DIFFERENTIAL DIAGNOSIS

The diagnosis of asthma is usually obvious. However, wheeze and dyspnoea may be caused by other illnesses, including left ventricular failure, aspiration, upper airway obstruction, inhaled foreign body, pulmonary embolism or hyperventilation syndromes. Wheeze and dyspnoea arising in hospitalised patients who were not admitted with asthma are less likely to be due to asthma. Clues to another or additional diagnosis include: (1) no past history of asthma; (2) sudden onset following vomiting or food intake; (3) focal or asymmetrical chest auscultation findings; (4) risk factors for thromboembolism; and (5) onset during hospitalisation when admitted with another condition.

MANAGEMENT

ESTABLISHED TREATMENTS

Initial therapy of acute severe asthma should include the following.

OXYGEN

Hypoxaemia contributes to life-threatening events that complicate acute severe asthma.[45] Current guidelines[46] recommend supplemental oxygen should be titrated to achieve a SpO2 94%–98% but clinicians should consider the risk of oxygen-induced increasing hypercapnia with co-existing chronic air-flow limitation or pre-existing chronic hypercapnia. This phenomenon was not believed to be relevant to the majority of patients with acute asthma; however, there is now emerging evidence that hyperoxia may be harmful to a more widespread group[47] by releasing pulmonary hypoxic vasoconstriction, worsening V/Q matching and increasing hypercapnia. A previous trial[40] showed a decrease in $PaCO_2$ in a group receiving 28% O_2 and an increase in $PaCO_2$ in a group receiving 100% FiO_2. A more recent trial[48] demonstrated patients receiving oxygen titrated to achieve target SpO_2 of 93%–95% had lower transcutaneous CO_2 levels after 1 hour than those receiving 8 L O_2/min by mask.

BETA AGONISTS

Short-acting beta agonists remain the first-line bronchodilator therapy of choice.[46,49] Agents include salbutamol (albuterol), terbutaline, isoproterenol (isoprenaline) and epinephrine (adrenaline). Salbutamol is generally the agent of first choice as it has relative β_2-selectivity, with decreased β_1-mediated cardiac toxicity. Long-acting beta agonists, such as salmeterol, have no role in status asthmaticus owing to the slow onset of action and association with fatalities in this setting.[17] Beta agonists cause bronchodilatation by stimulation of β_2-receptors on airway smooth muscle and may reduce bronchial mucosal oedema.

The standard approach is to start with nebulised salbutamol in high and repeated doses. The typical adult dose is 5–10 mg (in 2.5 to 5.0 mL diluent volume) every 2–4 hours, but more frequent doses with a higher total dose are often required in severe asthma. It should be noted that less than 10% of the nebulised drug reaches the lung even under ideal conditions.[50] Continuous nebulisation appears to be superior to intermittent doses and is commonly used at the beginning of treatment in severe asthma.[17,51] The nebuliser should be driven by oxygen with the flow at 10–12 L/min and a reservoir volume of 2–4 mL so as to produce particles in the desired 1–3 µm range.[52] The total dose should be modulated by response to treatment and the level of toxic side effects.

Beta agonists can also be delivered by metered dose inhaler (MDI). There are data to suggest that in non-intubated patients MDIs combined with a spacing device are as effective as or more effective than nebulisers and are cheaper to use.[53] In intubated patients both nebulisers and MDIs have been used effectively.[54] Two-thirds of acutely presenting patients will respond well to inhaled beta agonists[55] irrespective of the method of administration. The remaining one-third are refractory even to high doses and usually require longer periods of intense treatment including multiple other agents.

Intravenous beta agonists remain controversial. There is no clear evidence of benefit[56] and significant side effects. Despite this, intravenous beta agonists have a theoretical benefit of additional access to lung units with severe air-flow obstruction and poor nebulised drug delivery, and some studies have demonstrated improved response when intravenous beta agonist is used.[57] Intravenous beta agonists continue to be considered if the patient is not responding to continuous nebulisation.[58] The typical dose is 5–20 µg/min, but doses greater than 10 µg/min should be used for the first 4–6 hours because of side effects, which should be monitored closely. Salbutamol 100–250 µg may also be given intravenously to non-intubated patients in extremis or delivered down an endotracheal tube should there be no time to gain intravenous access.

Side effects of beta agonists include tachycardia, dysrhythmias, hypertension, hypotension, tremor, hypokalaemia, worsening of ventilation–perfusion mismatch and hyperglycaemia,[59] but the most common side effect of parenteral beta agonists, also occasionally seen with continuous nebulised beta agonists, is lactic acidosis. This occurs in over 70% of patients with intravenous agonists; it has an onset within 2–4 hours of commencing an infusion or following an intravenous statim dose; the levels may reach 4–12 mmol/L; and may significantly add to a respiratory acidosis and respiratory distress.[43,60,61] Parenteral infusions should be initially limited to 10 µg/min and statim doses should not exceed 250 µg. Serum bicarbonate and lactate should be regularly monitored. If lactic acidosis becomes significant, the salbutamol infusion should be reduced or ceased. Lactic acidosis will generally resolve within 4–6 hours of infusion cessation and is seldom a problem with infusions in place for more than 24 hours.

Long-term high-dose beta-agonist use has been associated with increased mortality,[62] but whether high-dose beta agonists are a marker of disease severity, an indicator of suboptimal inhaled steroids or a direct cause of death is unclear. These concerns do not apply in the treatment of the acute asthma attack.

ANTICHOLINERGICS

Anticholinergics cause bronchodilatation by decreasing parasympathetic-mediated cholinergic bronchomotor tone. Ipratropium bromide is the most commonly used anticholinergic for asthma and is a quaternary derivative of atropine. Although some conclude there is insufficient evidence,[63] a number of studies and meta-analyses suggest clear additional benefit and few side effects when ipratropium bromide is added to the beta-agonist regimen.[64,65] Ipratropium is now widely used as first-line therapy for acute severe asthma in conjunction with beta-agonist

therapy. Preservative-induced bronchoconstriction has been reported in a few patients and can be prevented by using preservative-free solutions.[66] The bronchodilatation effect of ipratropium bromide appeared to be maximal with a dose of 250 µg when studied in children between 9 and 17 years of age. The optimal dose is not known in adults.[67] A reasonable regimen is ipatropium bromide 500 mcg nebulised 4–6 hourly for 24–48 hours with a frequency reduction thereafter.

CORTICOSTEROIDS

The role of corticosteroids in the acute asthma attack has been well established. Systemic steroids should be considered in all but mild exacerbations of asthma.[68] Their benefits include increased β-responsiveness of airway smooth muscle, decreased inflammatory cell response and decreased mucus secretion. Early treatment with corticosteroids has been shown to decrease the likelihood of hospitalisation and decrease the mortality rate from acute asthma. Systematic reviews[68,69] suggest that effects commence within 6–12 hours, that oral is as effective as intravenous and that there is little evidence of benefit for initial daily doses exceeding 800 mg/day of hydrocortisone (160 mg/day methylprednisolone) given in four divided doses.

Inhaled steroids have established long-term benefit and are believed to be a major factor in asthma mortality reduction.[1-3] Although some believe there is insufficient evidence,[63] there are data that inhaled steroids may also have a role during an acute attack[70,71] and it appears reasonable to use them routinely from day 1 as they may also enable more rapid dose reduction of parenteral steroids, potentially reducing side effects.

Parenteral corticosteroid dose reductions should commence after 1–3 days according to the severity of the attack, the degree of chronic inflammation and the response to treatment and should be converted to a reducing dose of oral steroids within 4–7 days (e.g. oral prednisolone starting at 40–60 mg/day).

Side effects of corticosteroids include hyperglycaemia, hypokalaemia, hypertension, acute psychosis and myopathy,[72,73] though they are usually well tolerated acutely. The immunosuppressive effects can increase the risk of infections including *Legionella*, *Pneumocystis jiroveci* and varicella[74,75] especially when the patient is on long-term corticosteroids. Allergic reactions including anaphylaxis have been reported with the use of most corticosteroid preparations.

MAGNESIUM SULPHATE

Magnesium sulphate is postulated to block calcium channels, and possibly acetylcholine release at the neuromuscular junction, leading to smooth muscle relaxation and bronchodilatation. It appeared to be well tolerated in early studies, and a number of some prospective randomised, double-blind trials of adding intravenous or nebulised magnesium sulphate to conventional therapy in adults with acute asthma were performed. Some showed benefit whereas others showed none.

The most recent Cochrane reviews[76,77] on this topic suggest that intravenous magnesium is useful for adults with acute severe asthma, although evidence for benefit in children is less clear. If given, recommended doses for adults are 5–10 mmol (1.25–2.5 g, 2.5–5.0 mL of 50% solution) given slowly over 20 minutes, but doses up to 40 mmol (10 g) can be given.[78] Side effects include hypotension, flushing, sedation, weakness, areflexia, respiratory depression and cardiac arrhythmias seen at higher serum levels (>5 mmol/dL or 12 mg/dL). Serum concentrations should be measured if repeated or high doses are used.

AMINOPHYLLINE

There have been conflicting reports regarding the efficacy of aminophylline in acute asthma ranging from no benefit to improved lung function and improved outcome. However, it is accepted that aminophylline is an inferior bronchodilator, with a narrow therapeutic range and frequent side effects[79] including headache, nausea, vomiting and restlessness, with cardiac arrhythmias and convulsions that can occur at serum levels above 200 µmol/L (40 mg/L). A Cochrane meta-analysis[80] identified no patient subgroup in which aminophylline was beneficial.

As a result, aminophylline is not a first-line treatment.[46,49,63] Aminophylline may be given to patients with acute asthma who are not showing a favourable response to full treatment with first-line agents. Careful administration and monitoring are required with an initial loading dose of 3 mg/kg (maximum 6 mg/kg, omitted if the patient is already taking oral theophylline) and an infusion of 0.5 mg/kg per hour. This should be reduced in patients with cirrhosis, cardiac failure or chronic obstructive airways disease and in patients taking cimetidine, erythromycin or antiviral vaccines. Drug levels should be taken after a loading dose (if given), and then 24 hours later aiming for a level of 30–80 µmol/L (5–12 mg/L). Levels should be repeated daily thereafter until stability has been achieved. The duration should be based on the response to treatment.

NON-ESTABLISHED TREATMENTS

A number of other therapies have reported benefit in acute severe asthma, but their role in addition to full standard therapy has not been clearly established and they are not advocated for routine use. However, these modes of therapy can be considered in the patient who is in extremis or remaining severe despite conventional treatment.

EPINEPHRINE

Epinephrine has some theoretical advantages over pure β_2-agonists in that its additional α-agonist actions

of vasoconstriction and mucosal shrinkage may improve airway calibre. However, in practice, nebulised epinephrine has not been shown to confer any advantage over nebulised β_2-agonists and is not recommended because of its cardiac side effects.[67] It may be tried in the patient who is failing to respond to conventional treatment. The nebulised dose is 2–4 mg in 2–4 mL (1% solution, 0.05 mL/kg) 1- to 4-hourly. Epinephrine by infusion may avert mechanical ventilation in very severe cases, but should be used with caution with electrocardiogram monitoring and preferably with central venous access. An initial intravenous dose of 0.1 mg (1 ml of 1:10,000 epinephrine) can be given slowly over 3–5 minutes. This may be followed by a continuous infusion of 1–10 μg/min, which is weaned when the acute attack subsides.[81]

The one situation where adrenaline is indicated is when acute severe bronchospasm is suspected to be caused by anaphylaxis. Intramuscular epinephrine should be administered immediately at a dose of 0.3–0.5 mg (0.3–0.5 mL of 1:1000 epinephrine), repeated if necessary 1–2 times over 5–10 minutes. If there is no improvement, consider intravenous epinephrine as above.

HELIOX

Inhalation of a helium:oxygen mixture reduces gas density and turbulence with reduced air-flow resistance. The most effective gas mixture is 70% helium (30% oxygen) and the minimum concentration likely to provide benefit is 60% helium. The work of breathing is decreased and pulmonary access of inhaled bronchodilators may be improved.[82] Small case series and reports have suggested benefit from heliox; randomised, prospective trials have both positive and negative results.[83] Meta-analyses[84,85] have shown trends towards improved aspects of lung function but insufficient evidence to recommend use of heliox in severe asthma. However, it otherwise appears safe and may be tried in critical asthma to avert intubation or during difficult mechanical ventilation provided the patient can tolerate 30%–40% O_2.

ANAESTHETIC AGENTS

Ketamine, a dissociative anaesthetic agent, has been used in severe asthma. It may cause bronchodilatation by both sympathomimetic potentiation and a direct effect on airway smooth muscle.[86] Small case series have suggested some benefit, although a small, randomised, controlled trial found no benefit with ketamine in the treatment of acute severe asthma[87] – ketamine may be a useful induction agent for endotracheal intubation (dose 0.5–1 mg/kg up to 2 mg/kg) as it may ameliorate the bronchoconstrictor response to intubation. It has been used as a continuous infusion in the dose range of 0.2–1 mg/kg per hour[87] to treat refractory asthma. Side effects include increased bronchial secretions, a hyperdynamic cardiovascular response and hallucinations; the hallucinations can be reduced with concomitant benzodiazepines.

The volatile inhalational agents including halothane, isoflurane and enflurane have been used in mechanically ventilated patients with severe asthma.[88] Clinical data are limited to small case-series, and side effects include direct myocardial depression, arrhythmias and hypotension.[89] The volatile anaesthetic agents should be used with great care and usually only as a prelude to or during invasive ventilation. An anaesthetic machine or custom-fitted ventilator is required for safe administration.

LEUKOTRIENE ANTAGONISTS

Leukotriene antagonists have shown benefit in chronic asthma[90] and there is some evidence of benefit in acute asthma.[91] There is insufficient evidence and the benefits were of insufficient magnitude to recommend these agents for acute severe asthma.[63]

BRONCHOALVEOLAR LAVAGE

Bronchoalveolar lavage has been used in severe refractory asthma to clear mucous plugging during mechanical ventilation.[92] It may have a role in ventilated patients with resistant mucus impaction, but it is rarely used.

THERAPIES NOT RECOMMENDED

Antibiotics are not routinely indicated[93] unless there is clear evidence of infection. Antihistamines are not effective. Inhaled mucolytics have been shown to have no benefit and may worsen air-flow obstruction. Sedation is unsafe in acute asthma. There is a clear association between their use and avoidable deaths.[94] Patients with severe asthma should not be sedated unless being intubated and ventilated, or in carefully monitored circumstances.

VENTILATION IN ASTHMA

DYNAMIC HYPERINFLATION

In all degrees of air-flow obstruction, slow expiratory air flow results in incomplete exhalation of gas during normal expiratory times. Gas is trapped in the lungs by the arrival of the next breath and the lungs are unable to return their normal passive relaxation volume (functional residual capacity [FRC]). Incomplete exhalation of each successive breath causes progressive accumulation of trapped gas called DHI (Fig. 35.2),[95] which continues until an equilibrium point is reached where the exhaled volume increases to match the inspired volume.[95] This equilibrium occurs because increasing lung volume increases small airway calibre and lung elastic recoil pressure, both of which improve expiratory air flow and allow the inspired tidal volume to be exhaled in the expiratory time available. There are three primary determinants of this equilibrium point: the volume inspired (V_t), the time for expiration

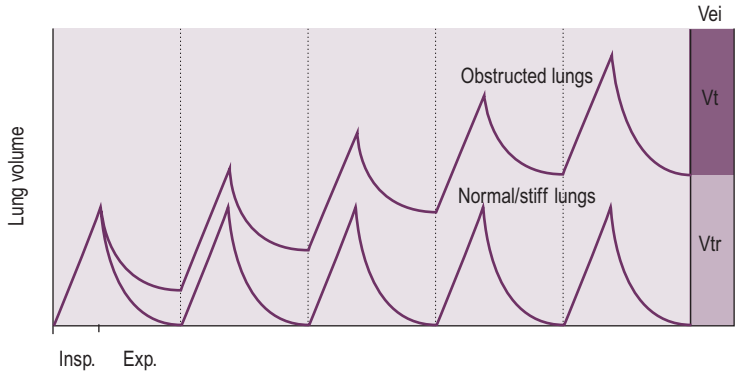


Figure 35.2 Dynamic hyperinflation. The volume history of normal or acutely injured lungs compared with that of obstructed lungs when commenced on controlled mechanical ventilation. This shows initial lung volume to be at the passive relaxation volume of the respiratory system or functional residual capacity. *Exp,* Expiratory time period; *Insp,* inspiratory time period; *Vei,* volume of the lung above functional residual capacity at the end of inspiration; *Vt,* tidal volume; *Vtr,* volume of gas trapped above functional residual capacity by the occurrence of the next breath.

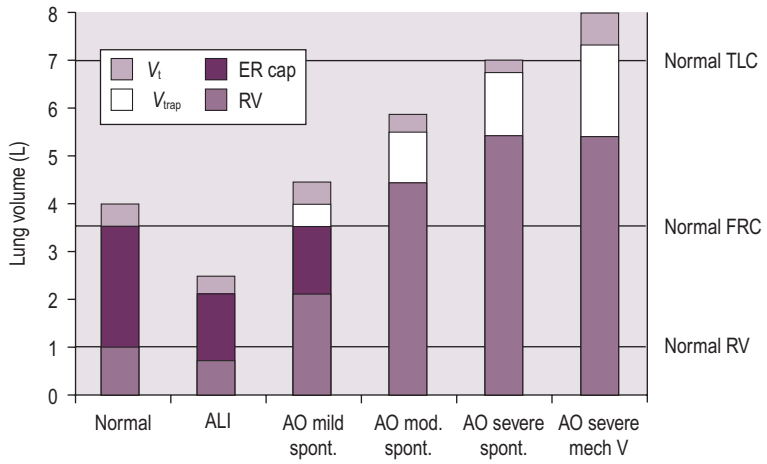


Figure 35.3 Comparison of lung volumes in patients with normal lungs, acute lung injury (ALI), and mild, moderate and severe air-flow obstruction (AO). Severe AO is shown during both spontaneous ventilation (spont) and mechanical ventilation (mech V). Functional residual capacity (FRC) is the static lung volume at the end of expiratory flow (60–90 seconds in severe AO). Expiratory reserve capacity (ER cap) is the additional gas expired with expiratory effort after FRC has been reached. Residual volume (RV) is the minimum lung volume possible after prolonged expiration and maximum expiratory effort. V_{trap} is the gas trapped by dynamic hyperinflation during tidal ventilation. *TLC*, Total lung capacity.

(t_e, which depends on both the ventilator rate or cycle time and the inspiratory flow or inspiratory time, t_i) and, of course, the severity of air-flow obstruction (the time constant of the lung). The first two determinants are controlled by the ventilator settings and compound to the minute ventilation (V_e) making this the most important determinant of DHI.

Gas trapped at the end of expiration exerts a positive pressure on the alveoli; this pressure is intrinsic positive end-expiratory pressure ($PEEP_i$) or auto-PEEP.[95,96] During expiration, sequential closure of the most severely obstructed airways occurs with only the less obstructed airways remaining in communication with the central airway at the end of tidal expiration.[97] As a consequence, measured $PEEP_i$ underestimates the true magnitude of $PEEP_i$ and is recognised as being insensitive to changes in severity.[97]

In mild air-flow obstruction, this process is adaptive as it allows the desired minute ventilation, which could not be achieved at FRC, to be achieved at a higher lung volume (Fig. 35.3, 'mild AO'). As asthma becomes more severe (see Fig. 35.3, 'mod AO') the static FRC that would be reached with a long expiratory time is elevated above the normal FRC by airway closure (static hyperinflation) and DHI further increases lung volume to a level where work of breathing is increased by lower lung compliance and respiratory muscles become less efficient from shortening and mechanical

disadvantage. At this level, some degree of dyspnoea is expected. When asthma is severe enough to risk requiring mechanical ventilation, static hyperinflation may increase FRC by 50%[98] and very little DHI is required to reach TLC (see Fig. 35.3, 'severe AO'). In this circumstance, the minute ventilation required to maintain normocapnia would cause hyperinflation beyond normal TLC. During spontaneous ventilation, the patient with severe asthma is unable to exceed TLC (see Fig. 35.3), has a much lower maximum minute ventilation capacity and as a result must become hypercapnic even at maximum respiratory effort with no fatigue.[99] When mechanical ventilation is commenced, increased tidal volume and rate delivery is easily able to increase minute ventilation and DHI well beyond normal TLC (see Fig. 35.3).[95] The consequences of this are commonly hypotension (due to increased intrathoracic pressure and decreased venous return) and barotrauma.[95,99–101]

NON-INVASIVE VENTILATION

Non-invasive ventilation (NIV) has been widely used for a variety of respiratory problems. In severe asthma there are a number of potential benefits. Externally applied PEEP may help overcome $PEEP_i$ due to gas trapping, and thus reduce the inspiratory threshold work of breathing. Augmentation of inspiration with NIV may further decrease the work of inspiration and increase tidal volume and minute ventilation. If tidal volume is increased with a shorter inspiratory time, then increased minute ventilation can occur without a proportional increase in DHI. Both inspiratory augmentation and PEEP may facilitate airspace opening, thus reducing V/Q mismatch.[102,103]

The role of NIV is well established in COPD where a number of randomised trials have shown benefit.[104,105] Although there have been no large randomised trials in acute asthma, there is increasing evidence of benefit from NIV for this indication with all studies reporting a positive outcome.[106,107] Non-randomised studies have reported improvements in respiratory acidosis and respiratory rate following the introduction of NIV, and low requirements for invasive ventilation. In small prospectively randomised studies of acute asthma, Soroksky et al.[107] showed better lung function and decreased hospitalisation rate, and Gupta et al.[108] found accelerated improvement in lung function, decreased inhaled bronchodilator requirement and shortened intensive care unit and hospital stay. In a retrospective cohort study, Murase et al.[98] found that NIV reduced the rate of endotracheal intubation from 18% (9/50) to 3.5% (2/57, $P = .01$).

There have been multiple reviews of NIV for acute severe asthma[109–112] including a Cochrane review[113] All concluded there is limited evidence for some benefits, insufficient data to be conclusive and that larger trials are needed. Where opinions were given, all recommended use of NIV in selected patients with asthma.[109–112] Indications for use are: (1) moderate to severe dyspnoea or respiratory distress, (2) hypercapnic acidosis and (3) respiratory rate greater than 25, accessory muscle use or paradoxical breathing. Contraindications to NIV include cardiac or respiratory arrest, a decreased conscious state, severe upper gastrointestinal bleeding, haemodynamic instability, facial trauma or surgery, inability to protect the airway and clear secretions and high risk of aspiration.

Nasal masks are usually not suitable in acute respiratory failure and full-face masks fitted to achieve comfort and a reliable seal are usually best.

NIV should be commenced with 5 cm H_2O continuous positive airway pressure (CPAP) (expiratory positive airway pressure 5 cm H_2O) and 8–10 cm H_2O pressure support (inspiratory positive airway pressure [IPAP] 13–15 cm H_2O). The aim is a respiratory rate less than 25 breaths/min and an exhaled tidal volume of 7 mL/kg. CPAP may be increased to 7 or 10 cm H_2O if there is difficulty initiating inspiration, or pressure support may be increased if tidal volume is low or respiratory rate remains high. It is not possible to reliably achieve total pressures (IPAP) greater than 20 cm H_2O. NIV should be undertaken in an area familiar with its use and where close observation is available.

Complications of NIV include nasal bridge ulceration, mask discomfort, nasal congestion, gastric insufflation, aspiration, hypotension and pneumothorax.[112] However, hypotension and pneumothorax are uncommon compared with their risk during mechanical ventilation. A recent uncontrolled series[114] suggest NIV is safe in this situation if conducted under careful supervision in a monitored environment.

INVASIVE VENTILATION

Invasive mechanical ventilation in acute severe asthma may be life saving, but can be associated with significant morbidity and mortality (Fig. 35.4).[100] Institution of invasive ventilation with endotracheal intubation carries the risk of inadvertent pulmonary hyperinflation[95,96,100] and potential aggravation of bronchospasm and a significant part of the morbidity and mortality has been attributed to pulmonary hyperinflation.[95,96,100] Despite these risks, the incidence of mechanical ventilation for asthma is decreasing and mortality of patients ventilated for asthma is also decreasing in some series (see Figs 35.1 and 35.4).[5,6]

The decision to intubate depends on both the clinical status of the patient and the natural history of the type of asthma present. Hyperacute asthma may present with marked hypercapnia ($PaCO_2$ >60 mm Hg [7.98 kPa]) due to mechanical limitations of ventilation as a result of DHI. Such patients may not initially be fatigued and may respond rapidly to treatment, thereby avoiding mechanical ventilation. Acute severe asthma that has been progressing for days may have

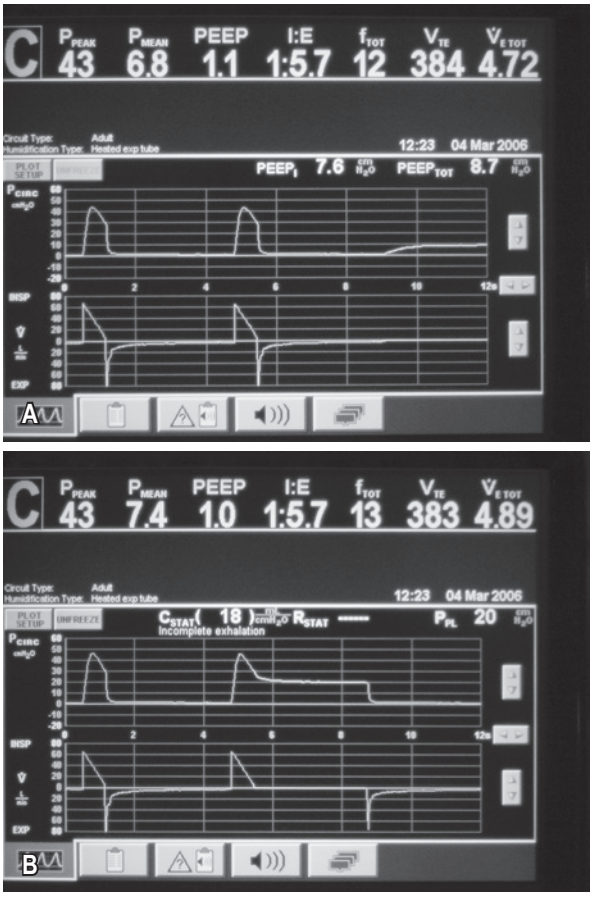


Figure 35.4 (a) The ventilator circuit pressure and flow traces versus time during controlled ventilation of a patient with severe air-flow obstruction. Note the use of a low rate, low V_t, a high inspiratory flow rate (V_i 80 L/min) and hence a short inspiratory time (t_e <1 second). This causes a high peak airway pressure but allows a long expiratory time (>4 seconds). Expiratory flow is low throughout expiration and appears close to baseline at the onset of the next breath (second on screen). Suggesting minimal gas trapping but when an intrinsic positive end-expiratory pressure ($PEEP_i$) manoeuvre is done (end-expiratory pause) these is a surprising degree of $PEEP_i$ present (7.6 cm H_2O). (b) The ventilator circuit pressure and flow traces versus time during controlled ventilation of the same patient in part a. When a P_{plat} manoeuvre is done (end-inspiratory pause) the P_{plat} is safe (20 cm H_2O) with this ventilator pattern despite the degree of PEEPi present. Note the low P_{plat} despite the high peak airway pressure.

less hypercapnia but will often respond poorly to treatment. The $PaCO_2$ may rise despite maximal treatment owing to fatigue and the patient may require intubation at a lower $PaCO_2$. The general principles are to use NIV early but to avoid mechanical ventilation if it is safe to do so.

The decision to intubate is based primarily on the degree of respiratory distress as assessed by an experienced clinician and the patient themselves. A patient with a high $PaCO_2$ (e.g. >70 mm Hg [9.31 kPa]) who is dyspnoeic but not distressed and who may respond to full treatment over a few hours needs close observation but not immediate intubation. Patients are often able to tolerate hypercapnia without requiring invasive ventilation.[115] A patient with a lower $PaCO_2$ (e.g. 50–60 mm Hg [6.66–7.98 kPa]) who has been unwell for days, and who has a deteriorating status despite treatment and significant respiratory distress, is likely to need intubation. A patient who complains of respiratory exhaustion is likely to need intubation. Absolute indications for intubation include cardiac or respiratory arrest, severe hypoxia or rapid deterioration of conscious state.[17,59]

Once the decision to intubate has been made, a safe option is to perform rapid sequence intubation using the orotracheal approach. As large as possible endotracheal tube should be used to reduce the work of breathing and to reduce the risk of tube occlusion by the tenacious secretions that often occur with asthma. Once the endotracheal tube is in place, slow hand ventilation (8–10 breaths/min) should maintain oxygenation until the ventilator can be connected.

INITIAL VENTILATOR SETTINGS

The principles of initial mechanical ventilation are to avoid excessive DHI[95,99–101,116] and to avoid excessive hypoventilation (Fig. 35.5) by commencing with a minute ventilation less than 115 mL/kg per minute (<8 L/min in a 70 kg patient) best achieved with a tidal volume of 5–7 mL/kg, a respiratory rate of 10–12 breaths/min and a short inspiratory time to ensure an expiratory time ≥4 seconds.[95,99–101,116] This degree of hypoventilation will usually result in hypercapnic acidosis and continued respiratory distress necessitating heavy sedation, and sometimes requires 1–2 bolus doses of a neuromuscular-blocking agent (NMBA).

The use of volume-controlled ventilation is most established for this ventilatory pattern. In volume control, a high inspiratory flow rate (70–100 L/min) is required to achieve a short inspiratory time. This will result in a high peak airway pressure (PIP), but this will lower DHI and P_{plat} and reduce barotrauma compared with lower inspiratory flow rates[95,100] Pressure-controlled or assisted modes have been used[117] without adverse consequences. The theoretical advantage of a safe pressure limit in pressure modes is offset by the fact that equilibrium with the set safe pressure cannot be reached during the short inspiratory times required, and thus either a higher pressure must be set or more than necessary hypoventilation may occur. It is not clear whether one mode is superior to the other.

If significant hypotension occurs this should be treated by reducing the respiratory rate, (thereby reducing DHI) and volume loading.

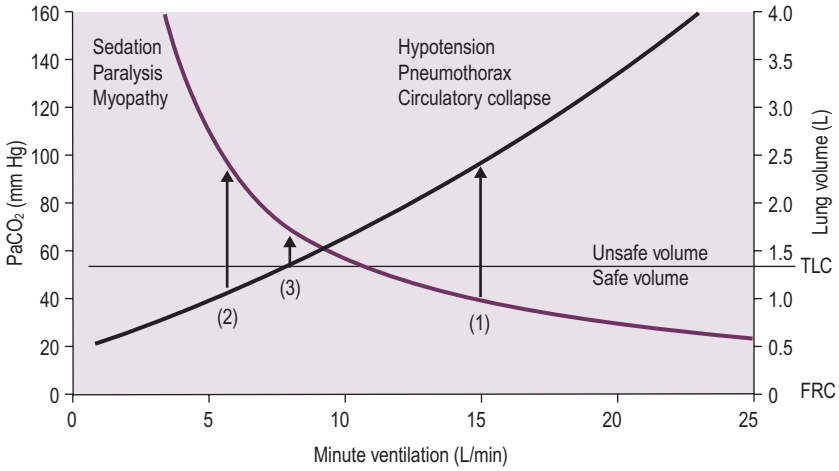


Figure 35.5 The effects of minute ventilation on $PaCO_2$ and end-inspiratory lung volume above functional residual capacity (FRC) in a typical patient with severe asthma. (1) The minute ventilation required for normocapnia; (2) profound hypoventilation; and (3) optimal hypoventilation. *TLC*, Total lung capacity.

POSITIVE END-EXPIRATORY PRESSURE

The role of extrinsic PEEP during mechanical ventilation of the patient with severe asthma requires careful consideration. During spontaneous breathing, CPAP has been shown to facilitate the initiation of the next breath and reduce the work of breathing in many patients with severe air-flow obstruction. However, during the initial controlled hypoventilation when there is an excessive level of PEEPi and DHI, and the work of breathing is not an issue, early work has shown that extrinsic PEEP will further increase lung volumes. As this conferred no benefit and risk of detriment, it has been recommended that extrinsic PEEP should not be used.[101] More recently, some research has suggested that low-level PEEP may improve the distribution of ventilation (as does hyperinflation) and reduce $PaCO_2$,[118] and one study[119] has found that extrinsic PEEP may paradoxically reduce hyperinflation in some patients ventilated with air-flow obstruction. The uncertain benefit and unpredictable responses to PEEP in these latter studies continue to suggest that extrinsic PEEP should not be routinely used during controlled ventilation for severe air-flow obstruction.[101]

ASSESSMENT OF DYNAMIC HYPERINFLATION

Once mechanical ventilation has started, the degree of DHI should be assessed by measurement of *plateau airway pressure* (P_{plat}). This is the airway pressure after transient expiratory occlusion at the end of inspiration. This may be achieved by an end-inspiratory hold function on most current ventilators, which delays the commencement of the next breath (see Fig. 35.4a), or by applying a 0.5 s 'plateau', which does not delay the onset of the next breath. The latter should be applied for a single breath only as application for several breaths in a row will decrease expiratory time and progressively increase DHI. This is the most easily measured estimate of average alveolar pressure at the end of inspiration and is directly proportional to the degree of hyperinflation and should be maintained at less than 25 cm H_2O.[95,100]

In patients with severe asthma, P_{plat} of 25 cm H_2O correlated with an average end-inspiratory lung volume of less than 20 mL/kg (1.4 L in a 70 kg patient, see Figs 35.2 and 35.3) above FRC. This has been shown to be a good predictor of complications during mechanical ventilation[100] and to correlate with a total lung volume at TLC.[99]

$PEEP_i$ is the airway pressure during occlusion of expiratory flow at the end of expiration (see Fig. 35.4b). This is also an automated end-inspiratory hold function on most current ventilators. However, this measurement is known to underestimate true $PEEP_i$, as a consequence of small-airway closure during expiration resulting in many higher-pressure alveoli not communicating with the central airway at the end of expiration.[97] Because of this, $PEEP_i$ can be used to show the presence of DHI but is not recommended to regulate the mechanical ventilation. Ideally, $PEEP_i$ should be less than 12 cm H_2O, although the exact safe level is unknown.

Assessment of the change in blood pressure and central venous pressure should be made during a period of transient ventilator disconnection (1–2 minutes) or transient ventilator rate reduction (4–6 breaths/min for 2–4 minutes). If DHI has been suppressing circulation then a significant increase in blood pressure and reduction in central venous pressure will occur.

ADJUSTMENT OF VENTILATION

Ventilatory patterns with excessive minute ventilation risk hypotension and barotrauma, and are associated with a high mortality. The use of profound hypoventilation will guarantee avoidance of these complications,

but usually necessitates heavy sedation and neuromuscular blockade (see Fig. 34.5). This, in association with parenteral steroids, has a high probability of myopathy,[72,120,121] which may cause severe prolonged disability. To minimise the risk of both these complications, DHI should be carefully assessed and the minimum amount of hypoventilation used to achieve a safe level of DHI (see Fig. 35.5) in association with less sedation and minimal or no use of NMBA.

Ventilation should be adjusted based on assessment of DHI, not on $PaCO_2$ or pH. If P_{plat} is greater than 25 cm H_2O or circulatory suppression is present, the ventilator rate should be reduced.[95,122] If P_{plat} is low, ventilation can be liberalised by increasing the ventilator rate or reducing sedation and allowing spontaneous ventilation. Hypercapnia is usually present but is well tolerated[123] and does not appear to depress cardiac function. There is no evidence of benefit from sodium bicarbonate, but it may reduce acidaemia-induced respiratory distress, and it may be given if the pH is less than 7.1.

When air-flow obstruction improves (decreasing P_{plat} and $PEEP_i$), sedation may be decreased, ventilator rate reduced and spontaneous ventilation assisted with pressure support ventilation. Pressure support of 10–16 cm H_2O may be used. Once spontaneous ventilation has commenced and when DHI is no longer critical, 3–7 cm H_2O CPAP may be introduced to assist ventilator triggering and reduce the work of breathing.

COMPLICATIONS OF INVASIVE VENTILATION IN ASTHMA

Hypotension may be caused by sedation, DHI, pneumothoraces or arrhythmias.[95,100] Hypovolaemia may be a contributory factor but is rarely a cause. Hypotension may be mild or life threatening.[124] Hypotension due to DHI may be diagnosed by the recovery of blood pressure during apnoea of 60 seconds (the 'apnoea test')[124] or by a longer period of low ventilator rate (4–6 breaths/min for 2–4 minutes). If this occurs, ventilation should be continued at a lower rate.

Circulatory arrest with apparent electromechanical dissociation (EMD) is a recognised complication that may occur within 10 minutes of intubation, and can lead to death or severe cerebral ischaemic injury if not managed correctly.[124–126] Standard mechanical ventilation recommendations (minute ventilation 115 mL/kg per minute) have been estimated to be safe for 80% of patients requiring mechanical ventilation for acute severe asthma, with the remaining 20% requiring a small to moderate reduction in minute ventilation to return DHI to a safe level.[100] A small percentage of patients with unusually severe asthma can rapidly develop excessive DHI during initial uncontrolled mechanical ventilation leading to EMD, sometimes despite 'safe' levels of minute ventilation. If the cause of this is not immediately recognised, it can lead to prolonged and unnecessary cardiopulmonary resuscitation, unsafe procedures (e.g. intercostal vascular access needles or pericardial taps) and can risk cerebral injury and death.[124–126] When this occurs, immediate disconnection from ventilation for 60–90 seconds (the 'apnoea test', above) or profound hypoventilation (2–3 breaths/min)[59] will diagnose and improve this situation. An even smaller percentage of patients may remain hypotensive despite profound hypoventilation with marked hypercapnia, fluid loading and inotropes. These patients may require heliox delivered by the mechanical ventilator[127] or extracorporeal membrane oxygenation.[126,128–130]

Pneumothoraces were common before the advent of protective ventilatory strategies. DHI during mechanical ventilation was probably the major causative factor involved.[95,100] Pneumothoraces may also occur in association with subclavian central venous catheter insertion and as a consequence of intercostal needle insertion for suspected tension pneumothorax during circulatory arrest (above). Asthma continues to remain one of the three most common conditions (with acute respiratory distress syndrome [ARDS] and interstitial lung disease) associated with barotrauma during mechanical ventilation with a risk rate of 6.3% compared with an overall risk rate of 2.9% for all mechanically ventilated patients.[131] The presence of severe air-flow obstruction prevents lung collapse and favours gas loss through the ruptured alveoli, with the result that tension is almost always present in the pneumothorax. Once a unilateral tension pneumothorax is present, this will necessarily reduce ventilation to that lung and redistribute ventilation to the contralateral lung, thereby further increasing DHI in the second lung, and bilateral tension pneumothoraces may result with severe adverse consequences.

As soon as a tension pneumothorax is suspected, the ventilator rate should be immediately reduced to decrease the risk to the second lung. Clinical diagnosis of a tension pneumothorax can be difficult as the lungs in severe asthma are already overexpanded and hyper-resonant with poor air entry. An urgent chest X-ray is always advisable for confirmation prior to intercostal catheter insertion unless severe hypotension is present. Intercostal catheters should always be inserted by blunt dissection. If intercostal needles are inserted for suspected pneumothorax, an intercostal catheter should always be inserted soon thereafter because if a tension pneumothorax was not present it is highly likely to present after the intercostal needles.

Acute necrotising myopathy is a serious complication that may occur in patients who are invasively ventilated for asthma and receive NMBA or very deep sedation.[72,120,121,132,133] It is characterised by weakness with electromyographic evidence of myopathy and increased serum creatine kinase levels. Muscle biopsy reveals two patterns: myonecrosis with muscle cell vacuolisation or predominant type II fibre atrophy.[72,132] Recovery can be slow with prolonged weaning from

mechanical ventilation and the need for rehabilitation. Incomplete recovery after 12 months has been reported in a few patients.[133,134] The aetiology of the myopathy appears to be a combination of the effects of corticosteroids and NMBA with the duration of paralysis a strong predictor of myopathy.[133,134] The type of NMBA used seems to make no difference to the incidence of myopathy.[132] Effective paralysis by deep sedation without the use of NMBAs also confers the risk of severe weakness in this patient group.[134] Gehlbach et al.[10] found that the risk factors for prolonged mechanical ventilation were female gender, the use of NMBAs, the requirement for inhaled corticosteroids prior to admission and a high illness severity score (APACHE II). The relative contributions of corticosteroids versus NMBAs in the causation of myopathy are unclear. It seems wise to minimise the dose of parenteral corticosteroids with early introduction of nebulised agents, to minimise or avoid NMBAs if possible and to minimise deep sedation.

MORTALITY, LONG-TERM OUTCOME AND FOLLOW-UP

Prior to the year 2000,[60] there was a high overall mortality of 12.4% for patients requiring mechanical ventilation for asthma with a progressive reduction in reported mortality during that period (Fig. 35.6). A selection of reports[5,7,9,10,25] published since 2000 have shown continued reduction in overall mortality (see Fig. 35.6) but with mortalities as high as 21% still occurring in one series.[9] The largest and most comprehensive recent series[5] reported 1899 patients admitted to 22 Australian intensive care units over an 8-year period (1996–2003). This series reported a requirement for mechanical ventilation for 36% of patients admitted with severe asthma and a progressive reduction in annual mortality of the ventilated patients from 10% to 3% over the 8-year period.

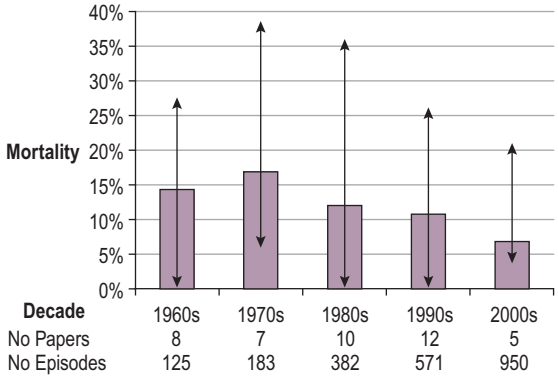


Figure 35.6 Comparison of reported mortality associated with the mechanical ventilation of patients with severe asthma over the last five decades. Mortality shown as mean with minimum and maximum mortality within the reported series for that decade.

The need for invasive ventilation increases the risk of death,[5,9] and survivors of these near-fatal episodes of asthma have an increased risk of intensive care readmission and an increased risk of death after hospital discharge.[38,135] For these reasons, patients who have an episode of asthma severe enough to require hospitalisation – particularly intensive care admission – need careful follow-up. This should include active identification and avoidance of precipitants, aggressive bronchodilator therapy including inhaled steroids, regular medical review, regular measurement of lung function, management plans for a deteriorating status and ready access to emergency services. Patients with difficult asthma may benefit from detailed psychological and sometimes speech therapy assessment.[18]

REFERENCES

1. Abramson MJ, Bailey MJ, Couper FJ, et al. Are asthma medications and management related to deaths from asthma? *Am J Respir Crit Care Med*. 2001;163(1):12–18.
2. McCaul KA, Wakefield MA, Roder DM, et al. Trends in hospital readmission for asthma: has the Australian National Asthma Campaign had an effect? *Med J Aust*. 2000;172(2):62–66.
3. Suissa S, Ernst P, Benayoun S, et al. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med*. 2000;343(5):332–336.
4. Pearce N, Aït-Khaled N, Beasley R, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2007;62(9):758–766.
5. Stow P, Pilcher D, Wilson J, et al. Improved outcomes from acute severe asthma in Australian intensive care units (1996–2003). *Thorax*. 2007;62(10):842–847.
6. Wilson D, Tucker G, Frith P, et al. Trends in hospital admissions and mortality from asthma and chronic obstructive pulmonary disease in Australia, 1993–2003. *Med J Aust*. 2007;186(8):408–411.
7. Elsayegh D, Saito S, Eden E, et al. Increasing severity of status asthmaticus in an urban medical intensive care unit. *J Hosp Med*. 2008;3(3):206–211.
8. Kaza V, Bandi V, Guntupalli KK. Acute severe asthma: recent advances. *Curr Opin Pulm Med*. 2007;13(1):1–7.
9. Afessa B, Morales I, Cury JD. Clinical course and outcome of patients admitted to an ICU for status asthmaticus. *Chest*. 2001;120(5):1616–1621.
10. Gehlbach B, Kress JP, Kahn J, et al. Correlates of prolonged hospitalization in inner-city ICU patients receiving noninvasive and invasive positive pressure ventilation for status asthmaticus. *Chest*. 2002;122(5):1709–1714.
11. Reddel H, Sawyer S, Everett P, et al. Asthma control in Australia: a cross-sectional web-based

survey in a nationally representative population. *Med J Aust*. 2015;202(9):492–497.
12. Goeman D, Abramson M, McCarthy E, et al. Asthma mortality in Australia in the 21st century: a case series analysis. *BMJ Open*. 2013;3(5):e002539.
13. Tay T, Abramson M, Hew M. Closing the million patient gap of uncontrolled asthma. *Med J Aust*. 2016;204(6):216–217.
14. Royal College of Physicians. *Why Asthma Still Kills: the National Review of Asthma Deaths (NRAD) Confidential Enquiry Report*. London: RCP; 2014. http://www.rcplondon.ac.uk/sites/default/files/why-asthma-still-kills-full-report.pdf.
15. Reddel H, Bateman E, Becker A, et al. A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J*. 2015;46(3):622–639.
16. Chung K. Asthma phenotyping: a necessity for improved therapeutic precision and new targeted therapies. *J Intern Med*. 2016;279:192–204.
17. Werner HA. Status asthmaticus in children: a review. *Chest*. 2001;119(6):1913–1929.
18. Harrison BD. Difficult asthma in adults: recognition and approaches to management. *Intern Med J*. 2005;35(9):543–547.
19. Daley D. The evolution of the hygiene hypothesis: the role of early-life exposures to viruses and microbes and their relationship to asthma and allergic diseases. *Curr Opin Allergy Clin Immunol*. 2014;14(5):390–396.
20. Bégin P, Nadeau K. Epigenetic regulation of asthma and allergic disease. *Allergy Asthma Clin Immunol*. 2014;10(1):27.
21. Hew M, Bhavsar P, Torrego A, et al. Relative corticosteroid insensitivity of peripheral blood mononuclear cells in severe asthma. *Am J Respir Crit Care Med*. 2006;174(2):134–141.
22. Busse WW, Lemanske RF Jr. Asthma. *N Engl J Med*. 2001;344(5):350–362.
23. Tay T, Radhakrishna N, Hore-Lacy F, et al. Comorbidities in difficult asthma are independent risk factors for frequent exacerbations, poor control and diminished quality of life. *Respirology*. 2016;21(8):1384–1390.
24. Moghaddas F, Smith C, Pilcher D, et al. Need for intensive care in patients admitted for asthma: red flags from the social history. *Respirology*. 2016;21(7):1251–1254.
25. Sekiya K, Sugino K, Hojyo T, et al. Clinical evaluation of severe asthma attacks requiring tracheal intubation and mechanical ventilation. *Allergol Int*. 2009;58(2):289–294.
26. Radhakrishna N, Hew M. Addressing ethnic disparity in asthma trials. *Respirology*. 2014;19(6):775–776.
27. Sandford AJ, Chagani T, Zhu S, et al. Polymorphisms in the IL4, IL4RA, and FCERIB genes and asthma severity. *J Allergy Clin Immunol*. 2000;106(1 Pt 1):135–140.
28. Restrepo RD, Peters J. Near-fatal asthma: recognition and management. *Curr Opin Pulm Med*. 2008;14(1):13–23.
29. Bai TR, Cooper J, Koelmeyer T, et al. The effect of age and duration of disease on airway structure in fatal asthma. *Am J Respir Crit Care Med*. 2000;162(2 Pt 1):663–669.
30. Jeffery PK. Bronchial biopsies and airway inflammation. *Eur Respir J*. 1996;9(8):1583–1587.
31. Wasserfallen J, Schaller M, Feihl F, et al. Sudden asphyxic asthma: a distinct entity? *Am Rev Respir Dis*. 1990;142:108–111.
32. Kolbe J, Fergusson W, Garrett J. Rapid onset asthma: a severe but uncommon manifestation. *Thorax*. 1998;53(4):241–247.
33. Woodruff PG, Emond SD, Singh AK, et al. Sudden-onset severe acute asthma: clinical features and response to therapy. *Acad Emerg Med*. 1998;5(7):695–701.
34. Hew M, Sutherland M, Thien F, et al. The Melbourne thunderstorm asthma event: can we avert another strike. *Intern Med J*. 2017;47:485–487.
35. Evans TW. International Consensus Conferences in Intensive Care Medicine: non-invasive positive pressure ventilation in acute respiratory failure. Organised jointly by the American Thoracic Society, the European Respiratory Society, the European Society of Intensive Care Medicine, and the Societe de Reanimation de Langue Francaise, and approved by the ATS Board of Directors, December 2000. *Intensive Care Med*. 2001;27(1):166–178.
36. Pinski M. Cardiopulmonary interactions associated with airflow obstruction. In: Hall J, Corbridge T, Rodrigo C, et al, eds. *Acute Asthma: Assessment and Management*. New York, NY: McGraw-Hill; 2000:105–123.
37. Rossi A, Ganassini A, Brusasco V, et al. Airflow obstruction and dynamic hyperinflation. In: Hall J, Corbridge T, Rodrigo C, eds. *Acute Asthma: Assessment and Management*. New York, NY: McGraw-Hill; 2000:57–82.
38. McFadden ER Jr. Acute severe asthma. *Am J Respir Crit Care Med*. 2003;168(7):740–759.
39. Carruthers DM, Harrison BD. Arterial blood gas analysis or oxygen saturation in the assessment of acute asthma? *Thorax*. 1995;50(2):186–188.
40. Rodrigo GJ, Rodriquez Verde M, Peregalli V, et al. Effects of short-term 28% and 100% oxygen on $PaCO_2$ and peak expiratory flow rate in acute asthma: a randomized trial. *Chest*. 2003;124(4):1312–1317.
41. Byrne A, Bennett M, Chatterji R, et al. Peripheral venous and arterial blood gas analysis in adults: are they comparable? A systematic review and meta-analysis. *Respirology*. 2014;19(2):168–175.
42. Manthous CA. Lactic acidosis in status asthmaticus: three cases and review of the literature. *Chest*. 2001;119(5):1599–1602.
43. Prakash S, Mehta S. Lactic acidosis in asthma: report of two cases and review of the literature. *Can Respir J*. 2002;9(3):203–208.
44. Rodrigo G, Rodrigo C. Assessment of the patient with acute asthma in the emergency

department. A factor analytic study. *Chest*. 1993; 104(5):1325–1328.
45. Beasley R, Pearce N, Crane J, et al. Asthma mortality and inhaled beta agonist therapy. *Aust NZ J Med*. 1991;21:753–763.
46. British Thoracic Society. Scottish Intercollegiate Guidelines Network. *British Guideline on the Management of Asthma*. London: BTS; 2016. https://www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2016/.
47. Chien JW, Ciufo R, Novak R, et al. Uncontrolled oxygen administration and respiratory failure in acute asthma. *Chest*. 2000;117(3):728–733.
48. Perrin K, Wijesinghe M, Healy B, et al. Randomised controlled trial of high concentration versus titrated oxygen therapy in severe exacerbations of asthma. *Thorax*. 2011;66(11):937–941.
49. *Australian Asthma Handbook 2016*. Melbourne: National Asthma Council Australia; 2016. Available from: www.asthmahandbook.org.au.
50. Bisgaard H. Delivery of inhaled medication to children. *J Asthma*. 1997;34(6):443–467.
51. Papo MC, Frank J, Thompson AE. A prospective, randomized study of continuous versus intermittent nebulized albuterol for severe status asthmaticus in children. *Crit Care Med*. 1993;21(10):1479–1486.
52. Dolovich MA. Influence of inspiratory flow rate, particle size, and airway caliber on aerosolized drug delivery to the lung. *Respir Care*. 2000;45(6):597–608.
53. Cates C, Rowe B, Bara A. *Holding chamber versus nebulisers for beta-agonist treatment of acute asthma (Cochrane Review)*. Cochrane Library, Oxford, UK: 2002;(2):CD000052.
54. Manthous C, Hall J, Schmidt G, et al. Metered-dose inhaler versus nebulized albuterol in mechanical ventilated patients. *Am Rev Respir Dis*. 1993;148:1567–1570.
55. Rodrigo C, Rodrigo G. Therapeutic response patterns to high and cumulative doses of salbutamol in acute severe asthma. *Chest*. 1998; 113(3):593–598.
56. Travers A, Milan S, Jones A, et al. Addition of intravenous beta(2)-agonists to inhaled beta(2)-agonists for acute asthma. *Cochrane Database Syst Rev*. 2012;(12):CD010179.
57. Browne GJ, Penna AS, Phung X, et al. Randomised trial of intravenous salbutamol in early management of acute severe asthma in children. *Lancet*. 1997;349(9048):301–305.
58. Boulet L, Becker A, Berube D, et al. Canadian Asthma Consensus Report: management of patients with asthma in the emergency department and in the hospital. *CMAJ*. 1999;161(suppl 11):S1–S62.
59. Corbridge SJ, Corbridge TC. Severe exacerbations of asthma. *Crit Care Nurs Q*. 2004;27(3):207–228, quiz 29–30.
60. Tuxen D. Mechanical ventilation in asthma. In: Evans T, Hinds C, eds. *Recent Advances in Critical Care Medicine Number 4*. London, UK: Churchill Livingstone; 1996:165–189.
61. Willmot D. A 24 year old woman admitted to the critical care unit, with 'resistant' asthma and a metabolic acidosis. *Crit Care Resusc*. 2000;2(3):228–229.
62. Spitzer WO, Suissa S, Ernst P, et al. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med*. 1992;326(8): 501–506.
63. Papiris SA, Manali ED, Kolilekas L, et al. Acute severe asthma: new approaches to assessment and treatment. *Drugs*. 2009;69(17):2363–2391.
64. Stoodley RG, Aaron SD, Dales RE. The role of ipratropium bromide in the emergency management of acute asthma exacerbation: a metaanalysis of randomized clinical trials. *Ann Emerg Med*. 1999;34(1):8–18.
65. Rodrigo GJ, Rodrigo C. The role of anticholinergics in acute asthma treatment: an evidence-based evaluation. *Chest*. 2002;121(6):1977–1987.
66. Bryant D, Rogers P. Effects of ipratropium bromide nebuliser solution with and without preservatives in the treatment of acute and stable asthma. *Chest*. 1992;102:742–747.
67. Rodrigo GJ, Rodrigo C, Hall JB. Acute asthma in adults: a review. *Chest*. 2004;125(3):1081–1102.
68. Bateman E, Hurd S, Barnes P, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J*. 2008;31(1): 143–178.
69. Rowe B, Spooner C, Ducharme F, et al. *Early Emergency Department Treatment of Acute Asthma With Systemic Corticosteroids (Cochrane Review)*. Oxford, UK: Update Software; 2001.
70. Rodrigo GJ, Rodrigo C. Triple inhaled drug protocol for the treatment of acute severe asthma. *Chest*. 2003;123(6):1908–1915.
71. Edmonds ML, Camargo CA Jr, Pollack CV Jr, et al. The effectiveness of inhaled corticosteroids in the emergency department treatment of acute asthma: a meta-analysis. *Ann Emerg Med*. 2002;40(2):145–154.
72. Douglass J, Tuxen D, Horne M, et al. Myopathy in severe asthma. *Am Rev Respir Dis*. 1992;146(2):517–519.
73. Klein-Gitelman MS, Pachman LM. Intravenous corticosteroids: adverse reactions are more variable than expected in children. *J Rheumatol*. 1998;25(10):1995–2002.
74. Abernathy-Carver KJ, Fan LL, Boguniewicz M, et al. Legionella and Pneumocystis pneumonias in asthmatic children on high doses of systemic steroids. *Pediatr Pulmonol*. 1994;18(3):135–138.
75. Kasper WJ, Howe PM. Fatal varicella after a single course of corticosteroids. *Pediatr Infect Dis J*. 1990;9(10):729–732.
76. Kew K, Kirtchuk L, Michell C. Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department. *Cochrane Database Syst Rev*. 2014;(5):CD010909.

77. Griffiths B, Kew K. Intravenous magnesium sulfate for treating children with acute asthma in the emergency department. *Cochrane Database Syst Rev*. 2016;(4):CD011050.
78. Sydow M, Crozier T, Zielman S, et al. High-dose intravenous magnesium sulfate in the management of life threatening status asthmaticus. *Intensive Care Med*. 1993;19:467–471.
79. Parameswaran K, Belda J, Rowe B, et al. *Addition of Intravenous Aminophylline to Beta2-Agonists in Adults With Acute Asthma (Cochrane Review)*. Oxford, UK: Update Software; 2002.
80. Nair P, Milan S, Rowe B. Addition of intravenous aminophylline to inhaled beta(2)-agonists in adults with acute asthma. *Cochrane Database Syst Rev*. 2012;(12):CD002742.
81. Tirot P, Bouachour G, Varache N, et al. Use of intravenous adrenaline in severe acute asthma. *Rev Mal Respir*. 1992;9(3):319–323.
82. Kress JP, Noth I, Gehlbach BK, et al. The utility of albuterol nebulized with heliox during acute asthma exacerbations. *Am J Respir Crit Care Med*. 2002;165(9):1317–1321.
83. Kass JE, Terregino CA. The effect of heliox in acute severe asthma: a randomized controlled trial. *Chest*. 1999;116(2):296–300.
84. Rodrigo GJ, Rodrigo C, Pollack CV, et al. Use of helium-oxygen mixtures in the treatment of acute asthma: a systematic review. *Chest*. 2003;123(3):891–896.
85. Colebourn CL, Barber V, Young JD. Use of helium-oxygen mixture in adult patients presenting with exacerbations of asthma and chronic obstructive pulmonary disease: a systematic review. *Anaesthesia*. 2007;62(1):34–42.
86. Sato N, Matsuki A, Zsigmond E, et al. Ketamine relaxes and airway smooth muscle contracted by endothelium. *Anesth Analg*. 1997;84(4):900–906.
87. Howton JC, Rose J, Duffy S, et al. Randomized, double-blind, placebo-controlled trial of intravenous ketamine in acute asthma. *Ann Emerg Med*. 1996;27(2):170–175.
88. Vaschetto R, Bellotti E, Turucz E, et al. Inhalational anesthetics in acute severe asthma. *Curr Drug Targets*. 2009;10(9):826–832.
89. Tobias JD, Garrett JS. Therapeutic options for severe, refractory status asthmaticus: inhalational anaesthetic agents, extracorporeal membrane oxygenation and helium/oxygen ventilation. *Paediatr Anaesth*. 1997;7(1):47–57.
90. Dockhorn RJ, Baumgartner RA, Leff JA, et al. Comparison of the effects of intravenous and oral montelukast on airway function: a double blind, placebo controlled, three period, crossover study in asthmatic patients. *Thorax*. 2000;55(4):260–265.
91. Camargo CA Jr, Smithline HA, Malice MP, et al. A randomized controlled trial of intravenous montelukast in acute asthma. *Am J Respir Crit Care Med*. 2003;167(4):528–533.
92. Smith D, Deshazo R. Bronchoalveolar lavage in asthma. State of the art. *Am Rev Respir Dis*. 1993; 148:523–532.
93. Graham V, Lasserson T, Rowe B, eds. *Antibiotics for Acute Asthma (Cochrane Review)*. Oxford, UK: Update Software; 2002.
94. Joseph KS, Blais L, Ernst P, et al. Increased morbidity and mortality related to asthma among asthmatic patients who use major tranquillisers. *BMJ*. 1996;312(7023):79–82.
95. Tuxen D, Lane S. The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe airflow obstruction. *Am Rev Respir Dis*. 1987;136:872–879.
96. Pepe P, Marini J. Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction. *Am Rev Respir Dis*. 1982;126:166–170.
97. Leatherman J, Ravenscraft S. Low measured auto-positive end-expiratory pressure during mechanical ventilation of patients with severe asthma: hidden auto-positive end-expiratory pressure. *Crit Care Med*. 1996;24(3):541–546.
98. Murase K, Tomii K, Chin K, et al. The use of non-invasive ventilation for life-threatening asthma attacks: changes in the need for intubation. *Respirology*. 2010;15(4):714–720.
99. Tuxen D, Williams T, Scheinkestel C, et al. Use of a measurement of pulmonary hyperinflation to control the level of mechanical ventilation in patients with severe asthma. *Am Rev Respir Dis*. 1992;146(5):1136–1142.
100. Williams T, Tuxen D, Scheinkestel C, et al. Risk factors for morbidity in mechanically ventilated patients with acute severe asthma. *Am Rev Respir Dis*. 1992;146(3):607–615.
101. Tuxen D. Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. *Am Rev Respir Dis*. 1989;140:5–9.
102. International Consensus Conferences in Intensive Care Medicine: noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med*. 2001;163(1):283–291.
103. Mehta S, Hill NS. Noninvasive ventilation. *Am J Respir Crit Care Med*. 2001;163:540–577.
104. Brochard L. Noninvasive ventilation for acute respiratory failure. *JAMA*. 2002;288(8): 932–935.
105. Kramer N, Meyer T, Meharg J, et al. Randomised prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med*. 1995;151:1799–1806.
106. Fernandez MM, Villagra A, Blanch L, et al. Non-invasive mechanical ventilation in status asthmaticus. *Intensive Care Med*. 2001;27(3):486–492.
107. Soroksky A, Stav D, Shpirer I. A pilot prospective, randomised placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack. *Chest*. 2003;123:1018–1025.

108. Gupta D, Nath A, Agarwal R, et al. A prospective randomized controlled trial on the efficacy of noninvasive ventilation in severe acute asthma. *Respir Care*. 2010;55(5):536–543.
109. Soroksky A, Klinowski E, Ilgyev E, et al. Noninvasive positive pressure ventilation in acute asthmatic attack. *Eur Respir Rev*. 2010; 19(115):39–45.
110. Murase K, Tomii K, Chin K, et al. Non-invasive ventilation in severe asthma attack, its possibilities and problems. *Panminerva Med*. 2011;53(2):87–96.
111. Boldrini R, Fasano L, Nava S. Noninvasive mechanical ventilation. *Curr Opin Crit Care*. 2012; 18(1):48–53.
112. Pallin M, Naughton M. Noninvasive ventilation in acute asthma. *J Crit Care*. 2014;29(4):586–593.
113. Lim W, Mohammed Akram R, Carson K, et al. Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. *Cochrane Database Syst Rev*. 2012;(12):CD004360.
114. Pallin M, Hew M, Naughton M. Is non-invasive ventilation safe in acute severe asthma? *Respirology*. 2015;20(2):251–257.
115. Mountain R, Sahn S. Clinical features and outcome in patients with acute asthma presenting with hypercapnia. *Am Rev Respir Dis*. 1988;138:535–539.
116. Peigang Y, Marini J. Ventilation of patients with asthma and chronic pulmonary disease. *Curr Opin Crit Care*. 2002;8:70–78.
117. Mansel J, Stogner S, Petrini M, et al. Mechanical ventilation in patients with acute severe asthma. *Am J Med*. 1990;89:42–48.
118. Marini JJ. Does positive end-expiratory pressure improve CO(2) exchange in controlled ventilation of acute airflow obstruction? *Crit Care Med*. 2011;39(7):1841–1842.
119. Caramez MP, Borges JB, Tucci MR, et al. Paradoxical responses to positive end-expiratory pressure in patients with airway obstruction during controlled ventilation. *Crit Care Med*. 2005;33(7):1519–1528.
120. Hansen-Flaschen J, Cowen J, Raps E. Neuromuscular blockade in the intensive care unit. More than we bargained for. *Am Rev Respir Dis*. 1993;147:234–236.
121. Nates J, Cooper D, Tuxen D. Acute weakness syndromes in critically ill patients – a reappraisal. *Anaesth Intensive Care*. 1997;25(5):502–513.
122. Leatherman JW, McArthur C, Shapiro RS. Effect of prolongation of expiratory time on dynamic hyperinflation in mechanically ventilated patients with severe asthma. *Crit Care Med*. 2004;32(7):1542–1545.
123. Bellomo R, McLaughlan P, Tai E, et al. Asthma requiring mechanical ventilation. A low morbidity approach. *Chest*. 1994;105:891–896.
124. Rosengarten P, Tuxen D, Dziukas L, et al. Circulatory arrest induced by intermittent positive pressure ventilation in a patient with severe asthma. *Anaesth Intensive Care*. 1990;19:118–121.
125. Kollef M. Lung hyperinflation caused by innappropriate ventilation resulting in electromechanical dissociation: a case report. *Heart Lung*. 1992;21:74–77.
126. Mabuchi N, Takasu H, Ito S, et al. Successful extracorporeal lung assist (ECLA) for a patient with severe asthma and cardiac arrest. *Clin Intensive Care*. 1991;2:292–294.
127. Gluck E, Onorato D, Castriotta R. Helium-oxygen mixtures in intubated patients with status asthmaticus and respiratory acidosis. *Chest*. 1990;98:693–698.
128. King D, Smales C, Arnold A, et al. Extracorporeal membrane oxygenation as emergency treatment for life threatening acute severe asthma. *Postgrad Med J*. 1986;62:555–557.
129. Mikkelsen ME, Pugh ME, Hansen-Flaschen JH, et al. Emergency extracorporeal life support for asphyxic status asthmaticus. *Respir Care*. 2007;52(11):1525–1529.
130. Tajimi K, Kasai T, Nakatani T, et al. Extracorporeal lung assist (ECLA) for a patient with hypercapnia due to status asthmaticus. *Intensive Care Med*. 1988;14:588–589.
131. Anzueto A, Frutos-Vivar F, et al. Incidence, risk factors and outcome of barotrauma in mechanically ventilated patients. *Intensive Care Med*. 2004;30(4):612–619.
132. Behbehani NA, Al-Mane F, D'Yachkova Y, et al. Myopathy following mechanical ventilation for acute severe asthma: the role of muscle relaxants and corticosteroids. *Chest*. 1999;115(6): 1627–1631.
133. Leatherman J, Fluegel W, David W, et al. Muscle weakness in mechanically ventilated patients with severe asthma. *Am J Respir Crit Care Med*. 1996;153:1686–1690.
134. Kesler SM, Sprenkle MD, David WS, et al. Severe weakness complicating status asthmaticus despite minimal duration of neuromuscular paralysis. *Intensive Care Med*. 2009;35(1):157–160.
135. McFadden ER Jr, Warren EL. Observations on asthma mortality. *Ann Intern Med*. 1997;127(2): 142–147.

36

Pneumonia

Kai Man Chan, Charles David Gomersall

The management of pneumonia is based on four findings and premises:

- Pneumonia is associated with a wide range of largely non-specific clinical features.
- Pneumonia can be caused by over 100 organisms.
- The relationship between specific clinical features and aetiological organism is insufficiently strong to allow a clinical diagnosis of the causative organism.[1,2]
- Early administration of appropriate antibiotics is important.[1,3]

The net result is that the differential diagnosis is wide and treatment should be started before the aetiological agent is known. The differential diagnosis and the likely causative organisms can be narrowed by using epidemiological clues, the most important of which are whether the pneumonia is community acquired or hospital acquired, and whether the patient is immunocompromised. Note that the flora and antibiotic resistance patterns vary between countries, hospitals and even intensive care units (ICU) and this must be taken into account.

COMMUNITY-ACQUIRED PNEUMONIA

Evidence-based guidelines have been issued by the UK National Institute for Health and Care Excellence (NICE, www.nice.org.uk/guidance/cg191) and the British Thoracic Society.[3] A summary of overlap and differences between the guideline is given at https://www.brit-thoracic.org.uk/document-library/clinical-information/pneumonia/adult-pneumonia/annotated-bts-cap-guideline-summary-of-recommendations/.

DEFINITION

An acute infection of the pulmonary parenchyma associated with at least some symptoms of acute infection, accompanied by an acute infiltrate on a chest X-ray (CXR) or auscultatory findings consistent with pneumonia (e.g. altered breath sounds, localised crackles) in a patient not hospitalised prior to the onset of symptoms.

The overall incidence is 3–40 per 1000 inhabitants per year with 40%–60% requiring hospital admission. Overall, 10% of patients are admitted to ICU. The overall mortality of hospitalised patient is approximately 10%.[4]

AETIOLOGY

Table 36.1 gives possible aetiological agents based on epidemiological clues. *Streptococcus pneumoniae* is the most commonly isolated organism. The next most common bacterial pathogens in patients admitted to ICU are: *Legionella* spp., *Haemophilus influenzae,* Enterobacteriaceae spp., *Staphylococcus aureus* and *Pseudomonas* spp.[8]

CLINICAL PRESENTATION

Pneumonia produces both systemic and respiratory manifestations. Common clinical findings include fever, sweats, rigors, cough, sputum production, pleuritic chest pain, dyspnoea, tachypnoea, pleural rub and inspiratory crackles. Classic signs of consolidation occur in less than 25% of cases. Multiorgan dysfunction or failure may occur depending on the type and severity of pneumonia.

The diagnosis of pneumonia may be more difficult in the elderly. Although the vast majority of elderly patients with pneumonia have respiratory symptoms and signs, over 50% may also have non-respiratory symptoms and over one-third may have no systemic signs of infection.

INVESTIGATIONS[4,5]

Investigations should not delay the administration of antibiotics, as a delay is associated with an increase in mortality.[1] Important investigations include:

1. Imaging: CXR usually shows infiltrates but may be normal in 25%–30% of patients with pneumonia. Lung ultrasound appears to be similarly or more sensitive,[9,10] but computed tomography (CT) is the most sensitive.
2. Arterial blood gases or oximetry.

ABSTRACT

Pneumonia should be treated urgently, prior to the identification of the causative organism. The choice of antimicrobial is therefore empirical initially, and is based on epidemiological clues, the most important of which are whether pneumonia is community or hospital acquired and whether the patient is immunocompromised. Recent changes in the management of chest infections include: the increasing recognition that invasive pulmonary aspergillosis may occur in critically ill patients without overt severe immunocompromise, decreased emphasis on routine use of invasive sampling of respiratory specimens, shorter duration of antibiotic therapy, procalcitonin-guided duration of antibiotic therapy and the use of a polymerase chain reaction to identify causative organisms.

KEYWORDS

Pneumonia
empyema
pleural effusion
antibiotics
bacterial infection
fungal infection
viral infection
immunocompromise
tuberculosis

Table 36.1 Possible aetiological agents based on epidemiological clues

EXPOSURE TO ANIMALS	
Handling turkeys, chickens, ducks or psittacine birds or their excreta	*Chlamydia psittaci*
Exposure to birds in countries in which avian flu has been identified in birds	Influenza A H5N1, H7N9, H5N6
Handling infected parturient cats, cattle, goats or sheep or their hides	*Coxiella burneti*
Handling infected wool	*Bacillus anthracis*
Handling infected cattle, pigs, goats or sheep or their milk	*Brucella* spp.
Insect bite. Transmission from rodents and wild animals (e.g. rabbits) to laboratory workers, farmers and hunters	*Francisella tularensis*
Insect bites or scratches. Transmission from infected rodents or cats to laboratory workers and hunters	*Yersinia pestis*
Contact with infected horses (very rare)	*Pseudomonas mallei*
Exposure to mice or mice droppings	Hantavirus
GEOGRAPHICAL FACTORS	
Immigration from or residence in countries with high prevalence of TB	*M. tuberculosis*
N. America. Contact with infected bats or birds or their excreta. Excavation in endemic areas	*Histoplasma capsulatum*
Southwest United States	*Coccidiodes* spp., *Hantavirus*
United States. Inhalation of spores from soil	*Blastomyces dermatitidis*
Middle East or contact with confirmed Middle East respiratory syndrome (MERS) case or exposure to camels	*MERS coronavirus*
Asia, Pacific, Caribbean, N. Australia. Contact with local animals or contaminated skin abrasions	*Burkholderia pseudomallei*
HOST FACTORS	
Diabetic ketoacidosis	*Strep. pneumoniae, S. aureus*
Alcoholism	*Strep. pneumoniae, S. aureus, Klebsiella pneumoniae,* oral anaerobes, *M. tuberculosis, Acinetobacter* spp.
Chronic obstructive pulmonary disease or smoking	*Strep. pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella* spp., *Pseudomonas aeruginosa*
Sickle cell disease	*Strep. pneumoniae*
Pneumonia complicating whooping cough	*Bordatella pertussis*
Pneumonia complicating influenza	*Strep. pneumoniae, S. aureus, CA-MRSA*
Pneumonia severe enough to necessitate artificial ventilation	*Strep. pneumoniae, Legionella* spp. *S. aureus, Haemophilus influenzae, Mycoplasma pneumoniae,* enteric gram-negative bacilli, *Chlamydia pneumoniae, Mycobacterium tuberculosis,* viral infection, endemic fungi
Nursing home residency	Treat as healthcare associated pneumonia
Poor dental hygiene	Anaerobes
Suspected large volume aspiration	Oral anaerobes, Gram-negative enteric bacteria
Structural disease of lung (e.g. bronchiectasis, cystic fibrosis)	*Pseudomonas aeruginosa, Burkholderia cepacia, S. aureus*

Table 36.1 Possible aetiological agents based on epidemiological clues—cont'd

Lung abscess	Community acquired methicillin resistant *S. aureus*, oral anaerobes, endemic fungi, *M. tuberculosis*, atypical mycobacteria
Endobronchial obstruction	Anaerobes, *Strep. pneumoniae, H. influenzae, S. aureus*
Intravenous drug addict	*S. aureus, CA-MRSA,* anaerobes, *M. tuberculosis, Strep. pneumoniae*
End-stage renal failure	*CA-MRSA*
OTHERS	
Epidemic	*Mycoplasma pneumoniae,* influenza virus (H1N1, H3N2, influenza B), parainfluenza
Air-conditioning cooling towers, hot tubs or hotel or cruise ship stay in previous 2 weeks	*Legionella pneumophilia*
Presentation of a cluster of cases over a very short period of time	Bioterrorist agents: *Bacillus anthracis, Franciscella tularensis, Yersinia pestis*

See references 1, 5–7.

3. Full blood count.
4. Serum creatinine, urea and electrolytes.
5. Liver function tests.
6. Blood cultures (×2) prior to the administration of antimicrobials.
7. Sputum (if immediately available) for urgent Gram stain and culture. The usefulness of sputum tests remains debatable because of contamination by upper respiratory tract commensals. However, a single or predominant organism on a Gram stain of a fresh sample or a heavy growth on culture of purulent sputum is likely to be the organism responsible. The finding of many polymorphonuclear cells (PMN) with no bacteria in a patient who has not already received antibiotics can reliably exclude infection by most ordinary bacterial pathogens.

   Specimens should be obtained by deep cough and be grossly purulent. Ideally, the specimen should be obtained before treatment with antimicrobials – if this does not delay administration of antibiotics – and be transported to the laboratory immediately for prompt processing to minimise the chance of missing fastidious organisms (e.g. *Strep. pneumoniae*). Acceptable specimens (in patients with normal or raised white blood cell [WBC] counts) should contain less than 25 PMN per low power field (LPF) and less than 10–25 squamous epithelial cells (SEC)/LPF or less than 10 PMN per SEC. These criteria should not be used for *Mycobacteria* and *Legionella* infection.

   Certain organisms are virtually always pathogens when recovered from respiratory secretions (Table 36.2).

   Patients with risk factors for tuberculosis (TB) (see Table 36.6), particularly those with cough for more than 1 month, other common symptoms of TB and suggestive radiographic changes should have sputum examined for *M. tuberculosis*.

   Sputum cannot be processed for culture for anaerobes due to contamination by the endogenous anaerobic flora of the upper respiratory tract. In addition to the factors listed in Table 36.1, foul smelling sputum, lung abscess and empyema should raise suspicion of anaerobic infection.
8. Aspiration of pleural fluid for Gram stain, culture, protein, lactate dehydrogenase (LDH), pH and leukocyte count – all patients with a pleural effusion less than 1 cm thick on a lateral decubitus CXR or less than 2–2.5 cm on CT.
9. Urinary *Legionella* antigen. This test is specific (>95%). In patients with severe Legionnaires disease sensitivity is 88%–100% for *L. pneumophilia* serogroup 1 (the most commonly reported cause of legionella infection). A positive result is virtually diagnostic of *Legionella* infection, but a negative result does not exclude it. In areas where other

Table 36.2 Organisms that are virtually always pathogens when recovered from respiratory secretions

Legionella
Chlamydia
Tuberculosis
Influenza, para-influenza virus, respiratory syncytial virus, adenovirus, hantavirus, SARS coronavirus
Stronglyloides stercoralis
Toxoplasma gondi
Histoplasma capsulatum
Coccidiodes immitis
Blastomycoses dermatitidis
Cryptococcus neoformans

Legionella species are more common (e.g. South Australia), this test is less helpful.

10. Urinary pneumococcal antigen has moderate sensitivity (50%–80%) and high specificity (>90%).
11. Polymerase chain reaction (PCR) for *Mycoplasma pneumoniae* and *Chlamydophilia*. PCR assays are more sensitive than culture for *Mycoplasma* and *Chlamydophilia* species and at least as sensitive for *Legionella*.[9] PCR assays also detect Legionella strains other than serogroup 1. The British Thoracic Society guidelines[3] recommend PCR of the lower respiratory tract sample or, if unavailable, a throat swab for the diagnosis of Mycoplasma pneumonia. PCR for *Chlamydophilia* should be performed when invasive respiratory samples are collected from patients with severe community-acquired pneumonia (CAP).
12. HIV serological status.

Other investigations should be considered in patients with risk factors for infection with unusual organisms. Bronchoalveolar lavage may be useful in immunocompromised patients, those who fail to respond to antibiotics or those in whom sputum samples cannot be obtained.[11]

Molecular diagnosis (e.g. PCR-based methods) has the advantages of a quick result (within 3 hours), enhanced sensitivity, independence of organism viability and hence previous antibiotics and the theoretical possibility for determining antimicrobial susceptibility.[9] For example, PCR for pneumococcus is positive in 62% of blood samples from adult patients with confirmed or probable pneumococcal pneumonia,[11] while blood cultures are positive in only 37%. It is most useful when performed on specimens from a normally sterile site. In respiratory specimens, PCR testing may increase the sensitivity of detection, but false positive results from upper respiratory tract contamination and lower respiratory tract colonisation may occur.

MANAGEMENT

GENERAL SUPPORTIVE MEASURES

A general approach should be made to organ support with an emphasis on correcting hypoxia. The use of nasal high-flow oxygen was associated with a lower 90-day mortality (compared to patients treated with non-invasive ventilation) in a randomised controlled trial of patients with acute respiratory failure, of whom 80% had pneumonia.[12] However, there was no difference in the primary outcome (need for intubation) and these data should be considered hypothesis-generating only.

ANTIMICROBIAL REGIMES

Increased mortality among those who do not receive empiric antibiotics that cover the infecting pathogen(s) is well documented.[13] Each unit should have its own regimens tailored to the local flora and antibiotic resistance patterns. In the absence of such regimens, the regimen outlined in Fig. 36.1 may be helpful. This should be modified in the light of risk factors

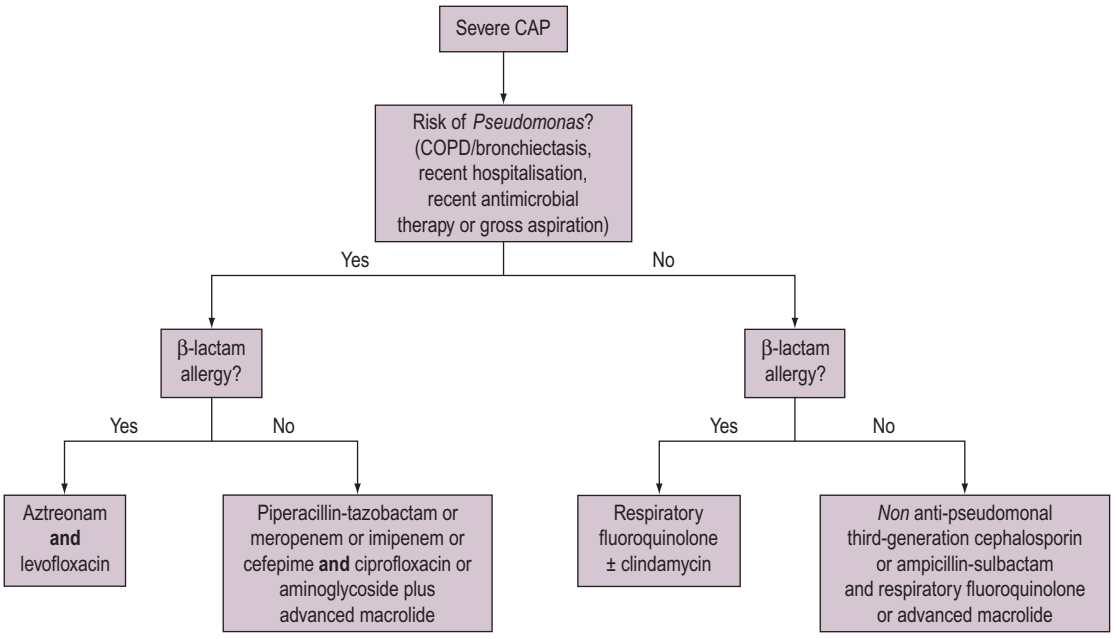


Figure 36.1 Antibiotic regimes for treatment of severe community acquired pneumonia (CAP) in critically ill patients.[5,8] Respiratory fluoroquinolones include moxifloxacin and levofloxacin. Advanced macrolides include azithromycin and clarithromycin. Non–anti-pseudomonal third-generation cephalosporins include cefotaxime and ceftriaxone. *COPD*, Chronic obstructive pulmonary disease.

(see Table 36.1). Quinolones may be less appropriate in areas with a high prevalence of TB as their use may mask concurrent TB infection. Patients infected with Panton-Valentine Leukocidin toxin-producing *S. aureus* (most community-acquired MRSA and some MSSA) may benefit from antimicrobials that also reduce toxin production (e.g. linezolid, rifampicin or clindamycin).[13] Antimicrobials should be administered to patients with sepsis within 1 hour of diagnosis.[14] There is controversy regarding the de-escalation of empiric therapy based on microbiological findings.[4,5] Changing to narrower spectrum antimicrobial cover may result in inadequate treatment of the 5%–38% of patients with polymicrobial infection. Increasing evidence demonstrates improved outcome with combination antimicrobial, including a macrolide, compared to monotherapy, particularly in severely ill patients with bacteraemic pneumococcal pneumonia.[15,16] The odds ratio of death was 1.5 to 6 for monotherapy compared to combination therapy.[4] A recent meta-analysis showed a trend towards an improved outcome when a beta-lactam was combined with a macrolide rather than a fluoroquinolone.[16] For the treatment of drug-resistant *Strep. pneumoniae* the regimes in Table 36.2 are probably suitable for isolates with a penicillin minimum inhibitory concentration (MIC) less than 4 mg/L.[5] If the MIC is ≥4 mg/L an antipneumococcal fluoroquinolone, vancomycin, teicoplanin or linezolid should be given.[4]

DURATION OF THERAPY

There are no clinical trials that have specifically addressed this issue. Courses as short as 5 days may be sufficient.[17] NICE guidelines recommend 7- to 10-day courses for patients with moderate or severe pneumonia. Short courses may be suboptimal for patients with bacteraemic *S. aureus* pneumonia, meningitis or endocarditis complicating pneumonia or infection with less common organisms (e.g. *Burkholderia pseudomallei* or fungi) or *Pseudomonas aeruginosa*. Procalcitonin may be useful to guide antibiotic therapy, allowing a reduction in antibiotic duration without an adverse effect on mortality in both CAP[18] and sepsis, and septic shock.[19]

CORTICOSTEROIDS

Limited data suggest that the administration of steroids (methylprednisolone 30 mg/day for 7 days) may decrease the risk of acute respiratory distress syndrome, reduce hospital and ICU stay and time to stability, but has no effect on mortality.[20] Routine use is not recommended by NICE.

RESPONSE TO THERAPY[5,6,21]

A response is usually seen within 1–3 days of starting therapy; this can be assessed on the basis of respiratory symptoms, fever, oxygenation, WBC count, bacteriology, CXR changes, C-reactive protein reduction and procalcitonin reduction. The average time to defervescence varies with organism, severity and patient age (7 days in elderly patients, 2.5 days in young patients with pneumococcal pneumonia, 6–7 days in bacteraemic patients with pneumococcal pneumonia, 1–2 days in patients with *M. pneumoniae* pneumonia and 5 days in patients with *Legionella* pneumonia). Both blood and sputum cultures are usually negative within 24–48 hours of treatment, although *P. aeruginosa* and *M. pneumoniae* may persist in the sputum despite effective therapy. CXR changes lag behind clinical changes with the speed of change depending on the organism, the severity of illness, the age of the patient and the presence of co-morbid illnesses. The CXRs of most young or middle-aged patients with bacteraemic pneumococcal pneumonia are clear by 4 weeks but resolution is slower in elderly patients and patients with underlying illness, extensive pneumonia on presentation or *Legionella pneumophilia* pneumonia.

If the patient fails to respond, consider the following questions:

- Has the patient got pneumonia?
- Are there host factors which explain the failure (e.g. obstruction of bronchus by a foreign body or tumour, inadequate host response)?
- Has a complication developed (e.g. empyema, superinfection, bronchiolitis obliterans organising pneumonia, metastatic abscess)?
- Is the right drug being given in an adequate dose by the right route?
- Is the organism resistant to the drug being given?
- Are there other organisms?
- Is the fever a drug fever?

Useful investigations include CT of the chest, thoracocentesis, bronchoalveolar lavage (Table 36.3) and transbronchial or open lung biopsy.

PREDICTION OF ADVERSE OUTCOME AND ADMISSION TO INTENSIVE CARE UNIT

The CURB65 score can be used to risk-stratify patients. Patients with three or more of the following features have a greater than 15% mortality risk: new confusion or abbreviated mental test score ≤8; urea greater than 7 mmol/L (blood urea nitrogen >19.6 mg/dL); low blood pressure, diastolic ≤60 mm Hg or systolic ≤90 mm Hg; age ≥65 years.

Viral pneumonia

Viral infection is common in patients with CAP. Estimates suggest that it occurs in approximately 25% of patients hospitalised with pneumonia. The most commonly identified viruses are influenza, rhinovirus and respiratory syncytial virus (RSV). Although viral and bacterial pneumonia have a similar short-term mortality, dual infection with both bacteria and virus is associated with a higher mortality (odds ratio 2:1).[22] The diagnosis is based on reverse transcriptase PCR of nasal or lower respiratory tract aspirates.

Table 36.3 Procedure for obtaining microbiological samples using bronchoscopy and protected specimen brushing and/or bronchoalveolar lavage

Infection control	In patients suspected of having a disease which is transmitted by the airborne route (e.g. tuberculosis): • the risk of transmission should be carefully weighed against the benefits of bronchoscopy, which may generate large numbers of airborne particles. • perform bronchoscopy in a negative-pressure isolation room • consider the use of a muscle relaxant in ventilated patients, to prevent coughing • staff should wear personal protective equipment which should include a fit-tested negative-pressure respirator (N95, FFP2 or above) as a minimum. Use of a powered air-purifying respirator should be considered
General recommendations	Suction through the endotracheal tube should be performed before bronchoscopy Avoid suction or injection through the working channel of the bronchoscope Perform protected specimen brushing before bronchoalveolar lavage
Ventilated patients	Set Fio_2 at 1.0 Set peak pressure alarm at a level that allows adequate ventilation Titrate ventilator settings against exhaled tidal volume Consider neuromuscular blockade in addition to sedation in patients at high risk of complications who are undergoing prolonged bronchoscopy
Protected specimen brushing (PSB)	Sample the consolidated segment of lung at subsegmental level If purulent secretions are not seen advance the brush until it can no longer be seen but avoid wedging it in a peripheral position Move brush back and forth and rotate it several times
Bronchoalveolar lavage (BAL)	Wedge tip of bronchoscope into a subsegment of the consolidated segment of lung Inject, aspirate and collect 20 mL of sterile isotonic saline. Do not use this sample for quantitative microbiology or identification of intracellular organisms. It can be used for other microbiological analysis Inject, aspirate and collect additional aliquots of 20–60 mL The total volume of saline injected should be 60–200 mL
Complications	Hypoxaemia (possibly less with smaller BAL volumes) Arrhythmia Transient worsening in pulmonary infiltrates Bleeding (particularly following PSB) Fever (more common after BAL)
Positive results	>5% of cells in cytocentrifuge preparations of BAL fluid contain intracellular bacteria OR $\geq 10^3$ colony forming units/mL in PSB specimen OR $\geq 10^4$ colony forming units/mL in BAL fluid

Meduri GU, Chastre J. The standardization of bronchoscopic techniques for ventilator-associated pneumonia. *Chest*. 1992;102(5 S1):557S–564S.

Influenza pneumonia is typically preceded by a prodrome of fever, chills, sore throat, myalgia and non-productive cough. CXR usually shows bilateral infiltrates. Multiorgan failure may occur, but the pattern of organ failure appears to vary between strains. A complicated course is more common in the elderly and very young, and those with chronic medical conditions.[23] Oseltamivir is recommended for critically ill patients although there is no direct evidence of outcome benefit. Glucocorticoids do not appear to be useful[21] and may prolong viral replication. Bacterial superinfection should be considered, with Gram-positive cocci being most frequently isolated.[22] Droplet and contact precautions should be followed routinely. Airborne precautions are recommended where aerosol-generating procedures are frequent.

Rhinovirus infection is difficult to distinguish from influenza, although a cough may be less common, and septic shock is a less common presentation to the ICU. Patients with severe infection (requiring mechanical ventilation or with septic shock) are more likely to be immunocompromised than patients with influenza. Mortality in the two groups is similar (approximately 50% in one series).[24]

RSV tends to present with wheezes, crackles and a pneumonic infiltrate in adults, but it is difficult to distinguish it from other viral infections on clinical grounds. There is no established therapy. Ribavirin and palivizumab have been used in immunocompromised patients. The use of corticosteroids to treat wheezing is controversial. Droplet and contact precautions should be adopted.[23,25]

Hospital-acquired pneumonia and ventilator-associated pneumonia

Hospital-acquired pneumonia (HAP) is defined as pneumonia with an onset occurring after 48 hours of hospital admission.[26] It occurs in 0.5%–5% of hospitalised patients, with a higher incidence in certain groups (e.g. postoperative patients and patients in ICU). Diagnosis may be difficult as many non-infectious conditions (e.g. atelectasis, pulmonary embolus, aspiration, heart failure, pulmonary haemorrhage and cancer) can cause chest infiltrates. Identification of the organism responsible is even more difficult than in patients with community-acquired pneumonia due to the high incidence of oropharyngeal colonisation by Gram-negative bacteria. Blood cultures are only positive in about 6% of cases of HAP. Ventilator-associated pneumonia (VAP) is pneumonia arising after 48 hours of invasive mechanical ventilation. The reported incidence of VAP is 10%–20% for those who receive mechanical ventilation for more than 48 hours.[23] The previously used term 'healthcare-associated pneumonia' is now obsolete in the latest Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) hospital acquired pneumonia (HAP)/ventilator associated pneumonia (VAP) guidelines.[26]

PATHOGENESIS

HAP/VAP is thought to result from microaspiration of bacteria colonising the upper respiratory tract. Other routes of infection include macroaspiration of gastric contents, inhaled aerosols, haematogenous spread, spread from pleural space and direct inoculation from ICU personnel.

CLINICAL DIAGNOSIS

Diagnosis is based on the findings of new or progressive chest infiltrates plus either clinical features with simple laboratory investigations or the results of quantitative microbiology. In clinical terms, pneumonia is diagnosed by the finding of a new infiltrate or a change in an infiltrate on chest radiograph, and the growth of pathogenic organisms from sputum plus one of the following: WBC count greater than 12×10^5/L, core temperature ≥38.3°C or purulent sputum.

INVESTIGATIONS

These are broadly similar to those required in community-acquired pneumonia

- CXR: although studies using a histological diagnosis as the gold standard have demonstrated that pneumonia may be present despite a normal CXR, most definitions of HAP/VAP require the presence of new persistent infiltrates on a CXR.
- Respiratory secretions: considerable controversy surrounds the issue of whether invasive sampling of respiratory secretions is necessary, and whether quantitative culture improves diagnostic accuracy. Whether invasive (bronchoscopic BAL, protected specimen brushing or blind bronchial miniBAL, see Table 36.3) or non-invasive (tracheal aspirates) sampling is used, empiric broad-spectrum antibiotics should be started while results are awaited. The results of microbiological analysis of specimens are used to either stop antibiotics or narrow the spectrum.[26] Using histopathology as reference standard, tracheal aspirate using semi-quantitative culture has higher sensitivity but lower specificity compared to quantitative tracheal aspirate ($\geq 10^5$ colony-forming unit [CFU]/mL) or BAL ($\geq 10^4$ CFU/mL). Quantitative BAL and quantitative tracheal aspirate have similar sensitivity (approximately 50%) and specificity (approximately 80%). A meta-analysis of randomised trials shows that sampling sites and culture techniques do not affect clinical outcomes, such as the duration of mechanical ventilation, the ICU length of stay or mortality.[26] The latest IDSA/ATS guidelines[26] favour the use of non-invasive sampling with semi-quantitative culture for the diagnosis of VAP *(weak recommendation, low quality of evidence)*. While tracheal aspirates may predominantly reflect the organisms colonising the upper airway, they may be useful in indicating which organisms are not responsible for the pneumonia, thus allowing the antimicrobial cover to be narrowed.[26] This interpretation is based on the premise that the predominant route of infection is via the upper respiratory tract. From this it can be assumed that if the organism is not present in the upper respiratory tract, the probability of it being present in the lung parenchyma is low. Certain organisms are virtually always pathogens when recovered from respiratory secretions (see Table 36.2). Of note, the respiratory specimens should be processed within 2 hours if kept at room temperature and within 24 hours if kept at 4°C.
- Blood cultures: Blood cultures should be taken from all patients with HAP/VAP. Although only 8%–20% VAP patients are bacteraemic, bacteraemia is associated with a worse prognosis. Of note, at least 25% of positive blood cultures in patients with suspected VAP are from non-pulmonary source of sepsis, with important implications in antimicrobials treatment and source control.
- Newer techniques such as PCR/electrospray ionisation-mass spectrometry show promise as methods to provide rapid detection of microbiological pathogens in blood cultures and respiratory specimens.[27]

MANAGEMENT

Management is based on the finding that early treatment with antimicrobials that cover all likely pathogens results in a reduction in morbidity and mortality.[3]

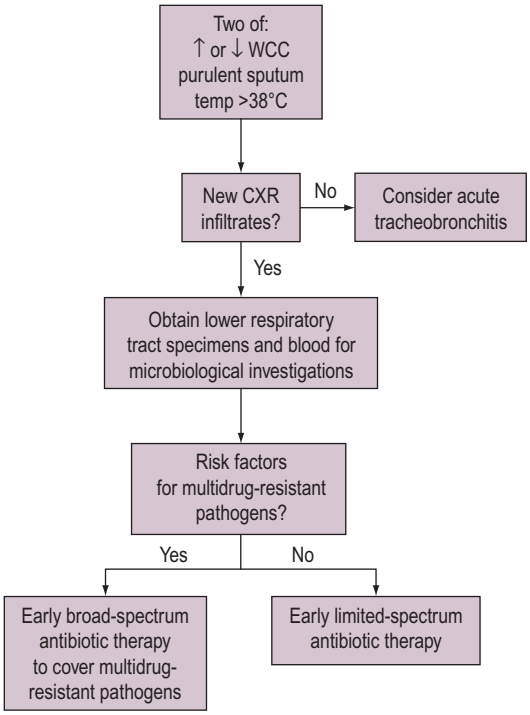


Figure 36.2 An outline of initial management of HAP/VAP based on a non-invasive clinical approach. *CXR*, Chest x-ray; *HAP*, hospital-acquired pneumonia; *VAP*, ventilator-associated pneumonia.

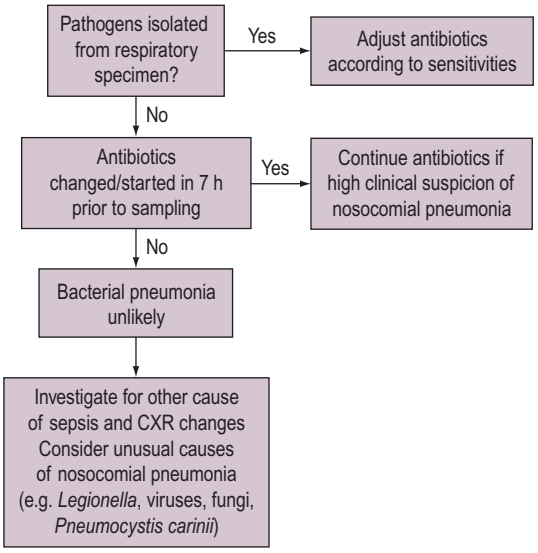


Figure 36.3 Subsequent management of nosocomial pneumonia based on a non-invasive clinical approach. *CSR*, Chest x-ray.

The initial selection of antimicrobials is based on risk factors for multidrug resistant (MDR) organisms and the local ICU/hospital antibiogram (Fig. 36.2, Table 36.4). *S. aureus*, *P. aeruginosa* and other Gram-negative bacilli should be covered in all empirical therapies *(strong recommendation, low-quality evidence)*. The results of microbiological investigations are used to narrow antimicrobial cover later. Treatment should be reassessed after 2–3 days or sooner if the patient deteriorates (Fig. 36.3).

DURATION OF THERAPY

Current IDSA/ATS guidelines[26] recommend 7 days rather than 8–15 days of antimicrobial treatment for both VAP and HAP *(strong recommendation, moderate-quality evidence)*. Systematic reviews confirmed no difference in important clinical outcomes such as mortality, length of stay and duration of mechanical ventilation. Short-course antibiotics increase 28-day antibiotic-free days and decrease recurrent VAP due to MDR organisms. There is concern in VAP caused by non-glucose fermenting Gram-negative bacilli (*Pseudomonas sp.* and *Acinetobacter sp.*) that 8-day therapies may have more recurrent infection when compared to 15-day therapies.[28] Although this finding is not universal, caution should be applied when considering short courses of antibiotics for non-glucose fermenting Gram-negative bacilli. Serial measurement of procalcitonin can be used to guide the duration of antibiotics,[19] but it is uncertain whether this can decrease antibiotic exposure in settings when a short-course of 7-day antibiotics is used.

RESPONSE TO THERAPY

Clinical improvement is usually not apparent for 48–72 hours and therapy should not be changed in this time. The CXR is of limited value for assessing response: initial deterioration is common and improvement often lags behind clinical response. However a rapidly deteriorating CXR pattern with a less than 50% increase in size of infiltrate in 48 hours, new cavitation or a significant new pleural effusion should raise concern. If a patient fails to respond, consider the diagnosis, host factors (e.g. immunosuppressed, debilitated), bacterial factors (e.g. virulent organism) and therapeutic factors (e.g. wrong drug, inadequate dose). Review the antibiotics and repeat cultures. It may be useful to broaden the antimicrobial cover while waiting for the results of investigations. Consider invasive sampling of respiratory secretions, CT or ultrasound of the chest (to look for an empyema or abscess), another source of infection, an open lung biopsy to establish diagnosis and aetiology, or the administration of steroids.

Mortality and morbidity attributable to ventilator-associated pneumonia

Substantial morbidity and mortality associated with VAP has previously been reported.[23] However, causal

Table 36.4 Recommended initial empiric treatment for nosocomial pneumonia

SITUATION	ANTIBIOTICS
No risk factors for multidrug-resistant pathogens	Piperacillin-tazobactam 4.5 g q6h *or* cefepime 2 g q8h *or* Levofloxacin 750 mg q24h *or* meropenam 1 g q8h, imipenam 500 mg q6h
Risk factors for multidrug-resistant organisms: • Prior intravenous antimicrobial therapy within 90 days • Hospitalisation for ≥5 days prior to onset of VAP • Septic shock at time of VAP • ARDS preceding VAP • Acute renal replacement therapy prior to VAP onset *or* • High frequency of antibiotic resistance in the local ICU/hospital antibiogram • >10%–20% *Staph aureus* isolates being resistant to methicillin • >10% of Gram-negative isolates being resistant to an agent considered for monotherapy) *or* Immunosuppression *or* Bronchiectasis *or* Cystic fibrosis	One of: Antipseudomonal cephalosporin (e.g. cefepime 2g q8h, ceftazidime 2g q8h) *or* Antipseudomonal carbapenem (e.g. meropenem 1 g q8h or imipenem-cilastin 500 mg q8h) *or* ß-lactam/ß-lactamase inhibitor (e.g. piperacillin-tazobactam 4.5g q6h, cefoperazone-sulbactam 2 g q8h) *or* Monobactam (aztreonam 2 g q8h) *PLUS* one of: Aminoglycoside 15–20 mg/kg q24h or Antipseudomonal quinolone (e.g. levofloxacin 750 mg q24h, ciprofloxacin 400 mg q8h) PLUS one of the following for patients at high risk of methicillin-resistant *Staphylococcus aureus* (MRSA) infection: Linezolid 600 mg q12h or vancomycin load 25–30 mg/kg, 15 mg/kg q12–8h

The use of dual therapy in susceptible Gram-negative isolates is not well supported by evidence but it does reduce the probability that the pathogen is resistant to the drugs being given. If an extended spectrum β lactamase-producing strain or an *Acinetobacter* spp. is suspected, a carbapenem should be given. If *Legionella pneumophilia* is suspected, use a quinolone. The risk factor for MDR HAP, MRSA HAP/VAP, MDR pseudomonas HAP/VAP was prior use of intravenous antibiotics within 90 days.

ARDS, Acute respiratory distress syndrome; *HAP*, hospital-associated pneumonia; *ICU*, intensive care unit; *MDR*, multidrug resistant; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *VAP*, ventilator-associated pneumonia.

American Thoracic Society and Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare associated pneumonia. *Am J Respir Crit Care Med*. 2005;171:388–416.

inference is difficult to be established. It should be noted that patients who developed VAP tended to be more severely ill and at a higher risk of death, not only at the time of ICU admission, but also throughout the course of their illness. While VAP is associated with a significantly longer ICU length of stay (mean of 6.1 days; 95% CI: 5.32–6.87), mechanical ventilation and increased health care cost,[23] recent studies suggest that mortality directly attributable to VAP is small.[25,26] While the attributable mortality for VAP was 4.4% on the 30th day of ICU and 5.9% on the 60th day, mortality directly due to the effect of VAP was found to be 1% and 1.5%, respectively, after controlling the evolution of severity of illness.[26] In another meta-analysis using pooled individual patients' data from 24 randomised controlled trials of VAP prevention, the attributable mortality of VAP was 13%. After using competing analysis, the increased risk of dying in ICU was concluded to be merely due to the results of prolonging ICU length of stay rather than a direct effect on VAP on mortality.[29]

PREVENTION

Several guidelines for prevention of VAP and HAP have been published, but these vary in the advice given. A consensus summary, based on literature review followed by a Delphi approach, is given in Table 36.5.[30]

TUBERCULOSIS

The main risk factors are listed in Table 36.6. Typical clinical features include fever, sweating, weight loss, lassitude, anorexia, cough productive of mucoid or purulent sputum, haemoptysis, chest wall pain, dyspnoea, localised wheeze and apical crackles. Patients

Table 36.5 Consensus strategies for prevention of ventilator-associated pneumonia

Positioning	Nurse in semirecumbent position (≥30 degrees)
Minimise duration of invasive mechanical ventilation	Assess daily for readiness to wean using spontaneous awakening trials and spontaneous breathing trials Facilitate use of non-invasive ventilation
Suctioning	Use subglottic suctioning in patients expected to be intubated for >72 h Use closed endotracheal suctioning and change catheters only as needed. Use standard precautions while suctioning respiratory tract secretions Avoid non-essential tracheal suctioning
Ventilator circuit	Change ventilator circuits only when damaged or soiled. Remove condensate from circuits, keeping circuit closed during removal and making sure condensate does not drain towards patient Change heat and moisture exchangers every 5–7 days or if clinically indicated
General care	Oral care at least 6 times per day, with chlorhexidine at least twice per day Use an early mobilisation protocol Avoid gastric overdistension
General infection control measures	Perform hand hygiene Avoid use of prophylactic systemic antimicrobials

Table 36.6 Risk factors for pulmonary tuberculosis

Living in or originating from a developing country
Age (<5 yrs, middle-aged and elderly men)
Alcoholism and/or drug addiction
HIV infection
Diabetes mellitus
Lodging house dwellers
Immunosuppression
Close contact with smear positive patients
Silicosis
Poverty and/or malnutrition
Previous gastrectomy
Smoking

may also present with unresolved pneumonia, pleural effusions, spontaneous pneumothorax and hoarseness, or with enlarged cervical nodes or other manifestations of extrapulmonary disease. In the most recent (retrospective) study, the in-hospital mortality for all patients with TB requiring ICU admission was 25.9%, but in those requiring mechanical ventilation it rose to 50%.[31] The presentation and management of TB in HIV-positive patients is different (see later).

INVESTIGATION OF PULMONARY TUBERCULOSIS[32]

IDENTIFICATION OF MYCOBACTERIA

Multiple[33,34] sputum samples should be collected, preferably on different days, for fluorescent microscopy for acid-fast bacilli (AFB) and culture. If sputum is not available, bronchial washings taken at bronchoscopy and gastric lavage or aspirate samples should be obtained. Gastric aspirates need to be neutralised immediately on collection. Bronchoscopy and transbronchial biopsy may be useful in patients with suspected TB but who have a negative sputum smear. Pleural biopsy is often helpful and mediastinoscopy is occasionally needed in patients with mediastinal lymphadenopathy. Part of any biopsy specimen should always be sent for culture. The Xpert MTB/RIF gene probe system is able to simultaneously identify the presence of *M. tuberculosis* and rifampicin resistance. As rifampicin is strongly associated with isoniazid resistance, the system can give a strong indication of multidrug resistance. In sputum samples, the system has a sensitivity of approximately 90% (compared to 65% for a single AFB smear) with a specificity of 99%. Sensitivity (67%) is lower in smear-negative patients and patients with HIV (approximately 80%).[33]

CHEST X-RAY

A normal CXR almost excludes TB (except in HIV infected patients) but endobronchial lesions may not be apparent, and early apical lesions can be missed. Common appearances include patchy/nodular shadowing in the upper zones (often bilateral), cavitation, calcification, hilar or mediastinal lymphadenopathy (may cause segmental or lobar collapse), pleural effusion, tuberculomas (dense round or oval shadows) and diffuse fine nodular shadowing throughout the lung fields in miliary TB. Inactivity of disease cannot be inferred from the CXR alone. This requires three negative sputum samples *and* failure of any lesion seen on CXR to progress. CXR appearances in HIV-positive patients with TB differ from non–HIV-infected patients.

TREATMENT OF PULMONARY TUBERCULOSIS[34,35]

The decision to initiate anti-TB treatment should be based on the level of clinical suspicion, the results of the AFB smear or the gene probe, and sometimes mycobacterial culture. If the initial clinical suspicion is strong and the patient is seriously ill attributable to possible TB, treatment should be initiated promptly, sometimes before the result of the AFB smear. Subsequent positivity of the AFB smear or the gene probe provides support for the continuation of treatment. Combination chemotherapy consisting of four drugs is necessary for maximal efficacy. Treatment is divided into the initial phase and the continuation phase. The most commonly used initial regimen consists of 8 weeks of rifampicin 600 mg daily (450 mg for patients <50 kg), isoniazid 300 mg daily, pyrazinamide 2 g daily (1.5 g for patients <50 kg) and ethambutol 15 mg/kg daily as an initial phase treatment. Ethambutol should only be used in patients who have reasonable visual acuity and who are able to appreciate and report visual disturbances. This excludes patients who require sedation. Visual acuity and colour perception must be assessed (if ethambutol is to be used) and liver and renal function checked before treatment is started. Steroids are recommended for children with endobronchial disease and, possibly, for patients with TB pleural effusions. Pyridoxine 10 mg daily should be given to prevent isoniazid-induced neuropathy to those at increased risk (e.g. patients with diabetes mellitus, chronic renal failure or malnutrition, or alcoholic or HIV-positive patients). A negative AFB smear should not delay initial treatment if clinical suspicion remains high. Supporting features included chronic cough, weight loss, characteristic CXR findings, emigration from a high incidence country, no other immediate diagnosis and a positive tuberculin test.

INFECTION CONTROL

Patients admitted to an ICU with infectious TB or suspected of having active pulmonary TB should be managed in an isolation room with special ventilation characteristics, including negative pressure. Patients should be considered infectious if they are coughing or undergoing cough-inducing procedures, or if they have positive AFB smears and they are not on or have just started chemotherapy, or have a poor clinical or bacteriological response to chemotherapy.[35,36] Patients with non–drug-resistant TB should be non-infectious after 2 weeks of treatment that includes rifampicin and isoniazid.[35] As TB is spread through aerosols it is probably appropriate to isolate patients who are intubated, even if only their bronchial washings are smear positive. Staff caring for patients for patients who are smear positive should wear personal protective equipment including a fit-tested negative-pressure respirator (N95, FFP2 or higher). The use of a powered air-purifying respirator should be considered when bronchoscopy is being performed, particularly if the patient has not received effective treatment, is smear positive and if the bronchoscopy is being carried out in a room with less than 12 air changes per hour.[36]

PNEUMONIA IN THE IMMUNOCOMPROMISED

The lungs are amongst the most frequent target organs for infectious complications in the immunocompromised. The incidence of pneumonia is highest amongst patients with haematological malignancies, bone marrow transplant (BMT) recipients and patients with AIDS.

The speed of progression of pneumonia, the CXR changes (Table 36.7) and the type of immune defect provide clues to the aetiology. Bacterial pneumonias progress rapidly (1–2 days), while fungal and protozoal pneumonias are less fulminant (several days to a week or more). Viral pneumonias are usually not fulminant, but on occasion they may develop quite rapidly. Bronchoscopy is a major component of the investigation of these patients. Empiric management based on CXR appearances is outlined in Table 36.6. There is some evidence that early non-invasive ventilation may reduce the need for intubation amongst immunocompromised patients with fever and bilateral infiltrates,[37] but it did not reduce the need for intubation nor the mortality in patients with haematological malignancy or solid-organ transplants.[38]

PNEUMOCYSTIS JIROVECI PNEUMONIA[39]

Most cases occur in patients with HIV who are not receiving HIV care or who have advanced immunosuppression, or in patients with other causes of immunosuppression (e.g. haematological malignancy). The onset is usually insidious with dry cough, dyspnoea and fever on a background of fatigue and weight loss. Crackles in the chest are rare. A rise in LDH is common but non-specific. Approximately 15% of patients have a concurrent cause for respiratory failure (e.g. Kaposi sarcoma, TB, bacterial pneumonia). Useful investigations are:

1. CXR: classical appearance is diffuse bilateral perihilar interstitial shadowing, but in the early stages this is very subtle and easily missed. The initial CXR is normal in 10%. In a further 10% the changes are atypical with focal consolidation or coarse patchy shadowing. None of the changes are specific for pneumocystis jiroveci pneumonia (PCP) and may be seen in other lung diseases associated with AIDS. Pleural effusions, hilar or mediastinal lymphadenopathy are unusual in PCP, but are common in mycobacterial infection, Kaposi's sarcoma or lymphoma.

Table 36.7 Causes of CXR changes and empiric treatment of pneumonia in the immunocompromised

CHEST X-RAY APPEARANCE	CAUSES	EMPIRIC TREATMENT FOR SUSPECTED PNEUMONIA
Diffuse infiltrate	Cytomegalovirus (CMV) and other herpes viruses Pneumocystis carinii Bacteria Aspergillus (advanced) Cryptococcus (uncommon) Non-infectious causes (e.g. drug reaction, non-specific interstitial pneumonitis, radiation pneumonitis [uncommon], malignancy, leucoagglutinin reaction, heart failure secondary to cardiotoxic chemotherapy)	Broad-spectrum antibiotics for at least 48 h (e.g. third-generation cephalosporin and aminoglycoside). Cotrimoxazole. Lung biopsy or lavage within 48 h or full 2-week course of cotrimoxazole (depends on patient tolerance of invasive procedure)
Focal infiltrate	Gram-negative rods Staph aureus Aspergillus Cryptococcus Nocardia Mucor Pneumocystis carinii (uncommon) Tuberculosis Legionella Non-infectious causes (e.g. malignancy, nonspecific interstitial pneumonitis, radiation pneumonitis)	Broad-spectrum antibiotics. If response seen continue treatment for 2 weeks If disease progresses lung biopsy/aspirate within 48–72 h or empiric trial of anti-fungal ± macrolide

2. Induced sputum. In this technique the patient inhales nebulised hypertonic saline from an ultrasonic nebuliser. This provokes bronchorrhoea and the patient coughs up material containing cysts and trophozoites. This is time consuming and requires meticulous technique, and is less sensitive than bronchoscopy but less invasive. The possibility of concurrent TB should be considered and steps taken to minimise the risk of spread of infection.
3. Bronchoscopy with bronchoalveolar lavage leads to the diagnosis in over 90% of cases. Specimens should be sent for cytology. PCR is a sensitive method of detecting PCP but may not be able to distinguish colonisation from infection. The role of PCR in diagnosing PCP is mainly limited to non-HIV patients, in whom conventional microscopy and staining of induced sputum and BAL has a lower sensitivity than in HIV patients.[12]

Anti-pneumocystis treatment should be started as soon as the diagnosis is suspected. Treatment should not be delayed to obtain specimens as organisms persist in specimens for days to weeks after effective treatment is initiated. The treatment of choice is trimethoprim plus sulphamethoxazole (co-trimoxazole) 20 mg/kg per day + 100 mg/kg per day for 3 weeks. In patients with HIV infection, give adjunctive steroids as soon as possible and within 72 hours: prednisolone 40 mg orally twice daily for 5 days followed by 20 mg twice daily for 5 days and then 20 mg/day until the end of PCP treatment. Side effects of cotrimoxazole are common (nausea, vomiting, skin rash, myelotoxicity, nephrotoxicity, hepatotoxicity). The dose should be reduced by 25% if the WBC count falls. Patients who are intolerant of cotrimoxazole should be treated with:

- Pentamidine 4 mg/kg per day intravenously or
- Primaquine with clindamycin

Response to treatment is usually excellent, with a response time of 4–7 days. If the patient deteriorates or fails to improve by 8 days of treatment: consider (re-) bronchoscopy (is the diagnosis correct?), treat co-pathogens and consider a short course of high-dose intravenous methylprednisolone and/or diuretics (patients often fluid overloaded). Approximately 70% of patients with HIV-related PCP, but only 40% of patients with non–HIV-related PCP, who require mechanical ventilation survive to hospital discharge.[40]

Antiretroviral therapy should be initiated, when possible, in patients who are not already receiving it and who present with HIV-related PCP, within 2 weeks of the diagnosis of PCP. Although this may precipitate paradoxical immune reconstitution inflammatory syndrome, the syndrome is rarely life threatening and early antiretroviral therapy is associated with better outcomes (Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents).

For more detailed advice on management of patients with HIV-associated PCP go to https://aidsinfo.nih.gov/guidelines.

BACTERIAL PNEUMONIA[41]

This is the most common cause of acute respiratory failure in HIV-positive patients. Bacterial pneumonia is more common in HIV-infected patients than in the general population and tends to be more severe. *Strep. pneumoniae, H. influenza, Pseudomonas aeruginosa* and *S. aureus* are the most common organisms. *Nocardia* and Gram negatives should also be considered. Atypical pathogens (e.g. *Legionella*) are rare. The response to appropriate antibiotics is usually good but may require protracted courses of antibiotics because of the high tendency to relapse. Patients with severe immunodeficiency ($CD4^+$ T lymphocyte count <100/μL) and a history of *Pseudomonas* infection or bronchiectasis or neutropenia should receive antibiotics that cover *P. aeruginosa* as well as other Gram negatives. The possibility of concurrent PCP or TB should be excluded.

TUBERCULOSIS

TB may be the initial presentation of AIDS, particularly in sub-Saharan Africa. The pattern of TB in HIV patients depends on the degree of immunosuppression. In patients with $CD4^+$ T lymphocytes greater than 200 cells/μL the clinical presentation is similar to TB in non–HIV-infected patients although extrapulmonary disease is more common. In patients with $CD4^+$ T lymphocytes less than 200 cells/μL, extrapulmonary disease (pleuritis, pericarditis, meningitis) is common. Severely immunocompromised patients ($CD4^+$ T lymphocytes <100 cells/μL) may present with severe systemic disease with high fever and rapid progression sepsis. In these patients, lower and middle lobe disease is more common; miliary disease is common; and cavitation is less common. Sputum smears and culture may be positive even with a normal CXR.

Response to treatment is usually rapid. Initial treatment should be the same as non–HIV-infected patients, except in those receiving antiretrovirals. Management of TB in in these patients is complex due to numerous drug interactions, and consultation with an expert in treatment HIV-related TB should be strongly considered. The National Institutes of Health guidelines for doses of first-line drugs are given at https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/356/tb-drug-dosing.

CYTOMEGALOVIRUS (CMV) PNEUMONITIS[42,43]

The risk of infection is highest following haematological stem cell transplantation, followed by lung transplantation, pancreas transplantation and then liver, heart and renal transplantation and advanced AIDS. If both the recipient and the donor are seronegative then the risk of both infection and disease are negligible. If the recipient is seropositive, the risk of infection is approximately 70% but the risk of disease is only 20%, regardless of the serostatus of the donor. However, if the recipient is seronegative and the donor is seropositive the risk of disease is 70%. If steroid pulses and antilymphocyte globulin are given for the treatment of acute rejection, the risk of developing disease is markedly increased. Infection may be the result of primary infection or reactivation of latent infection. It is clinically important, but often difficult, to distinguish between CMV infection and CMV disease, and a definitive diagnosis can only be made histologically. Quantitative PCR can be used to quantify viral load in blood and BAL fluid, which will aid the distinction. Treatment consists of intravenous ganciclovir for at least 14 days. Foscarnet can be used if ganciclovir fails.

FUNGAL PNEUMONIA

Fungi are rare but important causes of pneumonia. They can be divided into two main groups based on the immune response required to combat infection with these organisms. Histoplasma, blastomycosis, coccidioidomycosis, paracoccidioidomycosis and cryptococcus require specific cell-mediated immunity for their control and thus, in contrast to infections, which are controlled by phagocytic activity, the diseases caused by these organisms can occur in otherwise healthy individuals, although they cause much more severe illness in patients with impaired cell-mediated immunity (e.g. patients infected with HIV, and organ transplant recipients). With the exception of cryptococcus, these organisms are rarely seen outside North America. Aspergillus and mucor spores are killed by non-immune phagocytes, so these fungi rarely result in clinical illness in patients with normal neutrophil numbers and function.

CANDIDIASIS

Primary *Candida* pneumonia (i.e. isolated lung infection) is uncommon[44–46] and the isolation of *Candida* from respiratory secretions most commonly reflects benign colonisation of the airway. Where it is associated with infection, pulmonary lesions are usually only one manifestation of disseminated candidiasis. Echinocandins are the recommended first-line treatment in the critically ill.

INVASIVE ASPERGILLOSIS[47]

Invasive aspergillosis was previously believed to be almost exclusively associated with severe immunocompromise. However, recent data suggest that the majority of cases in the ICU are not severely immunocompromised, with chronic obstructive pulmonary disease and decompensated liver disease being significant patient risk factors. Exposure to construction, demolition or renovation work is an important environmental risk factor. Definitive diagnosis requires both histological evidence of acute-angle branching,

Table 36.8 Diagnostic criteria for putative invasive pulmonary aspergillosis

CRITERIA			
Aspergillus isolate AND	Positive isolate from respiratory tract specimen		
Clinical features At least one feature AND	Fever refractory to ≥3 days' appropriate antibiotic therapy Unexplained recurrence of fever, while still on antibiotics after a defervescence of ≥48 h Pleuritic chest pain Dyspnoea Haemoptysis Worsening respiratory failure despite appropriate antibiotics and ventilatory support		
Imaging AND	Abnormal chest X-ray or CT scan of lungs		
Risk factors or invasive cultures	Neutropaenia before or on ICU admission Malignancy treated with cytotoxic agents Glucocorticoid treatment (prednisolone >20 mg/day or equivalent) Immunodeficiency	OR	Semi-quantitative Aspergillus +ve culture of BAL fluid (+ or ++), without bacterial growth together with +ve smear showing branching hyphae

BAL, Bronchoalveolar lavage; *CT*, computed tomography; *ICU*, intensive care unit.

septated non-pigmented hyphae measuring 2–4 µm in width, and cultures yielding *Aspergillus* species from biopsy specimens of involved organs, but this is rarely practical in critically ill patients. The new diagnostic category, putative invasive pulmonary aspergillosis (Table 36.8) provides a more useful guide for clinicians caring for critically ill patients. The criteria have a 61% specificity and 92% sensitivity for invasive pulmonary aspergillosis. Recovery of *Aspergillus* species from respiratory secretions in immunocompromised, but not immunocompetent, patients may indicate invasive disease with a positive predictive value as high as 80%–90% in patients with leukaemia or BMT recipients. Galactomannan antigen detection has high specificity for invasive pulmonary aspergillosis in both serum and BAL fluid, but has much greater sensitivity in BAL fluid.

Early intravenous treatment is important. First-line therapy is voriaconazole. Liposomal amphotericin is an alternative and echinocandins can be used as salvage therapy.[48]

PARAPNEUMONIC EFFUSION

This may be an uncomplicated effusion that resolves with appropriate treatment of the underlying pneumonia, or a complicated effusion that develops into an empyema unless drained. Complicated effusions tend to develop 7–14 days after initial fluid formation. They are characterised by increasing pleural fluid volume, continued fever and pleural fluid with low pH (<7.2) and high LDH concentration (>1000 IU/L),[49] which contains a large number of neutrophils and may reveal organisms on Gram staining or culture.

EMPYEMA[49]

DEFINITION

Collection of pus in the pleural space

AETIOLOGY

This most commonly follows bacterial pneumonia and parapneumonic effusion. Other causes include bronchial carcinoma, oesophageal rupture, extension of subdiaphragmatic infection, chest trauma, mediastinitis and infections of the thoracic or cervical spine. Anaerobic bacteria, usually streptococci or Gram-negative rods are responsible for 76% of cases.

DIAGNOSIS

The diagnosis should be considered in all patients with a pleural effusion and pneumonia or unexplained sepsis. Failure of clinical improvement within a few days in a patient with pneumonia should prompt investigation to identify a pleural effusion. Imaging should include a CXR ± ultrasound. Ultrasound may reveal loculated effusions that are obscured by consolidation on the CXR. CT scanning may reveal loculations, show features indicative of infection, demonstrate the underlying cause and distinguish between an abscess and an empyema. The diagnosis is confirmed by the aspiration of pus. In the absence of pus, measure the pleural fluid pH and LDH. A pH <7.2 or LDH >1000 IU/L are predictive of complicated parapneumonic effusions that require drainage. Pleural fluid taken at the time of pleurocentesis should be sent for culture. Fluid from drains gives unreliable results.

TREATMENT

The mainstay of treatment is image-guided drainage. There is controversy regarding the optimal drain size. The traditional belief is that small-bore catheters are ineffective for drainage of thick pus or in the presence of extensive septation within the empyema, but there a few data to provide guidance. Routine flushing of the drain (e.g. 20 mL normal saline every 6 hours) reduces the risk of drain occlusion. The adequacy of drainage should be monitored with repeated thoracic CT. Any undrained loculations should be treated by the use of larger or additional drains. Intrapleural-tissue-plasminogen-activator and DNase may be beneficial in patients with more advanced disease, but are not routinely indicated in patients with early empyema. Failure to achieve complete drainage or failure to improve should prompt a referral to a thoracic surgeon. Antibiotics have only an adjunctive role. Broad-spectrum antibiotic regimes with anaerobic cover should be used until the results of microbiological analysis of the aspirated pus are available.

Acknowledgements

All tables and figures are reproduced from ICU web (www.aic.cuhk.edu.hk/web8) with the permission of the author.

REFERENCES

1. American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia. *Am J Respir Crit Care Med*. 2001;163: 1730–1754.
2. Fang GD, Fine M, Orloff J, et al. New and emerging etiologies for community-acquired pneumonia with implications for therapy. A prospective multicenter study of 359 cases. *Medicine (Baltimore)*. 1990;69(5):307–316.
3. Dupont H, Mentec H, Sollet JP, et al. Impact of appropriateness of initial antibiotic therapy on the outcome of ventilator-associated pneumonia. *Intensive Care Med*. 2001;27:355–362.
4. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J*. 2005;26(6):1138–1180.
5. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(S2):S27–S72.
6. Bartlett JG, Dowell SF, Mandell LA, et al. Practice guidelines for the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2000;31:347–382.
7. Mandell LA, Marrie TJ, Grossman RF, et al; the Canadian Community-Acquired Pneumonia Working Group. Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. *Clin Infect Dis*. 2001;31: 383–421.
8. File TM Jr. Community-acquired pneumonia. *Lancet*. 2003;362(9400):1991–2001.
9. Llamas-Álvarez AM, Tenza-Lozano EM, Latour-Pérez J. Accuracy of lung ultrasonography in the diagnosis of pneumonia in adults. *Chest*. 2016;151(2):374–382.
10. Schenck EJ, Rajwani K. Ultrasound in the diagnosis and management of pneumonia. *Curr Opin Infect Dis*. 2016;29(2):223–228.
11. van der Eerden MM, Vlaspolder F, de Graaff CS, et al. Value of intensive diagnostic microbiological investigation in low- and high-risk patients with community-acquired pneumonia. *Eur J Clin Microbiol Infect Dis*. 2005;24(4):241–249.
12. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med*. 2015;372(23):2185–2196.
13. Bender MT, Niederman MS. Improving outcomes in community-acquired pneumonia. *Curr Opin Pulm Med*. 2016;22(3).
14. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock. *Intensive Care Med*. 2016;2017:1–74.
15. Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. *Arch Intern Med*. 2001;161(15):1837–1842.
16. Sligl WI, Asadi L, Eurich DT, et al. Macrolides and mortality in critically ill patients with community-acquired pneumonia: a systematic review and meta-analysis. *Crit Care Med*. 2014;42(2).
17. Dunbar LM, Wunderink RG, Habib MP, et al. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. *Clin Infect Dis*. 2003;37(6):752–760.
18. Schuetz P, Briel M, Christ-Crain M, et al. Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. *Clin Infect Dis*. 2012;55(5):651–662.
19. de Jong E, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. *Lancet Infect Dis*. 2016;16(7):819–827.
20. Wan YD, Sun TW, Liu ZQ, et al. Efficacy and safety of corticosteroids for community-acquired pneumonia. *Chest*. 2016;149(1):209–219.
21. O'Grady NP, Barie PS, Bartlett JG, et al. Practice guidelines for evaluating new fever in critically ill adult patients. *Clin Infect Dis*. 1998;26:1042–1059.
22. Burk M, El Kersh K, Saad M, et al. Viral infection in community-acquired pneumonia: a systematic review and meta-analysis. *Eur Respir Rev*. 2016;25(140):178.
23. Ramsey CD, Kumar A. Influenza and endemic viral pneumonia. *Crit Care Clin*. 2013;29(4):1069–1086.

24. Choi SH, Huh JW, Hong SB, et al. Clinical characteristics and outcomes of severe rhinovirus-associated pneumonia identified by bronchoscopic bronchoalveolar lavage in adults: comparison with severe influenza virus-associated pneumonia. *J Clin Virol*. 2015;62:41–47.
25. Lee N, Qureshi ST. Other viral pneumonias. *Crit Care Clin*. 2013;29(4):1045–1068.
26. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63(5):e61–e111.
27. Vincent J-LMPF, Brealey DM, Libert NM, et al. Rapid diagnosis of infection in the critically ill, a multicenter study of molecular detection in bloodstream infections, pneumonia, and sterile site infections. *Crit Care Med*. 2015;43(11):2283–2291.
28. American Thoracic Society and Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare associated pneumonia. *Am J Respir Crit Care Med*. 2005;171: 388–416.
29. Melsen WG, Rovers MM, Groenwold RH, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. *Lancet Infect Dis*. 2013;13(8):665–671.
30. Speck K, Rawat N, Weiner NC, et al. A systematic approach for developing a ventilator-associated pneumonia prevention bundle. *Am J Infect Control*. 2016;44(6):652–656.
31. Erbes R, Oettel K, Raffenberg M, et al. Characteristics and outcome of patients with active pulmonary tuberculosis requiring intensive care. *Eur Respir J*. 2006;27(6):1223.
32. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: diagnosis of tuberculosis in adults and children. *Clin Infect Dis*. 2017;64(2):111–115.
33. Cudahy P, Shenoi SV. Diagnostics for pulmonary tuberculosis. *Postgrad Med J*. 2016;92(1086):187.
34. Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis*. 2016;63(7):e147–e195.
35. National Collaborating Centre for Chronic Conditions. *Tuberculosis. Clinical Diagnosis and Management of Tuberculosis and Measures for its Prevention*. London, UK: Royal College of Physicians; 2006.
36. Centers for Disease Control and Prevention. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR Morb Mortal Wkly Rep*. 2005;54 (RR–17):1–119.
37. Hilbert G, Gruson D, Vargas F, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med*. 2001;344(7):481–487.
38. Lemiale V, Mokart D, Resche-Rigon M. Effect of noninvasive ventilation vs oxygen therapy on mortality among immunocompromised patients with acute respiratory failure: a randomized clinical trial. *JAMA*. 2015;314(16):1711–1719.
39. Maschmeyer G, Helweg-Larsen J, Pagano L, et al. ECIL guidelines for treatment of Pneumocystis jirovecii pneumonia in non-HIV-infected haematology patients. *J Antimicrob Chemother*. 2016;71(9):2405–2413.
40. Monnet X, Vidal-Petiot E, Osman D, et al. Critical care management and outcome of severe Pneumocystis pneumonia in patients with and without HIV infection. *Crit Care*. 2008;12(1):R28.
41. Benson CA, Kaplan JE, Masur H, et al. Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *Clin Infect Dis*. 2005;40:S131–S235.
42. Tan BH. Cytomegalovirus treatment. *Curr Treat Options Infect Dis*. 2014;6(3):256–270.
43. van der Bij W, Speich R. Management of cytomegalovirus infection and disease after solid-organ transplantation. *Clin Infect Dis*. 2001;33(suppl 1):S32–S37.
44. Meersseman W, Lagrou K, Spriet I, et al. Significance of the isolation of Candida species from airway samples in critically ill patients: a prospective, autopsy study. *Intensive Care Med*. 2009;35(9):1526–1531.
45. Tamm M. The lung in the immunocompromised patient. Infectious complications part 2. *Respiration*. 1999;66(3):199–207.
46. Pappas PG, Rex JH, Sobel JD, et al. Guidelines for treatment of candidiasis. *Clin Infect Dis*. 2004;38:161–189.
47. Koulenti D, Garnacho-Montero J, Blot S. Approach to invasive pulmonary aspergillosis in critically ill patients. *Curr Opin Infect Dis*. 2014;27(2):174–183.
48. Patterson TF, Thompson III, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63(4):e1–e60.
49. Shen KR, Bribriesco A, Crabtree T, et al. The American Association for Thoracic Surgery consensus guidelines for the management of empyema. *J Thorac Cardiovasc Surg*. 2017;153(6): e129–e146.

37

Non-invasive ventilation

Graeme J Duke, Andrew D Bersten

Non-invasive ventilation (NIV) is a valuable therapeutic option in the management of acute and chronic respiratory failure – for certain diagnoses it is the preferred option. The application of NIV predates the introduction of laryngoscopy (early 1900s) and the widespread use of positive-pressure mechanical ventilation (MV) via an endotracheal tube in the 1950s.[1] The clinical benefit of NIV in acute respiratory failure (ARF) was first publicised in 1936.[2]

NIV is defined as ventilatory support without an (invasive) endotracheal airway. NIV should be considered as standard therapy in the early management of rapidly reversible ARF,[3,4] and in domiciliary management of chronic respiratory failure due to obstructive sleep apnoea (OSA) and neuromuscular disease.

NIV may be achieved either through the delivery of positive pressure to the airway (P_{ao}) or the application of a negative-pressure generator to the chest ('chest box' or cuirass) or body ('iron lung'). A conceptual framework is shown in Fig. 37.1.

Negative-pressure generators may be used for the management of acute or chronic respiratory disease.[5] Major limitations to the use of negative-pressure generators include the induction of OSA, lack of fractional inspired oxygen (Fi_{O_2}) control, equipment bulk and size.[6] However, external negative-pressure generators suit some patients with chronic respiratory failure, particularly as there is no oral or nasal prosthesis.

This chapter deals primarily with the use of positive-pressure NIV to treat ARF. The clinical efficacy of NIV depends upon: (1) the ventilatory mode selected and (2) the nature and severity of the underlying respiratory pathophysiology.[7,8] Correctly applied NIV reduces morbidity and mortality, whereas incorrect or inappropriate application may delay definitive therapy and adversely affect the outcome.[9] The physiological rationale for NIV will assist the clinician in understanding the indications and benefits, and predict the side effects of each mode of NIV.

PHYSIOLOGY OF NON-INVASIVE VENTILATION

Several important aspects regarding ventilatory support are discussed in Chapter 31, and this chapter will focus on those aspects specific to NIV.

The physiological benefits of NIV are similar to those of invasive ventilatory support. NIV can reverse many of the adverse physiological and mechanical derangements associated with ARF, through a combination of:

- augmentation of alveolar ventilation (V_A) to reverse respiratory acidosis and hypercarbia
- alveolar recruitment and increased Fi_{O_2} to reverse hypoxia
- reduction in work of breathing (W_{mus}) to reduce or prevent respiratory muscle insufficiency
- stabilisation of the chest wall in the presence of chest trauma or surgery
- reduction in left ventricular (LV) afterload that may lead to improved cardiac function
- reduction of right ventricular (RV) afterload and improved RV function.[10]

In brief, the respiratory effort (pressure–volume work) required to achieve a desired minute volume (V_E) may be viewed as the summation of the individual forces that must be overcome to generate inspiratory flow, namely: elastic work (or 'stretch'; W_{el}), flow-resistive work (air-flow obstruction; W_{res}) and threshold work. Intrinsic positive end-expiratory pressure (PEEPi) and dynamic hyperinflation are absent in the healthy lung, but are common in the presence of tachypnoea or expiratory airflow obstruction. During flow limitation, PEEPi impedes the onset (triggering) of inspiratory support modes (inspiratory positive airway pressure [IPAP] and pressure support ventilation [PSV]). Threshold load (PEEPi) must be counterbalanced by additional inspiratory effort before inspiratory flow can commence. External PEEP (CPAP) that matches PEEPi will aid in reducing this component of elastic work W_{el}.

Since the volume component is constant the equation of motion can be written as:

$$P_{mus} = P_{el} + P_{res} \quad (37.1)$$

(See Chapter 31, for more detailed explanation.)

With the addition of a device for ventilatory support, the respiratory muscle effort (P_{mus}) required by the patient is equivalent to the difference between the applied P_{ao} and the total work required to maintain V_E:

ABSTRACT

Non-invasive ventilation (NIV) has been successfully applied in patients with acute respiratory failure (ARF) caused by cardiogenic pulmonary oedema (CPO), chronic obstructive pulmonary disease (COPD) and chronic respiratory failure due to sleep apnoea and neuromuscular disorders. NIV should be considered as standard therapy for respiratory support in these patients before considering invasive mechanical ventilation. Continuous positive airway pressure (CPAP) alone appears to be beneficial in ARF due to CPO and COPD with threshold load. Bilevel (or pressure support ventilation with CPAP) is beneficial in patients with hypercapnic ARF secondary to respiratory muscle insufficiency, high inspiratory workloads or reduced alveolar ventilation. NIV does not appear to benefit patients with severe pneumonia, acute respiratory distress syndrome or postoperative respiratory failure. Its role in ARF due to pneumonia in immune-compromised subjects, acute asthma and blunt chest trauma remains unclear.

KEYWORDS

Non-invasive ventilation
acute respiratory failure
hypoxia
cardiogenic pulmonary oedema
chronic obstructive pulmonary disease
pneumonia
CPAP
BiPAP

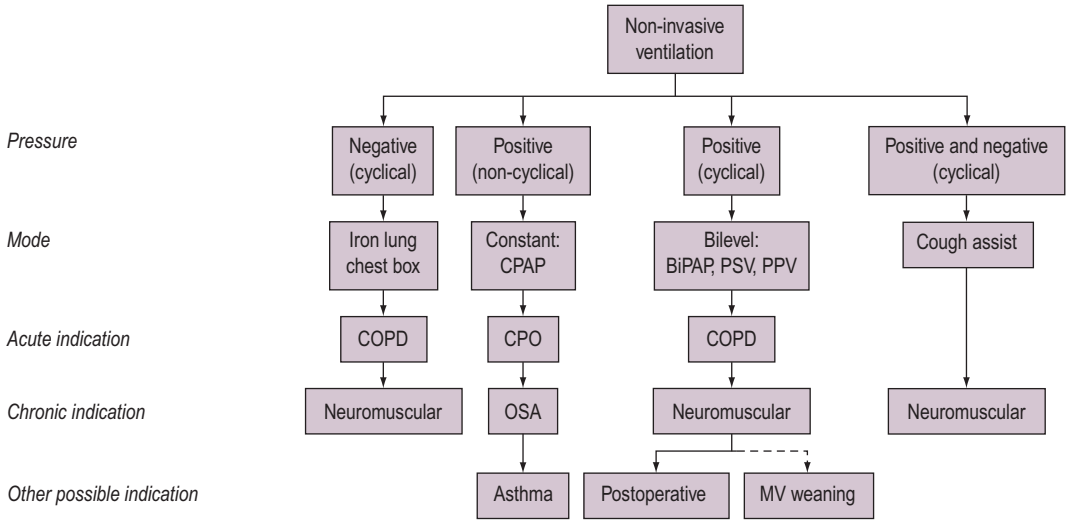


Figure 37.1 Conceptual non-invasive ventilation paradigm. *BiPAP*, Biphasic positive airway pressure; *CPAP*, continuous positive airway pressure; *COPD*, chronic obstructive pulmonary disease; *CPO*, cardiogenic pulmonary oedema; *MV*, mechanical ventilation; *OSA*, obstructive sleep apnoea; *PPV*, positive-pressure ventilation; *PSV*, pressure support ventilation.

$$P_{mus} = (P_{el} + P_{res}) - P_{ao} \quad (37.2)$$

This relationship may be rearranged into its individual components, as follows:

$$P_{mus} + P_{ao} = E \bullet V + R \bullet \dot{V} + \text{PEEPi} \quad (37.3)$$

where E is the respiratory elastance (inverse of compliance), V is the volume of gas, R is the respiratory and circuit flow resistance, $\dot{V}$ is the inspiratory flow rate and PEEPi is the intrinsic PEEP.

It is important to remember that breathing via a circuit will create additional air-flow resistance (R) adding to breathing work (P_{mus}), and thus attention to circuit design is important (see below).

Respiratory failure occurs when the forces opposing inspiration – namely elastic (P_{el}), resistive (P_{res}) and threshold (PEEPi) work – exceed the respiratory muscle effort (P_{mus}) required to maintain V_E. Hypermetabolic states (e.g. trauma, sepsis) increase basal V_E, whereas pulmonary and chest wall diseases increase respiratory workload and neuromuscular disease impairs respiratory muscle effort. NIV may prevent respiratory failure by counterbalancing the increased respiratory workload and/or reducing respiratory muscle effort, and thus maintain V_A.

Any invasive MV mode may be delivered non-invasively, and four are commonly described in clinical research: CPAP, PSV, bilevel or biphasic positive airway pressure (BiPAP) and pressure- or volume-limited intermittent positive-pressure ventilation. Other modes under investigation include high-frequency and proportional assist ventilation.

All NIV modalities utilise semiclosed or closed circuits and are thus capable of reliably delivering high Fi_{O_2}. This is an important mechanism by which NIV improves oxygenation, independently of other mechanisms discussed below.

CONTINUOUS POSITIVE AIRWAY PRESSURE

CPAP is a form of NIV because it provides respiratory support even though the P_{ao} applied is constant throughout the respiratory cycle. This mode addresses a number of the objectives of ventilatory support, namely:

- reduction in the work of breathing by:
  - alveolar recruitment and reduction in elastic work
  - reducing threshold load created in the presence of PEEPi
- reversing hypoxia through the delivery of high Fi_{O_2}, alveolar recruitment, and the reduction of intrapulmonary shunt
- reduction of LV transmural pressure (afterload).[10,11]

INSPIRATORY POSITIVE AIRWAY PRESSURE AND PRESSURE SUPPORT VENTILATION

Positive inspiratory airway pressure without expiratory pressure (e.g. PSV or IPAP), provides respiratory support by reducing both the elastic and the resistive components of respiratory work resulting in:

- augmentation of tidal volume (V_E) and minute volume (V_E) and reduction in $PaCO_2$
- reduction in P_{mus} with diminished, or the prevention of, respiratory muscle insufficiency
- induction of pulmonary surfactant release through alveolar inflation above resting tidal volume.[12]

Bilevel positive airway pressure allows separate settings for inspiratory (IPAP) and expiratory (EPAP) airway pressure levels; it is equivalent to PSV plus CPAP.[13] Respiratory frequency is usually patient-dependent but may be mechanically time cycled and independent of patient effort.

CONTROLLED VENTILATION

NIV may also be administered as volume- or pressure-limited MV applied via a mask (instead of an endotracheal airway).

PATIENT–VENTILATOR INTERACTION

This is discussed in Chapter 31, and subdivided into: (1) triggering of inspiration, (2) inspiration and (3) cessation of inspiration. Asynchrony is a common cause of NIV failure arising from gas leaks due to poor mask fit.[14] Mask leaks interfere with the ability to sense the end of expiration because there is continued 'expiratory' gas flow.

NON-INVASIVE VENTILATION EQUIPMENT

Equipment design varies according to NIV mode and purpose (e.g. critical care or domiciliary setting), and significant variations in performance characteristics have been documented.[1,15] The important characteristics of an efficient NIV circuit include:

- high gas flow to match peak inspiratory air flow – high flows may be generated by a pressurised gas supply, a gas turbine or a jet venturi mechanism: a device providing continuous flow imposes less circuit work than a demand flow device
- an expiratory (threshold) resistor capable of maintaining the desired PEEP, yet offering a low resistance to expiratory flow to reduce fluctuations in the delivered P_{ao} – this may be a threshold resistor or flow resistor; the optimal position for the expiratory valve is as close to the patient's airway as possible
- short wide-bore tubing to reduce turbulence and flow resistance
- a flow or pressure sensor to identify inspiratory effort and facilitate triggering of the predetermined inspiratory pressure support (e.g. PSV or IPAP)
- ability to control and deliver a wide range of Fi_{O_2}
- other desirable features include the humidification, pressure-relief safety valves, battery back-up, apnoea back-up support, acoustic suppression and monitoring of volume and P_{ao}. These are important for management of ARF and less important for domiciliary (long-term) NIV devices.

Several varieties of mask design are also available and the optimal configuration depends upon the purpose and mode of NIV, patient anatomy, and preference. These include intranasal, nasal, and oronasal, full-face and helmet (full-head) masks. Desirable features of a mask include lightweight and transparent materials affording a comfortable airtight seal, minimal dead space, and separate inspiratory and expiratory ports to minimise air-flow turbulence[15] and rebreathing.[16] In lung model studies, expiratory ports over the nasal bridge reduce dead space,[17] which may prove to be clinically advantageous. Orofacial masks have a lower dead space than full-face masks or helmet designs,[18] but a higher risk of air leak.[14]

Mask discomfort, arising from the mask seal, air leaks, humidification or claustrophobia, are common causes of non-compliance. Masks that cover nose and mouth tend to produce more reliable and constant P_{ao} because they are unaffected by mouth breathing – a common problem in the critically ill patient. Nasal masks are less restrictive on the patient's ability to talk, eat/drink and expectorate, and therefore gain higher compliance in long-term and domiciliary applications. To effectively compensate for air leaks, nasal masks should be used with circuits capable of rapidly augmenting and delivering high gas flow (>100 L/min).

Fibreoptic bronchoscopy can be safely performed during NIV,[19-21] using a full-face mask with at least two ports. One of these can be modified to provide a simple valve for insertion of the bronchoscope, and the other used for NIV. Provided there is adequate flow reserve during suction, this can be performed during any mode of NIV. This technique may allow both diagnostic and therapeutic bronchoscopic intervention without intubation even in critically ill patients.

COMPLICATIONS AND ASSESSMENT OF EFFICACY

Contraindications and complications specific to NIV are listed in Box 37.1. Acutely unwell patients requiring NIV should be managed in a critical care ward, or similar area with appropriately trained on-site medical and nursing staff. Although availability of sophisticated, portable non-invasive ventilators makes it easy to provide NIV in any environment, its benefits may diminish outside the critical care environment.[22,23]

The reversal of hypoxia and the reduction in respiratory effort is commonly observed with the commencement of NIV, yet they are a poor guide to the efficacy of NIV. More reliable clinical measures of NIV efficacy include the reversal of hypercarbia, a sustained improvement in respiratory function and outcomes, such as a reduction in intubation, nosocomial pneumonia and mortality.

Box 37.1 Contraindications and complications of non-invasive ventilation

Contraindications
- Respiratory arrest
- Unprotected airway (coma, sedation)
- Upper airway obstruction
- Inability to clear secretions
- Untreated pneumothorax
- Marked haemodynamic instability

Complications
- Mask discomfort, patient intolerance
- Facial or ocular abrasions
- Nasal congestion, sinus pain
- Oronasal dryness
- ↑ Intraocular pressure (particularly in patients with glaucoma)
- ↑ Intracranial pressure (particularly in patients with neurotrauma)
- ↓ Blood pressure (if hypovolaemic)
- Aspiration pneumonia (rare)
- Aerophagy and gastric distension (uncommon; routine gastric decompression is unnecessary)

NON-INVASIVE VENTILATION AND ACUTE RESPIRATORY FAILURE

CARDIOGENIC PULMONARY OEDEMA

Cardiogenic pulmonary oedema (CPO) is a common cause of severe reversible ARF. Since the 1930s, the therapeutic benefits of all modes of NIV, particularly CPAP have been well documented.[24-26] CPO leads to an increase in elastic workload (P_{el}) and, to a lesser extent, resistive workload (P_{res}), an increase in lung water and impaired surfactant function. CPAP reverses hypoxia, recruits alveoli and reduces intrapulmonary shunt and LV afterload. The redistribution of extravascular lung water from alveoli to the interstitial space is aided by the recruitment of alveoli and improved surfactant function.

Over 30 prospective, randomised, controlled trials of NIV in CPO have consistently demonstrated physiological improvements in hypoxic and hypercapnic respiratory failure, and a significant reduction in the need for intubation (relative risk 95% confidence interval [RR 95% CI]), duration of respiratory support, hospital length of stay, and improved survival (RR 95% CI = 0.44–0.92).[22,24]

NIV should be considered part of standard therapy for CPO.[1,22] The optimal mode of NIV in CPO appears to be CPAP.[27] The optimal P_{ao} level remains to be resolved, although 10 cm H_2O appeared to be safe and effective in the majority of subjects. The addition of a differential inspiratory pressure (e.g. IPAP and PSV) may be as effective as CPAP in avoiding (95% CI, RR = 0.33–0.86) intubation without survival benefit[28,29] and may increase the rate of myocardial infarction (95% CI, RR = 0.92–2.42).[24]

Benefits appear to be greater in those with acute coronary syndrome as the primary aetiology.[24] CPAP reduces preload and afterload[10,11,30] and myocardial catecholamine release,[31] whereas the cyclical P_{ao} (of bilevel NIV) may cause fluctuation in the preload and afterload during respiration.

ACUTE RESPIRATORY FAILURE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) patients have an elevated resistive work (P_{res}), often coupled with an elevated basal V_E and elastic work (P_{el}) as a result of the pre-existing parenchymal damage. Threshold load (PEEPi) is frequently present as a consequence of air-flow obstruction, and is exacerbated during ARF by further increases in P_{res} and the respiratory rate. Reversible ARF is a common complication of COPD.

The importance of NIV in hypercapnic ARF is now supported by at least 14 well-performed prospective, randomised, controlled studies[32,33] in more than 600 patients. Most investigators reported a low prevalence of side effects and a significant decrease in intubation rates and in-hospital mortality. A meta-analysis of NIV trials reveals significant reductions in mortality (95% CI, RR = 0.35–0.76) and the need for intubation (95% CI, RR = 0.33–0.53) – the number of patients needed to treat to avoid one intubation or death being as few as 4 and 10, respectively.[33] Risk reduction appears to be proportional to the severity of respiratory acidosis.[35] The incidence of nosocomial pneumonia is lower with NIV[34,35] and this may explain some of the survival benefit associated with NIV.

Current evidence supports the use of NIV in hypercapnic ARF as standard therapy in COPD subjects.[34] This is supported by several respiratory medicine societies.[22,32,36]

All modes of NIV appear to have a role but the optimal mode and pressure settings remain unresolved.[22] Patients with ARF arising predominantly from reversible air-flow obstruction (P_{res}) and/or threshold load are likely to respond to CPAP alone. Hypercapnic patients often experience reduced alveolar ventilation or respiratory muscle insufficiency and are likely to benefit from the addition of inspiratory support (PSV or IPAP).

A trial of NIV is indicated by the presence of respiratory acidosis (pH <7.37) or persistent breathlessness.[33] It is poorly tolerated in those without acidosis.

Inspiratory support (usually 5–20 cm H_2O) should be titrated to improve V_E as indicated by an improvement in tidal volume and pH, and a reduction in respiratory rate and/or $PaCO_2$. Low levels of CPAP or EPAP (4–8 cm H_2O) are usually required to counterbalance threshold load and trigger inspiratory support. Clinical observation and judgement are required to

titrate this to a level that minimises the effort required to trigger inspiratory support (PSV or IPAP). Fi_{O_2} is titrated to reverse hypoxia.

Early predictors of NIV success in COPD patients include improvements in pH and $PaCO_2$ (but not Pa_{O_2}) within the first 1–2 hours of therapy.[33,37] Predictors of NIV failure include persistent mask intolerance, severe acidosis (pH <7.25), tachypnoea (>35/min), impaired conscious state and poor clinical response to initial therapy. The bedside care plan should address management should the trial of NIV fail. Mask intolerance, nursing workload and failure rates are greater during NIV for COPD than those reported in CPO. These patients benefit from a critical care setting where expertise and equipment are available, and where reported outcomes appear better.[23,33]

While reported success rates are high (70%–90%), NIV failure (requiring intubation) appears to increase with the severity of respiratory acidosis. For the poorly compliant patient, reassurance and explanation together with a trial of different size and/or type of mask or initiation with lower-pressure settings, plus brief periods of NIV will sometimes assist. Low-dose anxiolytic drugs may be beneficial where anxiety is a recurrent precipitant of dyspnoea, but should be used with caution because of their respiratory depressant side effects.

Late failure (>48 hours) occurs in 10%–20% of patients[38] despite an initial improvement with NIV. This group of patients has a high mortality risk.[37] Whether this reflects the severity of the underlying disease or the delayed initiation of MV remains unclear.

ASTHMA

Asthma is an acute inflammatory lung disease that increases resistive (P_{res}) and threshold (PEEPi) respiratory work. Clinical improvement[39-41] and physiological improvement[42,43] has been demonstrated in acute asthmatics with the application of CPAP and bilevel NIV.

The role of NIV in the management of acute asthma, and thus the optimal mode and pressure settings, remains to be clarified. Nebulised drugs can be effectively delivered even in the presence of a high-flow NIV circuit.[44] Controlled clinical studies with robust end-points are awaited.[39] Low-level CPAP (5 cm H_2O) may be effective in moderate to severe asthma unresponsive to steroids and continuous inhaled bronchodilators. Mask intolerance is the most frequent cause of NIV failure. NIV must be delivered in a high-acuity environment where the appropriately skilled staff members are immediately available should the patient require urgent intubation.

ACUTE RESPIRATORY DISTRESS SYNDROME

Like CPO, acute respiratory distress syndrome (ARDS) leads to an increase in elastic workload (P_{el}) and, to a lesser extent, resistive workload (P_{res}) arising from an increase in alveolar–capillary permeability, the release of inflammatory mediators and impaired surfactant function. Even though PEEP is beneficial in ARDS, and NIV has a lower prevalence of nosocomial pneumonia,[34,35] current data do not support the routine use of NIV in ARDS, non-CPO or undifferentiated hypoxaemic ARF.[45,46]

Despite numerous publications reporting the successful use of NIV in the setting of community-acquired pneumonia[47] (without COPD) and other forms of ARDS, the failure rate remains high.[45-51] This may reflect the differences in duration, severity, and the pathophysiology of pneumonia and ARDS compared with CPO. Apparent benefit may be due to the inclusion of subjects with CPO[49] or COPD[52,53] – subgroups that benefit from NIV.

PNEUMONIA IN THE IMMUNOCOMPROMISED PATIENT

MV is associated with high morbidity and mortality in immunocompromised patients with hypoxic respiratory failure.[54-56] These patients may benefit from an early trial NIV,[57] although early evidence for improved survival is not supported by a recent large randomised trial.[58] Whether NIV benefits this group by reducing unnecessary exposure to a high-morbidity therapy (MV)[34] or by identifying responders (with a rapidly reversible form of ARF) remains unclear. It seems reasonable, based on the current evidence, to offer NIV to these patients[22,56] with a clear plan for patient management should the trial of NIV fail.

POSTOPERATIVE AND POST-TRAUMATIC ACUTE RESPIRATORY FAILURE

ARF in postoperative and trauma patients may arise from a number of reversible pathological processes associated with increases in elastic workload (P_{el}) and impaired respiratory muscle function (P_{mus}), including dependent atelectasis, impaired chest-wall mechanics, poor cough, nosocomial infection, aspiration pneumonitis and non-respiratory trauma or sepsis.

Mask CPAP consistently improves intermediate physiological parameters (e.g. oxygenation and respiratory rate) and may reduce the risk of intubation in general surgical[59] and cardiothoracic patients[60,61] with mild postoperative hypoxic respiratory failure, but evidence for a survival benefit is lacking,[62] particularly when high rates of failure are reported in the control groups of favourable trials. NIV may improve survival in certain subgroups, such as postoperative lung resection,[61] but many of these patients have underlying COPD, and extrapolation of these results to non-COPD patients awaits further study.

Mask CPAP has been shown to be superior to MV in patients with isolated severe chest trauma,[63,64] but

the benefit of CPAP plus PSV remains unclear. NIV is contraindicated in the presence of neurotrauma, intracranial hypertension, facial trauma or the presence of an undrained pneumothorax.

NON-INVASIVE VENTILATION-ASSISTED WEANING

Since NIV is effective in reducing the need for intubation and MV, it has been postulated that NIV may reduce the risk of failed extubation. Therefore NIV has been recommended to expedite early weaning from MV[65] or as rescue therapy following failed[66] or accidental extubation. The putative advantages relate to a reduction in the duration and the risks of MV (e.g. nosocomial pneumonia).

For COPD patients there appears to be a survival benefit,[67,68] but it cannot be recommended in the non-COPD group where reported failure (intubation) rates are unacceptably high,[69] NIV offers no benefit[18,70,71] and mortality risk may be higher.[68] Thus NIV is a post-extubation rescue therapy for COPD patients, but it is not a substitute for weaning strategies to the risk of extubation failure.[69]

HIGH-FLOW INTRANASAL OXYGEN THERAPY

High-flow intranasal oxygen therapy (HFNO) systems deliver humidified oxygen at high flows (up to 60 L/min) via nasal cannula, with or without a pressure seal. Humidification improves patient tolerance and high flows create low levels of CPAP in the hypopharynx, reduce dead space and improve lung volumes.[70] This form of therapy is useful in neonates (see Chapter 107). Its benefit and role in adult ARF are less clear. HFNO consistently improves oxygenation but failure (intubation) is frequent and improved survival remains controversial.[71]

NON-INVASIVE VENTILATION AND CHRONIC RESPIRATORY DISEASE

NIV is an important modality for the long-term treatment of severe chronic respiratory failure associated with obstructive and central sleep apnoea syndromes[22,72] and chronic hypoventilation syndromes associated with extrapulmonary disease, such as neuromuscular disease,[73] and thoracic deformities,[74] COPD with hypercapnia[75] and cystic fibrosis (CF).[76,77]

These patients may require short-term respiratory support during an acute illness or as an aid to perioperative care in a critical care environment. NIV (plus minitracheostomy for secretion removal) may improve outcome compared with intubation and MV,[78] but failure rates appear to be higher.[79] Diagnosis of these underlying disorders during admission for the treatment of severe ARF should prompt referral and assessment for long-term NIV.

NON-INVASIVE VENTILATION AND SLEEP APNOEA SYNDROMES

Moderate or severe OSA results in nocturnal hypoventilation and episodic hypoxia that can lead to pulmonary and systemic hypertension, cardiac failure, plus daytime hypercapnia and somnolence.[80,81] Many of these complications can be arrested or reversed through the appropriate use of nocturnal CPAP.[22,72,80] Patients with suspected sleep apnoea require accurate assessment by a respiratory physician, including sleep studies, prior to the routine use of domiciliary CPAP. Bilevel or controlled ventilation is required when there is inadequate central respiratory drive or increased elastic work. In many patients, respiratory drive will improve and they can then be managed with CPAP after a period of bilevel or controlled ventilation.

Intercurrent illness, surgery or the use of sedatives and opioid analgesics, will increase the frequency and duration of hypopnoea, apnoea and hypoxia. CPAP should be available even for those patients who do not require admission to a critical care ward.

NON-INVASIVE VENTILATION AND CHRONIC HYPOVENTILATION SYNDROMES

Domiciliary NIV (predominantly using inspiratory support modes or NIPPV) should be considered in all patients presenting with severe chronic respiratory failure due to neuromuscular disease.[78,83-86] Early referral and consideration of domiciliary NIV are recommended because of improved outcomes and quality of life.[83] As mentioned earlier, there are recent data to support NIV in CF[77] and chronic hypercapnic COPD patients.[75]

Assessment of these patients for domiciliary NIV includes respiratory function tests, blood gas analysis and sleep studies, together with trials of NIV modes and pressure settings. In general, indications for long-term NIV include the demonstration of symptomatic respiratory failure, daytime hypercapnia and a significantly reduced (<20% predicted) vital capacity. The use of nocturnal or intermittent NIV has been shown to improve daytime respiratory and cardiac function,[83] to improve exercise endurance, to slow the progression of respiratory dysfunction and to reduce the frequency of hospitalisation.[78,86]

REFERENCES

1. Mehta S, Hill NS. Noninvasive ventilation. State of the art. *Am J Respir Crit Care Med*. 2001;163:540–577.
2. Poulton EP, Oxon DM. Left-sided heart failure with pulmonary oedema. Its treatment with the 'pulmonary plus pressure' machine. *Lancet*. 1936;231:981–983.
3. Carlucci A, Richard JC, Wysocki M, et al. Noninvasive versus conventional mechanical ventilation. An epidemiologic survey. *Am J Respir Crit Care Med*. 2001;163:874–880.

4. Schnell D, Timsit JF, Darmon M, et al. Noninvasive mechanical ventilation in acute respiratory failure: trends in use and outcomes. *Intensive Care Med*. 2014; 40(4):582–591.
5. Corrado A, Confalonieri M, Marchese S, et al. Iron lung vs mask ventilation in the treatment of acute on chronic respiratory failure in COPD patients. A multicenter study. *Chest*. 2002;121:189–195.
6. Brochard L. Negative pressure ventilation. *JAMA*. 2003;289:983.
7. Duke GJ, Bersten AD. Noninvasive ventilation for acute respiratory failure. Part 1. *Crit Care Resusc*. 1999; 1:187–198.
8. Duke GJ, Bersten AD. Non-invasive ventilation for adult acute respiratory failure. Part 2. *Crit Care Resusc*. 1999;1:199–210.
9. Carrillo A, Gonzalez-Diaz G, Ferrer M, et al. Non-invasive ventilation in community-acquired pneumonia and severe acute respiratory failure. *Intensive Care Med*. 2012;38(3):458–466.
10. Lamia B, Van Mossevelde S, Molano L-C, et al. Echocardiographic speckle tracking strain analysis to quantify right ventricular function in acute respiratory failure patients. *Changes during non invasive ventilation*. San Francisco: A4631 American Thoracic Society International Conference. 2012.
11. Naughton MT, Rahman A, Hara K, et al. Effect of continuous positive airway pressure on intrathoracic and left ventricular transmural pressures in patients with congestive heart failure. *Circulation*. 1995;91:1725–1731.
12. Nicholas TE, Power JH, Barr HA. The pulmonary consequences of a deep breath. *Respir Physiol*. 1982; 49:315–324.
13. Girault C, Leroy J, Bonmarchand G, et al. Comparative physiologic effects of noninvasive assist-control and pressure support ventilation in acute hypercapnic respiratory failure. *Chest*. 1997;111(6):1639–1648.
14. Carteaux G, Lyazidi A, Córdoba-Izquierdo A, et al. Patient-ventilator asynchrony during noninvasive ventilation. *Chest*. 2012;142(2):367–376.
15. Lofaso F, Brochard L, Hang T, et al. Home versus intensive care pressure support devices. *Am J Respir Crit Care Med*. 1996;153:1591–1599.
16. Ferguson GF, Gilmartin M. CO_2 rebreathing during BiPAP ventilatory assistance. *Am J Respir Crit Care Med*. 1995;151:1125–1135.
17. Saatci E, Miller DM, Stell IM, et al. Dynamic dead space in face masks used with noninvasive ventilators: a lung model study. *Eur Respir J*. 2004;23: 129–135.
18. Fodil R, Lellouche F, Mancebo J, et al. Comparison of patient–ventilator interfaces based on their computerized effective dead space. *Intensive Care Med*. 2011;37:257–262.
19. Hill NS, Brennan J, Garpestad E, et al. Noninvasive ventilation in acute respiratory failure. *Crit Care Med*. 2007;35(10):2402–2407.
20. Esquinas A, Zuil M, Scala R, et al. Bronchoscopy during non-invasive mechanical ventilation: a review of techniques and procedures. *Arch Bronconeumol*. 2013;49(3):105–112.
21. Heunks LMA, de Bruin CJR, Van Der Hoeven JG, et al. Non-invasive mechanical ventilation for diagnostic bronchoscopy using a new face mask: an observational feasibility study. *Intensive Care Med*. 2009;36(1):143–147.
22. American Thoracic Society. International Consensus Conferences in Intensive Care Medicine: noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med*. 2001;163:283–291.
23. Plant PK, Owen JL, Parrott S, et al. Cost effectiveness of ward based non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease: economic analysis of randomised controlled trial. *BMJ*. 2003;326:956–961.
24. Weng C-L, Zhao Y-T, Liu Q-H, et al. Meta-analysis: noninvasive ventilation in acute cardiogenic pulmonary edema. *Ann Intern Med*. 2010;152(9):590–600.
25. Bersten AD, Holt AW, Vedig AE, et al. Treatment of severe cardiogenic pulmonary oedema with continuous positive airway pressure delivered by face mask. *N Engl J Med*. 1991;325:1825–1830.
26. Bellone A, Vettorello M, Monari A, et al. Noninvasive pressure support ventilation vs. continuous positive airway pressure in acute hypercapnic pulmonary edema. *Intensive Care Med*. 2005;31:807–811.
27. Peter JV, Moran JL. Noninvasive ventilation in exacerbations of chronic obstructive pulmonary disease: implications of different meta-analytic strategies. *Ann Intern Med*. 2004;141:78–79.
28. Mehta S, Jay GD, Woolard RH, et al. Randomized, prospective trial of bilevel versus continuous positive airway pressure in acute pulmonary edema. *Crit Care Med*. 1997;25:620–628.
29. Nava S, Carbone G, DiBattista N, et al. Noninvasive ventilation in cardiogenic pulmonary edema. A multicenter randomized trial. *Am J Respir Crit Care Med*. 2003;168:1432–1437.
30. Duke GJ. Cardiovascular effects of mechanical ventilation. *Crit Care Resusc*. 1999;1(4):388–399.
31. Kaye DM, Mansfield D, Aggarwal A, et al. Acute effects of continuous positive airway pressure on cardiac sympathetic tone in congestive heart failure. *Circulation*. 2001;103:2336–2338.
32. British Thoracic Society Standards of Care Committee. Non-invasive ventilation in acute respiratory failure. *Thorax*. 2002;57:192–211.
33. Ram FSF, Picot J, Lightowler J, et al. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2009. Available: http://summaries.cochrane.org/CD004104/.
34. Girou E, Brun-Buisson C, Taille S, et al. Secular trends in nosocomial infection and mortality associated with noninvasive ventilation in patients with exacerbation of COPD and pulmonary edema. *JAMA*. 2003;292:2985–2991.

35. Demoule A, Girou E, Richard JC, et al. Benefits and risks of success or failure of noninvasive ventilation. *Intensive Care Med*. 2006;32:1756–1765.
36. Abramson MJ, Crockett AJ, Frith PA, et al. COPDX: an update of guidelines for the management of chronic obstructive pulmonary disease with a review of recent evidence. *Med J Aust*. 2006;184: 342–345.
37. Confalonieri M, Garuti G, Cattaruzza MS, et al. A chart of failure risk for noninvasive ventilation in patients with COPD exacerbation. *Eur Respir J*. 2005;25:348–355.
38. Moretti M, Cilione C, Tampieri A, et al. Incidence and causes of non-invasive mechanical ventilation failure after initial success. *Thorax*. 2000;55: 819–825.
39. Lim WJ, Mohammed Akram R, Carson KV, et al. Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. *Cochrane Database Syst Rev*. 2012;(12):CD004360, doi:10.1002/14651858. CD004104.pub3.
40. Soroksky A, Stav D, Shpirer I. A pilot prospective, randomized, placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack. *Chest*. 2003;123:1018–1025.
41. Gupta D, Nath A, Agarwal R, et al. A prospective randomized controlled trial on the efficacy of noninvasive ventilation in severe acute asthma. *Respir Care*. 2010;55(5):536–543.
42. Martin JG, Shore S, Engel LA. Effect of continuous positive airway pressure on respiratory mechanics and pattern of breathing in induced asthma. *Am Rev Respir Dis*. 1982;126:812–817.
43. Shivaram U, Miro AM, Cash ME, et al. Cardiopulmonary responses to continuous positive airway pressure in acute asthma. *J Crit Care*. 1993;8: 87–92.
44. Parkes SN, Bersten AD. Aerosol kinetics and bronchodilator efficacy during continuous positive airway pressure delivered by face mask. *Thorax*. 1997;52:171–175.
45. Antonelli M, Conti G, Moro ML, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. *Intensive Care Med*. 2001; 27:1718–1728.
46. Thille AW, Contou D, Fragnoli C, et al. Non-invasive ventilation for acute hypoxemic respiratory failure: intubation rate and risk factors. *Crit Care*. 2013;17(6):R269.
47. Jolliet P, Abajo B, Pasquina P, et al. Non-invasive respiratory support ventilation in severe community-acquired pneumonia. *Intensive Care Med*. 2001;27:812–821.
48. Masclans JR, Pérez M, Almirall J, et al. Early non-invasive ventilation treatment for severe influenza pneumonia. *Clin Microbiol Infect*. 2013; 19(3):249–256.
49. Delclaux C, L'Her E, Alberti C, et al. Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask. A randomized controlled trial. *JAMA*. 2000;284:2352–2360.
50. Ferrer M, Esquinas A, Leon M, et al. Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. *Am J Respir Crit Care Med*. 2003;168:1438–1444.
51. Kramer N, Meyer TJ, Meharg J, et al. Randomized prospective trial of non-invasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med*. 1995;151:1799–1806.
52. Confalonieri M, Potena A, Carbone G, et al. Acute respiratory failure in patients with severe community acquired pneumonia. *Am J Respir Crit Care Med*. 1999;160:1585–1591.
53. Phua J, Kong K, Lee KH, et al. Noninvasive ventilation in hypercapnic acute respiratory failure due to chronic obstructive pulmonary disease vs. other conditions: effectiveness and predictors of failure. *Intensive Care Med*. 2005;31:533–539.
54. Hilbert G, Gruson D, Vargas F, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever and acute respiratory failure. *N Engl J Med*. 2001;344:481–487.
55. Antonelli M, Conti G, Bufi M, et al. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. *JAMA*. 2000;283:235–241.
56. Gristina GR, Antonelli M, Conti G, et al. Noninvasive versus invasive ventilation for acute respiratory failure in patients with hematologic malignancies: a 5-year multicenter observational survey. *Crit Care Med*. 2011;39(10):2232–2239.
57. Del Sorbo L, Jerath A, Dres M, et al. Non-invasive ventilation in immunocompromised patients with acute hypoxemic respiratory failure. *J Thorac Dis*. 2016;8(3):E208–E216.
58. Lemiale V, Mokart D, Resche-Rigon M, et al. Effect of noninvasive ventilation vs oxygen therapy on mortality among immunocompromised patients with acute respiratory failure. *JAMA*. 2015;314(16):1711–1719.
59. Squadrone V, Coha M, Cerutti E, et al. Continuous positive airway pressure for treatment of postoperative hypoxemia: a randomized controlled trial. *JAMA*. 2005;293:589–595.
60. Richter-Larsen K, Ingwersen U, Thode S, et al. Mask physiotherapy in patients after heart surgery: a controlled study. *Intensive Care Med*. 1995;21: 469–474.
61. Auriant J, Jallot A, Herve P, et al. Noninvasive ventilation reduces mortality in acute respiratory failure following lung resection. *Am J Respir Crit Care Med*. 2001;164:1231–1235.
62. Chiumello D, Chevallard G, Gregoretti C. Non-invasive ventilation in postoperative patients: a systematic review. *Intensive Care Med*. 2011;37(6): 918–929.

63. Bolliger CT, Van Eeden SF. Treatment of multiple rib fractures. Randomised controlled trial comparing ventilatory with non-ventilatory management. *Chest*. 1990;97:943–948.
64. Gunduz M, Unlugenc H, Ozalevli M, et al. A comparative study of continuous positive airway pressure (CPAP) and intermittent positive pressure ventilation (IPPV) in patients with flail chest. *Emerg Med J*. 2005;22:325–329.
65. Burns KEA, Adhikari NKJ, Keenan SP, et al. Noninvasive positive pressure ventilation as a weaning strategy for intubated adults with respiratory failure. *Cochrane Database Syst Rev*. 2010;8:doi:10.1002/14651858.
66. Varga F, Clavel M, Sanchez P, et al. Sequential and early use of noninvasive ventilation after extubation in patients with chronic respiratory disorders. San Francisco: A6487 American Thoracic Society International Conference; 2012.
67. Nava S, Ambrosino N, Clini E, et al. Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial. *Ann Intern Med*. 1998;128:721–728.
68. Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med*. 2004;350(24):2452–2460.
69. Ferreyra G, Fanelli V, Del Sorbo L, et al. Are guidelines for non-invasive ventilation during weaning still valid? *Minerva Anestesiol*. 2011;77(9): 921–926.
70. Nishimura M. High-flow nasal cannula oxygen therapy in adults. *J Intensive Care*. 2015;3(1): 2985–2988.
71. Frat J-P, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med*. 2015;372(23): 2185–2196.
72. National Association for Medical Direction of Respiratory Care. Clinical indications for non-invasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation – a consensus conference report. *Chest*. 1999;116: 521–553.
73. Gomez-Merino E, Bach JR. Duchenne muscular dystrophy: prolongation of life by noninvasive ventilation and mechanically assisted coughing. *Am J Phys Med Rehabil*. 2002;8:411–415.
74. Tuggey JM. Randomised crossover study of pressure and volume non-invasive ventilation in chest wall deformity. *Thorax*. 2005;60(10):859–864.
75. Struik FM, Lacasse Y, Goldstein R, et al. Nocturnal non-invasive positive pressure ventilation for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2013;(6):CD002878, doi:10.1002/14651858.CD002878.pub2.
76. Madden BP, Kariyawasam H, Siddiqi AJ, et al. Noninvasive ventilation in cystic fibrosis patients with acute or chronic respiratory failure. *Eur Respir J*. 2002;19:310–313.
77. Flight WG, Shaw J, Johnson S, et al. Long-term non-invasive ventilation in cystic fibrosis – Experience over two decades. *J Cyst Fibros*. 2012;11(3): 187–192.
78. Vianello A, Bevilacqua M, Arcaro G, et al. Non-invasive ventilatory approach to treatment of acute respiratory failure in neuromuscular disorders. A comparison with endotracheal intubation. *Intensive Care Med*. 2000;26:384–390.
79. Robino C, Faisy C, Diehl J-L, et al. Effectiveness of non-invasive positive pressure ventilation differs between decompensated chronic restrictive and obstructive pulmonary disease patients. *Intensive Care Med*. 2003;29:603–610.
80. American Thoracic Society. Indications and standards for use of nasal continuous positive airway pressure (CPAP) in sleep apnoea syndromes. *Am J Respir Crit Care Med*. 1994;150:1738–1745.
81. Giles T, Lasserson TJ, Smith BJ, et al. Continuous positive airway pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev*. 2006;(3):CD001106, Available: http://summaries.cochrane.org/CD001106/.
82. Kaneko Y, Floras JS, Usui K, et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnoea. *N Engl J Med*. 2003;348:1233–1241.
83. Granton JT, Naughton MT, Benard DC, et al. CPAP improves respiratory muscle strength in patients with heart failure and central sleep apnoea. *Am J Respir Crit Care Med*. 1996;153:277–287.
84. Annane D, Orlikowski D, Chevret S, et al. Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. *Cochrane Database Syst Rev*. 2007;(4):CD001941, Available: http://summaries.cochrane.org/CD001941/.
85. Radunovic A, Annane D, Jewitt K, et al. Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database Syst Rev*. 2009;(4):CD004427, Available: http://summaries.cochrane.org/CD004427/.
86. Aboussouan LS, Khan SU, Meeker DP, et al. Noninvasive positive-pressure ventilation on survival in amyotrophic lateral sclerosis. *Ann Intern Med*. 1997;127:450–453.

38

Respiratory monitoring

Andrew D Bersten

History and respiratory examination are particularly important in the critically ill patient. Particular attention should be directed at the respiratory rate (f), the most poorly documented vital sign, the quantity and nature of sputum, and evidence of excessive inspiratory and/or expiratory pleural pressure changes and effort, which include accessory muscle use, tracheal tug, supraclavicular and intercostal indrawing, paradoxical abdominal movement (which is suggestive of diaphragmatic fatigue),[1] and pulsus paradoxus. During spontaneous ventilation, an excessive fall in blood pressure during inspiration (>10 mm Hg) is found both in low-output states such as cardiac tamponade, cardiogenic shock, pulmonary embolism, hypovolaemic shock, and in acute respiratory failure. The fall in pleural pressure during spontaneous inspiration has a curvilinear relationship with the fall in blood pressure. However, as there is marked variation between individuals,[2] pulsus paradoxus is most useful in following trends. A reduction in the degree of paradox may reflect improvement with a fall in the negative pleural pressure needed for ventilation, or may reflect respiratory muscle insufficiency, and an inability to generate the same negative pleural pressure.

Additional information can be gained from blood gases and pulse oximetry (see Chapter 18), and capnography, ventilatory pressures, and waveform analysis in patients receiving respiratory assistance. This chapter will focus on tests of respiratory function that are directly relevant to critically ill patients.

MONITORING GAS EXCHANGE

OXYGENATION

This is reviewed in Chapter 18, and is only briefly discussed here. Hypoxaemia may be due to a low partial pressure of inspired O_2 (rare), hypoventilation, diffusion impairment (rare), ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch, and shunt. Inert gas analysis has been used to quantitate $\dot{V}/\dot{Q}$ mismatch, and has demonstrated that hypoxaemia in acute respiratory distress syndrome (ARDS) is predominantly due to alveoli that are perfused but not ventilated (shunt),[3] consistent with computed tomography (CT) scan evidence of increased dependent lung density. The alveolar gas equation is a common but less accurate method to assess hypoxaemia:

$$(38.1)\quad P\mathrm{A}_{\mathrm{O}_2} = \text{inspired } P_{\mathrm{O}_2} - \mathrm{PaCO}_2 \text{ respiratory quotient}$$

where $P\mathrm{A}_{\mathrm{O}_2}$ is the alveolar PO_2, and this is usually simplified to:

$$(38.2)\quad P\mathrm{A}_{\mathrm{O}_2} = (760 - 47) \times F\mathrm{i}_{\mathrm{O}_2} - \mathrm{PaCO}_2/0.8$$

where 760 is atmospheric pressure in mm Hg, and 47 is the saturated vapour pressure of water at 37°C, since gas at the alveolus is fully humidified. The normal $P\mathrm{A}_{\mathrm{O}_2}$ to $P\mathrm{a}_{\mathrm{O}_2}$ gradient is less than 15 mm Hg, but increases to 25 mm Hg in the elderly. This normal A–a gradient is due to some venous admixture through the lungs, and a small right-to-left shunt through both the bronchial veins, and the thebesian veins of the coronary circulation. This equation removes hypercarbia as a direct cause of hypoxaemia, and an increase in the A–a gradient will usually be due to $\dot{V}/\dot{Q}$ mismatch or right-to-left shunt. A commonly used alternative measure of hypoxaemia is the $P\mathrm{a}_{\mathrm{O}_2}/F\mathrm{i}_{\mathrm{O}_2}$ ratio. However, this does not account for the effect of a raised $PaCO_2$, and both measures are influenced by a number of factors (e.g. cardiac output, Hb, $F\mathrm{i}_{\mathrm{O}_2}$) in addition to the extent of venous admixture, which may be estimated from the intrapulmonary shunt equation:

$$(38.3)\quad \dot{Q}_s/\dot{Q}_t = \mathrm{Cc}'_{\mathrm{O}_2} - \mathrm{Ca}_{\mathrm{O}_2} / \mathrm{Cc}'_{\mathrm{O}_2} - \mathrm{Cv}_{\mathrm{O}_2}$$

where $\dot{Q}_s$ is the intrapulmonary shunt blood flow, $\dot{Q}_t$ is the total pulmonary blood flow, $\mathrm{Cc}'_{\mathrm{O}_2}$ is the end-capillary O_2 content calculated from the $P\mathrm{A}_{\mathrm{O}_2}$, and $\mathrm{Ca}_{\mathrm{O}_2}$ and $\mathrm{Cv}_{\mathrm{O}_2}$ are the O_2 contents of arterial and mixed venous blood, respectively.

CARBON DIOXIDE

$PaCO_2$ is determined by alveolar ventilation ($\dot{V}_A$), and CO_2 production ($\dot{V}_{\mathrm{CO}_2}$):

$$(38.4)\quad P\mathrm{a}_{\mathrm{CO}_2}\ (\text{mm Hg}) = \dot{V}_{\mathrm{CO}_2}\ (\text{mL/min STPD}) \times 0.863/\dot{V}_{\mathrm{A}}\ (\text{L/min BTPS})$$

ABSTRACT

Respiratory monitoring can usefully assist clinical assessment of patients requiring respiratory support. Pulse oximetry is almost universally available, and continuously monitored. Capnography should be used to confirm endotracheal or tracheostomy placement, and to continuously monitor tube position during ventilatory assistance; however, arterial blood gases are still required when the absolute value of $PaCO_2$ is needed. In combination with an understanding of the methodology, various measures of respiratory mechanics including plateau pressure (Pplat), intrinsic PEEP (PEEPi), and respiratory system compliance and resistance, and observation of respiratory waveforms both help adjust ventilator support, reduce asynchrony and monitor responses to treatment. The clinical role of bedside measures of stress and strain remain uncertain.

KEYWORDS

Pulse oximetry
capnography
respiratory mechanics
compliance
resistance
respiratory waveforms
asynchrony

where $\dot{V}_A$ is the minute ventilation ($\dot{V}_E$) minus the wasted or dead space ventilation ($\dot{V}_D$). The modified Bohr equation (assuming $PA_{CO_2} = PaCO_2$) calculates the proportion of the V_T that is wasted ventilation (i.e. physiological dead space; V_{Dphys}):

$$(38.5) \qquad V_{Dphys}/V_T = PaCO_2 - P\bar{E}_{CO_2}/PaCO_2$$

where $P\bar{E}_{CO_2}$ is the mixed expired P_{CO_2}, and V_{Dphys} is composed of anatomical dead space (V_{Danat}) and alveolar dead space (V_{Dalv}) – notionally due to alveoli that are ventilated but not perfused. Normally V_{Dalv} is minimal and V_{Danat} comprises 30% of V_T. Since the volume of an endotracheal tube is less than the mouth or nose, and pharynx, intubation may reduce V_{Danat}; however, when the connection from the endotracheal tube is taken into account, there is little change in dead space. Positive-pressure ventilation increases dead space by distension of the airways increasing V_{Danat}, and through a tendency to increase alveoli that are ventilated but not perfused. In patients with ARDS, marked increases in V_{Dalv} lead to marked increases in the V_{Dphys}/V_T ratio (exceeding 0.6), which is an independent prognostic factor.[4]

CAPNOGRAPHY

Capnography measures and displays exhaled CO_2 throughout the respiratory cycle, with sampling usually by a mainstream sensor as side-stream systems tend to become blocked by secretions. However, when capnography is used in non-intubated patients, side-stream sampling is commonly used (e.g. modified nasal cannulae). Infrared spectroscopy measures the fraction of energy absorbed and converts this to a percentage of CO_2 exhaled. During expiration, the capnogram initially reads no CO_2, but as anatomical dead space is exhaled there is a rise in the exhaled CO_2 to a plateau, which falls to 0% CO_2 with the onset of inspiration. In patients with significant respiratory disease, a plateau may never be achieved. The end-tidal CO_2 (PE'_{CO_2}) is the value at the end of the plateau, and is normally only slightly less than the $PaCO_2$. However, this gradient will increase when alveolar dead space (V_{Dalv}) increases, such as low cardiac output, pulmonary embolism and elevated alveolar pressure. Consequently, the PE'_{CO_2} may not reflect $PaCO_2$ in critically ill patients. Nevertheless, in a stable patient the gradient will be fairly constant, and can be used to guide $\dot{V}_E$ during transport,[5] and when other factors including the adequacy of minute ventilation are unchanged, then sudden changes in the PE'_{CO_2} may provide an early signal. Indeed, PE'_{CO_2} directly correlates with cardiac output, and PE'_{CO_2} monitoring has been used to assess adequacy of cardiopulmonary resuscitation, and its prognosis.[6]

The presence of exhaled CO_2 confirms endotracheal tube placement, and is recommended even when the tube is seen to pass through the vocal cords,[7] since clinical assessment is not always reliable. Simple colorimetric devices may be used for this purpose. However, detection of expired CO_2 is not infallible[7] as false positives can rarely occur following ingestion of carbonated liquids, and false negatives may be due to extremely low pulmonary blood flow, or very large alveolar dead space such as pulmonary embolus or severe asthma. Capnography is also recommended during transport,[8] in all patients receiving intubated ventilator support,[9] and should be available for every anaesthetised patient.[10]

Sidestream capnography should also be considered during conscious sedation, as this is associated with reduced hypoxaemic episodes, and in morbidly obese patients or those receiving significant parenteral opiates in the intensive care unit (ICU).[11] Supplemental oxygen in these circumstances is routine but also reduces the sensitivity of pulse oximetry to detect ventilator problems.

GAS TRANSFER (DIFFUSING CAPACITY)

This is a test of the transfer of a gas, typically carbon monoxide (CO), across the alveolocapillary barrier. The transfer factor is calculated as:

$$(38.6) \qquad \text{volume of CO taken up}/(PA_{CO} - Pc_{CO})$$

and, as CO is so completely taken up by Hb, Pc_{CO} is taken as zero. This test is usually performed as an outpatient, is not usually measured in ICU, and diffusion abnormality is rarely a cause of hypoxaemia. The transfer factor is often corrected for lung volume since diseases such as emphysema and pulmonary fibrosis may affect both lung volume and diffusion. In chronic heart failure, diffusing capacity is reduced and correlates with exercise performance and chronic heart failure (CHF) severity and prognosis due to a reduction in the volume of alveolar tissue and amount of blood participating in gas exchange.[12]

LUNG VOLUME AND CAPACITIES

The tidal volume (V_T) is the volume of gas inspired and expired with each breath, and the volume at end expiration and zero positive end-expiratory pressure (PEEP) is the functional residual capacity (FRC); the end-expiratory lung volume (EELV) is the volume at end-expiration at a specified PEEP so that at PEEP 0 cm H_2O FRC is equal to EELV (Fig. 38.1). The residual volume (RV) is the FRC minus the expiratory reserve volume (ERV). If a maximum inspiratory effort is made from FRC, this is termed a vital capacity (VC) manoeuvre when the total lung capacity (TLC) is reached. Clinically, the most important of these are the FRC, EELV, V_T and VC, and the latter two are easily measured using a spirometer or integrated from flow.

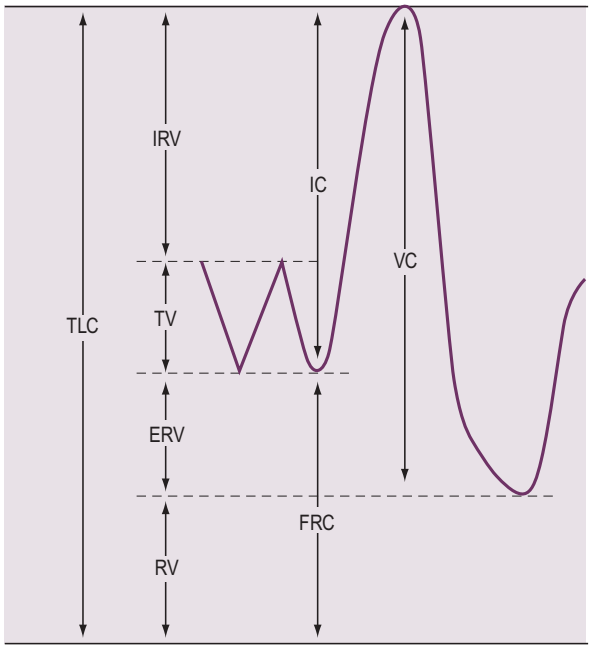


Figure 38.1 Lung volumes and capacities. *ERV*, Expiratory reserve volume; *FRC*, functional residual capacity; *IC*, inspiratory capacity; *IRV*, inspiratory reserve volume; *RV*, residual volume; *TLC*, total lung capacity; *TV*, tidal volume; *VC*, vital capacity.

TIDAL VOLUME

Minute volume is composed of f and V_T – normally ~17 breaths/min and ~400 mL, respectively, in adults.[13] Rapid shallow breathing is common in patients with respiratory distress, and in those failing weaning. Although the f/V_T ratio greater than 100 was initially shown to be highly predictive of weaning failure,[14] subsequent studies have reported varying results.

VITAL CAPACITY

At TLC, inspiratory muscle forces are counterbalanced by elastic recoil of the lung and chest wall (CW). Both these parameters and the size of the lung, which varies with body size and gender (Box 38.1), determine TLC. Vital capacity, the difference between TLC and FRC, is also reduced by factors that reduce FRC (e.g. increased abdominal CW elastance and premature airway closure in chronic obstructive pulmonary disease [COPD]). The normal VC is ~70 mL/kg; although reduction to 12–15 mL/kg has been suggested as an indication for mechanical ventilation, many other factors need to be considered, including the patient's general condition, the strength of the expiratory muscles, glottic function, and the response to non-invasive ventilation. Indeed, many chronically weak patients are able to manage at home with extremely low VC with the assistance of non-invasive ventilation.

Box 38.1 Factors that decrease vital capacity

Decreased muscle strength
- Myopathy
- Neuropathy
- Spinal cord injury

Increased lung elastance
- Pulmonary oedema
- Atelectasis
- Pulmonary fibrosis
- Loss of lung tissue

Increased chest wall elastance
- Pleural effusion
- Haemothorax
- Pneumothorax
- Kyphoscoliosis
- Obesity
- Ascites

Reduced functional residual capacity
- Atelectasis
- Premature airway closure (e.g. chronic obstructive pulmonary disease)

END-EXPIRATORY LUNG VOLUME

Direct measurement of EELV is rare in the ICU. Anatomical rather than functional estimates of EELV can be derived from CT scan, and while this remains a research standard it is not used clinically due to logistics. Techniques such as nitrogen or oxygen washout[15] are becoming available on modern ventilators but concerns regarding accuracy limit their use to changes in EELV greater than 200 mL.[16] When EELV is less than the closing volume, the lung volume at which airway closure is present during expiration, there is a marked increase in $\dot{V}/\dot{Q}$ mismatch. Consequently, PEEP is commonly used to elevate EELV. Increases in lung volume above resting lung volume can also be directly measured from a prolonged expiration to atmospheric pressure using either a spirometer or integration of flow,[17] or by repeated EELV measurements.[18] FRC is decreased in ARDS and pulmonary oedema, in patients with abdominal distension, and following abdominal and thoracic surgery. Increased FRC places the diaphragm at a mechanical disadvantage, and is seen with severe air-flow limitation and dynamic overinflation, and when there is loss of elastic recoil (e.g. emphysema).

ELECTRICAL IMPEDANCE TOMOGRAPHY

Electrical impedance tomography (EIT) uses impedance variation (as gas is a poor conductor) derived from multiple CW electrodes to monitor regional tidal ventilation. This is usually performed following a recruitment manoeuvre or change in PEEP setting.[19] Care must be taken to differentiate the diaphragm from collapsed lung, as the diaphragm moves cephalad both during

expiration and at lower lung volumes. EIT can be calibrated to volume, and used to examine changes in EELV but not FRC itself. PEEP may be adjusted to these changes and to indices of heterogeneity of ventilation. Automated summary analyses are being developed which may help assess variables such as the balance between non-aerated and overdistended lung.[20] Other developments include the assessment of lung perfusion and regional pulmonary function testing; however, clinical trials are needed prior with the potential to influence patient care to widespread use.

MEASUREMENT OF LUNG MECHANICS

The forces the respiratory muscles must overcome during breathing are the elastic recoil of the lung and CW, and airway and tissue resistance. During controlled mechanical ventilation, the ventilatory pressures reflect the work done to overcome these forces; however, during partial ventilatory support, the pressure at the airway opening reflects both these forces and those generated by the respiratory muscles. Estimates of respiratory mechanics are often readily available, and can assist titration of ventilatory support.

ELASTIC PROPERTIES OF LUNG AND CHEST WALL

The respiratory system (RS) is composed of the lung (L) and CW, which is comprised of the rib cage and abdomen. Although it is often convenient to consider RS mechanics as implying information about the lung, abnormal CW compliance can markedly influence these measurements.[21–25]

The pressure gradient across the lung (P_L) that generates gas flow is equal to the difference between the pressure at the airway opening (P_{ao}) and the mean pleural pressure (P_{pl}), which is estimated as the oesophageal pressure (P_{es}):

$$P_L = P_{ao} - P_{es} \quad (38.7)$$

Although the P_{es} is not always an accurate measure of the absolute P_{pl}, the change in P_{es} reflects the change in P_{pl}. However, this requires an appropriately positioned and functioning oesophageal balloon. In spontaneously breathing subjects, a thin latex balloon sealed over a catheter is introduced into the lower third of the oesophagus and P_{es} and P_{ao} measured simultaneously during an end-expiratory airway occlusion. A well-positioned oesophageal balloon will have a ratio of $\Delta P_{es}/\Delta P_{ao}$ of ~1.[26] This technique is reliable in supine, intubated spontaneously breathing patients[27] and in paralysed subjects it appears that a similar pressure change, induced by manual rib cage pressure,[28] can be used to verify oesophageal balloon function.

CW mechanics are derived from P_{es} referenced to atmospheric pressure and, in ventilated relaxed subjects, RS mechanics are derived from P_{ao} referenced to atmospheric pressure. It is not surprising then that $P_{RS} = P_L + P_{CW}$. Finally, abdominal mechanics can be estimated as either intravesical or intragastric pressure. However, despite these provisos, useful information can be obtained from RS mechanics.

Measuring the slope of the V–P relationship of the lung or RS allows a simple estimate of the elastic properties of the lung. Since the E_{RS} is directly related to its components ($E_{RS} = E_L + E_{CW}$), it is preferred to compliance, which is inversely related: $1/C_{RS} = 1/C_L + 1/C_{CW}$. The normal E_{RS} is 10–15 cm H_2O/L and the normal C_{RS} is 60–100 mL/cm H_2O in ventilated patients.

POSITIVE END-EXPIRATORY PRESSURE-TITRATION USING TRANSPULMONARY PRESSURE

Using a V_T of 6 m/kg pbw in patients with ARDS, PEEP-titration to achieve an end-expiratory transpulmonary pressure (Ptp; PEEP – oesophageal pressure) based on a Ptp Fi_{O_2} scale resulted in higher PEEP and plateau pressure (Pplat) levels, with both improved oxygenation, and Crs compared with conventional PEEP-titration[29] (ARDSnet protocol).[30] There was a trend to improved mortality but the trial was small (n = 61), and clinical outcomes, not physiologic data, should drive decision making; comparing V_T of 6 versus 12 mL/kg pbw oxygenation was worse in the lower V_T, lower-mortality group for the first 3 days.[30] However, there continues to be strong interest in using transpulmonary pressure to guide mechanical ventilation in ARDS.[31]

MEASUREMENT OF ELASTANCE

Elastance and resistance are frequency dependent, and respiratory mechanics depend upon the volume and volume history of the lung.[32] With increasing frequency of breathing, total RS resistance falls and elastance increases, and this is particularly obvious in patients with air-flow obstruction.[33,34] Consequently, these factors must be taken into account when interpreting respiratory mechanics. In a passively ventilated subject, P_{ao} is the sum of: (1) the pressure required to overcome airway, endotracheal tube and circuit resistance (P_{res}), (2) the elastic pressure required to expand the lung and CW (P_{el}), (3) the elastic recoil pressure at end expiration or total PEEP (P_o), and (4) the inertial pressure required to generate gas flow (P_{inert}):

$$P_{ao} = P_{el} + P_{res} + P_o + P_{inert} \quad (38.8)$$

Since the elastance (E) is equal to $\Delta P/\Delta V$, with the resistance (R) equal to $\Delta P/\Delta \dot{V}$, and ignoring the inertance,[35] this can be rewritten as the single-compartment equation of motion:

$$P_{ao} = E_{RS}V + R_{RS}\Delta\dot{V} + P_o \quad (38.9)$$

Elastance can then be measured using either static techniques, where cessation of gas flow allows dissipation of P_{res}, or dynamic techniques, where flow is not interrupted.

END-INSPIRATORY OCCLUSION METHOD

The simplest estimate of E_{RS} can be made using a rapid end-inspiratory airway occlusion during a constant flow breath, provided that the respiratory muscles are relaxed (Fig. 38.2). If a plateau is introduced at end inspiration, there is a sudden initial pressure drop due to dissipation of flow resistance ($P_{pk} - P_1$) followed by a slower, secondary pressure drop to a plateau ($P_{dif} = P_1 - P_2$) due to stress relaxation. At least 1–2 seconds are taken for this plateau to be achieved, and P_2 is often called the plateau pressure; however, if P_{plat} is measured too soon it will lie somewhere between P_1 and P_2.

Stress adaptation

Stress relaxation of the RS is due to both tissue viscoelasticity and time constant inequalities of the RS (pendelluft). In the normal lung, pendelluft has a minimal contribution to stress relaxation.[36] However, heterogeneity of regional resistance and elastance can markedly influence stress relaxation.[37] Pulmonary surfactant and its contribution to changes in surface tension, parenchymal factors including elastic fibres in the lung, contractile elements such as the alveolar duct muscle and changes in pulmonary blood volume have all been implicated in the viscoelastic properties of the lung. In the abnormal lung, it is difficult to separate either of these factors or the role of pendelluft in stress adaptation. However, pendelluft may contribute to lung injury in ARDS during triggered or supported ventilation.[38]

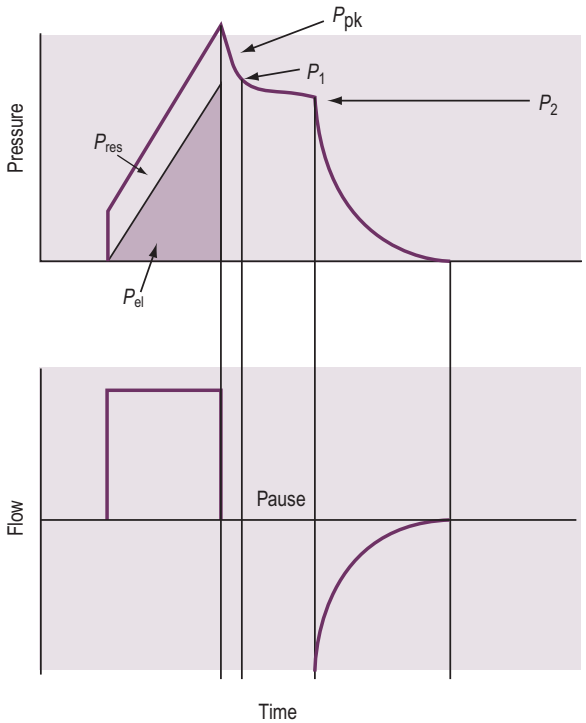


Figure 38.2 Schematic diagram of a volume-controlled breath with constant inspiratory flow. A period of no inspiratory gas flow has been interposed before expiration (pause) to illustrate dissipation of lung resistance as airways resistance (fall from P_{pk} to P_1) and tissue resistance (fall from P_1 to P_2). The inspiratory pressure due to the elastic properties of the respiratory system is illustrated in the top panel as the filled area (P_{el}), and the lung resistive pressure is labeled as P_{res}. (See text for more detail.)

Calculation of respiratory mechanics

Returning to Fig. 38.2, it is now simple to estimate RS resistance and elastance from P_{ao}. The static elastance ($E_{rs,st}$) and the dynamic elastance ($E_{rs,dyn}$) are calculated as:

$$E_{rs,st} = (P_2 - P_o)/V_T \quad (38.10)$$

$$E_{rs,dyn} = (P_1 - P_o)/V_T \quad (38.11)$$

where P_o is the total PEEP (extrinsic plus intrinsic PEEP). The difference between $P_{el,dyn}$ and $P_{el,st}$ is the effective recoil pressure of the RS during mechanical ventilation. Consequently, additional work is performed during inspiration to overcome stress adaptation, and this is stored and dissipated during expiration. This contributes to the hysteresis seen in dynamic volume-pressure curves during mechanical ventilation, and to the generation of expiratory flow. This latter component may be important in patients with air-flow obstruction since the imposition of a pause at end inspiration results in a 32% dissipation of the total energy loss within the RS.[39]

THE STATIC VOLUME–PRESSURE CURVE

The quasistatic volume–pressure (V–P) curve is infrequently performed, and the relevance of a measurement performed on a single occasion is questionable when lung mechanics are not constant. Various techniques have been described, but the overall concept is that incremental volume and pressure points are made after a sufficient period of no flow has allowed P_{res} to be dissipated. This allows definition of a sigmoidal-shaped curve with upper and lower inflection points, and a mid-section with relatively linear V–P relations, allowing inflation elastance to be measured as this slope at a given lung volume. If similar measures are made during deflation, a deflation curve and its hysteresis can also be described.

The V–P curve provides an advantage over an end-inspiratory elastance as, with the latter, it is not possible to know which part of the V–P curve is being measured. Consequently, this 'chord' elastance may span either inflection point, yielding a falsely high

figure. The upper inflection point represents a sudden decrease in elastance with increasing volume, and this has been interpreted as lung overdistention. The lower inflection point represents a sudden decrease in elastance with increased volume, and this has been interpreted as recruitment of atelectatic air spaces. Ventilation between these two inflection points should minimise both shearing forces secondary to repetitive collapse and reopening of alveoli, and overstretch of alveoli. However, this interpretation of the V–P curve has been questioned. In patients with ARDS, recruitment occurs well above the lower inflection point, along the entire V–P curve and above the upper inflection point.[40,41] An alternative interpretation is that the lower inflection point represents a zone of rapid recruitment, and that the upper inflection point is due to a reduced rate of recruitment.[42]

Conventionally the static V–P curve has been measured in paralysed ventilated patients with the 'supersyringe' method.[43] In a paralysed patient, the RS is progressively inflated from FRC in 100 mL steps up to ~1700 mL or a predefined pressure limit. After each step, sufficient time is allowed for a well-defined plateau to become apparent (using a pause of 3–6 seconds). The effects of temperature, humidity, gas compression and ongoing gas exchange during the manoeuvre need to be taken into account,[44,45] and the volume history standardised before it is performed. Many patients become hypoxaemic following disconnection from the ventilator during the 60 seconds or so without PEEP. An alternative is to randomly insert a range of single-volume inflations, followed by a prolonged pause,[46] during normal mechanical ventilation at 0 cm H_2O PEEP. Advantages include simplicity, the patient is not disconnected from the ventilator, the volume history is the same for each measurement and gas exchange during the measurement is negligible. However, again, many patients will become hypoxaemic due to prolonged periods without PEEP (this procedure may take ~15 minutes), particularly following a small-volume breath. Finally, an automated low-flow V–P curve method allowing subtraction of P_{res} is available on some ventilators, takes around 20 seconds to perform, and correlates well with the static occlusion technique.[47,48]

THE DYNAMIC VOLUME–PRESSURE CURVE

Dynamic P_{ao}, $\dot{V}$ and V are displayed by many ventilators, but the volume signal is not referenced to FRC and the signals are not readily available for quantitative analysis. However, $\dot{V}$ is readily measured with a heated pneumotachograph, and volume can then be derived by simple integration. If P_{ao} is also collected, it is relatively simple to measure dynamic mechanics.

The dynamic V–P curve appears to show hysteresis, due to the effects of airway and tissue resistance; however, during tidal breathing even the static V–P does not show hysteresis.[49] In contrast to static V–P relations, dynamic mechanics are collected during normal ventilation so they do not interfere with patient care, and they provide a 'functional' description of respiratory mechanics. Indeed, the 'effective' alveolar distending pressure is more accurately $P_{el,dyn}$, not $P_{el,st}$. Since dynamic mechanics are potentially continuous, they could also be used to servo-control ventilatory strategies.

There are a number of ways to analyse dynamic V–P data. A line can be drawn between no-flow points at end inspiration and end expiration to determine elastance; however, this is relatively inaccurate as it is based on two points that can be hard to exactly identify. Multiple linear regression analysis is now the technique most commonly employed. The patient does not need to be paralysed,[50] provided the respiratory muscles are not active during ventilation. The signal can also be split to allow analysis of inspiratory and expiratory mechanics.

Provided the model fit is acceptable, elastance and resistance are accurately and reproducibly calculated using the single compartment equation of motion:

$$P_{ao} = E_{RS}V + R_{RS}\Delta\dot{V} + P_o \quad (38.12)$$

Static intrinsic PEEP ($PEEP_i$) is accurately calculated, as $P_o - PEEP_e$, when compared with either an end-expiratory airway occlusion method[51] or by direct measurement of end-expiratory alveolar pressure.[52] However, the single compartment model only approximates the RS, and frequency and volume dependence of the derived mechanics are observed.

Changes in elastance during tidal breathing can be modelled with the stress index derived from power analysis of the P_{ao}–t curve ($P_{ao} = a^t + c$),[53] and addition of a volume-dependent term to the equation of motion[15,54]:

$$P_{ao} = (E_1 + E_2V)V + R_{RS}\Delta\dot{V} + P_o \quad (38.13)$$

$$E_{rs} = E_1 + E_2V \quad (38.14)$$

Since power analysis requires a constant inspiratory $\dot{V}$ pattern to discount resistive effects, it is not as versatile as the volume-dependent technique, which models resistance and can be applied to any inspiratory $\dot{V}$ pattern. Both measures correlate highly with each other, suggesting they measure the same parameter.

High stress, and possibly overinflation, is inferred when the stress index is greater than 1.1 and when the volume-dependent elastance increases, which may be quantified:

$$\%E_2 = 100E_2V/E_{rs} \quad (38.15)$$

A stress index below 0.9 and a negative volume dependence (negative $\%E_2$) suggest significant atelectasis during tidal breathing. Provided both V_T and

$\dot{V}$ are constant, the change in driving pressure, either $P_{pk} - PEEP_{tot}$ or $P_1 - PEEP_{tot}$ 20–30 minutes following a change in PEEP, is highly correlated with $\%E_2$.[15] Using the 95% predictive interval for these data, an increase in $\Delta P > 2$ cm H_2O, consistent with a significant increase in elastance, suggests high stress and overinflation. Similarly, the lowest E_{rs} during PEEP titration targets the best balance between recruitment and overinflation, and may be superior to the stress index or $\%E_2$ in laboratory models.[55]

Both the stress index and volume-dependent elastance also vary with stress relaxation, and high stress may not mean overinflation; in COPD, bullous lung disease is due to a loss of lung tissue and elastic recoil. This may be measured on CT as hyperaerated; however, the associated wall stress may be high or low depending upon the degree of inflation.

INTERPRETATION OF ELASTANCE

Elastance may be increased due to a reduction in lung volume or to an increase in specific elastance, the product of E and FRC. Small body size, female gender, lung resection and reduced aerated lung volume (e.g. ARDS) are important factors in reducing effective lung volume. Specific elastance is increased in ARDS, pulmonary oedema and pulmonary fibrosis.

MEASUREMENT OF THE RESISTANCE OF THE LUNG AND CHEST WALL

Lung resistance (R_L) is the sum of airway (R_{aw}) and tissue resistance (R_{ti}). Resistance is flow-, volume- and frequency-dependent, and R_L decreases as f increases. It is also important to compare measurements at similar lung volumes since there is a hyperbolic relation between lung volume and R. This is particularly obvious in ARDS, where the incremental administration of PEEP can result in a decrease in R_{aw} due to concurrent recruitment and an increase in lung volume. Indeed, although the absolute values are increased, when corrected for EELV R_L, R_{aw} and R_{ti} are unchanged in ARDS,[17] although specific R_{ti} did increase with PEEP.[21] Finally, since gas flow may be a mixture of laminar and turbulent flow, resistance is often flow-dependent.

END-INSPIRATORY OCCLUSION TECHNIQUE

The total inspiratory R_{aw}, including the endotracheal tube and associated ventilatory apparatus, can be calculated in a relaxed patient following an inspiratory pause (see Fig. 38.2) as:

$$R_{aw} = (P_{pk} - P_1)/\dot{V} \quad (38.16)$$

and R_L calculated by using P_2 instead of P_1. Since the endotracheal tube and apparatus will make a significant contribution to R_{aw}, it is best to measure P_{ao} distal to the endotracheal tube with an intratracheal catheter. An alternative approach is to calculate and subtract endotracheal tube resistance using the Rohrer equation ($R = K_1 + K_2\dot{V}$),[56] and this is now automatically included in some ventilators. However, as in vivo endotracheal tube resistance is often greater than in vitro resistance[57] due to the effect of secretions and interaction with the tracheal wall, these corrections may be inaccurate. Despite these provisos, this simple measure of resistance, or the P_{pk} to P_{plat} difference at a constant $\dot{V}$, can be clinically useful in both the diagnosis and monitoring of air-flow obstruction.[58]

DYNAMIC TECHNIQUES

Total, inspiratory and expiratory R can also be estimated, using either multiple linear regression analysis or from linear interpolation of the V–P curve at a constant volume. However, this latter technique assumes a constant elastance during tidal inflation, and may be inaccurate because it relies on only two measurements. Finally, an average expiratory R can be calculated from the time constant (τ) derived from passive expiration if the E is known, since:

$$\tau = R/E \quad (38.17)$$

However, the lung does not empty as a single compartment in patients with air-flow obstruction, and E is assumed to be constant over the tidal expiration.

OTHER MEASUREMENT TECHNIQUES

The interrupter technique consists of a series of short (100–200 ms) interruptions to relaxed expiration by a pneumatic valve.[59] This results in an expiratory plateau in P_{ao} following equilibration with alveolar pressure. From the V, P and $\dot{V}$ data, the expiratory elastance and the expiratory P–$\dot{V}$ relationship are measured. This technique does not make assumptions about the behaviour of the RS and can identify dynamic air-flow limitation.

Assuming that the RS behaves linearly, it can be analysed following a forced-flow oscillation at the airway opening.[60] The resultant pressure waveform depends upon the impedance of the RS, which can be analysed following Fourier analysis of the P and $\dot{V}$ waveforms into resistance and reactance. This will then allow measurement of R_{aw}, R_{ti}, E_{rs} and inertance, and information can be gained regarding small airways disease by examining R_{aw} at different oscillatory frequencies.

FORCED EXPIRATORY FLOW

Maximum expiratory flow rates from TLC, the forced vital capacity (FVC), the forced expiratory volume in the first second of expiration (FEV_1) and the peak expiratory flow rate (PEFR) are commonly measured in cooperative subjects with a spirometer or flow meter. The PEFR is cheap but is relatively effort-dependent, and is less specific and reliable than the FEV_1. It is most useful for office or home use. The normal PEFR

is 450–700 L/min in males and 300–500 L/min in females. It is reduced with obstructive diseases and gross muscle weakness.

The FEV_1 is usually expressed as a ratio of the FVC since both may be reduced in restrictive disease, with a normal ratio. The FEV_1 is normally 50–60 mL/kg and 70%–83% of FVC. In asthma and COPD, the FEV_1 is reduced out of proportion to the FVC to a ratio less than 70%.

MEASUREMENT OF INTRINSIC POSITIVE END-EXPIRATORY PRESSURE

$PEEP_i$ (1) may have unrecognised haemodynamic consequences,[61] (2) adds an elastic load to inspiratory work during assisted and supported ventilatory modes, which may be reduced by application of small amounts of $PEEP_e$,[62] and (3) reflects dynamic hyperinflation with the consequent risks of barotrauma[63] and right heart failure. If $PEEP_i$ is not taken into account during calculation of chord compliance, an incorrect denominator is used, which may result in gross error.[64] As automated measures of mechanics do not account for $PEEP_i$, estimates of elastance must be corrected.

The two most commonly described techniques for measuring $PEEP_i$ are end-expiratory airway occlusion in a relaxed subject and the fall in oesophageal pressure during inspiration prior to initiation of inspiratory $\dot{V}$. However, these are not really comparable measures since static and dynamic $PEEP_i$, respectively, are measured. Static $PEEP_i$ is measured as the plateau P_{ao} that is reached following an end-expiratory occlusion; typically a plateau is reached in ~5 seconds, but this will be shorter in ARDS and longer in severe COPD. With the cessation of gas flow, alveolar pressure equilibrates with P_{ao}. Since the lung is composed of non-homogeneous units, this will represent the average static $PEEP_i$. All respiratory effort must be absent since muscle pressure will increase end-expiratory P_{ao}. End expiration must be accurately identified. This is most easily done by the ventilator itself either using an end-expiratory hold manoeuvre or by using the next inspiration, the onset of which is concurrent with expiratory valve closure, to close a valve that directs inspiratory flow to atmosphere and seals the circuit. Static $PEEP_i$ is a surrogate measure of dynamic hyperinflation, and this volume may be directly measured using a spirometer[61] or a pneumotachograph[15] during a prolonged expiration.

Dynamic $PEEP_i$ is measured as the pressure change required to initiate inflation. In ventilated subjects, this will be the change in P_{ao} prior to initiation of inspiratory $\dot{V}$,[62] and in spontaneously breathing subjects the change in oesophageal[60] or transdiaphragmatic[65] pressure from their end-expiratory relaxation values prior to inspiratory $\dot{V}$. Measurement of dynamic $PEEP_i$ in spontaneously breathing subjects is not particularly straightforward. The changes in pressure are small and influenced by cardiogenic oscillations, which are preferably filtered out.[66] Furthermore, dynamic $PEEP_i$ is not constant, with breath-to-breath variation probably due to variation in the extent of dynamic hyperinflation. Many patients with air-flow obstruction have an active expiration that 'falsely' increases $PEEP_i$, at least with respect to its elastic load since cessation of active expiration does not require work.[67] Consequently, it is preferable to concurrently measure intragastric pressure as a measure of active expiration.

Finally, $PEEP_i$ can be measured as P_o from dynamic P, V and $\dot{V}$ data in ventilated subjects. This is thought to be a measure of dynamic $PEEP_i$ since static $PEEP_i$ systematically yields a slightly greater result,[51] with similar discrepancies reported between other dynamic measures of $PEEP_i$ and static $PEEP_i$.[68,69] This systematic difference correlates with, and is thought to be due to, the viscoelastic properties and regional time constant inequalities of the RS.[68] This has clinical significance as, although matching dynamic $PEEP_i$ with $PEEP_e$ reduces respiratory work through a decrease in elastic load,[62] it does not counterbalance these forces.

PATIENT–VENTILATOR ASYNCHRONY

Asynchrony between the patient and ventilator is more common than usually recognised during both intubated and non-invasive ventilatory support, and is often due to patient effort failing to trigger the ventilator. Clinical findings include agitation and anxiety, tachycardia, tachypnoea, and increased work of breathing. Careful observation of the patient–ventilator interaction, including waveforms, can be used to further identify and help match ventilatory assistance to neural drive.[70] (See also Chapter 31.)

INSPIRATION

TRIGGERING OF INSPIRATION

Ineffective respiratory efforts are best detected from the P_{es} waveform; however, this is rarely monitored. Ineffective triggering due to $PEEP_i$ may be detected from the expiratory $\dot{V}$ waveforms as an abrupt decrease in $\dot{V}$ at either the onset of inspiratory muscle activity or relaxation of the expiratory muscles. Monitoring of P_{ao} is less sensitive unless the circuit expiratory resistance is increased (e.g. heat and moisture exchanger [HME] or poorly functioning expiratory valve) so that small changes in expiratory $\dot{V}$ are reflected in P_{ao}. Sensing P_{ao} at the Y-piece may not offer any advantage, as the pressure signal needs to travel the same distance, usually via separate gas tubing to the ventilator expiratory block. Inadequate sensitivity may also lead to ineffective triggering with similar but more obvious waveform effects.

Autotriggering, a triggered assisted or supported breath without patient effort, may occur owing to

excessively low trigger threshold or to P_{ao} or $\dot{V}$ distortion, as commonly seen with large cardiogenic oscillations, hiccups, condensate in tubing or a circuit leak. Again, waveform analysis may help detect and manage the problem; for example, it may be necessary to reduce trigger sensitivity to prevent cardiogenic oscillations from being detected as inspiratory effort.

INSPIRATION

During an assisted volume control breath, P_{ao} may fall, often seen as a scalloped shape, if there is excessive inspiratory muscle effort as seen in $\dot{V}$ starvation. Expiratory muscle effort, as may be seen with an excessive V_T or prolonged inspiratory time (T_i), leads to a rise in P_{ao}. During an assisted pressure control breath or during pressure support, changes in patient effort are detected from the $\dot{V}$ waveform. Finally, excessively rapid development of the set delivered pressure, a rapid rise time, may be detected by an overshoot in P_{ao}; an excessively long rise time will be seen as a rounded inspiratory $\dot{V}$ profile, similar to that seen with continued inspiratory muscle effort.

CESSATION OF INSPIRATION

Mismatch of the mechanical and neural T_i can be detected from waveform changes at the cessation of inspiration.

Mechanical T_i shorter than neural T_i

There will be prolonged inspiratory muscle effort during early expiration; if this leads to a sufficient fall in P_{ao} or $\dot{V}$, an early triggered breath follows. During pressure-cycled ventilation this will lead to a second small I_T breath due to the high baseline lung volume, but in assist volume control P_{ao} will be excessive. Typically this is seen with a stiff RS, $PEEP_i$ or inadequate pressure support.

Mechanical T_i longer than neural T_i

This leads to features of passive inflation such as a linear increase in P_{ao} during assist volume control ventilation; during pressure-cycled ventilation there may be an increase in P_{ao} due to loss of inspiratory effort, or an unexplained fall in $\dot{V}$.

EXPIRATION

Changes in P_{ao} during expiration are usually small unless expiratory circuit resistance is abnormally high. However, in patients with expiratory flow limitation, the expiratory $\dot{V}$ waveform shows a typical 'tick' pattern; there is a rapid spike in expiratory flow due to dynamic compression of large conducting airways at the beginning of expiration, and this is followed by low, slowly declining expiratory $\dot{V}$ due to high $\dot{V}$ expiratory resistance. When $PEEP_i$ is present, the expiratory $\dot{V}$ fails to cease prior to the inspiratory trigger; however, this may be difficult to detect due to the poor fidelity present on most commercial ventilators.

MONITORING NEUROMUSCULAR FUNCTION

INSPIRATORY OCCLUSION PRESSURE

The pressure 100 ms (P_{100} or $P_{0.1}$) after a random occlusion timed at the beginning of inspiration is a measure of respiratory drive. There is a large range of normal values (1.5–5 cm H_2O), but it is reproducible in an individual patient. In ventilated patients, the $P_{0.1}$ correlates with the work of breathing during pressure support ventilation, and changes in the same direction as $PEEP_e$ is increased if work is reduced.[71] Consequently, $P_{0.1}$ may prove to be a useful method of titrating $PEEP_e$ in patients with dynamic hyperinflation; however, this is not valid when flow triggering is used.

MAXIMUM MOUTH PRESSURES

Maximum inspiratory (MIP) and expiratory (MEP) mouth pressures can be used to estimate the power of the respiratory muscles. MIP is usually measured in ventilated patients using a unidirectional expiratory valve for ~20 seconds.[72] This ensures the procedure is performed from a low lung volume and does not require patient cooperation. However, despite this the results are quite variable.[73] Normal values vary with age and gender; young females may exceed ~–90 cm H_2O, and young males ~–130 cm H_2O. A MIP <–20 cm H_2O is predictive of weaning failure; however, this is associated with too many false positives and negatives to be useful.[13] MEP may be useful in myopathic patients with expiratory muscle weakness. Transdiaphragmatic pressure is assessed using an oesophageal and gastric balloon to measure the pressure in these two cavities.

WORK OF BREATHING

The work of breathing (W_B) is the sum of elastic work (W_{el}), flow-resistive work (W_{res}) and inertial work (negligible), and can be estimated from V–P data during spontaneous or assisted ventilation. An oesophageal balloon is used to examine changes in pleural pressure, $\dot{V}$ is measured with a pneumotachograph, and volume is derived as its integral. Although conceptually W_B is the inspiratory area of a V–P loop, this needs to be referenced to the CW V–P curve, and the appropriate area measured from a Campbell diagram.[74]

The normal W_B is ~0.5 J/L of $\dot{V}_E$, and this may be significantly increased in patients with acute respiratory failure, and by additional work imposed by ventilatory apparatus including the endotracheal tube and connector, humidifier and ventilator circuit.[75] The consequences of a large increase in W_B may include an increase in the $\dot{V}O_2$ attributable to breathing ($\dot{V}O_{2resp}$), respiratory muscle insufficiency, CO_2 retention and acute respiratory failure. However, W_B is rarely measured outside of research projects since

the Campbell diagram is a relatively tedious approach. Simplifications have been used, but these are not as accurate, and W_B only estimates energy expenditure during muscle shortening with relatively poor correlation with $\dot{V}O_{2resp}$.[76] Consequently, the pressure-time product (PTP), which does correlate with $\dot{V}O_{2resp}$,[77] is more commonly measured.[10]

PRESSURE–TIME PRODUCT

PTP is usually calculated from the oesophageal pressure-time integral during inspiration. In mechanically ventilated patients, the oesophageal pressure during assisted breathing is compared with that during a controlled breath, or that pressure calculated from the CW elastance and lung volume.[10] However, the early correlation of $\dot{V}O_{2resp}$ with PTP used the transdiaphragmatic pressure in spontaneously breathing subjects.[74] Using either technique, importantly, the effort expended before $\dot{V}$ occurs due to $PEEP_i$ is measured, probably accounting for the better correlation of $\dot{V}O_{2resp}$ with PTP than W_B.[74] Although incremental pressure support ventilation may reduce PTP in COPD patients, the effect can be variable with some patients also showing evidence of expiratory muscle activity due to delayed sensing of neural expiration.[10]

ELECTRICAL ACTIVITY OF THE DIAPHRAGM

Using a modified nasogastric tube, electrical activity of the diaphragm (EAdi) can be monitored, and used to drive neutrally assisted ventilation.[78] While EAdi and transdiaphragmatic pressure (Pdi) usually show a strong correlation, suggesting that EAdi could replace the need for P_{es} monitoring in some circumstances, electromechanical uncoupling may occur when the diaphragm is placed under mechanical disadvantage such as the presence of PEEPi.[31] During triggered ventilation, EAdi may help diagnose and manage asynchrony, and this technique offers assistance diagnosing and managing neuromuscular disorders, particularly those with minimal peripheral muscle manifestations.

ULTRASOUND

Lung ultrasound is covered in Chapter 40. Ultrasound can also be used to measure diaphragm thickness at the zone of apposition, and fractional thickening is predictive of weaning trial outcome.[79]

KEY REFERENCES

14. Yang K, Tobin MJ. A prospective study of indices predicting outcome of trials of weaning from mechanical ventilation. *N Engl J Med*. 1991;324:1445–1450.
30. Mauri T, Yoshida T, Bellani G, et al. Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives. *Intensive Care Med*. 2016;42:1360–1373.
55. Carvalho AR, Spieth PM, Pelosi P, et al. Ability of dynamic airway pressure curve profile and elastance for positive end-expiratory pressure titration. *Intensive Care Med*. 2008;34:2291–2299.
62. Petrof BJ, Legare M, Goldberg P, et al. Continuous positive airway pressure reduces work of breathing and dyspnea during weaning from mechanical ventilation in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1990;141:281–289.
70. Georgopoulos D, Prinianakis G, Kondili E. Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies. *Intensive Care Med*. 2006;32:34–47.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Cohen CA, Zagelbaum G, Gross D, et al. Clinical manifestations of inspiratory muscle fatigue. *Am J Med*. 1982;73:308–316.
2. Martin J, Jardin J, Sampson M, et al. Factors influencing pulsus paradoxus in asthma. *Chest*. 1981; 80:543–549.
3. Dantzker DR, Brook CJ, Dehart P, et al. Ventilation–perfusion distributions in the adult respiratory distress syndrome. *Am Rev Respir Dis*. 1979;120:1039–1052.
4. Nuckton TJ, Alonso AJ, Kallet RH, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. *N Engl J Med*. 2002;346:1281–1286.
5. Palmon SC, Liu M, Moore LE, et al. Capnography facilitates tight control of ventilation during transport. *Crit Care Med*. 1996;24:608–611.
6. Levine RL. End-tidal CO_2: physiology in pursuit of clinical applications. *Intensive Care Med*. 2000; 26:1595–1597.
7. Deakin CD, Nolan JP, Soar J, et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 4. Adult advanced life support. *Resuscitation*. 2010;81:1305–1352.
8. Australasian College for Emergency Medicine, Joint Faculty of Intensive Care Medicine; Australian and New Zealand College of Anaesthetists. Minimum standards for transport of critically ill patients. Review IC-10 (2003). *Emerg Med (Fremantle)*. 2003; 15(2):197–201.
9. *Minimum standards for intensive care units*. Joint Faculty of Intensive Care, Medicine, Review IC-1. 2003.
10. Guidelines on Monitoring During Anaesthesia, Australian and New Zealand College of Anaesthetists (ANZCA) - PS18, 2015.
11. *Capnography for Monitoring End-Tidal CO2 in Hospital and Pre-hospital Settings: A Health Technology Assessment*. Issue Number: 142, Publication Date: March 2016.
12. Agostoni O, Bussotti M, Cattadori G, et al. Gas diffusion and alveolar–capillary unit in chronic heart failure. *Eur Heart J*. 2006;27:2538–2543.
13. Jubran A. Advances in respiratory monitoring during mechanical ventilation. *Chest*. 1999;116:1416–1425.
14. Yang K, Tobin MJ. A prospective study of indices predicting outcome of trials of weaning from mechanical ventilation. *N Engl J Med*. 1991;324: 1445–1450.
15. Henderson WR, Sheel AW. Pulmonary mechanics during mechanical ventilation. *Resp Physiol Neurobiol*. 2012;180:162–172.
16. Richard J-C, Pouzot C, Pinzon AM, et al. Reliability of the nitrogen washin-washout technique to assess end-expiratory lung volume at variable PEEP and tidal volumes. *Intensive Care Med Exp*. 2014;2:10.
17. Bersten AD. Measurement of overinflation by multiple linear regression analysis in patients with acute lung injury. *Eur Respir J*. 1998;12:526–532.
18. Dellamonica J, Lerolle N, Sargentini C, et al. PEEP-induced changes in lung volume in acute respiratory distress syndrome. Two methods to estimate alveolar recruitment. *Intensive Care Med*. 2011;37:1595–1604.
19. Lundin S, Stenqvist O. Electrical impedance tomography: potentials and pitfalls. *Curr Opin Crit Care*. 2012;18:35–41.
20. Frerichs I, Amato MBP, Kaam AH, et al. Chest electrical impedance tomography examination, data analysis, terminology, clinical use and recommendations: consensus statement of the Translational EIT development study group. *Thorax*. 2017;72(1):83–93. doi:10.1136/thoraxjnl-2016-208357.
21. Pelosi P, Cereda M, Foti G, et al. Alterations of lung and chest wall mechanics in patients with acute lung injury: effects of positive end-expiratory pressure. *Am J Respir Crit Care Med*. 1995;152: 531–537.
22. Mergoni M, Martelli A, Volpi A, et al. Impact of positive end-expiratory pressure on chest wall and lung pressure-volume curve in acute respiratory failure. *Am J Respir Crit Care Med*. 1997;156: 846–854.
23. Ranieri VM, Brienza N, Santostasi S, et al. Impairment of lung and chest wall mechanics in patients with acute respiratory distress syndrome: role of abdominal distension. *Am J Respir Crit Care Med*. 1997;156:1082–1091.
24. Gattinoni L, Pelosi P, Suter PM, et al. Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes? *Am J Respir Crit Care Med*. 1998;158:3–11.
25. Baydur A, Behrakis PK, Zin WA, et al. A simple method for assessing the validity of the esophageal balloon technique. *Am Rev Respir Dis*. 1982;126:788–791.
26. Higgs BD, Behrakis PK, Bevan DR, et al. Measurement of pleural pressure with esophageal balloon in anesthetized humans. *Anesthesiology*. 1983; 59:340–343.
27. Lanteri CJ, Kano S, Sly PD. Validation of esophageal pressure occlusion test after paralysis. *Pediatr Pulmonol*. 1994;17:56–62.
28. Talmor D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med*. 2008;359:2095–2104.
29. Ventilation with lower tidal volumes as compared with traditional volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000;342:1301–1308.
30. Mauri T, Yoshida T, Bellani G, et al. Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives. *Intensive Care Med*. 2016;42:1360–1373.
31. Fredberg JJ, Stamenovic D. On the imperfect elasticity of lung tissue. *J Appl Physiol*. 1989;67: 2408–2419.

32. Grimby G, Takishima T, Graham W, et al. Frequency dependence of flow resistance in patients with obstructive lung disease. *J Clin Invest*. 1968;47:1455–1465.
33. Woolcock AJ, Vincent NJ, Macklem PT. Frequency dependence of compliance as a test for obstruction in the small airways. *J Clin Invest*. 1969;48: 1097–1106.
34. Mead J. Measurement of inertia of the lungs at increased ambient pressure. *J Appl Physiol*. 1956; 9:208–212.
35. Bates JH, Rossi A, Milic-Emili J. Analysis of the behavior of the respiratory system with constant inspiratory flow. *J Appl Physiol*. 1985;58:1840–1848.
36. Otis AB, McKerrow CB, Bartlett RA, et al. Mechanical factors in distribution of pulmonary ventilation. *J Appl Physiol*. 1956;8:427–443.
37. Yoshida T, Torsani V, Gomes S, et al. Spontaneous effort causes occult pendelluft during mechanical ventilation. *Am J Respir Crit Care Med*. 2013;188: 1420–1427.
38. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med*. 2017;195:438–442.
39. Jonson B, Beydon L, Brauer K, et al. Mechanics of respiratory system in healthy anesthetized humans with emphasis on viscoelastic properties. *J Appl Physiol*. 1993;75:132–140.
40. Jonson B, Richard J-C, Straus R, et al. Pressure-volume curves and compliance in acute lung injury: evidence for recruitment above the lower inflection point. *Am J Respir Crit Care Med*. 1999;159: 1172–1178.
41. Crotti S, Mascheroni D, Caironi P, et al. Recruitment and derecruitment during acute respiratory failure: a clinical study. *Am J Respir Crit Care Med*. 2001;164: 131–140.
42. Hickling KG. The pressure–volume curve is greatly modified by recruitment. A mathematical model of ARDS lungs. *Am J Respir Crit Care Med*. 1998;158: 194–202.
43. Matamis D, Lemaire F, Harf A, et al. Total respiratory pressure-volume curves in the adult respiratory distress syndrome. *Chest*. 1984;86: 58–66.
44. Gattinoni L, Mascheroni D, Basilico E, et al. Volume/pressure curve of total respiratory system in paralysed patients: artefacts and correction factors. *Intensive Care Med*. 1987;13:19–25.
45. Dall'ava-Santucci J, Armaganidis A, Brunet F, et al. Causes of error of respiratory pressure-volume curves in paralyzed subjects. *J Appl Physiol*. 1988; 64:42–49.
46. Levy P, Similowski T, Corbeil C, et al. A method for studying volume-pressure curves of the respiratory system during mechanical ventilation. *J Crit Care*. 1989;4:83–89.
47. Servillo G, Svantesson C, Beydon L, et al. Pressure–volume curves in acute respiratory failure: automated low flow inflation versus occlusion. *Am J Respir Crit Care Med*. 1997;155:1629–1636.
48. Lu Q, Vieira SRR, Richecoeur J, et al. A simple automated method for measuring pressure-volume curves during mechanical ventilation. *Am J Respir Crit Care Med*. 1999;159:275–282.
49. Beydon L, Svantesson C, Brauer K, et al. Respiratory mechanics in patients ventilated for critical lung disease. *Eur Respir J*. 1996;9:262–273.
50. Peslin R, da Silva JF, Chabot F, et al. Respiratory mechanics studied by multiple linear regression in unsedated ventilated patients. *Eur Respir J*. 1992;5:871–878.
51. Eberhard L, Guttmann J, Wolff G, et al. Intrinsic PEEP monitored in the ventilated ARDS patient with a mathematical method. *J Appl Physiol*. 1992;73: 479–485.
52. Nicolai T, Lanteri C, Freezer N, et al. Non-invasive determination of alveolar pressure during mechanical ventilation. *Eur Respir J*. 1991;4:1275–1283.
53. Grasso S, Terragni P, Mascia L, et al. Airway pressure–time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury. *Crit Care Med*. 2004;32:1018–1027.
54. Kano S, Lanteri CJ, Duncan AW, et al. Influence of nonlinearities on estimates of respiratory mechanics using multilinear regression analysis. *J Appl Physiol*. 1994;77:1185–1197.
55. Carvalho AR, Spieth PM, Pelosi P, et al. Ability of dynamic airway pressure curve profile and elastance for positive end-expiratory pressure titration. *Intensive Care Med*. 2008;34:2291–2299.
56. Sullivan M, Paliotta J, Saklad M. Endotracheal tube as a factor in measurement of respiratory mechanics. *J Appl Physiol*. 1976;41:590–592.
57. Wright PE, Marini JJ, Bernard GR. In vitro versus in vivo comparison of endotracheal tube airflow resistance. *Am Rev Respir Dis*. 1989;140:10–16.
58. Manthous CA, Hall JB, Schmidt GA, et al. Metered-dose inhaler versus nebulized albuterol in mechanically ventilated patients. *Am Rev Respir Dis*. 1993;148:1567–1570.
59. Gottfried SB, Rossi A, Higgs BD, et al. Noninvasive determination of respiratory system mechanics during mechanical ventilation for acute respiratory failure. *Am Rev Respir Dis*. 1985;131:414–420.
60. Peslin R, Fredberg JJ. Oscillation mechanics of the respiratory system. In: *Handbook of Physiology. The Respiratory System: Mechanics of Breathing*. Bethesda, MD: American Physiological Society; 1986:145–177.
61. Pepe PE, Marini JJ. Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction: the auto-PEEP effect. *Am Rev Respir Dis*. 1982;126:166–170.
62. Petrof BJ, Legare M, Goldberg P, et al. Continuous positive airway pressure reduces work of breathing and dyspnea during weaning from mechanical ventilation in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1990;141:281–289.

63. Tuxen DV, Lane S. The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe air-flow obstruction. *Am Rev Respir Dis*. 1987;136:872–879.
64. Rossi A, Gottfried SB, Zocchi L, et al. Measurement of static compliance of the total respiratory system in patients with acute respiratory failure during mechanical ventilation. The effect of intrinsic positive end-expiratory pressure. *Am Rev Respir Dis*. 1985;131:672–677.
65. Lessard MR, Lofaso F, Brochard L. Expiratory muscle activity increases intrinsic positive end-expiratory pressure independently of dynamic hyperinflation in mechanically ventilated patients. *Am J Respir Crit Care Med*. 1995;151:562–569.
66. Schuessler TF, Gottfried SB, Goldberg P, et al. An adaptive filter to reduce cardiogenic oscillations on esophageal pressure signals. *Biomed Eng*. 1998;26: 260–267.
67. Ninane V, Yernault JC, de Troyer A. Intrinsic PEEP in patients with chronic obstructive pulmonary disease. Role of expiratory muscles. *Am Rev Respir Dis*. 1993;148:1037–1042.
68. Maltais F, Reissmann H, Navalesi P, et al. Comparison of static and dynamic measurements of intrinsic PEEP in mechanically ventilated patients. *Am J Respir Crit Care Med*. 1994;150:1318–1324.
69. Yan S, Kayser B, Tobiasz M, et al. Comparison of static and dynamic intrinsic positive end-expiratory pressure using the Campbell diagram. *Am J Respir Crit Care Med*. 1996;154:938–944.
70. Georgopoulos D, Prinianakis G, Kondili E. Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies. *Intensive Care Med*. 2006;32:34–47.
71. Mancebo J, Albaladejo P, Touchard D, et al. Airway occlusion pressure to titrate positive end-expiratory pressure in patients with dynamic hyperinflation. *Anesthesiology*. 2000;93:81–90.
72. Caruso P, Friedrich C, Denari SDC, et al. The unidirectional valve is the best method to determine maximal inspiratory pressure during weaning. *Chest*. 1999;115:1096–1101.
73. Multz AS, Aldrich TK, Prezant DJ, et al. Maximal inspiratory pressure is not a reliable test of inspiratory muscle strength in mechanically ventilated patients. *Am Rev Respir Dis*. 1990;142: 529–532.
74. Banner MJ, Jaeger MJ, Kirby RR. Components of the work of breathing and implications for monitoring ventilator-dependent patients. *Crit Care Med*. 1994;22:515–523.
75. Bersten AD, Rutten AJ, Vedig AE, et al. Additional work of breathing imposed by endotracheal tubes, breathing circuits and intensive care ventilators. *Crit Care Med*. 1989;17:671–680.
76. Annat G, Viale J-P. Measuring the breathing workload in mechanically ventilated patients. *Intensive Care Med*. 1990;16:418–421.
77. Field S, Sanci S, Grassino A. Respiratory muscle oxygen consumption estimated by the diaphragmatic pressure-time index. *J Appl Physiol*. 1984;57: 44–51.
78. Piquilloud L, Vignaux L, Bialais E, et al. Neurally adjusted ventilatory assist improves patient-ventilator interaction. *Intensive Care Med*. 2011;37: 263–271.
79. DiNio E, Gartman EJ, Sethi J, et al. Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. *Thorax*. 2014;69: 423–427.

39

Chest imaging

Simon PG Padley, Patrick MT Wong

RADIOLOGICAL TECHNIQUES

Of the imaging techniques available for investigating patients in the intensive care unit (ICU), the chest radiograph remains the most important, with ultrasound being utilised in a selected group of patients. High-resolution and computed tomography (CT) allow further investigation of these patients in certain situations.

CHEST RADIOGRAPHY

The views of the chest most frequently performed in the ambulant patient are the erect posteroanterior (PA) and lateral projections, taken with the patient breath-holding at total lung capacity. While portable or mobile chest radiography, as undertaken on an ICU, has the obvious advantage that the examination can be done without moving the patient from the ward, there are many disadvantages. These include:

- shorter focus–film distance causing magnification
- limited X-ray output necessitating long exposure times with resultant movement blurring
- difficulties with satisfactory patient positioning.

COMPUTED TOMOGRAPHY

CT relies on differing absorption of X-rays by tissues with constituents of differing atomic number, so slight differences in X-ray absorption can be interpreted to produce a cross-sectional image. The components of a CT scanner are an X-ray tube, which rotates around the patient, and an array of X-ray detectors opposite the tube.

Spiral (also known as volume or helical) scanning entails sustained patient exposure by the rotating X-ray tube during continuous movement of the examination couch through the CT gantry aperture. In this way, a continuous data set or 'spiral' of information may be acquired in a single breath-hold.

INTRAVENOUS CONTRAST ENHANCEMENT

The inherent high contrast on CT between vessels and surrounding air in the lung, and vessels and surrounding fat within the mediastinum reduces the need for intravenous contrast enhancement in most instances. However, in some circumstances, for example to aid the distinction between hilar vessels and a soft-tissue mass or to detect a pulmonary artery embolus, contrast is required. The timing of the injection of contrast media depends on the technical attributes of the CT scanner. Rapid scanning protocols with automated injectors tend to improve contrast enhancement of vascular structures at the expense of enhancement of solid lesions because of the rapidity of scanning. Timing of image acquisition is vital for accurate diagnosis of pulmonary embolism. However, when examining inflammatory lesions such as the reaction around an empyema, it may be necessary to delay scanning by 60 seconds to allow contrast to diffuse into the extravascular space.

CLINICAL APPLICATIONS OF HIGH-RESOLUTION COMPUTED TOMOGRAPHY IN THE INTENSIVE CARE UNIT PATIENT

High-resolution computed tomography (HRCT) is increasingly being used to confirm the impression of an abnormality seen on a chest radiograph. HRCT may also be used to achieve a histospecific diagnosis in some patients with obvious but non-specific radiographic abnormalities. Furthermore, HRCT has provided a number of useful insights into chest disease in the severely ill patient in an ICU setting.

High-resolution computed tomography in uncomplicated acute respiratory distress syndrome[1]

- HRCT reveals that the apparently homogeneous opacification apparent on the chest radiograph has an anterior-to-posterior graded increase in density – an appearance referred to as a gravitational gradient (Fig. 39.1).
- HRCT demonstrates early dilatation of the smaller airways within areas of ground-glass density, an appearance that suggests development of fibrosis, and may prompt anti-inflammatory treatment.
- HRCT demonstrates that a shift from the supine to the prone position results in redistribution of

ABSTRACT

This chapter discusses an approach to chest imaging useful for intensivists. An approach to plain film interpretation is described. Common intensive care conditions are presented with a focus on important imaging considerations.

KEYWORDS

Radiology
X-ray
CT
ICU
ARDS
trauma

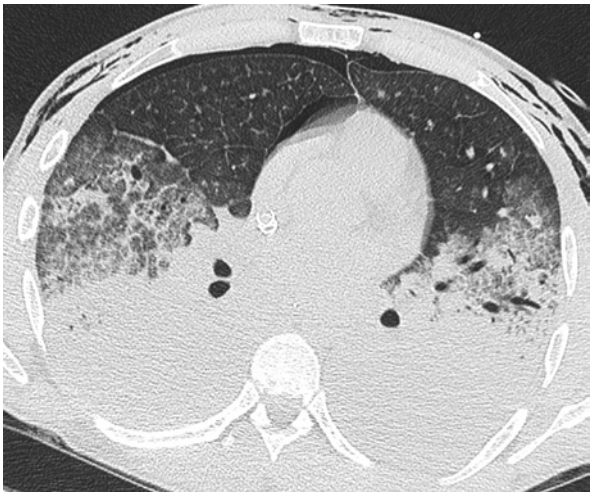


Figure 39.1 Computed tomography of a patient with acute respiratory distress syndrome. Note the marked anterior-to-posterior-density gradient. The anterior lung is of almost normal density, becoming of ground-glass attenuation in the mid part of the lung before fading into consolidation posteriorly. There are small pneumothoraces bilaterally and surgical emphysema.

the previously dependent dense parenchymal opacification to the now dependent anterior lung, a phenomenon that may be accompanied by improvements in patient oxygenation.

High-resolution computed tomography of complications of acute respiratory distress syndrome

- Infection is common in acute respiratory distress syndrome (ARDS). Diagnosis may be difficult. Radiographically there may be a lack of specific findings, often due to superimposition of changes attributable to ARDS. This is a particular problem in the critically ill patient when the usual indicators of pneumonia are also unreliable. Although the diagnosis may still be in question following HRCT, associated pneumonic changes such as abscess formation, empyema and mediastinal disease, as well as development of non-dependent areas of consolidation, are all useful pointers to superadded infection (see Fig. 39.1).
- Barotrauma – mediastinal and interstitial emphysema, as well as pneumothorax, are all increasingly common at higher levels of peak end-expiratory pressure (PEEP). The incidence of barotrauma has been reported to be as high as 50%.
- HRCT allows the exact location of loculated air collections to be defined.

NORMAL RADIOGRAPHIC ANATOMY

THE MEDIASTINUM, CENTRAL AIRWAYS AND HILAR STRUCTURES

Appreciation of abnormality requires a sound grasp of normal radiological anatomy. The mediastinum is delimited by the lungs on each side, the thoracic inlet above, the diaphragm below and the vertebral column posteriorly. Because the various structures that make up the mediastinum are superimposed on each other on the chest radiograph, they cannot be separately identified. Key points include:

- Only the outline of the mediastinum and the air-containing trachea and bronchi (and sometimes oesophagus) are clearly seen on a normal chest radiograph.
- The right superior mediastinal border is formed by the right brachiocephalic vein and superior vena cava (SVC), and becomes less distinct as it reaches the thoracic inlet. The right side of the superior mediastinum can appear to be considerably widened in patients with an abundance of mediastinal fat.
- The left mediastinal border above the aortic arch is the result of summation of the left carotid and left subclavian arteries together with the left brachiocephalic and jugular veins.
- The left cardiac border comprises the left atrial appendage, which merges inferiorly with the left ventricle. The silhouette of the heart should always be sharply outlined. Any blurring of the border is due to loss of immediately adjacent aerated lung, usually by collapse or consolidation.
- The density of the heart shadow to the left and right of the vertebral column should be identical and any difference indicates pathology (e.g. an area of consolidation or a mass in a lower lobe).
- The trachea and main bronchi should be visible through the upper and middle mediastinum.
- In older individuals, the trachea may be displaced by a dilated aortic arch. In approximately 60% of normal subjects, the right wall of the trachea (the right paratracheal stripe) can be identified as a line of uniform thickness (less than 4 mm in width); when it is visible it excludes the presence of an adjacent space-occupying lesion, most usually lymphadenopathy.
- The carinal angle is usually less than 80 degrees. Splaying of the carina is an insensitive sign of subcarinal disease, either in the form of massive subcarinal lymphadenopathy, or a markedly enlarged left atrium.
- The origins of the lobar bronchi, where they are projected over the mediastinal shadow, can usually be identified but the segmental bronchi within the lungs are not generally seen on plain radiography.

- Normal hilar shadows on a chest radiograph represent the summation of the pulmonary arteries and veins.
- The hila are approximately the same size and the left hilum normally lies between 0.5 cm and 1.5 cm above the level of the right hilum. The size and shape of the hila show remarkable variation in normal individuals, making subtle abnormalities difficult to identify.

THE PULMONARY FISSURES, VESSELS AND BRONCHI

The two lungs are separated by the four layers of pleura behind and in front of the mediastinum. The resulting posterior and anterior junction lines are often visible on chest radiographs as nearly vertical stripes, the posterior junction line lying higher than the anterior.

The upper and lower lobes of the left lung are separated by the major (or oblique) fissure. The upper, middle and lower lobes of the right lung are separated by the major fissure and the minor (horizontal or transverse) fissure. The minor fissure is visible in over half of normal PA chest radiographs. The major fissures are not visible on a frontal radiograph and are inconstantly identifiable on lateral radiographs. In a few individuals, fissures are incompletely developed – a point familiar to thoracic surgeons performing a lobectomy because of incomplete cleavage between lobes. Accessory fissures are occasionally seen.

All of the branching structures seen within normal lungs on a chest radiograph represent pulmonary arteries or veins. It is often impossible to distinguish arteries from veins in the lung periphery. On a chest radiograph taken in the erect position, there is a gradual increase in the diameter of the vessels, at equidistant points from the hilum, travelling from lung apex to base; this gravity-dependent effect disappears if the patient is supine or in cardiac failure.

THE DIAPHRAGM AND THORACIC CAGE

The interface between aerated lung and the diaphragm is sharp and the highest point of each dome is normally medial to the midclavicular line. The right dome of the diaphragm is higher than the left by up to 2 cm in the erect position unless the left dome is elevated by air in the stomach (Fig. 39.2).

Filling-in or blunting of these costophrenic angles usually represents pleural disease, either pleural thickening or an effusion.

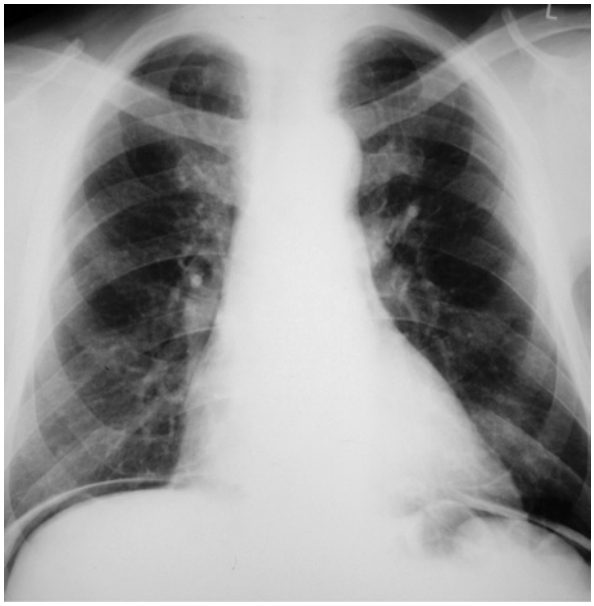


Figure 39.2 Erect chest radiograph of a patient with a pneumoperitoneum demonstrating the normal thickness in position of the hemidiaphragms. The right lies slightly higher than the left.

POSITIONING OF TUBES AND LINES[3]

CENTRAL VENOUS CATHETERS

The end of a central venous catheter (CVC) needs to be intrathoracic, and is ideally in the SVC. CVCs may be introduced via an antecubital, subclavian or jugular vein. Subclavian venous puncture carries a risk of pneumothorax and mediastinal haematoma. Rarely, perforation of the subclavian vein leads to fluid collecting in the mediastinum or pleura. All catheters have a potential risk of coiling, misplacement, knotting and fracture (Fig. 39.3). The tip should not abut the vessel wall at an obtuse angle.

PULMONARY ARTERY FLOTATION CATHETERS

Ideally, the end of the catheter should be maintained less than 5–8 cm (2–3 inches) beyond the bifurcation of the main pulmonary artery in either the right or left pulmonary artery (see Fig. 39.3). When the pulmonary artery occlusion pressure is measured, the balloon is inflated, and the flow of blood carries the catheter tip peripherally, to an occluded position. After the measurement has been made, the balloon is deflated and the catheter returns to a central position; otherwise, there is a risk of pulmonary infarction. The inflation balloon is radiolucent. The balloon should normally be kept deflated.

NASOGASTRIC TUBES

These should reach the stomach but may coil in the oesophagus or occasionally are inserted into the tracheobronchial tree (Fig. 39.4).

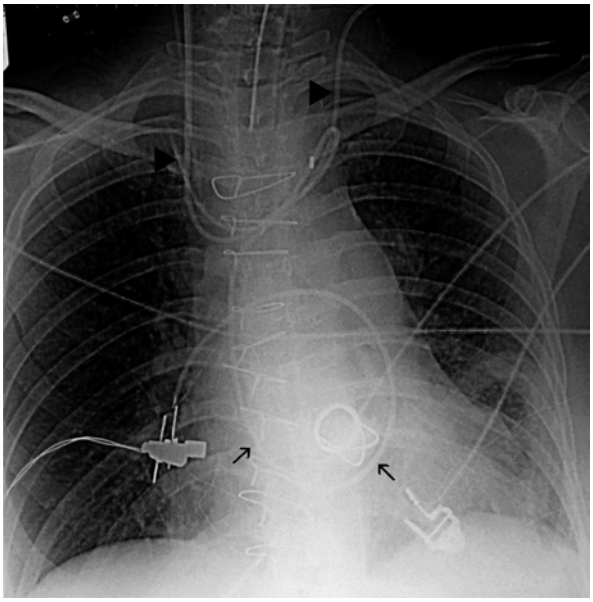


Figure 39.3 Intensive care unit patient with multiple tubes and lines in place. The endotracheal tube tip position is satisfactory, and there are sternotomy wires, an intra-aortic balloon pump (radiopaque tip in the proximal descending aorta) and a prosthetic heart valve. The central line inserted into the left internal jugular vein passes into the right internal jugular vein. The Swan–Ganz catheter, which has been inserted via the right internal jugular vein, loops into the left brachiocephalic vein, before taking a satisfactory course through the cardiac chambers *(black arrows)*.

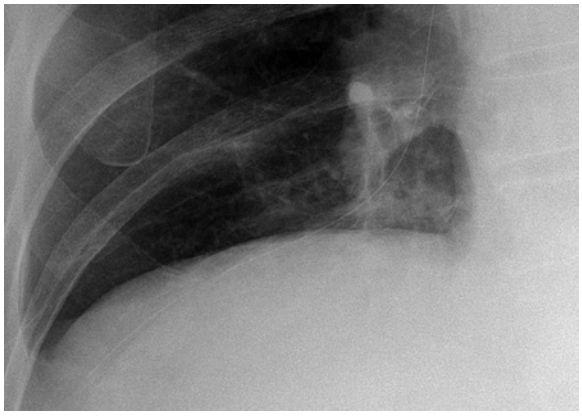


Figure 39.4 Misplaced nasogastric tube.

ENDOTRACHEAL TUBES

Extension and flexion of the neck may make the tip of an endotracheal tube move by as much as 5 cm. With the neck in neutral position, the tip of the tube should ideally be about 4–5 cm above the carina. A tube that is inserted too far usually passes into the right bronchus, with the risk of non-ventilation or collapse of the left lung (Fig. 39.5).

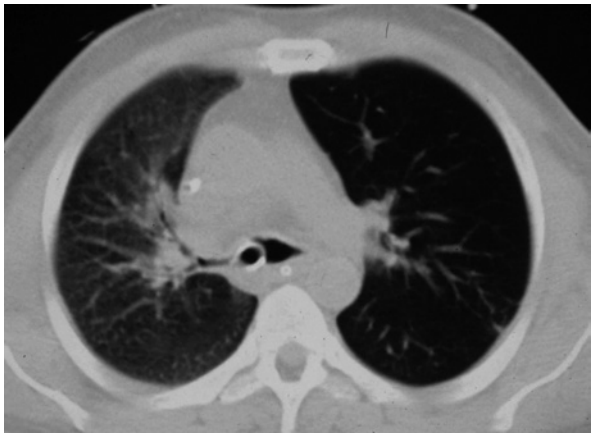


Figure 39.5 Endotracheal tube inserted into the right main bronchus as demonstrated on computed tomography. This image, obtained in expiration, demonstrates air trapping in the left lung.

TRACHEOSTOMY TUBES

The tube tip should be situated centrally in the airway at the level of T_3. Acute complications of tracheostomy include pneumothorax, pneumomediastinum and subcutaneous emphysema. Long-term complications include tracheal ulceration, stenosis and perforation.

PLEURAL TUBES

These are used to treat pleural effusions and pneumothoraces. A radiopaque line usually runs along pleural tubes and is interrupted where there are side holes. It is important to check that all the side holes are within the thorax. Tracks may remain on the chest X-ray following removal of chest tubes, causing tubular or ring shadows. When doubt remains about tube position, then CT scanning should be considered (Fig. 39.6).

MEDIASTINAL DRAINS

These are usually present following sternotomy. Apart from their position, they look like pleural tubes.

INTRA-AORTIC BALLOON PUMP

These are used in patients with cardiogenic shock, often following cardiac surgery. The ideal position of the catheter tip is just distal to the origin

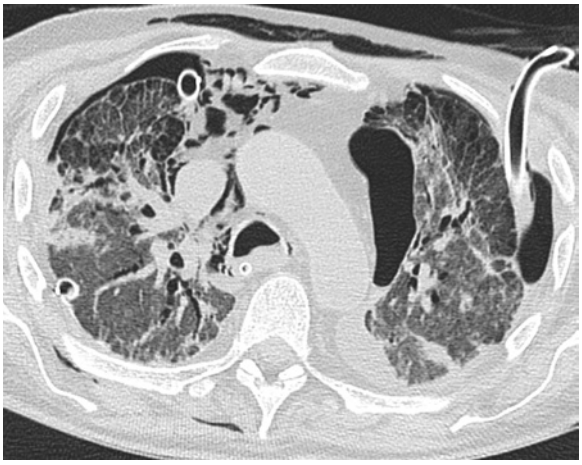


Figure 39.6 Computed tomography scan demonstrating bilateral pneumothoraces in a patient with acute respiratory distress syndrome. Note is made of bilateral chest drains.

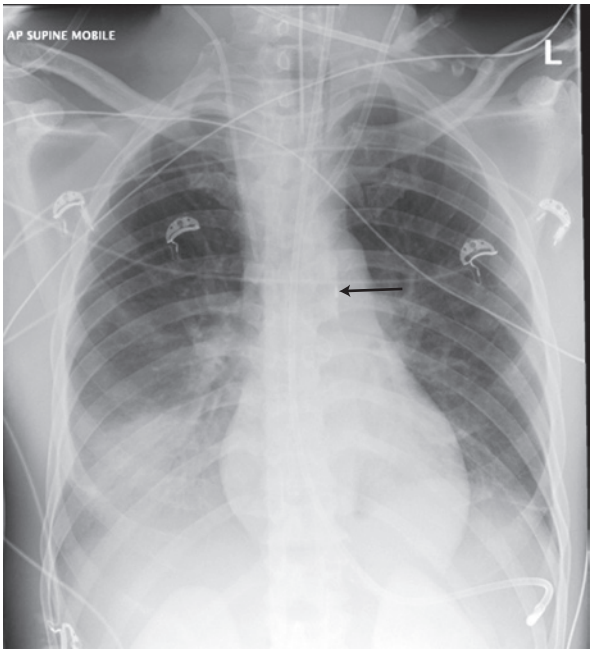


Figure 39.7 Intra-aortic balloon pump. The tip *(arrow)* is seen appropriately positioned in the proximal descending aorta. The patient suffered septic cardiomyopathy due to multilobar pneumococcal pneumonia.

of the left subclavian artery (Fig. 39.7). If the catheter tip is advanced too far it may occlude the left subclavian artery, and if it is too distal the balloon may occlude branches of the abdominal aorta. The intra-aortic balloon pump may be visible only by its radiopaque tip.

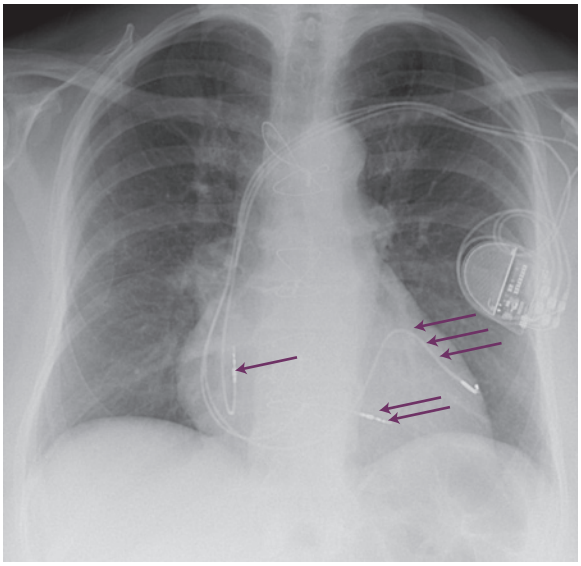


Figure 39.8 Biventricular pacemaker. Note the right atrial lead *(arrow)*, right ventricular lead *(double arrows)* and coronary sinus lead *(triple arrows)*.

PACEMAKERS

These may be permanent or temporary (Fig. 39.8). Temporary epicardial wires are sometimes inserted during cardiac surgery, and may be seen as thin, almost hair-like metallic opacities overlying the heart. Temporary pacing electrodes are usually inserted transvenously via a subclavian or jugular vein. If a patient is not being paced properly, a chest radiograph may reveal that the position of the electrode tip is unstable, or that a fracture in the wire has occurred.

EXTRACORPOREAL MEMBRANE OXYGENATION

Extracorporeal membrane oxygenation (ECMO) cannulae are large bore, and can be classified as veno-venous or veno-arterial based on line location.

Veno-venous ECMO: the venous drainage cannula should be placed in the proximal SVC or inferior vena cava (IVC) and return cannula should be placed in the right atrium (Fig. 39.9). Veno-arterial ECMO: the venous drainage cannula should be placed in the right atrium, distal IVC or SVC and the return cannula should be within the aorta or its branches (Fig. 39.10).

Line-associated complications include venous tear, arterial pseudoaneurysm, haemorrhage and thrombosis, which can be identified on CT. Systemic complications include thrombosis, pulmonary or systemic emboli (including ischaemic stroke), disseminated intravascular coagulation, systemic haemorrhage and especially intracranial haemorrhage (Fig. 39.11).

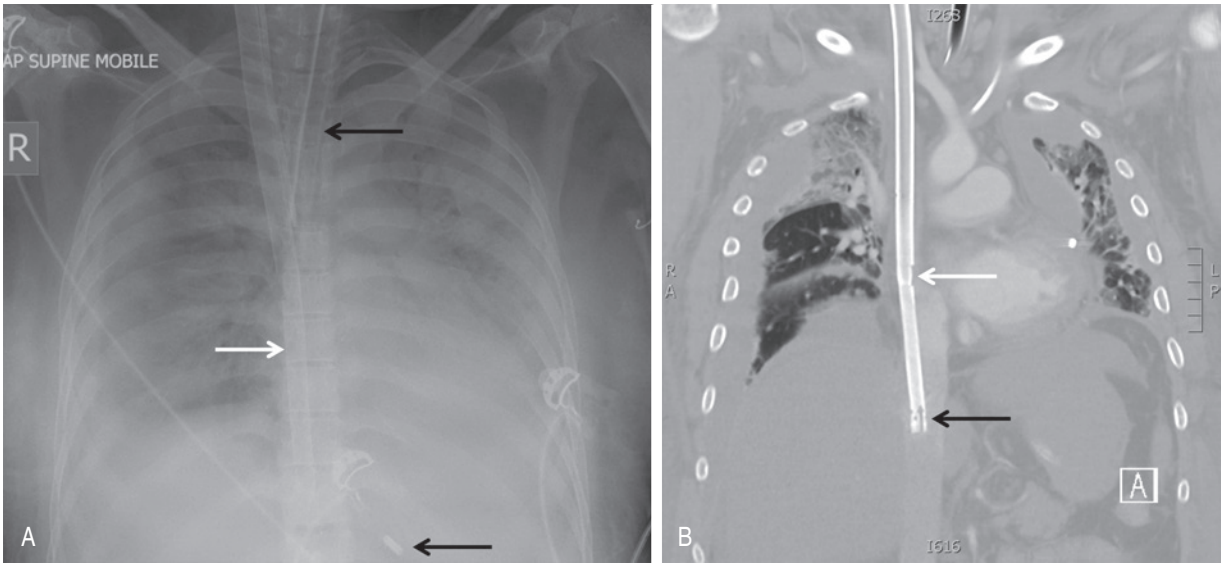


Figure 39.9 (a) Chest radiograph of an adult male patient with acute respiratory distress syndrome demonstrating the single puncture dual lumen venovenous-extracorporeal membrane oxygenation Avalon catheter in situ *(white arrow)*. The draining and returning holes cannot be demonstrated on plain radiographs. Endotracheal and nasogastric tubes are also in situ *(black arrows)*. (b) Maximum intensity projection (MIP) coronal images on lungs windows demonstrate the position of the Avalon cannula inserted via the right internal jugular vein (RIJV), the holes of the draining lumen *(black arrow)* and the hole of the return lumen *(white arrow)*.

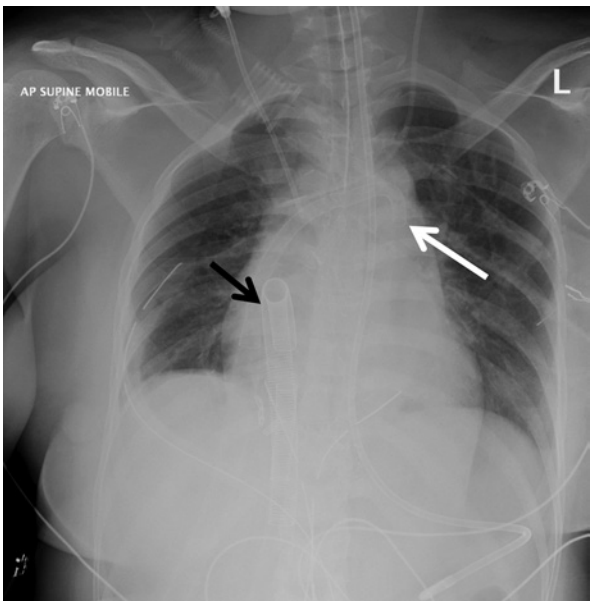


Figure 39.10 Venoarterial-extracorporeal membrane oxygenation in a patient with massive pulmonary embolism. The drainage cannula is in the right atrium *(black arrow)*. The return cannula is in the proximal descending aorta *(white arrow)*.

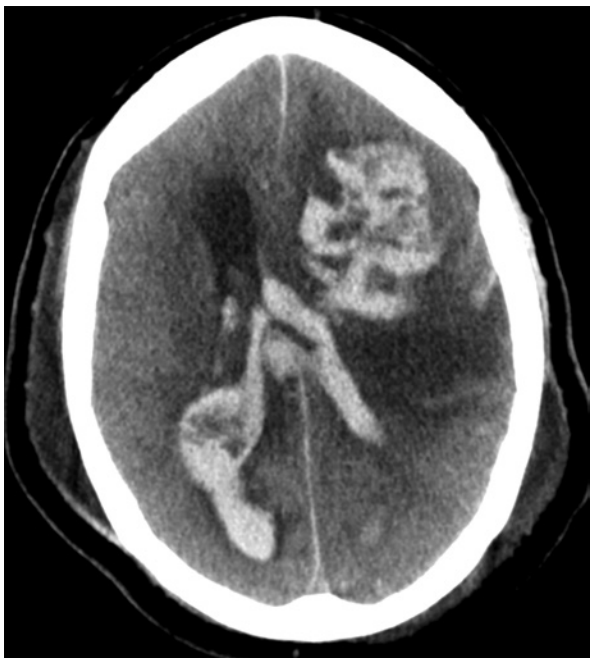


Figure 39.11 Unenhanced axial computed tomography head image of a 71-year-old male on venoarterial-extracorporeal membrane oxygenation post aortic aneurysm repair. There is a large intraparenchymal, subarachnoid and intraventricular haemorrhage.

RADIOGRAPHIC SIGNS OF PATHOLOGY

CONSOLIDATION

Consolidation, or synonymously air space shadowing, is due to opacification of the air-containing spaces of the lung, usually without a change in volume of the affected area. It is not possible to tell what the air space filling is due to in the absence of a clinical history, except perhaps for shadowing due to cardiogenic alveolar oedema, when there will be associated signs of cardiac failure. Typical features of all forms of consolidation (Fig. 39.12) include:

- ill-defined margins, except where it directly abuts a pleural surface
- sharply demarcated by fissures
- loss of vascular markings
- air bronchograms – the bronchi, usually invisible, may become apparent in negative contrast to the air space opacification
- acinar opacities, due to individual acini or secondary pulmonary lobules being opacified but still surrounded by normally aerated lung, usually seen at the periphery of a more confluent area of consolidation, and 0.5–1 cm in diameter
- ground-glass opacification, when consolidation has caused only partial filling of the air spaces
- silhouette sign – consolidation abutting a soft-tissue structure causes the silhouette of that structure to be lost.

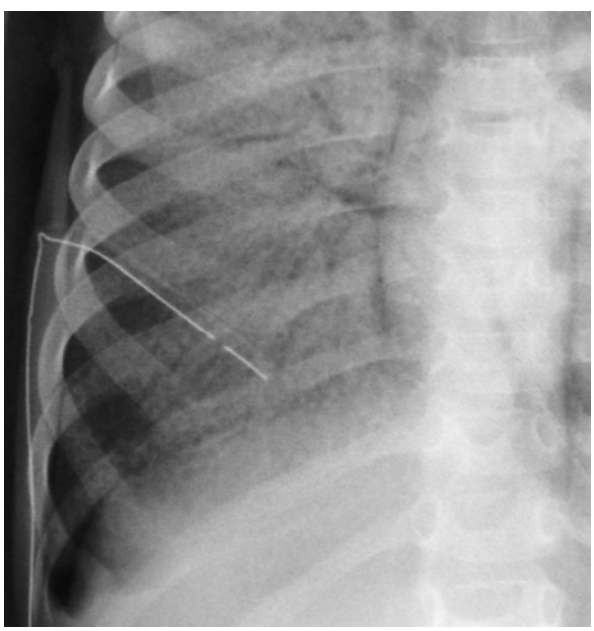


Figure 39.12 Close-up view of an area of consolidation adjacent to the right heart border, which is obscured. Air bronchograms can be identified passing through this area. A chest tube is in situ.

When an area of consolidation undergoes necrosis, due to either infection or infarction, then liquefaction may result, and if there is either a gas-forming organism or communication with the bronchial tree, then an air-fluid level may develop in addition to cavity formation.

The radiographic signs of a lobar consolidation are similar to those of lobar collapse (see section on Collapse, below), with the exception that there is no volume loss.

COLLAPSE

When there is partial or complete volume loss in a lung or lobe, this is referred to as collapse or atelectasis, implying a diminished volume of air in the lung with associated reduction of lung volume. There are several different mechanisms for lung or lobar collapse, for example relaxation or passive collapse, when fluid or air accumulates in the pleural space; cicatrisation collapse, when volume loss is associated with pulmonary fibrosis; adhesive collapse, as in ARDS; and resorption collapse, as in bronchial obstruction.

The radiographic appearance in pulmonary collapse depends upon a number of factors. These include the mechanism of collapse, the extent of collapse, the presence or absence of consolidation in the affected lung and the pre-existing state of the pleura. This latter factor includes the presence of underlying pleural tethering or thickening and the presence of pleural fluid.

The direct signs of collapse include:

- displacement of interlobar fissures
- loss of aeration resulting in increased density or the presence of the silhouette sign
- crowding of vessels and bronchi.

The indirect signs of collapse include:

- elevation of the hemidiaphragm, especially with lower lobe collapse
- mediastinal displacement, especially in upper lobe collapse
- hilar displacement, where the hilum is elevated in upper lobe collapse and depressed in lower lobe collapse
- compensatory hyperinflation of remaining normal lung, resulting in increased transradiancy or herniation across the midline from the normal side
- crowding of the ribs reflecting diminished overall volume of the affected hemithorax.

COMPLETE LUNG COLLAPSE

Complete collapse (Fig. 39.13) will cause complete opacification of the hemithorax, with displacement of the mediastinum to the affected side and elevation of the hemidiaphragm. Compensatory hyperinflation of the contralateral lung with herniation across

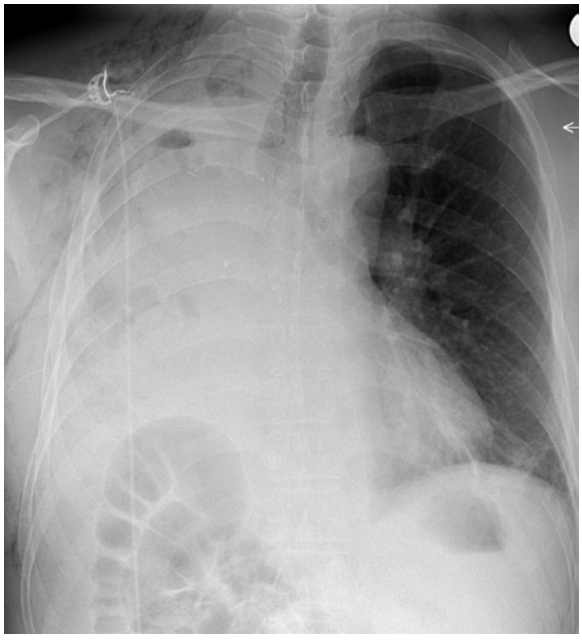


Figure 39.13 Complete lung collapse. There was an obstructing tumour in the right main bronchus. The right hemithorax is opaque, the mediastinum has shifted and the trachea is deviated to the right.

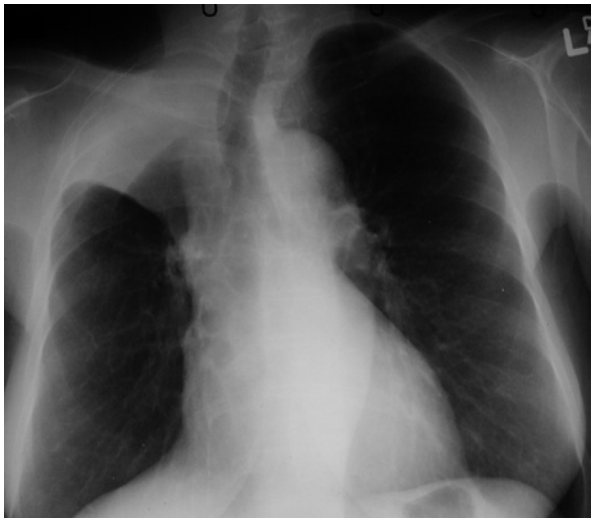


Figure 39.14 Right upper lobe collapse. The horizontal fissure has become elevated and the right upper lobe has become a wedge-shaped density extending from the hilum to the right lung apex. There is evidence of volume loss with shift of the trachea to the right side.

the midline may be apparent. Herniation may occur in the retrosternal space, anterior to the ascending aorta, or may be posterior to the heart.

INDIVIDUAL OR COMBINED LOBAR COLLAPSE

In any situation, some or all of the signs may be present.

Right upper lobe collapse (Fig. 39.14)

- Horizontal fissure moves upwards and medially towards the superior mediastinum.
- Trachea deviates to the right.
- Compensatory hyperinflation of the right middle and lower lobes.

Middle lobe collapse (Fig. 39.15)

- Horizontal fissure and lower half of the oblique fissure move towards each other – best seen on the lateral projection.
- Frontal radiograph changes may be subtle, with obscuration of the right heart border.
- Indirect signs of volume loss are rarely obvious.

Right lower lobe collapse

- There is partial depression of the horizontal fissure.
- There is triangular opacity of the collapsed lower lobe on the frontal projection, usually obscuring the diaphragm but preserving the right heart border.

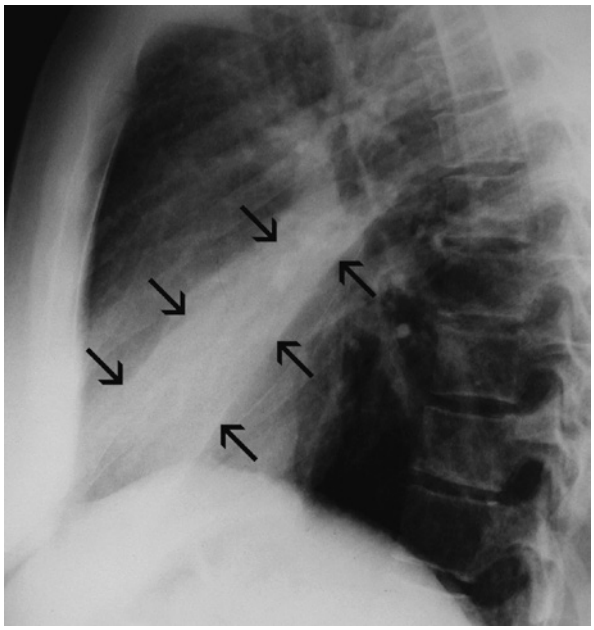


Figure 39.15 Middle lobe collapse. The horizontal fissure is depressed and demarcates the collapsed middle lobe as a wedge-shaped density best demonstrated on the lateral *(arrows)*.

- Eventually a completely collapsed lower lobe may be so small that it flattens and merges with the mediastinum, producing a thin, wedge-shaped shadow.

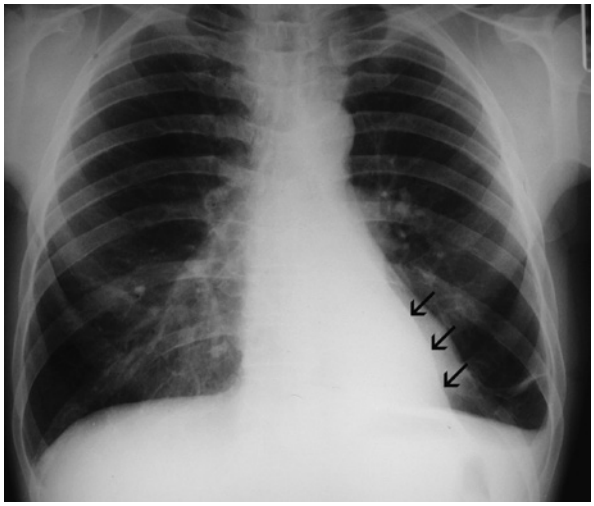


Figure 39.16 Left lower lobe collapse. The left lower lobe has become a wedge-shaped density behind the heart, forming a double left heart border *(arrows)*. The left hilar vessel to the lower lobe has disappeared as a result of collapse.

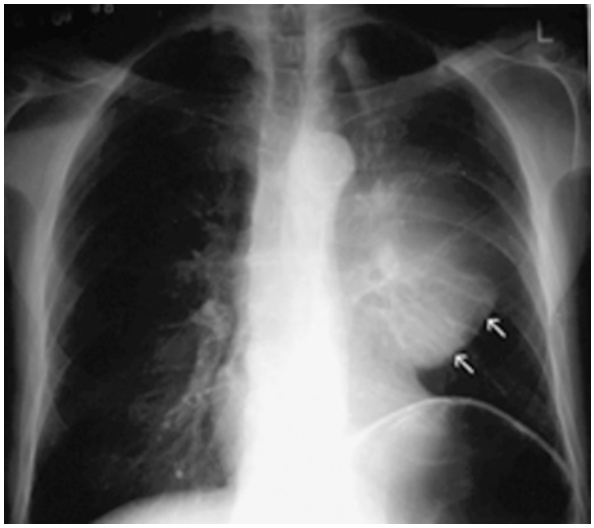


Figure 39.17 Left upper lobe collapse. A hazy opacity extends from the hilum towards the left lung apex. It is sharply demarcated inferiorly and laterally *(white arrows)* owing to the presence of a large tumour at the left hilum, which is obstructing the left upper lobe bronchus. Note the signs of volume loss, particularly the elevation of the left hemidiaphragm.

Left lower lobe collapse (Fig. 39.16)

- Collapsed lobe may be obscured by the heart and a penetrated view may be required.
- Mediastinal structures and the diaphragm adjacent to the non-aerated lobe are obscured.
- Extreme volume loss may cause the lobe to be so small as to be invisible as a separate opacity.
- There is loss of lower lobe artery silhouette at the hilum.

Lingula collapse

- Is often involved in collapse of the left upper lobe.
- May collapse individually, leading to focal blurring of the central left heart border.
- Radiographic features are similar to those of middle lobe collapse.

Left upper lobe collapse (Fig. 39.17)

- Lateral view demonstrates anterior displacement of the entire oblique fissure, oriented almost parallel to the anterior chest wall, demarcating the posterior surface of the upper lobe as an elongated opacity extending from the apex almost reaching the diaphragm and lying anterior to the hilum.
- Eventually the upper lobe retracts posteriorly and loses contact with the anterior chest wall.
- Frontal radiograph demonstrates an ill-defined hazy opacity in the upper, mid and sometimes lower zones, with loss of hilar clarity.
- Hilum is often elevated, and the trachea deviated to the left.

COMBINED COLLAPSE

Right lower and middle lobe collapse is the most common pairing since a lesion may occur in the bronchus intermedius. The appearances are similar to right lower lobe collapse except that the horizontal fissure is not apparent, and the opacification reaches the lateral chest wall on the frontal radiograph, and similarly extends to the anterior chest wall on the lateral view.

Right upper and middle lobe collapse is much less common because of the distance between the origins of their bronchi, and can generally be taken to imply the presence of more than one lesion. This combination will produce appearances almost identical to those of left upper lobe collapse (see Fig. 39.17). On occasion, isolated right upper lobe collapse will also produce appearances that are identical to left upper lobe collapse.

UNILATERAL INCREASED TRANSRADIANCY

The commonest causes are technical and include:

- patient rotation
- poor beam centring
- offset grid.

Pathological causes include:

- chest wall changes
- mastectomy

- congenital unilateral absence of pectoral muscles, known as Poland syndrome
- reduced vascularity when interruption or significant reduction in the blood supply to one lung may cause that lung to be of increased transradiancy
- lung hyperexpansion due to air trapping or asymmetric emphysema.

When there is relative increased transradiancy of one hemithorax for which there is no obvious cause, then the possibility of generalised increase in radiopacity of the opposite side should be considered – for example, the posterior layering of a pleural effusion in a supine patient. Usually hypertransradiancy due to technical factors can be identified by comparison of the soft tissues around the shoulder girdle, and particularly over the axillae.

ABNORMALITIES OF THE MEDIASTINUM

Pneumomediastinum or mediastinal emphysema is the presence of air between the tissue planes of the mediastinum (see section on Injuries to the mediastinum). Chest radiography may show vertical translucent streaks in the mediastinum, representing air separating the soft-tissue planes. The air may extend up into the neck and over the chest wall, causing subcutaneous emphysema, and also over the diaphragm. The mediastinal pleura may be displaced laterally and then be visible as a thin stripe alongside the mediastinum.

Acute mediastinitis is usually due to perforation of the oesophagus, pharynx or trachea and chest radiograph usually shows widening of the mediastinum and pneumomediastinum.

Mediastinal haemorrhage may occur from venous or arterial bleeding. The mediastinum appears widened, and blood may be seen tracking over the lung apices. It is imperative to identify a life-threatening cause such as aortic rupture.

Aortic dissection or aneurysmal dilatation may also cause widening of the mediastinal silhouette on chest radiography (Fig. 39.18).

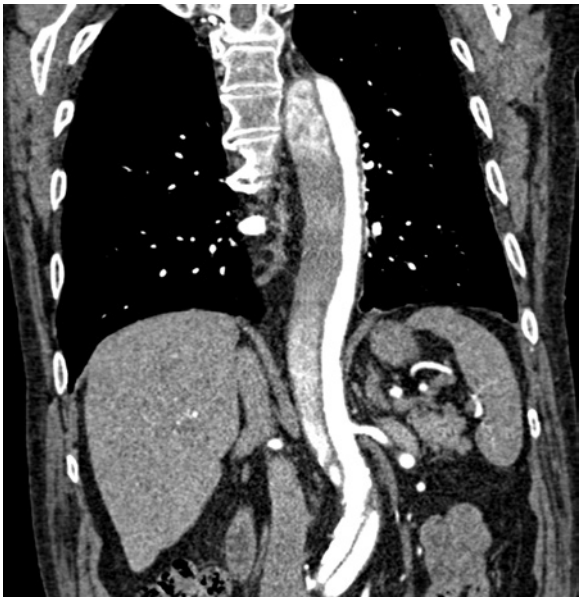


Figure 39.18 Aortic dissection. Coronal computed tomographic image showing intimal flap in the descending aorta.

PLEURAL FLUID

The most dependent recess of the pleural space is the posterior costophrenic angle and this is where a small effusion will tend to collect. As little as a few millilitres of fluid may be detected using decubitus views with a horizontal beam, ultrasound or CT. Larger volumes of fluid eventually fill in the costophrenic angle on the frontal view, and with increasing fluid a homogeneous opacity spreads upwards, obscuring the lung base (Fig. 39.19). The fluid usually demonstrates a concave upper edge, higher laterally than medially, and obscures the diaphragm. Fluid may track into the fissures. A massive effusion may cause complete opacification of a hemithorax with passive atelectasis. The space-occupying effect of the effusion may push the mediastinum towards the opposite side, especially when the lung does not collapse significantly. Effusions in a supine patient redistribute into the

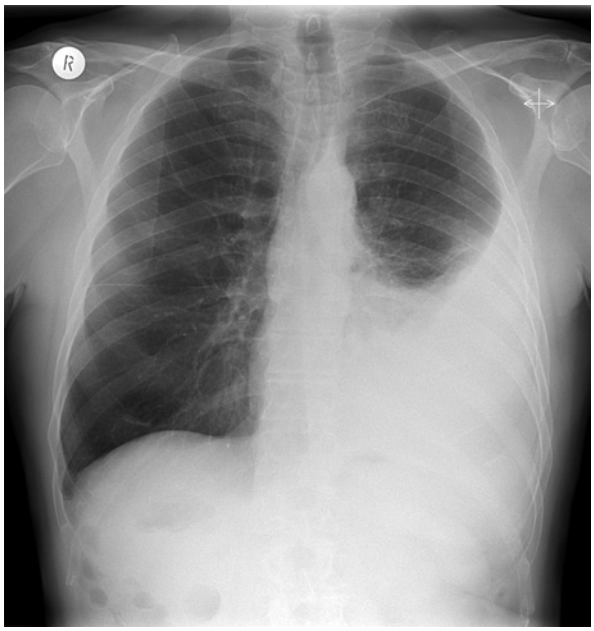


Figure 39.19 Left pleural effusion. There is a typical configuration of the left upper border, a meniscus extending up the lateral chest wall.

paravertebral sulcus and produce an even increased density throughout that hemithorax.

Lamellar effusions are shallow collections between the lung surface and the visceral pleura, sometimes sparing the costophrenic angle, and occur early in heart failure.

Subpulmonary effusions accumulate between the diaphragm and undersurface of a lung, mimicking elevation of the hemidiaphragm, altering the diaphragmatic contour so the apex moves more laterally than usual. When left-sided, there is increased distance between the gastric air bubble and lung base.

Fluid may become loculated in the interlobar fissures and is most frequently seen in heart failure. Loculated interlobar effusions may disappear rapidly and are sometimes known as pulmonary pseudotumours.

Differentiation between a simple effusion and a complicated parapneumonic effusion or an empyema usually requires thoracentesis. Loculation is best demonstrated with ultrasound.

PNEUMOTHORAX

In an erect patient, air will usually collect at the apex (Fig. 39.20). The lung retracts towards the hilum and on a frontal chest film the sharp white line of the visceral pleura will be visible, separated from the chest wall by the radiolucent pleural space, which is devoid of lung markings. This should not be confused with a skin fold, which mostly occurs in supine or recumbent patients. The lung usually remains aerated, although perfusion is reduced in proportion to ventilation and therefore the radiodensity of the partially collapsed lung remains relatively normal. A large pneumothorax may lead to complete retraction of the lung, with some mediastinal shift towards the normal side. Since it is a medical emergency, tension pneumothorax is often treated before a chest radiograph is obtained. However, if a radiograph is taken in this situation it will show marked displacement of the mediastinum. Radiographically the lung may be squashed against the mediastinum or herniate across the midline, and the ipsilateral hemidiaphragm may be depressed. A supine pneumothorax may produce increased transradiancy towards the diaphragm, and a deep sulcus sign.

COMPLICATIONS OF PNEUMOTHORAX

Pleural adhesions may limit the distribution of a pneumothorax and result in a loculated or encysted pneumothorax (see Fig. 39.6). The usual appearance is an ovoid air collection adjacent to the chest wall, and it may be radiographically indistinguishable from a thin-walled subpleural pulmonary cyst or bulla. Pleural adhesions are occasionally seen as line shadows

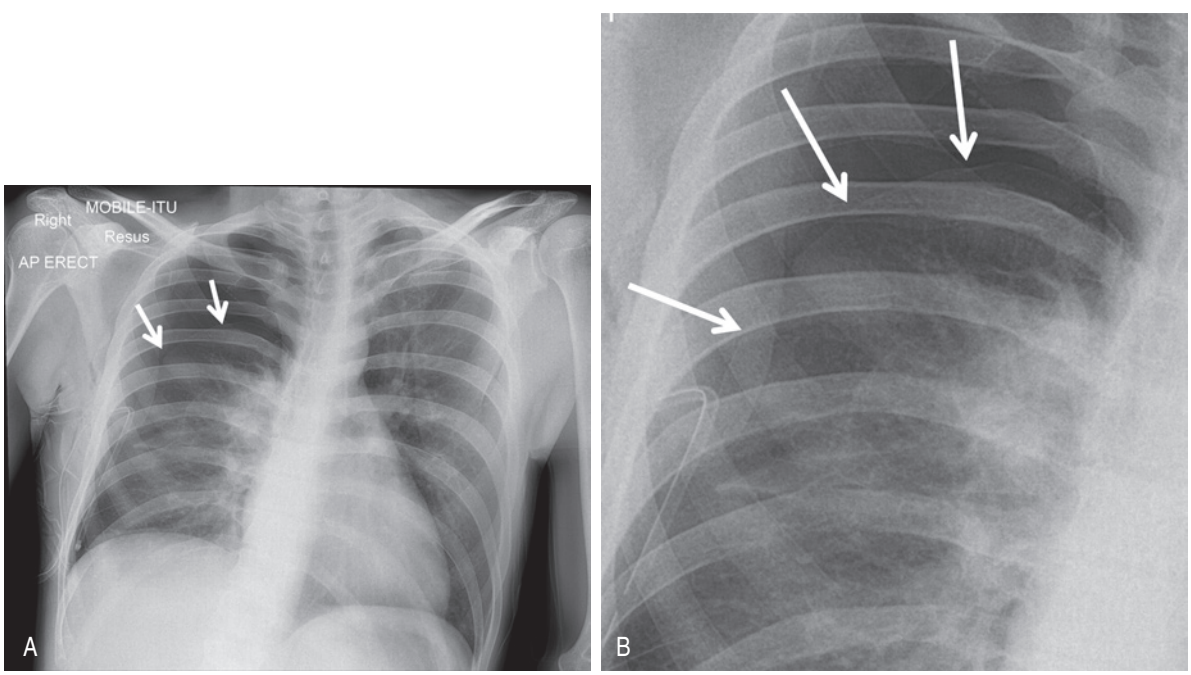


Figure 39.20 Pneumothorax. (a) This patient, with underlying lung abnormality, has developed a pneumothorax. The fine white line that represents the visceral pleura delineates the edge of the lung *(arrows)*. (b) Close-up of the pleural line. Note how there are no vascular markings beyond this point.

stretching between the two pleural layers, preventing relaxation of the underlying lung. Rupture of an adhesion may produce a haemopneumothorax. Collapse or consolidation of a lobe or lung in association with a pneumothorax is important because it may delay re-expansion of the lung.

Since the normal pleural space contains a small volume of fluid, blunting of the costophrenic angle by a short fluid level is commonly seen in a pneumothorax. In a small pneumothorax this fluid level may be the most obvious radiological sign. A larger fluid level usually signifies a complication and represents exudate, pus or blood, depending on the aetiology of the pneumothorax. A hydropneumothorax is a pneumothorax containing a significant amount of fluid (Fig. 39.21). On a radiograph obtained with a horizontal beam, a fluid level is evident. A hydro- or pyopneumothorax may arise as a result of a bronchopleural fistula, and may be a complication of surgery, tumour or infection.

PULMONARY EMBOLISM

CT has excellent reported sensitivity and specificity for the detection of pulmonary embolus down to the segmental level.[3] Pulmonary emboli are identified as filling defects in the contrast opacified pulmonary arteries (Fig. 39.22). CT pulmonary angiography (CTPA) also allows evaluation of clot burden, right heart strain and pulmonary infarction. In addition, even with a negative study, CTPA also allows other diagnoses to be made that explain the symptoms of chest pain or dyspnoea.

TRAUMA AND THE INTENSIVE CARE UNIT PATIENT

SKELETAL INJURY

Following trauma, rib fractures are common and may be single, multiple, unilateral or bilateral. In cases of

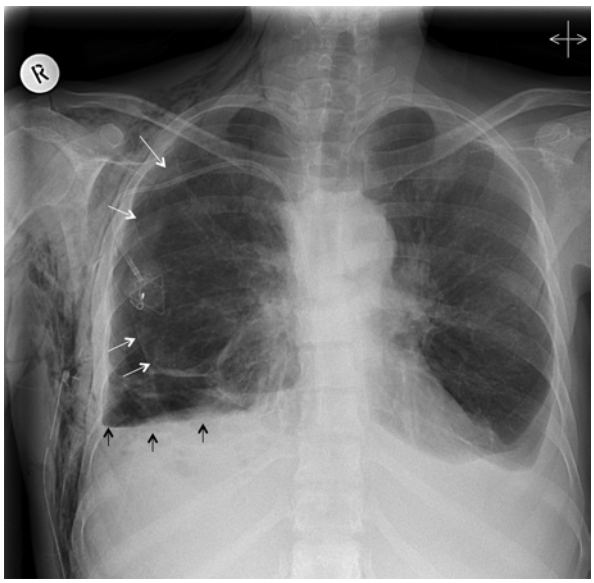


Figure 39.21 Hydropneumothorax post biopsy. There is a thin white line due to pneumothorax *(white arrows)* associated with an air-fluid level *(black arrows)* due to fluid. The intercostal catheter has dislodged into the chest wall, causing surgical emphysema.

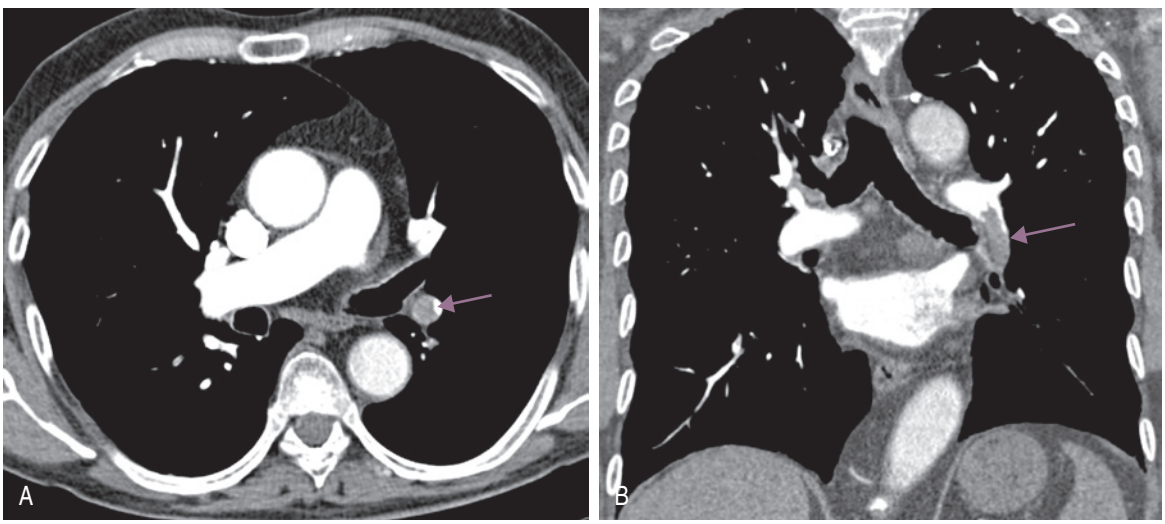


Figure 39.22 Pulmonary embolism: (a) axial and (b) coronal computed tomographic image of an embolus in the left lower lobe pulmonary artery *(arrows)*.

chest trauma, the chest X-ray is more important in detecting a complication of rib fracture than the fracture itself. Fracture of one of the first three ribs is often associated with major intrathoracic injury, and fracture of the lower three ribs may be associated with important hepatic, splenic or renal injury. Complications of rib fracture include a flail segment, pneumothorax, haemothorax and subcutaneous emphysema. A flail segment is usually apparent clinically and radiologically. The fractured ends of ribs may penetrate underlying pleura and lung and cause a pneumothorax, haemothorax, haemopneumothorax or intrapulmonary haemorrhage. Air may also escape into the chest wall and cause subcutaneous emphysema. Fractures of the sternum usually require a lateral film or CT for visualisation. Fractures of the thoracic spine may be associated with a paraspinal shadow, which represents haematoma. Fractures of the clavicle may be associated with injury to the subclavian vessels or brachial plexus, and posterior dislocation of the clavicle at the sternoclavicular joint may cause injury to the trachea, oesophagus, great vessels or nerves of the superior mediastinum.[4]

DIAPHRAGMATIC INJURY[5]

Laceration of the diaphragm may result from penetrating or non-penetrating trauma to the chest or abdomen. Rupture of the left hemidiaphragm is encountered more frequently in clinical practice than rupture on the right (Fig. 39.23). The typical plain film appearance is of obscuration of the affected hemidiaphragm and increased shadowing in the ipsilateral hemithorax due to herniation of stomach, omentum, bowel or solid viscera, although such herniation may be delayed. Ultrasound may demonstrate diaphragmatic laceration and free fluid in both the pleura and peritoneum. Barium studies may be useful to confirm herniation of stomach or bowel into the chest.

PLEURAL INJURY[6-8]

Pneumothorax may be a complication of rib fracture, and is then usually associated with a haemothorax. If no ribs are fractured, pneumothorax is secondary to a pneumomediastinum, pulmonary laceration or penetrating chest injury. Pneumothorax due to a penetrating injury is liable to develop increased pressure, resulting in a tension pneumothorax, which may require emergency decompression. Haemothorax may also occur with or without rib fractures, and is due to laceration of intercostal or pleural vessels. If a pneumothorax is also present, a fluid level will be seen on a horizontal-beam film. Pleural effusion may also result from trauma. Open injuries to the pleura are prone to infection and development of an empyema.

INJURIES TO THE LUNG[6-8]

Pulmonary contusion is due to haemorrhagic exudation into the alveoli and interstitial spaces and appears as patchy, non-segmental consolidation within the first

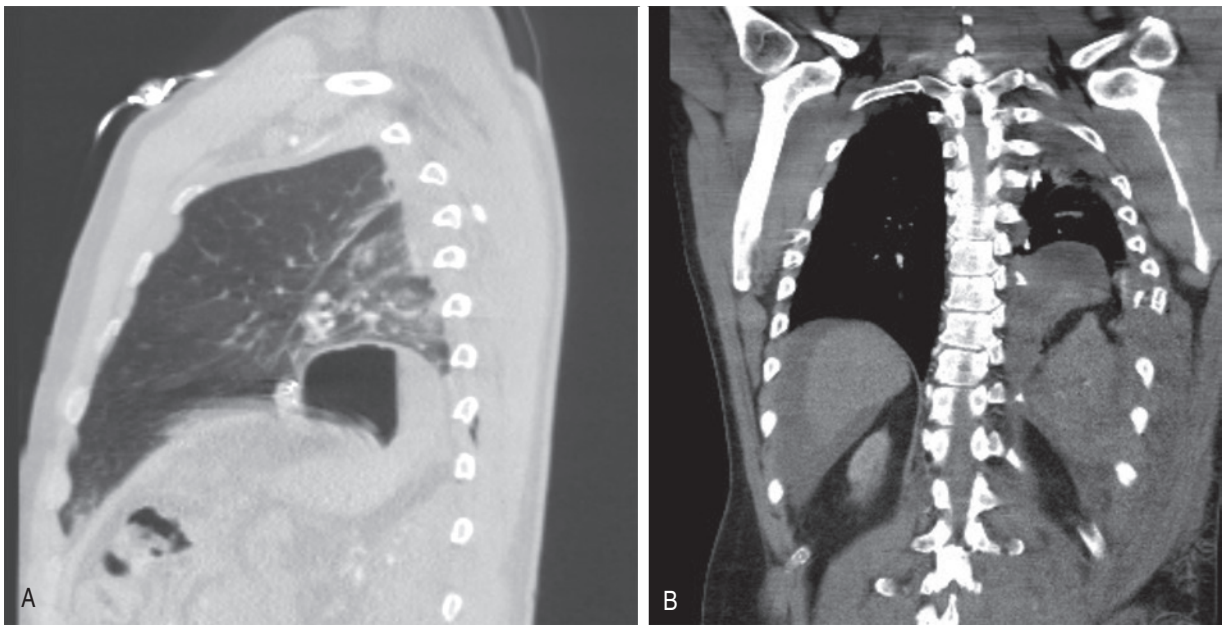


Figure 39.23 Traumatic diaphragmatic hernia on computed tomography. Axial lung windows demonstrate the stomach is above the diaphragm. The defect is best seen on the coronal soft tissue reformats.

few hours of penetrating or non-penetrating trauma. There is usually improvement within 2 days and clearance within 3–4 days. Pulmonary lacerations may be obscured by pulmonary contusion, but, as this resolves, the laceration will become evident. If filled with blood it appears as a homogeneous round opacity, and if partly filled with blood it may show a fluid level (Fig. 39.24). Such pulmonary haematomas or blood cysts gradually decrease in size, but may take a few months to resolve completely. Fat embolism is a rare complication of multiple fractures, with poorly defined nodular opacities throughout both lungs, which resolve within a few days.

INJURIES TO THE TRACHEA AND BRONCHI[9,10]

Laceration or rupture of a major airway is an uncommon result of severe chest trauma. Fracture of the first three ribs and mediastinal emphysema and pneumothorax may also be evident. The injury is usually in the trachea just above the carina, or in a main bronchus just distal to the carina. If the bronchial sheath is preserved there may be no immediate signs or symptoms, but tracheostenosis or bronchiectasis may occur later. CT may be helpful in diagnosis, but bronchoscopy is the best diagnostic method in the acute stage.

INJURIES TO THE MEDIASTINUM[11,12]

Pneumomediastinum and mediastinal emphysema, discussed in the section, Abnormalities of the mediastinum, are the presence of air between the tissue planes of the mediastinum. Air may reach here as a result of pulmonary interstitial emphysema, perforation of the oesophagus, trachea or bronchus, or from a penetrating chest injury. Pulmonary interstitial emphysema is a result of alveolar wall rupture due to high intra-alveolar pressure, and may occur during violent coughing, severe asthma or crush injuries, or be due to positive-pressure ventilation. Air dissects centrally along the perivascular sheath to reach the mediastinum. Rarely, air may dissect into the mediastinum from a pneumoperitoneum. A pneumomediastinum may extend beyond the thoracic inlet into the neck, and over the chest wall. Pneumothorax is a common complication of pneumomediastinum, but the converse rarely occurs. Pneumomediastinum usually produces vertical translucent streaks in the mediastinum. This represents gas separating and outlining the soft-tissue planes and structures of the mediastinum. Gas shadows may extend up into the neck, or dissect extrapleurally over the diaphragm, or extend into the soft-tissue planes of the chest wall, causing subcutaneous emphysema. The mediastinal pleura may be displaced laterally, and become visible as a linear soft-tissue shadow parallel to the mediastinum. If mediastinal air collects beneath the pericardium the central part of the diaphragm may be visible, producing the 'continuous diaphragm' sign. Mediastinal haemorrhage may result from penetrating or non-penetrating trauma, and be due to venous or arterial bleeding. Many cases are probably unrecognised, as clinical and radiographic signs are absent. Important causes include automobile accidents, aortic rupture and dissection, and introduction of CVCs. There is usually bilateral mediastinal widening, but a localised haematoma may occur.

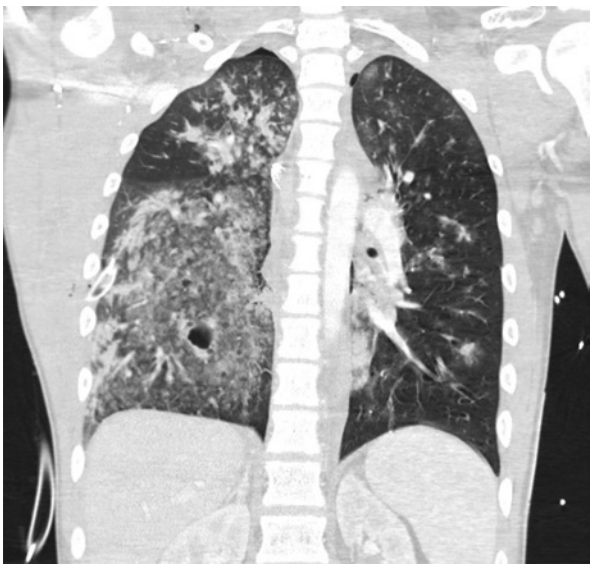


Figure 39.24 Pulmonary contusion. Computed tomography shows diffuse ground-glass opacity of the right lung, and there is also a laceration causing a traumatic pneumatocele (air cyst) of the right lower lobe.

ACUTE AORTIC INJURY

Aortic rupture (Fig. 39.25) is usually the result of an automobile accident. Most non-fatal aortic tears occur at the aortic isthmus, the site of the ligamentum arteriosum. Only 10%–20% of patients survive the acute episode, but a small number may develop a chronic aneurysm at the site of the tear. The commonest acute radiographic signs of traumatic aortic injury (Fig. 39.26) are widening of the superior mediastinum, and obscuration of the aortic knuckle. Other radiographic signs include deviation of the left main bronchus anteriorly, inferiorly and to the right, and rightward displacement of the trachea, a nasogastric tube or the right parasternal line. A left apical extrapleural cap or a left haemothorax may be visible.

CARDIAC INJURY[13]

This is rare but may result from penetrating or blunt trauma. Penetrating injuries are usually rapidly fatal but may cause tamponade, ventricular aneurysm or

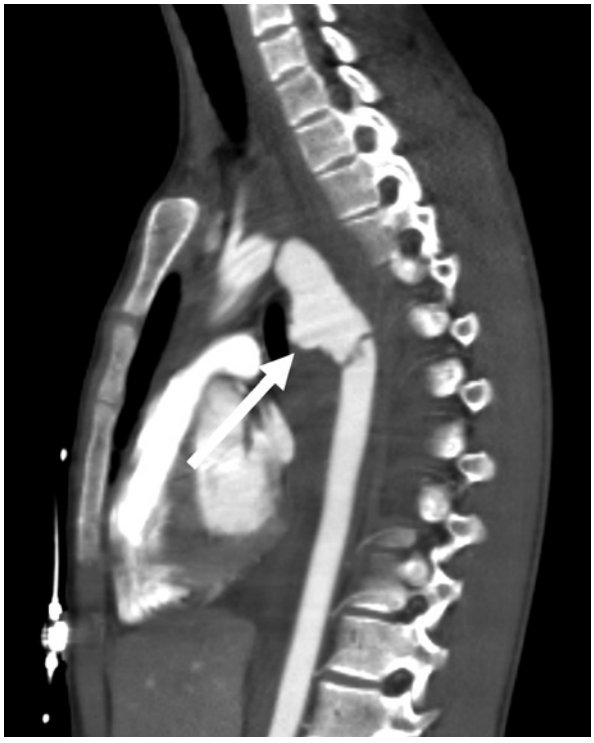


Figure 39.25 Traumatic aortic injury on computed tomography thoracic angiogram. Usually best seen on sagittal reformats, there is an intimal tear leading to abnormal contour, causing pseudoaneurysm formation *(arrow)*. There is surrounding haematoma.

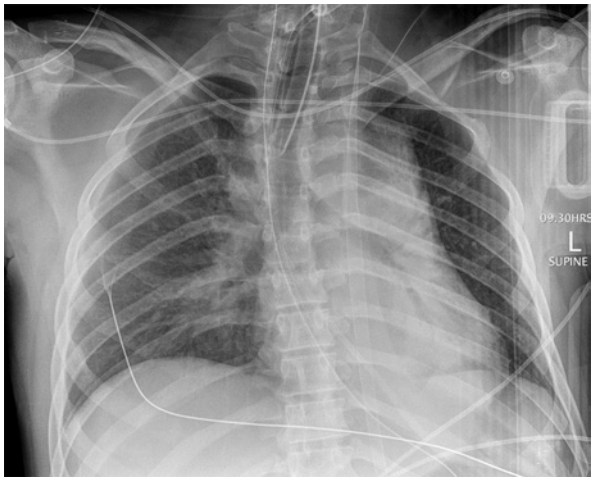


Figure 39.26 Traumatic aortic injury on chest X-ray. There is enlargement and obscuration of the aortic knuckle, causing superior mediastinal widening. The haematoma causes deviation of the left main bronchus downward and the nasogastric tube rightward. There is a small left apical extrapleural cap.

septal defects. Blunt trauma may cause myocardial contusion and infarction and may be associated with transient or more permanent rhythm disturbance.

OESOPHAGEAL RUPTURE[14]

This is usually the result of instrumentation or surgery, but occasionally occurs in penetrating trauma, and is rarely spontaneous and due to sudden increase of intraoesophageal pressure (Boerhaave syndrome). Clinically there is acute mediastinitis; radiographically there are signs of pneumomediastinum, with or without a pneumothorax or hydropneumothorax, which is usually left-sided. The diagnosis should be confirmed by a CT swallow (Fig. 39.27). This should initially be with water-soluble contrast medium in order to avoid the small risk of granuloma formation in the mediastinum that has been described following barium leakage. Chylothorax due to damage to the thoracic duct may become apparent hours or days after trauma. Thoracic surgery is the commonest cause.

THE POSTOPERATIVE CHEST

THORACIC COMPLICATIONS OF GENERAL SURGERY

ATELECTASIS

Atelectasis is the commonest pulmonary complication of thoracic or abdominal surgery. The chest X-ray usually shows elevation of the diaphragm due to a poor inspiration. Linear opacities are present in the lower zones, and represent a combination of subsegmental volume loss and consolidation. The shadows usually appear about 24 hours postoperatively and resolve within 2–3 days.

PLEURAL EFFUSIONS

Pleural effusions are common immediately following abdominal surgery and usually resolve within 2 weeks. They may be associated with pulmonary infarction. Effusions due to subphrenic infection usually occur later.

PNEUMOTHORAX

Pneumothorax, when it complicates extrathoracic surgery, is usually a complication of positive-pressure ventilation or central venous line insertion. It may complicate nephrectomy.

ASPIRATION PNEUMONITIS

Aspiration pneumonitis is common during anaesthesia, but fortunately is usually insignificant. When significant, patchy consolidation appears within a few hours, usually basally or around the hila. Clearing occurs within a few days, unless there is superinfection.

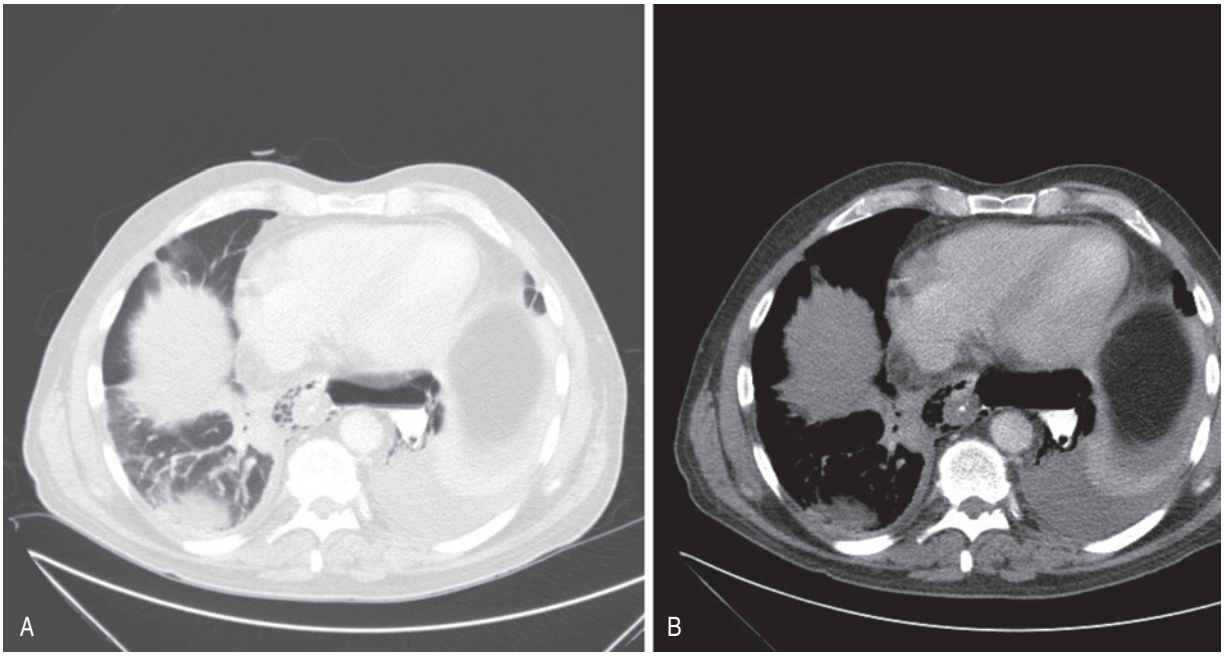


Figure 39.27 Oesophageal rupture. The patient swallowed oral contrast just prior to the computed tomography scan. The contrast has leaked into the posterior mediastinum, to the left of the lower oesophagus adjacent to the gastro-oesophageal junction. There is a pre-existing pneumomediastinum due to oesophageal rupture.

PULMONARY OEDEMA

In the postoperative period, oedema may be cardiogenic or non-cardiogenic.

PNEUMONIA

Postoperative atelectasis and aspiration pneumonitis may be complicated by pneumonia. Postoperative pneumonias, therefore, tend to be associated with bilateral basal shadowing.

SUBPHRENIC ABSCESS

Subphrenic abscess usually produces elevation of the hemidiaphragm, pleural effusion and basal atelectasis. Loculated gas may be seen below the diaphragm, and fluoroscopy may show splinting of the diaphragm. Subphrenic abscess can be demonstrated by CT or ultrasound.

PULMONARY EMBOLISM

Pulmonary embolism may produce pulmonary shadowing, pleural effusion or elevation of the diaphragm, but is not excluded by a normal radiograph. In the ICU setting the radiological investigation of choice is CTPA.

THORACIC COMPLICATIONS OF CARDIAC SURGERY

Most cardiac operations are performed through a sternotomy incision, and wire sternal sutures are often seen on the postoperative films. Mitral valvotomy is now rarely performed via a thoracotomy incision, but this route is still used for surgery of coarctation of the aorta, patent ductus arteriosus, Blalock–Taussig shunts and pulmonary artery banding.

Widening of the cardiovascular silhouette is usual, and represents bleeding and oedema. Marked or progressive widening of the mediastinum suggests significant haemorrhage (Fig. 39.28). Some air commonly remains in the pericardium following cardiac surgery, so that the signs of pneumopericardium may be present.

Left basal shadowing is almost invariable, representing atelectasis. This shadowing usually resolves over a week or two. Small pleural effusions are also common in the immediate postoperative period.

Pneumoperitoneum is sometimes seen due to involvement of the peritoneum by the sternotomy incision. It is of no pathological significance (see Fig. 39.2).

Violation of left or right pleural space may lead to a pneumothorax. Damage to a major lymphatic vessel may lead to a chylothorax or a more localised chyloma. Phrenic nerve damage may cause paresis or paralysis of a hemidiaphragm.

Surgical clips or other metallic markers have sometimes been used to mark the ends of coronary artery bypass grafts. Prosthetic heart valves are usually visible radiographically, but they may be difficult to see on an underpenetrated film.

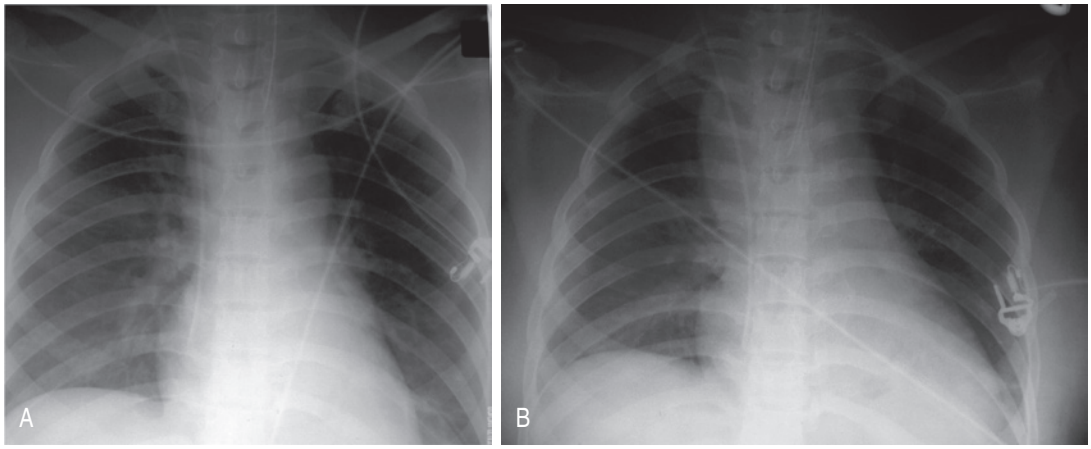


Figure 39.28 Following cardiac surgery (a) the postoperative chest radiograph appears satisfactory. A few hours later (b) the mediastinum has widened considerably due to mediastinal haemorrhage.

Sternal dehiscence may be apparent radiographically by a linear lucency appearing in the sternum and alteration in position of the sternal sutures on consecutive films. The diagnosis is usually made clinically and may be associated with osteomyelitis. A first or second rib may be fractured when the sternum is spread apart. The importance of this observation is that it may explain chest pain in the postoperative period.

Acute mediastinitis may complicate mediastinal surgery, although it is more commonly associated with oesophageal perforation or surgery. Radiographically there may be mediastinal widening or pneumomediastinum, and these features are best assessed by CT scan.

POST-PNEUMONECTOMY

The initial postoperative film will show an air-filled pneumonectomy space with volume loss. Thereafter, the pneumonectomy space fills with fluid, at approximately 2 ribs per day for a standing film. The residual air bubble in the pneumonectomy cavity should shrink over time. If, however, the air bubble increases in size, this is indicative of a bronchopleural fistula, and a CT is indicated. If the pleural effusion rapidly increases in size, this may indicate a haemothorax, which could be life threatening and best evaluated by CT.

REFERENCES

1. Sheard S, Rao P, Devaraj A. Imaging of acute respiratory distress syndrome. *Respir Care*. 2012;57:607–612.
2. Knutstad K, Hager B, Hauser M. Radiologic diagnosis and management of complications related to central venous access. *Acta Radiol*. 2003;44:508–516.
3. Bettmann MA, White RD, Woodard PK, et al. ACR Appropriateness Criteria acute chest pain – suspected pulmonary embolism. *J Thorac Imaging*. 2012;27:W28–W31.
4. Peters S, Nicolas V, Heyer CM. Multidetector computed tomography-spectrum of blunt chest wall and lung injuries in polytraumatized patients. *Clin Radiol*. 2010;65:333–338.
5. Desir A, Ghaye B. CT of blunt diaphragmatic rupture. *Radiographics*. 2012;32:477–498.
6. Dreizin D, Munera F. Blunt polytrauma: evaluation with 64-section whole-body CT angiography. *Radiographics*. 2012;32:609–631.
7. Palas J, Matos A, Mascarenhas V, et al. Multidetector computed tomography: evaluation of blunt chest trauma in adults. *Radiol Res Pract*. 2014;2014:864369.
8. Sridhar S, Raptis C, Bhalla S. Imaging of blunt thoracic trauma. *Semin Roentgenol*. 2016;51(3): 203–214.
9. Kiser C, O'Brien SM, Detterbeck FC. Tracheobronchial injuries: treatment and outcomes. *Ann Thorac Surg*. 2001;71:2059–2065.
10. Scaglione M, Romano S, Pinto A, et al. Acute tracheobronchial injuries: impact of imaging on diagnosis and management implications. *Eur J Radiol*. 2006;59:336–343.
11. Euathrongchit J, Thoongsuwan N, Stern EJ. Nonvascular mediastinal trauma. *Radiol Clin North Am*. 2006;44:251–817.
12. Gunn M, Clark RT, Linnau KF, et al. Current concepts in imaging evaluation of penetrating transmediastinal injury. *Radiographics*. 2014;34: 1824–1841.
13. Restrepo C, Gutierrez F, Marmolvelez J, et al. Imaging patients with cardiac trauma. *Radiographics*. 2012;32:633–649.
14. Holster IL, Kuipers EJ. Management of acute nonvariceal upper gastrointestinal bleeding: current policies and future perspectives. *World J Gastroenterol*. 2012;18:1202–1207.

40

Ultrasound in the intensive care unit

Ubbo F Wiersema

Point-of-care ultrasound has become established as an integral part of intensive care practice. An increasing number of clinical applications have been developed that facilitate time-critical therapeutic decision making and invasive diagnostic procedures.[1] This chapter will describe ultrasound techniques that have an established role in intensive care, and are readily acquired with a short period of training. Acquisition of ultrasound proficiency is best achieved with a combination of theoretical learning (basic physics of ultrasound, relevant anatomy, image interpretation), direct supervision of image acquisition and practice.[2,3]

EQUIPMENT

The ideal ultrasound machine for intensive care applications is compact, easily transportable and robust. The console should be waterproof and able to withstand repeated disinfection procedures. To avoid transmission of nosocomial skin flora between patients the transducer, console and electrocardiograph leads (if used) should be disinfected (e.g. with alcohol-based wipes) after each examination.[4,5] Single-use coupling gel should be used instead of multi-use bottles.

Different transducers (probes) are designed for different applications:

- A low-frequency (3–5 MHz) phased array transducer (transthoracic echocardiography transducer) is suitable for chest and abdominal ultrasound.
- A mid-frequency (5–8 MHz) microconvex curved array transducer is also suitable for chest ultrasound and is sometimes useful for subclavian (SC) vein ultrasound.
- A high-frequency (6–13 MHz) linear array transducer is necessary for vascular access and ocular ultrasound.
- A low-frequency (2–5 MHz), large-footprint, curved array transducer provides optimal abdominal ultrasound imaging, but is not essential.

CHEST ULTRASOUND

Ultrasound waves are unable to penetrate aerated lung tissue. Historically, this has limited ultrasound of the chest largely to the evaluation of pleural effusions. In recent years, the recognition that analysis of ultrasound artefacts arising from the pleura can provide valuable information about underlying lung pathology has led to wider application of lung ultrasound, including the diagnosis of pneumothorax and parenchymal lung disease.[1,4] Compared with chest radiography and computed tomography (CT), ultrasound is rapid, inexpensive and safe from ionising radiation. Acute lung parenchymal pathology invariably abuts the pleura and can thus be detected by ultrasound. Diagnostic accuracy of ultrasound compares favourably with CT, and significantly exceeds clinical examination and plain radiography.[6]

EQUIPMENT

Several transducers can be used for chest ultrasound. The standard transthoracic echocardiography, phased array, low-frequency (3–5 MHz) transducer provides good depth penetration and sufficient resolution for most chest ultrasound applications. This transducer is ideally suited for evaluating pulmonary oedema and pleural effusions[7,8] and can therefore be used to complement echocardiographic assessment of cardiac function. A microconvex 5–8 MHz curved array transducer provides better artefact visualisation than lower-frequency transducers, but depth penetration may be insufficient for large patients. The microconvex design facilitates placement of the transducer between the ribs of thin patients.[4] A high-frequency linear array transducer (6–13 MHz) allows detailed pleural line analysis, and is optimal for pneumothorax detection (e.g. after venous cannulation) but has limited other applicability.

Imaging in 2D is adequate for most examinations. M-mode is useful for lung sliding analysis. Doppler imaging is not required.[4]

EXAMINATION TECHNIQUE

Mechanically ventilated patients can usually be satisfactorily examined in the supine or semi-recumbent position. Imaging of the posterior lungs is achieved by scanning along the posterior axillary line with the arm lifted out of the way over the anterior chest. A thorough examination of the lungs involves scanning

ABSTRACT

Point-of-care ultrasound provides a fast, simple and safe imaging modality for a range of diagnostic and procedural applications. Lung ultrasound may be used in the diagnosis of pneumothorax, pleural effusion, consolidation, alveolar-interstitial syndrome, and diaphragmatic dysfunction. Interpretation of lung ultrasound images is based in large part on the recognition of distinct artefacts generated at the pleural line. Abdominal ultrasound provides rapid assessment for free intraperitoneal fluid and abdominal aortic aneurysm. An integrated approach with lung, abdominal and deep vein ultrasound, plus echocardiography, may be used for diagnosis in undifferentiated respiratory or circulatory failure. Ultrasound should routinely be used to guide pleural or ascitic aspiration and central venous cannulation; it may also be used to guide arterial or peripheral venous cannulation.

KEYWORDS

Ultrasound
A lines
B lines
lung sliding
pneumothorax
pleural effusion
alveolar interstitial syndrome
cannulation
diaphragmatic dysfunction
FAST

bilaterally over four quadrants of the anterior chest wall (upper and lower zones laterally and medially), the upper and lower lateral chest wall (bounded by the anterior and posterior axillary lines), and upper, middle and lower zones of the posterior chest wall.[4,9] For a complete study, each intercostal space, along multiple vertical lines, should be imaged.[7,8,10] The findings for each space can then be documented in tabulated form. Only the dorsal lung segments behind the scapulae cannot be examined by ultrasound.

Fluid-filled chest pathology (e.g. pleural effusions, atelectasis) is gravity dependent and thus lies inferiorly. In contrast, aerated pathology (i.e. pneumothorax) is non-dependent, and lies superiorly. Detection of specific pathology should thus be directed accordingly, noting that in the supine patient the least dependent region is the basal anterior chest, which is where a small pneumothorax will collect.[9]

The examination sequence should commence with scanning of the lower lateral chest. Here identification of the diaphragm provides a useful landmark for further imaging. Subdiaphragmatic structures (liver, spleen and kidneys) may be identified to confirm the location of the diaphragm. Right-sided subdiaphragmatic structures are usually easier to visualise than left-sided structures. Diaphragmatic movement with tidal ventilation should be identified. The scanning depth should initially be set to 15–20 cm to evaluate basal lung pathology. The scanning depth can then be reduced to 10 cm (and use of a higher-frequency transducer considered) to facilitate artefact analysis and complete the examination over the whole chest wall.

For each region of interest, the transducer should be placed between the rib spaces and aligned with the longitudinal axis of the patient. The orientation marker on the transducer should face cephalad. By convention, the orientation marker is displayed on the upper left of the screen with abdominal ultrasound and displayed on the upper right of the screen with echocardiography. Choice of transducer and type of examination selected from the display menu will determine the default marker location on the screen.

IMAGE INTERPRETATION

For every region examined, image interpretation involves each of the following steps:

- identification of the pleural line between the ribs
- artefact analysis
- lung sliding analysis
- evaluation for pathology that can be directly visualised (e.g. pleural effusion, consolidation).

EXTRAPLEURAL LANDMARKS

In 2D mode, with the transducer aligned with the longitudinal axis of the patient, the ribs above and below the pleural space cast a dark shadow that extends down to the full depth of the image on the screen. Between the ribs, the pleural line can be identified as a bright (hyperechoic) horizontal line located 0.5 cm deep to the outer surface of the ribs (Fig. 40.1). The pleural line is the reference line for artefact analysis and lung sliding analysis.

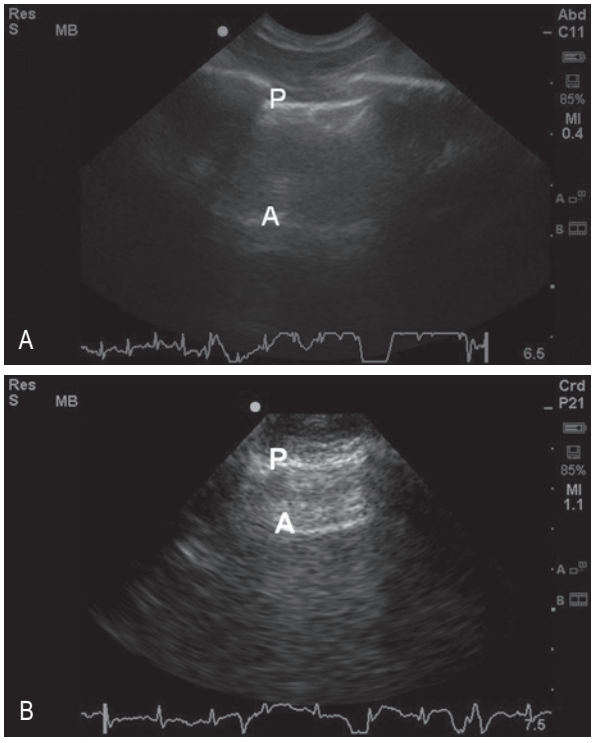


Figure 40.1 A lines demonstrated with a 5–8 MHz microconvex curved array transducer (A) and 1–5 MHz phased array transducer (B). Note the horizontal bright (hyperechoic) pleural line *(P)* and A line *(A)* flanked on each side by dark rib shadows.

ARTEFACT ANALYSIS

Ultrasound waves cannot be transmitted through aerated tissue. Normal lung parenchyma is thus not visible beyond the visceral pleura. The pleural line is formed by the reflection of ultrasound waves at the interface between the pleura and lung parenchyma (see Fig. 40.1). All artefacts used for analysis of lung pathology (except E lines) arise from the pleural line.

- *A-line artefacts* (see Fig. 40.1): these are bright horizontal repetitions of the pleural line due to reverberation artefacts, and are a normal finding.[4,11] The vertical distance between two adjacent A lines is the same as the distance between the skin and the pleural line. Usually only one or two A lines are visible, depending on image gain and depth settings. A lines are so-called because they are reminiscent of the cross bar of the capital letter A framed by the diagonal shadows cast by the ribs.

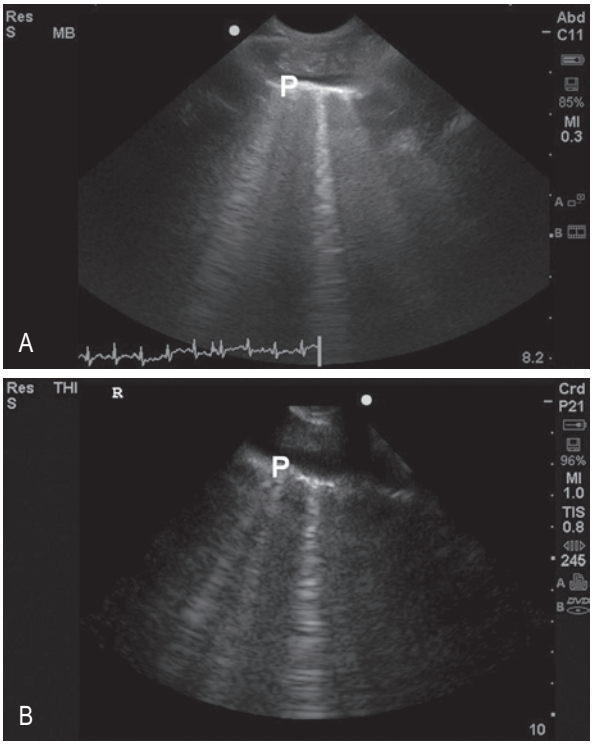


Figure 40.2 B lines demonstrated with 5–8 MHz microconvex curved array transducer (A) and 1–5 MHz phased array transducer (B). Note vertical bright (hyperechoic) lines originating at the pleural line *(P)* and extending to the bottom of the screen.

- *B-line artefacts* (Fig. 40.2): these were previously known as *comet-tail artefacts*[11] or *ultrasound lung comets*,[7] and are defined as discrete vertical bright lines originating at the pleural line and fanning out to the bottom of the screen without fading.[12] B lines arise from reverberation artefacts generated at the interface of fluid-filled or fibrosed interlobular septa abutting the visceral pleura.[11,13] The presence of multiple B lines, termed '*B pattern*', erases the A-line artefact. With greater loss of aeration, the B lines become more closely spaced, or confluent (*white-out*) (Fig. 40.3). B lines are equivalent to Kerley B lines seen on the chest radiograph, although they may be present before radiographic changes are visible. Isolated B lines or short, ill-defined vertical artefacts are of uncertain significance.
- *E-line artefacts* (Fig. 40.4): these have a very similar appearance to B lines, but arise superficial to the pleural line.[4,9] They occur with subcutaneous emphysema where pockets of air create an air–tissue interface that generates reverberation artefacts. It is important to distinguish B lines from E lines by clearly identifying the origin of vertical artefacts in relation to the pleural line, although subcutaneous emphysema is usually easy to detect clinically.

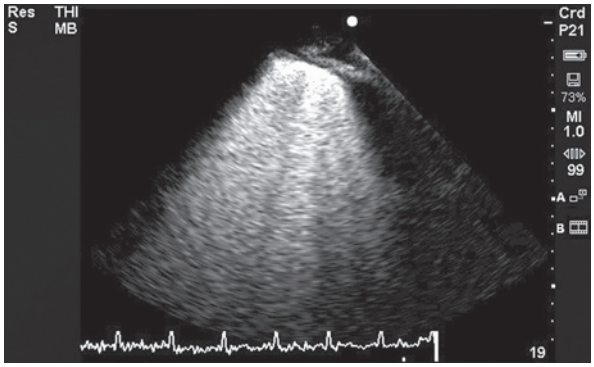


Figure 40.3 Confluent B lines creating a 'white out' appearance, demonstrated with a 1–5 MHz phased array transducer.

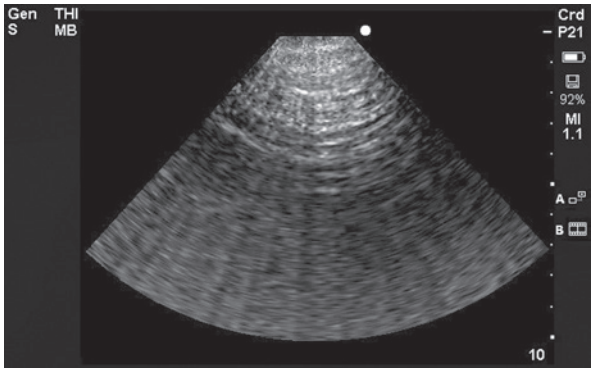


Figure 40.4 E lines demonstrated with a 1–5 MHz phased array transducer. Note the vertical bright (hyperechoic) lines originated above the pleural line, which is poorly defined.

LUNG SLIDING ANALYSIS

With tidal inflation of the normal lung, the visceral pleura slides against the parietal pleura. On ultrasound this is seen as movement below the pleural line. The movement is best appreciated using M-mode imaging, which shows an image reminiscent of the seashore: above the pleural line there are a series of horizontal lines created by extrapleural tissue static in time (the sea), and below the pleural line there is a grainy appearance due to reflection from moving visceral pleura (the beach) (Fig. 40.5).[4,9] The transducer must be held completely still on the chest wall. Diagnostic accuracy is improved if a higher-frequency transducer is used. Lung sliding is absent if the visceral pleura cannot be visualised because of air in the pleural space (pneumothorax) (Fig. 40.6), or if lung movement is abolished (e.g. pleural fibrosis, dense consolidation, atelectasis or apnoea). Lung sliding may appear absent in patients with chronic obstructive pulmonary disease, or at the apices with small volume tidal ventilation. The *lung pulse sign* (see section on Atelectasis) can be present only when lung sliding is absent (Fig. 40.7).[14]

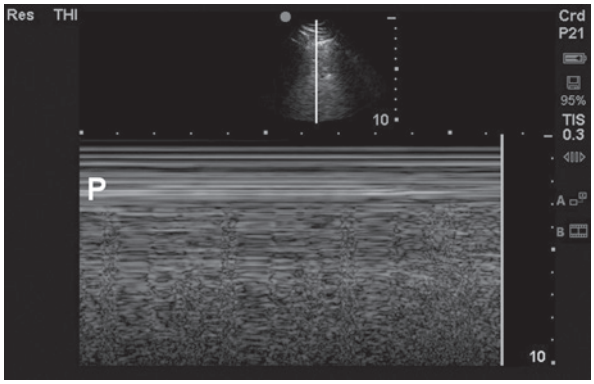


Figure 40.5 Lung sliding (seashore sign) demonstrated with a 1–5 MHz phased array transducer in M-mode. Note the smooth horizontal lines above the pleural line *(P)* (extrapleural tissues static over time), and the 'sandy' appearance below the pleural line (due to artefact from visceral pleural sliding with tidal ventilation).

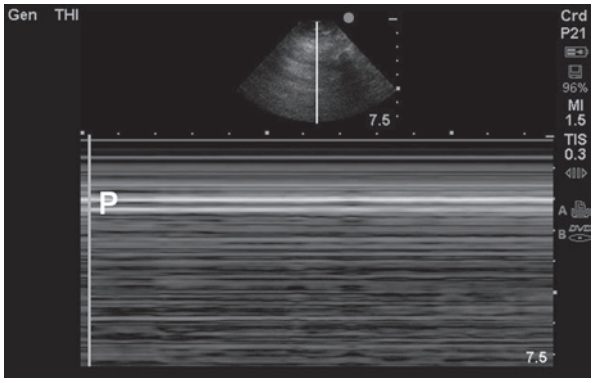


Figure 40.6 Absent lung sliding demonstrated with a 1–5 MHz phased array transducer in M-mode. Note the smooth horizontal lines above and below the bright (hyperechoic) pleural line *(P)*.

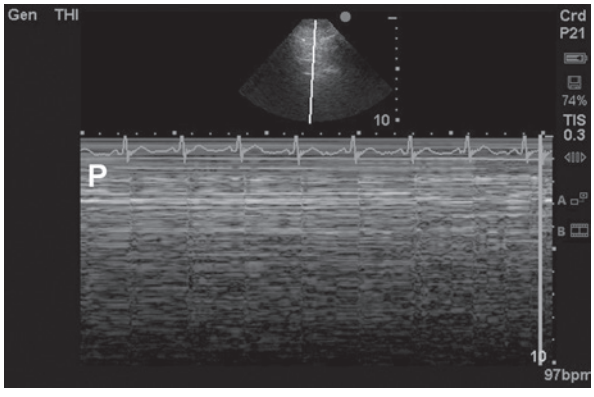


Figure 40.7 Lung pulse sign demonstrated with a 1–5 MHz phased array transducer in M-mode. Note the vertical lines below the pleural line *(P)* due to transmitted cardiac pulsations.

DIRECTLY VISUALISED PATHOLOGY

Ultrasound waves are able to penetrate non-aerated tissues. Thus pleural fluid, and non-aerated lung pathology (such as consolidation or complete atelectasis), can be readily visualised.

SPECIFIC PATHOLOGIES

The diagnostic accuracy of ultrasound is comparable to CT and superior to plain radiography for all the pathologies discussed in this section. Ultrasound is also sensitive to rapid changes in severity of disease and can thus be used to monitor disease progression and make timely clinical decisions.[15–17]

The ultrasound appearance of normal lung is characterised by the presence of A lines and lung sliding. About a quarter of normal individuals have one or two B lines at the lung bases, but other artefacts should be absent.[5,7,11]

Pleural effusion

Ultrasound enables the detection of small pleural effusions (<50 mL) not visible on chest radiography. Ultrasound also provides information about the nature of an effusion; septated pleural collections are better characterised with ultrasound than with CT.

Examination for pleural effusion commences with identification of the diaphragm on scanning over the lower lateral chest. The diaphragm appears as a smooth bright (hyperechoic) line overlying the abdominal contents (usually liver or spleen, with the kidneys deep and caudal to these). Pleural fluid manifests as a relatively homogeneous dark (hypoechoic) area between the diaphragm and parietal pleura (Fig. 40.8). As pleural fluid acts as an acoustic window, the

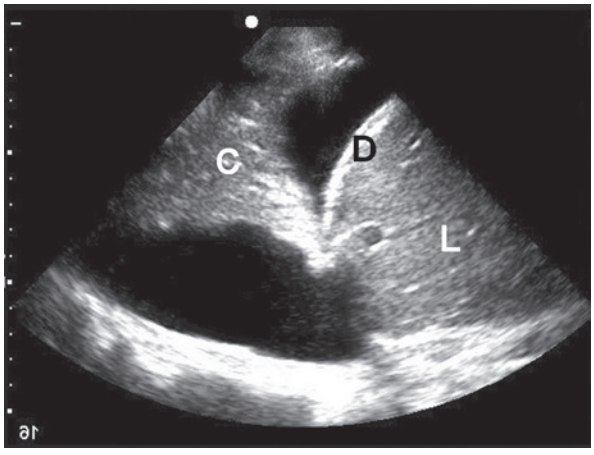


Figure 40.8 Liver *(L)*, diaphragm *(D)*, pleural effusion and collapsed/consolidated lung *(C)* demonstrated with a 1–5 MHz phased array transducer aligned with the longitudinal axis of the patient in the basal right mid-axillary line.

lung surface (visceral pleura) can be seen as a regular deep border to the effusion. Aerated lung will show a bright pleural line, often with B lines adjacent to the effusion. Normal lung will tend to float above an effusion, whereas collapsed or consolidated lung will float within a moderate or large effusion (see Fig. 40.8). A small pleural effusion confined to the costophrenic angle may be difficult to detect. However, its presence can be inferred if the dome of the diaphragm, which is normally obscured by aerated lung, can be seen. Large effusions allow direct visualisation of mediastinal structures (e.g. aorta and great vessels) if sufficient depth is imaged.

Pleural effusion quantification Various techniques have been described to estimate the volume of pleural fluid.

Measurements are made scanning in the basal intercostal spaces of the posterior axillary line with the transducer aligned in a transverse plane. In supine mechanically ventilated patients, a posterior pleural separation greater than 5 cm strongly predicts a drainage volume of greater than 500 mL.[18] In semi-recumbent (15 degrees) mechanically ventilated patients, the maximum pleural separation (in mm) multiplied by 20 gives an estimate of drainage volume (in mL).[19] Measurements can be made at either end-expiration or end-inspiration, but are not very reliable at estimating volumes of small or very large effusions. A multiplane method, obtained by multiplying the longitudinal extent of the effusion by the cross-sectional area at mid length, increases measurement accuracy.[20] However, a precise volume measurement is rarely necessary for clinical decision making.

Nature of pleural effusion Ultrasound characteristics may indirectly suggest the nature of an effusion and can be used to guide the decision whether to perform thoracocentesis. On ultrasound the appearance of an effusion can be categorised as simple, with a uniformly anechoic (black) appearance; or complex, with echogenic material (bright dots), or septa visible within the effusion. Complex effusions can be classified as complex non-septated with echogenic foci, complex septated or homogeneously echogenic.[21]

Transudates typically appear anechoic (see Fig. 40.8). In addition, the low viscosity of a transudate allows substantial movement of lung tissue with tidal ventilation. This is best appreciated as a sinusoidal pattern of the lung surface line with M-mode during tidal ventilation.[4] The pleural line is usually smooth.

Exudates are usually but not always complex. On M-mode imaging there is minimal sinusoidal movement with tidal ventilation if the exudate is very viscous. The pleural line may appear thickened and irregular from pleural inflammation. A homogeneously echogenic pattern may be almost tissue-like in appearance and should not be mistaken for an area of consolidation. In patients who clinically appear infected, a complex, relatively hyperechoic, septated, or homogeneously echogenic pattern suggests empyema. An anechoic or minimally hyperechoic pattern is unlikely to represent empyema.[19] Haemothoraces appear complex with septa and areas of differing echogenicity, depending on the age of the blood.

Thoracocentesis Ultrasound guidance of thoracocentesis decreases complications and improves fluid collection rates.[5] It allows identification of the optimal site for drainage, and measurement of the depth of the pleural space. Potential hazards such as the diaphragm or pleural adherences can be avoided, and the risk of intrafissural or intraparenchymal tube placement reduced. The decision to perform thoracocentesis is based on size, suspected nature of the effusion and clinical circumstances.

Alveolar consolidation

Consolidated lung (except bronchi) is not aerated and can therefore be directly visualised where it abuts the pleura, or where there is a pleural effusion between the chest wall and consolidated lung (Fig. 40.9).[14,22] Artefacts that arise from the pleural line are absent, although B lines may be seen at the edges of consolidated areas. Consolidation is rarely confined just to deeper lung tissue, almost always extending to involve peripheral lung tissue adjacent to pleura. The full extent of consolidation can thus usually be defined. In mechanically ventilated patients, consolidation preferentially affects the basal posterior lung segments. By contrast, with community-acquired pneumonia, consolidation may affect any lung region.

The echo-texture of consolidation resembles that of liver (hepatisation), although usually coarser in appearance (see Fig. 40.9). When examining the right basal chest, care should be taken to distinguish between consolidated lung and liver parenchyma by clearly

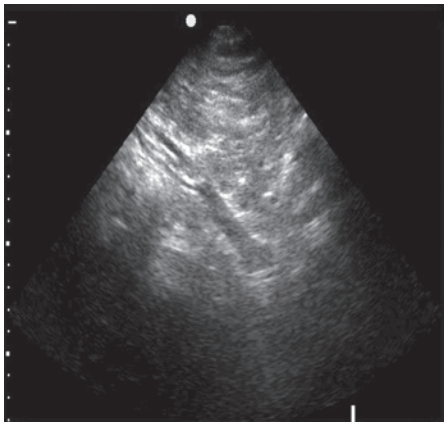


Figure 40.9 Consolidated lung demonstrated with a 1–5 MHz phased array transducer aligned with the longitudinal axis of the patient in the mid-left mid-axillary line. Note the dark (hypoechoic) diagonal region representing the oblique fissure, and the bright (hyperechoic) punctiform air bronchograms.

identifying the diaphragm (see Fig. 40.8). The borders of the consolidated area may be irregular at the junction with normal lung tissue, but will be regular if the full thickness of lung is affected.

Within consolidated lung, air bronchograms appear as bright (hyperechoic) punctiform or linear artefacts (see Fig. 40.9). The air bronchogram artefact moves with respiration (dynamic air bronchogram), outwards (towards the transducer) with inspiration and inwards (away from the transducer) with expiration.[23] The dynamic air bronchogram distinguishes consolidation from resorptive atelectasis.[23]

Atelectasis

Resorptive atelectasis commonly affects the dependent lung regions of mechanically ventilated patients. On ultrasound the affected lung appears consolidated, but air bronchograms are static with respiration.[23]

Complete lobar collapse may occur with bronchial intubation or mucus plugging. This can be detected immediately on ultrasound by absence of lung sliding and the lung pulse sign.[14] These signs are best appreciated using M-mode imaging with a high-frequency transducer. The lung pulse sign consists of vibrations in the M-mode trace (below the pleural line) due to transmitted cardiac pulsations (see Fig. 40.7). Over time, progressive absorption of gas leads to the development of consolidated lung (resorptive atelectasis).

Alveolar–interstitial syndrome

Alveolar–interstitial syndrome encompasses disease processes with which there is predominant interstitial involvement, and partial loss of lung aeration. In the acute setting this is most often due to hydrostatic or capillary leak pulmonary oedema. Less common causes include interstitial fibrosis (interstitial pneumonia) and opportunistic infection (in immunocompromised patients). Ultrasound has a high diagnostic accuracy for alveolar–interstitial syndrome.[11]

On ultrasound the hallmark of alveolar–interstitial syndrome is the presence of multiple (at least three) B lines largely independent of patient positioning.[7,11] The ultrasound pattern of B lines corresponds to the degree of lung aeration.[16] In mild disease, where thickening is confined to interlobular septa, the B lines are characteristically 7 mm apart (measured at the pleural line) (see Fig. 40.2). With progressive pulmonary oedema and increasing alveolar flooding, or with fine fibrosis, B lines are more closely spaced (approximately 3 mm apart). In severe cases B lines become confluent, creating a 'white-out' pattern (see Fig. 40.3); this pattern is equivalent to ground-glass opacification on CT.[5,11,24] Complete alveolar flooding is indistinguishable from primary alveolar consolidation.[16,24] With respiration, the B lines move to-and-fro across the screen with lung sliding.

In acute alveolar–interstitial syndrome, a number of ultrasound findings can be used to distinguish acute respiratory distress syndrome (ARDS) from cardiogenic pulmonary oedema.[24] ARDS is characterised by a non-uniform distribution of B lines, with areas of normal lung and areas of confluent B lines or white-out. Areas of consolidation are often present, particularly in the posterobasal regions. Lung sliding is reduced, or absent, in densely affected regions and the pleural line appears irregular, thickened and coarse when examined with a high-frequency transducer. In contrast, cardiogenic pulmonary oedema shows a homogeneous distribution of B lines. Consolidation is infrequent and pleural line abnormalities are absent. Pleural effusions are common.

With cardiogenic pulmonary oedema, a *lung comet score* can be used to provide a semiquantitative measure of extravascular lung water. The score is obtained by adding together the number of B lines seen from each intercostal space examined over the anterior and lateral chest.[7,8,10] The number of B lines has been shown to correlate with functional class, and severity of systolic and diastolic left ventricular dysfunction on cardiac echocardiography.[8] Reduction in lung comet score occurs with resolution of interstitial oedema.[17] An absence of B lines is consistent with a low pulmonary artery occlusion pressure.[25,26] During fluid resuscitation, the new appearance of B lines heralds the development of interstitial oedema before radiographic changes are visible.

In acute lung injury/ARDS, a lung ultrasound *reaeration score* based on the severity of interstitial changes (Table 40.1) provides a semiquantitative measure of positive end-expiratory pressure induced lung recruitment.[16] The lung ultrasound reaeration score has also been used to evaluate resolution of ventilator-associated pneumonia with antibiotics.[15]

Pneumothorax

The diagnosis of pneumothorax by ultrasound requires more expertise than other aspects of chest ultrasound[5] due to the reliance on artefact analysis and low incidence of pneumothorax. However, in experienced hands the diagnostic accuracy of ultrasound for occult

Table 40.1 Lung ultrasound reaeration score

LUNG PATHOLOGY	DEGREE OF AERATION	ULTRASOUND FINDINGS
Normal lung	More aeration	A lines
Interstitial infiltrate	↕	B lines
Alveolar-interstitial infiltrate	↕	White out (confluent B lines)
Alveolar consolidation	Less aeration	Consolidation

Loss of aeration may be due to oedema, inflammation or fibrosis.
See references 15, 16.

pneumothorax, defined as pneumothorax visible on CT but not plain radiograph, matches that of CT.[1,6,9]

As free pneumothorax is non-dependent, signs of pneumothorax should be sought anteroapically in the semi-recumbent patient or anterobasally in the supine patient. Where there is a pneumothorax, the parietal and visceral pleura are separated by air through which ultrasound waves cannot penetrate. Thus any lung pathology, or artefacts abutting or arising at the visceral pleura, cannot be visualised; lung sliding, B lines and the lung pulse sign must be absent. However, the A-line sign is present, generated at the tissue/air interface of the parietal pleura. The combination of A lines, absent B lines, absent lung sliding and absent lung pulse sign is 100% sensitive, but not specific for pneumothorax. Detection of the edge of the pneumothorax, termed the *lung point sign*, confirms the diagnosis of pneumothorax and allows a rough assessment of its size.[9] With the transducer held perfectly still, using 2D mode, the lung is seen to slide in and out of view with tidal ventilation. This can also be appreciated using M-mode imaging, which shows alternating lung sliding and absent lung sliding. The lung point sign will be visualised anteriorly with an occult or small pneumothorax and more laterally with a moderate-sized pneumothorax.[9] The lung point sign will be absent with a large pneumothorax, where lung sliding is absent over the entire chest.[9] In mechanically ventilated patients, care should be taken to avoid mistaking a temporary cessation of lung sliding, due to a pause in ventilation, for true lung sliding; the lung pulse sign should be present with pauses in ventilation.

A false-positive diagnosis of pneumothorax is more likely in patients with chronic obstructive pulmonary disease. If clinical uncertainty remains, then chest CT may be indicated. During cardiopulmonary resuscitation, the exclusion of pneumothorax may be particularly difficult because lung sliding will be absent unless there is effective ventilation, and the lung pulse sign will be absent during apnoeic periods because of the lack of cardiac contractility.

Subcutaneous emphysema is characterised by an air–liquid interface superficial to the pleural line. This creates E-line artefacts, which are similar in appearance to B lines but arise superficially to the pleural line (see Fig. 40.4). The presence of subcutaneous emphysema is suggestive of pneumothorax. Unfortunately, the presence of E lines precludes further ultrasound analysis for signs of pneumothorax or other lung pathology. In these circumstances, other imaging techniques may be required depending on the clinical circumstances.

DIAPHRAGMATIC DYSFUNCTION

Ultrasound provides a fast, simple and safe alternative to fluoroscopy or phrenic nerve conduction studies for the assessment of diaphragmatic dysfunction.[27] Ultrasound techniques are based on the measurement of either the extent of diaphragmatic excursion with respiration, or changes in diaphragm thickness with respiration.[27]

Diaphragmatic excursion is measured with a 3–5 MHz phased array probe placed below the right or left costal margin in the mid clavicular or anterior axillary line, directed to best visualise the posterior hemidiaphragm perpendicular to the ultrasound beam. Normal diaphragm movement with inspiration is caudal, towards the ultrasound probe in this view, and rostral (away from the probe) during expiration (Fig. 40.10). Measurements are made in M-mode. Normal values for diaphragmatic excursion during quiet spontaneous breathing are 1.8 ± 0.3 cm for males and 1.6 ± 0.3 cm for females.[28] Inaccuracies can arise from non-perpendicular alignment of the ultrasound beam with the hemidiaphragm.

Thickness of the hemidiaphragm is measured with a linear high frequency (7–11 MHz) probe placed over the zone of apposition of the hemidiaphragm to the rib cage, between the 8th and 10th intercostal space in the mid axillary line (Fig. 40.11). Measurements are made

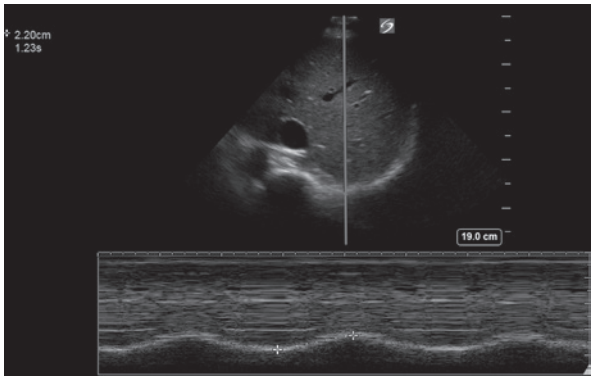


Figure 40.10 Diaphragmatic excursion demonstrated with a 1–5 MHz phased array transducer placed over the liver in the anterior axillary line, using M-mode.

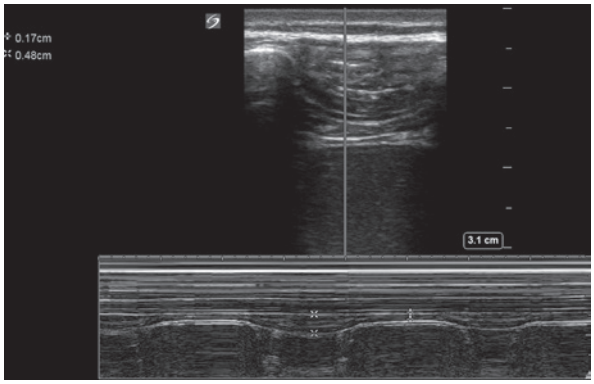


Figure 40.11 Diaphragmatic thickening demonstrated with a 6–13 MHz linear array transducer in the mid-axillary line, using M-mode.

in M-mode. Normal diaphragm thickness is 1.8–3 mm at end-expiration, with greater than 30% increase during active inspiration.

Assessment of diaphragmatic excursion and thickening during unsupported respiration provides a measure of work of breathing[29]; reduced excursion and reduced thickening predict failure to wean from mechanical ventilation.[27,30] Diaphragmatic atrophy (thinning and reduced excursion) can develop within a few days of controlled mechanical ventilation.[31] Diaphragmatic paralysis manifests as absent, or paradoxical diaphragmatic excursion during unsupported respiration. Patient ventilator synchrony may be assessed during supported mechanical ventilation by timing of diaphragmatic excursion in relation to the timing of the airway pressure waveform.[27]

DIAGNOSTIC ALGORITHMS

A number of algorithms exist that incorporate chest ultrasound in the diagnostic assessment of patients with undifferentiated respiratory failure, shock, trauma (E-FAST) or cardiac arrest.

The bedside lung ultrasound in emergency (BLUE) protocol combines lung ultrasound with deep-vein ultrasound to facilitate a diagnosis in patients with acute respiratory failure.[6,32] The A line, B line and lung sliding profile on lung ultrasound are used to differentiate pulmonary oedema, pneumonia and pneumothorax.[6,32] In patients with lung sliding and A lines throughout the chest (normal lung ultrasound), the presence of venous thrombosis on deep vein ultrasound makes pulmonary embolism the likely cause of acute respiratory failure,[6] averting the requirement for a diagnostic CT pulmonary angiography. Unnecessary CT pulmonary angiography may also be avoided if lung ultrasound or echocardiography clearly demonstrates an alternative diagnosis.[33]

Direct diagnosis of pulmonary embolism with lung ultrasound is unreliable.[34]

The fluid administration limited by lung sonography (FALLS) protocol combines lung ultrasound with echocardiography to aid the diagnosis of the cause of acute circulatory failure.[6] Firstly, obstructive shock is excluded by ultrasound examination for tension pneumothorax, pericardial tamponade and pulmonary embolism (right ventricular dilatation). Secondly, cardiogenic shock is excluded by examination for signs of left heart disease and B lines. Finally, patients with hypovolaemic or distributive shock will have A lines, indicating that fluid resuscitation can safely be administered, titrated until B lines appear. In this way fluid administration is limited by the development of pulmonary oedema, which coincides with loss of fluid responsiveness.[6,35] For undifferentiated hypovolaemic shock, abdominal ultrasound is added to detect free peritoneal fluid and abdominal aortic aneurysm.[36]

ABDOMINAL ULTRASOUND

A complete ultrasound examination of the abdomen requires radiological expertise. However, detection of haemoperitoneum (and haemopericardium) with focused assessment with sonography in trauma (FAST) is well established in emergency medicine,[37-39] and the same examination sequence can be readily applied to the intensive care patient to detect intraperitoneal fluid of any cause. Examples include detection of haemoperitoneum after abdominal surgery, or ascites in patients with chronic liver disease and portal hypertension. Once detected, if the ascites requires paracentesis, the optimal location for needle puncture can be determined by scanning more widely over the abdomen.

Low-frequency curved or phased array transducers are suitable for the FAST examination. The examination sequence consists of four standard views[37,38]:

- *Right upper quadrant:* with the transducer in the anterior or mid axillary line, at the level of the xiphisternum, aligned with the longitudinal axis of the patient (orientation marker cephalad). Three potential spaces where fluid may collect are examined in turn by moving the transducer cephalad and caudad: the subdiaphragmatic space, hepatorenal recess (Morison's pouch) and around the inferior pole of the kidney (Fig. 40.12). In the supine patient, the hepatorenal recess is the most dependent and sensitive site for detection of peritoneal fluid accumulation.
- *Left upper quadrant:* with the transducer aligned longitudinally along the posterior axillary line. The subdiaphragmatic, splenorenal and inferior renal

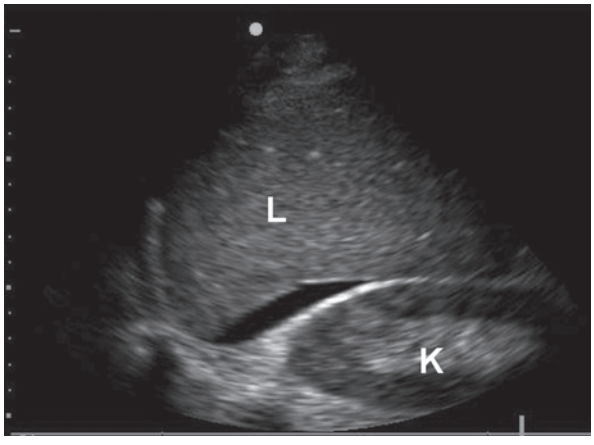


Figure 40.12 Right upper quadrant FAST scan (1–5 MHz phased array transducer) demonstrating free intraperitoneal fluid in the hepatorenal recess (Morison's pouch). Liver *(L)*, kidney *(K)*.

pole regions are examined. Fluid is more likely to be detected subdiaphragmatically than in the splenorenal recess because the phrenicocolic ligament closely apposes the spleen and kidney.[36]

- *Pelvis:* with the transducer just cephalad to the symphysis pubis and directed caudally. Images should be obtained in both longitudinal and transverse planes. The pelvis view is difficult to obtain if the bladder is decompressed (urinary catheter in situ) because the filled bladder is used as an 'acoustic window' to the pelvic peritoneal spaces.
- *Subcostal cardiac view:* to detect pericardial effusion.

The Extended-FAST (E-FAST) examination adds focused lung ultrasound for the detection of traumatic haemothorax and pneumothorax.[38] The basal anterior chest is examined bilaterally (supine patient) for signs of pneumothorax, and the basal posterolateral chest is examined for pleural fluid (haemothorax).

The abdominal aorta is imaged with the transducer placed over the epigastrium perpendicular to the abdominal wall. By convention the probe marker is pointed towards the patient's right side for the transverse view, and towards the patient's head for the longitudinal view. In the transverse view, the aorta lies to the left of the inferior vena cava and anterior to the vertebrae. The aorta appears round in cross section, thick walled and pulsatile. In the longitudinal view, the aorta can be distinguished from the inferior vena cava by its anatomical relation to the heart. The normal aortic diameter is less than 3 cm, measured from outer wall to outer wall. The entire length of the abdominal aorta should be imaged to look for aneurysmal dilatation by sliding the probe from the epigastrium to the umbilicus. The combination of abdominal aortic aneurysm and haemorrhagic shock should prompt consideration of ruptured abdominal aortic aneurysm, but retroperitoneal haemorrhage may be difficult to identify on ultrasound.

ULTRASOUND-GUIDED VASCULAR CANNULATION

Central venous cannulation is an essential component of intensive care practice. With the traditional 'landmark technique', location of the vein for cannulation is based on identification of skin surface anatomical landmarks and palpation, and is reliant on normal anatomy and venous patency. Complications include failure to cannulate the vein, pneumothorax, arterial puncture, haematoma, haemothorax and nerve injury. Risk of complication depends on operator experience, urgency and patient co-morbidities, with reported rates of 5%–20%.[40] Inclusion of ultrasound with the procedure improves first-pass success, leads to lower complication rates and is advocated by patient safety practice recommendations.[40–44] Ultrasound can also be used to aid arterial cannulation.[1,45]

ULTRASOUND TECHNIQUE

For the ultrasound novice, learning the necessary skills to image the central veins requires only a short period of supervised training, although developing good hand–eye coordination for real-time imaging during cannulation may take longer.

A high-frequency (7–11 MHz) linear transducer provides optimal image resolution suitable for vascular structures close to the skin surface. The vertical imaging depth should be set to ensure complete visualisation of the vein to be cannulated and significant structures (e.g. artery) deep to the vein. To avoid left–right confusion, the orientation marker on the screen should match the orientation of the transducer on the patient.

Ultrasound can be used in an indirect or direct way to assist cannulation. With the indirect (static) approach, imaging is used only prior to skin preparation to confirm location and patency of the vein. This avoids the need for a sterile transducer cover, but doesn't account for distortion of anatomy during needle puncture and may increase the risk of needle damage to the posterior vessel wall.[44] This technique is best suited to cannulation of large superficially located veins. The direct (dynamic) approach involves real-time ultrasound guidance of needle insertion. The vein can be imaged in a transverse or longitudinal plane. Transverse imaging gives a better view of the anatomical relationships of the vein to surrounding structures (Fig. 40.13). However, the full depth of the needle may be difficult to visualise (Fig. 40.14).[42–47] Longitudinal imaging provides optimal visualisation of the entire length of the needle and its depth of insertion,[47,48] but is technically more difficult than cannulation with transverse imaging.[42,44] The direct approach requires sterile gel and transducer cover.

VESSEL IDENTIFICATION

The anatomical position of the artery and vein may vary from the usual pattern, particularly in the neck. Certain characteristics are used to distinguish vein from artery and determine venous patency.[44] Veins are thin-walled, elliptical in cross-section and compressible with light external pressure (see Fig. 40.13). Arteries are thick-walled, circular in cross-section, and more pulsatile (during normal haemodynamic conditions). Veins are usually larger than the adjacent artery; however, the internal jugular vein may appear smaller due to anatomical variation or hypovolaemia, and will appear slit-like in the hypovolaemic patient who is not in the Trendelenburg position. Colour flow Doppler demonstrates pulsatile arterial blood flow during systole. Venous blood flow is visible on colour flow Doppler during both systole and diastole if a low-velocity (Nyquist) scale is used.

Thrombus appears as an irregular filling defect that is often quite mobile. Thrombus downstream from the site where the vein is being scanned may not be

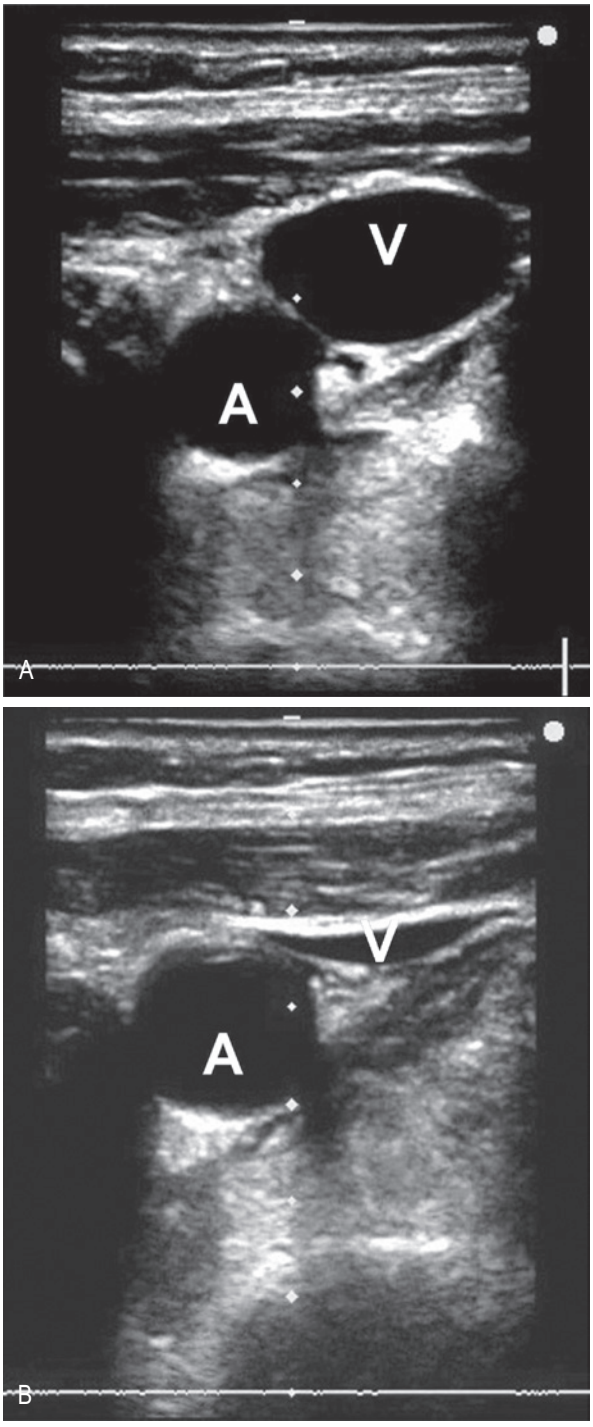


Figure 40.13 Right internal jugular vein *(V)* and carotid artery *(A)* imaged in a transverse (short-axis) plane with a 6–13 MHz linear array transducer. The vein has an oval contour without external compression (A), but appears slit-like when light external compression is applied (B). The depth markers down the centre of the image are at half-centimetre intervals.

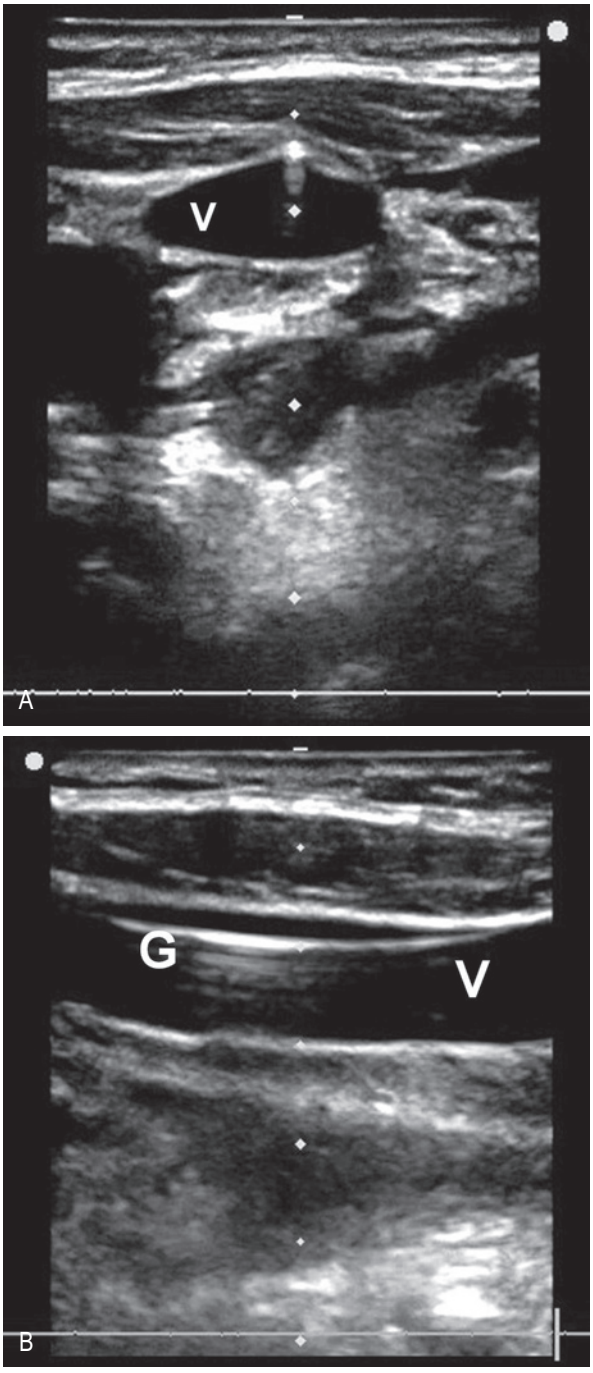


Figure 40.14 Right internal jugular vein cannulation demonstrated with a 6–13 MHz linear array transducer. In the transverse (short-axis) image (A), the needle is visualised in cross-section as a bright (hyperechoic) dot seen at the top of the vein *(V)*. Note that in this still image it is not possible to determine which part of the needle shaft is being visualised and thus at what depth the needle tip is. The longitudinal (long-axis) image (B) shows the guidewire *(G)* within the vein *(V)*.

visible, but its presence can be suspected if the vein is incompressible with light pressure. Absence of colour flow Doppler across part of the venous lumen may help to identify thrombus.

INTERNAL JUGULAR VEIN CANNULATION

Cannulation of the internal jugular (IJ) vein is ideally suited to ultrasound guidance because of the ease with which good images can be obtained, and the significant incidence of anatomical variants. The IJ vein is classically described as being located lateral to the carotid artery as it courses behind the sternocleidomastoid muscle between the anterior and posterior triangles of the neck. However, in a small proportion of patients the IJ vein runs medial to the carotid artery and in the majority of patients the vein overlies the artery to some extent.[42,44] The degree of overlap is increased by excessive head rotation away from the neutral position, and is more likely to occur with older age and obesity. In two-thirds of patients, the right IJ is larger than the left IJ.[49] A quarter of patients have one IJ vein less than 0.4 cm^2 in cross-sectional area.[49] As anatomical variation is not predictable a priori from skin surface features, ultrasound should be used for IJ vein cannulation (Box 40.1).[40,42,44]

SUBCLAVIAN VEIN CANNULATION

More consistent surface landmarks and less anatomical variation make the landmark technique for SC vein cannulation very reliable. However, if unsuccessful after two attempts, the risk of complications (pneumothorax, SC artery puncture) increases significantly with further attempts.[44] Ultrasound may be used to guide SC-vein cannulation, but the clavicle often obscures a clear image of the vein. A microconvex transducer (which is easier to place under the clavicle than a linear transducer) sometimes improves visualisation of the vein. Alternatively, cannulation can be attempted from a more lateral, axillary vein, approach, where the clavicle does not obscure imaging of the vein. This latter technique requires a steeper angle of needle entry with potential risk of pneumothorax, and should be attempted only under direct ultrasound guidance.[44] The axillary vein approach has been reported to be superior to the standard landmark technique with both novice and experienced operators.[51,52] Routine use of ultrasound for SC cannulation is not supported by current literature, but is recommended in high-risk patients to identify SC vein location and patency, or to guide an axillary vein approach.[44] Following the procedure, ultrasound can also be used to examine the lung for evidence of pneumothorax.

FEMORAL VEIN CANNULATION

The femoral vein can be reliably identified from surface landmarks and palpation of the femoral artery. The femoral vein is usually medial to the femoral artery, but significant vessel overlap may occur, particularly in children.[53] Ultrasound is recommended to identify vessel overlap and patency.[1,44] Evaluation for compressibility of the femoral and popliteal veins is a reliable method of diagnosing proximal deep vein thrombosis.[1]

Box 40.1 A suggested approach to direct ultrasound guidance of internal jugular vein cannulation using the Seldinger method

1. Obtain informed consent for procedure
2. Place patient in Trendelenburg position with head slightly rotated away from the side to be cannulated
3. Image IJ vein to determine suitability for cannulation; presence of unsuitable anatomy or thrombus should prompt cannulation of an alternative site
4. Ensure appropriate ultrasound depth, marker position and gain settings
5. Prepare and drape sterile field
6. With the help of an assistant, apply sterile sheath over transducer with coupling gel inside sheath and separate sterile coupling gel outside sheath
7. Scan along the vein to determine the optimal site for venous puncture: easy to access with the needle, large cross-sectional area and minimum overlap with the carotid artery. The degree of head rotation may need to be adjusted to minimise vessel overlap
8. For right-handed cannulation, hold the transducer with the left hand
9. If imaging in a transverse (short-axis) plane, advance the needle incrementally and then adjust the transducer position each time to ensure visualisation of the needle tip (see Fig. 40.14). With longitudinal (long-axis) imaging, puncture the skin with the needle directly underneath one end of the transducer; adjust the needle direction (not the transducer position) to ensure that it remains visible on the screen as the needle advances. With either method, needle damage to the posterior wall of the vein may be less with a bevel-downward rather than bevel-upward approach[50]
10. Once venous blood is aspirated, place the transducer on the drapes and hold the needle with the left hand whilst removing the syringe from the needle with the right hand
11. Insert the guidewire into the needle with the right hand
12. Remove the needle over the guidewire and then scan over the vein to confirm satisfactory guidewire placement (see Fig. 40.14)
13. Dilate and cannulate the vein over the guidewire to complete the procedure

OPTIC NERVE ULTRASOUND

Simple 2D ultrasound measurement of the diameter of the nerve sheath surrounding the optic nerve

provides a rapid, non-invasive method of detecting elevated intracranial pressure (ICP). In patients presenting to hospital with suspected traumatic brain injury, ultrasound-measured optic nerve sheath diameter (ONSD) identifies patients with elevated ICP who warrant further neuroimaging.[54,55] Furthermore, with traumatic brain injury changes in ONSD correlate with changes in invasively measured ICP.[56,57] However, invasive monitoring remains the gold standard for ICP measurement where this is not contraindicated by a risk of infection or haemorrhage. Validation of ultrasound ONSD in other clinical settings is limited.

A high-frequency (10–15 MHz) linear transducer is used with the image depth set to 3–4 cm. A thick layer of acoustic gel is applied over the closed upper eyelids, with the patient lying supine or 20 degrees head up. The transducer is then lightly placed over the upper, lateral eyelid, with the examiner's hand resting on the patient's forehead and the transducer held like a pencil. Care must be taken to ensure that no pressure is applied to the globe with the transducer. To reduce the risk of harmful effects (cavitation) of ultrasound acoustic output, the mechanical index (MI) should be set to less than 0.23. The possibility of thermal damage is limited by scanning for less than 5 minutes.

The optic nerve is seen as a hypoechogenic column beyond the globe and optic disk, surrounded bilaterally by the hyperechogenic optic nerve sheath (Fig. 40.15). With the optic nerve aligned directly opposite the transducer, the ONSD is measured perpendicular to the vertical axis of the imaging plane, at a depth of 3 mm from the optic disk (see Fig. 40.15). At this depth, detection of significant swelling is maximised, and distortion of ONSD measurement by artefactual shadowing is minimised. Normal values for ONSD are less than 5 mm. Values greater than 5.7–6.0 mm predict an elevated ICP (>20 cmH_2O).[55] Inaccuracies can arise if the transducer is orientated in a strictly axial imaging plane, with the optic nerve scanned along the visual axis.[58]

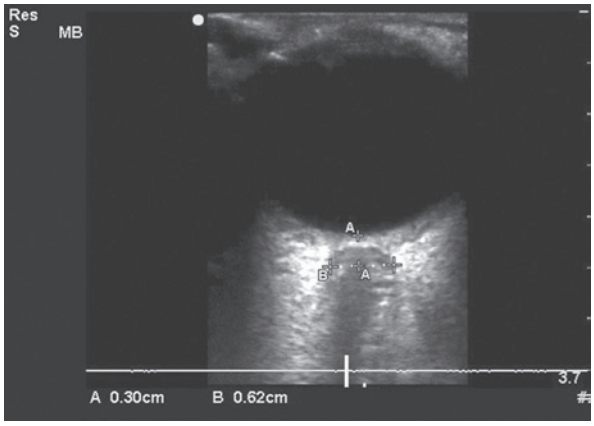


Figure 40.15 Globe and optic nerve demonstrated with a 6–13 MHz linear array transducer. Measurement of the optic nerve sheath diameter (vertical calliper) is demonstrated 3 mm deep (horizontal calliper) to the optic nerve head.

REFERENCES

1. Frankel HL, Kirkpatrick AW, Elbarbary M, et al. Guidelines for the appropriate use of bedside general and cardiac ultrasonography in the evaluation of critically ill patients – part 1: general ultrasonography. *Crit Care Med*. 2015;43:2479–2502.
2. Mayo PH, Beaulieu Y, Doelken P, et al. American College of Chest Physicians/La Société de Réanimation de Langue Française statement on competence in critical care ultrasonography. *Chest*. 2009;135:1050–1060.
3. Neri L, Storti E, Lichtenstein D. Toward an ultrasound curriculum for critical care medicine. *Crit Care Med*. 2007;35:S290–S304.
4. Lichtenstein DA. Ultrasound in the management of thoracic disease. *Crit Care Med*. 2007;35:S250–S261.
5. Bouhemad B, Zhang M, Lu Q, et al. Clinical review: bedside lung ultrasound in critical care practice. *Crit Care*. 2007;11:205.
6. Lichtenstein D. BLUE-protocol and FALLS-protocol. *Chest*. 2015;147:1659–1670.
7. Picano E, Frassi F, Agricola E, et al. Ultrasound lung comets: a clinically useful sign of extravascular lung water. *J Am Soc Echocardiogr*. 2006;19:356–363.
8. Frassi F, Gargani L, Gligorova S, et al. Clinical and echocardiographic determinants of ultrasound lung comets. *Eur J Echocardiogr*. 2007;8:474–479.
9. Lichtenstein DA, Meziere G, Lascols N, et al. Ultrasound diagnosis of occult pneumothorax. *Crit Care Med*. 2005;33:1231–1238.
10. Jambrik Z, Monti S, Coppola V, et al. Usefulness of ultrasound lung comets as a nonradiologic sign of extravascular lung water. *Am J Cardiol*. 2004;93:1265–1270.
11. Lichtenstein D, Mézière G, Biderman P, et al. The comet-tail artifact. An ultrasound sign of alveolar–interstitial syndrome. *Am J Respir Crit Care Med*. 1997;156:1640–1646.
12. Volpicelli G, Elbarbary M, Blavias M, et al. International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med*. 2012;38:577–591.
13. Soldati G, Copetti R, Sher S. Sonographic interstitial syndrome: the sound of lung water. *J Ultrasound Med*. 2009;28:163–174.
14. Lichtenstein DA, Lascols N, Prin S, et al. The "lung pulse": an early ultrasound sign of complete atelectasis. *Intensive Care Med*. 2003;29:2187–2192.
15. Bouhemad B, Liu ZH, Arbelot C, et al. Ultrasound assessment of antibiotic-induced pulmonary reaeration in ventilator-associated pneumonia. *Crit Care Med*. 2010;38:84–92.
16. Bouhemad B, Brisson H, Le-Guen M, et al. Bedside ultrasound assessment of positive end-expiratory pressure-induced lung recruitment. *Am J Respir Crit Care Med*. 2011;183:341–347.

17. Noble VE, Murray AF, Capp R, et al. Ultrasound assessment for extravascular lung water in patients undergoing hemodialysis. Time course for resolution. *Chest*. 2009;135:1433–1439.
18. Roch A, Bojan M, Michelet P, et al. Usefulness of ultrasonography in predicting pleural effusions >500 mL in patients receiving mechanical ventilation. *Chest*. 2005;127:224–232.
19. Balik M, Plasil P, Waldauf P, et al. Ultrasound estimation of volume of pleural fluid in mechanically ventilated patients. *Intensive Care Med*. 2006;32: 318–321.
20. Remérand F, Dellamonica J, Mao Z, et al. Multiplane ultrasound approach to quantify pleural effusion at the bedside. *Intensive Care Med*. 2010;36:656–664.
21. Tu CY, Hsu WH, Hsia TC, et al. Pleural effusions in febrile medical ICU patients: chest ultrasound study. *Chest*. 2004;126:1274–1280.
22. Lichtenstein DA, Lascols N, Meziere G, et al. Ultrasound diagnosis of alveolar consolidation in the critically ill. *Intensive Care Med*. 2004;30:276–281.
23. Lichtenstein D, Meziere G, Seitz J. The dynamic air bronchogram. A lung ultrasound sign of alveolar consolidation ruling out atelectasis. *Chest*. 2009; 135:1421–1425.
24. Copetti R, Soldati G, Copetti P. Chest sonography: a useful tool to differentiate acute cardiogenic pulmonary edema from acute respiratory distress syndrome. *Cardiovasc Ultrasound*. 2008;6:16.
25. Agricola E, Bove T, Oppozzi M, et al. "Ultrasound comet-tail images"; a marker of pulmonary edema: a comparative study with wedge pressure and extravascular lung water. *Chest*. 2005;127:1690–1695.
26. Lichtenstein DA, Mezière GA, Lagoueyte JF, et al. A-lines and B-lines: lung ultrasound as a bedside tool for predicting pulmonary artery occlusion pressure in the critically ill. *Chest*. 2009;136: 1014–1020.
27. Matamis D, Soilemezi E, Tsagourias M, et al. Sonographic evaluation of the diaphragm in critically ill patients. Technique and clinical applications. *Intensive Care Med*. 2013;39:801–810.
28. Boussuges A, Gole Y, Blanc P. Diaphragmatic motion studied by M-mode ultrasonography. *Chest*. 2009; 135:391–400.
29. Vivier E, Mekontso DA, Dimassi S, et al. Diaphragm ultrasonography to estimate the work of breathing during non-invasive ventilation. *Intensive Care Med*. 2012;38:796–803.
30. Kim WY, Suh J, Hong SB, et al. Diaphragm dysfunction assessed by ultrasonography: influence on weaning from mechanical ventilation. *Crit Care Med*. 2011;39:1–4.
31. Zambon M, Beccaria P, Matsuno J, et al. Mechanical ventilation and diaphragmatic atrophy in critically ill patients: an ultrasound study. *Crit Care Med*. 2016;44:1347–1352.
32. Lichtenstein DA, Mezière GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. *Chest*. 2008;134:117–125.
33. Koenig S, Chandra S, Alaverdian A, et al. Ultrasound assessment of pulmonary embolism in patients receiving CT pulmonary angiography. *Chest*. 2014; 145:818–823.
34. Aman J, Groeneveld J, van Nieuw Amerongen GP. Predictors of pulmonary edema formation during fluid loading in the critically ill with presumed hypovolemia. *Crit Care Med*. 2012;40:793–799.
35. Mathis G, Blank W, Reissig A, et al. Thoracic ultrasound for diagnosing pulmonary embolism: a prospective multicentre study of 352 patients. *Chest*. 2005;128:1531–1538.
36. Byrne MW, Hwang JQ. Ultrasound in the critically ill. *Ultrasound Clin*. 2011;6:235–259.
37. Hoff WS, Holevar M, Nagy KK, et al. Practice management guidelines for the evaluation of blunt abdominal trauma: the East practice management guidelines work group. *J Trauma*. 2002;53:602–615.
38. Kirkpatrick AW. Clinician-performed focused sonography for the resuscitation of trauma. *Crit Care Med*. 2007;35:S162–S172.
39. Melniker LA, Leibner E, McKenney MG, et al. Randomized controlled clinical trial of point-of-care, limited ultrasonography for trauma in the emergency department: the first sonography outcomes assessment program trial. *Ann Emerg Med*. 2006;48:227–235.
40. McGee DC, Gould MK. Preventing complications of central venous catheterization. *N Eng J Med*. 2003;348:1123–1133.
41. Milling TJ, Rose J, Briggs WM, et al. Randomized, controlled clinical trial of point-of-care limited ultrasonography assistance of central venous cannulation: The third sonography outcomes assessment program (SOAP-3) trial. *Crit Care Med*. 2005;33:1764–1769.
42. Maecken T, Grau T. Ultrasound imaging in vascular access. *Crit Care Med*. 2007;35:S178–S185.
43. Wigmore TJ, Smythe JF, Hacking MB, et al. Effect of the implementation of NICE guidelines for ultrasound guidance on the complication rates associated with central venous catheter placement in patients presenting for routine surgery in a tertiary referral centre. *Br J Anaesth*. 2007;99: 662–665.
44. Troianos CA, Hartman GS, Glas KE, et al. Guidelines for performing ultrasound guided vascular cannulation: recommendations of the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. *J Am Soc Echocardiogr*. 2011;24:1291–1318.
45. Shiloh AL, Savel RH, Paulin LM, et al. Ultrasound-guided catheterization of the radial artery: a systematic review and meta-analysis of randomized controlled trials. *Chest*. 2011;139:524–529.
46. Feller-Kopman D. Ultrasound-guided internal jugular access: a proposed standardized approach and implications for training and practice. *Chest*. 2007;132:302–309.
47. Blavias M, Adhikari S. An unseen danger: frequency of posterior vessel wall penetration by

needles during attempts to place internal jugular vein central catheters using ultrasound guidance. *Crit Care Med*. 2009;37:2345–2349.
48. Stone MB, Moon C, Sutijono D, et al. Needle tip visualization during ultrasound-guided vascular access: short-axis vs long-axis approach. *Am J Emerg Med*. 2010;28:343–347.
49. Lichtenstein D, Saifi R, Augarde R, et al. The internal jugular veins are asymmetric. Usefulness of ultrasound before catheterization. *Intensive Care Med*. 2001;27:301–305.
50. Lim T, Ryu HG, Jung CW, et al. Effect of the bevel direction of puncture needle on success rate and complications during internal jugular vein catheterization. *Crit Care Med*. 2012;40:491–494.
51. Gualtieri E, Scott D, Slippery ME, et al. Subclavian venous catheterization: greater success rate for less experienced operators using ultrasound guidance. *Crit Care Med*. 1995;23:692–697.
52. Fragou M, Gravvanis A, Dimitriou V, et al. Real-time ultrasound-guided subclavian vein cannulation versus landmark method in critical care patients: a prospective randomized study. *Crit Care Med*. 2011;39:1607–1612.
53. Warkentine FH, Clyde Pierce M, Lorenz D, et al. The anatomic relationship of femoral vein to femoral artery in euvolemic pediatric patients by ultrasonography: implications for pediatric femoral central venous access. *Acad Emerg Med*. 2008;15:426–430.
54. Geeraerts T, Launey Y, Martin L, et al. Ultrasonography of the optic nerve sheath may be useful for detecting raised intracranial pressure after severe brain injury. *Intensive Care Med*. 2007;33: 1704–1711.
55. Dubourg J, Javouhey E, Geeraerts T, et al. Ultrasonography of optic nerve sheath diameter for detection of raised intracranial pressure: a systematic review and meta-analysis. *Intensive Care Med*. 2011;37:1059–1068.
56. Geeraerts T, Merceron S, Benhamou D, et al. Non-invasive assessment of intracranial pressure using ocular sonography in neurocritical care patients. *Intensive Care Med*. 2008;34:2062–2067.
57. Cammarata G, Ristagno G, Cammarata A, et al. Ocular ultrasound to detect intracranial hypertension in trauma patients. *J Trauma*. 2011;71: 779–781.
58. Blehar DJ, Gaspari RJ, Montoya A, et al. Correlation of visual axis and coronal axis measurements of the optic nerve sheath diameter. *J Ultrasound Med*. 2008;27:407–411.

41

Extracorporeal membrane oxygenation

Vincent Pellegrino, Alexander (Sacha) Richardson

EXTRACORPOREAL MEMBRANE OXYGENATION FOR RESPIRATORY FAILURE

The management of severe lung injury remains a significant problem in critically ill patients. Despite the use of protective mechanical lung ventilation, the mortality of patients with severe acute respiratory distress syndrome (ARDS) remains high and increases with the severity of lung injury.[1,2] Protective lung ventilation in patients with severe ARDS may be limited by progressive hypoxaemia and hypercapnia, despite recourse to adjunctive therapies that improve oxygenation, such as inhaled nitric oxide (NO) or prone positioning.

Veno-venous extracorporeal membrane oxygenation (VV-ECMO) is an alternative form of lung support that provides non-pulmonary oxygen delivery and carbon dioxide removal, facilitates lung protective ventilation and provides time for lung recovery. Although previously predominantly used as a neonatal and paediatric support, it is now increasingly being used in adults.[3]

Current ECMO systems are mobile, can facilitate interhospital patient transport even over long distances, can be instituted quickly and provide support over days to months.

DEFINITIONS

EXTRACORPOREAL MEMBRANE OXYGENATION

This is a form of extracorporeal support comprising specialised *access cannula* to drain venous blood, an external circuit (*tubing*), a gas exchange device (*oxygenator*) where blood becomes enriched with oxygen (O_2) and has carbon dioxide (CO_2) removed, and a *return cannula* through which circuit blood returns to the patient. A pump drives the circuit blood flow and heat exchange is possible. A *fresh gas flow (FGF)* is delivered to the oxygenator. ECMO can provide adequate oxygenation and CO_2 clearance in patients with minimal or absent native lung function. ECMO may achieve circuit blood flows up to approximately 7 L of blood per minute.

MODE

The vessels from which ECMO circuit blood is obtained and returned define the *mode of ECMO*. VV-ECMO is the ECMO mode used for respiratory support. Blood is removed from the great veins and returned to the right atrium and the patient's native circulation is powered entirely by the heart. Veno-arterial extracorporeal membrane oxygenation (VA ECMO) should not be used to support isolated respiratory failure.

CONFIGURATION

The *configuration of VV-ECMO* refers to the manner in which the cannulae interact with the native circulation and is defined by the cannulae insertion sites, the type of cannula used and the tip positions (Table 41.1). *Access cannulae* drain blood from the venous system under negative pressure and may be either single stage or multistage. Single-stage cannulae drain blood from a short region near the tip only. Multistage cannulae drain blood through side holes over a long length of the cannula, in addition to the tip, and allow a greater negative pressure in the circuit. For this reason they can provide higher circuit blood flow. *Return cannulae* deliver blood back to the patient under positive pressure from the ECMO circuit and expel blood only near the cannula tip (single stage). A double-lumen cannula is available for adult VV-ECMO support (Avalon Elite) that contains both access and return lumens within a single cannula.[4]

EXTRACORPOREAL CO_2 REMOVAL

Extracorporeal CO_2 removal ($ECCO_2R$) systems differ from ECMO. They use smaller cannulae, low-blood-flow extracorporeal circuits and oxygenators, and predominantly remove CO_2.[5] Circuit blood flow is limited to less than 3 L/min and such systems cannot support patients with minimal lung function or severe hypoxaemia, but can eliminate virtually all the CO_2 produced. By controlling CO_2, they facilitate protective lung ventilation.[6] Recently, several new $ECCO_2R$ systems have become available. Current $ECCO_2R$ systems may be pump-driven veno-venous systems with a membrane oxygenator PALP (Maquet, Germany) or Hemolung RAS (ALung Technology)[7] or be 'pumpless' and use

ABSTRACT

Extracorporeal membrane oxygenation (ECMO), a form of extracorporeal life support, can provide mechanical pulmonary and circulatory support for patients with life-threatening respiratory failure or cardiogenic shock. The anatomical configuration of the access and return cannulas within the patient determine the mode of ECMO (veno-venous or veno-arterial), which correspond to isolated respiratory support (VV-ECMO) or cardio-respiratory support (VA ECMO). Current generation blood pumps, membrane oxygenators and circuit coatings have markedly improved the safety and reliability of ECMO, resulting in the expansion of its use worldwide.

KEYWORDS

Extracorporeal membrane oxygenation (ECMO)
VA ECMO
VV-ECMO
ECMO-CPR
ARDS
ECLS

Table 41.1 Configurations of veno-venous extracorporeal membrane oxygenation

CONFIGURATION	INSERTION SITE	CANNULA TIP POSITION	CANNULA TYPE AND SIZE	ADVANTAGES/ DISADVANTAGES
Femoro-femoral (fem-fem)	*Access:* Right or left femoral veins *Return:* Right or left femoral veins	*Access:* Hepatic IVC *Return:* Right atrium	*Access:* Multi- or single-stage (21–25F) *Return:* Single-stage (21–23F)	*Advantages:* Rapid to establish, safe, easy to secure and transport *Disadvantages:* Frequent problems with access insufficiency
Femoro/jugular–femoral (high-flow)	*Access:* Femoral vein and right jugular vein *Return:* Femoral vein	*Access:* Hepatic IVC and SVC *Return:* Right atrium	*Access:* Multi- or single-stage (21–25F) and short single-stage cannula (17–19F) *Return:* Single-stage (19–23F)	*Advantages:* Can fully support severe respiratory failure even in large patients *Disadvantages:* Multiple cannulations required
Femoro-jugular (fem-jug)	*Access:* Femoral vein *Return:* Right jugular vein	*Access:* Hepatic IVC *Return:* SVC/ right atrium	*Access:* Multistage (21–25F) *Return:* Short single-stage (19–21F)	*Advantages:* Full support and infrequent access insufficiency *Disadvantages:* Longer to insert, difficult to secure and maintain dressing, decannulation risk
Dual-lumen/two-stage (Avalon)	Right jugular vein	*Access:* Hepatic IVC and SVC *Return:* Right atrium	31F	*Advantages:* Single cannulation, allows ambulation *Disadvantages:* Difficult to secure and maintain dressings, high circuit pressures

In all cases, ECMO blood flow travels from the vena cavae to the atria (cavo-atrial flow) to minimise recirculation.
IVC, Inferior vena cava; *SVC*, superior vena cava.

an arterio-venous mode (iLA Membrane Ventilator Novalung)[8] or utilise a dialysis membrane in addition to the gas exchange membrane (Prismalung, Gambro-Baxter, DECAPsmart, Hemodec).[9]

GAS EXCHANGE PRINCIPLES IN VENO-VENOUS EXTRACORPOREAL MEMBRANE OXYGENATION

OXYGEN DELIVERY

Delivery of oxygen to the circuit blood by the oxygenator is governed by the oxygen-carrying capacity of the blood. Current adult membrane oxygenators can oxygenate up to 7 L of deoxygenated blood flow per minute. The quantity of oxygen that can be delivered to the patient on VV-ECMO depends on the quantity of blood arriving at the oxygenator (circuit blood flow), the pre-oxygenator O_2 saturation and the haemoglobin. Additional FGF to the oxygenator cannot increase the oxygen delivery to the circuit blood. *In the presence of a large pulmonary shunt, the patient's arterial oxygen saturation will depend predominantly on the proportion of deoxygenated venous return that can be captured by the VV-ECMO circuit.* Capturing additional deoxygenated venous blood with VV-ECMO will improve the arterial oxygen saturation. The oxygen consumption and haemoglobin will also affect the patient's arterial oxygen saturation in the presence of a large lung shunt.

CARBON DIOXIDE REMOVAL

Removal of CO_2 *by the membrane oxygenator is largely determined by the ratio of fresh gas flow to circuit blood flow in the oxygenator*. For a given circuit blood flow, increasing the FGF to the oxygenator will increase CO_2 removal. The FGF rate to the membrane oxygenator is titrated to achieve a desired partial pressure of CO_2 in the arterial blood. Normally, the ratio of FGF (L/min) to the circuit blood flow (L/min) at commencement of ECMO is approximately 1:1. With lung recovery, FGF can be gradually reduced while maintaining circuit blood flow. When the lung is capable of safely removing all CO_2 production, FGF is ceased to the oxygenator and extracorporeal respiration ceases.

RECIRCULATION

Optimal configuration of VV-ECMO must ensure adequate separation between the access and return cannulae within the venous system in order to minimise *recirculation* of ECMO circuit blood flow.[10] Blood

entering the oxygenator with high oxygen content can accept little additional oxygen owing to the nature of the oxygen content curve. This will greatly reduce the quantity of oxygen delivery the patient can receive from the ECMO circuit and may be a cause of arterial hypoxaemia. Some degree of recirculation is inevitable, particularly at higher pump blood flow rates. Clinically significant recirculation results in a reduced colour difference between pre- and post-oxygenator blood (both appear bright red) or an O_2 saturation of over 80% in the pre-oxygenator blood. In contrast, recirculation does not reduce CO_2 clearance.

HIGH OXYGEN CONSUMPTION

High cardiac output in conjunction with high oxygen consumption due to illness, patient size and fever may result in hypoxaemia, despite optimal VV-ECMO configuration and maximal circuit blood flow ≥7 L/min. This is associated with low pre-oxygenator oxygen saturation (<60%).

EQUIPMENT

Current generation blood pumps, membrane oxygenators and circuit coatings have improved the safety and reliability of ECMO.[11] This has allowed less-specialised bedside staffing and allowed ECMO care to be integrated into the scope of practice of ICU medical and nursing staff.[11] Major features are given below.

ROTARY PUMPS

Rotary pumps have largely superseded roller pumps and offer many advantages when used in circuits with low resistance to flow. These magnetically coupled pumps generate a rotational force, which drives blood radially within the pump head. A negative pressure is generated in the centre of the pump (inlet) and a positive pressure at the periphery (outlet). The pressure gradient within the pump head drives circuit blood flow, which is proportional to the rotational speed controlled by the operator. The pressure load across the circuit and the circuit resistance determine the actual circuit flow rate. The pressure load across a VV-ECMO circuit is negligible, as both access and return cannulae are sited in the venous system. Pump head thrombosis, which can cause rapid and very severe haemolysis, is rare with current rotary pump heads.

MEMBRANE OXYGENATORS

Membrane oxygenators made from polymethylpentene have markedly improved the safety and reliability of ECMO.[12] Plasma leak across the membrane seen in previous microporous membrane oxygenators has been eliminated. They allow high gas transfer with low resistance to blood flow and can be coated to minimise activation of coagulation. Acute oxygenator failure is now extremely rare.

SURFACE COATINGS

Surface coatings to reduce blood–surface interaction and activation of coagulation and inflammatory systems are present on all current ECMO components. The patient-centred benefits of one coating compared with another have not been established in ECMO.[13,14]

INDICATIONS AND PATIENT SELECTION

VV-ECMO is indicated for life-threatening forms of acute respiratory failure where the risks of less-invasive support are considered greater than the risks of ECMO (Fig. 41.1). It is predominantly used to provide support and allow time for recovery of the underlying condition where there is a reasonable expectation of long-term survival without severe

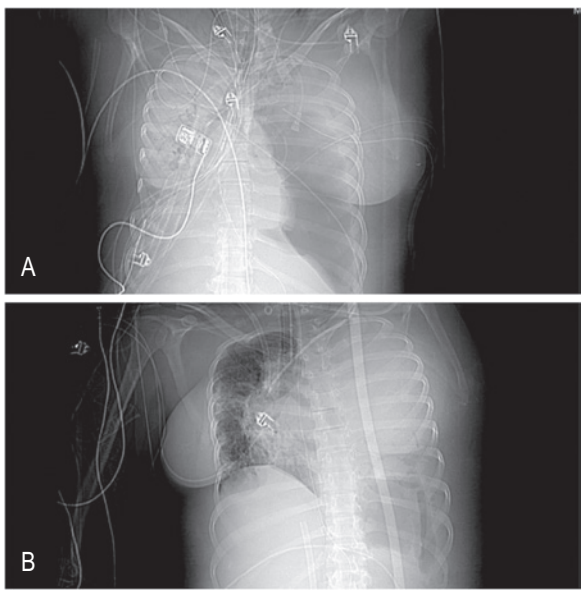


Figure 41.1 Veno-venous extracorporeal membrane oxygenation (VV-ECMO) for severe respiratory failure secondary to influenza. The patient was commenced on VV-ECMO urgently following the development of a tension pneumothorax during mechanical ventilation, which resulted in a cardiac arrest. (A) An extensive left-sided pneumothorax despite two intercostal catheters on day 1 of VV-ECMO support with extensive right-sided consolidation. By day 8 (B) the pneumonitis had resolved and the patient could be weaned from extracorporeal gas exchange despite the development of extensive left-sided haemothorax during ECMO support, which resulted in lung necrosis (noted at thoracotomy) and ultimately death.

disability. Cardiac function must be adequate, as VV-ECMO provides no direct cardiac support. Adult ECMO outcomes for respiratory support from case series from specialised centres suggest that outcomes are improving.[15,16] Increasing clinical experience with ECMO support has helped define conditions that are more likely to be associated with successful outcome.[17]

Conditions where the use of VV-ECMO is commonly associated with recovery and favourable outcomes (age <70) despite severe respiratory failure are:

- ARDS with primary lung injury from infection,[18] aspiration or direct trauma
- primary graft dysfunction following lung transplantation[18,19]
- pulmonary vasculitis (Goodpasture's, ANCA-associated, autoimmune)
- bronchopulmonary fistula with severe air leak.

Conditions where recovery is unlikely with the use of VV-ECMO as a rescue therapy in the event of severe respiratory failure are:

- respiratory failure associated with long-term immunosuppression (heart, renal, bone marrow transplant recipients, HIV, graft-versus-host disease)
- respiratory failure associated with malignancy[20]
- chronic lung transplant rejection[21]
- severe septic shock where multiple advanced organ failure and purpura are present prior to the initiation of ECMO.

ECMO is also used as a bridge to lung transplantation in selected patients with advanced forms of irreversible respiratory failure.[22] ECMO should be used for known cases of irreversible end-stage respiratory failure (cystic fibrosis, interstitial lung disease, chronic obstructive airways disease) only after careful case selection by lung transplant centres.

The decision to institute ECMO for severe respiratory failure is often complex and clinical triggers and logistic factors must be considered when determining the need for and the timing of ECMO. These include:

- severity of lung injury
- adequate trial of less invasive interventions
- rate of lung injury progression
- need for interhospital transport
- risk of bleeding.

Clinical triggers for VV-ECMO initiation in suitable patients[23] include:

- ratio of Pa_{O_2} mm Hg to Fi_{O_2} <75 (Sa_{O_2} <90%)
- hypercapnia with pH <7.15 with safe mechanical ventilation settings (plateau pressure ≤30 mm Hg (3.99 kPa) and tidal volume ≤6 mL/kg predicted body weight)
- extensive (3–4 quadrant) lung infiltrate consistent with acute lung injury

despite:

- optimising circulatory support (cardiac assessment with echocardiography) using inotropes or volume state therapy (where appropriate)
- trial of high positive end-expiratory pressure (PEEP) (18–22 cm H_2O) and recruitment manoeuvre (if not contraindicated)
- 2- to 12-hour trial of iNO or alternative pulmonary vasodilator (if available).

Rapidly progressive (6–12 hours) lung infiltrates and increasing ventilator requirements particularly in the early stages of hospital admission are often associated with a fulminant illness that reduces the time window when ECMO may be of benefit and generally favours the earlier use of ECMO.

Survival prediction models have been built using worldwide datasets of VV-ECMO patients, such as the RESP,[24] PRESERVE[25] and ECMOnet scores,[26] to aid in risk adjusting survival from differing institutions and provide a guide to expected outcomes.

ECMO is a mobile support that can be used across all patient transport modalities (road, fixed wing and helicopter) with very low rates of complications reported.[27-29] Unstable patients with severe respiratory failure requiring interhospital transport should be considered for ECMO prior to transfer.

CANNULATION FOR VENO-VENOUS EXTRACORPOREAL MEMBRANE OXYGENATION

ECMO cannulae can be safely inserted using a percutaneous dilation technique or by a surgical cut-down approach. Percutaneous dilation, which avoids skin cutting, can achieve a tight seal between skin, vessels and cannulae. This avoids bleeding associated with surgical dissection. It can also be performed quickly in a variety of settings without the need for surgical equipment or staffing.

Risks associated with 'blind' percutaneous cannulation for VV-ECMO can be greatly reduced with the use of real-time vascular ultrasound and echocardiography guidance prior to and during percutaneous dilation and cannulae advancement. Ultrasound guidance and echocardiography are increasingly being adopted in numerous hospital departments and equipment is widely available. Image intensifiers can also help prevent complications associated with VV-ECMO cannulation; however, they introduce additional patient transfers, require additional staffing, and may not be available in smaller centres (Table 41.2).

Utility of real-time vascular and cardiac ultrasound in VV-ECMO[30] includes:

- cardiac assessment
  - cardiac function
  - detection of proximal pulmonary artery emboli
  - detection of pericardial collections and extrinsic cardiac compression

Table 41.2 Potential major complications of cannulation for veno-venous extracorporeal membrane oxygenation

COMPLICATION	CAUSE	PREVENTION
Haemorrhage	Perforation of venous system	• Real-time guidewire localisation • Ensuring guidewire continually has free movement through dilators during dilator insertion • Use 'soft' tapered dilators • Enter femoral vessel below inguinal ligament
	Cannula site bleeding	• Maintain tight skin/tissue seal with cannula • Avoid arterial puncture • Avoid transfixing the inguinal ligament • Avoid surgical dissection
Cardiac injury	Femoral dilator/cannula advanced into interatrial septum	• Image intensifier or echocardiography guidance
	Jugular dual-lumen dilator/cannula advanced into right ventricle	• Image intensifier or echocardiography guidance
Cannula malposition	Femoral access cannula in lower IVC	• Image intensifier or echocardiography guidance
	Jugular dual-lumen cannula tip in hepatic vein or right ventricle	• Image intensifier or echocardiography guidance • Adequate cannula securing

IVC, Inferior vena cava.

- identification of proximal vein thrombosis prior to cannulation (unilateral occlusive jugular vein thrombosis is a contraindication to contralateral jugular vein cannulation owing to the risk of cerebral oedema)
- anatomical assessment of the target vessel and branches
  - reduces carotid or femoral artery puncture
  - prevents inadvertent sapheno–femoral junction cannulation
  - identifies abnormal anatomy
- maintenance of guidewire J-loop position in the right atrium
  - detects inadvertent guidewire entrapment ('kinking') during serial dilation
  - prevents excessive guidewire introduction and cardiac effects during cannula insertion
- guides optimal cannula tip placement
  - ensures femoral access cannulae are sited within the hepatic inferior vena cava (IVC)
  - ensures return cannula sited in the right atrium without encroachment on the interatrial septum
  - ensures optimal positioning of dual-lumen VV cannula (Avalon Elite) return port[31]
  - prevents dual-lumen VV cannula (Avalon Elite) tip being sited in the hepatic vein.[31]

EXTRACORPOREAL MEMBRANE OXYGENATION-SPECIFIC PATIENT CARE

MANAGEMENT OF CIRCUIT BLOOD FLOW SETTINGS

Rotary (constrained vortex) blood pumps generate circuit blood flow proportional to their pump speed and are afterload sensitive. In VV-ECMO, afterload across the pump is low and stable provided there are no circuit obstructions. Generally, the pump operates in a pump-speed-controlled mode where pump speed is the set variable and resulting pump flow is measured. Pump speed settings are chosen to deliver sufficient circuit blood flow to achieve required oxygen delivery. Depending on patient size, oxygen consumption and lung shunt, circuit blood flow between 4 and 7 L/min will be required to achieve safe arterial oxygen saturations of over 85%, while maintaining safe lung ventilation.

MONITORING OF CIRCUIT PRESSURE

The pressure in the extracorporeal circuit becomes progressively more negative from drainage cannula tip to the inflow to the pump head. The maximal positive circuit pressure occurs at the outlet of the pump head and falls progressively to the return cannula. The oxygenator is located distal to the pump head and receives blood under positive pressure. The pressure change across the oxygenator can be measured safely and easily without introducing circuit connectors and gives an indication of clot burden within the oxygenator. One current-generation ECMO pump (Cardiohelp-HLS, Maquet) has integrated pressure monitoring of pre- and post-oxygenator pressure in addition to negative-pressure monitoring at the pump head inlet.

ACCESS INSUFFICIENCY

As pump speed is increased, the negative pressure at the access cannula inlet also becomes more negative. If venous return to the access (draining) ECMO

cannula is inadequate for the degree of pump suction, venous 'suck-down' will occur and circuit blood flow will fall and become variable, usually with audible and visible effects on the inflow of the circuit. *Restricted and variable circuit flow with or without visible chaotic movement of the access tubing is termed access insufficiency.* This situation must be identified and rectified quickly (reducing pump speed) to prevent haemolysis and potential vascular injury.[32] Access insufficiency may prevent adequate circuit blood flow and oxygen delivery. Multistage access cannulae distribute the negative circuit pressure over a longer length of a vessel and deliver higher maximal blood flow than similar single-stage access cannulae.

Factors that increase the occurrence of access insufficiency include:

- femoral access cannula tip sited too low
- dual-lumen cannula not optimally sited
  - distal tip sited in the hepatic vein (instead of IVC)
  - catheter withdrawn and superior vena cava (SVC) access sited too high within the right brachiocephalic vein
- reduced venous return
  - blood or volume loss
  - vasodilation
  - raised intrathoracic or intra-abdominal pressure (coughing, dysynchronous breathing, constipation, abdominal distension)
- reduced venous capacitance
  - extrinsic right heart compression.

TITRATION OF FRESH GAS FLOW TO THE OXYGENATOR

FGF to the oxygenator maintains the diffusion gradients for O_2 delivery to, and CO_2 removal from, the circuit blood. FGF can be composed of dry air–oxygen mix or pure O_2. The partial pressure of O_2 in the FGF determines the post-oxygenator blood partial pressure O_2. The FGF rate determines the partial pressure of CO_2 in the post-oxygenator and its rate is chosen to achieve a desired partial pressure of CO_2 in the patient's arterial blood.

LUNG VENTILATION

Non-injurious lung ventilation is a primary goal of ECMO support in respiratory failure. Non-pulmonary gas exchange facilitates low pressure and volume strategies and several lung ventilation modes have been advocated during the different phases of ECMO support. PEEP levels are chosen to maintain lung aeration. Peak lung pressures can easily be maintained below 30 cm H_2O with ECMO support. A low driving pressure (plateau pressure – PEEP) may be beneficial[33]; as such, tidal volumes may be negligible and remain much less than the anatomical dead space of the lung during ECMO support. Improving lung compliance and the return of physiological tidal volume herald lung recovery from acute lung injury.

WEANING

As lung recovery occurs, it is standard to wean ECMO gas flow until it is off, at which point the patient is no longer receiving extracorporeal support. Cannulae are generally removed after a period of time off gas flow (usually 2–24 hours). There is no need to wean circuit blood flow below 3 L/min during weaning, which reduces the need for additional anticoagulation. Percutaneously inserted venous cannulae can be removed at the bedside (off anticoagulation) and skin sites compressed for 20 minutes.

In general, ECMO weaning and decannulation are performed in advance of airway extubation. Where ECMO is used in chronic respiratory failure conditions, it can be advantageous to extubate patients during ECMO support to maintain wakefulness and avoid the complications of sedation. Ambulant ECMO is highly desirable for cystic fibrosis patients being bridged to transplantation to maintain secretion clearance.[34] Whether ambulant ECMO provides additional benefit for patients with acute respiratory failure is currently uncertain.

ANTICOAGULATION

Anticoagulation for ECMO is given to reduce the rate of clot formation within the circuit, and reduce clot formation associated with cannulae.[35] Clotting is often seen in low-flow regions of the oxygenator but is not an indication for circuit change. It is generally accepted that systemic anticoagulation with heparin should be provided for all patients on ECMO *provided there is no bleeding and there is no anticipated or recent surgery.* Anticoagulation practices are based on patient bleeding risk profiles and VV-ECMO can be successfully run for days without anticoagulation in order to arrest bleeding. Essential surgery can also be performed during ECMO support.[36]

EXTRACORPOREAL MEMBRANE OXYGENATION-SPECIFIC PATIENT COMPLICATIONS

Prevention of complications is fundamental to successful ECMO care. Patients are at increased risk of bleeding, particularly from the injured lung, and have an increased risk of haemolysis. VV-ECMO can provide great stability to the patient with severe respiratory failure, but may also induce dangerous complications if the circuit is breached (accidental decannulation, circuit rupture) or the blood pump fails. Staff training and bedside resources to standardise decision making are important components of successful ECMO programmes. Avoiding excessive sedation, provision

of timely pressure care and physical therapy during VV-ECMO support are becoming routine.

BLEEDING

Bleeding remains the main complication of ECMO; however, many sources of bleeding can be prevented. Cannulation site bleeding should be uncommon in VV-ECMO if optimal percutaneous cannulation techniques are used and surgical dissection is avoided. Pulmonary bleeding is a frequent cause of death during VV-ECMO support for respiratory failure.[37] Insertion of intercostal catheters during ECMO is an extremely high-risk intervention and should not be performed unless no other alternative remains. In particular, intercostal catheters should not be inserted for pneumothoraces or pleural fluid drainage unless they are massive or cause haemodynamic compromise.[38] During VV-ECMO, pneumothoraces may be managed by increasing ECMO support and reducing (or ceasing) pulmonary ventilation, without the need for tube insertion. Fibrinolysis and secondary consumptive coagulopathy can occur during ECMO, particularly with older circuits and induce generalised bleeding. Monitoring of fibrinogen and D-dimer levels and elective ECMO circuit changes are required to control this process.

Therapies for managing severe bleeding during ECMO support are given in the section *ECMO for cardiac failure*.

HAEMOLYSIS

Haemolysis (repeated plasma free Hb >0.1 g/dL) is extremely uncommon with current-generation circuits; however, regular monitoring of plasma free Hb is still routine in many centres. Severe haemolysis (plasma free Hb >1.0 g/L or with hyperkalaemia or red urine) suggests pump head thrombosis and must be treated with an urgent circuit change.[39]

AIR EMBOLISM

Air will rapidly enter the circuit during pump operation if there is any breach in the negative pressure region of the circuit. Taps and other potential breaches on the negative (pre-pump) side of the circuit should be avoided. Air that enters the circuit will de-prime the pump head (reducing circuit flow), accumulate in the oxygenator and may reach the return line and cause patient air embolism. Staff education and circuit design are essential preventative measures. De-airing the circuit following air embolism is technically challenging.

CLINICAL TRIALS

ECMO has been used since 1966 as a rescue therapy for severe acute respiratory failure that is refractory to mechanical ventilation.[40] The process of establishing the clinical efficacy for this practice has a long and fascinating history owing to the unique ethical[41] and logistical challenges inherent in this form of support and the patient populations with this disease. In the 1970s and 1980s, uncontrolled observational reports suggested clinical benefits with the use of extracorporeal support, but these were not realised in subsequent randomised controlled trials (RCTs).[42,43]

In 2001 the CESAR trial,[44] a prospective randomised adult ECMO trial conducted in the United Kingdom, commenced enrolment. The results were published in 2009, and the intention-to-treat analysis showed that significantly more patients allocated to consideration for treatment including ECMO survived to 6 months without disability compared with those allocated to conventional management. This result represented a relatively large treatment effect, albeit with borderline precision and with a sample size that was less than initially planned. Reasonable concerns with regard to the basis of the efficacy, the quality of respiratory care in the control arm and the generalisability of the findings outside the United Kingdom have been raised.[45]

In 2011 Noah et al.[46] compared the outcomes of patients in the H1N1 flu pandemic referred to an ECMO centre to matched controls of H1N1 flu patients from the same pandemic who were not referred. Survival was 74% in the ECMO centre patients and 49% in the database matched pairs.

Currently, a French multinational adult ECMO trial for severe respiratory failure (EOLIA) has completed patient recruitment and is expected to report outcomes early in 2018. Mechanical ventilation strategies for both arms demand protective lung ventilation (ClinicalTrials.gov Identifier: NCT01470703).

EXTRACORPOREAL MEMBRANE OXYGENATION FOR CARDIAC FAILURE

Mortality from cardiogenic shock and refractory cardiac arrest is very high and frequently cannot be adequately managed with medical therapy. Veno-arterial extracorporeal membrane oxygenation (VA ECMO) is a rapidly deployable, short-term system for complete or partial support of the circulatory system. It can allow time for reversible forms of cardiac failure to recover and can prevent end-organ damage from under perfusion. It can provide organ support before, during or after therapeutic cardiovascular procedures. In patients with advanced chronic heart failure and secondary acute end-organ injury, it can provide a bridging support to longer-term devices and allow time for thorough case selection.

Traditionally, VA ECMO has been employed by surgical staff in the operative setting, but progressively it is being applied in non-operative settings by a number of trained specialists. Although previously

predominantly used as a neonatal and paediatric support, it is increasingly being used in adults.

Additional explanations of ECMO are given in the section on ECMO for respiratory support.

DEFINITIONS

MODE

VA ECMO is the ECMO *mode* used for cardiac support. Blood is removed from the right atrium and adjacent veins and then returned to the aorta, bypassing the native heart and lungs. VA ECMO comprises a specialised *access cannula* to drain venous blood, an external circuit (*tubing*), a gas exchange device (*oxygenator*) where blood becomes enriched with oxygen and has CO_2 removed, and a *return cannula* through which circuit blood returns to the arterial system. A pump drives the circuit blood flow and heat exchange is possible. A *FGF* is delivered to the oxygenator. ECMO circuit flows are adequate to provide complete systemic perfusion (5–7 L of blood per minute); however, it may not provide specific left ventricular 'unloading'.[47] Percutaneous cardiopulmonary bypass and temporary cardiopulmonary bypass are other terms for VA ECMO.

In veno-pulmonary artery (VPA) ECMO, venous blood is accessed from a large central vein and returned to the pulmonary arterial system via a specialised surgical conduit after it has passed through the oxygenator. It provides short-term right ventricular (and respiratory) support in the intraoperative setting following left ventricular assist device (VAD) insertion.[48]

CONFIGURATION

The *configuration of VA ECMO* determines the manner in which the ECMO circuit interacts with the native circulation. Cannulae insertion sites and the tip positions define configuration. Broadly, there are three adult VA ECMO configurations (Table 41.3):

- femoro-femoral
- jugulo-subclavian[49]
- central (including VPA ECMO).

Table 41.3 Configurations of veno-arterial extracorporeal membrane oxygenation

CONFIGURATION	INSERTION SITE	CANNULA TIP POSITION	CANNULA TYPE AND SIZE	ADVANTAGES/DISADVANTAGES
Femoro-femoral ECMO (fem-fem)	*Access:* Femoral vein *Return:* Common femoral artery (with distal perfusion cannula)	*Access:* Right atrium *Return:* Iliac artery or distal aorta	*Access:* Multistage (19–25F) *Return:* Single-stage (15–21F)	*Advantages:* Quick to deploy Surgery not required *Disadvantages:* High rate of limb ischaemia if distal perfusion cannula not used Unable to ambulate Allows cephalic differential hypoxaemia
Jugulo-subclavian ECMO[3]	*Access:* Right jugular vein *Return:* Right subclavian artery (tunnelled)	*Access:* Right atrium *Return:* Right subclavian artery (T-graft)	*Access:* Short single-stage (19–23F) *Return:* Specialised graftable	*Advantages:* Allows ambulation and unrestricted sitting Reduces cephalic differential hypoxia *Disadvantages:* Right arm swelling or axillary plexus injury
Central ECMO (atrio-aortic)	*Access:* Sternotomy or tunnelled subcostally *Return:* Sternotomy or tunnelled subcostally	*Access:* Right atrium via atrial appendage *Return:* Proximal ascending aorta	Standard by-pass cannulae (access and return) inserted via sternotomy (36–46F) *or* Specialised long-term surgical (graftable) arterial cannula and malleable atrial cannula (tunnelled with closed sternum) (36–46F)	*Advantages:* Accessible during cardiac surgery Large cannula and lower circuit resistance *Disadvantages:* Surgical site bleeding Restricted patient movement and pressure area care Respiratory effects of sternotomy
Femoro-pulmonary artery ECMO (VPA ECMO)[2]	*Access:* Femoral vein *Return:* Tunnelled via chest wall	*Access:* Right atrium *Return:* Main pulmonary trunk	*Access:* Multistage (19–25F) *Return:* Specialised surgical graft and short single-stage 19F cannula	*Advantages:* Maintains full LVAD flows Provides respiratory and right heart support Removal without surgery *Disadvantages:* Pulmonary artery vascular graft remains in situ

ECMO, Extracorporeal membrane oxygenation; *LVAD*, left ventricular assist device; *VPA*, veno-pulmonary artery.

DISTINCT FROM EXTRACORPOREAL MEMBRANE OXYGENATION

Short-term *VAD* may employ similar cannulae, circuit tubing and pumps to ECMO, but does not include an oxygenator and is configured to provide single ventricular mechanical support only. Left VAD (LVAD) is configured using a left heart access cannula with an aortic return cannula. Right VAD (RVAD) is configured using right heart access with a pulmonary artery return. Biventricular VAD support configurations (BiVAD) are distinct from VA ECMO.

BLOOD FLOW PRINCIPLES

VA ECMO blood flow bypasses the native heart and lungs. Two arterial circulations may be identifiable during VA ECMO support. In contrast to VV-ECMO, recirculation is not seen during VA ECMO support.

NATIVE CARDIAC OUTPUT

Native cardiac output produces pulsatile pulmonary and aortic blood flow during VA ECMO support. Cardiac function can vary from absent to near-complete during different phases of VA ECMO support. Oxygen and CO_2 gas tensions of the native cardiac output will reflect the pulmonary gas exchange and predominantly be delivered to the coronary and cephalic circulations. Because CO_2 is only delivered to the lung by the native cardiac output through the pulmonary circulation, airway end-tidal CO_2 excretion is also indicative of native cardiac output.

CIRCUIT BLOOD FLOW

The distribution of the returning VA ECMO circuit blood within the arterial tree is dependent on the particular VA ECMO configuration, ECMO circuit blood flow and the native cardiac output. The gas tensions in the ECMO circuit blood flow reflect gas exchange across the oxygenator. During complete VA support, ECMO circuit blood flow provides all systemic perfusion and arterial gas tensions will be similar to post-oxygenator readings. In this state, the arterial waveform is non-pulsatile. As cardiac function returns, pulsatility will be seen and arterial gas tensions will reflect the proportion of native and circuit blood flow reaching the sampling site.

DIFFERENTIAL OXYGENATION DURING VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION

A significant lung shunt in association with an improving native cardiac output can result in large degrees of differential oxygenation in patients supported with peripheral VA ECMO. With femoral arterial VA ECMO return, highly oxygenated blood is preferentially distributed to the caudal regions as native cardiac output improves while deoxygenated blood leaving the left ventricle predominantly perfuses the coronary and cephalic circulations. For this reason, patients on peripheral VA ECMO should have arterial oxygenation monitored via the right arm.

CIRCUIT PRESSURE

The pressure gradient across a VA ECMO circuit is greater than in VV-ECMO owing to the physiological systemic arteriovenous pressure. Consequently, in VA ECMO, it is normal to require higher pump speeds to achieve full support, and pressure monitoring in the circuit (see VV-ECMO) will record higher pressures at the membrane and in the return line. Such high ECMO circuit pressure may limit the ability for the provision of continuous renal replacement via the ECMO circuit.

INDICATIONS AND PATIENT SELECTION

VA ECMO is indicated for life-threatening forms of cardiac failure where the risks of less invasive support are considered greater than the risks of ECMO and there is a reasonable expectation of long-term survival without severe disability. Currently, ECMO is generally considered in patients up to the age of 70 without other chronic organ failures or terminal illnesses.

Common indications for VA ECMO support with a reasonable chance (>50%) of subsequent recovery and favourable outcomes include:

- acute fulminant myocarditis[50-52]
- cardiomyopathy (bridge to VAD)[53]
- acute myocardial infarction (AMI)-cardiogenic shock prior to multiple organ failure[54]
- drug overdose with profound cardiac depression or arrhythmia[55,56]
- pulmonary embolism with cardiogenic shock[57]
- primary graft failure: post heart[58,59]/heart–lung transplant.

The use of ECMO for refractory 'in-hospital' cardiac arrest (with ECMO commenced within 60 minutes)[60,61] is associated with recovery rates of approximately 30% (alive to discharge), which may be superior to standard treatment.[62]

Conditions where recovery is rare (<25%) despite the use of VA ECMO as a rescue therapy include:

- adult cardiogenic shock with established multiorgan failure
- adult septic shock with severe myocardial depression and multiorgan failure
- heart transplant with chronic rejection
- 'out of hospital' and prolonged cardiac arrest, although there is some evidence for improved outcomes compared to conventional cardiopulmonary resuscitation (CPR) in selected cases.[61-64]

Cardiac and vascular lesions that prevent the successful application of VA ECMO are:

- aortic dissection
- severe aortic regurgitation[65]
- severe mitral regurgitation.

ECMO is also used as a bridge to VAD and heart transplantation (the 'double bridge' strategy) in selected patients with advanced forms of irreversible cardiac failure.[66] Decisions regarding the choice of mechanical support modalities in this population should involve specialised transplant services.

CLINICAL TRIGGERS FOR VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION INITIATION IN SUITABLE PATIENTS WITH CARDIOGENIC SHOCK

Due to the rapid onset of end-organ damage with cardiogenic shock and refractory arrest, the timing of VA ECMO initiation is critical in patient outcome. A guide to the clinical triggers and logistic factors to be considered when determining the timing of ECMO for a deteriorating patient with cardiogenic shock is given below:

- pharmacological support of cardiac index and blood pressure is likely to exacerbate the underlying primary cardiac illness (e.g. AMI-cardiogenic shock or recurrent ventricular fibrillation [VF])
- cardiac index and blood pressure inadequate despite pharmacological support:
  - moderate- or high-dose inotropes (epinephrine [adrenaline] >0.3 µg/kg/min equivalent) in combination with an intra-aortic balloon pump (IABP), vasopressors and positive-pressure ventilation for predominately left ventricular failure
  - moderate- or high-dose inotropes (epinephrine [adrenaline] >0.3 µg/kg/min equivalent) in combination with pulmonary artery vasodilator and/or systemic vasopressors for predominantly right ventricular failure
- onset of secondary hepatic, renal or skin ischaemia despite pharmacological support
- lactate greater than 5 mmol/L and rising despite pharmacological support.

VA ECMO is a mobile support that can be used across all patient transport modalities (road, fixed wing and helicopter) with very low rates of complications reported.[67,68] Time delays incurred with ECMO retrieval must be considered during assessment.

EXTRACORPOREAL MEMBRANE OXYGENATION-CARDIOPULMONARY RESUSCITATION

Cardiac arrest refractory to conventional CPR and Advanced Cardiac Life Support (ACLS) therapies may be salvaged with ECMO. Favourable neurological outcome following cardiac arrest diminishes rapidly following prolonged conventional CPR without return of spontaneous circulation (ROSC) due to cerebral hypoperfusion. VA ECMO rapidly restores a perfusing circulation in the absence of native cardiac function, allowing more time for reversible causes of the arrest to be diagnosed and treated. There is observational data to suggest improved outcomes in selected patients undergoing ECMO-CPR (ECPR) who do not attain ROSC with conventional CPR for both in-hospital and out-of-hospital cardiac arrest[63,64,69,70]; however, the logistics required to appropriately deploy the therapy in a timely fashion for cardiac arrest are considerable and patient selection is key.[71]

CANNULATION FOR VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION

ECMO cannulae can be safely inserted using a percutaneous dilation technique or by a surgical cut-down approach. Percutaneous dilation, which avoids skin cutting, can achieve a tight seal between skin and cannulae. This avoids bleeding associated with surgical dissection. It can also be performed quickly in a variety of settings without the need for surgical equipment or staffing.[72]

Risks associated with 'blind' percutaneous cannulation for VA ECMO can be greatly reduced with the use of real-time vascular ultrasound and echocardiography guidance prior to and during percutaneous dilation and cannulae advancement. Ultrasound guidance and echocardiography are increasingly being adopted in numerous hospital departments and equipment is widely available. Image intensifiers can also help prevent complications associated with VV-ECMO cannulation; however, this introduces additional patient transfers, requires additional staffing and may not be available in smaller centres.

UTILITY OF REAL-TIME VASCULAR AND CARDIAC ULTRASOUND IN VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION

- Cardiac assessment[30]
  - Cardiac and valvular function
  - Detection of proximal pulmonary artery emboli
  - Detection of pericardial collections and extrinsic cardiac compression
  - Presence of aortic disease
  - Detection of intracardiac thrombosis
- Anatomical assessment of the target vessel and branches
  - Prevents inadvertent sapheno-femoral junction venous cannulation
  - Prevents inadvertent profunda femoris artery injury (arterial cannulation)
  - Identifies abnormal anatomy

- Immediate confirmation of needle entry in vein and confirmation of arterial cannulation prior to dilation (required during pulseless resuscitation)
- Maintenance of guidewire J-loop position during dilation
  - Detects inadvertent guidewire entrapment ('kinking') during serial dilation
  - Prevents excessive guidewire introduction and cardiac effects during cannula insertion
- Guides optimal cannula tip placement
- Weaning study from V ECMO[73,74]
  - LVOT (left ventricular outflow tract) blood flow assessment.

EXTRACORPOREAL MEMBRANE OXYGENATION-SPECIFIC PATIENT CARE

ASSESSMENT OF NATIVE CARDIAC OUTPUT

This is approximately assessed at the bedside using the pulsatility of the arterial blood pressure and end-tidal CO_2 trace (Fig. 41.2). It can be measured from velocity–time integration of blood flow through the LVOT with echocardiography, but not by thermodilution due to partial loss of indicator into the ECMO circuit. Native cardiac output must be assessed regularly during VA ECMO support to titrate lung ventilation in order to avoid gross abnormalities in lung V/Q ratios. It is also important in assessing the adequacy of overall systemic perfusion.

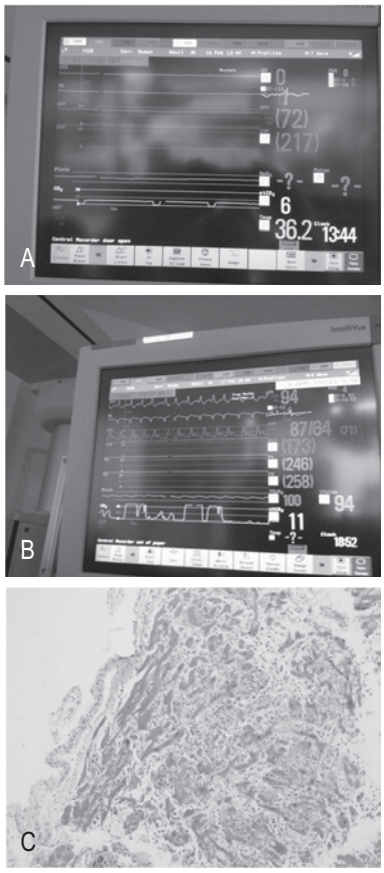


Figure 41.2 The stages of cardiac support with veno-arterial extracorporeal membrane oxygenation (VA ECMO) for a case of severe lymphocytic myocarditis. Arterial pulsatility was lost on day 1 following ECMO initiation for cardiogenic shock. On day 2 (A) after ECMO support the asystole and ventricular standstill were frequently seen for hours. By day 3 (B), pulsatility and end-tidal CO_2 signals returned with cardiac recovery following immunosuppressive therapy. The patient was decannulated by day 7 and extubated by day 9 and made a full recovery. (C) Cardiac biopsy on day 1 showing heavy lymphocytic infiltration.

MANAGEMENT OF CIRCUIT BLOOD FLOW SETTINGS

VA ECMO circuit blood flow settings are primarily chosen to achieve adequate overall systemic perfusion. ECMO circuit flow, which is continually measured, in combination with the native cardiac output equate to the total body blood flow. Adequate mechanical systemic perfusion allows inotropic support to be weaned or ceased and lowers myocardial work. Adequate mechanical circulatory support can allow safe performance of high-risk percutaneous cardiac procedures.

ACCESS INSUFFICIENCY

Access insufficiency can occur in all modes of ECMO and is described in the section on ECMO for respiratory failure.

TITRATION OF FRESH GAS FLOW TO THE OXYGENATOR

FGF to the oxygenator maintains the diffusion gradients for O_2 delivery to, and CO_2 removal from, the circuit blood (see ECMO for respiratory failure). Where VA ECMO provides partial circulatory support, significant CO_2 clearance will occur via the lungs and low rates of FGF to the oxygenator will be required to prevent respiratory alkalosis. Inadequate FGF during VA ECMO will prevent oxygenation of venous blood within the ECMO circuit and impose an extrapulmonary right-to-left shunt.

LUNG VENTILATION

Many patients on peripheral VA ECMO support do not require mechanical ventilation or sedation, in contrast to patients configured with central VA ECMO support. Positive-pressure ventilation is beneficial in the management of pulmonary oedema, which may develop

during VA ECMO support where left ventricular failure is more severe than right ventricular failure. Mechanical lung ventilation may also form part of the management of a lung shunt, which becomes evident during VA ECMO as native cardiac function returns (see below).

PREVENTION OF DISTAL LIMB ISCHAEMIA

All patients with a peripheral ECMO arterial return catheter should have a *distal perfusion cannula* inserted to prevent limb ischaemia occurring as a result of the occlusive and compressive effects of the return cannula.[75] The presence of normal lower limb perfusion should not prevent the insertion, as limb ischaemia may progress quickly. Distal perfusion cannulae are not required for specialised surgical cannulation using a 'T' graft.

DIFFERENTIAL HYPOXIA

Differential hypoxia occurs when hypoxaemic blood from the pulmonary circulation is ejected from the left heart while fully oxygenated blood enters the arterial circulation from the ECMO circuit. It develops during peripheral VA ECMO support as cardiac function returns when a large intrapulmonary shunt is present, and its development indicates cardiac recovery. It is not seen in central VA ECMO as the ECMO circuit blood enters the arterial tree at the proximal aorta. Its development can be anticipated in known cases of combined severe respiratory and cardiac failure, or it may only become apparent following successful resuscitation. Right subclavian artery return configuration will reduce the cerebral effects in peripheral ECMO, compared with femoral return.

Management includes weaning off any inotropic agents, treating the lung shunt with positive-pressure ventilation, PEEP, bronchoscopy, and inhaled NO if appropriate. Increasing the ECMO circuit blood flow should reduce the proportion of venous return able to reach the lungs. If severe hypoxaemia persists ($Sa_{O_2} < 85\%$) despite other measures, consideration of changing the mode of ECMO support from VA to VV should be considered.

LOSS OF PULSATILITY

The ability of the heart to open the aortic and pulmonary valves and contribute to cardiac output may be temporarily lost in severe forms of cardiac failure. The progressive loss of pulsatility during VA ECMO support may indicate extrinsic cardiac compression or progressive cardiac failure, and urgent echocardiography is required to establish the cause. Extrinsic cardiac compression from bleeding is more common in the postoperative cardiac setting and must be managed surgically.

Severe myocardial failure with loss of pulsatility is associated with increased risk of intracardiac thrombosis with arterial embolisation. Management is aimed at preservation of some intracardiac blood flow and higher anticoagulation targets. Increased inotropic support, reduction in arterial pressure and reduced ECMO circuit blood flow may improve cardiac blood flow.

MANAGEMENT OF LEFT VENTRICULAR FAILURE

Pathology that results in a predominance of left ventricular heart failure (LVF), compared with right ventricular failure (e.g. massive left ventricular AMI), the presence of aortic or mitral valve regurgitation or high mean arterial pressure can result in progressive distension of the left ventricle, and congestion of the pulmonary circulation and lungs during VA ECMO support. Non-surgical options for control of LVF during VA ECMO support include positive-pressure ventilation and high PEEP, reduction in mean arterial pressure and decreasing inotropic support (inotropes may increase RV function more than LV function in diseases of the LV). Surgical options include the addition of a left heart drainage cannula to the circuit, conversion from ECMO to a LVAD, or the use of minimally invasive transaortic valve axial pumps.[76-78]

PREVENTION AND MANAGEMENT OF BLEEDING

Prevention of bleeding remains the greatest challenge for ECMO patient care and preventative strategies are given in the section *ECMO for respiratory failure*. Surgical site bleeding is the most common cause of severe bleeding in VA ECMO. The management of severe bleeding during ECMO commonly involves the following responses and involvement of surgeons and specialist haematology support:

INITIAL RESPONSE TO BLEEDING

- Heparin should be ceased and not be recommenced until all bleeding has stopped for 12–24 hours.
- Aggressively replace all clotting element deficiencies:
  - cryoprecipitate until fibrinogen >1.5 g/dL
  - platelets until count is >80,000 and normal maximal amplitude (MA) on a thromboelastogram (TEG)
  - fresh frozen plasma (FFP) or human prothrombin complex (Prothrombinex) until international normalised ratio (INR) is <1.3 and there is normal reaction (R) time on TEG.

ADDITIONAL TREATMENTS IF THERE IS SEVERE OR REFRACTORY BLEEDING

- Fibrinolytic treatment[79,80]
- Factor VIIa treatment[81,82]
- Radiological or surgical intervention.

Protamine is not given to bleeding patients with heparin-bonded circuits owing to the risk of acute circuit thrombosis.

ANTICOAGULATION

Anticoagulation for ECMO in the setting of severe cardiac failure reduces the risk of clot formation within the heart, extracorporeal circuit and cannulae. Heparin is the first-line therapy despite both its limitations and the spectrum of heparin-induced thrombocytopenia and thrombosis (HITTs). Most centres target anticoagulation values below those for management of thromboembolic disease. Definitive recommendations for the titration of heparin therapy are lacking. Activated clotting time (ACT), activated partial thromboplastin time (APTT) and TEG are all used in different centres, but there remains poor correlation between tests and no relevant outcome data on which to base recommendations.[83]

HITT is a rare, but potentially devastating, complication of heparin therapy during ECMO support. Case reports of successful management with the use of intravenous direct thrombin inhibitors (heparin ceased) exist.[84]

WEANING AND DECANNULATION

VA ECMO for cardiac failure generally runs for 3–12 days, which allows time for assessment of cardiac recovery or planning for alternative support if indicated. Cardiac recovery is suggested by improving pulsatility with low or no inotropic support. A formal echocardiographic weaning study is required to assess suitability for decannulation.[85] During a weaning study, haemodynamics, ventricular function and native cardiac output are monitored and measured at progressively lower ECMO circuit blood flow rates (to 1 L/min in adults). Adequate recruitment in the native cardiac output during weaning and haemodynamic stability support the decision to schedule decannulation. Central and peripheral configurations of VA ECMO require surgical repair of the artery after decannulation.

EXPECTED PATIENT OUTCOMES

The clinical effectiveness of VA ECMO for cardiogenic shock and refractory cardiac arrest has not been evaluated in prospective clinical trials. A number of larger case series and cohort studies allow some assessment of the expected outcomes in the more common patient groups that received VA ECMO support. Successful patient outcomes from a complex intervention are likely to occur in centres with clinical leadership, training and competency programmes, adequate protocols and resources and governance programmes. The application of ECMO before end-organ damage and use in selected patients with either reversible conditions or suitable for longer-term treatment options will also probably be associated with improved outcomes.

In addition, the Extracorporeal Life Support Organization (ELSO), which was established in 1989, maintains a registry of ECMO use in registered ECMO centres around the world. The ELSO registry provides annual outcome data for members (see www.elsonet.org) in addition to educational programmes and resources.

REFERENCES

1. Phua J, Badia JR, Adhikari NK, et al. Has mortality from acute respiratory distress syndrome decreased over time?: a systematic review. *Am J Respir Crit Care Med*. 2009;179(3):220–227.
2. Cooke CR, Shah CV, Gallop R, et al. A simple clinical predictive index for objective estimates of mortality in acute lung injury. *Crit Care Med*. 2009;37(6): 1913–1920.
3. *ECLS Registry Report – International Summary*. 2016;1–26; ELSO.
4. Wang D, Zhou X, Liu X, et al. Wang-Zwische double lumen cannula-toward a percutaneous and ambulatory paracorporeal artificial lung. *ASAIO J*. 2008;54(6):606–611.
5. Gattinoni L, Kolobow T, Tomlinson T, et al. Control of intermittent positive pressure breathing (IPPB) by extracorporeal removal of carbon dioxide. *Br J Anaesth*. 1978;50(8):753–758.
6. Terragni P, Maiolo G, Ranieri VM. Role and potentials of low-flow CO(2) removal system in mechanical ventilation. *Curr Opin Crit Care*. 2012; 18(1):93–98.
7. Batchinsky AI, Jordan BS, Regn D, et al. Respiratory dialysis: reduction in dependence on mechanical ventilation by venovenous extracorporeal CO2 removal. *Crit Care Med*. 2011;39(6):1382–1387.
8. Bein T, Weber F, Philipp A, et al. A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. *Crit Care Med*. 2006;34(5): 1372–1377.
9. Terragni PP, Del Sorbo L, Mascia L, et al. Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. *Anesthesiology*. 2009;111(4):826–835.
10. Rich PB, Awad SS, Crotti S, et al. A prospective comparison of atrio-femoral and femoro-atrial flow in adult venovenous extracorporeal life support. *J Thorac Cardiovasc Surg*. 1998;116(4):628–632.
11. MacLaren G, Combes A, Bartlett RH. Contemporary extracorporeal membrane oxygenation for adult respiratory failure: life support in the new era. *Intensive Care Med*. 2012;38(2):210–220.
12. Khoshbin E, Roberts N, Harvey C, et al. Poly-methyl pentene oxygenators have improved gas exchange capability and reduced transfusion requirements in adult extracorporeal membrane oxygenation. *ASAIO J*. 2005;51(3):281–287.

13. Reser D, Seifert B, Klein M, et al. Retrospective analysis of outcome data with regards to the use of Phisio(R)-, Bioline(R)- or Softline(R)-coated cardiopulmonary bypass circuits in cardiac surgery. *Perfusion*. 2012;27(6):530–534.
14. Palatianos GM, Foroulis CN, Vassili MI, et al. A prospective, double-blind study on the efficacy of the bioline surface-heparinized extracorporeal perfusion circuit. *Ann Thorac Surg*. 2003;76(1): 129–135.
15. Holzgraefe B, Broome M, Kalzen H, et al. Extracorporeal membrane oxygenation for pandemic H1N1 2009 respiratory failure. *Minerva Anestesiol*. 2010;76(12):1043–1051.
16. Forrest P, Ratchford J, Burns B, et al. Retrieval of critically ill adults using extracorporeal membrane oxygenation: an Australian experience. *Intensive Care Med*. 2011;37(5):824–830.
17. Brogan TV, Thiagarajan RR, Rycus PT, et al. Extracorporeal membrane oxygenation in adults with severe respiratory failure: a multi-center database. *Intensive Care Med*. 2009;35(12):2105–2114.
18. Australia and New Zealand Extracorporeal Membrane Oxygenation Influenza Investigators, Davies A, Jones D, et al. *Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome*. *JAMA*. 2009;302(17): 1888–1895.
19. Aigner C, Wisser W, Taghavi S, et al. Institutional experience with extracorporeal membrane oxygenation in lung transplantation. *Eur J Cardiothorac Surg*. 2007;31(3):468–473, discussion 73–74.
20. Gow KW, Lao OB, Leong T, et al. Extracorporeal life support for adults with malignancy and respiratory or cardiac failure: the extracorporeal life support experience. *Am J Surg*. 2010;199(5):669–675.
21. Marasco SF, Vale M, Preovolos A, et al. Institution of extracorporeal membrane oxygenation late after lung transplantation—a futile exercise? *Clin Transplant*. 2012;26(1):E71–E77.
22. Mason DP, Thuita L, Nowicki ER, et al. Should lung transplantation be performed for patients on mechanical respiratory support? The US experience. *J Thorac Cardiovasc Surg*. 2010;139(3):765–773 e1.
23. Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. *N Engl J Med*. 2011;365(20):1905–1914.
24. Schmidt M, Bailey M, Sheldrake J, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. *Am J Respir Crit Care Med*. 2014;189(11):1374–1382.
25. Klinzing S, Wenger U, Steiger P, et al. External validation of scores proposed for estimation of survival probability of patients with severe adult respiratory distress syndrome undergoing extracorporeal membrane oxygenation therapy: a retrospective study. *Crit Care*. 2015;19:142.
26. Pappalardo F, Pieri M, Greco T, et al. Predicting mortality risk in patients undergoing venovenous ECMO for ARDS due to influenza A (H1N1) pneumonia: the ECMOnet score. *Intensive Care Med*. 2013;39(2):275–281.
27. Forrest P, Cheong JY, Vallely MP, et al. International retrieval of adults on extracorporeal membrane oxygenation support. *Anaesth Intensive Care*. 2011;39(6):1082–1085.
28. Javidfar J, Brodie D, Takayama H, et al. Safe transport of critically ill adult patients on extracorporeal membrane oxygenation support to a regional extracorporeal membrane oxygenation center. *ASAIO J*. 2011;57(5):421–425.
29. Isgro S, Patroniti N, Bombino M, et al. Extracorporeal membrane oxygenation for interhospital transfer of severe acute respiratory distress syndrome patients: 5-year experience. *Int J Artif Organs*. 2011;34(11):1052–1060.
30. Platts DG, Sedgwick JF, Burstow DJ, et al. The role of echocardiography in the management of patients supported by extracorporeal membrane oxygenation. *J Am Soc Echocardiogr*. 2012;25(2): 131–141.
31. Dolch ME, Frey L, Buerkle MA, et al. Transesophageal echocardiography-guided technique for extracorporeal membrane oxygenation dual-lumen catheter placement. *ASAIO J*. 2011; 57(4):341–343.
32. Toomasian JM, Bartlett RH. Hemolysis and ECMO pumps in the 21st century. *Perfusion*. 2011; 26(1):5–6.
33. Serpa Neto A, Schmidt M, Azevedo LC, et al. Associations between ventilator settings during extracorporeal membrane oxygenation for refractory hypoxemia and outcome in patients with acute respiratory distress syndrome: a pooled individual patient data analysis: mechanical ventilation during ECMO. *Intensive Care Med*. 2016;42(11):1672–1684.
34. Hayes D Jr, Kukreja J, Tobias JD, et al. Ambulatory venovenous extracorporeal respiratory support as a bridge for cystic fibrosis patients to emergent lung transplantation. *J Cyst Fibros*. 2012;11(1): 40–45.
35. Oliver WC. Anticoagulation and coagulation management for ECMO. *Semin Cardiothorac Vasc Anesth*. 2009;13(3):154–175.
36. Yen TS, Liau CC, Chen YS, et al. Extracorporeal membrane oxygenation resuscitation for traumatic brain injury after decompressive craniotomy. *Clin Neurol Neurosurg*. 2008;110(3):295–297.
37. Marasco SF, Preovolos A, Lim K, et al. Thoracotomy in adults while on ECMO is associated with uncontrollable bleeding. *Perfusion*. 2007;22(1):23–26.
38. *ELSO Guidelines General v1.3*. 2016:18.
39. Lehle K, Philipp A, Zeman F, et al. Technical-induced hemolysis in patients with respiratory failure supported with veno-venous ECMO—prevalence and risk factors. *PLoS ONE*. 2015;10(11): e0143527.
40. Gille JP, Bagniewski AM. Ten years of use of extracorporeal membrane oxygenation (ECMO)

in the treatment of acute respiratory insufficiency (ARI). *Trans Am Soc Artif Intern Organs*. 1976;22: 102–109.
41. Worrall J. Evidence and ethics in medicine. *Perspect Biol Med*. 2008;51(3):418–431.
42. Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. *JAMA*. 1979;242(20):2193–2196.
43. Morris AH, Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med*. 1994;149(2 Pt 1):295–305.
44. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009;374(9698):1351–1363.
45. Zwischenberger JB, Lynch JE. Will CESAR answer the adult ECMO debate? *Lancet*. 2009;374(9698): 1307–1308.
46. Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA*. 2011;306(15): 1659–1668.
47. Westaby S, Anastasiadis K, Wieselthaler GM. Cardiogenic shock in ACS. Part 2: role of mechanical circulatory support. *Nat Rev Cardiol*. 2012;9(4): 195–208.
48. De Silva RJ, Soto C, Spratt P. Extra corporeal membrane oxygenation as right heart support following left ventricular assist device placement: a new cannulation technique. *Heart Lung Circ*. 2012;21(4):218–220.
49. Javidfar J, Brodie D, Costa J, et al. Subclavian artery cannulation for venoarterial extracorporeal membrane oxygenation. *ASAIO J*. 2012;58(5): 494–498.
50. Mirabel M, Luyt CE, Leprince P, et al. Outcomes, long-term quality of life, and psychologic assessment of fulminant myocarditis patients rescued by mechanical circulatory support. *Crit Care Med*. 2011; 39(5):1029–1035.
51. Rajagopal SK, Almond CS, Laussen PC, et al. Extracorporeal membrane oxygenation for the support of infants, children, and young adults with acute myocarditis: a review of the Extracorporeal Life Support Organization registry. *Crit Care Med*. 2010;38(2):382–387.
52. Asaumi Y, Yasuda S, Morii I, et al. Favourable clinical outcome in patients with cardiogenic shock due to fulminant myocarditis supported by percutaneous extracorporeal membrane oxygenation. *Eur Heart J*. 2005;26(20):2185–2192.
53. Idelchik GM, Simpson L, Civitello AB, et al. Use of the percutaneous left ventricular assist device in patients with severe refractory cardiogenic shock as a bridge to long-term left ventricular assist device implantation. *J Heart Lung Transplant*. 2008;27(1):106–111.
54. Tsao NW, Shih CM, Yeh JS, et al. Extracorporeal membrane oxygenation-assisted primary percutaneous coronary intervention may improve survival of patients with acute myocardial infarction complicated by profound cardiogenic shock. *J Crit Care*. 2012;27(5):530 e1–e11.
55. de Lange DW, Sikma MA, Meulenbelt J. Extracorporeal membrane oxygenation in the treatment of poisoned patients. *Clin Toxicol (Phila)*. 2013; 51(5):385–393.
56. St-Onge M, Fan E, Megarbane B, et al. Venoarterial extracorporeal membrane oxygenation for patients in shock or cardiac arrest secondary to cardiotoxicant poisoning: a cost-effectiveness analysis. *J Crit Care*. 2015;30(2):437 e7–e14.
57. Yusuff HO, Zochios V, Vuylsteke A. Extracorporeal membrane oxygenation in acute massive pulmonary embolism: a systematic review. *Perfusion*. 2015;30(8):611–616.
58. Lima EB, Cunha CR, Barzilai VS, et al. Experience of ECMO in primary graft dysfunction after orthotopic heart transplantation. *Arq Bras Cardiol*. 2015;105(3):285–291.
59. Marasco SF, Vale M, Pellegrino V, et al. Extracorporeal membrane oxygenation in primary graft failure after heart transplantation. *Ann Thorac Surg*. 2010;90(5):1541–1546.
60. Avalli L, Maggioni E, Formica F, et al. Favourable survival of in-hospital compared to out-of-hospital refractory cardiac arrest patients treated with extracorporeal membrane oxygenation: an Italian tertiary care centre experience. *Resuscitation*. 2012;83(5):579–583.
61. Lee JJ, Han SJ, Kim HS, et al. Out-of-hospital cardiac arrest patients treated with cardiopulmonary resuscitation using extracorporeal membrane oxygenation: focus on survival rate and neurologic outcome. *Scand J Trauma Resusc Emerg Med*. 2016; 24:74.
62. Richardson AS, Schmidt M, Bailey M, et al. ECMO Cardio-Pulmonary Resuscitation (ECPR), trends in survival from an international multicentre cohort study over 12-years. *Resuscitation*. 2017;112:34–40.
63. Stub D, Bernard S, Pellegrino V, et al. Refractory cardiac arrest treated with mechanical CPR, hypothermia, ECMO and early reperfusion (the CHEER trial). *Resuscitation*. 2015;86:88–94.
64. Sakamoto T, Morimura N, Nagao K, et al. Extracorporeal cardiopulmonary resuscitation versus conventional cardiopulmonary resuscitation in adults with out-of-hospital cardiac arrest: a prospective observational study. *Resuscitation*. 2014;85(6):762–768.
65. Sidebotham D, Allen S, McGeorge A, et al. Catastrophic left heart distension following initiation of venoarterial extracorporeal membrane oxygenation in a patient with mild aortic regurgitation. *Anaesth Intensive Care*. 2012;40(3): 568–569.

66. Cheng R, Ramzy D, Azarbal B, et al. Device strategies for patients in INTERMACS profiles 1 and 2 cardiogenic shock: double bridge with extracorporeal membrane oxygenation and initial implant of more durable devices. *Artif Organs*. 2017; 41(3):224–232.
67. Vaja R, Chauhan I, Joshi V, et al. Five-year experience with mobile adult extracorporeal membrane oxygenation in a tertiary referral center. *J Crit Care*. 2015;30(6):1195–1198.
68. Broman LM, Frenckner B. Transportation of critically ill patients on extracorporeal membrane oxygenation. *Front Pediatr*. 2016;4:63.
69. Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: adult advanced cardiovascular life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132(18 suppl2): S444–S464.
70. Chen YS, Chao A, Yu HY, et al. Analysis and results of prolonged resuscitation in cardiac arrest patients rescued by extracorporeal membrane oxygenation. *J Am Coll Cardiol*. 2003;41(2):197–203.
71. Poppe M, Weiser C, Holzer M, et al. The incidence of 'load&go' out-of-hospital cardiac arrest candidates for emergency department utilization of emergency extracorporeal life support: a one-year review. *Resuscitation*. 2015;91:131–136.
72. Shinar Z, Bellezzo J, Paradis N, et al. Emergency department initiation of cardiopulmonary bypass: a case report and review of the literature. *J Emerg Med*. 2012;43(1):83–86.
73. Aissaoui N, Luyt CE, Leprince P, et al. Predictors of successful extracorporeal membrane oxygenation (ECMO) weaning after assistance for refractory cardiogenic shock. *Intensive Care Med*. 2011;37(11): 1738–1745.
74. Cavarocchi NC, Pitcher HT, Yang Q, et al. Weaning of extracorporeal membrane oxygenation using continuous hemodynamic transesophageal echocardiography. *J Thorac Cardiovasc Surg*. 2013; 146(6):1474–1479.
75. Yeo HJ, Yoon SH, Jeon D, et al. The utility of preemptive distal perfusion cannulation during peripheral venoarterial extracorporeal membrane oxygenation support. *J Interv Cardiol*. 2016;29(4):431–436.
76. Pappalardo F, Schulte C, Pieri M, et al. Concomitant implantation of Impella(R) on top of veno-arterial extracorporeal membrane oxygenation may improve survival of patients with cardiogenic shock. *Eur J Heart Fail*. 2017;19(3):404–412.
77. Barbone A, Malvindi PG, Ferrara P, et al. Left ventricle unloading by percutaneous pigtail during extracorporeal membrane oxygenation. *Interact Cardiovasc Thorac Surg*. 2011;13(3):293–295.
78. Alkhouli M, Narins CR, Lehoux J, et al. Percutaneous decompression of the left ventricle in cardiogenic shock patients on venoarterial extracorporeal membrane oxygenation. *J Card Surg*. 2016;31(3):177–182.
79. Downard CD, Betit P, Chang RW, et al. Impact of AMICAR on hemorrhagic complications of ECMO: a ten-year review. *J Pediatr Surg*. 2003;38(8):1212–1216.
80. Buckley LF, Reardon DP, Camp PC, et al. Aminocaproic acid for the management of bleeding in patients on extracorporeal membrane oxygenation: four adult case reports and a review of the literature. *Heart Lung*. 2016;45(3):232–236.
81. Anselmi A, Guinet P, Ruggieri VG, et al. Safety of recombinant factor VIIa in patients under extracorporeal membrane oxygenation. *Eur J Cardiothorac Surg*. 2016;49(1):78–84.
82. Repesse X, Au SM, Brechot N, et al. Recombinant factor VIIa for uncontrollable bleeding in patients with extracorporeal membrane oxygenation: report on 15 cases and literature review. *Crit Care*. 2013;17(2):R55.
83. Bolliger D, Zenklusen U, Tanaka KA. Point-of-care coagulation management algorithms during ECMO support: are we there yet? *Minerva Anestesiol*. 2016; 82(9):1000–1009.
84. Sanfilippo F, Asmussen S, Maybauer DM, et al. Bivalirudin for alternative anticoagulation in extracorporeal membrane oxygenation: a systematic review. *J Intensive Care Med*. 2017;32(5):312–319.
85. Aissaoui N, El-Banayosy A, Combes A. How to wean a patient from veno-arterial extracorporeal membrane oxygenation. *Intensive Care Med*. 2015; 41(5):902–905.

Part Five

Gastroenterological Emergencies

This page intentionally left blank

42

Acute gastrointestinal bleeding

Constantinos Simillis, Shahnawaz Rasheed

INTRODUCTION

Acute gastrointestinal bleeding (or haemorrhage) is a common major medical emergency and a common reason for admission to the intensive care unit (ICU).[1] It may result in significant morbidity and mortality, with mortality rates ranging from 4% to 10%.[1–4] The majority of cases die of causes not directly related to bleeding, but due to significant co-morbidities such as cardiopulmonary or multiorgan failure.[2,5,6] This observation emphasises the benefit of good supportive care in the ICU for patients presenting with gastrointestinal bleeding.

Upper gastrointestinal bleeding is that originating proximal to the ligament of Treitz, and this includes the oesophagus, stomach and duodenum. Lower gastrointestinal bleeding is that originating from the small bowel and colon. Peptic ulcer disease accounts for 75% of upper gastrointestinal bleeding. Bleeding from varices, oesophagitis, duodenitis and Mallory–Weiss syndrome each account for between 5% and 15% of cases.[2–4] About 20% of gastrointestinal bleeding arises from the lower gastrointestinal tract, commonly due to diverticular disease.[2–4] Common aetiological causes for gastrointestinal bleeding are listed in Box 42.1.

RESUSCITATION

Patients with acute gastrointestinal bleeding should have immediate and continual assessment with appropriate management of airway, breathing and circulation. Airway compromise should be managed with immediate basic airway manoeuvres or, if needed, advanced airway manoeuvres. The goals of managing a patient with acute gastrointestinal bleeding are, first, to resuscitate, second, to control active bleeding and, third, to prevent recurrence of haemorrhage. Either colloid or crystalloid solutions may be given through large-bore intravenous cannulae to achieve volume restoration prior to administering blood products. The local major haemorrhage protocol may be activated and patient is transfused with blood, platelets, and clotting factors. Anticoagulation medication, such as aspirin, clopidogrel, warfarin, new oral anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs), should be stopped in the acute setting. Patients on warfarin should be offered prothrombin complex concentrate. A multidisciplinary approach involving haematology, cardiology/neurology, and gastroenterology is necessary when managing patients on anticoagulant medications. Vital signs should be closely monitored. Significant gastrointestinal bleeding is indicated by syncope, haematemesis, systolic blood pressure below 100 mm Hg (13.3 kPa), postural hypotension and a blood transfusion requirement of more than four units of blood in 12 hours to maintain blood pressure. In patients with hypovolaemic shock, central venous pressure and hourly urine output should be observed.

UPPER GASTROINTESTINAL BLEEDING

CLINICAL PRESENTATION

Haematemesis and melaena are the most common presentations of acute upper gastrointestinal bleeding. Bright red haematemesis usually implies active haemorrhage from the oesophagus, stomach or duodenum. There may be epigastric pain, but bleeding ulcers can be painless, especially in elderly patients and users of NSAIDs. A history of vomiting and retching preceding haematemesis suggests Mallory–Weiss syndrome. Coffee-ground vomitus refers to the vomiting of black material which is assumed to be blood. Melaena is the passage of black tarry stools usually due to acute upper gastrointestinal bleeding. Haematochezia is the passage of bright red or maroon blood from the rectum, in the form of pure blood or blood mixed with stool, and usually represents a lower intestinal source of bleeding, although it may be a feature of massive upper gastrointestinal bleeding. In cases of massive gastrointestinal bleeding leading to hypovolaemic shock, the patient may exhibit symptoms and signs of tachycardia, tachypnoea, hypotension, anxiety or confusion, pallor, sweating and oliguria.

RISK ASSESSMENT

Risk factors associated with poor outcome in patients presenting with acute upper gastrointestinal bleeding include being an inpatient, older age (>60 years),

ABSTRACT

Acute gastrointestinal bleeding is a common major medical emergency which is associated with significant morbidity and mortality. The goals of managing acute gastrointestinal bleeding are, first, to resuscitate, second, to control active bleeding and, third, to prevent recurrence of haemorrhage. Patients with non-variceal upper gastrointestinal bleeding are assessed using formal risk assessment scoring systems to predict their risk of mortality and need for intervention. These patients should receive early diagnostic and therapeutic endoscopy and be given antacids. Patients with variceal upper gastrointestinal haemorrhage should be managed with a combination of terlipressin, somatostatin, antibiotics and endoscopic therapy. If this fails, further treatment may be given in the form of balloon tamponade or transjugular intrahepatic portosystemic shunt. Lower gastrointestinal bleed tends to resolve spontaneously and the main aim is to identify the source of bleeding. It may be managed with colonoscopy/sigmoidoscopy, angiogram with the option of angioembolisation, and rarely proceed with surgery.

KEYWORDS

Gastrointestinal bleeding
gastrointestinal haemorrhage
variceal bleeding
non-variceal bleeding
ulcer
diverticular disease
rectal bleeding
endoscopy

significant co-morbidity (especially cardiac failure or malignancy), liver disease/cirrhosis, known varices, haemodynamic disturbance (hypotension with systolic blood pressure <100 mm Hg, tachycardia with pulse ≥100 beats/min), and witnessed haematemesis or haematochezia (suspected continued bleeding after admission).[2,4,7–9]

To assess the risk of serious adverse events, or need for intervention, formal risk assessment scoring systems may be used such as the Rockall scoring system and the Blatchford scoring system.[5,10] The Rockall scoring system, which is used to predict rebleeding and mortality risk, is based on a combination of clinical and endoscopic findings.[5] The initial (pre-endoscopic) Rockall score is derived from age (0–2 points), shock (0–2 points) and co-morbidity (0–3 points). If the pre-endoscopic score is above 0, there is a significant risk of mortality (score 1: predicted mortality 2.4%; score 2: predicted mortality 5.6%) requiring hospital admission and endoscopy, whereas those patients scoring 0 can be safely discharged with outpatient follow-up.[5] The final post-endoscopy score has additional points for endoscopic diagnosis (0–2 points) and endoscopic stigmata of recent haemorrhage (0–2 points), giving a maximum score of 11 points (see Table 42.1). Patients with a post-endoscopic Rockall score less than 3 have a low risk of rebleeding or mortality and should be considered for early discharge and outpatient follow up. Increasing post-endoscopic Rockall score leads to higher risk of rebleeding and death, and should be used in association with other clinical factors in assigning patients to different levels of care.

The Blatchford risk score was derived to predict death and the need for treatment (transfusion, endoscopic treatment, surgery) (see Table 42.2).[10] The total Blatchford score can range from 0 to 23, where a score of 0 is the clinical cut-off above which patients are considered to be at risk of needing an intervention.[5,10] The full score was validated internally on 197 patients and performed better than the Rockall score in predicting the need for treatment.[10]

Box 42.1 Common causes of acute gastrointestinal bleeding

Upper gastrointestinal bleeding
Peptic ulcers (duodenal ulcer:gastric ulcer, 3:1)
Varices (oesophageal varices:gastric varices, 9:1)
Portal hypertensive gastropathy
Mallory–Weiss syndrome
Gastritis, duodenitis and oesophagitis

Lower gastrointestinal bleeding
Diverticular bleeding
Angiodysplasia and arteriovenous malformation
Colonic polyps or tumours
Meckel diverticulum
Inflammatory bowel diseases
Haemorrhoids, anal fissure

Table 42.1 The Rockall numerical risk scoring system

	SCORE*			
	0	*1*	*2*	*3*
Age†	<60	60–79	≥80	
Shock†	No shock (systolic blood pressure ≥100, pulse <100)	Tachycardia (systolic blood pressure ≥100, pulse ≥100)	Hypotension (systolic blood pressure <100)	
Co-morbidity†	No major co-morbidity		Cardiac failure, ischaemic heart disease, any major co-morbidity	Renal failure, liver failure, disseminated malignancy
Diagnosis‡	Mallory–Weiss tear, no lesion identified, and no stigmata of recent haemorrhage	All other diagnoses	Malignancy of upper gastrointestinal tract	
Major stigmata of recent haemorrhage‡	None or dark spot only		Blood in upper gastrointestinal tract, adherent clot, visible or spurting vessel	

*The total score can range from 0 to 11, with a score of 2 representing the clinical cut-off, above which patients are considered to be at high risk of death or rebleeding.

†Scores are calculated on admission.

‡Scores are added after endoscopy.

Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut.* 1996;38(3):316–321.

Table 42.2 The Blatchford numerical risk scoring system

RISK MARKER AT ADMISSION	SCORE
BLOOD UREA (mmol/L)	
≥6.5<8.0	2
≥8.0<10.0	3
≥10.0<25	4
≥25	6
HAEMOGLOBIN (g/L) FOR MEN	
≥120<130	1
≥100<120	3
<100	6
HAEMOGLOBIN (g/L) FOR WOMAN	
≥100<120	1
<100	6
SYSTOLIC BLOOD PRESSURE (mm Hg)	
100–109	1
90–99	2
<90	3
OTHER MARKERS	
Pulse ≥100 (beats/min)	1
Presentation with melaena	1
Presentation with syncope	2
Hepatic diseases	2
Cardiac failure	2

A total score can range from 0 to 23. A score of 0 is the clinical cut-off, above which patients are considered to be at risk of needing an intervention.

Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. *Lancet*. 2000;356(9238):1318–1321.

PHARMACOLOGICAL TREATMENT

Acid-suppressing drugs such as proton pump inhibitors (PPIs) and H_2-receptor antagonists are very effective drugs to promote ulcer healing. An acidic environment impairs platelet function and haemostasis; therefore, reducing the secretion of gastric acid optimises platelet aggregation and clot formation.[11] Pharmacological control without endoscopic haemostasis is inadequate and there is a lack of evidence to support pre-endoscopic treatment with PPIs, with no evidence of benefit in terms of mortality, rebleeding or need for surgery.[12,13] Patients with non-variceal upper gastrointestinal bleeding and stigmata of recent haemorrhage shown at endoscopy should be offered PPIs.[12–14] There is evidence that potent acid suppression using intravenous PPIs post-endoscopy results in reduced rebleeding, reduced need for surgery, and reduced need for repeated endoscopic treatment.[13,14] PPIs should be recommended in high-risk peptic ulcer bleeding patients as an adjuvant to endoscopic therapy and a combination of endoscopic and pharmacological therapy offers the best therapy for ulcer-bleeding patients.

Table 42.3 Stigmata of haemorrhage and risk of recurrent bleeding in peptic ulcers

STIGMATA OF HAEMORRHAGE	% RECURRENT BLEEDING
Spurter or oozer	85–90
Protuberant vessel	35–55
Adherent clot	30–40
Flat spot	5–10
None	5

ENDOSCOPY

Endoscopy is the investigation of choice, with potential therapeutic benefit, and should be offered within 24 hours of presentation to hospital to provide optimal clinical outcome.[15] Early endoscopy and endoscopic therapy (<24 hours from admission) is associated with a reduced transfusion need, a reduction in rebleeding, a lower need for surgery, and a reduction in length of stay compared to patients receiving later endoscopy.[15–17] Endoscopy allows identification of the site and nature of bleeding and treatment can be provided endoscopically. Endoscopy may induce serious hypoxia in patients with cardiorespiratory disease, and careful supervision with continuous monitoring of blood pressure, pulse and oxygen saturation with a pulse oximeter is mandatory.

HIGH-RISK LESIONS

Most patients with acute upper gastrointestinal haemorrhage stop bleeding spontaneously and have an uneventful recovery. No specific intervention is required in these patients. Endoscopic haemostasis should be used in patients with a high risk of persistent or recurrent bleeding. Stigmata of haemorrhage found during endoscopy are integral to the Rockall scoring system[5] and are important predictors of recurrent bleeding. These stigmata include localised active bleeding (i.e. pulsatile, arterial spurting or simple oozing), an adherent blood clot, a protuberant vessel, or a flat, pigmented spot on the ulcer base (Table 42.3).[16,18,19] Only high-risk lesions (active arterial bleeding, non-bleeding visible vessels or an adherent blood clot) should be treated endoscopically since only these are at risk of further bleeding.[16,18,19] The proximal postero-inferior wall of the duodenal bulb and the high lesser curve

of the stomach are common sites for severe recurrent bleeding, probably owing to their respective large arteries (gastroduodenal and left gastric arteries).

Adrenaline (epinephrine) injection

Endoscopic injection of adrenaline (1:10,000 dilution) into and around the ulcer bleeding point is an effective, cheap, portable and easy-to-learn method of haemostasis.[20] Injection into ulcers with adherent blood clot significantly reduces rebleeding from approximately 35%–10%.[18,21] Debate exists as to whether the haemostatic effect is a result of local tamponade by the volume injected or vasoconstriction by adrenaline, or a combination of both. When different volumes of adrenaline solution 1:10,000 are compared, there were no significant differences in the rate of initial haemostasis between three groups with 20, 30 and 40 mL of endoscopic injections, but the rate of peptic ulcer perforation was significantly higher in the group receiving 40 mL adrenaline, and the rate of recurrent bleeding was significantly higher in the 20 mL adrenaline group (20.3%) than in the 30 mL (5.3%) and 40 mL (2.8%) adrenaline groups.[22] Absorption of adrenaline into the systemic circulation has been documented, but without any significant effect on the haemodynamic status of the patient.[23]

Thermal

This method uses direct pressure and heat energy (heater probe) or electrocoagulation (bipolar coagulation probe [BICAP]) to control ulcer bleeding. The depth of tissue injury induced by these devices is minimal, as the bleeding vessel is tamponaded prior to coagulation. The overall efficacy of the heater probe and BICAP probe methods are comparable to the adrenaline injection,[24] and any complications, including mucosal perforation, are rare.[24,25]

Mechanical

The advantage of haemoclips over thermocoagulation is that there is no tissue injury induced and hence the risk of perforation is reduced. Studies comparing haemoclips with injection and thermocoagulation have shown favourable results for endoscopic clipping, including higher definitive haemostasis and reduced rebleeding compared to injection, and comparable efficacy to thermocoagulation.[26–28] However, the application of haemoclips in certain sites, for example lesser curve, gastric fundus and posterior wall of the duodenum, is technically difficult.

Combination

Combinations of endoscopic treatments, comprising an injection of adrenaline coupled with either a thermal or mechanical therapy, are superior to the use of a single modality treatment resulting in decreased rebleeding and emergency surgery rate, without increased risk of complications.[28,29]

Repeat endoscopy

Repeat endoscopy should be performed within 24 hours when initial endoscopic treatment was considered suboptimal due to difficult access, poor visualisation or technical difficulties. In addition, repeat endoscopy reduces the risk of rebleeding[28,30] and should be considered for patients in whom rebleeding is likely to be life threatening. For patients who rebleed after endoscopic therapy, they should be considered for repeat endoscopic treatment, selective arterial embolisation or surgery. In a study investigating the best salvage treatment for patients with recurrent bleeding after endoscopic therapy, repeat endoscopic therapy was found to be comparable to surgery in securing haemostasis, with similar 30-day mortality and transfusion requirements; however, morbidity was significantly higher after surgery compared to repeat endoscopy.[31]

ANGIOGRAPHY

Angiography and angioembolisation is a diagnostic and therapeutic option for gastrointestinal haemorrhage. Angiography alone can be helpful as a diagnostic tool to locate the site of bleeding for subsequent radiological or surgical intervention. In cases of the bleeding being very brisk and obscuring the endoscopic view, angiography may help to identify the source of bleeding. Once the bleeding point is identified, angiography may be also used to embolise the bleeding point with simultaneous superselective coil transcatheter embolisation. Agents can be delivered radiologically to occlude the vascular supply, such as coils or particles, with the aim of reducing blood flow to the bleeding vessel and thereby reduce perfusion pressure and enable clot formation at the bleeding site.[32] Studies reporting on the use of angiography and embolisation have demonstrated high rates of technical success, low rebleeding rate, and low complication rates.[33–36] An important complication of embolisation is the risk of ischaemia that can be caused by reducing the blood flow to the organ supplied by the target blood vessel (e.g. hepatic/splenic infarction and duodenal ischaemia) and also the risk of embolisation of an inappropriate vessel.[33–36] Angiography may be preferred to surgery in patients with multiple comorbidities where there is a high risk of postoperative morbidity and mortality, and its use is well established in managing haemorrhage secondary to peptic ulcer disease in patients that are high risk for surgery.[37,38]

SURGERY

Surgery remains the definitive method of stopping haemorrhage, but there is little agreement on the exact indications and best timing for surgical intervention. These issues are even less clear now that endoscopic treatment and angioembolisation are so effective. Accordingly, good cooperation among intensivists, gastroenterologists, radiologists and surgeons is essential. Indications for surgery can be:

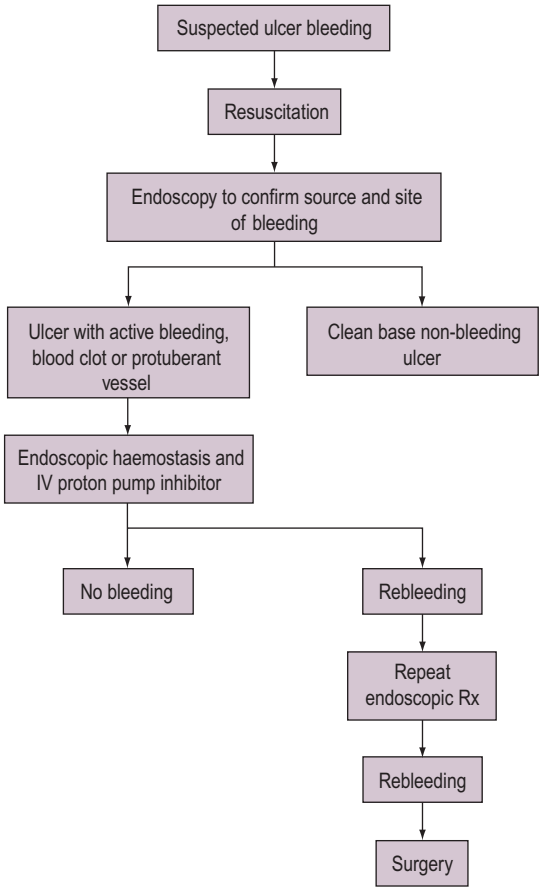


Figure 42.1 Management of peptic ulcer bleeding. *IV*, Intravenous; *Rx*, treatment.

- arterial bleeding that cannot be controlled by endoscopic haemostasis or angioembolisation
- massive transfusion (i.e. total of 6–8 units of blood) required to maintain blood pressure
- recurrent clinical bleeding after initial success in endoscopic haemostasis
- evidence suggestive of gastrointestinal perforation.

Surgical procedures include underrunning of the ulcer, underrunning plus vagotomy and drainage, and various types of gastrectomy. The overall mortality of emergency surgery for gastrointestinal bleeding is about 15%–20%. Early surgery should be considered in patients with hypovolaemic shock and/or large peptic ulcer with protuberant vessels. A protocol to manage bleeding peptic ulcer is shown in Fig. 42.1.[39]

PREVENTION OF REBLEEDING

ACID SUPPRESSION

Acid suppression therapy should be given to patients at high risk of rebleeding and to patients undergoing endoscopic therapy to achieve haemostasis, in order to maintain intragastric pH above 6 to stabilise clots and prevent rebleeding.[11] A meta-analysis concluded that in ulcer bleeding, PPIs reduce the risk of rebleeding and the need for surgery or repeat endoscopy, and decrease mortality among high-risk patients.[14]

TRANEXAMIC ACID

There is insufficient evidence to make recommendations regarding the use of antifibrinolytic agents such as tranexamic acid. Meta-analyses demonstrated that tranexamic acid did not significantly reduce the rate of rebleeding or need for surgery but significantly reduced mortality.[40,41]

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

NSAID use and *Helicobacter pylori* (*H. pylori*) infection increase the risk of upper gastrointestinal bleeding, with this risk increasing further when both factors are present.[42] The elderly and patients with a history of peptic ulcer could benefit the most from a reduction in NSAID gastrotoxicity. Clinical factors reported to increase the risk of developing NSAID-associated upper gastrointestinal complications include a history of ulcer or gastrointestinal bleeding, increasing age, concomitant anticoagulation or corticosteroid therapy and high-dose NSAID use.[43]

HELICOBACTER PYLORI

Eradication of *H. pylori* results in reduced recurrence of uncomplicated peptic ulcer disease[44] and prevents recurrent bleeding.[45] Treatment of *H. pylori* infection is more effective than antisecretory non-eradicating therapy in preventing recurrent bleeding from peptic ulcer.[45] The rapid urease test for *H. Pylori* is quick, easy to perform and inexpensive, but PPI therapy is associated with false negative rapid urease results. Therefore, when negative for this test, additional biopsies should be examined histologically, and mucosal biopsies should be obtained from the antrum and body of the stomach at the initial endoscopy prior to commencing PPI therapy.[46] For those patients who test positive for *H. pylori*, a 1-week course of eradication therapy should be prescribed with a further 3 weeks ulcer healing treatment.

ACUTE STRESS ULCERATION

Acute stress ulceration is associated with shock, sepsis, burns, multiple trauma, head injuries, spinal injuries and respiratory, renal and hepatic failure. Bleeding may be occult or overt, from 'coffee-ground' aspirates to frank haemorrhage. Lesions are most commonly seen in the gastric fundus, and range from mild erosions to acute ulcerations. The exact mechanism leading to acute mucosal erosion/ulceration in critically ill patients is still unclear. Hypoxia and hypoperfusion of the gastroduodenal mucosa are probably the most important factors, but haemodynamic instability,

respiratory failure and coagulopathy are also strong independent factors in critically ill patients. The reported incidence of stress-related mucosal bleeding in ICU patients ranges from 8% to 45%.[47] It has been declining in the last decade as a result of highly effective management of hypotension and hypoxaemia in the ICU.

Prophylactic treatment for acute stress ulceration, given in the oral form of the drug if possible, aims for gastric alkalinisation (gastric pH > 3.5), with the rationale that gastric acidity is the main cause of stress ulceration.[47] The incidence of stress ulceration appears to be lower with prophylactic gastric alkalinisation than with placebos, although an improvement in survival has not been shown.[48,49] Concerns have included gastric bacterial overgrowth and associated nosocomial pneumonia, but these have not been substantiated by existing data. On balance, prophylactic treatment should probably be reserved only for at-risk patients. Drugs given include the following:

- Antacids – Antacids can maintain gastric alkalinisation and contain magnesium, aluminium, calcium or sodium. Complications may arise from excessive intake of these minerals, and bowel stasis and diarrhoea can also be problems.
- Sucralfate – Sucralfate is effective in increasing mucus secretion, mucosal blood flow, and local prostaglandin production. It promotes ulcer healing and mucosal resistance against acid and pepsin (i.e. it is cytoprotective). As it does not alter gastric pH, Gram-negative bacterial colonisation of gastric juice is less likely. The incidence of nosocomial pneumonia may be less with sucralfate than with antacids or H_2-receptor antagonists, but this is debatable and is offset by the potential risk of aspiration.[49]
- H_2-receptor antagonists – These drugs suppress acid secretion by competing for the histamine receptor on the parietal cell.
- PPIs – These drugs block the final common pathway of acid secretion by the parietal cell, namely the proton pump. They were shown to protect critically ill patients requiring ventilation from the development of stress-related mucosal bleeding from the upper gastrointestinal tract.[50] All PPIs can be given as oral medications. Omeprazole and pantoprazole are also available in intravenous form for those who cannot be fed orally.

VARICEAL BLEEDING

Varices are abnormal, dilated veins at the junction between the portal and systemic venous systems, usually in the oesophagus (oesophageal varices, 90%) and less frequently in the stomach (gastric varices, 8%) or other sites (ectopic varices, 2%). Acute variceal bleeding is a serious complication of portal hypertension related to liver disease, with a high mortality. The degree of liver failure, using the Child–Pugh classification, is the most important prognostic factor for early rebleeding and survival.[51] The size of the varices and their propensity to bleed is directly related to the portal pressure, which, in most cases, is directly related to the severity of the underlying liver disease.

RESUSCITATION

Immediate resuscitation with whole blood and fluid is mandatory. Overtransfusion may cause a rebound increase in portal pressure (with a consequent increased risk of rebleeding) and must be avoided. Fresh frozen plasma and platelet transfusion may be indicated. A nasogastric cannula is often inserted for the removal of blood (and also for drug administration). Lactulose (15–30 mL every 4–6 hours) can be given to prevent or correct hepatic encephalopathy. When the patient is haemodynamically stable, upper gastrointestinal endoscopy should be performed to identify the source of bleeding. A protocol to manage variceal bleeding is shown in Fig. 42.2.

PHARMACOLOGICAL TREATMENT

Vasopressin

Vasopressin used to be the most widely used agent to reduce portal blood pressure and control variceal bleeding. Adverse effects of vasopressin such as cardiac ischaemia (in about 10% of patients) and worsening coagulopathy (by release of plasminogen activator) have discouraged the use of this drug in recent years. Terlipressin, a triglycyl synthetic analogue of vasopressin, has a longer half-life and fewer cardiac side-effects and appears more effective and safe when used in combination with glyceryl trinitrate.[52] Terlipressin used in the treatment of acute variceal haemorrhage results in a significant decrease in mortality.[53] When terlipressin was used specifically before endoscopy, it resulted in better bleeding control and decreased mortality, suggesting that terlipressin may be given prior to endoscopic diagnosis to patients suspected of variceal haemorrhage.[52] Terlipressin given after endoscopic diagnosis of acute variceal haemorrhage resulted in improved haemostasis.[54,55]

Somatostatin

Infusion of somatostatin and its analogues (octreotide, vapreotide) reduces portal blood pressure and azygos blood flow. They are safe and effective vasoactive agents to be used in acute variceal bleeding.[56] Although they do not reduce mortality, they result in a decrease in the amount of blood transfusion required and in the number of patients failing initial haemostasis.[57] When somatostatin was used before endoscopy, it resulted in improved haemostasis, but no reduction in rebleeding or mortality.[58] Somatostatin given after endoscopic confirmation of variceal haemorrhage made no difference in rebleeding or mortality.[59] The

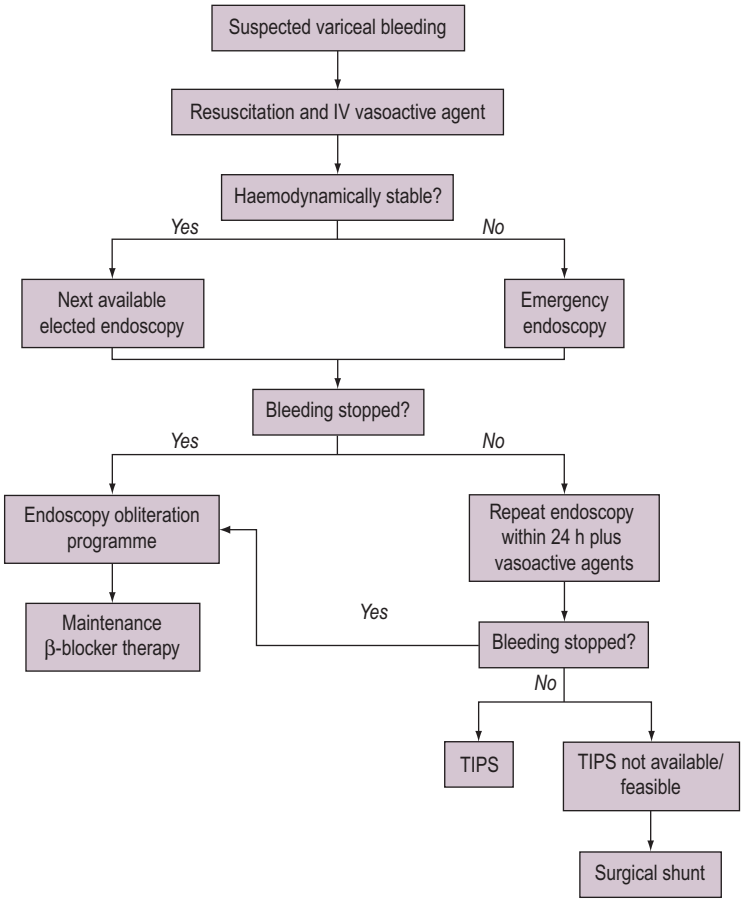


Figure 42.2 Management of variceal haemorrhage. *TIPS*, Transjugular intrahepatic portosystemic shunt. *IV*, Intravenous.

combination of somatostatin, octreotide or vapreotide, with endoscopic therapy was superior to endoscopic therapy alone, with improved haemostasis and decreased rebleeding, although there was no survival benefit.[60]

Antibiotics

Prophylactic antibiotic use in patients with cirrhosis and upper gastrointestinal bleeding was found to result in significantly reduced bacterial infections, all-cause mortality, bacterial infection mortality, rebleeding events and hospitalisation length.[61]

Propranolol

Propranolol monotherapy used for secondary prevention of variceal haemorrhage results in decreased risk of mortality and rebleeding.[62] The combination of beta blocker and nitrate is superior to beta blocker therapy alone and of equal efficacy to variceal band ligation.[63,64] Variceal band ligation combined with a beta blocker is recommended as secondary prevention for oesophageal variceal haemorrhage. In patients unsuitable for variceal band ligation, combination of non-selective beta blocker and nitrate would be the alternative.

ENDOSCOPIC VARICEAL LIGATION

Endoscopic variceal ligation is performed with rubber bands mounted on the banding device at the tip of the endoscope, which are released to strangulate the bleeding varices. Studies comparing endoscopic variceal ligation with endoscopic sclerotherapy showed that the technique is as effective as injection sclerotherapy in acute bleeding with fewer procedure-related complications, possibly because there is no tissue chemical irritation. A meta-analysis demonstrated that variceal band ligation therapy was superior to sclerotherapy in terms of rebleeding, all-cause mortality, and death due to bleeding in patients with bleeding oesophageal varices.[65] A further randomised controlled trial (RCT) demonstrated better control of oesophageal variceal bleeding with ligation than sclerotherapy, and complications were found to be greater in the sclerotherapy group, particularly in regard to sepsis and oesophageal ulceration.[66] Based on the current evidence,

patients with confirmed oesophageal variceal haemorrhage should undergo endoscopic variceal band ligation rather than injection sclerotherapy.

ENDOSCOPIC SCLEROTHERAPY

During endoscopy, sclerosants can be injected directly into the variceal columns (intravariceal injection) or into the mucosa adjacent to the varices (paravariceal injection) to cause venous thrombosis and inflammation, and tissue fibrosis. A commonly used sclerosant is cyanoacrylate. Possible complications include ulcer formation, fever, chest pain and mediastinitis. RCTs comparing the efficacy and complications of cyanoacrylate injection versus banding ligation for the management of bleeding gastric varices demonstrated better haemostasis, decreased rebleeding, and lower amount of blood transfusions required with injection treatment compared to banding.[67,68] Therefore, patients with confirmed gastric variceal haemorrhage should have endoscopic injection.

BALLOON TAMPONADE

Balloon tamponade is a temporary measure that can control massive variceal bleeding which does not respond to endoscopic therapy. Variceal bleeding can be controlled by exerting pressure directly on the bleeding point using a balloon. The Sengstaken–Blakemore tube has been replaced by the four-lumen Minnesota tube, which allows aspiration of gastric and oesophageal contents. Inflation of the gastric balloon (by 250–350 mL of water) is often sufficient to stop the bleeding by occluding the feeding veins to the oesophageal varices. If bleeding continues, the oesophageal balloon can be inflated by air and kept at a pressure of 50–60 mm Hg (6.7–8.0 kPa). Rates of haemostasis associated with balloon tamponade are reported to be 80%–95% in patients with either oesophageal or gastric varices.[69] Duration of using balloon tamponade should be limited to 24 hours to avoid tissue pressure necrosis. Other complications of balloon tamponade include pneumonia, oesophageal tears and discomfort. Because of available effective pharmacological and endoscopic therapies with lower complication rates, balloon tamponade should be used only in the exceptional cases when these therapies fail to control of bleeding.[70,71]

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT

Transjugular intrahepatic portosystemic shunt (TIPS) can be administered once the patient has been stabilised and is the definitive treatment of choice for uncontrolled variceal haemorrhage. Using a transjugular approach, a catheter is inserted into the hepatic vein, and advanced under fluoroscopic guidance into a branch of the portal vein.[72] By means of a guidewire and dilators, a self-expandable metal stent is introduced to create an intrahepatic portosystemic shunt. This procedure significantly reduces portal blood pressure and thus bleeding from varices. Major complications include intra-abdominal haemorrhage and stent occlusion. Hepatic encephalopathy has been reported in 25%–60% of patients. Nevertheless, this is an effective salvage treatment for uncontrolled variceal bleeding. Meta-analysis comparing TIPS with endoscopic therapy showed that the former has improved haemostasis but at the cost of increasing risk of hepatic encephalopathy.[73] TIPS should be reserved for the subset of patients who continue to bleed or develop recurrent bleeding after endoscopic therapy. Unlike shunt surgery, TIPS will not reduce the chance of future liver transplantation. A meta-analysis comparing portosystemic shunts (TIPS and surgical shunts) versus endoscopic therapy demonstrated a reduction in the rate of rebleeding with shunt therapy, but this was at the cost of an increased incidence of chronic hepatic encephalopathy with no difference in mortality.[74]

SURGERY

Surgical treatments for variceal bleeding include direct devascularisation of the lower oesophagus plus the proximal stomach and a variety of surgical shunts. The role of surgery has diminished since the advent of endoscopic treatment and TIPS.[75] Surgery is now used as a second-line treatment, when bleeding continues or recurs after two sessions of injection sclerotherapy or banding ligation. Both staple transection of the oesophagus and portocaval shunt surgery are highly effective emergency measures. Despite successful control of bleeding, long-term survival is not significantly improved.

Hepatic encephalopathy is one of the major complications of shunting operations.[74] Higher shunt dysfunction and reintervention was observed in TIPS patients compared to those receiving a distal splenorenal surgical shunt operation.[74] Expectations that the Warren distal splenorenal shunt will preserve antegrade portal flow and avoid accelerated deterioration of liver function have not been realised. The Warren shunt is technically more difficult, especially if performed as an emergency. Choice of surgery should be carefully made in those who are potential transplant candidates, as it may complicate subsequent surgery.

LOWER GASTROINTESTINAL BLEEDING

CLINICAL PRESENTATION

Common causes of lower gastrointestinal bleeding include diverticular disease, vascular malformations (angiodysplasia), ischaemic colitis, haemorrhoids, inflammatory bowel disease (e.g. ulcerative colitis, Crohn disease), post-polypectomy bleeding, colonic polyps, carcinoma, and radiation enteropathy. Haematochezia (bright-red blood) is the most common presentation of lower gastrointestinal bleeding. However, bleeding from small intestine and caecum/right colon

may also present as melaena (black, tarry stools). Abdominal pain preceding a massive bleeding episode suggests either ischaemia or inflammatory bowel disease. Painless massive bleeding is common in diverticulosis, angiodysplasia or from a Meckel diverticulum. In a patient with portal hypertension, haemorrhoids may present with massive haematochezia.

Risk factors associated with poor outcome in patients presenting with acute lower gastrointestinal bleeding include being an inpatient, older age (>60 years), evidence of acute haemodynamic instability at presentation (tachycardia, hypotension and syncope), ongoing bleeding, evidence of gross rectal bleeding, significant co-morbidity, specific drugs such as aspirin or NSAIDs, an elevated creatinine, and anaemia (initial hematocrit ≤35%).[76–80] Diverticular disease is the commonest cause of lower gastrointestinal bleeding, accounting for 23%–48% of cases, and with a 9% chance of recurrence at 1 year and 25% at 4 years.[81]

INVESTIGATIONS

Localisation of the site and determination of the cause of bleeding in acute colonic haemorrhage allows treatment to be appropriately focused. Haemorrhoids and rectal tumour can be identified by proctosigmoidoscopy, which should always be performed. Haematochezia associated with haemodynamic instability may be indicative of an upper gastrointestinal bleeding source and thus warrants an upper endoscopy. When both proctosigmoidoscopy and gastroscopy are negative, the lower gastrointestinal tract should be examined by colonoscopy, angiography or radionuclide scan.

COLONOSCOPY

Colonoscopy should be the initial diagnostic procedure for patients presenting with acute lower gastrointestinal bleeding.[82] The endoscopist should intubate the terminal ileum to rule out proximal blood suggestive of a small bowel lesion. The colonic mucosa should be carefully inspected during colonoscopy with aggressive attempts made to wash residual stool and blood in order to identify the bleeding site.[83] Visualisation is often unsatisfactory due to the dark discoloration of blood, and colonoscopy may yield better results after adequate colon preparation once bleeding has stopped. In studies of urgent colonoscopy without oral or rectal preparation, caecal intubation rates are low (55%–70%).[84,85] In addition, colonoscopy should be deferred until patients are haemodynamically stable and upper gastrointestinal bleeding has been excluded by upper endoscopy.[86] Urgent colonoscopy does not seem to be necessary as there is little difference in outcome when compared with elective colonoscopy, although studies support that urgent colonoscopy (defined variably as colonoscopy within 12–24 hours) improves diagnostic and therapeutic yield.[82,86,87]

COMPUTED TOMOGRAPHY ANGIOGRAPHY/ANGIOGRAPHY

Computed tomographic angiography and angiography should be considered in high-risk patients with ongoing bleeding who do not respond adequately to resuscitation and who are unlikely to tolerate bowel preparation and colonoscopy. It is also helpful when the view of endoscopy is completely obscured by active haemorrhage or when endoscopy could not identify the bleeding point. Furthermore, it is helpful in defining abnormal vasculatures including angiodysplasia, arteriovenous malformation and various inherited vascular anomalies (e.g. Rendu–Osler–Weber syndrome, pseudoxanthoma elasticum and Ehlers–Danlos syndrome). Angiography localises a lower gastrointestinal bleeding source in 25%–70% of exams,[88,89] although it relies on active brisk bleeding (more than 0.5 mL/min) to identify the bleeding point. Computed tomographic angiography is widely available, easy to perform, and accurate at localising the bleeding site, and is an acceptable first-line screening test if needed before angiography or emergent surgery.

RADIONUCLIDE SCAN

A red cell scan (99mTc labelled red blood cells) can localise a bleeding source in 65%–80% of exams, and may increase the diagnostic yield of angiography by enabling targeted contrast injection.[90,91] One advantage of the red cell scan is the ability to perform repeated scans after the initial injection of tagged cells, making red cell scans most suitable for the evaluation of intermittent, obscure-overt gastrointestinal bleeding.[90,92]

MANAGEMENT

CONSERVATIVE

A significant proportion of lower gastrointestinal bleeding (80%–85%) will stop bleeding spontaneously without any specific treatment.[81,93] The patient should be resuscitated, the coagulation corrected, and any anticoagulation medication withheld. Diverticular disease which is the most common cause of lower gastrointestinal bleed resolves spontaneously in 75% of cases.[81] NSAIDs should be avoided in patients with a history of acute lower gastrointestinal bleeding, particularly if secondary to diverticulosis or angioectasia. Patients with established cardiovascular disease who require aspirin (secondary prophylaxis) should generally resume aspirin as soon as possible after bleeding ceases, but aspirin for primary prevention of cardiovascular events should be avoided.[94,95] Dual antiplatelet therapy should not be discontinued in patients with an acute coronary syndrome within the past 90 days or coronary stenting within the past 30 days.[94,96] As with all patients with gastrointestinal bleed on anticoagulants, a multidisciplinary approach involving haematology, cardiology/neurology, and gastroenterology should be sought.

ENDOSCOPY

Endoscopic haemostasis therapy should be provided to patients with high-risk endoscopic stigmata of bleeding including active bleeding (spurting and oozing), non-bleeding visible vessel, or adherent clot.[97] The endoscopic haemostasis modality used is most often guided by the aetiology of bleeding, access to the bleeding site, and the endoscopist's experience with the various haemostatic modalities. Adrenaline injection therapy can be used to gain initial control of an active bleeding lesion and improve visualisation but should be used in combination with a second haemostatic modality, including mechanical or contact thermal therapy, to achieve definitive haemostasis.[82,87,97] Bleeding from colonic diverticula can be controlled with endoscopic clips, as clips may be safer in the colon than contact thermal therapy and are generally easier to perform than band ligation, particularly for right-sided colon lesions.[98] Bleeding from vascular anomalies or post-polypectomy can be treated by mechanical (clip) or contact thermal therapy, with or without the combined use of dilute adrenaline injection.[99,100] Bleeding colonic polyps can be removed by polypectomy or coagulated by thermocoagulation.

ANGIOGRAPHY AND ANGIOEMBOLISATION

Angiography alone can be helpful as a diagnostic tool to locate the site of bleeding for subsequent radiological or surgical intervention. Once the bleeding point is identified, angiography may be used to embolise the bleeding point with simultaneous superselective coil transcatheter angioembolisation. Studies have shown that angioembolisation is safe and effective in achieving immediate haemostasis, with high technical and clinical success rates, although it has a low risk of bowel ischaemia and late rebleeding.[88,101,102]

SURGERY

Surgery for acute lower gastrointestinal haemorrhage should be considered after all other therapeutic options have failed and should take into consideration the extent and success of prior bleeding control measures,

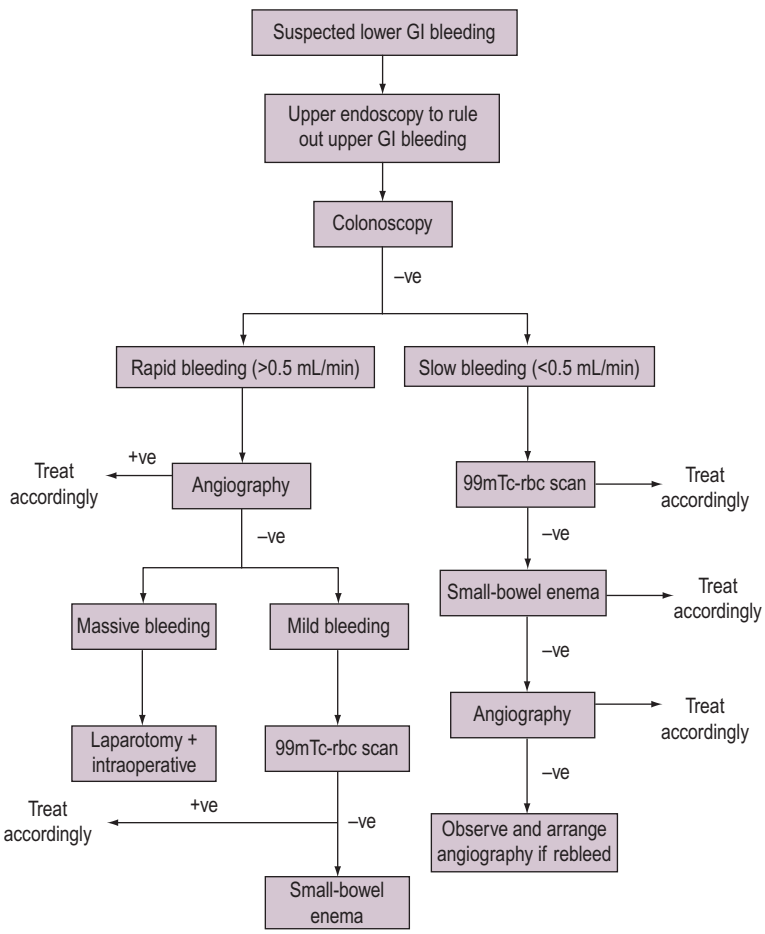


Figure 42.3 Management of lower gastrointestinal bleeding. *GI*, Gastrointestinal.

severity and source of bleeding, and the level of comorbid disease. Before surgery it is important to make all attempts to localise the source of bleeding to avoid continued or recurrent bleeding from an unresected culprit lesion or to avoid unnecessary extensive colonic resection. Localised segmental resection of the colon, with its associated risks of morbidity and mortality, is warranted after localisation of the bleeding site. When an obvious and refractory massive lower gastrointestinal bleeding is not identified by endoscopic or angiographic examinations, immediate laparotomy with possible subtotal colectomy should be offered.[103] A protocol to manage lower gastrointestinal bleeding is shown in Fig. 42.3.

REFERENCES

1. Hearnshaw SA, Logan RF, Lowe D, et al. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. *Gut*. 2011;60(10):1327–1335.
2. Blatchford O, Davidson LA, Murray WR, et al. Acute upper gastrointestinal haemorrhage in west of Scotland: case ascertainment study. *BMJ*. 1997;315(7107):510–514.
3. Holman RA, Davis M, Gough KR, et al. Value of a centralised approach in the management of haematemesis and melaena: experience in a district general hospital. *Gut*. 1990;31(5):504–508.
4. Rockall TA, Logan RF, Devlin HB, et al. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. Steering Committee and members of the National Audit of Acute Upper Gastrointestinal Haemorrhage. *BMJ*. 1995;311(6999):222–226.
5. Rockall TA, Logan RF, Devlin HB, et al. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut*. 1996;38(3):316–321.
6. Sung JJ, Tsoi KK, Ma TK, et al. Causes of mortality in patients with peptic ulcer bleeding: a prospective cohort study of 10,428 cases. *Am J Gastroenterol*. 2010;105(1):84–89.
7. Cameron EA, Pratap JN, Sims TJ, et al. Three-year prospective validation of a pre-endoscopic risk stratification in patients with acute upper-gastrointestinal haemorrhage. *Eur J Gastroenterol Hepatol*. 2002;14(5):497–501.
8. Klebl FH, Bregenzer N, Schofer L, et al. Comparison of inpatient and outpatient upper gastrointestinal haemorrhage. *Int J Colorectal Dis*. 2005;20(4):368–375.
9. Zimmerman J, Siguencia J, Tsvang E, et al. Predictors of mortality in patients admitted to hospital for acute upper gastrointestinal hemorrhage. *Scand J Gastroenterol*. 1995;30(4):327–331.
10. Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. *Lancet*. 2000; 356(9238):1318–1321.
11. Green FW Jr, Kaplan MM, Curtis LE, et al. Effect of acid and pepsin on blood coagulation and platelet aggregation. A possible contributor prolonged gastroduodenal mucosal hemorrhage. *Gastroenterology*. 1978;74(1):38–43.
12. Dorward S, Sreedharan A, Leontiadis GI, et al. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. *Cochrane Database Syst Rev*. 2006;(4): CD005415.
13. Lau JY, Sung JJ, Lee KK, et al. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. *N Engl J Med*. 2000;343(5):310–316.
14. Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor therapy for peptic ulcer bleeding: Cochrane collaboration meta-analysis of randomized controlled trials. *Mayo Clin Proc*. 2007;82(3):286–296.
15. Tsoi KK, Ma TK, Sung JJ. Endoscopy for upper gastrointestinal bleeding: how urgent is it? *Nat Rev Gastroenterol Hepatol*. 2009;6(8):463–469.
16. Barkun A, Bardou M, Marshall JK, et al. Consensus recommendations for managing patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med*. 2003;139(10):843–857.
17. Spiegel BM, Vakil NB, Ofman JJ. Endoscopy for acute nonvariceal upper gastrointestinal tract hemorrhage: is sooner better? A systematic review. *Arch Intern Med*. 2001;161(11):1393–1404.
18. Kahi CJ, Jensen DM, Sung JJ, et al. Endoscopic therapy versus medical therapy for bleeding peptic ulcer with adherent clot: a meta-analysis. *Gastroenterology*. 2005;129(3):855–862.
19. Rollhauser C, Fleischer DE. Current status of endoscopic therapy for ulcer bleeding. *Baillieres Best Pract Res Clin Gastroenterol*. 2000;14(3): 391–410.
20. Chung SS, Lau JY, Sung JJ, et al. Randomised comparison between adrenaline injection alone and adrenaline injection plus heat probe treatment for actively bleeding ulcers. *BMJ*. 1997;314(7090): 1307–1311.
21. Bleau BL, Gostout CJ, Sherman KE, et al. Recurrent bleeding from peptic ulcer associated with adherent clot: a randomized study comparing endoscopic treatment with medical therapy. *Gastrointest Endosc*. 2002;56(1):1–6.
22. Liou TC, Lin SC, Wang HY, et al. Optimal injection volume of epinephrine for endoscopic treatment of peptic ulcer bleeding. *World J Gastroenterol*. 2006;12(19):3108–3113.
23. Sung JY, Chung SC, Low JM, et al. Systemic absorption of epinephrine after endoscopic submucosal injection in patients with bleeding peptic ulcers. *Gastrointest Endosc*. 1993;39(1):20–22.
24. Sofia C, Portela F, Gregorio C, et al. Endoscopic injection therapy vs. multipolar electrocoagulation vs. laser vs. injection + octreotide vs. injection + omeprazole in the treatment of bleeding peptic ulcers. A prospective randomized study. *Hepatogastroenterology*. 2000;47(35):1332–1336.
25. Choudari CP, Rajgopal C, Palmer KR. Comparison of endoscopic injection therapy versus the heater

probe in major peptic ulcer haemorrhage. *Gut*. 1992;33(9):1159–1161.
26. Chung IK, Ham JS, Kim HS, et al. Comparison of the hemostatic efficacy of the endoscopic hemoclip method with hypertonic saline-epinephrine injection and a combination of the two for the management of bleeding peptic ulcers. *Gastrointest Endosc*. 1999;49(1):13–18.
27. Cipolletta L, Bianco MA, Marmo R, et al. Endoclips versus heater probe in preventing early recurrent bleeding from peptic ulcer: a prospective and randomized trial. *Gastrointest Endosc*. 2001;53(2): 147–151.
28. Sung JJ, Tsoi KK, Lai LH, et al. Endoscopic clipping versus injection and thermo-coagulation in the treatment of non-variceal upper gastrointestinal bleeding: a meta-analysis. *Gut*. 2007;56(10): 1364–1373.
29. Calvet X, Vergara M, Brullet E, et al. Addition of a second endoscopic treatment following epinephrine injection improves outcome in high-risk bleeding ulcers. *Gastroenterology*. 2004;126(2): 441–450.
30. Marmo R, Rotondano G, Bianco MA, et al. Outcome of endoscopic treatment for peptic ulcer bleeding: is a second look necessary? A meta-analysis. *Gastrointest Endosc*. 2003;57(1):62–67.
31. Lau JY, Sung JJ, Lam YH, et al. Endoscopic retreatment compared with surgery in patients with recurrent bleeding after initial endoscopic control of bleeding ulcers. *N Engl J Med*. 1999;340(10): 751–756.
32. Mirsadraee S, Tirukonda P, Nicholson A, et al. Embolization for non-variceal upper gastrointestinal tract haemorrhage: a systematic review. *Clin Radiol*. 2011;66(6):500–509.
33. Aina R, Oliva VL, Therasse E, et al. Arterial embolotherapy for upper gastrointestinal hemorrhage: outcome assessment. *J Vasc Interv Radiol*. 2001;12(2):195–200.
34. Defreyne L, Vanlangenhove P, De Vos M, et al. Embolization as a first approach with endoscopically unmanageable acute nonvariceal gastrointestinal hemorrhage. *Radiology*. 2001; 218(3):739–748.
35. Schenker MP, Duszak R Jr, Soulen MC, et al. Upper gastrointestinal hemorrhage and transcatheter embolotherapy: clinical and technical factors impacting success and survival. *J Vasc Interv Radiol*. 2001;12(11):1263–1271.
36. Yap FY, Omene BO, Patel MN, et al. Transcatheter embolotherapy for gastrointestinal bleeding: a single center review of safety, efficacy, and clinical outcomes. *Dig Dis Sci*. 2013;58(7):1976–1984.
37. Ljungdahl M, Eriksson LG, Nyman R, et al. Arterial embolisation in management of massive bleeding from gastric and duodenal ulcers. *Eur J Surg*. 2002;168(7):384–390.
38. Ripoll C, Banares R, Beceiro I. Comparison of transcatheter arterial embolization and surgery for treatment of bleeding peptic ulcer after endoscopic treatment failure. *J Vasc Interv Radiol*. 2004;15(5): 447–450.
39. Sung J. Current management of peptic ulcer bleeding. *Nat Clin Pract Gastroenterol Hepatol*. 2006; 3(1):24–32.
40. Gluud LL, Klingenberg SL, Langholz SE. Systematic review: tranexamic acid for upper gastrointestinal bleeding. *Aliment Pharmacol Ther*. 2008;27(9): 752–758.
41. Henry DA, O'Connell DL. Effects of fibrinolytic inhibitors on mortality from upper gastrointestinal haemorrhage. *BMJ*. 1989;298(6681):1142–1146.
42. Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet*. 2002;359(9300):14–22.
43. Hernandez-Diaz S, Rodriguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/ perforation: an overview of epidemiologic studies published in the 1990s. *Arch Intern Med*. 2000; 160(14):2093–2099.
44. Ford AC, Delaney BC, Forman D, et al. Eradication therapy for peptic ulcer disease in *Helicobacter pylori* positive patients. *Cochrane Database Syst Rev*. 2006;(2):CD003840.
45. Gisbert JP, Khorrami S, Carballo F, et al. *pylori* eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer. *Cochrane Database Syst Rev*. 2004;(2): CD004062.
46. Gisbert JP, Abraira V. Accuracy of *Helicobacter pylori* diagnostic tests in patients with bleeding peptic ulcer: a systematic review and meta-analysis. *Am J Gastroenterol*. 2006;101(4):848–863.
47. Cook DJ, Fuller HD, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. *N Engl J Med*. 1994;330(6):377–381.
48. Cook DJ, Witt LG, Cook RJ, et al. Stress ulcer prophylaxis in the critically ill: a meta-analysis. *Am J Med*. 1991;91(5):519–527.
49. Tryba M. Sucralfate versus antacids or H_2-antagonists for stress ulcer prophylaxis: a meta-analysis on efficacy and pneumonia rate. *Crit Care Med*. 1991;19(7):942–949.
50. Lasky MR, Metzler MH, Phillips JO. A prospective study of omeprazole suspension to prevent clinically significant gastrointestinal bleeding from stress ulcers in mechanically ventilated trauma patients. *J Trauma*. 1998;44(3):527–533.
51. Krige JE, Kotze UK, Bornman PC, et al. Variceal recurrence, rebleeding, and survival after endoscopic injection sclerotherapy in 287 alcoholic cirrhotic patients with bleeding esophageal varices. *Ann Surg*. 2006;244(5):764–770.
52. Levacher S, Letoumelin P, Pateron D, et al. Early administration of terlipressin plus glyceryl trinitrate to control active upper gastrointestinal

bleeding in cirrhotic patients. *Lancet*. 1995; 346(8979):865–868.
53. Ioannou G, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. *Cochrane Database Syst Rev*. 2003;(1):CD002147.
54. Freeman JG, Cobden I, Record CO. Placebo-controlled trial of terlipressin (glypressin) in the management of acute variceal bleeding. *J Clin Gastroenterol*. 1989;11(1):58–60.
55. Walker S, Stiehl A, Raedsch R, et al. Terlipressin in bleeding esophageal varices: a placebo-controlled, double-blind study. *Hepatology*. 1986;6(1):112–115.
56. D'Amico G, Politi F, Morabito A, et al. Octreotide compared with placebo in a treatment strategy for early rebleeding in cirrhosis. A double blind, randomized pragmatic trial. *Hepatology*. 1998;28(5):1206–1214.
57. Gotzsche PC, Hrobjartsson A. Somatostatin analogues for acute bleeding oesophageal varices. *Cochrane Database Syst Rev*. 2008;(3):CD000193.
58. Avgerinos A, Nevens F, Raptis S, et al. Early administration of somatostatin and efficacy of sclerotherapy in acute oesophageal variceal bleeds: the European Acute Bleeding Oesophageal Variceal Episodes (ABOVE) randomised trial. *Lancet*. 1997;350(9090):1495–1499.
59. Valenzuela JE, Schubert T, Fogel MR, et al. A multicenter, randomized, double-blind trial of somatostatin in the management of acute hemorrhage from esophageal varices. *Hepatology*. 1989;10(6):958–961.
60. Banares R, Albillos A, Rincon D, et al. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis. *Hepatology*. 2002;35(3):609–615.
61. Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila FI, et al. Antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding. *Cochrane Database Syst Rev*. 2010;(9): CD002907.
62. Cheng JW, Zhu L, Gu MJ, et al. Meta analysis of propranolol effects on gastrointestinal hemorrhage in cirrhotic patients. *World J Gastroenterol*. 2003;9(8):1836–1839.
63. Lo GH, Chen WC, Chen MH, et al. Banding ligation versus nadolol and isosorbide mononitrate for the prevention of esophageal variceal rebleeding. *Gastroenterology*. 2002;123(3):728–734.
64. Romero G, Kravetz D, Argonz J, et al. Comparative study between nadolol and 5-isosorbide mononitrate vs. endoscopic band ligation plus sclerotherapy in the prevention of variceal rebleeding in cirrhotic patients: a randomized controlled trial. *Aliment Pharmacol Ther*. 2006;24(4): 601–611.
65. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. *Ann Intern Med*. 1995;123(4):280–287.
66. Lo GH, Lai KH, Cheng JS, et al. Emergency banding ligation versus sclerotherapy for the control of active bleeding from esophageal varices. *Hepatology*. 1997;25(5):1101–1104.
67. Lo GH, Lai KH, Cheng JS, et al. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. *Hepatology*. 2001;33(5): 1060–1064.
68. Tan PC, Hou MC, Lin HC, et al. A randomized trial of endoscopic treatment of acute gastric variceal hemorrhage: N-butyl-2-cyanoacrylate injection versus band ligation. *Hepatology*. 2006; 43(4):690–697.
69. Panes J, Teres J, Bosch J, et al. Efficacy of balloon tamponade in treatment of bleeding gastric and esophageal varices. Results in 151 consecutive episodes. *Dig Dis Sci*. 1988;33(4):454–459.
70. Garcia-Compean D, Blanc P, Bories JM, et al. Treatment of active gastroesophageal variceal bleeding with terlipressin or hemostatic balloon in patients with cirrhosis. A randomized controlled trial. *Arch Med Res*. 1997;28(2):241–245.
71. Lo GH, Lai KH, Ng WW, et al. Injection sclerotherapy preceded by esophageal tamponade versus immediate sclerotherapy in arresting active variceal bleeding: a prospective randomized trial. *Gastrointest Endosc*. 1992;38(4):421–424.
72. Rossle M, Haag K, Ochs A, et al. The transjugular intrahepatic portosystemic stent-shunt procedure for variceal bleeding. *N Engl J Med*. 1994;330(3): 165–171.
73. Papatheodoridis GV, Goulis J, Leandro G, et al. Transjugular intrahepatic portosystemic shunt compared with endoscopic treatment for prevention of variceal rebleeding: a meta-analysis. *Hepatology*. 1999;30(3):612–622.
74. Khan S, Tudur Smith C, Williamson P, et al. Portosystemic shunts versus endoscopic therapy for variceal rebleeding in patients with cirrhosis. *Cochrane Database Syst Rev*. 2006;(4):CD000553.
75. Bornman PC, Krige JE, Terblanche J. Management of oesophageal varices. *Lancet*. 1994;343(8905): 1079–1084.
76. Newman J, Fitzgerald JE, Gupta S, et al. Outcome predictors in acute surgical admissions for lower gastrointestinal bleeding. *Colorectal Dis*. 2012;14(8):1020–1026.
77. Strate LL, Ayanian JZ, Kotler G, et al. Risk factors for mortality in lower intestinal bleeding. *Clin Gastroenterol Hepatol*. 2008;6(9):1004–1010, quiz 955.
78. Strate LL, Orav EJ, Syngal S. Early predictors of severity in acute lower intestinal tract bleeding. *Arch Intern Med*. 2003;163(7):838–843.
79. Strate LL, Saltzman JR, Ookubo R, et al. Validation of a clinical prediction rule for severe acute lower intestinal bleeding. *Am J Gastroenterol*. 2005;100(8):1821–1827.
80. Velayos FS, Williamson A, Sousa KH, et al. Early predictors of severe lower gastrointestinal bleeding and adverse outcomes: a prospective study. *Clin Gastroenterol Hepatol*. 2004;2(6):485–490.

81. Longstreth GF. Epidemiology and outcome of patients hospitalized with acute lower gastrointestinal hemorrhage: a population-based study. *Am J Gastroenterol*. 1997;92(3):419–424.
82. Strate LL, Syngal S. Timing of colonoscopy: impact on length of hospital stay in patients with acute lower intestinal bleeding. *Am J Gastroenterol*. 2003;98(2):317–322.
83. Jensen DM. Management of patients with severe hematochezia – with all current evidence available. *Am J Gastroenterol*. 2005;100(11):2403–2406.
84. Chaudhry V, Hyser MJ, Gracias VH, et al. Colonoscopy: the initial test for acute lower gastrointestinal bleeding. *Am Surg*. 1998;64(8):723–728.
85. Ohyama T, Sakurai Y, Ito M, et al. Analysis of urgent colonoscopy for lower gastrointestinal tract bleeding. *Digestion*. 2000;61(3):189–192.
86. Angtuaco TL, Reddy SK, Drapkin S, et al. The utility of urgent colonoscopy in the evaluation of acute lower gastrointestinal tract bleeding: a 2-year experience from a single center. *Am J Gastroenterol*. 2001;96(6):1782–1785.
87. Green BT, Rockey DC, Portwood G, et al. Urgent colonoscopy for evaluation and management of acute lower gastrointestinal hemorrhage: a randomized controlled trial. *Am J Gastroenterol*. 2005;100(11):2395–2402.
88. Ali M, Ul Haq T, Salam B, et al. Treatment of nonvariceal gastrointestinal hemorrhage by transcatheter embolization. *Radiol Res Pract*. 2013; 2013:604328.
89. Yi WS, Garg G, Sava JA. Localization and definitive control of lower gastrointestinal bleeding with angiography and embolization. *Am Surg*. 2013;79(4):375–380.
90. Gunderman R, Leef JA, Lipton MJ, et al. Diagnostic imaging and the outcome of acute lower gastrointestinal bleeding. *Acad Radiol*. 1998; 5(suppl 2):S303–S305.
91. Koh DC, Luchtefeld MA, Kim DG, et al. Efficacy of transarterial embolization as definitive treatment in lower gastrointestinal bleeding. *Colorectal Dis*. 2009;11(1):53–59.
92. Funaki B, Kostelic JK, Lorenz J, et al. Superselective microcoil embolization of colonic hemorrhage. *AJR Am J Roentgenol*. 2001;177(4):829–836.
93. Farrell JJ, Friedman LS. Gastrointestinal bleeding in the elderly. *Gastroenterol Clin North Am*. 2001;30(2): 377–407, viii.
94. Becker RC, Scheiman J, Dauerman HL, et al. Management of platelet-directed pharmacotherapy in patients with atherosclerotic coronary artery disease undergoing elective endoscopic gastrointestinal procedures. *Am J Gastroenterol*. 2009;104(12):2903–2917.
95. Sung JJ, Lau JY, Ching JY, et al. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. *Ann Intern Med*. 2010;152(1):1–9.
96. Eisenberg MJ, Richard PR, Libersan D, et al. Safety of short-term discontinuation of antiplatelet therapy in patients with drug-eluting stents. *Circulation*. 2009;119(12):1634–1642.
97. Jensen DM, Machicado GA, Jutabha R, et al. Urgent colonoscopy for the diagnosis and treatment of severe diverticular hemorrhage. *N Engl J Med*. 2000;342(2):78–82.
98. Kaltenbach T, Watson R, Shah J, et al. Colonoscopy with clipping is useful in the diagnosis and treatment of diverticular bleeding. *Clin Gastroenterol Hepatol*. 2012;10(2):131–137.
99. Guo SB, Gong AX, Leng J, et al. Application of endoscopic hemoclips for nonvariceal bleeding in the upper gastrointestinal tract. *World J Gastroenterol*. 2009;15(34):4322–4326.
100. Rex DK, Lewis BS, Waye JD. Colonoscopy and endoscopic therapy for delayed post-polypectomy hemorrhage. *Gastrointest Endosc*. 1992;38(2):127–129.
101. d'Othee BJ, Surapaneni P, Rabkin D, et al. Microcoil embolization for acute lower gastrointestinal bleeding. *Cardiovasc Intervent Radiol*. 2006;29(1):49–58.
102. Yata S, Ihaya T, Kaminou T, et al. Transcatheter arterial embolization of acute arterial bleeding in the upper and lower gastrointestinal tract with N-butyl-2-cyanoacrylate. *J Vasc Interv Radiol*. 2013;24(3):422–431.
103. Renzulli P, Maurer CA, Netzer P, et al. Subtotal colectomy with primary ileorectostomy is effective for unlocalized, diverticular hemorrhage. *Langenbecks Arch Surg*. 2002;387(2):67–71.

43

Acute pancreatitis

Aimée L Brame, Duncan LA Wyncoll

Acute inflammation of the pancreas produces a spectrum of symptoms, which may be mild and self-limiting, or reflect severe disease that rapidly leads to acute respiratory distress syndrome (ARDS), multiple-organ failure and death. In a majority of patients, a treatable underlying cause is identified. Although mild, interstitial, oedematous pancreatitis is more common, it is the more severe form – acute necrotising pancreatitis (ANP) – which accounts for the associated mortality, 17%–21% even in specialist centres.[1,2]

Management of patients with severe ANP is time consuming, labour and resource intensive. Long-term follow-up suggests that, although some survivors suffer permanent exocrine and endocrine insufficiency, most maintain a good quality of life.[3]

In the last 20 years there has been a gradual move towards aggressive supportive therapy for ANP. Numerous putative therapeutic interventions have been tried, but few have provided any objective evidence of clinical benefit.

AETIOLOGY

Biliary disease (35%–40%)[1] and alcohol (35%)[4] remain the two commonest causes of acute pancreatitis worldwide. Although no discernible cause is found in many of the remaining cases, there are well-established associations with a number of infections, certain drugs, hyperlipidaemias and trauma. See Box 43.1 for a more exhaustive list.

RANSON CRITERIA

Although the overall mortality rate for acute pancreatitis is approximately 5%–10%, the vast majority of deaths occur in those with the severe form of the disease. Since 1974 the standard means of documenting the severity of disease and risk of mortality has been by Ranson criteria (Box 43.2).[5] These factors were determined following the analysis of just 100 patients with predominantly alcohol-induced pancreatitis using clinical and laboratory data obtained at admission and after 48 hours, and the number of positive criteria should predict outcome. A decade later these criteria were re-evaluated and the first eight were found to be most predictive – this is now known as the Glasgow criteria, or Imrie score. This applies to both alcohol and non-alcohol induced pathology.[6]

SCORING

The Atlanta Symposium developed the first universally applicable classification system for acute pancreatitis in 1992.[7] This divided the disease into two broad categories, interstitial oedematous (without recognisable tissue necrosis) and acute necrotising (with parenchymal and peripancreatic necrosis).[7] The classification has since been revised (2012) and now includes clinical assessment of severity and organ failure (Modified Marshall Score) and defines terms for describing the local complications of acute pancreatitis (Box 43.3).[8]

The Modified Marshall score uses Pa_{O_2}/Fi_{O_2} ratio, serum creatinine and systolic blood pressure to define the presence of organ dysfunction and, hence, severity at 48 hours.[9] The Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system has also been used in predicting the severity of pancreatitis, and can be used daily throughout the patient's hospital admission rather than solely within the first 48 hours, thus potentially documenting progress or deterioration. However, such scoring systems are complex to perform and have been evaluated only prospectively 24–48 hours after the onset of pancreatitis, which means that the criteria may not be valid for patients subsequently admitted to the intensive care unit (ICU). Those factors with most predictive value for mortality include advanced age, presence of renal or respiratory insufficiency and presence of shock.

The scoring of patients with acute pancreatitis is important for a number of reasons. Firstly, the clinician can be alerted early to the presence of potentially severe disease. Secondly, comparisons of severity can be made both within and between patient series; and thirdly, rational selection of patients can be made for inclusion in trials of potential new treatments or interventions.

ABSTRACT

Acute pancreatitis is an acute inflammatory disorder of the pancreas and is one of the commonest gastrointestinal disorders requiring admission to hospital and critical care. The mortality rate is high and the treatment essentially supportive. There are multiple published guidelines and reviews; however, there are few high-quality randomised controlled trials as a result of the acuity of presentation and variability of disease aetiology and progression.

The aim of this review is to summarise the current evidence and best practice guidelines with regard to severity assessment, fluid management, imaging, pharmacological therapy, surgery and endoscopic intervention and nutrition.

KEYWORDS

Acute pancreatitis
necrotising pancreatitis
Atlanta classification
fluid therapy
SIRS
surgery
ERCP
antibiotics
steroids
nutrition

Box 43.1 Aetiology of acute pancreatitis

Excess alcohol ingestion
Biliary tract disease
Idiopathic
Metabolic
Hyperlipidaemia
Hyperparathyroidism
Diabetic ketoacidosis
End-stage renal failure
Pregnancy
Post renal transplant
Mechanical disorders
Post-traumatic, postoperative, post endoscopic retrograde cholangiopancreatography
Penetrating duodenal ulcer
Duodenal obstruction
Infections
Human immunodeficiency virus, mumps, Epstein–Barr virus, Mycoplasma, Legionella, Campylobacter, ascariasis
Vascular
Necrotising vasculitis – systemic lupus erythematosus, thrombotic thrombocytopenia
Atheroma
Shock
Drugs
Azathioprine, aminosalicylates, sulphonamides, thiazides, furosemide, tetracyclines, oestrogens, valproic acid, metronidazole, pentamidine, nitrofurantoin, erythromycin, tetracyclines, methyldopa, ranitidine and steroids
Toxins
Scorpion venom, organophosphates, methyl alcohol

Box 43.2 Adverse prognostic factors in acute pancreatitis ranson score

On admission
Age >55 years
White cell count >16,000/mm^3
Glucose 11 mmol/L
Lactate dehydrogenase 400 IU/L
Aspartate transaminase >250 IU/L
Within 48 hours of hospitalisation
Decrease in haematocrit >10%
Increase in blood urea >1.8 mmol/L
Calcium <2 mmol/L
PaO_2 <8 kPa
Base deficit >4 mmol/L
Fluid deficit >6 L

Risk factors	Mortality rate
0–2	<1%
3–4	≅15%
5–6	≅40%
>6	≅100%

Blamey et al.[6] found that only eight variables (not lactate dehydrogenase, base deficit and fluid deficit) were predictive and are often referred to as the Glasgow criteria or Imrie score.
Yang AL, Vadhavkar S, Singh G, Omary MB. Epidemiology of alcohol-related liver and pancreatic disease in the United States. *Arch Intern Med*. 2008;168(6):649–656.

Box 43.3 Severity grading for acute pancreatitis – revised atlanta classification 2012

Grades of severity
- Mild acute pancreatitis
  - No organ failure
  - No local or systemic complications
- Moderately severe acute pancreatitis
  - Transient organ failure (resolves <48 hours) ±
  - Local or systemic complications without persistent organ failure
- Severe acute pancreatitis
  - Persistent single or multiorgan failure (>48 hours)

Modified from Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis – 2012: Revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62:102–111.

THE MANAGEMENT OF SEVERE PANCREATITIS

IMAGING

Dynamic contrast-enhanced computed tomography (CT) provides the best means of accurately visualising the pancreas and diagnosing pancreatitis and its local complications. It may also be used for guiding percutaneous catheter drainage. Local complications are defined as peripancreatic fluid collections, necrosis (sterile or infected), pseudocysts and walled-off necrosis.[8]

In severe acute pancreatitis, there is lack of normal enhancement to contrast of all or part of the gland. This is consistent with pancreatic necrosis, defined as diffuse or focal areas of non-viable parenchyma. Microscopically, there is evidence of damage to the parenchymal network, acinar cells and pancreatic ductal system and necrosis of perilobular fat. Areas of necrosis are often multifocal, rarely involving the whole gland, and may be confined to the periphery with preservation of the core. Necrosis develops early in the course of the disease and is usually established 96 hours after the onset of symptoms. The extent of pancreatic necrosis and the degree of peripancreatic inflammation have been used to determine outcome. A grading system combining the two CT prognostic indicators (the extent of necrosis and the grade of peripancreatic inflammation) gives the 'CT severity index'.[10]

A strong correlation has been established between the CT depiction of necrosis and the development of complications and death.[11] In patients with necrosis in

the pancreatic head, the outcome is as severe as when the entire pancreas is affected. By contrast, for patients with necrosis in only the distal portion of the gland, the outcome is usually good, with few complications. The mechanism may be that necrosis in the pancreatic head causes obstruction of the pancreatic duct, and produces a rise in pressure in the acinar cells leading to damage and leakage of activated destructive proteases.

Following the initial CT scan, repeated scanning is indicated if the patient's clinical condition deteriorates, usually through the development of pancreatic necrosis, abscess or pancreatic pseudocyst, haemorrhage, or colonic ischaemia or perforation.

Ultrasonography in acute pancreatitis is less useful since visualisation of the gland may be obscured by 'gas-filled' bowel. Moreover, the degree of necrosis, which determines prognosis, cannot be assessed. However, there may be a role for this mode of imaging in demonstrating gallstones or duct dilatation, or in the subsequent management when ultrasound-guided fine-needle aspiration of the pancreas or surrounding tissue may help to establish the presence of infection.

FLUID THERAPY

Early aggressive intravenous fluid therapy is of paramount importance when treating patients with acute pancreatitis. Hypovolaemia arises from vomiting (± diarrhoea), poor oral intake, third spacing of fluid, oedema and diaphoresis. This results in hypotension, worsening tissue perfusion, exacerbating pancreatic tissue necrosis and precipitates dysfunction in other organ systems. Aggressive hydration (5–10 mL/kg/h)[12] with isotonic crystalloid solution should occur in all patients without contraindication and fluid status should be reassessed at frequent intervals in the first 24 hours.[12] Higher fluid administration rates may be required; however, one randomised controlled trial (RCT) demonstrated fluid volumes of 10–15 mL/kg/h were associated with increased need for mechanical ventilation (94% vs 65%), intra-abdominal compartment syndrome, sepsis and mortality (30.6% vs 10%) compared with 5–10 mL/kg/h strategy.[13]

SURGERY IN SEVERE PANCREATITIS

During the 1980s, most patients with acute pancreatitis of even moderate severity underwent operative intervention; this was particularly true for those patients thought to have infected pancreatic necrosis. The results were poor, with mortality rates in excess of 50%, although this was sometimes without ICU support. In the 1990s the concept of a conservative, non-surgical approach to severe ANP was developed. The aim now is often to postpone surgery for as long as possible and early referral to a specialist centre for supportive management is considered paramount.

Asymptomatic pseudocysts and pancreatic necrosis do not warrant surgical intervention, regardless of size and location, unless gastric outflow or bile duct patency is compromised.[12] In stable patients with infected necrosis, drainage should be delayed for a period of at least 4 weeks to allow formation of a fibrous wall and liquefaction of the necrotic tissue. Many patients improve such that intervention is unnecessary at this point.

Unstable patients with infected necrosis should receive a course of antibiotics to allow the inflammation to become organised prior to targeted, minimally invasive surgical intervention.[12,14]

Many centres report that a conservative approach and avoiding open necrosectomy result in lower mortality. Open surgery is reserved for concomitant intra-abdominal complications, such as perforation, bleeding or ischaemia.[15]

If severe acute pancreatitis is an unsuspected 'chance' finding at laparotomy, a T-tube should be inserted into the common bile duct, particularly if it has been explored and the opportunity taken for placement of a feeding jejunostomy tube. Some surgeons oppose this approach, as opening a hollow viscus risks peritonitis.

For those patients with mild gallstone pancreatitis, the risk of recurrence is high (18% at 90 days),[12] early cholecystectomy is advocated to prevent recurrent and potentially more serious disease. In more severe biliary acute pancreatitis (AP), cholecystectomy should be delayed until the inflammatory response and clinical picture have resolved.[16]

PANCREATIC ABSCESSES

Pancreatic abscesses are circumscribed collections of pus containing little or no pancreatic necrosis, which arise as a later consequence of severe acute pancreatitis or pancreatic trauma. They commonly occur about 3–4 weeks after the onset of severe pancreatitis, and a CT scan most accurately makes the diagnosis. If the appropriate expertise is available, percutaneous catheter drainage may be very successful. Some series report effective drainage of intra-abdominal collections with a single treatment in 70% of patients, increasing to 82% with a second attempt, although proceeding to open surgical drainage is more frequently required in pancreatic abscess, especially if complicated by yeast infection.[17]

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

Endoscopic retrograde cholangiopancreatography (ERCP) represents an alternative approach, particularly for patients with severe biliary pancreatitis or those who are too frail for surgery. In mild gallstone pancreatitis, early ERCP decreases morbidity and mortality in patients with acute pancreatitis and biliary sepsis/obstruction, whereas in mild pancreatitis

without cholangitis, the risks of intervention probably outweigh the benefits.[18]

This observation is confirmed by both a systematic review of the five ERCP trials[19] and by the recommendations of the 2013 International Association of Pancreatology on the management of severe acute pancreatitis in the critically ill.[14]

TREATMENT WITH PHARMACOLOGICAL AGENTS

Theories regarding the pathogenesis of acute pancreatitis have promoted the concept that autodigestion of the gland and peripancreatic tissue by activated pancreatic enzymes is a central component. This has led to the suggestion that the reduction of pancreatic exocrine secretion, thereby 'resting the pancreas', might improve outcome. The problem is that the secretory status of the pancreas in severe ANP is not known. Consequently, it is not clear whether inhibition of secretion actually occurs or whether this is beneficial. Therapies designed to inhibit pancreatic secretion, such as H_2-blockers, atropine, calcitonin, glucagon and fluorouracil, do not alter the course of the disease.

Other therapies are more controversial.

SOMATOSTATIN AND OCTREOTIDE

Somatostatin and its long-acting analogue octreotide are potent inhibitors of pancreatic secretion. They also stimulate activity of the reticuloendothelial system and play a regulatory role, mostly inhibitory, in the modulation of the immune response via autocrine and neuroendocrine pathways. Both are cytoprotective with respect to the pancreas.[20] Other effects include:

- Somatostatin also blocks the release of tumour necrosis factor and interferon-γ by peripheral mononuclear cells.
- Octreotide increases the phagocytotic activity of monocytes.

These actions may be important in the modulation of the pathogenesis of ARDS and septic shock, both of which can complicate severe ANP. Both agents are effective in experimental pancreatitis, and in the prevention of complications in patients undergoing surgery for chronic pancreatitis, but there are potential difficulties:

- Pre-emptive administration is not possible in the acute situation.
- Both agents are powerful splanchnic vasoconstrictors.
- The development of pancreatic necrosis has been linked to hypoperfusion of the gland and vasoconstrictors worsen the histological severity of experimental pancreatitis.[21]

Consequently, these agents have both beneficial and detrimental effects. Systematic evaluation suggests that there is insufficient evidence to support the use of octreotide or somatostatin in the treatment of patients with moderate to severe acute pancreatitis.[22,23] Octreotide may have a role in prophylaxis prior to ERCP[24] but the ideal delivery method and dosage are not clear.

Protease inhibitors

A further pathogenic mechanism involved in acute pancreatitis is autodigestion of the pancreas by the activation of proteases. More accurately, there is an imbalance between proteases and antiproteases. Aprotinin and gabexate mesilate are proteolytic enzyme inhibitors that act on serine proteases such as trypsin, phospholipase A_2, kallikrein, plasmin, thrombin and C1r and C1s esterases.

In a meta-analysis of 17 trials, protease inhibitors did not achieve a significant risk reduction in mortality, length of stay or need for surgery, even in severe disease.[25–27] The majority of published data is observational and to date there are no placebo-controlled randomised studies evaluating protease inhibitors in ANP.

The reason why these agents, in clinical practice, do not have the expected beneficial effect on outcome may be the lag time between the onset of pancreatitis and administration. Additionally, derangement to the microvascular control of the pancreas combined with increased vascular permeability may contribute. Continuous regional arterial infusion or intraperitoneal administration may be more advantageous in prophylaxis prior to ERCP,[28] but so far trials using these modes of administration have only involved small numbers of patients. At present, there is insufficient evidence to recommend protease inhibitors in ANP and their use is not supported in the majority of published guidelines.[29,30]

ANTI-INFLAMMATORY THERAPY

Patients with ANP exhibit a generalised uncontrolled inflammatory response. Potentially there is a therapeutic window between the onset of symptoms and the development of organ failure during which anti-inflammatory therapy might be successful. Potential targets include tumour necrosis factor-α, interleukin (IL)-1β, IL-6, IL-8, IL-10, platelet-activating factor and intracellular adhesion molecules.[31] Although many have been studied in animals, there are limited human data.

Changes in hypopituitary–adrenal axis hormone levels strongly suggest that the existence of relative adrenocortical insufficiency in patients with ANP is very comparable to that of severe sepsis and multiple-organ failure[32]; however, there are currently no positive published trials of corticosteroid therapy in patients with ANP, and no evidence for use as either therapy or prophylaxis.

NSAIDs have been evaluated in several studies and may provide a beneficial effect in prophylaxis post-ERCP and are also useful adjunctive analgesics.[33]

Recombinant IL-10, anti-TNF-α and platelet activating factor (Lexipafant) have all been investigated in animal models, but there is insufficient human data and the use of these agents is not recommended.[34]

PROPHYLACTIC ANTIBIOTICS

Bacterial infection of necrotic pancreatic tissue occurs in approximately 50% of patients with ANP, and infection is the major cause of morbidity and mortality. Early studies investigating the role of prophylactic antibiotics in acute pancreatitis showed no benefit, but most included patients with mild disease and employed agents (e.g. ampicillin) with inefficient penetration of pancreatic tissue. Subsequent studies have still not clarified their role, and prophylactic use remains widespread but controversial.

Carbapenems have exceptional penetration into pancreatic tissues and broad activity against most of the common pathogens encountered in this disease. In the 1990s there was hope that this new class of antibiotic would prove more useful, and some of the early trials did suggest a modest benefit with imipenem.[35] The incidence of septic complications was significantly reduced in the treated group (12.2% vs 30.3%), although there was only a trend towards decreased mortality (7% vs 12%). However, the most recent systematic review, which included 14 trials (but still only 841 patients), suggested antibiotic prophylaxis was not associated with a statistically significant reduction in mortality (relative risk [RR], 0.74 [95% confidence interval (CI), 0.50–1.07]), in the incidence of infected pancreatic necrosis (RR, 0.78 [95% CI, 0.60–1.02]) or in the incidence of non-pancreatic infections (RR, 0.70 [95% CI, 0.46–1.06]).[36] Of note, though, in the majority of these trials, patients with severe ANP and overt shock *were excluded*, leaving open the possibility that prophylactic antibiotics may still have a role in the very sickest patients.

Whilst antibiotic prophylaxis is not recommended, intravenous antibiotics should be given in cases of suspected infection of necrotising pancreatitis after aspiration or cultures have been performed.[12,14]

Patients with mild pancreatitis definitely do not benefit from antibiotics.

PROPHYLACTIC ANTIFUNGAL THERAPY

The incidence of fungal infection correlates with the extent of pancreatic necrosis, as well as the severity of disease on admission. Antibiotic administration has been claimed to promote fungal infection; however, up to 25% of patients with ANP who do not receive antibiotics also develop fungal infection with an associated mortality rate of up to 84%.[37] Advocates of prophylactic antifungal therapy argue that it may delay the need for surgery, which is associated with a better outcome. Routine administration of antifungal agents is not recommended.[12]

SELECTIVE DECONTAMINATION OF THE GUT

The original selective digestive decontamination (SDD) strategy contained three components: oropharyngeal and gastric decontamination with polymyxin E, tobramycin, and amphotericin B and intravenous cefotaxime for 4 days.[38] There is ongoing debate as to the effectiveness of this strategy and results are conflicting regarding any reduction in mortality, particularly when applied to a general critically ill population. However, more promising results have been seen in specific patient populations.

Severe acute pancreatitis may be a clinical situation which supports the hypothesis that gut hypoperfusion promotes bacterial translocation, leading to infection of the inflamed pancreas and peripancreatic tissue.[39,40] The only controlled trial of SDD in pancreatitis was performed in 102 patients[41] who were randomised to receive SDD: oral colistin, amphotericin and norfloxacin with addition of a daily dose of the three drugs given as a rectal enema and systemic cefotaxime until Gram-negative bacteria were successfully eliminated from the oral cavity and rectum. Surveillance samples were taken regularly to assess whether any subsequent infection was of exogenous or endogenous origin. There were 18 deaths (35%) in the control group, compared with 11 (22%) in the SDD group ($P < 0.05$). This difference was caused by a fall in late mortality due to significant reduction in the incidence of Gram-negative pancreatic infection. There was also a reduction in the mean number of laparotomies in the SDD patients. Since the SDD regimen used in this study incorporated intravenous cefotaxime, it could be argued that the improvement in outcome was not due to the colistin, amphotericin or norfloxacin components, but merely due to a systemic antibiotic effect.

Meta-analyses and even large randomised controlled trials of this intervention continue to suggest clear trends towards a reduction in mortality in critically ill patients.[42] However, the perhaps unfounded fear of the emergence of resistant Gram-positive cocci prevents widespread adoption of this strategy.

Probiotics have been investigated in three prospective randomised controlled double-blinded studies. The studies were relatively small and results contradictory. A non-significant reduction in mortality was seen in two of the studies.[43,44] The third study observed an increase in gut ischaemia (5.9% vs 0, $P = .004$) and mortality in the probiotic arm compared with the placebo (16% vs 6%, RR, 2.53; 95% CI, 1.22–5.25).[45] Probiotics are not recommended.

Nutritional support in acute necrotising pancreatitis

The provision of nutritional support for the patient with ANP is an essential component of supportive therapy, especially since many patients with pancreatitis are nutritionally depleted prior to their illness and face increased metabolic demands throughout the

course of their disorder. Failure to reverse or prevent malnutrition, and a prolonged negative nitrogen balance, increases mortality rates.

TOTAL PARENTERAL NUTRITION

Severe pancreatitis is still sometimes stated as an absolute contraindication to enteral nutrition (EN), and some physicians consider total parenteral nutrition (TPN) as 'standard' therapy. This is largely because it is regarded as a way of 'resting the pancreas', based on the assumption that the necrotic pancreas is still a secretor of activated enzymes. In fact, the secretory state of the pancreas has never been prospectively studied in severe necrosis. Several retrospective and prospective evaluations of TPN in acute pancreatitis have failed to demonstrate conclusively an effect on survival, or on the incidence and severity of organ failure.

ENTERAL NUTRITION

An increasing number of reports on the use of EN in severe ANP confirm that it is safe and feasible for all but the minority of patients. Enteral feeding maintains the gut mucosal barrier and helps prevent bacterial translocation and secondary infection of necrotic pancreatic tissue. Feeding should therefore commence early.

Enteral feeding can be oral, nasogastric or nasojejunal.[46] Nasogastric (NG) placement is easier than nasojejunal (NJ) and may therefore be preferential route; however, NG feeding is not tolerated by a number of patients. Intragastric delivery of nutrients may result in an increased volume of pancreatic protein and bicarbonate secretion, which, in combination with delayed gastric emptying, can precipitate vomiting and pain. It may therefore be preferable to place a nasojejunal tube with the tip distal to the third part of the duodenum, under radiological, endoscopic or magnetic guidance. The upper part of the duodenum contains cholecystokinin (CCK) secreting cells, stimulation of which causes gallbladder contraction and increased pancreatic exocrine secretion and may worsen the course of the disease. NJ feeding bypasses this area and conforms to the concept of 'pancreatic rest'.

EN is associated with reduced infectious complications, organ failure and mortality compared with parenteral nutrition (PN).[47] A number of comparisons of EN with PN have been made in mild and severe acute pancreatitis, all suggesting that EN is well tolerated without adverse effects on the course of the disease.[48]

In ANP, where there is often an ileus and slow bowel transit time, some patients do not tolerate EN and in some, additional nutritional support is required even after NJ insertion; in this situation TPN with normoglycaemic control should be used.

An international task force has recently made some recommendations,[49] which can be summarised as follows:

1. Most patients with mild or moderate uncomplicated pancreatitis do not benefit from nutritional support.
2. In moderate to severe pancreatitis, let hyperacute inflammation settle, then start a trial of EN.
3. In patients who require surgery for diagnosis or treatment, a jejunal tube should be placed, either pulled down from the stomach, or a separate jejunostomy.
4. TPN is indicated only if a 5- to 7-day trial of EN is not tolerated.
5. In all patients, whether fed enterally or parenterally, a protocol ensuring good glycaemic control is recommended.

CONCLUSION

The main determinant of outcome in severe acute pancreatitis is the extent of pancreatic necrosis and the subsequent risk for the development of infected necrosis. A thorough assessment using appropriate scoring systems and the early use of dynamic contrast-enhanced CT will highlight those patients likely to benefit from early critical care. Despite numerous suggested specific therapies, there is still no incontrovertible evidence that any one confers a significant mortality benefit. However, general supportive measures should include vigorous replacement of fluid losses to correct circulating volume, correction of electrolyte and glucose abnormalities, and respiratory, cardiovascular and renal support as necessary. Patients with sterile necrosis should receive a broad-spectrum prophylactic antibiotic that adequately penetrates pancreatic tissue if they develop shock. Due attention should also be paid to nutritional support, for which EN is recommended prior to initiation of TPN.

REFERENCES

1. Forsmark CE, Baillie J. AGA Institute technical review on acute pancreatitis. *Gastroenterology*. 2007; 132(5):2022–2044.
2. van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology*. 2011;141(4):1254–1263.
3. Tsiotos GG, Luque-De León E, Sarr MG. Long-term outcome of necrotizing pancreatitis treated by necrosectomy. *Br J Surg*. 1998;85(12):1650–1653.
4. Yang AL, Vadhavkar S, Singh G, et al. Epidemiology of alcohol-related liver and pancreatic disease in the United States. *Arch Intern Med*. 2008; 168(6):649–656.
5. Ranson JH, Rifkind KM, Roses DF, et al. Prognostic signs and the role of operative management in acute pancreatitis. *Surg Gynecol Obstet*. 1974;139(1):69–81.
6. Blamey SL, Imrie CW, O'Neill J, et al. Prognostic factors in acute pancreatitis. *Gut*. 1984;25(12): 1340–1346.
7. Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis,

Atlanta, Ga, September 11 through 13, 1992. *Arch Surg*. 1993;128(5):586–590.
8. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis – 2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2012;62:102–111.
9. Marshall JC, Cook DJ, Christou NV, et al. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med*. 1995;23(10): 1638–1652.
10. Bharwani N, Patel S, Prabhudesai S, et al. Acute pancreatitis: the role of imaging in diagnosis and management. *Clin Radiol*. 2011;66(2):164–175.
11. Casas JD, Diaz R, Valderas G, et al. Prognostic value of CT in the early assessment of patients with acute pancreatitis. *AJR Am J Roentgenol*. 2004;182(3): 569–574.
12. Tenner S, Baillie J, DeWitt J, et al. American College of Gastroenterology Guideline: Management of acute pancreatitis. *Am J Gastroenterol*. 2013;108(9): 1400–1415.
13. Mao EQ, Tang YQ, Fei J, et al. Fluid therapy for severe acute pancreatitis in acute response stage. *Chin Med J*. 2009;122(2):169–173.
14. Guidelines WGIAAP. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology*. 2013;13(4 suppl 2):e1–e15.
15. Wittau M, Scheele J, Golz I, et al. Changing role of surgery in necrotizing pancreatitis: a single-center experience. *Hepatogastroenterology*. 2010; 57(102–103):1300–1304.
16. Werner J, Feuerbach S, Uhl W, et al. Management of acute pancreatitis: from surgery to interventional intensive care. *Gut*. 2005;54:426–436.
17. Cinat ME, Wilson SE, Din AM. Determinants for successful percutaneous image-guided drainage of intra-abdominal abscess. *Arch Surg*. 2002;137(7): 845–849.
18. Fölsch UR, Nitsche R, Lüdtke R, et al. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. *N Engl J Med*. 1997; 336(4):237–242.
19. Tse F, Yuan Y. Early routine endoscopic retrograde cholangiopancreatography strategy versus early conservative management strategy in acute gallstone pancreatitis. *Cochrane Database Syst Rev*. 2012;(5):CD009779.
20. van Hagen PM, Krenning EP, Kwekkeboom DJ, et al. Somatostatin and the immune and haematopoetic system; a review. *Eur J Clin Invest*. 1994;24(2): 91–99.
21. Klar E, Rattner DW, Compton C, et al. Adverse effect of therapeutic vasoconstrictors in experimental acute pancreatitis. *Ann Surg*. 1991;214(2):168–174.
22. Cavallini G, Frulloni L. Somatostatin and octreotide in acute pancreatitis: the never-ending story. *Dig Liver Dis*. 2001;33(2):192–201.
23. Uhl W, Büchler MW, Malfertheiner P, et al. A randomised, double blind, multicentre trial of octreotide in moderate to severe acute pancreatitis. *Gut*. 1999;45:97–104.
24. Li ZS, Pan X, Zhang WJ, et al. Effect of octreotide administration in the prophylaxis of post-ERCP pancreatitis and hyperamylasemia: a multicenter, placebo-controlled, randomized clinical trial. *Am J Gastroenterol*. 2007;102(1):46–51.
25. Seta T, Noguchi Y, Shikata S, et al. Treatment of acute pancreatitis with protease inhibitors administered through intravenous infusion: an updated systematic review and meta-analysis. *BMC Gastroenterol*. 2014;14(1):102.
26. Zheng M, Chen Y, Yang X, et al. Gabexate in the prophylaxis of post-ERCP pancreatitis: a meta-analysis of randomized controlled trials. *BMC Gastroenterol*. 2007;7:6.
27. Yasunaga H, Horiguchi H, Hashimoto H, et al. Effect and cost of treatment for acute pancreatitis with or without gabexate mesylate: a propensity score analysis using a nationwide administrative database. *Pancreas*. 2013;42(2):260–264.
28. Otsuki M, Hirota M, Arata S, et al. Consensus of primary care in acute pancreatitis in Japan. *World J Gastroenterol*. 2006;12(21):3314–3323.
29. Banks PA, Freeman ML. Practice parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am J Gastroenterol*. 2006;101:2379–2400.
30. Whitcomb DC. Clinical practice. Acute pancreatitis. *N Engl J Med*. 2006;354(20):2142–2150.
31. Bhatia M. Novel therapeutic targets for acute pancreatitis and associated multiple organ dysfunction syndrome. *Curr Drug Targets Inflamm Allergy*. 2002;1(4):343–351.
32. De Waele JJ, Hoste EA, Baert D, et al. Relative adrenal insufficiency in patients with severe acute pancreatitis. *Intensive Care Med*. 2007;33(10): 1754–1760.
33. Murray B, Carter R, Imrie C, et al. Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. *Gastroenterology*. 2003;124(7):1786–1791.
34. Bang UC, Semb S, Nøjgaard C, et al. Pharmacological approach to acute pancreatitis. *World J Gastroenterol*. 2008;14(19):2968–2976.
35. Pederzoli P, Bassi C, Vesentini S, et al. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. *Surg Gynecol Obstet*. 1993;176(5):480–483.
36. Wittau M, Mayer B, Scheele J, et al. Systematic review and meta-analysis of antibiotic prophylaxis in severe acute pancreatitis. *Scand J Gastroenterol*. 2011;46(3):261–270.
37. Trikudanathan G, Navaneethan U, Vege SS. Intra-abdominal fungal infections complicating acute pancreatitis: a review. *Am J Gastroenterol*. 2011; 106(7):1188–1192.
38. Stoutenbeek CP, van Saene HK, Miranda DR, et al. The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. *Intensive Care Med*. 1984;10(4):185–192.

39. Medich DS, Lee TK, Melhem MF, et al. Pathogenesis of pancreatic sepsis. *Am J Surg*. 1993;165(1):46–50, discussion 1–2.
40. Fritz S, Hackert T, Hartwig W, et al. Bacterial translocation and infected pancreatic necrosis in acute necrotizing pancreatitis derives from small bowel rather than from colon. *Am J Surg*. 2010; 200(1):111–117.
41. Luiten EJ, Hop WC, Lange JF, et al. Controlled clinical trial of selective decontamination for the treatment of severe acute pancreatitis. *Ann Surg*. 1995;222(1):57–65.
42. de Smet AM, Kluytmans JA, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med*. 2009;360(1): 20–31.
43. Olah A, Belagyi T, Issekutz A, et al. Randomized clinical trial of specific lactobacillus and fibre supplement to early enteral nutrition in patients with acute pancreatitis. *Br J Surg*. 2002;89(9): 1103–1107.
44. Olah A, Belagyi T, Poto L, et al. Synbiotic control of inflammation and infection in severe acute pancreatitis: a prospective, randomized, double blind study. *Hepatogastroenterology*. 2007;54(74): 590–594.
45. Besselink MG, van Santvoort HC, Buskens E, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;371(9613): 651–659.
46. Petrov MS, Kukosh MV, Emelyanov NV. A randomized controlled trial of enteral versus parenteral feeding in patients with predicted severe acute pancreatitis shows a significant reduction in mortality and in infected pancreatic complications with total enteral nutrition. *Dig Surg*. 2006;23(5–6):336–344, discussion 44–45.
47. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med*. 2011;365(6):506–517.
48. McClave SA, Chang WK, Dhaliwal R, et al. Nutrition support in acute pancreatitis: a systematic review of the literature. *JPEN J Parenter Enteral Nutr*. 2006;30(2):143–156.
49. Mirtallo JM, Forbes A, McClave SA, et al. International consensus guidelines for nutrition therapy in pancreatitis. *JPEN J Parenter Enteral Nutr*. 2012;36(3):284–291.

44

Liver failure

Chris Willars, Hafiz Hamad Ashraf, Anand Damodaran, Julia Wendon

44.1 ACUTE HEPATIC FAILURE

DEFINITIONS

The manner in which acute deteriorations in hepatic function are described is not uniform. In this chapter, we use the term *acute hepatic failure* to describe both *acute liver failure* (ALF) and *acute-on-chronic liver failure* (ACLF) – which are distinct clinical entities that require very different management strategies.

ACUTE LIVER FAILURE

ALF is a rare condition, with about 400 cases per year in the United Kingdom. ALF arises in the context of massive parenchymal injury and results in a multisystem disorder that is phenotypically similar to severe septic shock. Liver damage is manifest by coagulopathy and encephalopathy, which occurs within days or weeks of the liver injury. There is diversity in terms of aetiology and clinical progression.

Patients with ALF may initially appear relatively well, but progression to multiorgan failure is rapid. The key to a successful outcome lies in prompt recognition, resuscitation and referral to a specialist centre. Only 40% of patients with ALF recover spontaneously, leaving many in need of a liver transplantation, and even those who do eventually recover are often gravely ill.[1]

CLASSIFICATION

The clinical classification described by O'Grady et al.[2] (Table 44.1.1) uses the time from jaundice to encephalopathy to differentiate between hyperacute, acute and subacute liver failure. It is particularly useful because it informs us of likely aetiology and clinical course.

Hyperacute liver failure progresses rapidly (the onset of encephalopathy is within 7 days of the development of jaundice) and is generally associated with profound coagulopathy, high-grade encephalopathy, severe organ dysfunction and a higher incidence of intracranial hypertension, but confers higher rates of spontaneous survival. The onset of encephalopathy often precedes clinical jaundice.

ALF has an intermediate course. Common aetiologies include the viral hepatitides and idiosyncratic drug reactions.

Subacute liver failure is associated with a later onset of encephalopathy, but with the worst outcomes in the absence of transplantation. Aetiology is frequently seronegative (idiopathic – the history suggests a viral or immune-mediated aetiology, but all serological tests are negative) or drug related. Jaundice is inevitable but the transaminitis is often less pronounced than in acute and hyperacute presentations. Patients frequently present with established ascites and so may be clinically difficult to distinguish from those with chronic liver disease (CLD).

AETIOLOGY

Determination of the aetiology of ALF (Box 44.1.1) is important for prognostication and because specific therapy may be available. There is a wide geographical variation in the aetiology of ALF. Acetaminophen (paracetamol) toxicity is responsible for the majority of cases of ALF seen in the United Kingdom and the United States, whereas viral hepatitis is the most common cause of ALF worldwide (Table 44.1.2).

A good history and review of the results of blood tests over the preceding weeks are essential to making a diagnosis. Any new drug ingestion (prescribed, recreational or over the counter) should be considered a potential culprit and discontinued if possible. In addition, any treatments that may be detrimental to liver recovery should be avoided.

DIAGNOSIS

A standardised investigative pathway ensures clinical consistency. *Laboratory tests* that may be useful in establishing a diagnosis are listed in Table 44.1.3. It is paramount that diagnosis proceeds in tandem with resuscitative measures.

ABSTRACT

Acute liver failure (ALF) is a life-threatening illness carrying high mortality. Progression to multiorgan failure can be rapid. Determination of the time from jaundice to encephalopathy allows the clinician to predict the likely aetiology and clinical progression.

Common aetiologies include drugs (especially acetaminophen), viruses, toxins and vascular events.

Diagnosis is established by the exploration of history, the identification of clinical features and the interpretation of serological and radiological investigations.

Patients are best managed in a specialist intensive care unit. Specific treatments are available where the cause is known. Proactive management of intracranial hypertension, prompt resuscitation of the cardiovascular system and the management of metabolic disarray is of paramount importance. Transplantation remains a cornerstone of treatment. Identification of patients who will not survive without urgent liver transplantation is not straightforward and good outcomes rely on the efforts of a multidisciplinary team.

KEYWORDS

Acute liver failure
liver transplant
fulminant liver failure
paracetamol
acetaminophen
critical care
hepatitis
cerebral oedema
intracranial hypertension

Table 44.1.1 Classification of acute liver failure

DEFINITION	TIME (DAYS)	COMMONEST AETIOLOGIES
Hyperacute	<7 days	Acetaminophen overdose, hepatitis A and B
Acute	8–28 days	Hepatitis A, B, E, idiosyncratic drug reactions
Subacute	29 days–8 weeks	Idiosyncratic drug reaction, seronegative hepatitis

Table 44.1.2 Geographical distribution of aetiology in acute liver failure

	U.K.	U.S.	FRANCE	INDIA	JAPAN
Paracetamol	54	40	2	–	–
Drug induced	7	12	15	5	–
Seronegative	17	17	18	24	45
Hepatitis A/B	14	12	49	33	55
Hepatitis E	–	–	–	38	–
Other	8	19	16	–	–

Box 44.1.1 Aetiology of acute liver failure

Viral hepatitis
Hepatitis A, B, D, E, seronegative hepatitis
Herpes simplex, cytomegalovirus, chickenpox – usually limited to immunocompromised hosts

Drug related
Acetaminophen
Antituberculous drugs
Recreational drugs (ecstasy, cocaine)
Idiosyncratic reactions (anticonvulsants, antibiotics, non-steroidal anti-inflammatory drugs [NSAIDs])
Aspirin in children may lead to Reye syndrome
Kava kava

Toxins
Carbon tetrachloride, phosphorous, *Amanita phalloides*, alcohol

Vascular events
Ischaemia, veno-occlusive disease, Budd–Chiari syndrome (hepatic vein thrombosis)
Hyperthermic liver injury

Pregnancy
Acute fatty liver of pregnancy, HELLP syndrome, liver rupture

Other
Wilson disease, autoimmune, lymphoma, carcinoma, haemophagocytic syndrome, trauma

HELLP, **H**aemolysis (microangiopathic haemolytic anaemia), **e**levated **l**iver enzymes and **l**ow **p**latelets.

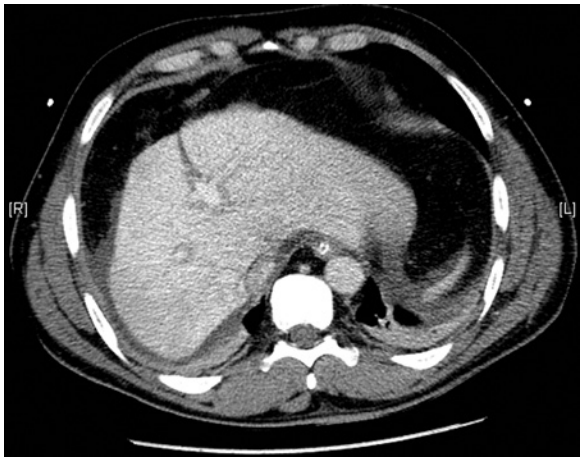


Figure 44.1.1 A collapsed liver in the case of a 42-year-old man with acute liver failure.

Doppler ultrasound is very useful in determining patency of the hepatic artery, vein and portal vein. Budd–Chiari syndrome, ischaemic hepatitis, portal vein thrombosis and even tricuspid regurgitation may be apparent. *Ultrasound examination* of the liver parenchyma may reveal heterogeneity, fatty infiltration (reflectivity) and tumour. Splenomegaly and ascites are evident, if present.

Axial computed tomography (CT) imaging provides additional information about other abdominal anatomy, lymphadenopathy and liver perfusion. Serial imaging in ALF may demonstrate a collapsing liver (Fig. 44.1.1). Nodularity of the liver should not be assumed to represent cirrhosis and CLD. The imaging pattern of subacute liver failure, with focal areas of collapse and regeneration, may be difficult to distinguish from cirrhosis.

Liver biopsy is rarely undertaken in the acute setting because of the high risk of bleeding. The contribution of histology to the assessment of ALF is controversial. Features suggestive of specific diagnoses, such as Wilson disease (cirrhosis), and autoimmune features may be evident and histology may be particularly useful if infiltration with tumour is suspected and a tissue diagnosis is required prior to consideration of systemic chemotherapy. However, in ALF, non-specific confluent necrosis is the commonest histological finding. Its severity has been used to assess prognosis: >50% necrosis is associated with poor prognosis. However, nodules of regeneration may occur randomly, particularly in subacute liver failure, and sampling error may thus make this a less than ideal tool for predicting outcome. The transjugular route is considered safest, although there is a risk of sampling error.

Echocardiography should be performed to exclude low cardiac output states as a cause of hypoxic hepatitis, and where transplantation is considered.

Table 44.1.3 Aetiology of acute liver failure and initial investigations

Hepatitis A virus (HAV)	Immunoglobulin M (IgM) anti-HAV
Hepatitis B + D viruses (HBV, HDV)	HBsAg, IgM anti-core, HBeAg, HBeAb, HBV DNA, delta antibody
Hepatitis E virus (HEV)	IgM antibody
Seronegative hepatitis	All tests negative: diagnosis of exclusion
Paracetamol	Drug levels in blood and clinical pattern of disease – may be negative on third or subsequent days after overdose; markedly elevated aspartate and alanine serum transaminase (often >10,000)
Idiosyncratic drug reactions	Eosinophil count may be elevated, although most diagnoses are based on temporal relationship
Ecstasy	Blood, urine, hair analysis and history
Autoimmune	Autoantibodies, immunoglobulin profile
PREGNANCY-RELATED SYNDROMES	
Fatty liver	Uric acid elevated, neutrophilia, often first pregnancy, history, CT scan for rupture and assessment of vessels
HELLP syndrome	Platelet count, disseminated intravascular coagulation a prominent feature; CT scan as above
Liver rupture	May be seen in association with pre-eclampsia, fatty liver and HELLP
Wilson disease	Urinary copper, ceruloplasmin (although low in many causes of acute liver failure), present up to second decade of life, Kayser–Fleischer rings, low alkaline phosphate levels
Amanita phalloides	History of ingestion of mushrooms, diarrhoea
Budd–Chiari syndrome	Ultrasound of vessels (HV signal lost, reverse flow in portal vein), CT angiography, ascites, prominent caudate lobe on imaging, haematological assessment
Malignancy	Imaging and histology; increased alkaline phosphate and LDH; often imaging may be interpreted as normal
Ischaemic hepatitis	Clinical context, marked elevation of transaminases (often >5000); may demonstrate dilated hepatic veins on ultrasound, echocardiogram
Heatstroke	Myoglobinuria and rhabdomyolysis are often prominent features

CT, Computed tomography; *HELLP,* **h**aemolysis (microangiopathic haemolytic anaemia), **e**levated **l**iver enzymes and **l**ow **p**latelets; *HbsAg,* hepatitis B surface antigen; *HIV,* human immunodeficiency virus; *HV*, high velocity; *LDH,* lactate dehydrogenase.

PARACETAMOL (ACETAMINOPHEN) TOXICITY

Paracetamol, taken intentionally or inadvertently, remains one of the commonest forms of acute hepatotoxicity. This incidence of paracetamol overdose has risen since the 1970s, and in 1998 the Medicines Control Agency (United Kingdom) introduced legislation to limit its availability, and paracetamol is now sold as 16 × 500 mg tablets; a maximum of 8 g per packet.

Cytochrome P450 enzymes convert ~5% of acetaminophen to *N*-acetyl *p*-benzoquinone imine (NAPQI), a metabolite that is normally detoxified by conjugation with hepatic glutathione. Hepatocellular glutathione becomes rapidly depleted in overdose, and NAPQI persists, causing damage to cell membranes leading to hepatocyte death unless NAC (N-acetylcysteine) or methionine is administrated in a timely fashion.

Following massive paracetamol ingestion, relatively small doses are absorbed and when NAC is administered early less than 1% of cases result in significant hepatotoxicity.

The recommended dosage schedule is 150 mg/kg in 5% dextrose over 15–60 minutes, followed by 50 mg/kg in 5% dextrose over 4 hours, and followed by 100 mg/kg in 5% dextrose over 16 hours. Ongoing administration at doses of 150 mg/kg over a 24-hour period may be indicated.

Even late administration of *N*-acetylcysteine (up to 36 hours after ingestion) may improve outcome. The risk factors listed in Table 44.1.4[3] confer a predisposition to paracetamol-induced hepatotoxicity:

The Prescott nomogram (Fig. 44.1.2) is used in the United Kingdom and Europe to determine the risk of acetaminophen toxicity. It can be applied only to a single acute overdose presenting within 16–24 hours.

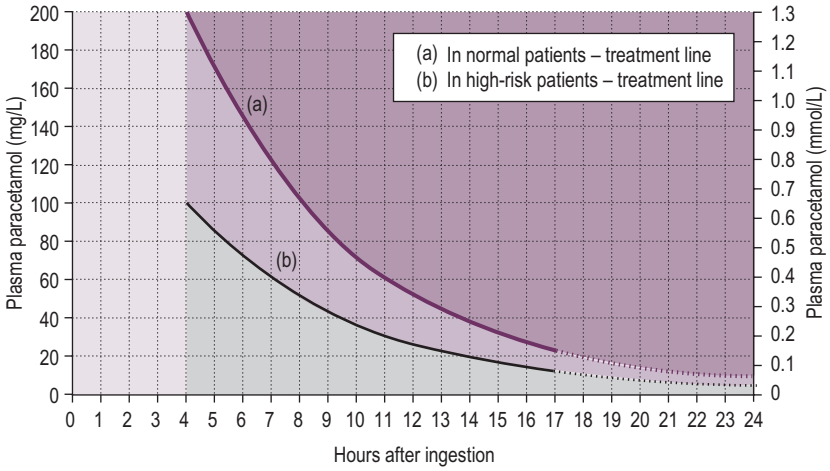


Figure 44.1.2 The Prescott nomogram.

Table 44.1.4 Risk factors for paracetamol hepatotoxicity

DECREASED HEPATIC GLUTATHIONE STORES	INDUCTION OF CYTOCHROME P450
Anorexia nervosa	Phenytoin
Bulimia	Carbamazepine
HIV	Rifampicin
Cystic fibrosis	Phenobarbital
Malnourishment	Long-term ethanol ingestion

HIV, Human immunodeficiency virus.

From Greene SL, Dargan PI, Jones AL. Acute poisoning: understanding 90% of cases in a nutshell. *Postgrad Med J.* 2005;81(954):204–216 (published by BMJ group).

If in doubt, commence treatment. NAC administration can be lifesaving, and adverse reactions and unpleasant side effects are rare.

It should be noted that negative paracetamol levels 16–24 hours after ingestion do not exclude the potential for hepatotoxicity. A staggered overdose is said to have occurred where there have been multiple ingestions over a period of time. Overdoses may be intentional or unintentional. Combined analgesics confer a risk of inadvertent overdose when they are abused for their narcotic content. A clear and detailed history is extremely important.

Patients with features of moderate or severe overdose should be managed in a critical care environment; the importance of early appropriate fluid resuscitation should not be underestimated. Contact should be made with a tertiary centre, and cases discussed with decision to transfer made in a timely fashion.

Early signs of nausea and vomiting after overdose are followed by signs of liver failure (see later) 48–72 hours after ingestion.

ACUTE VIRAL HEPATITIS

Acute viral hepatitis accounts for 40%–70% of patients with ALF worldwide.

Acute hepatitis A virus (HAV) infection rarely leads to ALF (0.35% of infections), but continues to account for up to 10% of cases; morbidity increases with the age of infection. It is hoped that the prevalence will decrease with improving hygiene standards generally and the uptake of vaccination.

Acute hepatitis B virus (HBV) causes 25%–75% of viral hepatitis-induced ALF. The liver injury is immunologically mediated with active destruction of infected hepatocytes. Diagnosis is by the presence of the immunoglobulin (Ig)M antibody to hepatitis B core antigen. Hepatitis B surface antigen (HbsAg) is frequently negative by the time of presentation. Hepatitis B DNA should also be assayed. ALF may also be seen with hepatitis D as either a co-infection or supra-infection.

Re-activation of hepatitis B is an increasing cause of ALF and should always be considered in a patient who has received steroids or chemotherapy. High-risk patients should be screened for sAg and HBV DNA and treated with antiviral agents if they are positive. This is not only a recognised problem in oncology and haematology but also it is a potential risk to patients in intensive care where steroids may be administered.

Hepatitis C virus (HCV) infection is commonly associated with CLD but *not* with ALF. It is detected by the presence of antibodies to HCV in serum. HCV-related cirrhosis will be discussed in detail in the subsequent chapter.

Hepatitis E virus (HEV), like hepatitis A, is transmitted via the faecal–oral route. It is particularly prevalent in the Indian subcontinent and Asia generally and is responsible for sporadic instances of ALF in the Western world. A particular genotype of hepatitis E can be transmitted via blood. HEV can be diagnosed

by the detection of antibodies to HEV in serum. Mortality can be as high as 25% in pregnant women.

Other viruses, such as herpes simplex 1 and 2, varicella zoster virus, cytomegalovirus, Epstein–Barr virus and measles virus, may all rarely cause ALF, but may be seen especially in the immunocompromised patient. Diagnosis is by serological and polymerase chain reaction (PCR) testing. Rift Valley fever, dengue fever, yellow fever, Lassa fever and the haemorrhagic fevers should be considered in those who are at risk.

SERONEGATIVE HEPATITIS

A cause for ALF can be established in approximately 60%–80% of patients.[4] Seronegative hepatitis (so-called) is seen in patients in whom there are no identifiable viral causes or obvious candidate drugs. Such patients may present with a prodromal illness and with acute or subacute manifestations of the disease. Prognosis is poorer than those with an identifiable virus, and once they have poor prognostic criteria the chances of survival without liver transplant are exceptionally small. A subgroup may represent an acute autoimmune form of ALF, although many will not have any positive immune markers such as elevated IgG or positive smooth-muscle or liver kidney antibodies. The pattern of markers shows an increased incidence of autoantibody positivity in seronegative cases and viral cases with elevated IgM in viral causes.[5,6]

DRUG-INDUCED LIVER INJURY (DILI)

Drug-induced hepatitis is responsible for approximately 15%–25% of cases of ALF. In some patients there appears to be a true hypersensitivity reaction, and symptoms develop after a sensitisation period of 1–5 weeks, recur promptly with re-administration of the drug and may be accompanied by fever, rash and eosinophilia. In others the clinical pattern is less acute and liver failure can manifest up to 6 months after exposure. Some herbal remedies are implicated as putative hepatotoxins, but their role is made more difficult to assess by the variable nature of the constituent parts. Halothane hepatitis is now almost unheard of.

RECREATIONAL DRUGS AND LIVER FAILURE

Ecstasy (methylenedioxymethamphetamine) may cause ALF, although, given the prevalence of exposure to the drug, the incidence is presumably low. Proposed mechanisms of injury include immune-mediated mechanisms and/or heatstroke. Cocaine use may result in ischaemic hepatitis. Yellow phosphorus, carbon tetrachloride, chloroform, trichloroethylene and xylene (glue sniffing) are very rare causes of ALF.

AMANITA PHALLOIDES

Mushroom poisoning can be seen even when only very small amounts have been ingested (e.g. *Amanita phalloides*). The initial presentation is often with diarrhoea. Patients subsequently develop signs of hepatic necrosis at 2–3 days after ingestion. The liver injury is caused by amatoxins. Forced diuresis may be helpful as large amounts of toxin are excreted in urine, but inadvertent dehydration may result in renal failure. Thioctic acid, silibinin (silybin) and penicillin have been advocated as therapy, but have not been subjected to controlled trials.

FULMINANT WILSON DISEASE

The characteristic features are those of cirrhosis, seen on imaging, with concomitant problems, such as thrombocytopenia, which may be long-standing, Kayser–Fleischer rings on examination and frequently non-immune-mediated haemolysis.

ACUTE BUDD–CHIARI SYNDROME (HEPATIC VENOUS OBSTRUCTION)

Hepatic venous obstruction (Budd–Chiari syndrome) may cause ALF. There are symptoms and signs of liver of necrosis, often with capsular pain from congestion and ascites. In Asia this may be associated with anatomical anomalies of the inferior vena cava, whereas in Europe and the United States the experience is normally of thrombosis of the hepatic veins, often with an underlying procoagulant condition (Fig. 44.1.3).

ISCHAEMIC HEPATITIS

Heat shock injury is now relatively rarely seen but ischaemic hepatitis remains relatively common. They are normally associated with a congested liver that is subjected to a secondary insult – hypoxia or decreased-flow arterial inflow. This is seen with hypoxaemic respiratory failure, cardiac arrhythmias and hypotension.

PREGNANCY-RELATED ACUTE LIVER FAILURE

Pregnancy-related liver failure includes HELLP (**h**aemolysis [microangiopathic haemolytic anaemia], **e**levated **l**iver enzymes and **l**ow **p**latelets), acute fatty liver of pregnancy and liver rupture, often in association with pre-eclampsia. The prognosis of pregnancy-related ALF is usually good, although some develop severe liver injury with small-vessel disease, liver ruptures may require packing and occasionally transplantation is required (Fig. 44.1.4).

MALIGNANCY

Malignancy may also present with ALF, albeit rarely. The clinical pattern normally is that of elevated biliary enzymes in addition to the transaminases. This pattern of disease may be seen in those with hepatic lymphoma, often with an elevated lactate

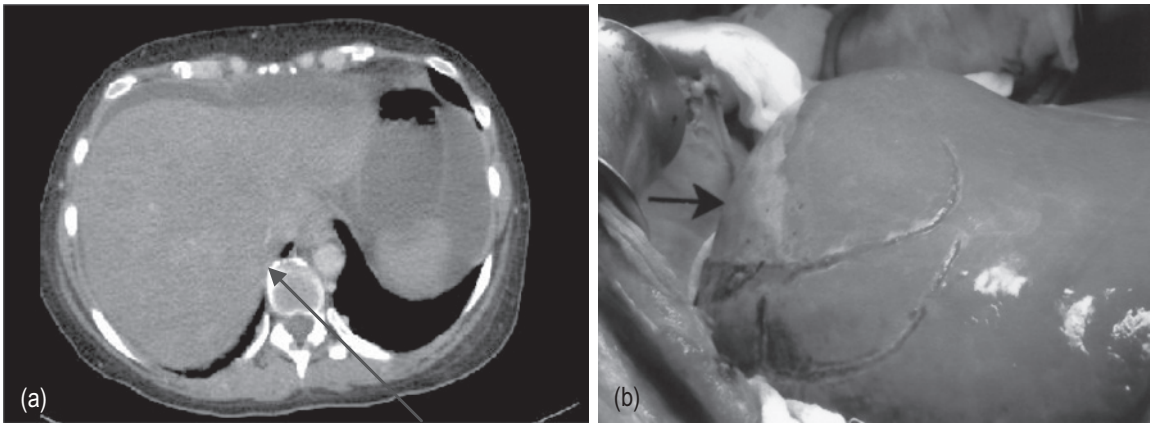


Figure 44.1.3 (a) Acute Budd–Chiari syndrome: The intrahepatic inferior vena cava (*arrow*) is grossly attenuated. (b) Budd–Chiari liver: The *arrow* shows liver necrosis; ischaemic/infarcted liver.

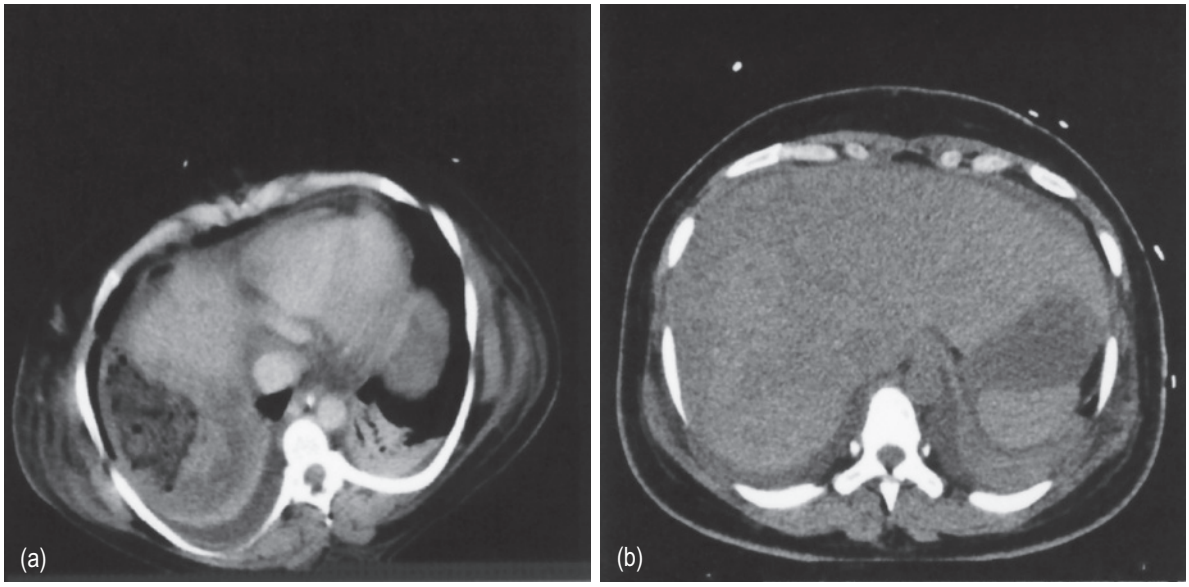


Figure 44.1.4 Liver computed tomography in pregnancy-related liver disease demonstrating abnormal perfusion (a and b) with rupture, packing (a) and associated areas of infarction. Major bleeding into the liver.

dehydrogenase or indeed with diffuse infiltration with other malignancies.

CLINICAL FEATURES

JAUNDICE

The above classification uses the time from jaundice to encephalopathy to describe ALF as either hyperacute, acute or subacute. In hyperacute liver failure (paracetamol toxicity, *Amanita* poisoning, acute viral hepatitis), encephalopathy may precede the onset of clinical jaundice.

ALF is frequently accompanied by a rapidly progressive syndrome of multiorgan failure requiring high levels of organ support.

HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is described by the modified Parsons–Smith scale (Table 44.1.5), which is based on functional impairment, changes in consciousness,

Table 44.1.5 Modified Parsons–Smith scale of hepatic encephalopathy

GRADE	CLINICAL FEATURES	NEUROLOGICAL SIGNS	GLASGOW COMA SCORE
0/subclinical	Normal	Seen only on neuropsychometric testing	15
1	Trivial lack of awareness, shortened attention span	Tremor, apraxia, incoordination	15
2	Lethargy, disorientation, personality change	Asterixis, ataxia, dysarthria	11–15
3	Confusion, somnolence to semi-stupor, responsive to stimuli	Asterixis, ataxia	8–11
4	Coma	±Decerebration	<8

cognitive function and behaviour. The presence of encephalopathy is essential for a diagnosis of ALF.

INTRACRANIAL HYPERTENSION

Hepatic encephalopathy is frequently complicated by cerebral oedema and intracranial hypertension with diminished cerebral perfusion and a risk of transtentorial herniation. The onset is rapid and allows little time for adaptive mechanisms (in contrast to patients with CLD where there is time for adaptation and control of cellular osmolarity). This has a significant implication in terms of the transfer of patients with ALF between hospitals. Intubation and ventilation with adequate sedation and implementation of neuroprotective strategies (see below) should be considered prior to transfer in any patient with progressive encephalopathy.

Patients with high-grade encephalopathy (coma) are at greatest risk of developing cerebral oedema. Elevated arterial ammonia levels, a higher MELD (model for end-stage liver disease) score, younger age, and requirement for vasopressor and renal replacement therapy (RRT) are independent risk factors for hepatic encephalopathy and arterial ammonia levels greater than 200 μmol/L are associated with cerebral herniation.[7,8]

Ammonia is produced by bacteria in the bowel and is taken up by cerebral astrocytes for deamination to glutamine. Water then moves into the intracellular compartment down its osmotic gradient. There are also induced changes in neurotransmitter synthesis and release, mitochondrial function and neuronal oxidative stress. The net result is astrocyte swelling and cerebral oedema.[9,10]

The association between the development of encephalopathy and markers of inflammation is well demonstrated, both in regard to systemic inflammatory response syndrome (SIRS) markers and inflammatory mediators such as tumour necrosis factor (TNF).[11,12] Curiously, a similar relationship between inflammation and encephalopathy is seen in patients with CLD.[13] What is not yet clear is whether treatments that modulate the inflammatory response will be of benefit. This and other avenues proposed from basic animal research may well result in several novel approaches to the treatment of cerebral oedema and possibly encephalopathy over the forthcoming years.

Blood–brain barrier injury, increased cerebral blood flow and hyperaemia accompanying astrocyte swelling can potentiate cerebral oedema independently of astrocyte glutamine concentration. Thus, cerebral oedema may be vasogenic with inflammatory disruption of the blood–brain barrier or cytotoxic with osmotic dysregulation.

Blood flow is intimately coupled to cerebral metabolic rate, arterial oxygen and carbon dioxide tensions and acid-base status. The 'toxic liver hypothesis' describes the situation whereby there is a massive release of pro-inflammatory cytokines in association with the profound systemic inflammatory response and accumulation of toxic metabolites that accompanies ALF. Altered cerebral blood flow and loss of autoregulation occurs in the face of this inflammatory milieu.

The Munro–Kellie hypothesis states that the intracranial cavity is essentially an incompressible box and that any increase in the volume of one of the intracranial components (blood, brain, cerebrospinal fluid) must be accompanied by a decrease in the volume of another. CT studies have demonstrated that effacement and ventricular attenuation are frequent radiological findings.

Diencephalic transtentorial herniation causes posterior cerebral artery insufficiency with temporal, thalamic, and occipital infarction; obstructive hydrocephalus; and brainstem ischaemia, compression and death.

The normal range for intracranial pressure (ICP) is between 7 and 15 mm Hg (0.93–2 kPa) in the supine adult. Many definitions of intracranial hypertension have been volunteered, but a pressure of greater than 20 mm Hg (2.66 kPa) for a period of 20 minutes should be considered worthy of treatment. The US Acute Liver Failure Study Group (USALFG) recommends osmotic therapy for patients with an ICP greater than 25 mm Hg (3.33 kPa).[14]

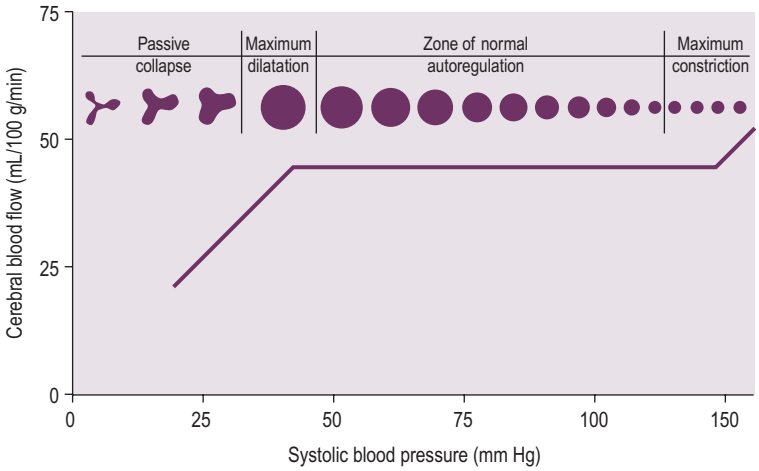


Figure 44.1.5 The relationship between systolic blood pressure and cerebral blood flow. Autoregulation may be lost, however, with flow pathologically dependent on pressure.

The clinical management of the cerebral complications of ALF has been developed pragmatically and by the extrapolation of data from the neurosurgical literature. The use of ICP monitoring is controversial. Advocates would point out that clonus, brisk reflexes and hypertonicity can be detected clinically, but pupillary changes, systemic hypertension and reflex bradycardia are not apparent until intracranial hypertension is established, and that radiographic changes are nonspecific. Sceptics would point out that there is no randomised controlled trial (RCT) evidence supporting an outcome benefit associated with ICP monitoring in ALF and that insertion confers a risk of intracranial haemorrhage. The USALFG found bleeding complications in up to 10% of patients, although many institutions use parenchymal monitors, which may be more accurate but confer a higher bleeding risk. At the authors' institution, standard practice is to use an epidural bolt, which may be slightly less accurate but confers a bleed rate of less than 1%. Bleeding associated with monitor insertion may be minimised by appropriate coagulation support at the time of placement. Some centres support coagulation at the time of insertion with plasma products and platelets, whereas others use recombinant factor VII. Non-invasive methods including transcranial Doppler ultrasonography, tympanometry and optic nerve ultrasound have been used but lack sensitivity and specificity.

Standard practice in the authors' institution is that patients whose conscious level deteriorates to grade 3/4 coma are electively intubated, sedated and ventilated with the head end elevated at 30 degrees. Stimulation is avoided. A combination of opiate (e.g. fentanyl) and propofol is commonly used. The decision to move to ICP monitoring is highly individual and is supported by a hyperacute presentation, younger age and higher arterial ammonia levels (>150 mmol/L). Decision making is frequently supported by reverse jugular venous oximetry and Doppler estimation of middle cerebral arterial flow.

A cerebral perfusion pressure of greater than 50 mm Hg (6.66 kPa) has been suggested as optimal. It is of note that patients with ALF often do not autoregulate to pressure and consequently increases in blood pressure may be associated with increased cerebral blood flow and potentially increased ICP, particularly if they are at a critical point on their pressure–volume curve. Sustained cerebral perfusion pressures less than 40 mm Hg (5.33 kPa) have been associated with very poor outcomes in some studies,[15] whereas others report good outcome despite periods of cerebral hypoperfusion (Fig. 44.1.5).

Invasive cardiovascular monitoring is mandatory (the authors advocate flow monitoring to guide fluid resuscitation). Norepinephrine (noradrenaline) and vasopressin are commonly used pressor agents. The use of terlipressin was associated with a rise in ICP in one study.[13]

In most patients, maintenance of P_{CO_2} 4.5–5.0 kPa is considered ideal. Cerebral blood flow is intimately coupled to arterial carbon dioxide tension and minute ventilation must therefore be carefully controlled. Lung injury/acute respiratory distress syndrome (ARDS) is relatively common and so protective ventilation strategies should be utilised.

Hyponatraemia and hyperammonaemia have been shown to be detrimental, whereas an RCT showed benefit to the patients whose serum Na was maintained between 145 and 155 mmol/L.[4] The use of hypertonic saline has been associated with a significant reduction in ICP, although the same study was not powered to detect a difference in outcome.

First-line treatment of a sustained rise in ICP remains mannitol 0.5 g/kg given as a bolus with an appropriate subsequent diuresis. It is essential that serum osmolarity is maintained at less than 320 mOsm

to avoid damage to the blood–brain barrier and worsening of vasogenic oedema. Hypertonic saline is increasingly used in this setting.

Hypothermia has been shown to reduce cerebral blood flow, ICP and cerebral ammonia uptake.[16,17] The role of hypothermia as an early preventive intervention in grade III/IV coma is contentious and the results of controlled studies are awaited. Fever should be avoided.

Other treatment options that have been shown to be potentially beneficial are thiopental and intravenous indomethacin (0.5 mg/kg).[18] Potential monitoring and treatment algorithms, as used by this unit, are detailed in Fig. 44.1.6.

SEPSIS

Sepsis is common in ALF and both culture-positive and negative SIRS are seen. Patients are functionally immunosuppressed in terms of impaired cell-mediated immunity, complement levels and phagocytosis.[17] Functional immunoparesis can only be observed and depression of human leucocyte antigen (HLA) DR expression correlates with the prognosis and severity of liver injury.[20,21] As such, scrupulous attention with regard to hand washing and line care needs to be applied to decrease the risk of nosocomial infection. Regular culture screens are required and antimicrobials are indicated in patients with any clinical suggestion of sepsis. Prophylactic intravenous antifungals should be considered, especially in those listed for transplantation. The choice of antimicrobial agent should be driven by local resistance patterns. Antimicrobial therapy should be reviewed in the light of culture results on a daily basis.

COAGULOPATHY

Coagulopathy is the hallmark of ALF, with prolongation predominantly of the prothrombin time and to lesser degrees the activated partial thromboplastin ratio (APTR). In a small percentage of patients the coagulopathy will respond, at least partially, to vitamin K. Intravenous vitamin K 10 mg is normally administered. Thrombocytopenia is common and frequently consumptive in nature. Bleeding is rare, although it may be seen in those with severe prolongation of APTR, low fibrinogen and severe thrombocytopenia. Coagulation or repletion of coagulation factors is necessary for clinical bleeding and prophylactically before major invasive procedures. Coagulation support is normally not given routinely so that the international normalised ratio (INR) can be monitored with regard to prognosis.

CARDIOVASCULAR CONSIDERATIONS

Patients with ALF develop a hyperdynamic circulation with peripheral vasodilation and central volume depletion. Hypotension is common and may initially respond to volume repletion. Assessment of volume responsiveness in the clinical setting may be difficult and pressure measurements are a poor indicator of volume status. Hypotension that does not respond to volume will normally require some form of invasive haemodynamic monitoring and frequently the institution of vasopressor agents. Increasingly it is recognised that volume responsiveness, as in general intensive care unit (ICU) patients, is best determined by dynamic rather than static variables.

The requirement for pressor agents should raise the possibility of adrenal dysfunction. Patients with ALF have been demonstrated to have impaired responses to adrenocorticotropic hormone (ACTH).[22,23] The response at 30 and 60 minutes in terms of cortisol should be examined following 250 µg ACTH in all patients with ALF who are requiring pressor agents. A subnormal response should result in consideration of hydrocortisone replacement therapy, normally given for a period of 10 days. Interestingly, adrenal dysfunction has similarly been reported in acute-on-chronic liver failure, and steroid replacement may result in improved outcome.[23,24]

Elevated troponin levels can be observed in patients with liver failure, especially those with cardiovascular failure.[25]

RESPIRATORY CONSIDERATIONS

Ventilatory support is frequently required in patients with ALF, usually because of a decreased conscious level rather than hypoxia, at least in the initial stages of disease.

Common respiratory complications are pleural effusions, atelectasis and intrapulmonary shunts. ARDS and acute lung injury may be seen and can be precipitated by extrapulmonary sepsis or inflammation.

Ventilatory strategies are influenced by both the respiratory and the multiorgan involvement that is characteristic of ALF. Thus patients with deep levels of coma and who are at risk of cerebral oedema will require close attention to CO_2 levels and tailored sedation regimens. Hypercapnia may have to be tolerated in patients progressing to ARDS. This requires balancing against the cerebral needs of these patients as hypercarbia and increased cerebral blood flow will tend to increase ICP. Pleural effusions may require drainage if they are impeding ventilation. Weaning may be facilitated by undertaking tracheostomy during the recovery period of ALF.

RENAL CONSIDERATIONS

Renal failure is common, with an incidence as high as 50%. Incidence is even higher up to 75% with paracetamol-induced liver failure, where the drug may also exert a directly toxic effect on the renal

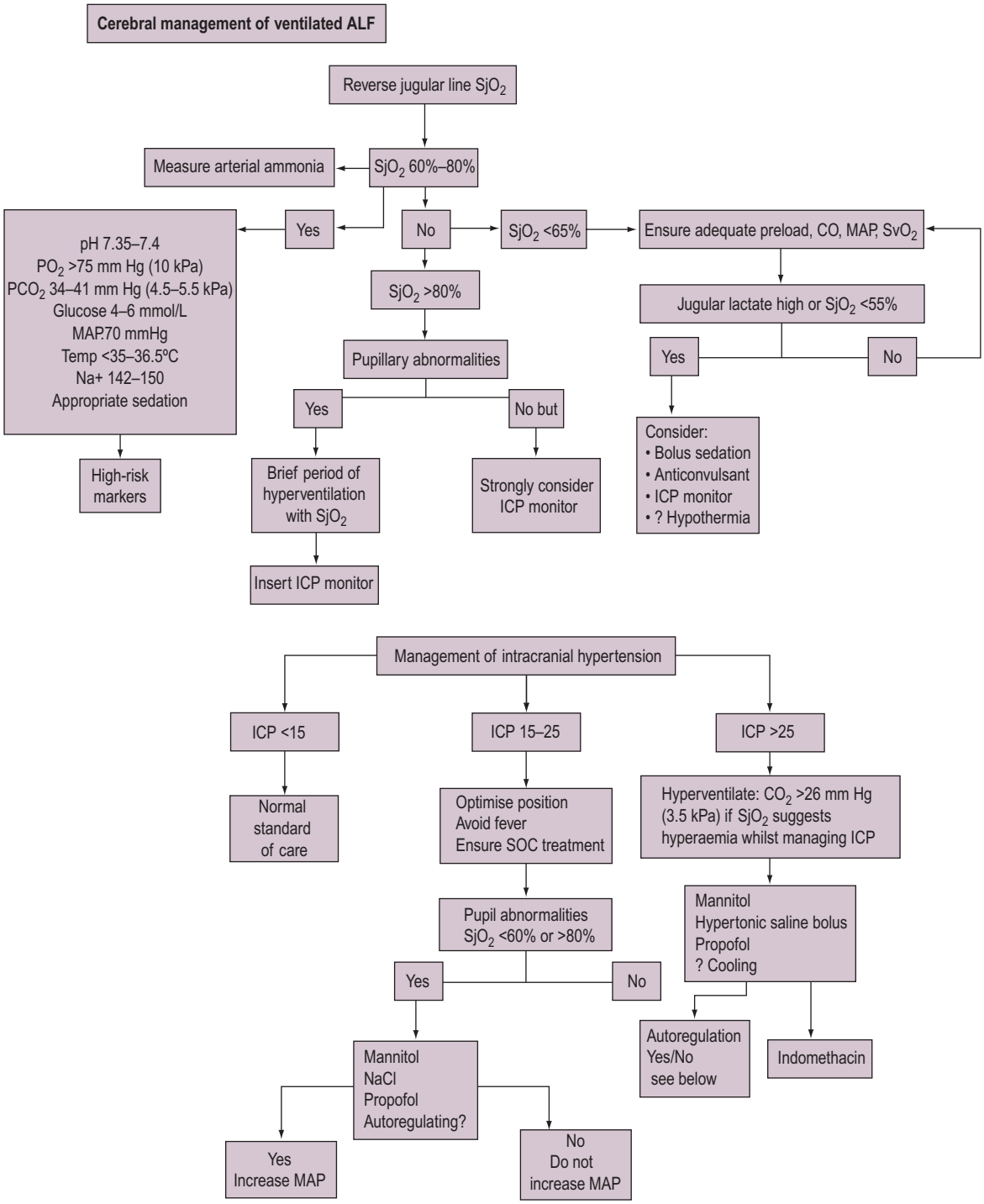


Figure 44.1.6 Treatment of raised intracranial pressure. *ALF*, Acute liver failure; *CO*, cardiac output; *ICP*, intracranial pressure; *MAP*, membrane-associated protein; *SjO_2*, jugular venous oxygen saturation; *SOC*, Standard of Care; *SvO_2*, venous oxygen saturation.

tubule.[26] The aetiology of acute renal dysfunction is frequently multifactorial, with hepatorenal failure being a rare occurrence. Acute tubular necrosis (ATN) and pre-renal renal failure are common. As such, volume therapy and maintenance of intrathoracic blood volume are essential in the management of such patients, as is the avoidance of nephrotoxins. Intra-abdominal hypertension is frequent and may reduce renal perfusion pressure and contribute to renal dysfunction; the measurement of intra-abdominal pressure may be a valuable component of monitoring.

Established renal failure requires the institution of RRT. In patients with ALF early consideration should be given to RRT to control fluid balance and acid-base disturbances and to avoid rapid changes in osmolarity. It may limit or control elevations of arterial ammonia and retard the development of cerebral complications. The haemodynamic instability and associated cerebral complications of this patient group have resulted in the application of continuous modes of RRT rather than intermittent haemodialysis. The inability of the liver to metabolise and utilise lactate or acetate buffer solutions results in the use of bicarbonate buffers.

A balance needs to be achieved between the risk of bleeding and platelet protection across an extracorporeal filter. A prostaglandin, such as epoprostenol, may be advantageous in terms of decreasing bleeding and prolonging filter life. Alternatively, circuits may be run without anticoagulation, with regional heparin or citrate or low-dose systemic heparin. In patients with thrombocytopenia, consideration should be given to the diagnosis of heparin-induced thrombocytopenia and, if confirmed, heparin should be withdrawn and circuits primed with an alternative agent (e.g. danaparoid).

METABOLISM AND FEEDING

Enteral nutrition should commence as soon as feasible after admission if there are no contraindications. In patients with large aspirates (>200 mL/4 h) a prokinetic agent should be commenced: erythromycin (250 mg intravenously 6-hourly) appears to be more effective than metoclopramide. Endoscopic placement of a post-pyloric feeding tube should be considered in refractory cases, although this may need to be delayed in patients with or at risk of cerebral oedema. In patients with profound coagulopathy, placement of a nasogastric tube may be associated with nasal/pharyngeal bleeding and oral tube placement may be preferred in ventilated patients. The optimal nature of the enteral feed used has not been investigated, but metabolic data on these patients show increased calorific requirements.[27,28] Patients with ALF demonstrate both peripheral and hepatological insulin resistance.[26] Tight glycaemic control would seem reasonable in this population. Hypokalaemia is common and may contribute to increased renal ammonia production.

Metabolic acidosis is a relatively frequent occurrence that may relate to lactic acidosis, hyperchloraemic acidosis or renal failure.

Hyperlactataemia may be secondary to volume depletion and hence will resolve with appropriate fluid loading or may reflect the inability of the liver to metabolise the lactate produced. A failure of blood lactate to normalise following volume loading is associated with a poor prognosis.[29,30] Metabolic acidosis may be a secondary effect of other drugs ingested as part of an episode of self-harm. Falls in serum phosphate levels are seen in ALF associated with liver regeneration and are associated with a good prognosis in paracetamol-induced ALF.[31] Pancreatitis is a common complication of ALF and should be actively sought.

SPECIFIC TREATMENTS

The management of ALF is largely supportive, providing an optimal environment for either regeneration or stability until a suitable liver becomes available. Once patients develop poor prognostic criteria the chances of effective liver regeneration and thus of spontaneous recovery are low; the prognosis is very poor without liver transplantation. The role of extracorporeal liver support systems remains a hope for the future, but at present no system has been shown to have a definitive survival benefit in a controlled trial.

- *N*-acetylcysteine is administered for paracetamol-induced ALF, as mentioned above. Its role in non–paracetamol-induced ALF remains undefined, although a US study[32] suggests that it may be of benefit in patients with ALF and grade 1–2 encephalopathy (presumably because transplantation is required to impact on the outcome when higher grades of encephalopathy are achieved).
- Chelating agents are not of benefit in patients with established ALF secondary to Wilson disease, but they play an important role in chronic presentations. The withdrawal of such treatments, or indeed non-compliance – especially in teenagers – may precipitate ALF.
- Antiviral therapy has a predominant role in preventing re-activation of hepatitis B in patients exposed to chemotherapy and steroids.
- Thrombolytic therapies may be of benefit in patients with early acute Budd–Chiari syndrome, although increasingly the treatment option would be to undertake a transhepatic portosystemic shunt (TIPS), decompressing the liver with a stent passed either through the hepatic vein (if the clot is soft enough) or via the inferior vena cava and through to the portal vein. Such procedures should be undertaken in units with the facilities to transplant as there is a risk of precipitating ALF. Chemotherapy may be offered

to those with lymphoma involving the liver and in these instances tissue is paramount, either of liver or from another diagnostic site.
- Steroid therapy is beneficial in acute autoimmune hepatitis but its role in autoimmune ALF has been less clear. A recent publication from the Paris group suggests that steroids for those with established ALF are potentially detrimental.[33]

PROGNOSIS

Prognostication is important in the management of ALF. Overall, survival rates in patients treated for ALF are greater than 60%.[34,35] It is essential not only to identify those patients who will not survive without liver transplant, but also to identify those who will succumb even if offered such a procedure.[36] Approximately 55% of patients will survive without needing a liver transplantation.[35]

Several risk stratification systems are presented in Box 44.1.2. The most commonly used are those of O'Grady and Clichy. The MELD has also been examined with regard to prognosis in ALF and may be particularly useful in non-paracetamol cases.[37] The Sequential Organ Failure Assessment (SOFA score) and the Acute Liver Failure Study Group (ALFSG) index are also used. It is essential that such systems are rigorously applied and in the context of paracetamol are only utilised at least 24 hours post-ingestion and following appropriate volume resuscitation.

44.2 CIRRHOSIS AND ACUTE-ON-CHRONIC LIVER DISEASE

CLD is said to be evident when liver dysfunction has been present for a period greater than 6 months. It presents far more commonly to the ICU than does ALF. Acute on chronic liver failure (ACLF) is a specific syndrome characterized by acute decompensation (AD), organ failure (OF) and high short-term mortality. AD refers to development of ascites, encephalopathy, gastrointestinal hemorrhage and/or intercurrent bacterial infections. OFs (liver, kidney, brain, coagulation, respiration, circulation) are defined by the CLIF-SOFA score (CLIF stands for chronic liver failure) (Box 44.2.1). High short-term mortality means a 28-day mortality rate ≥15%.[38] Acute decompensations in hepatic and extrahepatic organ function in the previously stable cirrhotic are frequently precipitated by infection and bleeding (often variceal), but may also reflect a trajectory of decline in liver function in a patient with end-stage disease. Acute decompensations are termed ACLF.

Box 44.1.2 Prognostic criteria for acute liver failure

O'Grady criteria
Paracetamol related
Acidosis (pH <7.3), *or*
Prothrombin time of >100 s (INR >6.5), creatinine > 300 mol/L and grade III/IV encephalopathy – all occurring within a 24-h timeframe
Non–paracetamol-related
Any three of the following in association with encephalopathy:
- Age <10 or >40 years
- Bilirubin >300 mol/L
- Time from jaundice to encephalopathy >7 days
- Aetiology: either non-A, non-B (seronegative hepatitis) *or* drug-induced
- Prothrombin time >50 s, *or*
- Prothrombin time >100 s/INR >6.5

French criteria (Clichy criteria)
The criteria are the presence of encephalopathy (coma or confusion), *and*
Age <20 years with factor V level <20%, *or*
Factor V levels <30% if >30 years of age 59

INR, International normalised ratio.

Box 44.2.1 CLIF Consortium Organ Failure score: simplified version of the CLIF-SOFA score

Organ/system	Variable	Score = 1	Score = 2	Score = 3
Liver	Bilirubin (mg/dl)	<6	6 to ≤12	>12
Kidney	Creatinine (mg/dl)	<2	2 to <3.5	≥3.5 or RRT
Brain	Encephalopathy grade (West Haven)	0	1–2	3–4
Coagulation	INR	<2	2 to <2.5	≥2.5
Circulation	MAP (mm Hg)	≥70	<70	Vasopressors
Respiratory	PaO_2/FiO_2	>300	≤300 and >200	≤200

CLIF, Chronic liver failure; *FiO_2*, fraction of inspired oxygen; *INR*, international normalised ratio; *MAP*, mean arterial pressure; *PaO_2*, partial pressure of arterial oxygen; *RRT*, renal replacement therapy; *SOFA*, sequential organ failure assessment.
Reproduced from Hernaez R, Solà E, Moreau R, Ginès P. Acute-on-chronic liver failure: an update. *Gut* 2017;66:541–553. doi:10.1136/gutjnl-2016-312670.

Box 44.2.2 Common aetiologies of chronic liver disease

- Chronic infection with hepatitis B and C viruses
- Alcohol
- Primary biliary cirrhosis
- Autoimmune chronic active hepatitis
- Primary sclerosing cholangitis
- Budd–Chiari syndrome
- Veno-occlusive disease
- Amyloidosis
- α_1-antitrypsin deficiency
- Wilson disease

AETIOLOGY OF CHRONIC LIVER DISEASE

There are myriad causes of CLD. Those most frequently encountered are listed in Box 44.2.2. It is beyond the scope of this chapter to discuss these in any depth, but we will focus on the management of decompensations, complications and extrahepatic organ failure.

The ICU physician is seldom involved in the management of stable CLD. Acute on chronic presentations are relatively common, however, and patients with previously unrecognised cirrhosis may decompensate following unrelated medical interventions. Wherever possible, planned interventions in patients with documented cirrhosis should be undertaken in specialist centres with appropriated peri-procedural supervision.

DECOMPENSATED CHRONIC LIVER DISEASE

ACLF commonly presents with one of the following:

- encephalopathy
- sepsis
- renal failure
- variceal bleeding
- cardiorespiratory failure.

The cause of decompensation should be sought in all cases when it is not clinically apparent. In addition to sepsis and bleeding, alcohol, dehydration, drug therapies (e.g. opiates and sedatives), hepatocellular carcinoma (HCC) and portal vein thrombosis should be considered. Ultrasound should be undertaken in all patients, examining the hepatic veins and portal veins for patency. In patients with ascites a diagnostic tap should always be undertaken for microbiological culture and cell count (a polymorphonuclear [PMN] count >250 mm^3 is indicative of bacterial peritonitis).

Signs of HCC should be sought on ultrasound, alpha-fetoprotein and axial imaging techniques. The therapies available for HCC have improved dramatically in recent years and prognosis can be good, especially with the option of cure with liver transplantation.

ENCEPHALOPATHY IN CHRONIC LIVER DISEASE

Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and/or portosystemic shunting; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.[39] Overt hepatic encephalopathy (OHE) will occur in 30%–40% of those with cirrhosis at some time during their clinical course and in the survivors in most cases repeatedly.[40] It may manifest as inattention, retardation in psychomotor speed and visuospatial ability progressing through personality changes and disturbance of the sleep–wake cycle to acute confusion with agitation, somnolence and coma. The International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus uses the onset of disorientation or asterixis as the onset of OHE. Hepatic encephalopathy is frequently seen in patients with cirrhosis and a systemic inflammatory response (and so sepsis should be actively sought and treated). Encephalopathy in CLD has pathophysiological and clinical features that are different from those seen in ALF. Importantly, the cirrhotic cohort does not normally develop intracranial hypertension and, as such, the management centres on the prevention of encephalopathy, the treatment of worsening encephalopathy, the control of the airway and the prevention of aspiration in those who are deeply encephalopathic.

Ammonia levels are frequently (but not always) elevated in encephalopathy and thus therapy includes bowel cleansing with agents such as lactulose and non-absorbable antibiotics such as rifaximin. There is little evidence-based research to support any particular avenue of treatment. Increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with CLD. A normal value calls for diagnostic reevaluation.[39]

A systematic review by Tsipotis et al. showed that extracorporeal liver support using albumin dialysis resulted in a net decrease in serum bilirubin level but not in serum ammonia or bile acids and although it achieved an improvement in hepatic encephalopathy relative to standard medical therapy, it did not result in increased survival.[41]

The role of inflammation seems to be of importance in the development of encephalopathy.[42,43] As many as 70% of patients with bacteraemia demonstrate a 'septic encephalopathy', which manifests as lethargy, confusion, agitation or even coma. The inflammatory response develops when inducers of inflammation are recognized by sensors that engage effectors of the response.[44] Microbial inducers trigger inflammation by using pathogen-associated molecular patterns (PAMPs) and virulence factors. PAMPs are unique molecular signatures that are recognized by pattern-recognition receptors (PRRs) which include toll-like receptors (TLRs). Virulence factors are detected

through the effects of their activity (functional feature recognition). Endogenous inducers called danger-associated molecular patterns (DAMPs) released by necrotic cells are recognized by host receptors inducing sterile inflammation.[45] The immune system then mounts a systemic response to fight the invading microbe. The final pathway is to induce responses to eliminate the invading microbe. This early systemic response can be excessive and lead to organ damage and multiorgan failure through a process called immunopathology.[45] There is some evidence that pro-inflammatory mediators mobilised during SIRS/sepsis modulate the action of ammonia on the brain. In 2004 Shawcross et al.[43] demonstrated that neuropsychological test scores deteriorate when hyperammonaemia is induced in cirrhotics with infection, during the inflammatory state, but not following its resolution. This synergism may be attributed to a number of possible mechanisms[46]:

- Systemic inflammation and ammonia induce neutrophil degranulation and release reactive oxygen species into peripheral circulation which may then cross the blood brain barrier.[47]
- Circulating endotoxin arising from the gut (bacterial translocation), superimposed sepsis and hyperammonemia upregulate the expression of microbial pattern recognition receptors such as Toll-like receptors (TLRs).[47]
- Dysregulation of cerebral blood flow, which occurs in cirrhosis, may be exaggerated in sepsis.

The prognosis in cirrhotic patients with sepsis is considerably worse following the onset of encephalopathy.

The role of feeding in the development of encephalopathy has always caused controversy. Recent guidance suggests that protein restriction is not appropriate and a study examining early versus slow introduction of protein into enteral nutrition showed no increase in encephalopathy and indeed appeared beneficial in respect of the nitrogen balance.[48,49]

SEPSIS IN CHRONIC LIVER DISEASE

A classical definition of sepsis is SIRS in response to a proven or suspected microbial event. This definition may not be universally applicable, however. The compensated and decompensated cirrhotic may demonstrate components of SIRS under resting conditions. For example, cirrhotics often have an elevated resting heart rate with a hyperdynamic circulation, hyperventilation due to the evolution of hepatic encephalopathy and reduced baseline PMN count owing to hypersplenism. Indeed, the response of the cirrhotic patient to infection may be characterised only by an exacerbation of circulatory changes already present at baseline, or may be distinctly uncharacteristic with, for example, blunting of the elevation in body temperature, which is usually seen in sepsis.

The mortality of cirrhotic patients who fulfil SIRS criteria is significantly higher than in those who do not,[50] and a majority of those with SIRS have intercurrent infection. It is often unclear whether SIRS acts as a predisposition to, or is a consequence of, infection in this cohort. In one retrospective analysis of non-transplanted patients with ACLF, bacteraemia was associated with increased illness severity, requirements for organ support, and mortality.[51] The same group found that severity of hepatic encephalopathy and SIRS score greater than 1 were predictive of bacteraemia.[52]

Bacterial infections are more common in cirrhosis than in the general population, and are higher still during episodes of decompensation. Cirrhotic individuals are significantly more likely to die while hospitalised (adjusted risk ratio [RR] 2.7), to have hospitalisations associated with sepsis (adjusted RR 2.6) and to die from sepsis (adjusted RR 2.0).[53]

The increased incidence of sepsis in those with underlying liver disease is multifactorial. Patients are frequently physically debilitated, deconditioned, malnourished and cachectic. Bactericidal and opsonic activity is reduced. Monocyte function is altered and there is depression of the phagocytic activity of the reticuloendothelial system owing to the presence of intra- and extrahepatic shunts through sinusoids without Kupffer cells, and reduced Kupffer cell numbers and function.[54] Serum complement levels are low. Ascites and peripheral oedema are often present, and iatrogenic factors may be contributory. There may be an associated genetic susceptibility to severe infection and sepsis.

The acquisition of a sepsis syndrome is frequently accompanied by encephalopathy, renal failure and worsening coagulopathy. The in-hospital mortality of septic cirrhotics is, accordingly, much higher and has been recently estimated at 70%,[55] and infection is responsible for 30%–50% of deaths in patients with cirrhosis.[56]

The main sites of infection in cirrhosis are ascites, urinary tract, lungs and blood. The commonest organisms are *Escherichia coli*, followed by *Staphylococcus aureus*, *Enterococcus faecalis, Streptococcus pneumoniae, Pseudomonas aeruginosa,* and *Staphylococcus epidermidis*. However, resistant Gram-positive organisms and extended spectrum beta lactamase (ESBL)-producing enterobacteria are becoming increasingly common (particularly in nosocomial infection). Cephalosporins therefore fail in a substantial proportion of infections acquired during hospitalisation.

The epidemiology of sepsis in cirrhosis is in a state of flux. Resistant organisms are increasing in prevalence both in nosocomial infection and in patients who require long-term antibacterial prophylaxis. Liver transplantation programmes have given chronic

cirrhotics a chance of salvation, and encourage physicians to treat episodes of sepsis more aggressively than ever before. Surveillance and early diagnosis of infection, coupled with adequate and appropriate antibiosis have led to improved outcomes in cirrhotic patients with spontaneous bacterial peritonitis (SBP) and other severe infections.

An enhanced inflammatory response can cause an exaggerated and damaging inflammatory response that may provoke single or multiple organ failures. Organ failure is an important determinant of outcome in patients with cirrhosis, with mortality increasing with the number of organ systems failing. Single-organ failure confers a mortality of 33%, double-organ failures a mortality of 73% and three-organ failure a mortality of 97%.[57,58]

Tissue hypoperfusion occurs secondary to systemic hypotension, microvascular dysfunction, shunting, microthrombi formation, vasoplegia, and reduced red blood cell deformity and tissue oedema. NO synthesis may be responsible for defective mitochondrial respiration. Direct tissue damage is caused by cellular infiltrates, particularly neutrophils releasing lysosomal enzymes and superoxide-derived free radicals.[59]

PATHOPHYSIOLOGY OF SEPSIS IN CIRRHOSIS

ENDOTOXIN SIGNALLING

The interaction between PAMPs (e.g. lipopolysaccharide on the outer membrane of Gram-negative bacteria) and PRRs leads to immune cell activation, initiation of pathogen clearance and secretion of proinflammatory cytokines culminating in T cell activation (Fig. 44.2.1).[60] Macrophages of the M1 phenotype release inflammatory mediators like TNF, IL-1B, IL-6 and IL-8 resulting in upregulation of adhesion molecules by endothelial cells, neutrophil recruitment and containment of the infection. The M2 phenotype is activated in the presence of IL-4 and IL-13. Disorganisation of the macrophage phenotypes in the presence of a programmed cell death protein receptor (PD-1R) intensifies the inflammatory response and suppresses macrophage function. This leads to an immunocompromised state.[60]

The Gram-negative flora of the intestine provides a reservoir of LPS. LPS is absorbed and transported in the portal vein where it is rapidly cleared by Kupffer cells. Under normal circumstances the liver does not show signs of excessive inflammation. In addition to its ability to clear LPS, the liver also responds to LPS

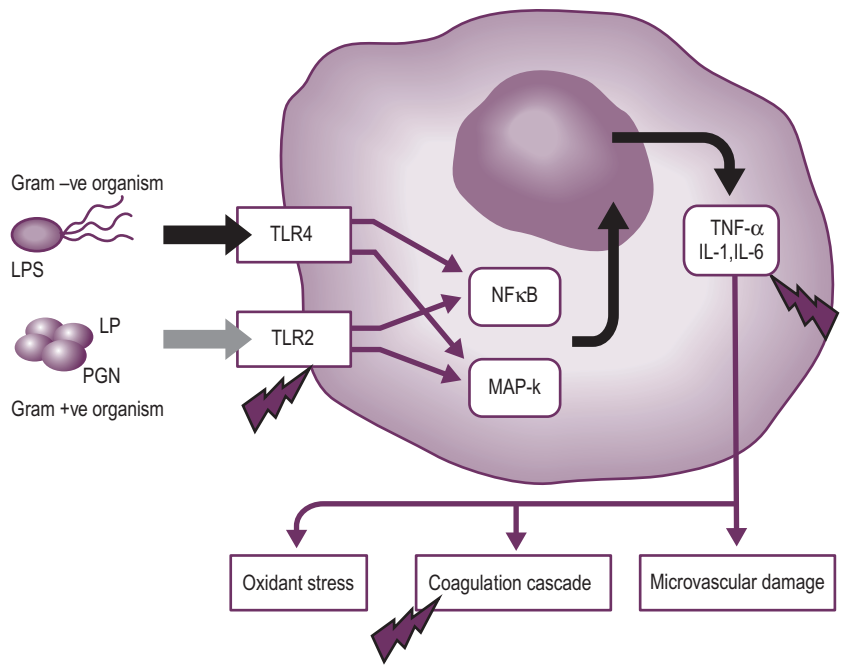


Figure 44.2.1 Endotoxin signalling pathway. The flashpoints represent changes in cirrhosis that make patients more susceptible to infection. *IL*, Interleukin; *LP*, lipopeptide; *LPS*, Lipopolysaccharide; *MAP*, membrane-associated protein; *NFκB*, nuclear factor-κB; *PGN*, peptidoglycan; *TLR*, Toll-like receptor; *TNF*, tumour necrosis factor. *Reproduced with permission from Wong F, Bernardi M, Balk R, et al. Sepsis in cirrhosis: report on the 7th meeting of the International Ascites Club.* Gut. *2005;54:718–725.*

with the production of cytokines and reactive oxygen intermediates, primarily by Kupffer cells.

In many types of CLD, levels of endotoxin[61] are elevated and tend to increase progressively as liver function deteriorates. Mortality is higher in patients with significant endotoxaemia than in those without.[62]

Cytokines, such as TNFα, IL-6 and IL-1 are essential components of the immune defence mechanism, but may propagate overwhelming septic shock. These may be over-produced and/or up-regulated in CLD, although the absolute levels of inflammatory cytokines are extremely variable in cirrhotic cohorts with septic complications. NO production is enhanced in cirrhosis, and is further increased in sepsis, with the induction of NO synthase by LPS exacerbating tissue hypoperfusion.

BACTERIAL TRANSLOCATION

Bacterial translocation is the migration of bacteria or bacterial products from the intestinal lumen to mesenteric lymph nodes or other extraintestinal organs and sites.[63] As mentioned above, elevated levels of endotoxin are a frequent finding in CLD, and levels tend to increase with disease severity (Child classification). Chromogenic assay in patients undergoing angiographic intervention demonstrates a gradient in terms of endotoxin level between portal and systemic circulations,[64] suggesting that the bowel is the source of the endotoxaemia. Moreover, only a single layer of intestinal epithelial cells form a barrier between the sterile host and trillions of live bacteria.[65]

Small bowel hypomotility, alterations in intestinal flora and disruption of mucosal barrier function promote bacterial translocation in the cirrhotic population. It is proposed that bacterial translocation is one of the main causes of spontaneous infection in this cohort and may perpetuate the persistent hyperdynamic state. Portal hypertension, ascites and increased severity of liver dysfunction are risk factors for bacterial translocation in this cohort. The epithelium demonstrates structural changes in cirrhosis, with widening of the intercellular spaces, and there is increased intestinal permeability.[66] Intestinal permeability is increased with portal hypertension (NO may be implicated in disruption of the intestinal epithelium).[67] Permeability is increased further if there is concomitant alcohol intake.

Organisms are usually removed from intestinal tissue by phagocytes. The intestinal immune system is centred on the gut-associated lymphoid tissue (GALT), which is comprised of Peyer's patches, lamina propria lymphocytes, intraepithelial lymphocytes and mesenteric lymph nodes. The innate immune response is centred on the stimulation of TLRs, a cytokine response and bacterial killing by monocytes and lamina propria lymphocytes. Under normal circumstances, any organism breaching the intestinal mucosal barrier is killed. Thus, in order for translocation to become clinically significant, there needs to be an overall failure of local and systemic immune defence.

The currently available therapies are directed towards reducing translocation by promoting gut motility, decreasing bacterial overgrowth or changing the composition of the gut flora. Selective digestive decontamination has been shown to be effective in preventing infection in patients with gastrointestinal haemorrhage,[68] and in prophylaxis in patients with ascites.

IMMUNE PARESIS

As stated above, there is up-regulation of TLRs, increased levels of circulating cytokines and activation of monocytes in cirrhotics. This does not, however, correspond to increased bacterial killing. Rather, the innate immune system is impaired with decreased phagocytosis and opsonisation.[63] This has been described as a 'sepsis-like immune paralysis'.[69]

GENETIC SUSCEPTIBILITY

It is recognised that a genetic variables may confer a predisposition towards the acquisition of infection in cirrhotic patients.

The management of sepsis in patients with liver failure should proceed along the same lines as in the cohort without liver failure. However, consideration should be given to some of the issues outlined below, which are peculiar to this population.

MANAGEMENT OF SEPSIS IN CIRRHOSIS

The principles of early goal-directed therapy in the treatment of sepsis are valid; that is, the early restoration of the circulating volume and maintenance of an adequate cardiac output, but the manner by which adequacy is assessed is complex. The circulation is frequently hyperdynamic in patients with acute or chronic liver failure – with or without infection. The oxygen extraction ratio is not uniform and shunting may occur. As a consequence, central venous oxygen saturations may be artificially high and not representative of an inadequately resuscitated patient. Early goal-directed therapy titrated to central venous oxygen saturation as outlined by Rivers et al.[70] may therefore not be applicable to this cohort. Furthermore, the use of the central venous pressure has been demonstrated to be unreliable[71] as a marker for preload-responsiveness. The authors would therefore advocate the early use of a cardiac output monitor, several of which are in widespread use. These provide markers of preload and preload responsiveness. Stroke volume response to fluid challenge or passive leg raising may be used in the mechanically ventilated or the spontaneously breathing patient.

Lactate levels have been used as markers of the adequacy of fluid resuscitation in sepsis.[72] In sepsis, lactate levels are elevated due to a higher metabolic rate and the inhibition of pyruvate dehydrogenase, and reflect

uptake by the liver. In liver disease, this uptake is markedly diminished and elevated lactate levels may not therefore imply anaerobic metabolism. Lactate levels are thus inadequate markers in this cohort, although elevated levels still unquestionably identify the sicker patients.

In terms of fluid resuscitation, albumin does not confer a mortality benefit over crystalloid in the critically unwell cohort. It does have a specific role in the treatment of patients undergoing large-volume paracentesis and has been demonstrated to preserve haemodynamics and attenuate a tendency towards hepatorenal syndrome (HRS).[73,74] A small, non-blinded, RCT suggested that 20% albumin was more effective in terms of improving systemic haemodynamics than a 6% hydroxyethyl starch (HES) solution in SBP.[75]

Vasopressor therapy is often required for the maintenance of adequate mean arterial pressure. Norepinephrine (noradrenaline) is the most frequently used pressor agent in the author's unit, with α-agonism attenuating a vasodilated, hyperdynamic systemic circulation and β-agonism augmenting ventricular function (which is frequently impaired in this cohort). Dopamine has no benefit over norepinephrine in the critically unwell and may be associated with a greater number of adverse events.[76] It is also not preferred in the liver failure cohort as it may cause dilatation of the superior mesenteric artery, leading to increased portal pressures. Vasopressin is used in refractory shock and to mitigate very high norepinephrine requirements.

In general terms, ventilatory management should proceed as per management in the general intensive care cohort, with attention paid to protective ventilatory strategies if ARDS is clinically apparent (limiting tidal volumes to ~6 mL/kg and plateau pressure to <30 cmH_2O). Endotracheal intubation is performed for airway protection in advanced (grade III/IV) encephalopathy and for the treatment of respiratory failure. It is worth noting that raised ICP is not normally a feature of CLD.

Both ALF and chronic cirrhosis are hypermetabolic states with marked catabolism and a net negative nitrogen balance. Assessment of the degree of malnutrition and muscle wasting in the chronic cirrhotic is often difficult owing to the presence of ascites and oedema. Dysphagia and gastroparesis are common in patients with cirrhosis and portal hypertension,[77] and the development of encephalopathy of any grade may be associated with a risk of aspiration. In both sepsis and liver failure the potential for both cholestasis and steatosis is significant. In the event of variceal bleeding, it is usual practice at the authors' institution to wait for 48 hours before placement of a nasogastric feeding tube owing to the risk of precipitating further bleeding. Immunonutrition has not been studied in critically unwell patients with liver failure.

The protein load associated with enteral feeding may predispose to hyperammonaemia, which is common in the (decompensated) cirrhotic. Lactulose, L-ornithine L-aspartate and non-absorbable antibiotics – such as neomycin, rifaximin, metronidazole, oral vancomycin and oral quinolones – have been administered in an effort to decrease the colonic concentration of ammoniagenic bacteria. Branched chain amino acid-enriched formulae may provide protein supplementation in the patient with troublesome hepatic encephalopathy.

Hyperglycaemia is common in sepsis and may be pro-coagulant, induce apoptosis and inhibit neutrophil function. Landmark clinical trials have suggested that the strict maintenance of glycaemic control is beneficial in critically unwell surgical patients.[78] The same group failed to demonstrate a mortality benefit in a medical cohort.[79] Meier et al.[80] compared the consequences of intensive glycaemic control (3.5–6.5 mmol/L) with loose glycaemic control (5.0–8.0 mmol/L). The incidences of hypoglycaemia and of bacteraemia were higher in the tight control group, with a trend towards worsened survival at 21 days. There are no RCTs examining the efficacy of tight glycaemic control in the cirrhotic population, and there is a high prevalence of hypoglycaemic events in this cohort.

The efficacy of high-volume continuous venovenous hemofiltration (CVVH) in severe sepsis and septic shock has generated a great deal of interest in the critical care community in recent years. It is proposed that the removal of mediators of the inflammatory cascade such as IL-2, IL-6, IL-8, IL-10, TNFα, C3a and C5a may attenuate the inflammatory response, improve haemodynamics and thereby end-organ perfusion and function. Animal studies were initially encouraging. A series of observational, interventional, randomised (but small scale and uncontrolled) studies showed beneficial cardiovascular effects and an improvement in predicted hospital and 28-day mortality.[81] However, a recent large randomised study demonstrated that intensive renal support in critically ill patients with acute kidney injury did not decrease mortality, improve recovery of kidney function, or reduce the rate of non-renal organ failure compared with less-intensive therapy.[82] There is consequently a lack of consensus on the optimal timing for the commencement of RRT, the appropriate dose or the type of membrane (pore size, surface area) for critically ill patients. Data for the septic/cirrhotic cohort are lacking.

SPONTANEOUS BACTERIAL PERITONITIS

SBP is infection of cirrhosis-related ascites. It may cause a florid sepsis syndrome with shock and renal failure, or have an onset that is insidious and detected only at paracentesis. The incidence and severity of infection in cirrhosis is greater than in the population without cirrhosis. Infection with multiresistant organisms is common, end organ damage is greater in cirrhotics with delays in diagnosis and treatment initiation

leading to higher mortality particularly in hypotensive patients with cirrhosis.[83] Pyrexia, changes in mental state and abdominal tenderness are common. Routine paracentesis demonstrates an incidence of SBP of up to 27% at the time of hospital admission.[84] Mortality rates for patients surviving their first hospital admission are 70% at 1 year, and 80% at 2 years. Prolonged bacteraemia, immune paresis and intrahepatic shunting probably play a role in the aetiology of SBP.

The bacterial concentration in ascitic fluid tends to be comparatively low and so 10–20 mL of ascitic fluid are introduced into blood culture bottles at the bedside to increase the diagnostic yield. Clinical factors associated with an increased risk of infection are poor liver function, variceal bleeding, low ascitic fluid protein levels, prior SBP and hospitalization.[83]

It is extremely important, in terms of management, to differentiate SBP from secondary peritonitis. The mortality rate of SBP approaches 100% if appropriate surgical intervention is omitted. However, the mortality rate is about 80% if a patient with SBP receives an unnecessary exploratory laparotomy.[85] Culture in SBP tends to reveal a single responsible pathogen.

There has been an emergence of enterobacteria strains harbouring ESBLs or beta lactamases, which are able to hydrolyse cephalosporins and broad-spectrum penicillins and other resistant bacteria, such as *P. aeruginosa*, methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci (VRE) and *E. faecium*. Predispositions for the acquisition of multi-resistant organisms include hospitalisation, antibiotic exposure and norfloxacin prophylaxis. Authors have suggested that quinolones should be avoided in the treatment of SBP or any other infection in patients on long-term norfloxacin prophylaxis.[86] Pathological bacterial translocation may be considered an end result of intestinal barrier dysfunction, genetic predisposition to infection and immune dysfunction resulting in an excessive proinflammatory response and tissue damage ('immunopathology'), organ failure (kidney injury, cerebral oedema, disseminated intravascular coagulation, variceal bleed, adrenal insufficiency and shock).[83]

The choice of empirical antimicrobials is made based upon the type and severity of infection and on local antibiotic resistance patterns. A response to antimicrobials must be assessed by a second paracentesis 48 hours after commencement of treatment. A failure of reduction in neutrophil count by more than 25% may be considered treatment failure and antibiotics must then be changed.[83] Through as yet unclear mechanisms, the intravenous administration of 20% albumin has been shown to reduce the incidence of renal failure and decrease mortality rates from 29% to 10%.[87]

The use of prophylactic antibiotics must be restricted to patients at high risk of infections (upper GI bleed, previous SBP, advanced cirrhosis and low total protein content in ascitic fluid). Oral quinolones (norfloxacin or ciprofloxacin) are effective in the prevention of SBP recurrence. Rifaximin, a non-absorbable broad spectrum antimicrobial that reaches high faecal concentrations, causes minimal alterations to gut microflora and reduces expression of bacterial virulence factors, has been shown to have significant benefit in prophylaxis of SBP in patients with encephalopathy.[88]

RENAL FAILURE IN CHRONIC LIVER DISEASE

Acute kidney injury and hypervolaemic hyponatraemia are the major determinants of poor prognosis in advanced cirrhosis.[89] Renal failure occurs in 27% of septic cirrhotics in the absence of SBP and in 33% with SBP.[90] HRS is a prerenal failure that does not respond to fluid therapy. The diagnostic criteria are listed in Box 44.2.3.[91]

There is an association with renal/splanchnic insufficiency. Infections, bleeding and large-volume paracentesis without adequate volume replacement are common precipitating factors. Type 1 HRS progresses rapidly, and often occurs in the setting of haemodynamic compromise. Type 2 HRS is said to be characterised by a slowly progressive deterioration in renal indices and is frequently associated with ascites. HRS is associated with a diminished survival probability (Fig. 44.2.2). Liver transplantation is the final treatment of HRS types 1 and 2 and must be considered in all patients.

Ischaemic ATN is common in patients with acute or chronic liver failure who develop SIRS/sepsis. The administration of 20% albumin was associated with a reduction in the incidence of renal failure and of mortality.[92] Terlipressin may also have a role in the treatment of HRS.[93,94] More recent data suggest that norepinephrine may be equally applied.[95-98]

Ascitic drainage should be undertaken with appropriate albumin loading if large-volume drainage is undertaken, or in patients at risk of central volume depletion.[99]

Box 44.2.3 Diagnostic criteria for hepatorenal syndrome

- Cirrhosis with ascites
- Creatinine >1.5 mg/dL
- No improvement in serum creatinine (>1.5) after 2 days of diuretic withdrawal and volume expansion with albumin (1 g/kg/day up to 100 g/day)
- Absence of shock
- No nephrotoxins
- Absence of parenchymal kidney disease (proteinuria >500 mg/day, microhaematuria >50 red blood cells per high-power field) and/or abnormal renal ultrasound

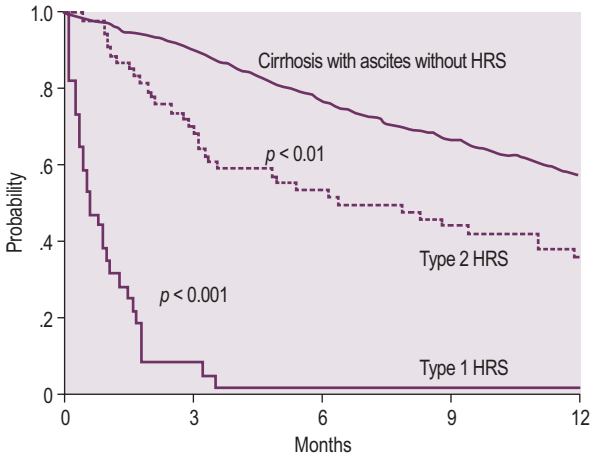


Figure 44.2.2 Actuarial survival probability in cirrhotic patients with hepatorenal syndrome (HRS). *With permission from Salerno F, Gerbes A, Gines P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis.* Gut. *2007;56:1310–1318.*

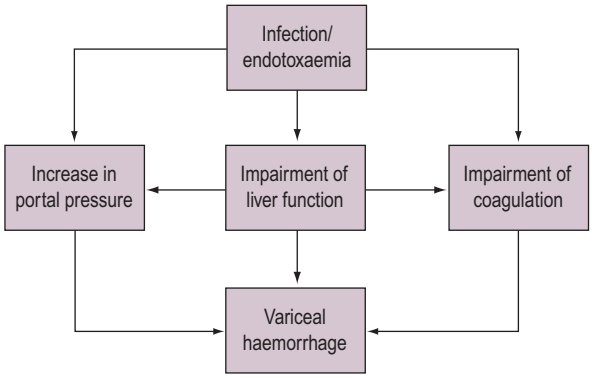


Figure 44.2.3 Pathophysiology of variceal bleeding in acute on chronic liver failure. *With permission from Thalheimer U, Triantos CK, Samonakis DN, et al. Infection, coagulation and variceal bleeding in cirrhosis.* Gut. *2005;54:556–563.*

VARICEAL BLEEDING IN CHRONIC LIVER DISEASE

The development of infection in cirrhosis is associated with a failure to control variceal bleeding and with early variceal rebleeding. The incidence of sepsis is also higher in patients with uncontrolled bleeding (Fig. 44.2.3).

Propranolol, which is used to lower portal pressures following variceal haemorrhage, was shown to lower the incidence of infection from 42% to 15% in a cohort of 73 cirrhotics.[100] It is not clear whether this effect is attributable to increased gut motility, and thus reduced bacterial translocation. Variceal band ligation is offered if there are contraindications to a non-cardioselective beta blocker. Proton pump inhibitors, isosorbide mononitrate monotherapy, sclerotherapy and TIPS are not recommended as primary prophylaxis.[101]

Infection may predispose to variceal bleeding because of an elevation in sinusoidal pressure – and hence portal pressure – and a worsening of coagulopathy. NO synthesis (the circulating form is *S*-Nitrosothiol) attenuates platelet aggregation, and heparinoid synthesis by endothelial cells increases.

It is recommended that patients with bleeding complications be treated with antibiotics.[102] The management of variceal haemorrhage remains that of basic resuscitation and care of the airway. Coagulation factors require appropriate supplementation along with other blood products. Cultures should be taken and all patients with variceal haemorrhage should be given antibiotics, which has been shown to decrease the risk of rebleeding.[103,104] Splanchnic vasoconstrictors, such as terlipressin, are beneficial in controlling oesophageal haemorrhage, but their role in gastric variceal haemorrhage per se has not been examined.[95,105] Octreotide is an alternative if terlipressin is unavailable.[101] Banding ligation therapy remains the treatment of choice for oesophageal haemorrhage, with tissue adhesives being utilised in gastric varices.

Failure to control variceal bleeding after two endoscopic sessions should result in consideration of TIPS insertion.[106,107] In patients in whom TIPS (Fig. 44.2.4) might be considered to be of benefit in controlling variceal bleeding, consideration needs to be given to the severity of the underlying liver disease that may in its own right make TIPS ill-advised.[108]

CARDIORESPIRATORY FAILURE

Cirrhotics display altered haemodynamics at baseline, with a hyperkinetic, vasodilated circulation. Patients tend to be tachycardic and hypotensive, with high cardiac output and low peripheral vascular resistance. Despite this, cirrhotic patients may have markedly abnormal tissue oxygenation, with arteriovenous O_2 content difference and O_2 uptake.[109] These changes become more profound with the onset of the septic state. Fluid resuscitation is complex, and probably best guided by the use of a cardiac output monitor. Patients may not respond to vasopressors as vigorously as the non-cirrhotic septic cohort. Left ventricular dilatation and dysfunction may be apparent on echocardiography.

Respiratory failure is common in the cirrhotic cohort. Intubation is often required for airway protection in encephalopathy. Ventilator-associated pneumonia is common. Alveolar macrophage activity may be diminished.

Tense ascites inhibits diaphragmatic descent and predisposes to basal atelectasis/collapse. There may

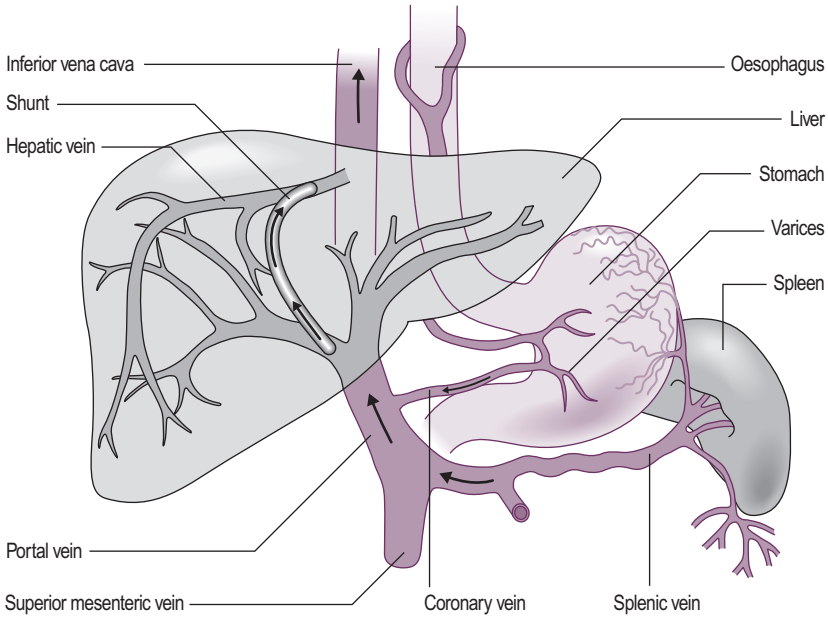


Figure 44.2.4 Transjugular intrahepatic portal systemic shunt.

be an accumulation of fluid owing to increased capillary membrane permeability, which may be exacerbated by attempts to resuscitate a relatively vasoplegic circulation.

There is a relatively high incidence of ARDS in cirrhosis. Mortality rates in ventilated cirrhotics are high.

DECOMPENSATIONS IN LIVER FUNCTION DURING THE SEPTIC EPISODE

Sepsis has the potential to worsen liver function, particularly in chronic cirrhotics. ACLF has been defined as 'a syndrome characterised by the acute deterioration of liver function in a patient with compensated or decompensated, but hitherto stable cirrhosis. It is commonly precipitated by an acute event/precipitating factor and associated with failure in the function of extra-hepatic organs' (European Association for the Study of Liver failure, EASL). The mechanisms underlying decrements in liver function are likely to be multifactorial.

As outlined above, levels of pro-inflammatory cytokines are increased in many forms of CLD. It is now believed that Kupffer cell induction by bacterial cell wall products may mediate hepatic inflammation. Hepatic stellate cells (HSCs), the main fibrogenic cells in the liver, are also mediators of inflammation, regulating leucocyte trafficking and activation.[110] Activation of HSCs by LPS has been proposed as a potential direct link between inflammation and hepatic fibrosis. Activation of the stellate cell to a myofibroblast-like phenotype allows the production of fibrillar collagens and other matrix proteins that characterise the fibrotic response.[111]

There is a large body of evidence to support the role of endotoxin and LPS derived from Gram-negative bacteria in the development of hepatic inflammation. Alcohol exposure (acute and chronic) increases gut permeability to LPS, resulting in increased LPS serum levels.[110] Injury to the liver may be attenuated by selective digestive decontamination and by colectomy, whereas the addition of LPS may augment liver injury caused by alcohol.[112]

What is, perhaps, unclear are the relative roles that Gram-negative and Gram-positive bacteria play in the pathogenesis of sepsis-related liver injury. There may be synergy between the TLR-2- and TLR-4-mediated pathways.[111]

COAGULOPATHY

The liver is responsible for the synthesis of the zymogens of both pro- and anticoagulant factors. Cirrhosis is associated with a relative deficiency of the procoagulant factors II, V, VII and X, and the anticoagulant factors protein C, protein S and antithrombin. Cirrhotic patients with severe sepsis have relatively lower levels of zymogen forms of clotting factors when compared with cirrhotic patients with infection (but not severe sepsis) and uninfected cirrhotics. Decreased zymogen levels are independently correlated with an elevated Child–Pugh score (Box 44.2.4) and are associated with significant increases in the relative RRs of in-hospital death.[113] Thrombocytopenia is secondary to hypersplenism and becomes more profound in sepsis.

Box 44.2.4 The Child–Pugh classification is a means of assessing the severity of liver cirrhosis

Score	Bilirubin (micromol/L)	Albumin (g/L)	Prolonged prothrombin time (s)	Encephalopathy	Ascites
1	<34	>35	<4	None	None
2	34–50	28–35	4–6	Mild	Mild
3	>50	<28	>6	Marked	Marked

If there is primary biliary cirrhosis or sclerosing cholangitis then bilirubin is classified as <68 = 1; 68–170 = 2; >170 = 3.
The individual scores are summed and then grouped as:

- <7 = A
- 7–9 = B
- >9 = C

The haemostatic profile of patients with liver disease is different to that of healthy individuals. Even though laboratory tests often show a natural bleeding tendency, this assumption is false; the patient with liver disease is in a state of 'rebalanced haemostasis' which can easily be tipped towards both bleeding and thrombosis. Thromboprophylaxis must also not be withheld in patients with cirrhosis or acute liver failure.[114]

ACUTE ALCOHOLIC HEPATITIS

Alcoholic hepatitis refers to a clinical syndrome of recent onset of jaundice and/or ascites in a patient with ongoing alcohol misuse. Alcohol steatohepatitis (ASH) is the predominant cause of this syndrome and is defined by the coexistence of steatosis, hepatocyte ballooning and a neutrophil inflammatory infiltrate. Alcoholic hepatitis is a frequent cause of decompensation and requires aggressive treatment. The severity can be assessed using the Glasgow score, MELD score or Maddrey score, and in high-risk patients steroid therapy may be considered.[115,116] Severe forms of ASH are defined as a Maddrey discriminant function ≥32. Response to steroids over the first 7 days is associated with improved outcome.[117] The role of antioxidants has been examined but no benefit was seen.[118,119] Another approach has been to look at the value of enteral feeding, which was comparable with steroid treatment over a 4-week period, albeit in a small study.[120] The use of pentoxifylline has been reported in a single-centre study to decrease the risk of developing hepatorenal failure and hence impacts the outcome.[121] Pentoxifylline has antioxidant and anti-TNF properties and patients with severe alcoholic hepatitis treated with the drug exhibited a higher 6-month survival. Other drugs that have been tried include anti-TNF agents (infliximab) and *N*-acetylcysteine. The latter may have synergistic effects with corticosteroids.

KEY REFERENCES

44.1 ACUTE HEPATIC FAILURE

1. http://www.aasld.org/practiceguidelines/Documents/AcuteLiverFailureUpdate2011.pdf.
4. Lidofsky SD. Liver transplantation for fulminant hepatic failure. *Gastroenterol Clin North Am*. 1993;22(2):257–269.
6. Bernal W, Ma Y, Smith HM, et al. The significance of autoantibodies and immunoglobulins in acute liver failure: a cohort study. *J Hepatol*. 2007;47:664–670.
12. Vaquero J, Polson J, Chung C, et al. Infection and the progression of hepatic encephalopathy in acute liver failure. *Gastroenterology*. 2003;125:755–764.
14. Stravitz RT, Kramer AH, Davern T, et al. Intensive care of patients with acute liver failure: recommendations of the U.S. Acute Liver Failure Study Group. *Crit Care Med*. 2007;35(11):2498–2508.

44.2 CIRRHOSIS AND ACUTE-ON-CHRONIC

43. Shawcross DL, Davies NA, Williams R, et al. Systemic inflammatory response exacerbates the neuropsychological effects of induced hyperammonemia in cirrhosis. *J Hepatol*. 2004;40:247–254.
51. Karvellas CJ, Pink F, McPhail M, et al. Bacteremia, acute physiology and chronic health evaluation II and modified end stage liver disease are independent predictors of mortality in critically ill nontransplanted patients with acute on chronic liver failure. *Crit Care Med*. 2010;38(1):121–126.
55. Gustot T, Durand F, Lebrec D, et al. Severe sepsis in cirrhosis. *Hepatology*. 2009;50(6):2022–2033. Erratum in: 2010; 51(2):725.
56. Wong F, Bernardi M, Balk R, et al. Sepsis in cirrhosis: report on the 7th meeting of the International Ascites Club. *Gut*. 2005;54:718–725.
63. Wiest R, Garcia-Tsao G. Bacterial translocation (BT) in cirrhosis. *Hepatology*. 2005;41(3):422–433.
91. Salerno F, Gerbes A, Gines P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut*. 2007;56:1310–1318.
93. Triantos CK, Samonakis D, Thalheimer U, et al. Terlipressin therapy for renal failure in cirrhosis. *Eur J Gastroenterol Hepatol*. 2010;22(4):481–486.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

44.1 ACUTE HEPATIC FAILURE

1. http://www.aasld.org/practiceguidelines/Documents/AcuteLiverFailureUpdate2011.pdf.
2. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. *Lancet*. 1993;342:273–275.
3. Greene SL, Dargan PI, Jones AL. Acute poisoning: understanding 90% of cases in a nutshell. *Postgrad Med J*. 2005;81(954):204–216.
4. Lidofsky SD. Liver transplantation for fulminant hepatic failure. *Gastroenterol Clin North Am*. 1993;22(2):257–269.
5. Lee WM. Acute liver failure in the United States. *Semin Liver Dis*. 2003;23:217–226.
6. Bernal W, Ma Y, Smith HM, et al. The significance of autoantibodies and immunoglobulins in acute liver failure: a cohort study. *J Hepatol*. 2007;47:664–670.
7. Bernal W, Hall C, Karvellas CJ, et al. Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. *Hepatology*. 2007;46:1844–1852.
8. Clemmesen JO, Larsen FS, Kondrup J, et al. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. *Hepatology*. 1999;29:648–653.
9. Albrecht J, Norenberg M. Glutamine: a Trojan horse in ammonia neurotoxicity. *Hepatology*. 2006;44:788–794.
10. Norenberg MD, Rao KV, Jayakumar AR. Mechanisms of ammonia-induced astrocyte swelling. *Metab Brain Dis*. 2005;20:303–318.
11. Rolando N, Wade J, Davalos M, et al. The systemic inflammatory response syndrome in acute liver failure. *Hepatology*. 2000;32:734–739.
12. Vaquero J, Polson J, Chung C, et al. Infection and the progression of hepatic encephalopathy in acute liver failure. *Gastroenterology*. 2003;125:755–764.
13. Shawcross DL, Davies NA, Mookerjee RP, et al. Worsening of cerebral hyperemia by the administration of terlipressin in acute liver failure with severe encephalopathy. *Hepatology*. 2004;39:471–475.
14. Stravitz RT, Kramer AH, Davern T, et al. Intensive care of patients with acute liver failure: recommendations of the U.S. Acute Liver Failure Study Group. *Crit Care Med*. 2007;35(11):2498–2508.
15. Hoofnagle JH, Carithers RL Jr, Shapiro C, et al. Fulminant hepatic failure: summary of a workshop. *Hepatology*. 1995;21:240–252.
16. Jalan R, Damink SW, Deutz NE, et al. Moderate hypothermia for uncontrolled intracranial hypertension in acute liver failure. *Lancet*. 1999;354:1164–1168.
17. Jalan R, Olde Damink SW, Deutz NE, et al. Restoration of cerebral blood flow autoregulation and reactivity to carbon dioxide in acute liver failure by moderate hypothermia. *Hepatology*. 2001;34:50–54.
18. Tofteng F, Larsen FS. The effect of indomethacin on intracranial pressure, cerebral perfusion and extracellular lactate and glutamate concentrations in patients with fulminant hepatic failure. *J Cereb Blood Flow Metab*. 2004;24:798–804.
19. Wade J, Rolando N, Philpott-Howard J, et al. Timing and aetiology of bacterial infections in a liver intensive care unit. *J Hosp Infect*. 2003;53:144–146.
20. Antoniades CG, Berry PA, Davies ET, et al. Reduced monocyte HLA-DR expression: a novel biomarker of disease severity and outcome in acetaminophen-induced acute liver failure. *Hepatology*. 2006;44:34–43.
21. Clapperton M, Rolando N, Sandoval L, et al. Neutrophil superoxide and hydrogen peroxide production in patients with acute liver failure. *Eur J Clin Invest*. 1997;27:164–168.
22. Harry R, Auzinger G, Wendon J. The clinical importance of adrenal insufficiency in acute hepatic dysfunction. *Hepatology*. 2002;36:395–402.
23. Marik PE. Adrenal-exhaustion syndrome in patients with liver disease. *Intensive Care Med*. 2006;32:275–280.
24. Fernandez J, Escorsell A, Zabalza M, et al. Adrenal insufficiency in patients with cirrhosis and septic shock: effect of treatment with hydrocortisone on survival. *Hepatology*. 2006;44:1288–1295.
25. Parekh NK, Hynan LS, De Lemos J, et al. Elevated troponin I levels in acute liver failure: is myocardial injury an integral part of acute liver failure? *Hepatology*. 2007;45:1489–1495.
26. Hoofnagle JH, Carithers RL Jr, Shapiro C, et al. Fulminant hepatic failure: summary of a workshop. *Hepatology*. 1995;21(1):240–252.
27. Fernandez J, Escorsell A, Zabalza M, et al. Adrenal insufficiency in patients with cirrhosis and septic shock: effect of treatment with hydrocortisone on survival. *Hepatology*. 2006;44:1288–1295.
28. Walsh TS, Wigmore SJ, Hopton P, et al. Energy expenditure in acetaminophen-induced fulminant hepatic failure. *Crit Care Med*. 2000;28:649–654.
29. Clark SJ, Shojaee-Moradie F, Croos P, et al. Temporal changes in insulin sensitivity following the development of acute liver failure secondary to acetaminophen. *Hepatology*. 2001;34:109–115.
30. Bernal W, Donaldson N, Wyncoll D, et al. Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study. *Lancet*. 2002;359:558–563.
31. Schmidt LE, Dalhoff K. Serum phosphate is an early predictor of outcome in severe acetaminophen-induced hepatotoxicity. *Hepatology*. 2002;36:659–665.
32. Lee WM, Hynan LS, Rossaro L, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute

liver failure. *Gastroenterology*. 2009;137(3):856–864, 864.e1.
33. Ichai P, Duclos-Vallee JC, Guettier C, et al. Usefulness of corticosteroids for the treatment of severe and fulminant forms of autoimmune hepatitis. *Liver Transpl*. 2007;13:996–1003.
34. Ostapowicz G, Fontana RJ, Schiødt FV, et al. Acute Liver Failure Study Group. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med*. 2002;137(12):947–954.
35. Reuben A, Tillman H, Fontana RJ, et al. Outcomes in adults with acute liver failure between 1998 and 2013: an observational cohort study. *Ann Intern Med*. 2016;164(11):724–732. doi:10.7326/M15-2211.
36. Blei AT. Selection for acute liver failure: have we got it right? *Liver Transpl*. 2005;11(suppl 2):S30–S34.
37. Yantorno SE, Kremers WK, Ruf AE, et al. MELD is superior to King's College and Clichy's criteria to assess prognosis in fulminant hepatic failure. *Liver Transpl*. 2007;13:822–828.

44.2 CIRRHOSIS AND ACUTE-ON-CHRONIC

38. Arroyo V, Moreau R, Jalan R, et al. Acute-on-chronic liver failure: a new syndrome that will re-classify cirrhosis. *J Hepatol*. 2015;62:S131–S143.
39. Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. *J Hepatol*. 2014;http://dx.doi.org/10.1016/j.jhep.2014.05.042.
40. Amodio P, Del Piccolo F, Pettenò E, et al. Prevalence and prognostic value of quantified electroencephalogram (EEG) alterations in cirrhotic patients. *J Hepatol*. 2001;35:37–45.
41. Tsipotis E, Shuja A, Jaber BL. Albumin dialysis for liver failure: a systematic review. *Adv Chronic Kidney Dis*. 2015;22(5):382–390. http://www.sciencedirect.com/science/journal/15485595/22/5.
42. Shawcross DL, Wright G, Olde Damink SW, et al. Role of ammonia and inflammation in minimal hepatic encephalopathy. *Metab Brain Dis*. 2007;22:125–138.
43. Shawcross DL, Davies NA, Williams R, et al. Systemic inflammatory response exacerbates the neuropsychological effects of induced hyperammonemia in cirrhosis. *J Hepatol*. 2004;40:247–254.
44. Arroyo V, Moreau R, Kamath PS, et al. Acute-on-chronic liver failure in cirrhosis. *Nat Rev Dis Primers*. 2016;2:16041.
45. Hernaez R, Solà E, Moreau R, et al. Acute-on-chronic liver failure: an update. *Gut*. 2017;66:541–553. doi:10.1136/gutjnl-2016-312670.
46. Blei AT. Infection, inflammation and hepatic encephalopathy, synergism redefined. *J Hepatol*. 2004;40:327–330.
47. Tranah TH, Vijay GK, Ryan JM, et al. Systemic inflammation and ammonia in hepatic encephalopathy. *Metab Brain Dis*. 2013;28(1):1–5. https://link.springer.com/journal/11011/28/1/page/1.
48. Marchesini G, Bianchi G, Rossi B, et al. Nutritional treatment with branched-chain amino acids in advanced liver cirrhosis. *J Gastroenterol*. 2000;35(suppl 12):7–12.
49. Alvarez MA, Cabre E, Lorenzo-Zuniga V, et al. Combining steroids with enteral nutrition: a better therapeutic strategy for severe alcoholic hepatitis? Results of a pilot study. *Eur J Gastroenterol Hepatol*. 2004;16:1375–1380.
50. Thabut D, Massard J, Gangloff A, et al. Model for end-stage liver disease and systemic inflammatory response are major prognostic factors in patients with cirrhosis and acute functional renal failure. *Hepatology*. 2004;46:1872–1882.
51. Karvellas CJ, Pink F, McPhail M, et al. Bacteremia, acute physiology and chronic health evaluation II and modified end stage liver disease are independent predictors of mortality in critically ill nontransplanted patients with acute on chronic liver failure. *Crit Care Med*. 2010;38(1):121–126.
52. Karvellas CJ, Pink F, McPhail M, et al. Predictors of bacteraemia and mortality in patients with acute liver failure. *Intensive Care Med*. 2009;35(8):1390–1396.
53. Foreman MG, Mannino DM, Moss M. Cirrhosis as a risk factor for sepsis and death: analysis of the National Hospital Discharge Survey. *Chest*. 2003;124(3):1016–1020.
54. Thalheimer U, Triantos CK, Samonakis DN, et al. Infection, coagulation and variceal bleeding in cirrhosis. *Gut*. 2005;54:556–563.
55. Gustot T, Durand F, Lebrec D, et al. Severe sepsis in cirrhosis. *Hepatology*. 2009;50(6):2022–2033. Erratum in: 2010; 51(2):725.
56. Wong F, Bernardi M, Balk R, et al. Sepsis in cirrhosis: report on the 7th meeting of the International Ascites Club. *Gut*. 2005;54:718–725.
57. Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA*. 2001;286:1754–1758.
58. Wheler M, Kokoska J, Reulbach U, et al. Short-term prognosis in critically ill patients with cirrhosis assessed by prognostic scoring systems. *Hepatology*. 2001;34:255–261.
59. Gustot T, Moreau R. *Mechanisms, consequences and management of infections in liver disease. Postgraduate Course: Management of Acute Critical Conditions in Hepatology*. Helsinki: EASL International Liver Congress; 2010:53–61.
60. Philips CA, Sarin SK. Sepsis in cirrhosis: emerging concepts in pathogenesis, diagnosis and management. *Hepatol Int*. 2016;10:871–882. doi:10.1007/s12072-016-9753-2.
61. Lin CY, Tsai IF, Ho YP, et al. Endotoxemia contributes to the immune paralysis in patients with cirrhosis. *J Hepatol*. 2007;46(5):816–826.

62. Chan CC, Hwang SJ, Lee FY, et al. Prognostic value of plasma endotoxin levels in patients with cirrhosis. *Scand J Gastroenterol*. 1997;32(9): 942–946.
63. Wiest R, Garcia-Tsao G. Bacterial translocation (BT) in cirrhosis. *Hepatology*. 2005;41(3):422–433.
64. Lumsden AB, Henderson JM, Kutner MH. Endotoxin levels measured by a chromogenic assay in portal, hepatic and peripheral venous blood in patients with cirrhosis. *Hepatology*. 1988;8:232–236.
65. Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. *J Hepatol*. 2014;60:197–209.
66. Campillo B, Pernet P, Bories PN, et al. Intestinal permeability in liver cirrhosis: relationship with severe septic complications. *Eur J Gastroenterol Hepatol*. 1999;11:755–759.
67. Wiest R, Rath HC. Gastrointestinal disorders of the critically ill. Bacterial translocation in the gut. *Best Pract Res Clin Gastroenterol*. 2003;17:397–425.
68. Rimola A, Bory F, Teres J, et al. Oral, nonabsorbable antibiotics prevent infection in cirrhotics with gastrointestinal haemorrhage. *Hepatology*. 1985; 5:463–467.
69. Wasmuth HE, Kunz D, Yagmur E, et al. Patients with acute or chronic liver failure display 'sepsis-like' immune paralysis. *J Hepatol*. 2005;42:195–201.
70. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19): 1368–1377.
71. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest*. 2008;134:172–178.
72. Jones AE, Shapiro NI, Trzeciak S, et al. Lactate vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA*. 2010;303(8):739–746.
73. Choi CH, Ahn SH, Kim DY, et al. Long-term clinical outcome of large volume paracentesis with intravenous albumin in patients with spontaneous bacterial peritonitis: a randomized prospective study. *J Gastroenterol Hepatol*. 2005; 20:1215–1222.
74. Fernandez J, Navasa M, Garcia-Pagan JC, et al. Effect of intravenous albumin on systemic and hepatic hemodynamics and vasoactive neurohormonal systems in patients with cirrhosis and spontaneous bacterial peritonitis. *J Hepatol*. 2004;41:384–390.
75. Fernandez J, Monteagudo J, Bargallo X, et al. A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. *Hepatology*. 2005;42:627–634.
76. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362(9):779–789.
77. Canabal JM, Kramer DJ. Management of sepsis in patients with liver failure. *Curr Opin Crit Care*. 2008;14:189–197.
78. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359–1367.
79. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006;354(5):449–461.
80. Meier R, Béchir M, Ludwig S, et al. Differential temporal profile of lowered blood glucose levels (3.5 to 6.5 mmol/l versus 5 to 8 mmol/l) in patients with severe traumatic brain injury. *Crit Care*. 2008;12:R98.
81. Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. *Lancet*. 2000;356: 26–30.
82. VA/NIH Acute Renal Failure Trial Network, Palevsky PM, Zhang JH, et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med*. 2008;359(1):7–20.
83. Jalan R, Fernandez J, Wiest R, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. *J Hepatol*. 2014;60:1310–1324.
84. Gines P, Arroyo V, Rodes J. Therapy of ascites and spontaneous bacterial peritonitis. In: Cohen S, Davis GL, Gianella RA, et al, eds. *Therapy of Digestive Disorders: A Companion to Sleisenger and Fortran's Gastrointestinal and Liver Disease*. Philadelphia, PA: WB Saunders; 2000:373–384.
85. Alaniz C, Regal R. Spontaneous bacterial peritonitis: a review of treatment options. *P T*. 2009; 34(4):204–210.
86. Fernandez J. *Changes in the epidemiology of infections in cirrhosis. The role of antibiotic resistance,* Clostridium difficile *infection, viral and fungal sepsis; EASL Postgraduate Course: Management of Acute Critical Conditions in Hepatology*. Helsinki: 45th International Liver Congress; 2010:62–67.
87. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med*. 1999;341:403–409.
88. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med*. 2010;362:1071–1081.
89. Møller S, Krag A, Bendtsen F. Kidney injury in cirrhosis: pathophysiological and therapeutic aspects of hepatorenal syndromes. *Liver Int*. 2014;34:1153–1163. doi:10.1111/liv.12549.
90. Follo A, Llovet JM, Navasa M, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence clinical course, predictive factors and prognosis. *Hepatology*. 1994;20: 1495–1501.
91. Salerno F, Gerbes A, Gines P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut*. 2007;56:1310–1318.

92. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med*. 1999;341(6):403–409.
93. Triantos CK, Samonakis D, Thalheimer U, et al. Terlipressin therapy for renal failure in cirrhosis. *Eur J Gastroenterol Hepatol*. 2010;22(4):481–486.
94. Fabrizi F, Dixit V, Messa P, et al. Terlipressin for hepatorenal syndrome: a meta-analysis of randomized trials. *Int J Artif Organs*. 2009;32(3):133–140.
95. Gluud LL, Kjaer MS, Christensen E. Terlipressin for hepatorenal syndrome. *Cochrane Database Syst Rev*. 2006;(4):CD005162.
96. Alessandria C, Ottobrelli A, Debernardi-Venon W, et al. Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. *J Hepatol*. 2007;47:499–505.
97. Moreau R, Durand F, Poynard T, et al. Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome: a retrospective multicenter study. *Gastroenterology*. 2002;122:923–930.
98. Moreau R, Lebrec D. The use of vasoconstrictors in patients with cirrhosis: type 1 HRS and beyond. *Hepatology*. 2006;43:385–394.
99. Moreau R, Asselah T, Condat B, et al. Comparison of the effect of terlipressin and albumin on arterial blood volume in patients with cirrhosis and tense ascites treated by paracentesis: a randomised pilot study. *Gut*. 2002;50:90–94.
100. Chelarescu O, Chelarescu D, Tircoveanu E, et al. Propranolol administration on post surgical infections in cirrhotic patients. *J Hepatol*. 2003;38(suppl 2):A173.
101. Tripathi D, Stanley AJ, Hayes PC, et al. UK guidelines on the management of variceal haemorrhage in cirrhotic patients. *Gut*. 2015;64:1680–1704. doi:10.1136/gutjnl-2015-309262.
102. Goulis J, Patch D, Burroughs AK. Bacterial infection in the pathogenesis of variceal bleeding. *Lancet*. 1999;353:139–142.
103. Hou MC, Lin HC, Liu TT, et al. Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: a randomized trial. *Hepatology*. 2004;39:746–753.
104. Fernandez J, Ruiz del Arbol L, Gomez C, et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. *Gastroenterology*. 2006;131:1049–1056, quiz 285.
105. Escorsell A, Ruiz del Arbol L, Planas R, et al. Multicenter randomized controlled trial of terlipressin versus sclerotherapy in the treatment of acute variceal bleeding: the TEST study. *Hepatology*. 2000;32:471–476.
106. Khan S, Tudur Smith C, Williamson P, et al. Portosystemic shunts versus endoscopic therapy for variceal rebleeding in patients with cirrhosis. *Cochrane Database Syst Rev*. 2006;(4):CD000553.
107. Thabut D, Bernard-Chabert B. Management of acute bleeding from portal hypertension. *Best Pract Res Clin Gastroenterol*. 2007;21:19–29.
108. Schepke M, Roth F, Fimmers R, et al. Comparison of MELD, Child-Pugh, and Emory model for the prediction of survival in patients undergoing transjugular intrahepatic portosystemic shunting. *Am J Gastroenterol*. 2003;98:1167–1174.
109. Moreau R, Lee SS, Soupison T, et al. Abnormal tissue oxygenation in patients with cirrhosis and liver failure. *J Hepatol*. 1988;7(1):98–105.
110. Paik YH, Schwabe RF, Bataller R, et al. Toll-like receptor 4 mediates inflammatory signaling by bacterial lipopolysaccharide in human hepatic stellate cells. *Hepatology*. 2003;37(5):1043–1055.
111. Iredale JP. Regulating hepatic inflammation: pathogen-associated molecular patterns take their toll. *Hepatology*. 2003;37(5):979–982.
112. Su GL. Lipopolysaccharides in liver injury: molecular mechanisms of Kupffer cell activation. *Am J Physiol Gastrointest Liver Physiol*. 2002;283(2):G256–G265.
113. Plessier A, Denninger MH, Consigny Y, et al. Coagulation disorders in patients with cirrhosis and severe sepsis. *Liver Int*. 2003;23:440–448.
114. Weeder PD, Porte RJ, Lisman T. Hemostasis in liver disease: implications of new concepts for perioperative management. *Transfus Med Rev*. 2014;28(3):107–113. http://www.sciencedirect.com/science/journal/08877963/28/3.
115. Forrest EH, Evans CD, Stewart S, et al. Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow alcoholic hepatitis score. *Gut*. 2005;54:1174–1179.
116. Forrest EH, Morris J, Stewart S, et al. The Glasgow alcoholic hepatitis score identifies patients who may benefit from corticosteroids. *Gut*. 2007;56:1743–1746.
117. Mathurin P, Abdelnour M, Ramond MJ, et al. Early change in bilirubin levels is an important prognostic factor in severe alcoholic hepatitis treated with prednisolone. *Hepatology*. 2003;38:1363–1369.
118. Phillips M, Curtis H, Portmann B, et al. Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis – a randomised clinical trial. *J Hepatol*. 2006;44:784–790.
119. Stewart S, Prince M, Bassendine M, et al. A randomized trial of antioxidant therapy alone or with corticosteroids in acute alcoholic hepatitis. *J Hepatol*. 2007;47:277–283.
120. Cabre E, Rodriguez-Iglesias P, Caballeria J, et al. Short- and long-term outcome of severe alcohol-induced hepatitis treated with steroids or enteral nutrition: a multicenter randomized trial. *Hepatology*. 2000;32:36–42.
121. Akriviadis E, Botla R, Briggs W, et al. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology*. 2000;119:1637–1648.

45

Abdominal surgical catastrophes

Stephen J Streat

Intra-abdominal surgical catastrophes are common in intensive care units (ICUs) and typically occur in older, co-morbid patients. They may be initiated by a traumatic, vascular or inflammatory event but often become complicated by sepsis (primarily or secondarily), multiple organ failure, multiple surgical procedures and a long intensive care stay.[1] Mortality remains comparatively high[2,3] both during and after the ICU period; hospitalisation is often very long and both reduced functional status[4,5] and life-expectancy may follow.

Treating clinicians must carefully and repeatedly assess the costs, including iatrogenic suffering,[6] and benefits[7] of treatment during an illness that can seem to have the character of a tragic saga[8] or the game of Snakes and Ladders (*"… implicit in the game is unchanging twoness of things, the duality of up against down, good against evil; the solid rationality of ladders balances the occult sinuosities of the serpent; in the opposition of staircase and cobra we can see, metaphorically, all conceivable oppositions."*).[9]

The clinical issues are themselves challenging and complex. Few randomised controlled trials are available to inform strategic, rather than tactical, decision making. Many patients have idiotypic features which make generalising from literature to the individual patient a risky endeavour. New treatments and treatment strategies continue to be introduced or to be subject to 'indication creep', often without robust evidence. All this is occurring in association with a 'shifting baseline' of slow continuous improvements in clinical outcomes in sepsis[10] and other critical illnesses, confounding inferences which some are tempted to draw between specific treatments and outcomes.

Herein lies considerable potential for conflict to arise between intensivists and other involved clinicians, particularly surgeons, whose relationship with the patient may reflect a different 'moral economy'[11] and who may have different views of what constitutes realistic goals and reasonable strategies[12] for patients who are often near the end of life.[13] Families may hold different views about 'what is reasonable to expect and to strive for' or about 'what the patient might want for themselves'. Most patients are not able to participate in strategic discussions while in the midst of such an illness, but any opportunities to ascertain the values, preferences and goals of the at-risk patients themselves should be recognised and taken (e.g. before anaesthesia for elective or emergency surgery).[13] Intensivists treating these patients must maintain expertise in: 'realistically seeing the big picture' while refraining from prematurely deciding that the situation is irrecoverable, maintaining appropriate patience, equipoise and commitment of the entire treating team, facilitating communication and cooperation and negotiating and maintaining consensus between all members of the treating team and the family, as well as in ensuring that the clinical care provided is holistic and meticulous in its detail.[6,13]

Vascular catastrophes, intra-abdominal sepsis and some serious abdominal complications are discussed in this chapter; trauma, gastrointestinal bleeding and pancreatitis are covered elsewhere (Chapters 76–81, 42 and 43, respectively).

VASCULAR CATASTROPHES

ABDOMINAL AORTIC ANEURYSM

Abdominal aortic aneurysm (AAA) is a disease of the elderly, and remains up to six times more common in men than women.[14] The prevalence of AAA, defined as infrarenal aortic diameter of 30 mm or more detected by ultrasound screening, was ~2% in Swedish 65-year-old men in 2009,[15] around half of what had been found in UK studies a decade earlier. Population-based screening of asymptomatic men (but not women) aged 65 years and older has been widely adopted and, with early elective repair, has reduced AAA rupture and associated mortality.[16,17]

Aortic diameter is the strongest predictor of the risk of rupture, which is below 1% per year with aortic diameter less than 5 cm and about 17% per year with aortic diameter of 6 cm or more. The risk of rupture is higher in women (who have faster aneurysm growth rates than men)[18] and is increased by current smoking and hypertension. Aortic aneurysm expansion is around 0.3 cm per year for aneurysms smaller than 5 cm and around 0.5 cm per year for those larger than 5 cm.

Elective endovascular aortic repair (EVAR) of unruptured aneurysms was rapidly adopted[19] because

ABSTRACT

Intra-abdominal surgical catastrophes are common in intensive care units (ICUs), typically occurring in older, co-morbid patients. They may be initiated by a traumatic, vascular, infective or inflammatory event but often become complicated by sepsis, multiple organ failure, multiple surgical procedures and prolonged intensive care stay. Mortality remains comparatively high; hospitalisation is prolonged and full recovery may not occur. Intensivists must see the big picture while refraining from prematurely deciding that the situation is irrecoverable, should maintain their own patience and stamina and support the entire treating team, facilitate communication and consensus with the family, and ensure that the clinical care provided is comprehensive and meticulous. This chapter discusses vascular catastrophes and intra-abdominal sepsis together with some serious abdominal complications including abdominal compartment syndrome, the open abdomen, enterocutaneous fistulas and colonic pseudo-obstruction which may later develop as a result and contribute to the syndrome of 'abdominal surgical catastrophe'.

KEY WORDS

Aortic aneurysm
mesenteric ischaemia
intra-abdominal sepsis
abdominal compartment syndrome
open abdomen
enterocutaneous fistula

of lower perioperative mortality than open repair. Perioperative mortality has fallen for both treatments, but is probably now plateauing at ~1% for EVAR and 2%–3% for open repair.[14]

RUPTURE OF AN ABDOMINAL AORTIC ANEURYSM

Rupture of an AAA remains highly lethal – a French national epidemiological study in 2013 identified 1117 patients with ruptured aortic aneurysm from death records and hospital databases. Only 43% survived rupture, with 22% dying before hospital admission, and a further 35% in hospital.[20]

The clinical features of rupture of an abdominal aortic (or iliac artery) aneurysm include the sudden onset of shock and back pain or abdominal pain or tenderness in an elderly patient. The diagnosis may be missed initially,[21] as a pulsatile abdominal mass is commonly not detectable[22] and some patients may not have shock when first seen.

Immediate bedside ultrasound may sometimes confirm the clinical diagnosis but risks delaying vascular surgical referral and repair without diagnostic benefit.[23] It is sometimes appropriate to not proceed to repair[24] (severe co-morbidity or functional impairment) and this decision should be very carefully considered.[6,8,25]

Computed Tomography (CT) angiography is usually performed[24] unless the patient has frank shock and this is now increasingly followed by EVAR rather than open repair, although robust evidence of the overall superiority of EVAR is not yet available. Despite a large number of non-randomised studies showing increasing EVAR use and often lower mortality in EVAR-treated patients, the most recent Cochrane review[26] based on data from 868 patients in only four randomised controlled trials (RCTs) found no early mortality advantage (Odds Ratio [OR], 0.88; 95% Confidence Interval [CI], 0.66–1.16), but a suggestion of reduced bowel ischaemia with EVAR (OR, 0.37; 95% CI, 0.14–0.94).

A very small number (~0.6%) of patients with aortic aneurysm have infection of the aneurysm[27] and usually present acutely with pain and commonly with rupture. Infection of the aneurysm should be suspected in patients with impaired immunity and when there are signs of systemic inflammation at presentation. A wide variety of organisms can occur, most commonly with streptococci, staphylococcus aureus or salmonella.

A period of intensive care after aneurysm repair is appropriate for most patients. During this time, common physiological abnormalities (e.g. hypothermia, dilutional coagulopathy, minor bleeding, circulatory shock, renal tubular dysfunction) can be corrected and serious complications can be sought and if possible treated (e.g. major bleeding, abdominal compartment syndrome, renal failure, myocardial infarction, acute lung injury, peripheral ischaemia, stroke, pulmonary embolism, persistent ileus, mesenteric ischaemia, pancreatitis and acalculous cholecystitis).

Abdominal compartment syndrome (ACS) occurs in ~15% of patients with ruptured aortic aneurysm undergoing either open repair or EVAR.[28] It is more likely in patients with blood loss greater than 5 L. Around 10% of patients undergoing open repair have the abdomen left open postoperatively and a further 5% have a later decompressive laparotomy for ACS. Around 7% of patients having EVAR develop ACS and most undergo later decompressive laparotomy. ACS is associated with much higher 30-day mortality (42% vs. 24%) and greatly increases the risk of major complications including myocardial infarction, acute kidney injury, multiple organ failure, intestinal ischaemia and resection and prolonged ICU stay.[28]

Rapid ventilator weaning and extubation is recommended in patients without major complications, perhaps with thoracic epidural anaesthesia[29] if coagulation allows. In others, an assessment of overall progress should be made after 24–48 hours. Severe or progressive multiple organ failure[30] or major cerebral, visceral or limb infarction should lead to a reappraisal of the appropriateness of continued intensive therapies.

ACUTE AORTIC OCCLUSION

This is a rare syndrome presenting with painful lower limb paraparesis or paraplegia and absent distal circulation and is usually due to thrombotic occlusion of a stenotic or aneurysmal aorta and less often to saddle embolism. Minimising delay to revascularisation is of the essence, but hospital mortality (~30%) remains high.[31]

MESENTERIC ISCHAEMIA

Mesenteric ischaemia is an uncommon condition which presents with two distinct syndromes[32] – occlusive ischaemia and non-occlusive mesenteric ischaemia (NOMI).

Occlusive ischaemia may occur after atherosclerotic arterial thrombosis or arterial embolism and less often after venous occlusion. Patients present with abdominal severe pain, and often nausea, vomiting and diarrhoea, followed later by distension, rigidity and shock. Although outcomes have improved[33] with a multidisciplinary approach including endovascular revascularisation, surgery (often gut resection) and intensive care, mortality remains very high.[34]

In a single-centre French study,[35] NOMI was confirmed (by endoscopy or laparotomy) in ~0.8% of around 12,500 predominantly 'medical' ICU admissions and had a mortality of 76%. The syndrome develops usually a few days after ICU admission in the setting of severe circulatory failure (due to bleeding, sepsis or cardiac failure), and should be suspected when there are signs of severe gastrointestinal disturbance, tissue ischaemia, often in association with acute

kidney injury or ischaemic hepatitis. CT scan findings include gas in the portal veins, intestinal pneumatosis or dilatation, and absence of bowel contrast enhancement. Endoscopy can confirm ischaemia and at laparotomy segmental intestinal necrosis may allow for resection or may be so extensive as to preclude this option. Measures should be taken to improve intestinal blood flow (including reduction in splanchnic vasoconstrictors and perhaps abdominal decompression).[36]

AORTIC DISSECTION AND INTRAMURAL HAEMATOMA

Aortic dissection has a commonly reported incidence of 5–30 per million per year,[37] but the true incidence is probably several times that if cases outside specialist surgical centres and those who die before hospital are also included.[38] The typical patient is an elderly hypertensive[39] and presents with pain in a distribution corresponding to the site of dissection. Cases have been reported in young people and in circumstances suggesting acute situational hypertension. Pericardial tamponade, haemothorax, myocardial infarction, stroke, paraplegia due to spinal cord ischaemia, anuria or an acute abdomen may be present. Most aortic dissections originate in the ascending thoracic aorta. Some dissections extend to involve the abdominal aorta, but spontaneous dissection of the abdominal aorta alone is rare. Acute intramural aortic haematoma has similar clinical features to aortic dissection and accounts for ~10% of cases of what is now termed 'acute aortic syndrome'.[40] Diagnosis is best established by CT aortography. In all cases, pain, blood pressure and heart rate should all be controlled after which Type A dissections (involving the thoracic aorta, sometimes including the descending aorta) are probably best treated surgically whereas type B dissections (involving the descending aorta alone) may be more suitable for endovascular repair.[40,41] An abdominal catastrophe may subsequently develop due to mesenteric ischaemia, often associated with acute kidney injury. Mortality remains high (somewhat lower for intramural haematoma)[40] but is falling in association with earlier diagnosis and treatment.[37]

SPONTANEOUS RETROPERITONEAL HAEMORRHAGE

Spontaneous retroperitoneal haemorrhage (excluding aortic aneurysm rupture) is uncommon and usually associated with anticoagulant therapy, including warfarin, unfractionated heparin, low-molecular-weight heparin and antiplatelet agents,[42] or with vascular or malignant disease of the kidney or adrenal gland and less commonly with spontaneous rupture of the retroperitoneal veins. The presentation is most often with acute abdominal pain, shock and a palpable abdominal or groin mass, and CT will confirm the diagnosis.[43,44] Transfusion, correction of coagulopathy and interventional radiological embolisation[44] may control some situations, but surgery may be required in others, either to stop bleeding or to relieve intra-abdominal hypertension. Mortality remains high.

INTRA-ABDOMINAL SEPSIS

Intra-abdominal sepsis is very common in the ICU; indeed, in many countries the abdomen is the most common cause of sepsis in ICU admissions. The issue of sepsis is covered in Chapter 70.

The general principles of the treatment of severe sepsis[45] are to support oxygen transport with ventilator support, fluid therapy and inotropic support, to identify and if possible remove the septic source[45,46] and to give appropriate antimicrobial therapy.[45,47] A clear role for other therapies is not yet established.[45] Sepsis is a time-critical condition wherein delay in the execution of these principles is likely to worsen outcome.[45]

In the critically ill patient with intra-abdominal sepsis, effective source control usually involves surgery, although occasionally interventional procedures may suffice. Laparotomy is recommended (without delay or further investigation) for most patients presenting acutely with shock and clinical evidence of peritonitis.[48] Diagnostic peritoneal aspiration or lavage, ultrasonography, CT scanning or laparoscopy may have limited applicability in some circumstances.

Common syndromes[49] include:

- Faecal peritonitis
  - Primarily – usually due to diverticular disease or colonic malignancy
  - Secondarily – after prior anterior resection
- Perforated upper abdominal viscus (usually of a gastric or duodenal ulcer)
- Biliary obstruction (sometimes with perforation)
- Intestinal infarction without perforation (usually adhesive, less commonly ischaemic)
- Appendicitis (often perforated in older patients).

Less common syndromes include localised intra-abdominal abscess, acalculous cholecystitis, toxic megacolon, perforation of a fallopian tube abscess, spontaneous bacterial peritonitis (SBP) (in end-stage liver disease or nephrotic syndrome) and chronic ambulatory peritoneal dialysis (CAPD)-associated peritonitis (some of which is surgical).

SURGICAL SOURCE CONTROL

Surgical source control should remove the septic focus at the first ('damage control') operation, but definitive surgery may not be feasible or desirable at this time. The abdomen may be left open (with a temporary fascial closure) if required for intra-abdominal hypertension or to facilitate repeat laparotomy.

Initial surgery[46] involves:

- Removal of all peritoneal contamination (both macroscopically and by generous lavage)

- Drainage of abscesses
- Resection of devitalised tissue
- Defunctioning of the gut (diverting the enteric stream) to prevent ongoing contamination.

Failure of the sepsis syndrome to settle ('failure to thrive') after apparently definitive surgical source control should suggest (early) ongoing contamination or ischaemia or (after some days) the development of abscess. Repeat laparotomy on clinical grounds is recommended when early postoperative progress is unsatisfactory,[50] whereas CT scanning followed by directed laparotomy or interventional radiological drainage is recommended when late abscess is suspected.

INTESTINAL-SOURCE PERITONITIS

Peritonitis secondary to contamination by intestinal contents usually results in mixed aerobic (most often due to Gram-negative and some Gram-positive organisms – usually enterococci) and anaerobic infection, although yeasts are commonly cultured from abdominal fluid samples.[51] Recommended antibiotic regimens[52] are based on a paucity of randomised controlled trial evidence and usually involve either monotherapy with a carbapenem (or piperacillin–tazobactam) or combination therapy with a third- or fourth-generation cephalosporin and metronidazole. Similar antibiotic regimens are appropriate in sepsis following intestinal infarction without perforation.

BILIARY SEPSIS

Biliary ultrasound, followed by endoscopic sphincterotomy and stone removal without delay, is recommended for critically ill patients with cholangitis.[53] Antibiotic regimens should cover aerobic Gram-negative bacilli and enterococci.

ACALCULOUS CHOLECYSTITIS

Acalculous cholecystitis is a rare but serious condition in intensive care units. A small number of patients with the syndrome of acute cholecystitis will have acalculous cholecystitis, but these patients have low mortality and do not present to intensive care units. Of greater concern are the perhaps half of all cases of acalculous cholecystitis which develop insidiously in intensive care patients already critically ill for another reason (e.g. recent trauma or surgery) and can therefore go unrecognised until gangrene, perforation or abscess develop. The gallbladder histology in such patients usually includes prominent ischaemia and arteriosclerosis and low cardiac output may predispose to the condition. There should be a high index of suspicion in an intensive care patient who develops new abdominal pain or clinical signs of sepsis. Although scintigraphy, CT scanning, ultrasound and laparoscopy[54] have all been used to help establish the diagnosis, none perform reliably.[55] Percutaneous cholecystostomy[46,56] may be preferable to open cholecystectomy in critically ill patients.

TOXIC MEGACOLON

Toxic megacolon[57] is a rare indication for intensive care admission. It is characterised by systemic toxicity accompanying a dilated, inflamed colon and is usually due to inflammatory bowel disease, although other causes including infection by Clostridium difficile, cytomegalovirus (in patients with HIV disease or immunosuppression) or rarely other organisms may be becoming more common. The diagnosis should be considered in patients with diarrhoea and abdominal distension. Limited sigmoidoscopy (despite the risk of perforation) and biopsy may both yield important microbiological information and help in the decision to operate. Supportive therapy in the ICU is usually recommended and includes both antibiotics as for colonic perforation and, in inflammatory bowel disease, steroids (equivalent of ~400 mg/day of hydrocortisone). Other immunosuppression (with calcineurin inhibitors or anti-tumour necrosis factor monoclonal antibody) has support from randomised controlled trials in severe ulcerative colitis, but is not recommended in the setting of toxic megacolon where there is a high risk of perforation and sepsis.[57] Frequent surgical reassessment and abdominal X-rays are used to monitor progress. Intravenous nutrition may help to reduce the activity of Crohn's disease but does not reduce hospital stay or the need for surgery in ulcerative colitis. A period of several days of careful observation may be reasonable to assess the response to medical treatment but urgent surgery (subtotal colectomy with end-ileostomy) is indicated for increasing colonic dilatation, perforation, bleeding or progressive systemic toxicity. Parenteral metronidazole may be effective in severe pseudomembranous colitis without megacolon (but early surgery is often recommended if megacolon develops).

RUPTURE OF A TUBO-OVARIAN ABSCESS

Rupture of a tubo-ovarian abscess is a rare cause of peritonitis presenting to intensive care units and is best treated with surgical extirpation. Antibiotic therapy should include activity against anaerobic organisms.

SPONTANEOUS BACTERIAL PERITONITIS

SBP is usually a monomicrobial infection, but both aerobic Gram-negative bacilli and a variety of Gram-positive organisms (especially enterococci) are equally commonly isolated.[58] The development of SBP in patients with end-stage liver disease is often followed by hepatic decompensation and multiple organ failure.

Those who recover are at high risk of death without liver transplantation. Early albumin supplementation has been shown to reduce both renal failure and mortality in SBP associated with end-stage liver disease.[59]

Treatment with a broad-spectrum beta-lactam antibiotic is usual[60] but may not be appropriate in view of the incidence and lethality of infection with enterococci.[58] Recovery should be followed by secondary oral antibiotic prophylaxis.

CAPD-ASSOCIATED PERITONITIS

CAPD-associated peritonitis rarely necessitates intensive care admission and such patients should be assessed for an unrecognised gastrointestinal septic source,[61] abscess formation or the presence of unusual organisms including fungi.

TERTIARY PERITONITIS

Tertiary peritonitis ('peritonitis in the critically ill patient that persists or recurs at least 48 hours after the apparently adequate management of primary or secondary peritonitis')[62] occurs occasionally in ICU patients with prior laparotomy. It is commonly due to *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Enterococcus* spp., *Enterobacter* spp., resistant *Bacteroides* or *Candida* spp.[62,63] and antimicrobial treatment should reflect these organisms until guided by cultures. When infection is due to *Candida* spp., other antimicrobial agents should be discontinued and any foreign bodies removed if possible, and treatment with echinocandins is increasingly recommended.[64]

COMPLICATIONS

THE ABDOMINAL COMPARTMENT SYNDROME

Intra-abdominal hypertension can occur in critically ill patients, particularly after laparotomy for trauma or sepsis and in association with obesity[65] and excessive fluid administration. Intra-abdominal hypertension has been defined as intra-abdominal pressure (IAP) greater than 12 mm Hg (1.6 kPa) and abdominal compartment syndrome as IAP greater than 20 mm Hg (2.66 kPa) with associated organ dysfunction.[66] IAP can be measured via intravesical pressure,[66] is normally 5–7 mm Hg (0.66–0.93 kPa) in critically ill adults and is increased in patients with increased body mass index. Physiological impairment (including cardiorespiratory, renal, splanchnic and neurological) can occur with acute increases in IAP to levels above 12 mm Hg. However, in the absence of evidence from randomised controlled trials, expert opinion[67] continues to suggest that the development of the abdominal compartment syndrome (IAP >20 mm Hg with associated organ dysfunction) should prompt a search for decompressive measures. Traditionally this involved urgent decompressive laparotomy and temporary fascial closure; however, other measures with potentially less risk should also be sought including sedation and analgesia, neuromuscular blockade, avoidance of the prone position, gastric and colonic decompression, neostigmine or other prokinetic agents, diuresis or ultrafiltration, or percutaneous drainage of intraperitoneal fluid or gas.[67]

THE OPEN ABDOMEN AND ABDOMINAL REPAIR

In 2009 and with the objectives of describing the clinical course, standardising clinical guidelines and facilitating research design, a classification of the open abdomen was produced and more recently was amended[68] with these resultant grades:

- Grade 1, without adherence between bowel and abdominal wall or fixity of the abdominal wall (lateralisation), subdivided into: 1A, clean; 1B, contaminated; and 1C, with enteric leak. (An enteric leak controlled by closure, exteriorisation into a stoma, or a permanent enterocutaneous fistula is considered clean.)
- Grade 2, developing fixation, subdivided into: 2A, clean; 2B, contaminated; and 2C, with enteric leak.
- Grade 3, frozen abdomen, subdivided into: 3A clean and 3B contaminated.
- Grade 4, an established enteroatmospheric fistula, is defined as a permanent enteric leak into the open abdomen, associated with granulation tissue.

The use of a negative-pressure wound technique over porous materials is increasingly recommended[69,70] and has facilitated the care of the patient with an open abdomen including providing decompression and allowing repeat laparotomy, removal of ascitic fluid, prevention of evisceration and encouraging abdominal repair as soon as possible.[71] The management of grade 4 open abdomen remains problematic as proximal defunctioning is often impossible and control of wound contamination may be difficult to achieve, even with the use of a negative-pressure wound care system.

ENTEROCUTANEOUS FISTULAS – INTESTINAL, BILIARY AND PANCREATIC

These are rare complications in intensive care patients but they usually present formidable problems because of their common associations with serious gastrointestinal co-morbidity (e.g. inflammatory bowel disease, intestinal malignancy, pancreatitis) and concurrent severe sepsis. In addition, fistulation through an open abdomen, complex fistulation with multiple collections, inability to proximally defunction or distal intestinal obstruction are commonly present. A standard approach to fistula management should apply[72]

including attention to drainage of sepsis, control of the fistula by drainage or if necessary by proximal defunctioning, protection of the skin from the deleterious effects of the fistula fluid, nutritional support and replacement of fluid and electrolyte losses. Somatostatin analogues reduce enterocutaneous fistula output, shorten time to closure and increase the likelihood of spontaneous closure[72] but may increase the risk of biliary stasis, cholelithiasis, liver dysfunction, and both hypoglycaemia and hyperglycemia. Parenteral nutrition is usually recommended for high output or more proximal enterocutaneous fistulas but more distal intestinal, biliary or pancreatic fistulas can probably be safely treated (after patient stability and good skin protection) with a trial of enteral nutrition.[72] Persistent high-output fistula should lead to investigation of possible causes including complete disruption of the gut lumen, distal obstruction or persistent intra-abdominal sepsis. Definitive operative treatment for fistulas that do not close should await clinical recovery and if possible nutritional repletion.

COLONIC PSEUDO-OBSTRUCTION

Colonic pseudo-obstruction (Ogilvie's syndrome, a severe form of colonic ileus) is not uncommonly encountered in critically ill patients.[73] The syndrome may contribute to ventilatory difficulty, intra-abdominal hypertension and failure of enteral feeding and carries a small risk of spontaneous perforation with high resultant mortality. Conventional conservative treatment includes nasogastric drainage, intravenous fluid replacement and avoidance of opioids and anticholinergic agents. Treatment with neostigmine has been found to be highly effective[74] but may cause symptomatic bradycardia and even cardiac arrest.[75] Colonoscopy or surgery may be required if these measures fail.[73]

KEY REFERENCES

2. Al-Temimi MH, Griffee M, Enniss TM, et al. When is death inevitable after emergency laparotomy? Analysis of the American College of Surgeons National Surgical Quality Improvement Program database. *J Am Coll Surg*. 2012;215(4):503–511.
5. Merlani P, Chenaud C, Mariotti N, et al. Long-term outcome of elderly patients requiring intensive care admission for abdominal pathologies: survival and quality of life. *Acta Anaesthesiol Scand*. 2007;51(5):530–537.
6. Ely EW. The ABCDEF bundle: science and philosophy of how ICU liberation serves patients and families. *Crit Care Med*. 2017;45(2):321–330.
10. Kaukonen KM, Bailey M, Suzuki S, et al. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. *JAMA*. 2014;311(13):1308–1316.
11. Cassell J, Buchman TG, Streat S, et al. Surgeons, intensivists, and the covenant of care: administrative models and values affecting care at the end of life – Updated. *Crit Care Med*. 2003;31(5):1551–1557.
13. Australian and New Zealand Intensive Care Society. *The ANZICS statement on care and decision-making at the end of life for the critically ill. Melbourne: ANZICS*. Online. http://www.anzics.com.au/.
14. Lilja F, Mani K, Wanhainen A. Editor's choice – Trend-break in abdominal aortic aneurysm repair with decreasing surgical workload. *Eur J Vasc Endovasc Surg*. 2017;53(6):811–819.
17. Wanhainen A, Hultgren R, Linné A, et al. Outcome of the Swedish nationwide abdominal aortic aneurysm screening program. *Circulation*. 2016;134(16):1141–1148.
20. Robert M, Juillière Y, Gabet A, et al. Time trends in hospital admissions and mortality due to abdominal aortic aneurysms in France, 2002–2013. *Int J Cardiol*. 2017;234:28–32.
26. Badger S, Forster R, Blair PH, et al. Endovascular treatment for ruptured abdominal aortic aneurysm. *Cochrane Database Syst Rev*. 2017;(5):CD005261.
28. Ersryd S, Djavani-Gidlund K, Wanhainen A, et al. Editor's choice – Abdominal compartment syndrome after surgery for abdominal aortic aneurysm: a nationwide population based study. *Eur J Vasc Endovasc Surg*. 2016;52(2):158–165.
31. Robinson WP, Patel RK, Columbo JA, et al. Contemporary management of acute aortic occlusion has evolved but outcomes have not significantly improved. *Ann Vasc Surg*. 2016;34:178–186.
32. Reginelli A, Iacobellis F, Berritto D, et al. Mesenteric ischemia: the importance of differential diagnosis for the surgeon. *BMC Surg*. 2013;13(suppl 2):S51.
35. Bourcier S, Oudjit A, Goudard G, et al. Diagnosis of non-occlusive acute mesenteric ischemia in the intensive care unit. *Ann Intensive Care*. 2016;6(1):112.
37. Erbel R, Alfonso F, Boileau C, et al. Task force on aortic dissection, European Society of Cardiology. Diagnosis and management of aortic dissection. *Eur Heart J*. 2001;22(18):1642–1681.
40. Mussa FF, Horton JD, Moridzadeh R, et al. Acute aortic dissection and intramural hematoma: a systematic review. *JAMA*. 2016;316(7):754–763.
44. Caleo O, Bocchini G, Paoletta S, et al. Spontaneous non-aortic retroperitoneal hemorrhage: etiology, imaging characterization and impact of MDCT on management. A multicentric study. *Radiol Med*. 2015;120(1):133–148.
45. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017;43(3):304–377.
46. Marshall JC, Maier RV, Jimenez M, et al. Source control in the management of severe sepsis and septic shock: an evidence-based review. *Crit Care Med*. 2004;32(suppl 11):S513–S526.
48. Azuhata T, Kinoshita K, Kawano D, et al. Time from admission to initiation of surgery for source control is a critical determinant of survival in patients with gastrointestinal perforation with associated septic shock. *Crit Care*. 2014;18(3):R87.

56. Treinen C, Lomelin D, Krause C, et al. Acute acalculous cholecystitis in the critically ill: risk factors and surgical strategies. *Langenbecks Arch Surg*. 2015;400(4):421–427.
57. Autenrieth DM, Baumgart DC. Toxic megacolon. *Inflamm Bowel Dis*. 2012;18(3):584–591.
58. Friedrich K, Nüssle S, Rehlen T, et al. Microbiology and resistance in first episodes of spontaneous bacterial peritonitis: implications for management and prognosis. *J Gastroenterol Hepatol*. 2016;31(6):1191–1195.
59. Salerno F, Navickis RJ, Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: a meta-analysis of randomized trials. *Clin Gastroenterol Hepatol*. 2013;11(2):123–130.
60. Chavez-Tapia NC, Soares-Weiser K, Brezis M, et al. Antibiotics for spontaneous bacterial peritonitis in cirrhotic patients. *Cochrane Database Syst Rev*. 2009;(1): CD002232.
61. Carmeci C, Muldowney W, Mazbar SA, et al. Emergency laparotomy in patients on continuous ambulatory peritoneal dialysis. *Am Surg*. 2001;67(7): 615–618.
62. Marshall JC, Innes M. Intensive care unit management of intra-abdominal infection. *Crit Care Med*. 2003;31(8):2228–2237.
63. De Waele J, Lipman J, Sakr Y, et al. Abdominal infections in the intensive care unit: characteristics, treatment and determinants of outcome. *BMC Infect Dis*. 2014;14:420.
66. Malbrain ML, Cheatham ML, Kirkpatrick A, et al. Results from the international conference of experts on intra-abdominal hypertension and abdominal compartment syndrome. I. Definitions. *Intensive Care Med*. 2006;32(11):1722–1732.
67. Kirkpatrick AW, Roberts DJ, De Waele J, Pediatric Guidelines Sub-Committee for the World Society of the Abdominal Compartment Syndrome, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med*. 2013;39(7):1190–1206.
70. Cristaudo A, Jennings S, Gunnarsson R, et al. Complications and mortality associated with temporary abdominal closure techniques: a systematic review and meta-analysis. *Am Surg*. 2017;83(2):191–216.
71. Sugrue M. Abdominal compartment syndrome and the open abdomen: any unresolved issues? *Curr Opin Crit Care*. 2017;23(1):73–78.
72. Kumpf VJ, de Aguilar-Nascimento JE, Diaz-Pizarro Graf JI, et al. ASPEN-FELANPE Clinical Guidelines: Nutrition support of adult patients with enterocutaneous fistula. *JPEN J Parenter Enteral Nutr*. 2017;41(1):104–112.
73. Ross SW, Oommen B, Wormer BA, et al. Acute colonic pseudo-obstruction: defining the epidemiology, treatment, and adverse outcomes of Ogilvie's syndrome. *Am Surg*. 2016;82(2):102–111.
74. Ponec RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med*. 1999;341(3):137–141.


Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Streat SJ, Plank LD, Hill GL. Overview of modern management of patients with critical injury and severe sepsis. *World J Surg*. 2000;24(6):655–663.
2. Al-Temimi MH, Griffee M, Enniss TM, et al. When is death inevitable after emergency laparotomy? Analysis of the American College of Surgeons National Surgical Quality Improvement Program database. *J Am Coll Surg*. 2012;215(4):503–511.
3. Hutchins RR, Gunning MP, Lucas DN, et al. Relaparotomy for suspected intraperitoneal sepsis after abdominal surgery. *World J Surg*. 2004;28(2): 137–141.
4. Iwashyna TJ, Ely EW, Smith DM, et al. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010;304(16):1787–1794.
5. Merlani P, Chenaud C, Mariotti N, et al. Long-term outcome of elderly patients requiring intensive care admission for abdominal pathologies: survival and quality of life. *Acta Anaesthesiol Scand*. 2007;51(5):530–537.
6. Ely EW. The ABCDEF bundle: science and philosophy of how ICU liberation serves patients and families. *Crit Care Med*. 2017;45(2):321–330.
7. Sznajder M, Aegerter P, Launois R, et al. A cost-effectiveness analysis of stays in intensive care units. *Intensive Care Med*. 2001;27(1):146–153.
8. Cassell J. *Life and Death in Intensive Care*. Philadelphia, PA: Temple University Press; 2005.
9. Rushdie S. *Midnight's Children*. New York, NY: Random House; 2006:160.
10. Kaukonen KM, Bailey M, Suzuki S, et al. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. *JAMA*. 2014;311(13):1308–1316.
11. Cassell J, Buchman TG, Streat S, et al. Surgeons, intensivists, and the covenant of care: administrative models and values affecting care at the end of life – updated. *Crit Care Med*. 2003;31(5):1551–1557.
12. Rabow MW, Hardie GE, Fair JM, et al. End-of-life care content in 50 textbooks from multiple specialties. *JAMA*. 2000;283(6):771–778.
13. Australian and New Zealand Intensive Care Society. *The ANZICS statement on care and decision-making at the end of life for the critically ill. Melbourne: ANZICS*. Online. http://www.anzics.com.au/.
14. Lilja F, Mani K, Wanhainen A. Editor's choice – trend-break in abdominal aortic aneurysm repair with decreasing surgical workload. *Eur J Vasc Endovasc Surg*. 2017;53(6):811–819.
15. Svensjö S, Björck M, Gürtelschmid M, et al. Low prevalence of abdominal aortic aneurysm among 65-year-old Swedish men indicates a change in the epidemiology of the disease. *Circulation*. 2011; 124(10):1118–1123.
16. Ali MU, Fitzpatrick-Lewis D, Miller J, et al. Screening for abdominal aortic aneurysm in asymptomatic adults. *J Vasc Surg*. 2016;64(6): 1855–1868.
17. Wanhainen A, Hultgren R, Linné A, et al. Outcome of the Swedish nationwide abdominal aortic aneurysm screening program. *Circulation*. 2016; 134(16):1141–1148.
18. Mofidi R, Goldie VJ, Kelman J, et al. Influence of sex on expansion rate of abdominal aortic aneurysms. *Br J Surg*. 2007;94(3):310–314.
19. Levin DC, Rao VM, Parker L, et al. Endovascular repair vs open surgical repair of abdominal aortic aneurysms: comparative utilization trends from 2001 to 2006. *J Am Coll Radiol*. 2009;6:506–509.
20. Robert M, Juillière Y, Gabet A, et al. Time trends in hospital admissions and mortality due to abdominal aortic aneurysms in France, 2002-2013. *Int J Cardiol*. 2017;234:28–32.
21. Rose J, Civil I, Koelmeyer T, et al. Ruptured abdominal aortic aneurysms: clinical presentation in Auckland 1993–1997. *ANZ J Surg*. 2001;71(6): 341–344.
22. Aburahma AF, Woodruff BA, Stuart SP, et al. Early diagnosis and survival of ruptured abdominal aortic aneurysms. *Am J Emerg Med*. 1991;9(2): 118–121.
23. Acheson AG, Graham AN, Weir C, et al. Prospective study on factors delaying surgery in ruptured abdominal aortic aneurysms. *J R Coll Surg Edinb*. 1998;43(3):182–184.
24. Starnes BW, Quiroga E, Hutter C, et al. Management of ruptured abdominal aortic aneurysm in the endovascular era. *J Vasc Surg*. 2010;51(1):9–17.
25. Prance SE, Wilson YG, Cosgrove CM, et al. Ruptured abdominal aortic aneurysms: selecting patients for surgery. *Eur J Vasc Endovasc Surg*. 1999;17(2): 129–132.
26. Badger S, Forster R, Blair PH, et al. Endovascular treatment for ruptured abdominal aortic aneurysm. *Cochrane Database Syst Rev*. 2017;(5):CD005261.
27. Sörelius K, Wanhainen A, Furebring M, et al. Nationwide study of the treatment of mycotic abdominal aortic aneurysms comparing open and endovascular repair. *Circulation*. 2016;134(23): 1822–1832.
28. Ersryd S, Djavani-Gidlund K, Wanhainen A, et al. Editor's choice – Abdominal compartment syndrome after surgery for abdominal aortic aneurysm: a nationwide population based study. *Eur J Vasc Endovasc Surg*. 2016;52(2):158–165.
29. Rodgers A, Walker N, Schug S, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. *BMJ*. 2000;321(7275): 1493–1497.
30. Meesters RC, van der Graaf Y, Vos A, et al. Ruptured aortic aneurysm: early postoperative prediction of mortality using an organ system failure score. *Br J Surg*. 1994;81(4):512–516.
31. Robinson WP, Patel RK, Columbo JA, et al. Contemporary management of acute aortic occlusion has evolved but outcomes have not significantly improved. *Ann Vasc Surg*. 2016;34:178–186.

32. Reginelli A, Iacobellis F, Berritto D, et al. Mesenteric ischemia: the importance of differential diagnosis for the surgeon. *BMC Surg*. 2013;13(suppl 2):S51.
33. Corcos O, Castier Y, Sibert A, et al. Effects of a multimodal management strategy for acute mesenteric ischemia on survival and intestinal failure. *Clin Gastroenterol Hepatol*. 2013;11(2):158–165.
34. Leone M, Bechis C, Baumstarck K, et al. Outcome of acute mesenteric ischemia in the intensive care unit: a retrospective, multicenter study of 780 cases. *Intensive Care Med*. 2015;41(4):667–676.
35. Bourcier S, Oudjit A, Goudard G, et al. Diagnosis of non-occlusive acute mesenteric ischemia in the intensive care unit. *Ann Intensive Care*. 2016;6(1):112.
36. Zagli G, Prosperi P, Parodo J, et al. Conservative treatment of non-occlusive mesenteric ischaemia with temporary vacuum-assisted closure therapy. *Br J Anaesth*. 2011;106(1):151–152.
37. Erbel R, Alfonso F, Boileau C, et al. Task force on aortic dissection, European Society of Cardiology. Diagnosis and management of aortic dissection. *Eur Heart J*. 2001;22(18):1642–1681.
38. Kurz SD, Falk V, Kempfert J, et al. Insight into the incidence of acute aortic dissection in the German region of Berlin and Brandenburg. *Int J Cardiol*. 2017;241:326–329.
39. Meszaros I, Morocz J, Szlavi J, et al. Epidemiology and clinicopathology of aortic dissection. *Chest*. 2000;117(5):1271–1278.
40. Mussa FF, Horton JD, Moridzadeh R, et al. Acute aortic dissection and intramural hematoma: a systematic review. *JAMA*. 2016;316(7):754–763.
41. Alfson DB, Ham SW. Type B aortic dissections: current guidelines for treatment. *Cardiol Clin*. 2017;35(3):387–410.
42. Ivascu FA, Janczyk RJ, Bair HA, et al. Spontaneous retroperitoneal hemorrhage. *Am J Surg*. 2005;189(3):345–347.
43. Nazarian LN, Lev-Toaff AS, Spettell CM, et al. CT assessment of abdominal hemorrhage in coagulopathic patients: impact on clinical management. *Abdom Imaging*. 1999;24(3):246–249.
44. Caleo O, Bocchini G, Paoletta S, et al. Spontaneous non-aortic retroperitoneal hemorrhage: etiology, imaging characterization and impact of MDCT on management. A multicentric study. *Radiol Med*. 2015;120(1):133–148.
45. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017;43(3):304–377.
46. Marshall JC, Maier RV, Jimenez M, et al. Source control in the management of severe sepsis and septic shock: an evidence-based review. *Crit Care Med*. 2004;32(suppl 11):S513–S526.
47. Thomas MG, Streat SJ. Infections in intensive care patients. In: Finch R, Greenwood D, Norrby R, et al., eds. *Antibiotic and Chemotherapy*. 9th ed. London, UK: Churchill Livingstone; 2010.
48. Azuhata T, Kinoshita K, Kawano D, et al. Time from admission to initiation of surgery for source control is a critical determinant of survival in patients with gastrointestinal perforation with associated septic shock. *Crit Care*. 2014;18(3):R87.
49. Sartelli M, Catena F, Ansaloni L, et al. Complicated intra-abdominal infections in Europe: a comprehensive review of the CIAO study. *World J Emerg Surg*. 2012;7(1):36.
50. van Ruler O, Lamme B, Gouma DJ, et al. Variables associated with positive findings at relaparotomy in patients with secondary peritonitis. *Crit Care Med*. 2007;35(2):468–476.
51. de Ruiter J, Weel J, Manusama E, et al. The epidemiology of intra-abdominal flora in critically ill patients with secondary and tertiary abdominal sepsis. *Infection*. 2009;37(6):522–527.
52. Wong PF, Gilliam AD, Kumar S, et al. Antibiotic regimens for secondary peritonitis of gastrointestinal origin in adults. *Cochrane Database Syst Rev*. 2005;(2):CD004539.
53. Lan Cheong Wah D, Christophi C, Muralidharan V. Acute cholangitis: current concepts. *ANZ J Surg*. 2017;87(7–8):554–559. doi:10.1111/ans.13981.
54. Ceribelli C, Adami EA, Mattia S, et al. Bedside diagnostic laparoscopy for critically ill patients: a retrospective study of 62 patients. *Surg Endosc*. 2012;26(12):3612–3615.
55. Kalliafas S, Ziegler DW, Flancbaum L, et al. Acute acalculous cholecystitis: incidence, risk factors, diagnosis, and outcome. *Am Surg*. 1998;64(5):471–475.
56. Treinen C, Lomelin D, Krause C, et al. Acute acalculous cholecystitis in the critically ill: risk factors and surgical strategies. *Langenbecks Arch Surg*. 2015;400(4):421–427.
57. Autenrieth DM, Baumgart DC. Toxic megacolon. *Inflamm Bowel Dis*. 2012;18(3):584–591.
58. Friedrich K, Nüssle S, Rehlen T, et al. Microbiology and resistance in first episodes of spontaneous bacterial peritonitis: implications for management and prognosis. *J Gastroenterol Hepatol*. 2016;31(6):1191–1195.
59. Salerno F, Navickis RJ, Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: a meta-analysis of randomized trials. *Clin Gastroenterol Hepatol*. 2013;11(2):123–130.
60. Chavez-Tapia NC, Soares-Weiser K, Brezis M, et al. Antibiotics for spontaneous bacterial peritonitis in cirrhotic patients. *Cochrane Database Syst Rev*. 2009;(1):CD002232.
61. Carmeci C, Muldowney W, Mazbar SA, et al. Emergency laparotomy in patients on continuous ambulatory peritoneal dialysis. *Am Surg*. 2001;67(7):615–618.
62. Marshall JC, Innes M. Intensive care unit management of intra-abdominal infection. *Crit Care Med*. 2003;31(8):2228–2237.
63. De Waele J, Lipman J, Sakr Y, et al. Abdominal infections in the intensive care unit: characteristics, treatment and determinants of outcome. *BMC Infect Dis*. 2014;14:420.

64. Bailly S, Leroy O, Azoulay E, et al. Impact of echinocandin on prognosis of proven invasive candidiasis in ICU: a post-hoc causal inference model using the AmarCAND2 study. *J Infect*. 2017;74(4):408–417.
65. Kim IB, Prowle J, Baldwin I, et al. Incidence, risk factors and outcome associations of intra-abdominal hypertension in critically ill patients. *Anaesth Intensive Care*. 2012;40(1):79–89.
66. Malbrain ML, Cheatham ML, Kirkpatrick A, et al. Results from the international conference of experts on intra-abdominal hypertension and abdominal compartment syndrome. I. Definitions. *Intensive Care Med*. 2006;32(11):1722–1732.
67. Kirkpatrick AW, Roberts DJ, De Waele J, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med*. 2013;39(7):1190–1206.
68. Björck M, Kirkpatrick AW, Cheatham M, et al. Amended classification of the open abdomen. *Scand J Surg*. 2016;105(1):5–10.
69. Atema JJ, Gans SL, Boermeester MA. Systematic review and meta-analysis of the open abdomen and temporary abdominal closure techniques in non-trauma patients. *World J Surg*. 2015;39(4):912–925.
70. Cristaudo A, Jennings S, Gunnarsson R, et al. Complications and mortality associated with temporary abdominal closure techniques: a systematic review and meta-analysis. *Am Surg*. 2017;83(2):191–216.
71. Sugrue M. Abdominal compartment syndrome and the open abdomen: any unresolved issues? *Curr Opin Crit Care*. 2017;23(1):73–78.
72. Kumpf VJ, de Aguilar-Nascimento JE, Diaz-Pizarro Graf JI, et al. ASPEN-FELANPE Clinical Guidelines: nutrition support of adult patients with enterocutaneous fistula. *JPEN J Parenter Enteral Nutr*. 2017;41(1):104–112.
73. Ross SW, Oommen B, Wormer BA, et al. Acute colonic pseudo-obstruction: defining the epidemiology, treatment, and adverse outcomes of Ogilvie's syndrome. *Am Surg*. 2016;82(2):102–111.
74. Ponec RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med*. 1999;341(3):137–141.
75. Maher L, Young PJ. Cardiac arrest complicating neostigmine use for bowel opening in a critically ill patient. *Crit Care Resusc*. 2011;13(3):192–193.

46

Implications of solid tumours for intensive care

Timothy Wigmore, Pascale Gruber

The term solid tumour refers to masses of tissue not containing cysts or liquid. There are over 200 types and they are classified according to the tissue of origin. The majority arise from epithelial tissues and are termed carcinomas. They are further differentiated into squamous cell (which include tumours of skin, oropharynx, oesophagus, cervix and lung) and adeno (which include those originating in lung, colon, breast, pancreas and stomach). Rarer tumours originate from connective tissue (sarcomas), the neuroectoderm (gliomas, glioblastomas, neuroblastomas, medulloblastomas) or germ cells (teratomas, seminomas and choriocarcinomas).

There were 12.7 million new cancer cases worldwide in 2008 and this number is expected to reach 26 million by 2030.[1] This increase is attributable to an ageing population and lifestyle changes, with diet, lack of physical activity and obesity all playing a role. The most common cancers worldwide are lung (12.7% of the total), breast (10.9%) and colorectal cancers (9.7%) whilst the commonest causes of cancer deaths are lung (18.2% of the total), stomach (9.7%) and liver cancer (9.2%).

This case load presents a substantial challenge to intensive care physicians. In the SOAP (Sepsis Occurrence in Acutely Ill Patients) study,[2] cancer patients accounted for 15% of all intensive care unit (ICU) admissions, 85% of which were solid tumours. The Intensive Care National Audit and Research Centre case-mix review of 128 adult general ICUs in the United Kingdom demonstrated that bowel and oesophageal tumours accounted for the fourth and eighth most common reason for ICU admission, respectively.[3]

Patients with solid cancers present to ICU either postoperatively, with complications of cancer treatment, as a result of the underlying cancer itself or with other co-morbidities unrelated to the cancer.

CANCER TREATMENTS

Cancer treatments fall broadly into the three main categories: chemotherapy, radiotherapy and surgery. Many patients have a combination of all three, and it is increasingly common for patients to receive neoadjuvant chemotherapy prior to surgery to facilitate surgical resection. Chemotherapeutic agents affect DNA synthesis, structure or repair and are usually unselective in that they affect all rapidly dividing cells. They may therefore also affect cells in the gut (with resulting mucositis and diarrhoea), bone marrow (leading to thrombocytopenia, anaemia and immunosuppression) and hair (causing alopecia). Additionally, many chemotherapeutic drugs have agent-specific side effects which may have implications for the ICU (Table 46.1). For example, anthracycline or trastuzumab-related cardiomyopathy, bleomycin-related lung injury or ifosfamide-induced encephalopathy.

Agents commonly used in combinations are represented by acronyms. Confusingly, the same agent may be represented by different letters depending on whether the generic or brand name has been used, and equally multiple agents may be represented by the same letter (Table 46.2).

SPECIFIC CHEMOTHERAPY-INDUCED TOXICITIES

BLEOMYCIN-RELATED LUNG INJURY

Bleomycin is an antibiotic derived from Streptomyces spp. which causes DNA scission through the generation of oxygen superoxide radicals. It is used for the treatment of head and neck squamous cell carcinomas, cancers of the cervix and germ cell tumours. It causes a pneumonitis in up to 40% of patients, with subsequent mortality in up to 2%.[4] Toxicity is caused by the generation of oxygen free radicals with subsequent alveolitis and fibrosis. This is exacerbated by high oxygen concentrations.

IFOSFAMIDE NEUROTOXICITY

Ifosfamide is an alkylating agent used in the treatment of head and neck, cervical, ovarian, breast and lung cancers. It causes encephalopathy in between 10% and 30% of patients, with a severity ranging from mild confusion to coma. The diagnosis is essentially

ABSTRACT

The number of patients affected by cancer continues to increase, as does the range of treatments on offer and survival. As a consequence, many more patients are now presenting to the critical care unit with treatment-related organ dysfunction, complications of their cancer or intercurrent illnesses. Treatment complexity has also increased, and a knowledge of common regimes and their associated toxicities is a necessity, as is a knowledge of the common cancer-related emergencies. In this chapter we consider both and also detail management, prognostication and emerging trends in outcome.

KEYWORDS

Cancer
solid tumour
chemotherapy
immunotherapy
radiotherapy
SVC obstruction
superior mediastinal syndrome
spinal cord compression

Table 46.1 Characteristic toxicities of commonly used chemotherapeutic agents

DRUG NAME OR GROUP	SOLID TUMOURS FOR WHICH TYPICALLY USED	MODE OF ACTION	CHARACTERISTIC TOXICITIES
Anthracyclines – doxorubicin, idarubicin	Breast, bladder, stomach, lung, ovary, thyroid	Intercalates DNA	Cardiotoxicity, 'hand-foot syndrome'
Alkylating agents – cyclophosphamide, ifosfamide	Many	Inhibits DNA replication	Immunosuppression, haemorrhagic cystitis, LV dysfunction, hyponatraemia
• Ifosfamide	Ovarian, breast, lung, testicular		Neurotoxicity
• Melphalan	Multiple myeloma, ovarian		Myelosuppression, interstitial pneumonitis
Bleomycin	Squamous cell, testicular	Induces DNA strand breaks	Pulmonary fibrosis
Cyproterone	Prostate	Inhibit tumour 'flare'	Hepatotoxicity
Fluouracil	Colorectal, pancreatic	Thymidylate synthase inhibitor	Cardiotoxicity, neurodegeneration
Ipilimumab	Metastatic melanoma	Anti-CTLA4 antibody	Diarrhoea, colitis, fatigue, transaminitis, hypophysitis
Methotrexate	Choriocarcinoma	Inhibits folic acid metabolism	Mucositis, pulmonary fibrosis, hepatitis, immunosuppression
Nivolumab	Metastatic melanoma, renal	Anti-PD-1 antibody	Colitis, dermatitis, pneumonitis, hepatitis, lymphopenia, nephritis
Platinum analogues, e.g. carboplatin, cisplatin, oxaliplatin	Lymphoma, sarcoma, ovarian, small cell lung	Selective inhibition of tumour DNA synthesis	Myelosuppression, nephro/oto/neurotoxicity, hypomagnesaemia with cisplatin
Procarbazine	Glioblastoma multiforme	Causes free radical formation	Myelosuppression, hypersensitivity rash
Monoclonal antibodies			
• Bevacizumab (Avastin)	Colon, non–small-cell lung	Inhibits VEGF, inhibiting cell growth	Mucocutaneous bleeding, GI perforation
• Cetuximab	Colorectal, squamous cell, head and neck	Binds to EGFR, inhibits cell division	Severe hypersensitivity reactions
• Trastuzumab (Herceptin)	Breast	Binds HER2 receptor, inhibits cell division	Cardiotoxicity, hypersensitivity
Tamoxifen	Breast	Oestrogen receptor antagonist	Thrombosis, endometrial Ca, strokes
Taxanes, e.g. docetaxel, paclitaxel	Breast, prostate, non–small-cell lung	Impair mitosis	Cardiac conduction defects, peripheral neuropathy, hypersensitivity
Topoisomerase inhibitors, e.g. irinotecan, topotecan	Colon	Inhibits DNA replication	Acute cholinergic syndrome
Vinca alkaloids – vincristine, vinblastine	Nephroblastoma	Inhibits assembly of microtubules arresting mitosis	Neuropathic ileus, peripheral neuropathy, hyponatraemia

EGFR, Epidermal growth factor receptor; *GI*, gastrointestinal; *HER2*, human epidermal growth factor 2; *LV*, left ventricular; *PD-1*, programmed death receptor-1; *VEGF*, vascular endothelial growth factor.

Table 46.2 Examples of commonly used chemotherapy regimes

AC	Breast cancer	Adriamycin, cyclophosphamide
BEP	Germ cell tumours	Bleomycin, etoposide, cisplatin
CAV	Lung cancer	Cyclophosphamide, adriamycin, vincristine
CEF	Breast cancer	Cyclophosphamide, epirubicin, fluorouracil
FOLFOX	Colorectal tumours	Fluorouracil, leucovorin (folinic acid), oxaliplatin
FOLFIRI	Colorectal tumours	Fluorouracil, leucovorin (folinic acid), irinotecan
PCV	Brain tumours	Procarbazine, CCNU (lomustine), vincristine
VIP	Germ cell tumours	Ifosfamide, cisplatin, etoposide

one of exclusion with normal brain imaging and an electroencephalography (EEG) demonstrating metabolic encephalopathy. The aetiology is thought to be related to direct toxicity from metabolites of ifosfamide, notably chloroacetaldehyde or dicarboxylic acid. The incidence is greater in those with pre-existing low albumin, raised creatinine or with cisplatin pretreatment.[5] The natural history of the encephalopathy is to regress over a period of days to weeks after cessation of ifosfamide. Methylene blue (50 mg 4-hourly intravenously) has been shown to ameliorate or even terminate symptoms.[6]

ANTHRACYCLINE CARDIOMYOPATHY

Anthracylines, such as daunorubicin, doxorubicin and epirubicin, are widely used anti-cancer agents. Anthracyclines can cause both acute and chronic cardiac dysfunction. Acutely, 5% of patients suffer from arrhythmias or acute cardiac failure that resolves with standard treatment. Chronically, anthracyclines cause a dose-dependent cardiomyopathy which becomes apparent anywhere between 3 months and several years after treatment and can result in severe myocardial dysfunction. Initial treatment is with ACE inhibition, but the full range of medical therapies for heart failure may be required, including cardiac resynchronization.[7]

TRASTUZUMAB (HERCEPTIN) CARDIOTOXICITY

Trastuzumab may cause a non–dose-related, reversible myocardial dysfunction. This appears to involve an element of myocardial stunning rather than myocyte destruction. It is often asymptomatic but can cause symptoms of cardiac failure in approximately 12% of patients after 5 years of treatment.[8] Trastuzumab is commonly combined with anthracyclines, which increases the incidence of heart failure at 5 years to 20%. Its occurrence does not preclude future dosing providing cardiac function has recovered prior to further use.[9]

IMMUNOTHERAPY

Immunotherapy is being increasingly utilised in the treatment of solid tumours, with impressive results being obtained in tumours such as metastatic melanoma that would have previously carried an almost universal poor prognosis. Check point inhibitors that augment the ability of the immune system to target tumour cells through the targeting of receptors (check points) such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death receptor-1 (PD-1) that inhibit the proliferation and function of T cells is one such group of drugs. Examples include ipilimumab (a CTLA-4 inhibitor) and nivolumab (a PD-1 inhibitor). Side effects are related to immune dysfunction, with colitis, dermatitis, hepatitis, pneumonitis, uveitis and encephalopathy all being commonly encountered, with an incidence of over 60% in patients receiving ipilimumab. Some 10%–15% of these patients will have grade 3–4 toxicity (life threatening) which may require admission to the ICU. Patients may also manifest with endocrine dysfunction, with thyroiditis, diabetes and hypophysitis observed.

Management is supportive plus treatment with immunosuppressants (steroids, infliximab which is a TNF-alpha inhibitor, tacrolimus and mycophenolate). The majority of patients recover spontaneously, but approximately 25% of patients will have long-term sequelae.[10]

RADIOTHERAPY

Radiotherapy causes damage to cells through the production of oxygen free radicals by the ionisation of water molecules. These in turn cause damage to cellular DNA. Damage to healthy surrounding tissue is minimised by targeting the radiation beam through multiple planes that intersect within the tumour. Despite this, radiation commonly causes acute inflammation and subsequent fibrosis in the tissues through which it passes. Common examples are pericarditis, pericardial, myocardial and lung fibrosis. This can cause organ dysfunction, particularly when combined with a chemotherapeutic agent known to have toxicities associated with that same organ.

DISEASE-RELATED ADMISSIONS

A number of oncological emergencies can occur that require admission to the ICU.

TUMOUR LYSIS SYNDROME

Tumour lysis occasionally follows treatment for bulky solid tumours, particularly small cell lung tumours, neuroblastomas and breast carcinomas.[11,12] The syndrome results from the rapid death of large numbers of tumour cells. This may occur spontaneously but usually follows chemotherapy, radiotherapy and occasionally surgery, with a consequent release of high concentration of intracellular contents. This results in a constellation of metabolic abnormalities, specifically hyperuricaemia (and subsequent nephropathy due to deposition of uric acid crystals in the distal tubules), hyperkalaemia, hyperphosphataemia and hypocalcaemia (due to the precipitation of calcium phosphate). The priority with tumour lysis syndrome is prevention, and patients with high- or intermediate-risk tumours should receive intravenous hydration and rasburicase (recombinant urate oxidase) as prophylaxis.[13] Rasburicase has generally replaced allopurinol as the agent of choice. Rasburicase catalyses the formation of water-soluble allantoin from uric acid, resulting in a rapid reduction in uric acid levels. In contrast, allopurinol prevents uric acid formation through the inhibition of xanthine oxidase which results in a slower decrease in uric acid concentration and increases the concentrations of xanthine which can result in xanthinuria, in itself a cause of renal failure.[14] Urinary alkinisation reduces the risk of uric acid precipitation by rendering it more water-soluble but simultaneously increases the risk of calcium phosphate precipitation in the kidneys and other organs. Hyperkalaemia and hyperphosphataemia sometimes require renal replacement therapy.

SPINAL CORD COMPRESSION

Breast, prostate, lung and kidney cancers have a predilection for bony metastasis. High spinal cord compression may require semi-urgent invasive mechanical ventilation. Treatment usually takes the form of steroids followed either by surgery or by radiotherapy.

CARDIAC TAMPONADE

Pericardial effusions due to epicardial metastasis or mediastinal lymph drainage obstruction are relatively common with advanced lung and breast cancers.[15] Cardiac tamponade is less frequent and may develop with pericardial effusions as small as 200 mL if accumulated rapidly. On echocardiography, cardiac tamponade classically demonstrates right atrial or ventricular diastolic collapse, increase in right ventricular size or failure of inferior vena cava collapse on inspiration. The management of cardiac tamponade in the acute setting is pericardiocentesis with subsequent pericardial window formation. For some tumours, treatment of the underlying cancer with chemotherapy and/or radiotherapy will result in longer-term resolution.

ELECTROLYTE DISORDERS

Rapid and life-threatening changes in electrolyte concentrations may result from paraneoplastic disorders, losses from treatment-induced diarrhoea or renal dysfunction. Paraneoplastic disorders result from the secretion of hormones or hormone-like substances from tumours. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) typically occurs in the setting of small cell lung carcinomas which account for 80% of the total incidences of SIADH. SIADH also occurs with pancreatic, colonic, prostate, duodenal and head and neck tumours. It can be seen with cisplatin, ifosfamide, vincristine, vinblastine and cyclophosphamide use. Hyponatraemia is particularly marked when secondary to cyclophosphamide due to concurrent fluid loading to reduce the risk of haemorrhagic cystitis.[16] Chronic mild hyponatraemia (Na+> 125 mmol/L) rarely requires intervention while severe hyponatraemia (Na+<125 mmol/L) should be cautiously corrected to avoid osmotic demyelination.

Hypercalcaemia represents the most common metabolic consequence of solid tumours and occurs in 10%–20% of patients.[17] The release of parathyroid hormone-related peptides from lung, head and neck, kidney and pancreatic cancers, together with osteolytic calcium release from tumours with bony metastases (e.g. breast and prostate) can result in life-threatening hypercalcaemia. Treatment of hypercalcaemia is with a combination of saline rehydration, calcitonin, and bisphosphonates (e.g. pamidronate). Saline corrects hypercalcaemic-induced dehydration, calcitonin reduces resorption from bone by blocking osteoclast maturation and increasing renal calcium excretion, and bisphosphonates cause osteoclasts to apoptose.[18] The response to furosemide is variable and often requires the use of high doses resulting in electrolyte abnormalities, and is therefore not recommended.[19] The effect of bisphosphonates may be poor in those with parathyroid hormone related protein (PTHrP) induced hypercalcaemia, although zoledronic acid may be useful.[20,21]

Hypokalaemia requiring admission to the ICU is often the result of diarrhoea due to chemotherapy or radiotherapy. Hypokalaemia may also be caused by adrenocorticotropic hormone (ACTH)-producing lung tumours or from tumours that produce insulin.

Electrolyte disorders may be of sufficient severity to be life threatening requiring immediate correction with intravenous replacement. They are also often accompanied by a normal anion gap hyperchloraemic metabolic acidosis caused by concomitant bicarbonate loss. This can result in marked acidaemia with consequent respiratory compensation that can lead to exhaustion in an already debilitated patient. It is best managed

with bicarbonate replacement, although care needs to be taken to avoid worsening hypokalaemia.

SUPERIOR MEDIASTINAL SYNDROME

Patients with anterior mediastinal compression typically present to the ICU either postoperatively or as an emergency with airway obstruction, cardiac compression or superior vena cava (SVC) obstruction. The aetiology in adults is most commonly a thymoma, although lymphomas, germ cell tumours and sarcomas can also be responsible.[22] Airway obstruction may occur due to compression of the trachea or bronchi. In an emergency there is often little time for formal assessment. Imaging may be available in the form of computed tomography (CT) or magnetic resonance imaging (MRI) demonstrating the level and degree of compression. A decrease in cross-sectional area of 50% is predictive of airway complications.[23,24] If supine imaging is unavailable, and symptoms permit, a CT scan can be conducted with the patient at 20–30 degrees of head up, or in lateral or prone position to minimise airway compromise. Flow volume loops can demonstrate intrathoracic or extrathoracic airway obstruction, although correlation with subsequent airway obstruction is variable.

Induction of anaesthesia may result in catastrophic airway obstruction due to a reduction in intrathoracic volume, increased size of (often very vascular) tumours with increased central blood volume, and increased compressibility of airways with reduction in smooth muscle tone. Equally, cardiovascular collapse may occur due to compression of the pulmonary arteries or SVC. Should it be necessary to intubate the patient with superior mediastinal syndrome, there are a number of key points that need to be considered.[25,26]

1. Establish venous access in the lower half of the body in case of superior vena caval obstruction which would result in significantly slowed transit of administered drugs and fluids.
2. Have intravenous fluid administration established to minimise the cardiovascular effects of vascular obstruction during induction.
3. In high-risk cases, establishment of femoral venovenous bypass under local anaesthesia prior to induction offers a route out in the event of complete airway obstruction. Having bypass on 'standby' is unlikely to be adequate due to the time required to establish it in the event of emergency.
4. Gaseous induction with preservation of spontaneous respiration or, if circumstances permit, an awake fibreoptic intubation to assess the degree of airway obstruction is advisable.
5. Neuromuscular blockade is best avoided. Subsequent positive-pressure ventilation (in concert with smooth muscle relaxation) may cause worsened bronchiolar obstruction leading to atelectasis and ventilation/perfusion mismatch. It will also increase the pressure of the mass on mediastinal structures such as the SVC, heart and pulmonary arteries with consequent potential cardiovascular collapse. If blockade is absolutely necessary, a trial of short-acting paralysis (e.g. with suxamethonium) should be undertaken first.
6. Should airway obstruction or cardiovascular collapse occur following intubation, repositioning the patient either sitting up, laterally or prone may be effective by reducing the mass effect. If this is ineffective and venovenous bypass is not possible, then emergency thoracotomy with manual displacement of the mass can be considered.

SUPERIOR VENA CAVA COMPRESSION

SVC compression may be part of superior mediastinal syndrome but often occurs in isolation. When caused by tumour, the aetiology is normally lung cancer, lymphoma or a germ cell tumour.[27] The clinical presentation depends on the time period during which the compression has evolved as collaterals involving the azygos, internal mammary or oesophageal vessels develop over time and relieve the pressure. Patients typically present with facial and arm swelling, dyspnoea, cough and dysphagia. Those presenting to the ICU are likely to have more immediately life-threatening features either of airway obstruction or cerebral oedema, in which case they may have stridor and a headache or a decreased level of consciousness.[28] In the absence of these features, SVC obstruction does not represent a true emergency and management should await histological diagnosis if one has yet to be made.[29] Endovascular stenting results in rapid resolution of symptoms in the vast majority of cases[30] and can be undertaken even in cases of complete obstruction. Radiotherapy is also effective in reducing tumour burden and achieving disease control in those cancers that are radiosensitive, (which includes the majority responsible for SVC obstruction), but takes up to 4 weeks to take effect and can make subsequent histological diagnosis impossible. Steroids such as dexamethasone have a role in cases where the tumour is known to be steroid sensitive (for example, with lymphomas or thymomas) but are otherwise not indicated.[31]

NEUTROPENIA

Neutropenia is a common occurrence following the administration of chemotherapy and obviously predisposes the patient to infection. Care of the neutropenic patient in the intensive care setting is detailed in the chapter 'Haematological malignancies and critical care'.

USE OF CHEMOTHERAPY IN THE INTENSIVE CARE UNIT SETTING

There is little published data on the administration of chemotherapy for solid tumours in the ICU.

Chemotherapy in the ICU should be considered if its administration results in amelioration of life-threatening symptoms or a significant chance of improved patient outcome.[32] Prognostic indicators following chemotherapy administration appear to be similar to those for the general critically ill patient with cancer.[33]

THE EFFECT OF CRITICAL CARE ON CANCER

There has been little work looking into the effect of an ICU stay on tumour progression but much of what happens to a patient during this period (be it disease or treatment mediated) has an impact on the function of the immune system and a potential consequent effect on tumour growth and metastases. The systemic inflammatory response syndrome associated with critical illness has been shown to decrease 5-year survival in patients with lung cancer.[34] Studies conducted in animals have shown that surgery in itself promotes metastasis. This is likely due to a combination of production of pro-inflammatory stimulators of tumour growth, the release of tumour cells directly into the circulation and the stress response. The stress response is mediated through the effect of catecholamines. Adrenaline acts via beta-2 receptors to decrease the number and activity of cytotoxic T and natural killer (NK) cells, both of which are known to destroy cancer cells. Noradrenaline has a similar effect, and has been found to induce the production of metastases in a rat model.[35,36] Interestingly, this effect was abolished by the administration of beta-blockers. Tumours such as breast, colon and prostate seem to express beta-receptors which up-regulate growth when stimulated.

Hypoxia is tumour stimulating. Hypoxia leads to the production of cellular proliferative and angiogenic growth factors (notably vascular endothelial growth factor) via the generation of hypoxia-inducible factors 1-alpha and and 2-alpha. Invasive mechanical ventilation, a common response to hypoxia, may similarly have a role to play; it results in the generation of immunomodulatory cytokines that add to the complex interplay of pro- and anti-inflammatory pathways.[37]

Blood transfusion can also increase the risk of tumour progression, particularly in the case of colorectal tumours. This is again thought to be related to immunosuppression. However, leucodepletion appears to make no difference to the impact on cancer recurrence after transfusion, and animal studies have suggested that transfusion of older blood may be implicated.[38]

Sedatives, induction agents and analgesics are also known to impact on cancer progression. Thiopentone, ketamine and propofol all decrease NK activity and numbers, with propofol having the least effect.[39] Morphine and fentanyl both decrease NK activity. Morphine has also been reported to promote angiogenesis and increase breast tumour cell growth in mice.

In summary, admission to the ICU for a patient with cancer carries a significant potential risk of promoting tumour growth and metastasis.

OUTCOMES FOR PATIENTS ADMITTED TO THE INTENSIVE CARE UNIT WITH SOLID TUMOURS

The traditional view of the outcome for the critically ill cancer patient has been almost universally poor. However, for those with solid tumours, recent evidence has challenged and indeed overturned this view. Survival figures for those admitted to the ICU have steadily improved over the past 15 years and approach those of patients admitted with non-oncological diagnoses in the most recent publications.[40–42] The aetiology of the improvement relates to improvements in general critical care, less cytotoxicity in chemotherapeutic regimes, novel antibacterials and antifungals and, crucially, a recognition that the admission of a patient with cancer to the ICU does not carry a universally poor outcome.

That said, the concept of considering all patients with solid tumours as a homogenous group is flawed. A substantial proportion of the patients that present to the ICU with an underlying diagnosis of solid tumour will be there for postoperative management. They have a similar mortality to patients admitted following any other major operative procedure. Critically ill patients with cancer and a medical diagnosis have a higher mortality than their compatriots without cancer. In the largest study to date (of 12,290 patients across 80 units in the Netherlands), such patients had higher acuity, ICU and hospital mortality (30.4% vs. 16.2% in the ICU, and 44.6% vs. 23.7% in hospital), with a greater need for organ support. Significant differences in outcomes according to cancer diagnosis were also present; respiratory tract cancers were associated with an odds ratio (OR) of 2.15 and upper gastrointestinal (GI) cancers 1.42 for death in the ICU.[43]

In addition to pre-morbid characteristics, the degree of physiological impairment at the point of presentation is a strong predictor of short-term mortality. Vasopressor use and the need for mechanical ventilation is commonly predictive and, in Puxty's systematic review, the need for the latter increased ICU mortality by nearly six times.[41] Additional organ support, in particular the requirement for renal replacement therapy, is also associated with poorer outcome.[44] Continued progression of organ dysfunction over the succeeding 72 hours after ICU admission has also been shown to be indicative of poor outcome[45] and in these patients differ little from patients admitted to the ICU with a non-oncological diagnoses.

RETURN TO INTENDED ONCOLOGICAL THERAPY

Given that the intention in most cases of an admission of critically ill cancer patients to the ICU is to enable

return to intended oncological therapy, there is a surprising dearth of data. In two studies with a total of 171 patients with advanced lung cancer admitted to the ICU, only 15 received further cancer treatment.[46,47]

QUALITY OF LIFE AND LONG-TERM OUTCOMES

There are also few studies reporting either quality of life measures or long-term outcomes (1 year or more). In the two largest studies, quality of life (as measured by SF-36 and EurQoL-5D) was poor in survivors at 3 months but recovered somewhat at a year,[48] whilst the probability of quality-adjusted survival in medical patients at 18 months was just 19.1%.[49]

REFERENCES

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;127(12):2893–2917.
2. Taccone FS, Artigas AA, Sprung CL, et al. Characteristics and outcomes of cancer patients in European ICUs. *Crit Care*. 2009;13:R15.
3. Harrison D. Case mix, outcome and length of stay for admissions to adult, general critical care units in England, Wales and Northern Ireland: the Intensive Care National Audit & Research Centre Case Mix Programme Database. *Crit Care*. 2004;9: S1–S13.
4. Simpson AB, Paul J, Graham J, et al. Fatal bleomycin toxicity in the west of Scotland 1991-1995: a review of patients with germ cell tumours. *Br J Cancer*. 1998; 78:1061–1066.
5. Ajithkumar T, Parkinson C, Shamshad F, et al. Ifosfamide encephalopathy. *Clin Oncol*. 2007;19(2): 108–114.
6. Pelgrims J, De Vos F, Van den Brande J, et al. Methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy: report of 12 cases and a review of the literature. *Br J Cancer*. 2000;82:291–294.
7. Horan PG, McMullin MF. Anthracycline cardiotoxicity. *Eur Heart J*. 2006;27(10):1137–1138.
8. Bowles EJA, Wellman R, Feigelson HS, et al. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. *J Natl Cancer Inst*. 2012; 104(17):1293–1305.
9. Guarneri V, Lenihan DJ, Valero VSO. Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center experience. *J Clin Oncol*. 2012;24(25):4107–4111.
10. Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: a systematic review of case reports. *PLoS ONE*. 2016;11(7): e0160221.
11. Kalemkerian GP, Darwish B, Varterasian ML. Tumor lysis syndrome in small cell carcinoma and other solid tumors. *Am J Med*. 1997;103(5):363–367.
12. Gemici C. Tumour lysis syndrome in solid tumours. *Clin Oncol*. 2006;18(10):773–780.
13. Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol*. 2008;26(16):2767–2778.
14. Cheuk DK, Chiang AK, Chan GC, et al. Urate oxidase for the prevention and treatment of tumor lysis syndrome in children with cancer. *Cochrane Database Syst Rev*. 2010;(6):CD006945.
15. Press OW, Livingston R. Management of malignant pericardial effusion and tamponade. *JAMA*. 1987;257(8):1088–1092.
16. Bressler RB, Huston DP. Water intoxication following moderate-dose intravenous cyclophosphamide. *Arch Intern Med*. 1985;145(3):548–549.
17. Mundy GR, Ibbotson KJ, D'Souza SM, et al. The hypercalcemia of cancer. Clinical implications and pathogenic mechanisms. *N Engl J Med*. 1984;310(26): 1718–1727.
18. Stewart A. Hypercalcemia associated with cancer. *N Engl J Med*. 2005;542(4):373–379.
19. LeGrand SB, Leskuski D, Zama I. Narrative review: furosemide for hypercalcemia: an unproven yet common practice. *Ann Intern Med*. 2008;149: 259–263.
20. Walls J, Ratcliffe WA, Howell A, et al. Response to intravenous bisphosphonate therapy in hypercalcaemic patients with and without bone metastases: the role of parathyroid hormone-related protein. *Br J Cancer*. 1994;70(1):169–172.
21. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol*. 2001;19(2):558–567.
22. Kim J, Hofsetter W. Tumours of the mediastinum and chest wall. *Surg Clin North Am*. 2010;90:1019–1040.
23. Shamberger RS, Holzman RS, Griscom NT, et al. CT quantitation of tracheal cross-sectional area as a guide to the surgical and anesthetic management of children with anterior mediastinal masses. *J Pediatr Surg*. 1991;26:138–142.
24. Anghelescu DL, Burgoyne LL, Liu T. Clinical and diagnostic imaging findings predict anesthetic complications in children presenting with malignant mediastinal masses. *Pediatr Anesth*. 2007; 17:1090–1098.
25. Erdos G, Tzanova I. Perioperative management of mediastinal mass in adults. *Eur J Anaesthesiol*. 2009; 26:627–632.
26. Slinger P, Karsli C. Management of the patient with a large anterior mediastinal mass: recurring myths. *Curr Opin Anaesthesiol*. 2007;20(1):1–3.
27. Wilson L, Detterbeck FC, Yahalom J. Superior vena cava syndrome with malignant causes. *N Engl J Med*. 2007;356:1862–1869.
28. Rice TW, Rodriguez RM, Light RW. The superior vena cava syndrome: clinical characteristics and evolving etiology. *Medicine (Baltimore)*. 2006;85(1): 37–42.

29. Schraufnagel DE, Hill R, Leech JA, et al. Superior vena caval obstruction. Is it a medical emergency? *Am J Med*. 1981;70(6):1169–1174.
30. Nguyen NP, Borok TL, Welsh J. Safety and effectiveness of vascular endoprosthesis for malignant superior vena cava syndrome. *Thorax*. 2009;64: 174–178.
31. Rowell NP, Gleeson FV. Steroids, radiotherapy, chemotherapy and stents for superior vena caval obstruction in carcinoma of the bronchus: a systematic review. *Clin Oncol (R Coll Radiol)*. 2002; 14(5):338–351.
32. Darmon M, Thiery G, Ciroldi M, et al. Intensive care in patients with newly diagnosed malignancies and a need for cancer chemotherapy. *Crit Care Med*. 2005;33:2488–2493.
33. Song J, Suh GY, Chung MP. Risk factors to predict outcome in critically ill cancer patients receiving chemotherapy in the intensive care unit. *Support Care Cancer*. 2011;19(4):491–495.
34. Iwasaki A, Shirakusa T, Maekawa T. Clinical evaluation of systemic inflammatory response syndrome (SIRS) in advanced lung cancer (T3 and T4) with surgical resection. *Eur J Cardiothorac Surg*. 2005;27:14–18.
35. Ben-Eliyahu S, Shakhar G, Page G. Suppression of NK cell activity and of resistance to metastasis by stress: a role for adrenal catecholamines and β-adrenoceptors. *Neuroimmunomodulation*. 2000;8: 154–164.
36. Ben-Eliyahu S, Page G, Yirmiya R, et al. Evidence that stress and surgical interventions promote tumor development by suppressing natural killer cell activity. *Int J Cancer*. 1999;80:880–888.
37. Kelly P. The cancer critical care paradox. *Curr Anaesth Crit Care*. 2008;19:91–95.
38. Atzil S, Arad M, Glasner A. Blood transfusion promotes cancer progression: a critical role for aged erythrocytes anesthesiology. *Anesthesiology*. 2008;109(6):989–997.
39. Snyder GL, Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. *Br J Anaesth*. 2010;105(2):106–115.
40. Taccone FS, Artigas A, Charles L, et al. Characteristics and outcomes of cancer patients in European ICUs. *Crit Care*. 2009;13(1):R(15).
41. Puxty K, McLoone P, Quasim T, et al. Survival in solid cancer patients following intensive care unit admission. *Intensive Care Med*. 2014;40(10):1409–1428.
42. Staudinger T, Stoiser B, Mullner M. Outcome and prognostic factors in critically ill cancer patients admitted to the intensive care unit. *Crit Care Med*. 2000;28(5):1322–1327.
43. Bos MM, de Keizer NF, Meynaar IA, et al. Outcomes of cancer patients after unplanned admission to general intensive care units. *Acta Oncol*. 2012;51(7):897–905.
44. Soares M, Salluh JI, Carvalho MS, et al. Prognosis of critically ill patients with cancer and acute renal dysfunction. *J Clin Oncol*. 2006;24(24):4003–4010.
45. Lecuyer L, Chevret S, Thiery G, et al. The ICU Trial: a new admission policy for cancer patients requiring mechanical ventilation. *Crit Care Med*. 2007;35(3):808–814.
46. Andréjak C, Terzi N, Thielen S, et al. Admission of advanced lung cancer patients to intensive care unit: a retrospective study of 76 patients. *BMC Cancer*. 2011;11(1):159.
47. Kim YJ, Kim MJ, Cho YJ, et al. Who should be admitted to the intensive care unit? The outcome of intensive care unit admission in stage IIIB–IV lung cancer patients. *Med Oncol*. 2014;31(3):1–7.
48. Oeyen SG, Benoit DD, Annemans L. Long-term outcomes and quality of life in critically ill patients with hematological or solid malignancies: a single center study. *Intensive Care Med*. 2013;39(5):889–898.
49. Normilio-Silva K, de Figueiredo AC, Pedroso-de-Lima AC, et al. Long-term survival, quality of life, and quality-adjusted survival in critically ill patients with cancer. *Crit Care Med*. 2016;44(7):1327–1337.

Part Six

Acute Renal Failure

This page intentionally left blank

47

Acute kidney injury

Rinaldo Bellomo

INTRODUCTION

Acute Kidney Injury (AKI), formerly referred to as acute renal failure, is the new international consensus term for a condition that remains a major complication of critical illness and a therapeutic challenge for the intensivist. The term AKI has been introduced to emphasise a gradation of dysfunction and abnormality that begins long before 'failure' occurs.[1] In the intensive care units (ICUs), AKI describes a syndrome characterised by a rapid (hours to days) decrease in the kidney's ability to eliminate a variety of small and middle molecular weight solutes, including nitrogen waste products such as urea and creatinine, which are measured to estimate the extent of such functional loss. Other typical clinical manifestations include decreased urine output, metabolic acidosis, and hyperkalaemia. More recently, an additional manifestation that has been clearly identified is the release of biomarkers of injury into the urine.[2,3]

AKI can now be defined and classified using changes in serum creatinine and urine output using the so-called Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[4] This classification divides AKI into the stages of severity. Using this or similar classifications, it is clear that AKI is a major ICU syndrome with an incidence of some degree of renal dysfunction being reported in greater than 50% in large studies of critically ill patients[5] and in more than one third of patients on day 1 in Australia and New Zealand ICUs.[6]

ASSESSMENT OF RENAL FUNCTION

Renal function is complex but, in the clinical context, monitoring of renal function is reduced to the indirect assessment of glomerular filtration rate (GFR) by the measurement of plasma urea and, more accurately, serum creatinine in blood. These waste products of nitrogen metabolism, however, are insensitive markers of GFR and are heavily modified by many factors and by dilution with the administration of intravenous fluids.[7] Furthermore, they start becoming abnormal only after more than 50% of GFR is lost and do not reflect dynamic changes in GFR. The use of creatinine clearance (2- or 4-hour collections) or of calculated clearance by means of formulae may be a more accurate reflection of GFR but rarely changes clinical management and is, therefore, uncommonly performed. The use of more sophisticated radionuclide-based tests is only useful for research purposes.

DIAGNOSIS AND CLINICAL CLASSIFICATION

The most practically useful approach to the aetiological diagnosis of AKI is to divide its causes according to the probable source of renal injury: pre-renal, renal (parenchymal or intrinsic) and post-renal.

PRE-RENAL RENAL FAILURE

This form of AKI is by far the most common in the ICU and is considered, at least in its initial phases, to be *functional* in nature (i.e. there are no histopathological changes to renal tissue). The term indicates that the kidney malfunctions predominantly because of systemic factors outside the kidney, which decrease GFR (decreased cardiac output, hypotension, sepsis and the like). If the systemic cause of AKI is rapidly removed or corrected, renal function improves and relatively rapidly returns to near normal levels. However, if intervention is delayed or unsuccessful, renal injury may become established and AKI may persist for several days or weeks. Several urine tests (measurement of urinary sodium, fractional excretion of sodium and other derived indices) have been promoted to help clinicians identify the development of such 'established' AKI. Unfortunately, their accuracy is doubtful[8] and their clinical utility is negligible. Furthermore, pre-renal AKI and established AKI are part of a continuum, and their separation has limited clinical implications.[9] More recently, other diagnostic tests have been developed which rely on the identification of molecules which are released in the urine as a consequence of renal injury. Such novel renal injury biomarkers[2,3] appear in the urine before changes in serum creatinine take place and have good to excellent accuracy for the prediction on subsequent increases in serum creatinine. Their commercialisation and

ABSTRACT

Acute kidney injury (AKI) is a major complication of critical illness typically characterised by oliguria and increased blood concentrations of nitrogen waste products. It is now defined by presence of consensus criteria and is associated with increased mortality. Its clinical subdivision into pre-renal, renal and post-renal causes provides a useful diagnostic framework of reference. More recently, the discovery of biomarkers of renal injury has helped identify at-risk patients earlier and may make preventive interventions more successful. The pathophysiology of AKI, however, is likely complex and remains poorly understood. For septic AKI (the most common type of AKI in intensive care unit [ICU]), changes in microvascular flow may be particularly important. For other unique syndromes (rhabdomyolysis and hepatorenal syndrome), specific factors are likely to be responsible for loss of renal function.

Prevention relies upon early recognition, treatment or removal of the likely cause, avoidance or removal of nephrotoxins, and optimisation of systemic haemodynamics (cardiac output and blood pressure). The non-dialytic management of AKI is also focused on preventing or rapidly treating the complications of AKI (hyperkalaemia, acidosis, fluid overload). Such treatment may ultimately require renal replacement therapy (RRT) in some patients. Although most patients recover renal function once their illness resolves, some do not. Moreover, an episode of AKI carries significant risk of subsequent chronic kidney disease, highlighting the importance of prevention.

KEY WORDS

Urea
creatinine
potassium
dialysis
pre-renal
post-renal
intrinsic acute kidney injury
fluid overload
resuscitation
nephrotoxin
hyperkalaemia
recovery

greater uptake in clinical medicine in the next 5 years appears likely.

PARENCHYMAL (INTRINSIC) RENAL FAILURE

This term is used to define a syndrome where the principal source of damage is within the kidney and where *structural* changes can be seen on microscopy. Disorders which affect the glomeruli or renal tubules can be responsible (Box 47.1).

Among these, nephrotoxins are particularly important, especially in hospital patients. The most common nephrotoxic drugs affecting ICU patients are listed in Box 47.2. Many cases of drug-induced AKI rapidly improve upon removal of the offending agent. Accordingly, a careful history of drug administration is *mandatory* in all patients with AKI. In some cases of parenchymal AKI, a correct working diagnosis can be obtained from history, physical examination and radiological and laboratory investigations. In such patients, one can proceed to a therapeutic trial without the need to resort to renal biopsy. However, if immunosuppressive therapy is considered, renal biopsy is recommended.

Box 47.1 Causes of intrinsic (parenchymal) acute kidney injury

- Glomerulonephritis
- Vasculitis
- Interstitial nephritis
- Malignant hypertension
- Pyelonephritis
- Bilateral cortical necrosis
- Amyloidosis
- Malignancy
- Nephrotoxins
- Cholesterol embolism

Box 47.2 Drugs which may contribute to acute kidney injury in the intensive care unit

- Radiocontrast agents
- Starch continuing fluids
- Aminoglycosides
- Amphotericin
- Non-steroidal anti-inflammatory drugs
- β-lactam antibiotics (interstitial nephropathy)
- Sulphonamides
- Acyclovir
- Methotrexate
- Cisplatin
- Cyclosporin A
- Tacrolimus
- Sirolimus

More than a third of patients who develop AKI in the ICU have chronic renal dysfunction due to factors such as age-related changes, long-standing hypertension, diabetes or atheromatous disease of the renal vessels. Such chronic renal dysfunction may be manifest by a raised serum creatinine. However, this is not always the case. Often, what may seem to the clinician to be a relatively trivial insult, which does not fully explain the onset of AKI in a normal patient, is sufficient to unmask lack of renal functional reserve in another patient.

Beyond all the above considerations, however, the most common type of so-called intrinsic AKI falls under the traditional name of acute tubular necrosis (ATN). The term ATN is often used to describe a form of 'intrinsic' AKI, which follows from severe and persistent pre-renal AKI. It is assumed that such ATN results from such continued hypoperfusion. This approach is widely accepted and used by textbooks and clinicians, but is likely misleading and inaccurate.[10] This is because the term ATN conflates a histological diagnosis (tubular necrosis) that is rarely confirmed by biopsy with a complex clinical syndrome (typically AKI of >72 hours from multiple causes). Such syndrome, in many cases, has *not* been convincingly linked with the specific histopathological appearance of ATN either in animal experiments or in human disease.[10,11] Moreover, ATN is believed to represent the consequence of sustained or severe pre-renal azotemia. Unfortunately, the term 'pre-renal azotemia' is, like ATN, conceptually flawed[12,13] because it implies that clinicians can know with a sufficient degree of certainty, by taking a history, examining the patient and performing urine and blood tests, that there is no histopathological injury to the tubules. Finally, all such concepts are biologically flawed because they imply that AKI does not represent (like all other diseases known to man) a continuum of injury but rather a yes-or-no phenomenon in terms of histological damage. For these reasons, terms like pre-renal azotemia and ATN are increasingly being challenged.[9,12] In addition to the above syndromes, the specific clinical syndrome of 'intrinsic' AKI deserves special attention.

HEPATORENAL SYNDROME

This condition is a form of AKI, which occurs in the setting of severe liver dysfunction in the absence of other known causes of AKI.[14] Typically, it presents as progressive oliguria with a very low urinary sodium concentration (<10 mmol/L). Its pathogenesis is not well understood. New consensus definitions, however, now define HRS as any development of AKI in the setting of advanced liver disease that is not due to other intrinsic causes. Thus, sepsis, paracentesis-induced hypovolaemia, raised intra-abdominal pressure due to tense ascites, diuretic-induced hypovolaemia, lactulose-induced hypovolaemia, and any combination

of these, which in the past were used to exclude HRS, are now acknowledged triggers of this condition.[14] The avoidance of hypovolaemia by albumin administration in patients with spontaneous bacterial peritonitis has been shown to decrease the incidence of HRS.[15] More importantly, multiple observational studies, several controlled trials, and growing clinical experience have led to the acceptance and widespread use of terlipressin to improve GFR in this condition.[16]

RHABDOMYOLYSIS-ASSOCIATED ACUTE KIDNEY INJURY

This condition accounts for close to 5%–10%[17] of cases of AKI in the ICU depending on the setting. Its pathogenesis involves pre-renal, renal and post-renal factors. It is now typically seen following major trauma, drug overdose with narcotics, vascular embolism and in response to a variety of agents, which can induce major muscle injury. The principles of treatment are based on retrospective data. They include prompt and aggressive fluid resuscitation, elimination of causative agents, correction of compartment syndromes, alkalinisation of urine (pH >6.5), and maintenance of polyuria (>300 mL/h).

POST-RENAL RENAL FAILURE

Obstruction to urine outflow is the most common cause of functional renal impairment in the community,[18] but is uncommon in the ICU. The clinical presentation of obstruction may be acute or acute-on-chronic in patients with long-standing renal calculi. It may not always be associated with oliguria. If obstruction is suspected, ultrasonography can be easily performed at the bedside. However, not all cases of acute obstruction have an abnormal ultrasound and, in many cases, obstruction occurs in conjunction with other renal insults (e.g. staghorn calculi and severe sepsis of renal origin). Assessment of the role of each factor and overall management should be conducted in conjunction with an urologist. Finally, the sudden and unexpected development of anuria in an ICU patient should always suggest obstruction of the urinary catheter as the cause. Appropriate flushing or changing of the catheter should be implemented in this setting.

PATHOGENESIS OF ACUTE KIDNEY INJURY

The pathogenesis of obstructive AKI involves several humoral responses as well as mechanical factors. The pathogenesis of parenchymal renal failure as seen with glomerulonephritis is typically immunological. It varies from vasculitis to interstitial nephropathy and involves an extraordinary complexity of immunological mechanisms. The pathogenesis of pre-renal AKI is of greater direct relevance to the intensivist.

The overwhelming majority of our conceptions of the pathophysiology of pre-renal AKI are derived from animal models[19,20] using ischemia by the acute and complete occlusion of the arterial vascular supply to the kidney. Unfortunately, the clinical relevance of such models is limited, and is negligible to conditions like sepsis,[21,22] now the most common trigger of AKI in hospital and ICU patients. However, models of septic AKI, which fully resemble the human phenotype, are difficult to develop. When a hyperdynamic sepsis phenotype with AKI is produced in large animals, renal blood flow actually increases to supranormal levels and renal histopathology is essentially normal.[23,24] Moreover, kidney adenosine triphosphate (ATP) levels are highly preserved in animal models of septic shock (Fig. 47.1). If experimental septic AKI can occur in the setting of increased renal blood flow and preserved ATP levels, it is impossible to know for sure that this does not also happen in humans, where histopathological assessment remains confined to rapid postmortem assessment, and assessment of renal blood flow is similarly extremely difficult and confined to invasive techniques.

Despite all of the above observations, activation of the renin-angiotensin system (RAAS), activation of the renal sympathetic system,[25] and activation of the tubulo-glomerular feedback (TGF) system may play a role.[26] However, it remains unclear which particular pathway of injury has *primacy* in terms of *importance or timing* or *both*. Finally, recent evidence suggests that intrarenal shunting contributes to decreased GFR and ischemia of the renal medulla.[27,28] Such shunting may also be coupled with changes in the microcirculation, suggesting that even if one could measure global renal blood flow with reasonable accuracy, unless the microcirculation is also assessed, our understanding of AKI will remain poor.

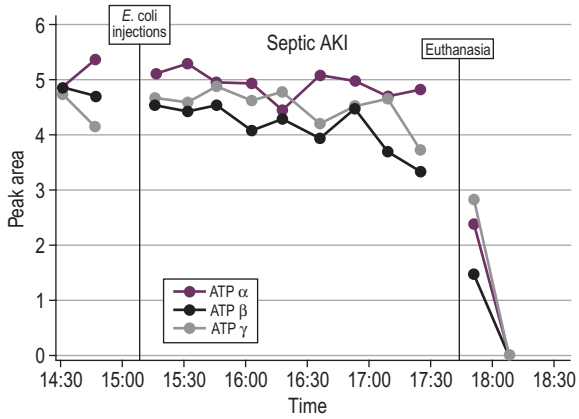


Figure 47.1 Graphic representation of the changes in magnetic resonance spectroscopy-derived ATP levels in the kidney during experimental septic shock. There are no significant changes until euthanasia is performed. *AKI*, Acute kidney injury.

THE CLINICAL PICTURE

The most common clinical picture seen in the ICU is that of a patient who has sustained/is experiencing a major systemic insult (trauma, sepsis, myocardial infarction, severe haemorrhage, cardiogenic shock, major surgery and the like). When the patient arrives in the ICU, resuscitation should typically be well under way or surgery may have just been completed. Despite such efforts, the patient may already be anuric or oliguric, the serum creatinine may be rising and a metabolic acidosis may be developing. Potassium and phosphate levels may be rising as well. Mechanical ventilation and need for vasoactive drugs is common in this setting. Fluid resuscitation is typically undertaken in the ICU under the guidance of invasive haemodynamic monitoring. Vasoactive drugs are often used to restore mean arterial pressure (MAP) to 'acceptable' levels (typically >65–70 mm Hg). The patient may improve over time and urine output may return with or without the assistance of diuretic agents. If urine output does not return, however, renal replacement therapy (RRT) needs to be considered. Once the cause of AKI has been removed and the patient has become physiologically stable, slow (days to weeks) recovery typically occurs. If the cause of AKI has not been adequately remedied, the patient remains gravely ill, the kidneys do not recover and death from multiorgan failure may occur.

PREVENTING ACUTE KIDNEY INJURY

The fundamental principle of AKI prevention is to treat its cause. If pre-renal factors contribute, these must be identified and haemodynamic resuscitation quickly instituted.

RESUSCITATION

Intravascular volume must be maintained or rapidly restored, and this is often best done using invasive haemodynamic monitoring (central venous catheter, arterial cannula, and pulmonary artery catheter or pulse contour cardiac output catheters, or echocardiography in some cases). Oxygenation must be maintained. An adequate hemoglobin concentration (at least >70 g/L) must be maintained or immediately restored. Once intravascular volume has been restored, some patients remain hypotensive (MAP <70 mm Hg). In these patients, autoregulation of renal blood flow may be lost. Restoration of MAP to near normal levels may increase GFR. Such elevations in MAP, however, require the addition of vasopressor drugs.[29] The nephroprotective role of additional fluid therapy in a patient with a normal or increased cardiac output and blood pressure is questionable. Despite these resuscitation measures, AKI may still develop if cardiac output is inadequate. This may require a variety of interventions from the use of inotropic drugs to the application of ventricular assist devices.

NEPHROPROTECTIVE DRUGS

Following haemodynamic resuscitation and removal of nephrotoxins, it is unclear whether the use of additional pharmacological measures is of further benefit to the kidney.

A phase III trial in critically ill patients showed that low-dose dopamine is as effective as placebo in the prevention of renal dysfunction in ICU patients.[30]

The use of loop diuretics is controversial and not supported by high-quality evidence. Other agents such as *theophylline, urodilatin, anaritide* (a synthetic atrial natriuretic factor), or *fenoldopam* have failed to show consistent benefits.

In patients receiving radiocontrast, saline infusion to maintain intravascular fluid expansion may be helpful in attenuating kidney injury. However, the relevance of such treatment in critically ill patients remains unclear. The benefits of n-acetylcysteine and bicarbonate infusion as protective strategies in this context also remain highly controversial.

DIAGNOSTIC INVESTIGATIONS

An aetiological diagnosis of AKI must always be established. While this may be obvious on clinical grounds, in other cases, investigations including the examination of urinary sediment and exclusion of a urinary tract infection (most if not all patients), exclusion of obstruction when appropriate (some patients) and the careful exclusion of nephrotoxins (all patients) may be needed.

In specific situations, other investigations are necessary to establish the diagnosis, such as creatine kinase and free myoglobin for possible rhabdomyolysis. A chest radiograph, a blood film, the measurement of non-specific inflammatory markers, and the measurement of specific antibodies (anti GBM, anti-neutrophil cytoplasm, anti-DNA, anti-smooth muscle, etc.) may help diagnose vasculitis or certain types of collagen disease or glomerulonephritis. If thrombotic-thrombocytopenic purpura is suspected, the additional measurement of lactic dehydrogenase, haptoglobin, unconjugated bilirubin and free haemoglobin are needed. In some patients, specific findings (cryoglobulins, Bence-Jones proteins) are almost diagnostic. In a few rare patients, a renal biopsy might become necessary.

NOVEL BIOMARKERS OF ACUTE KIDNEY INJURY

Using new search techniques based on proteomics, investigators have identified novel biomarkers of AKI.[31]

The identification of these biomarkers may change our classification and treatment of this condition in the near future. These biomarkers appear to change significantly earlier than changes in serum creatinine.[32] They appear to reflect different aspects of renal injury. For example, cystatin C appears to reflect changes in GFR, while neutrophil gelatinase associated lipocalin (NGAL) appears to reflect tubular stress/injury. They also appear to dynamically change with treatment or recovery, which suggests that they can be used to monitor interventions. They may identify subpopulations of patients who do not have AKI according to creatinine-based criteria, but actually have a degree of kidney stress/injury that can be detected by biomarkers and is associated with worse outcomes.[32] Finally, by identifying possible mechanisms of injury they may increase our understanding of the pathogenesis of AKI. Their therapeutic implications, however, remain unclear.

MANAGEMENT OF ESTABLISHED ACUTE KIDNEY INJURY

The principles of management of established AKI are the treatment or removal of its cause, the avoidance of nephrotoxins, and the maintenance of physiological and, in particular, haemodynamic homeostasis while recovery takes place. Complications such as encephalopathy, pericarditis, myopathy, neuropathy, electrolyte disturbances or other major electrolyte, fluid or metabolic derangement should never occur in a modern ICU. Their prevention may include several measures, which vary in complexity from fluid restriction to the initiation of extracorporeal RRT.

Nutritional support should be started early and should contain adequate calories (20–30 Kcal/kg/day) as a mixture of carbohydrates and lipids. Adequate protein (at least 1 g/kg/day) should be administered. There is no evidence that specific renal nutritional solutions are useful. Vitamins and trace elements should be administered at least according to their recommended daily allowance. The role of newer immunonutritional solution remains controversial. The enteral route is preferred to the use of parenteral nutrition.

Hyperkalaemia (>6 mmol/L) must be promptly treated either with insulin and dextrose administration, the infusion of bicarbonate if acidosis is present, the administration of nebulised salbutamol, or all of the above together. If the 'true' serum potassium is greater than 7 mmol/L or electrocardiographic signs of hyperkalaemia appear, calcium gluconate (10 mL of 10% solution IV) should also be administered. The above measures are temporising actions while RRT is being set up. The presence of hyperkalaemia is a major indication for the immediate institution of RRT.

Metabolic acidosis is almost always present but rarely requires treatment per se. Anaemia requires correction to maintain a haemoglobin level of at least greater than 70 g/L. More aggressive transfusion needs individual patient assessment. Drug therapy must be adjusted to take into account the effect of the decreased clearances associated with loss of renal function. Stress ulcer prophylaxis is advisable. Assiduous attention should be paid to the prevention of infection.

Fluid overload can be prevented by the use of loop diuretics in polyuric patients. However, if the patient is oliguric, the only way to avoid fluid overload is to institute RRT at an early stage (see specific chapter). Marked azotemia ([urea] >40 mmol/L or [creatinine] >400 µmol/L) is undesirable and should probably be treated with RRT unless recovery is imminent or already under way and a return towards normal values is expected within 24–48 hours. It is recognised, however, that no randomised controlled trials (RCTs) exist to define the ideal time for intervention with artificial renal support. Moreover, recent trials have reported controversial findings.[33,34]

PROGNOSIS

The mortality of critically ill patients with AKI remains high (40%–50% depending on case-mix). It is frequently stated that patients die with renal failure rather than of renal failure. However, much indirect evidence supports a careful and proactive approach to the treatment of patients with AKI, which is based on the prevention of uncontrolled uraemia and the maintenance of low-urea levels throughout the patient's illness. Finally, ICU patients with AKI typically recover to baseline or near baseline function even when suffering from severe AKI and long-term dialysis is an uncommon complication.[35] However, it is now clear that even a single episode of AKI is associated with a significantly increased risk of subsequent chronic kidney disease.[36,37] Accordingly, it seems advisable to refer patients treated in the ICU for severe AKI to follow-up nephrology care.

REFERENCES

1. Kellum JA, Bellomo R, Ronco C. Kidney attack. *JAMA*. 2012;307:2265–2266.
2. Nickolas TL, Schmidt-Ott KM, Canetta P, et al. Diagnostic and prognostic stratification in the emergency department using urinary biomarkers of nephron damage. *J Am Coll Cardiol*. 2012;59:246–255.
3. Kashani K, Al-Khafaji A, Ardiles T, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care*. 2013;17:R25.
4. KDIGO AKI Writing Group Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int*. 2012;(suppl 2):1–141.
5. Hoste EAJ, Clermont G, Kersten A, et al. RIFLE criteria for acute kidney injury are associated with

hospital mortality in critically ill patients: a cohort analysis. *Crit Care*. 2006;10:R73–R83.
6. Bagshaw SM, George C, Bellomo R. Changes in the incidence and outcome for early acute kidney injury in a cohort of Australian intensive care units. *Crit Care*. 2007;11:R68–R74.
7. Liu K, Thomson T, Ancukiewics M, et al. Acute kidney injury with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. *Crit Care Med*. 2011;39:2665–2671.
8. Langenberg C, Wan L, Bagshaw SM, et al. Urinary biochemistry in experimental septic acute renal failure. *Nephrol Dial Transplant*. 2006;21(12):3389–3397.
9. Uchino S, Bellomo R, Bagshaw SM, et al. Transient azotemia is associated with a high risk of death in hospitalised patients. *Nephrol Dial Transplant*. 2010;25:1833–1839.
10. Langenberg C, Bagshaw S, May CN, et al. The histopathology of septic acute kidney injury: a systematic review. *Crit Care*. 2008;6(12):R38–R44.
11. Lerolle N, Nochy D, Guérot E, et al. Histopathology of septic shock induced acute kidney injury: apoptosis and leukocytic infiltration. *Intensive Care Med*. 2010;36:471–478.
12. Bellomo R, Bagshaw SM, Langenberg C, et al. Pre-renal azotemia: a flawed paradigm in critically ill septic patients? *Contrib Nephrol*. 2007;156:1–9.
13. Macedo E, Mehta RL. Prerenal failure: from old concepts to new paradigms. *Curr Opin Crit Care*. 2009;15:467–473.
14. Nadim MK, Kellum JA, Davenport A, et al. Hepatorenal syndrome: the 8th international consensus conference of the Acute Dialysis Quality Initiative (ADQI) group. *Crit Care*. 2012;16:R23.
15. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impariment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med*. 1999;341: 403–409.
16. Narahara Y, Kanazawa H, Sakamoto C, et al. The efficacy and safety of terlipressin and albumin in patients with type 1 hepatorenal syndrome: a multicentrer, open-label, explorative study. *J Gastroenterol*. 2012;47:313–320.
17. Uchino S, Kellum J, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA*. 2005;294:813–818.
18. Feest TG, Round A, Hamad S. Incidence of severe acute renal failure in adults: results of a community-based study. *BMJ*. 1993;306:481–483.
19. Heyman SN, Rosenberger C, Rosen S. Experimental ischemia-reperfusion: biases and myths – the proximal vs. distal hypoxic tubular injury debate revisited. *Kidney Int*. 2010;77:9–16.
20. Heyman SN, Lieberthal W, Rogiers P, et al. Animal models of acute tubular necrosis. *Curr Opin Crit Care*. 2002;8:526–534.
21. Langenberg C, Wan L, May CN, et al. Animal models of septic acute renal failure. In: Ronco C, Bellomo R, Kellum JA, eds. *Critical Care Nephrology*. Philadelphia, PA: Saunders Elsevier; 2009:237–250.
22. Ishikawa K, May CN, Gobe G, et al. Pathophysiology of septic acute kidney injury: a different view of tubular injury. *Contrib Nephrol*. 2010;165:18–27.
23. Langenberg C, Wan L, Egi M, et al. Renal blood flow in experimental septic acute renal failure. *Kidney Int*. 2006;69:1996–2002.
24. Maiden MJ, Otto S, Brealey JK, et al. Structure and function of the kidney in septic shock. A prospective controlled experimental study. *Am J Resp Crit Care Med*. 2016;194:692–700.
25. Ramchandra R, Wan L, Hood SG, et al. Septic shock induces distinct changes in sympathetic nerve activity to the heart and kidney in conscious sheep. *Am J Physiol Regul Integr Comp Physiol*. 2009;297: R1247–R1253.
26. Schrier RW, Wang W. Acute renal failure and sepsis. *N Engl J Med*. 2004;351:159–169.
27. Post EH, Kellum JA, Bellomo R, et al. Renal perfusion in sepsis: from macro- to microcirculation. *Kidney Int*. 2016;91:45–60.
28. Calzavacca P, Evans RG, Bailey M, et al. Cortical and medullary tissue perfusion and oxygenation in experimental septic acute kidney injury. *Crit Care Med*. 2015;43:e431–e439.
29. Asfar P, Meziani F, Hamel JE, et al. High versus low blood pressure target in patients with septic shock. *N Engl J Med*. 2014;370:1583–1593.
30. ANZICS Clinical Trials Group. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. *Lancet*. 2000;356:2139–2143.
31. Devarajan P, Krawczeski CD, Nguyen MT, et al. Proteomic identification of early biomarkers of acute kidney injury after cardiac surgery in children. *Am J Kidney Dis*. 2010;56:632–642.
32. Haase M, Devarajan P, Haase-Fielitz A, et al. The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury a multicenter pooled analysis of prospective studies. *J Am Coll Cardiol*. 2011;57:1752–1761.
33. Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. *JAMA*. 2016;315:2190–2199.
34. Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. *New Engl J Med*. 2016;375: 122–133.
35. Gallagher M, Cass A, Bellomo R, et al. Long-term survival and dialysis dependency following acute kidney injury in intensive care: extended follow-up of a randomized contorlled trial. *PLoS Med*. 2014;11:e1001601.
36. Kellum JA, Silenau FE, Bihorac A, et al. Recovery after acute kidney injury. *Am J Respir Crti Care Med*. 2017;195(6):784–791.
37. Goldstein SL, Chawla L, Ronco C, et al. Renal recovery. *Crit Care*. 2014;18:301.

48

Renal replacement therapy

Rinaldo Bellomo

INTRODUCTION

When acute kidney injury (AKI) is severe, resolution can take several days or weeks. During this time, the kidneys may be unable to maintain homeostasis of fluid, potassium, metabolic acid and waste products. If this pathophysiological state is prolonged, life-threatening complications frequently develop. In these patients, extracorporeal techniques of blood purification become necessary to prevent such complications. These techniques broadly referred to as renal replacement therapy (RRT) include continuous haemofiltration (HF) and its technical variations, intermittent haemodialysis (IHD), and peritoneal dialysis (PD) – each with its technical variations. All of these techniques rely on the principle of removing unwanted solutes and water through a semipermeable membrane, which is either biological (peritoneum) or artificial (haemodialysis or HF membranes), and each technique offers several advantages, disadvantages and limitations.

PRINCIPLES

The principles of RRT have been extensively studied and described.[1-3] Here we summarise several key aspects, which are relevant to the critical care physician.

WATER REMOVAL

The removal of unwanted solvent (water) is therapeutically probably as important as the removal of unwanted solutes (acids, uraemic toxins, potassium, and the like). During RRT, water is removed through a process called *ultrafiltration*. This process is essentially the same as that performed by the glomerulus. It requires a driving pressure to move water across a semipermeable membrane because such fluid would normally be kept within the circulation due to oncotic pressure. This pressure is achieved by:

1. Generating a *transmembrane pressure* though the pumping of blood (as in HF or during IHD) through the semipermeable membrane. This positive pressure is greater than the oncotic pressure that would retain water in the circulation, and generates ultrafiltration.
2. Increasing osmolarity of the dialysate (as in PD), which then draws water across the semipermeable membrane (the peritoneum).

SOLUTE REMOVAL

The removal of unwanted solutes (uraemic toxins, nitrogen waste products, and organic acids) can be achieved by:

1. Creating an electrochemical gradient across the membrane using a flow-past system with toxin-free dialysate (*diffusion*) as in IHD and PD.
2. Creating a transmembrane pressure driven 'solvent drag', where solutes move together with solvent (*convection*) across the membrane, are discarded together with the solvent, and then replaced with toxin-free replacement fluid as in HF.

The rate of diffusion of a given solute depends on its molecular weight (MW), the porosity of the membrane, the blood flow rate, the dialysate flow rate, the degree of protein binding and its concentration gradient across the membrane. If synthetic high-flux membranes are used (cut-off at 10–20 kilo Daltons [kD] MW in vivo) molecules with a MW below these values can be removed. However, with these membranes, convection is superior to diffusion in achieving the clearance of middle molecules (those with a MW >1000).

INDICATIONS FOR RENAL REPLACEMENT THERAPY

In the critically ill patient, RRT can be initiated early, prior to the development of complications. Fear of early RRT stems from historical experience with the adverse effects of conventional IHD, especially haemodynamic instability, and from the risks and limitations of continuous or intermittent PD.[4,5] However, continuous renal replacement therapy (CRRT)[6,7] or slow low efficiency daily dialysis (SLEDD)[8] minimise these effects. The criteria for the initiation of RRT in patients with chronic renal failure may not be appropriate in many critically ill patients.[9,10] A set of modern criteria, which can be considered sufficient for the initiation of RRT in the intensive care unit (ICU) is presented in Box 48.1.

ABSTRACT

In the intensive care unit (ICU) setting in patients with acute kidney injury (AKI), renal replacement therapy (RRT) becomes necessary when renal function is insufficient to preserve adequate control of fluid, acid-base and waste product homeostasis. The principles of RRT are based on solute and solvent movement across a semipermeable membrane. These principles apply to all modalities of RRT from intermittent haemodialysis (IHD) to continuous haemofiltration, from slow low efficiency daily dialysis (SLEDD) to peritoneal dialysis. Continuous RRT (CRRT) is the dominant form of RRT in developed countries, especially in haemodynamically unstable patients. IHD is typically used in stable patients or in the recovery phase just before and after general ward transfer. CRRT circuit anticoagulation is often challenging. However, regional anticoagulation with citrate is emerging as the safest and most effective option. Although large, randomised, controlled trials have made it possible to have strong evidence to guide intensity selection, several aspects of RRT remain to be explored, especially the timing of its initiation.

KEY WORDS

Haemodialysis
haemofiltration
CRRRT
peritoneal dialysis
SLEDD
CVVH
CVVHD
CVVHDF
anticoagulation
citrate
heparin
haemoperfusion
MARS

Box 48.1 Modern criteria for the initiation of renal replacement therapy in the intensive care unit

1. Oliguria (urine output <200 mL/12 h)
2. Anuria (urine output: 0–50 mL/12 h)
3. (Urea) >35 mmol/L
4. (Creatinine) >400 µmol/L
5. (K^+) >6.5 mmol/L or rapidly rising*
6. Pulmonary oedema unresponsive to diuretics
7. Uncompensated metabolic acidosis (pH <7.1)
8. (Na^+) <110 and >160 mmol/L
9. Temperature >40°C
10. Uraemic complications (encephalopathy/myopathy/neuropathy/pericarditis)
11. Overdose with a dialyzable toxin (e.g. lithium).

*Please be aware of differences between plasma versus serum measurement in your laboratory.

If one criterion is present, RRT should be considered. If two criteria are simultaneously present, RRT is strongly recommended.

RRT, Renal replacement therapy.

With either IHD, or CRRT or SLEDD, there are limited data on what is the 'adequate' intensity of dialysis. However, the concept of dialytic adequacy should include the maintenance of homeostasis at all levels[10] and better uraemic control may translate into better survival.[11,12] An appropriate target urea might be 15–25 mmol/L, with a protein intake around 1.5 g/kg/day. This can be easily achieved using CRRT at urea clearances of 20–25 mL/kg/h depending on the catabolic rate. If intermittent therapy is used, daily and extended treatment as described with SLEDD may be desirable in the ICU.[13]

MODALITY OF RENAL REPLACEMENT THERAPY

There is a great deal of controversy as to which modality of RRT is 'best' in the ICU due to the lack of randomised, controlled trials comparing different modalities (IHD or CRRT). In their absence, modalities of RRT may be judged on the basis of the following criteria:

1. Haemodynamic side effects
2. Ability to control fluid status
3. Biocompatibility
4. Risk of infection
5. Uraemic control
6. Avoidance of cerebral oedema
7. Ability to allow full nutritional support
8. Ability to control acidosis
9. Absence of specific side effects
10. Cost.

In relation to the above criteria, CRRT and SLEDD offer many advantages over PD and conventional IHD (3–4 h/day, 3–4 times/week),[13] and, therefore, CRRT or SLEDD are almost exclusively used in Australia and New Zealand ICUs,[14] with IHD only being used prior to discharge or after discharge to the general wards. Irrespective of the choice of modality, some salient aspects of CRRT, IHD and PD require discussion.

CONTINUOUS RENAL REPLACEMENT THERAPY

First described in 1977, CRRT has undergone several technical modifications. It is now performed using double-lumen catheters and peristaltic blood pumps with control of the ultrafiltration rate. If no dialysate is used and effluent is replaced with substitution solutions, the technique is called continuous veno-venous haemofiltration (CVVH). During CVVH, ultrafiltration rates of 2 L/h yield urea clearances of approximately 25 mL/kg/h in the average 80 kg patient (Fig. 48.1).

In a veno-venous system, dialysate can also be delivered countercurrent to blood flow (continuous veno-venous haemodialysis – CVVHD) to achieve either almost pure diffusive clearance (Fig. 48.2) or as a mixture of diffusive and convective clearance (continuous veno-venous haemodiafiltration – CVVHDF) (Fig. 48.3).

No matter what technique is used, the following outcomes are predictable:

1. Continuous control of fluid status
2. Haemodynamic stability
3. Control of acid-base status
4. Ability to provide protein-rich nutrition while achieving uraemic control
5. Control of electrolyte balance, including phosphate and calcium balance
6. Prevention of swings in intracerebral water
7. Minimal risk of infection
8. High level of biocompatibility.

However, CRRT mandates the presence of specifically trained nursing and medical staff 24 hours a day and the issues of continuous circuit anticoagulation or the potential risk of bleeding have been of concern.

CIRCUIT ANTICOAGULATION DURING CONTINUOUS RENAL REPLACEMENT THERAPY

The flow of blood through an extracorporeal circuit causes activation of the coagulation cascade and promotes clotting of the filter and circuit itself. In order to delay this and achieve acceptable operational lives (approximately 24 hours) for the circuit, anticoagulants are frequently used.[15] However, circuit anticoagulation increases the risk of bleeding. Therefore, the risks and benefits of more or less intense anticoagulation and alternative strategies (Box 48.2) must be considered.

In the vast majority of patients, low-dose heparin (<500 IU/h) is sufficient to achieve adequate (approximately 24 hours) circuit life; it is easy and cheap to

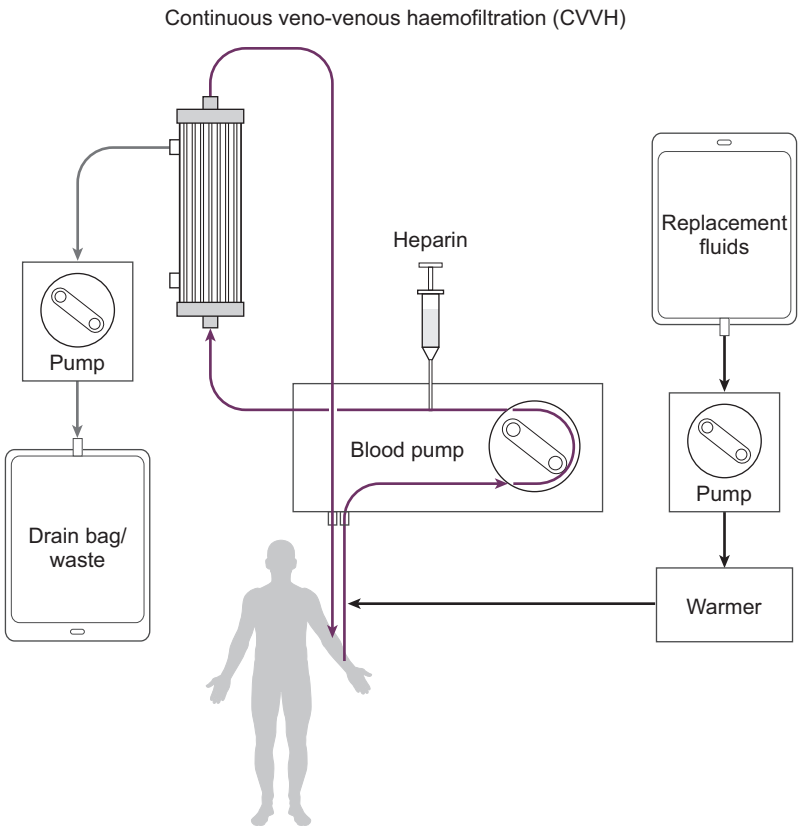


Figure 48.1 Diagram illustrating a continuous veno-venous haemofiltration circuit (CVVH).

Box 48.2 Strategies for circuit anticoagulation during continuous renal replacement therapy

1. No anticoagulation
2. Low-dose pre-filter heparin (<500 IU/h)
3. Regional citrate anticoagulation (pre-filter citrate and post-filter calcium and magnesium – special calcium free dialysate needed or citrate containing replacement fluid delivered pre-filter)
4. Medium-dose pre-filter heparin (500–1000 IU/h)
5. Full heparinisation
6. Regional anticoagulation (pre-filter heparin and post-filter protamine usually at a 100 IU to 1 mg ratio) (1500 IU/h) of heparin pre-filter and 15 mg/h of protamine post-filter
7. Low-molecular-weight heparin
8. Prostacyclin
9. Heparinoids

administer, and has almost no effect on the patient's coagulation tests. In some patients, a higher dose (800–1000 IU/h) is necessary. In others (pulmonary embolism, myocardial ischaemia) full heparinisation may actually be concomitantly indicated.

Regional citrate anticoagulation is very effective, but requires a special dialysate or replacement fluid.[16] Nonetheless, several randomised, controlled trials have now established that citrate anticoagulation is the safest and most effective way of achieving anticoagulation.[17,18] However, although it is safe and effective in patients who do not have significantly impaired liver function, in these patients citrate may accumulate and induce coagulopathy. The biochemical signs of citrate accumulation are an increasing base deficit, an increasing requirement for calcium administration to maintain the target level of calcaemia and widening of the total calcium to ionised calcium ratio. Magnesium supplementation is also needed. Due to the development of commercially available dialysate and replacement fluids to facilitate citrate anticoagulation and new CRRT machine technology to enable such anticoagulation to be performed with minimal risk, the use of citrate anticoagulation is now rapidly expanding.[17,18]

Regional heparin/protamine anticoagulation is also somewhat complex, but is simpler than citrate anticoagulation, and may be useful if frequent filter clotting occurs and further anticoagulation of the patient is considered dangerous.[18] Low MW heparin is also easy to administer, but is more expensive. If enoxaparin is

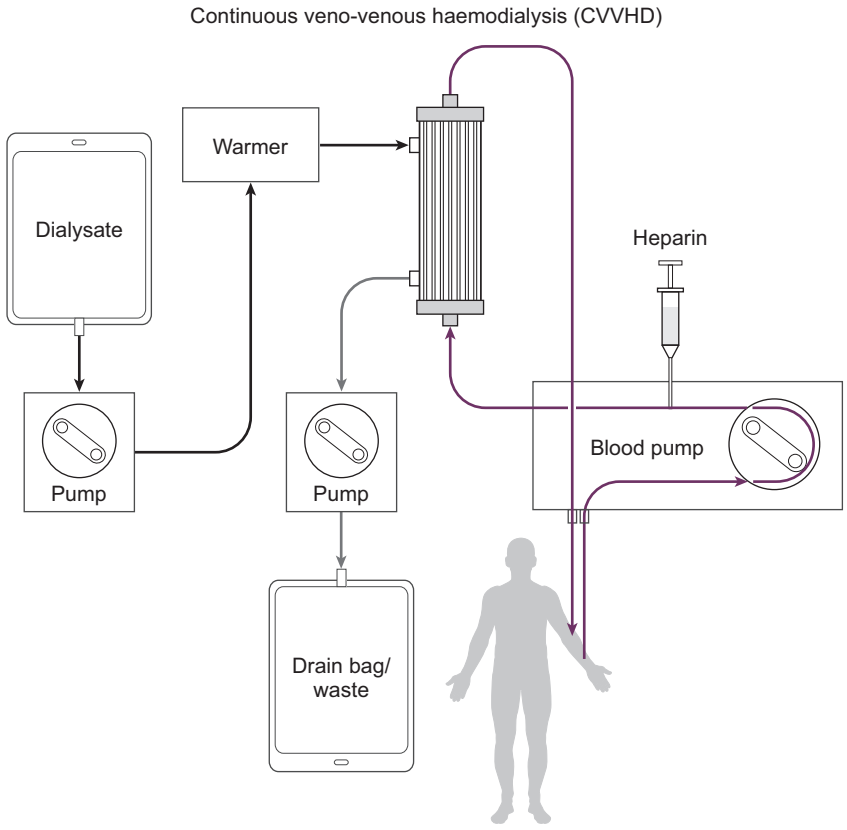


Figure 48.2 Diagram illustrating a continuous veno-venous haemodialysis circuit (CVVHD).

used, its dose should be adjusted for the loss of renal function. Heparinoids and prostacyclin may be useful if the patient has developed heparin-induced thrombocytopoenia and thrombosis. Finally, in perhaps 10%–20% of patients, anticoagulation of any kind is best avoided because of endogenous severe coagulopathy or recent surgery or inability to metabolise citrate. In such patients, adequate filter life can be achieved provided that blood flow is kept at about 200 mL/min and vascular access is reliable.[19]

Many circuits clot for *mechanical reasons* (inadequate access, unreliable blood flow from double-lumen catheter depending on patient position, kinking of catheter).[20] Responding to frequent filter clotting by simply increasing anticoagulation without making the correct aetiological diagnosis (checking catheter flow and position, taking a history surrounding the episode of clotting, identifying the site of clotting) is often futile and exposes the patient to unnecessary risk. Particular attention needs to be paid to the adequacy/ease of flow through the double lumen catheter. Smaller (11.5 Fr) catheters in the subclavian position are a particular problem. Larger catheters (13.5 Fr) in the femoral position or internal jugular position appear to perform more reliably.[21]

CONTINUOUS RENAL REPLACEMENT THERAPY TECHNOLOGY

The increasing use of veno-venous CRRT has led to the development of a field of CRRT technology, which offers different kinds of machines to facilitate its performance.[22] Some understanding of these devices is important to the successful implementation of CRRT in any ICU. These machines are safer and have much more sophisticated pump control systems, alarms and graphic displays. They are much more user friendly, especially with the set-up procedure. They provide information on outflow pressure (the suction pressure applied to the outflow lumen of the dialysis catheter and a marker of its performance), the transmembrane pressure (a marker of membrane fouling and clotting) and inflow pressure (a marker of resistance to inflow). Such pressures are often useful is assessing catheter function and the aetiology of circuit loss.[20]

The choice of membrane is also a matter of controversy. There are no controlled studies to show that one of them confers a clinical advantage over the others. The AN 69 is the most commonly used CRRT membrane in Australia. The issue of membrane size is also controversial as no controlled studies have compared

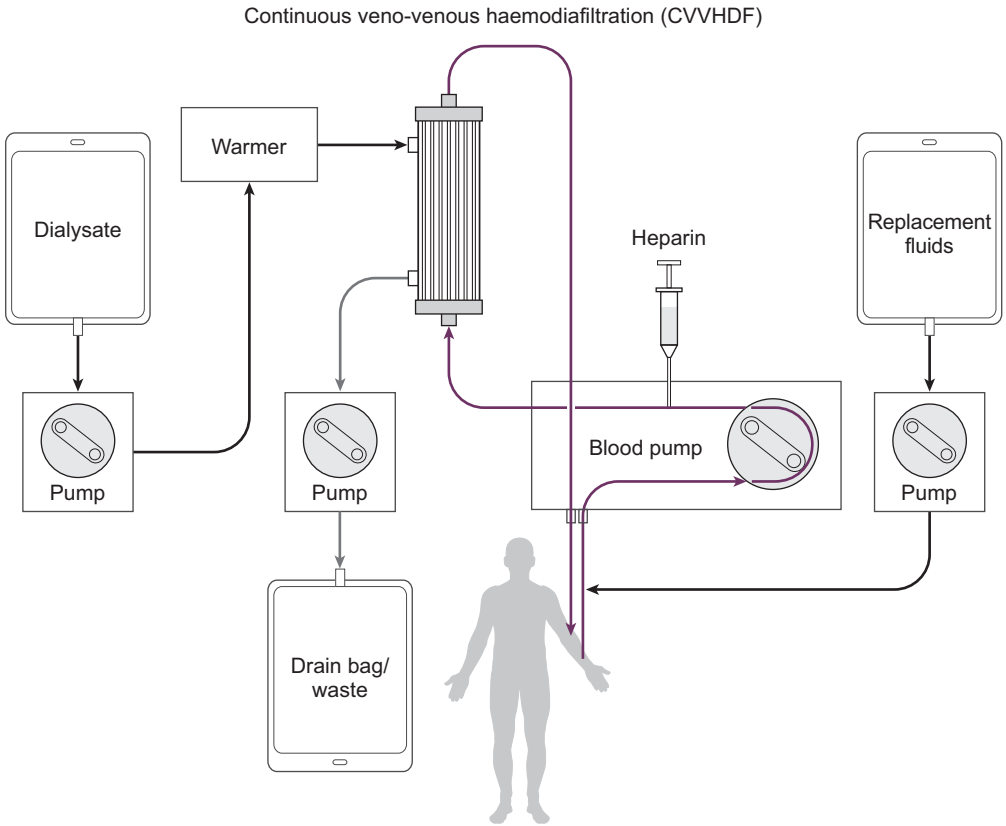


Figure 48.3 Diagram illustrating a continuous veno-venous haemodiafiltration circuit (CVVHDF).

different membrane surface sizes. However, if high-volume haemofiltration is planned the membrane surface needs to be in the 1.6–2 m^2 range.

INTENSITY OF CONTINUOUS RENAL REPLACEMENT THERAPY

The optimal dose (expressed at effective effluent/kg/h) of CRRT has been the subject of controversy for almost a decade. Several studies had initially suggested that a higher dose may translate into a better outcome.[23–25] However, such studies had been single centre in nature and were considered to require confirmation in multicentre, randomised, controlled trials. Two trials, completed in 2008[26] and 2009[27], showed no difference with increasing the intensity of RRT indicating that, in current practice, the prescribed dose of RRT should be equivalent to 25–30 mL/kg/h to take into account the impact of 'down time' on the delivered dose. Moreover, essentially all AKI patients on vasopressor support received CRRT in the Acute Renal Failure Trial Network (ATN) and Randomized Evaluation of Normal vs Augmented Level renal replacement therapy (RENAL) trials. Thus, by practice consensus, CRRT has now been become the de facto standard of care in haemodynamically unstable patients. Renal recovery was much greater in the RENAL trial (with essentially exclusive use of CRRT) than in the ATN trial (with substantial use of IHD), suggesting that the use of CRRT might facilitate renal recovery – a finding supported by large observational data.[28]

INTERMITTENT HAEMODIALYSIS

Acute vascular access for IHD is typically by double lumen catheter as in continuous HF. The circuit is also the same. Countercurrent dialysate flow is used as in CVVHD. The major differences are that standard IHD uses high dialysate flows (>400 mL/min) and generates dialysate by mixing purified water and concentrate. Treatment is conventionally applied for short periods of time (3–4 hours), usually every second day. These differences have important implications. First, volume has to be removed over a short period of time and this may cause hypotension. Repeated hypotensive episodes may delay renal recovery.[4,28] Secondly, solute removal is episodic. This translates into inferior uraemic[29] and acid-base control. Limited fluid and uraemic control imposes unnecessary limitations on nutritional support. Finally, rapid solute shifts increase brain water content and raise intracranial pressure.[30]

The limitations of applying 'standard' IHD to the treatment of AKI has led to the development of new approaches (so-called 'hybrid techniques'), such as slow low efficiency daily dialysis –SLEDD.[13] These techniques seek to adapt IHD to the clinical circumstances, decrease the rate of volume removal, decrease the rate of solute removal and thereby increase tolerance and overall clearances. However, the uptake of SLEDD has remained limited.[26] The multiple techniques of RRT and their complex names and many abbreviations (CVVHD, CVVH, CVVHDF, SLEDD, IHD) can lead to confusion and miscommunication. Accordingly, recent consensus statements on principles and nomenclature for RRT have been published for reference.[31,32]

PERITONEAL DIALYSIS

This technique is now uncommonly used in the treatment of adult AKI in developed countries, but remains relatively common in children and in patients with AKI in developing countries.[23] This is because it may be a cheap and adequate technique in developing countries, or in children where the peritoneal membrane has a greater relative surface or where alternatives are considered too expensive, too invasive or are not available. Typically, access is by the insertion of an intraperitoneal catheter. Glucose rich (hypertonic) dialysate is then inserted into the peritoneal cavity and acts as the 'dialysate'. After a given 'dwell time' it is removed and discarded with the extra fluid and toxins that have moved from the blood vessels of the peritoneum to the dialysate fluid. Machines are also available that deliver and remove dialysate at higher flows, providing intermittent treatment or higher solute clearances. Several major shortcomings make PD suitable for chronic dialysis but relatively unsuited to the treatment of adult AKI:

1. Limited and sometimes inadequate solute clearance
2. High risk of peritonitis
3. Unpredictable hyperglycaemia
4. Fluid leaks
5. Protein loss
6. Interference with diaphragm function.

In developed countries, there have not been any reports of the sole use of PD for the treatment of adult patients with AKI in the last 15 years. A randomised trial comparing PD to CVVH found that PD was associated with increased mortality.[23]

OTHER BLOOD PURIFICATION TECHNIQUES

HAEMOPERFUSION

During haemoperfusion, blood is circulated through a circuit similar to one used for CVVH. However, a charcoal cartridge is perfused with blood instead of a dialysis membrane. In some cases, an ion exchange resin (Amberlite) has been used. Charcoal microcapsules effectively remove molecules of 300–500 D in molecular weight including some lipid-soluble and protein-bound substances. Heparinisation is necessary to prevent clotting. Also, attention must be paid to changes in intravascular volume at the start of therapy because of the large priming volume of the cartridge (260 mL). Glucose absorption is significant and the monitoring of blood glucose is necessary to avoid hypoglycaemia. Also, thrombocytopoenia is common, and can be marked. The role of haemoperfusion is controversial as no controlled trials have ever shown it to confer clinically significant advantages. However, it may be useful in patients with life-threatening theophylline overdose because it removes the agent effectively.

PLASMAPHERESIS OR PLASMA EXCHANGE

With this technique, plasma is removed from the patient and exchanged with fresh frozen plasma (FFP) and a mixture of colloid and crystalloid solutions. This technique also can be performed in an ICU familiar with CRRT techniques. A plasmafilter (a filter that allows the passage of molecules up to 500 kD) instead of a haemofilter is inserted in the CVVH circuit, and the filtrate (plasma) is discarded. Plasmapheresis can also be performed with special machines using the principles of centrifugation. The differences, if any, between centrifugation and filtration technology are unclear. Replacement (post-filter) will occur as in CVVH, using a 50/50 combination of FFP and albumin, for example. Plasmapheresis has been shown to be effective treatment for thrombotic thrombocytopenic purpura (TTP) and for several diseases mediated by abnormal antibodies (Guillain-Barré syndrome, cryoglobulinaemia, myasthenia gravis, Goodpasture syndrome, etc.) in which antibody removal appears desirable. Its role in the treatment of sepsis remains uncertain.[33]

BLOOD PURIFICATION TECHNOLOGY OUTSIDE OF ACUTE KIDNEY INJURY

There is growing interest in the possibility that blood purification may provide a clinically significant benefit in patients with severe sepsis/septic shock by removing circulating 'mediators'. A variety of techniques, including plasmapheresis, high-volume HF, very-high volume HF, coupled plasma filtration adsorption and large pore HF are being studied in animals and in phase I/II studies in humans.[34–36] Initial experiments supported the need to continue exploring this therapeutic option. However, a recent multicentre, randomised, controlled trial of high volume haemofiltration in septic shock failed to show any benefit.[37] Also, albumin-based dialysis has been developed

Table 48.1 Drug dosage during dialytic therapy

DRUG	CRRT	IHD
Aminoglycosides	Normal dose q. 36 h	50% normal dose q. 48 h–2/3 re-dose after IHD
Cefotaxime or ceftazidime	1 g q. 8–12 h	1 g q. 12–24 h after IHD
Imipenem	500 mg q. 8 h	250 mg q. 8 h and after IHD
Meropenem	500 mg q. 8 h	250 mg q. 8 h and after IHD
Metronidazole	500 mg q. 8 h	250 mg q. 8 h and after IHD
Co-trimoxazole	Normal dose q. 18 h	Normal dose q. 24 h after IHD
Amoxycillin	500 mg q. 8 h	500 mg daily and after IHD
Vancomycin	1 g q. 24 h	1 g q. 96–120 h
Piperacillin	3–4 g q. 6 h	3–4 g q. 8 h and after IHD
Ticarcillin	1–2 g q. 8 h	1–2 g q. 12 h and after IHD
Ciprofloxacin	200 mg q. 12 h	200 mg q. 24 h and after IHD
Fluconazole	200 mg q. 24 h	200 mg q. 48 h and after IHD
Acyclovir	3.5 mg/kg q. 24 h	2.5 mg/kg/d and after IHD
Gancyclovir	5 mg/kg/d	5 mg/kg/48 h and after IHD
Amphotericin B	Normal dose	Normal dose
Liposomal amphotericin	Normal dose	Normal dose
Ceftriaxone	Normal dose	Normal dose
Erythomycin	Normal dose	Normal dose
Milrinone	Titrate to effect	Titrate to effect
Amrinone	Titrate to effect	Titrate to effect
Catecholamines	Titrate to effect	Titrate to effect
Ampicillin	500 mg q. 8 hourly	500 mg daily and after IHD

The above values represent approximations and should be used as a general guide only. Critically ill patients have markedly abnormal volumes of distribution for these agents, which will affect dosage. CRRT is conducted at variable levels of intensity in different units also requiring adjustment. The values reported here relate to CVVH at 2 L/h of ultrafiltration. Vancomycin is poorly removed by CVVHD. IHD may also differ from unit to unit. The values reported here relate to standard IHD with low-flux membranes for 3–4 hours every second day.
CRRT, Continuous renal replacement therapy; *d*, day; *h*, hours; *IHD*, intermittent haemodialysis; *q,* frequency.

to deal with protein-bound toxins in patients with liver failure. This system – known as MARS (molecular adsorption re-circulating system) – has shown benefits in patients' elevated intracranial pressure and/or acute or chronic liver failure, but not in patients with fulminant liver failure.[38] More recently, new techniques based on advanced sorbents with high adsorption capabilities for cytokines have been developed and are being used in small studies with promising biological effect.[39]

DRUG PRESCRIPTION DURING DIALYTIC THERAPY

Acute renal failure and RRT profoundly affect drug clearance. A comprehensive description of changes in drug dosage according to the technique of RRT, residual creatinine clearance, and other determinants of pharmacodynamics is beyond the scope of this chapter and can be found in specialist texts.[40] Table 48.1 provides general guidelines for the prescription of drugs commonly used in the ICU.

AREAS OF ONGOING CONTROVERSY AND CLINICAL RESEARCH

In the area of RRT, the area of greater controversy and clinical research priority relates to the timing of the initiation of such RRT.[41]

This issue has been recently addressed by two important trials.[42,43] Unfortunately, these two studies (one from France and the other from Germany) had

opposing findings, leaving the issue unresolved. Accordingly, a definitive, very large (>2000 patients) international, randomised, controlled trial has just started and will be randomising patients over the next 3–4 years.[44] Its findings will likely shape RRT practice in the next decade, much as the ATN[26] and RENAL[27] trials have done over the last decade.

SUMMARY

The field of RRT has undergone remarkable changes over the last 10 years and is continuing to evolve rapidly. Technology is being improved to facilitate the clinical application, and new areas of research are developing. CRRT is now firmly established throughout the world as perhaps the most commonly used form of RRT. However, conventional dialysis, which was slowly losing ground, is reappearing in the form of extended, slow-efficiency treatment, especially in the United States. Two large phase III trials (>1000 patients) have been completed in the United States and in Australia and New Zealand to define the optimal dose of RRT in ICU patients; the results indicate that a dose of 25 mL/kg/h of effluent generation provides appropriate therapy in this setting. In the meantime, the use of novel membranes, sorbents and different intensities of treatment are being explored in the area of sepsis management and liver support.

REFERENCES

1. Sargent J, Gotch F. Principles and biophysics of dialysis. In: Maher J, ed. *Replacement of Renal Function by Dialysis*. Dordrecht, the Netherlands: Kluwer Academic Publishers; 1989:87–102.
2. Henderson L. Biophysics of ultrafiltration and hemofiltration. In: Maher J, ed. *Replacement of Renal Function by Dialysis*. The Netherlands: Kluwer Academic Publishers; 1989:300–332.
3. Nolph KD. Peritoneal dialysis. In: Brenner BM, Rector FC, eds. *The Kidney*. 1st ed. Philadelphia, PA: WB Saunders; 1986:1791–1845.
4. Conger JD. Does hemodialysis delay recovery from acute renal failure? *Seminars Dial*. 1990;3:146–145.
5. Howdieshell TR, Blalock WE, Bowen PA, et al. Management of post-traumatic acute renal failure with peritoneal dialysis. *Am Surg*. 1992;58:378–382.
6. Bellomo R, Boyce N. Continuous veno-venous hemodiafiltration compared with conventional dialysis in critically ill patients with acute renal failure. *ASAIO J*. 1993;39:M794–M797.
7. Gettings LG, Reynolds HN, Scalea T. Outcome in post-traumatic acute renal failure when continuous renal replacement therapy is applied early vs. late. *Intensive Care Med*. 1999;25:805–881.
8. Chatoth DK, Shaver MJ, Marshall MR, et al. Daily 12-hour sustained low-efficiency hemodialysis (SLED) for the treatment of critically ill patients with acute renal failure: initial experience. *Blood Purif*. 1999;17:Abstract 16.
9. Paganini EP. Dialysis is not dialysis is not dialysis! Acute dialysis is different and needs help! *Am J Kidney Dis*. 1998;32:832–833.
10. Bellomo R, Ronco C. Adequacy of dialysis in the acute renal failure of the critically ill: the case for continuous therapies. *Int J Artif Organs*. 1996;19:129–142.
11. Kanagasundaram NS, Paganini EP. Critical care dialysis – a Gordian knot (but is untying the right approach? *Nephrol Dial Transplant*. 1999;14: 2590–2594.
12. Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomized trial. *Lancet*. 2000;355: 26–30.
13. Marshall MR, Golper TA, Shaver MJ. et al. Hybrid renal replacement modalities for the critically ill. *Contrib Nephrol*. 2001;132(252):257.
14. Cole L, Bellomo R, Silvester W, et al. A prospective, multicenter study of the epidemiology, management and outcome of severe acute renal failure in a 'closed' ICU system. *Am J Respir Crit Care Med*. 2000; 162:191–196.
15. Mehta R, Dobos GJ, Ward DM. Anticoagulation procedures in continuous renal replacement. *Seminars Dial*. 1992;5:61–68.
16. Naka T, Egi M, Bellomo R, et al. Low-dose citrate continuous veno-venous hemofiltration and acid-base balance. *Int J Artif Organs*. 2005;28: 222–228.
17. Morgera S. Regional anticoagulation with citrate: expanding its indications. *Crit Care Med*. 2011;39: 399–400.
18. Gattas DJ, Rajbhandari D, Bradford C, et al. A randomized controlled trial of regional citrate versus regional heparin anticoagulation for continuous renal replacement therapy in critically ill adults. *Crit Care Med*. 2015;43(8):1622–1629.
19. Tan HK, Baldwin I, Bellomo R. Hemofiltration without anticoagulation in high-risk patients. *Intensive Care Med*. 2000;26:1652–1657.
20. Zhang L, Tanaka A, Zhu G, et al. Patterns and mechanisms of artificial kidney failure during continuous renal replacement therapy. *Blood Purif*. 2016;41:254–263.
21. Parienti JJ, Thirion M, Fischer MO, et al. Catheter dysfunction and dialysis performance according to vascular access among 736 critically ill adults requiring renal replacement therapy: a randomized controlled trial. *Crit Care Med*. 2010;38:1118–1125.
22. Ronco C, Brendolan A, Bellomo R. Current technology for continuous renal replacement therapies. In: Ronco C, Bellomo R, eds. *Critical Care Nephrology*. Dordrecht, The Netherlands: Kluwer Academic Publishers; 1998:1327–1334.
23. Phu NH, Hien TT, Mai NT, et al. Hemofiltration and peritoneal dialysis in infection-associated acute renal failure in Vietnam. *N Engl J Med*. 2002;347: 895–902.
24. Ronco C, Bellomo R, Homel P, et al. Effect of different doses in CVVH on outcomes of acute

renal failure: a prospective randomized trial. *Lancet*. 2000;356:26–30.
25. Saudan P, Niederberger M, De Seigneux S, et al. Adding a dialysis dose to continuous hemofitlration increases survival in patients with acute renal failure. *Kidney Int*. 2006;70:1312–1317.
26. Palevsky PM, Zhang JH, O'Connor TZ, et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med*. 2008;359:7–20.
27. The RENAL Replacement Therapy Study Investigators. Intensity of continuous renal replacement therapy in critically ill patients. *N Engl J Med*. 2009;361:1627–1638.
28. Wald R, Shariff SZ, Adhikari NK, et al. The association between renal replacement therapy modality and long-term outcomes among critically ill adults with acute kidney injury: a retrospective cohort study. *Crit Care Med*. 2014;42:868–877.
29. Macias WL, Clark WR. Azotemia control by extracorporeal therapy in patients with acute renal failure. *New Horiz*. 1995;3:688–693.
30. Davenport A. The management of renal failure in patients at risk of cerebral edema/hypoxia. *New Horiz*. 1995;3:717–724.
31. Neri M, Villa G, Garzotto F, et al. Nomenclature for renal replacement therapy in acute kidney injury: basic principles. *Crit Care*. 2016;20:318.
32. Villa G, Neri M, Bellomo R, et al. Nomenclature for renal replacement therapy and blood purification techniques in critically ill patients: practical applications. *Crit Care*. 2016;20:283.
33. Reeves JH, Butt WW, Shann F, et al. Continuous plasmafiltration in sepsis syndrome. *Crit Care Med*. 1999;27:2096–2104.
34. Bellomo R, Baldwin I, Ronco C. High-volume hemofiltration. *Contrib Nephrol*. 2001;132:375–382.
35. Mao H, Yu S, Yu X, et al. Effect of coupled plasma filtration adsorption on endothelial cell function in patients with multiple organ dysfunction syndrome. *Int J Artif Organs*. 2011;34:288–294.
36. Naka T, Haase M, Bellomo R. Super high-flux or high cut-off hemofiltration and hemodialysis. *Contrib Nephrol*. 2010;166:181–189.
37. Joannes-Boyau O, Honore P, Perez P, et al. High-volume versus standard volume hemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicenter randomized controlled trial. *Intensive Care Med*. 2013;39:1535–1546.
38. Kobashi-Margain RA, Gavilanes-Espinar JG, Gutierrez-Grobe Y, et al. Albumin dialysis with molecular adsorbent recirculating system (MARS) for the treatment of hepatic encephalopathy in liver failure. *Ann Hepatol*. 2011;10:S70–S76.
39. Kellum JA, Song M, Venkataraman R. Hemoadsorption removes tumor necrosis factor, interleukin-6, and interleukin-10, reduces nuclear factor-kappa B DNA binding and improves short term survival in lethal endotoxemia. *Crit Care Med*. 2004;32:801–805.
40. Buckmaster J, Davies AR. Guidelines for drug dosing during continuous renal replacement therapies. In: Ronco C, Bellomo R, eds. *Critical Care Nephrology*. Dordrecht, The Netherlands: Kluwer Academic Publishers; 1998:1327–1334.
41. Wald R, Bagshaw SM. The timing of renal replacement therapy initiation in acute kidney injury. *Semin Nephrol*. 2016;36:78–84.
42. Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. *JAMA*. 2016;315:2190–2199.
43. Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med*. 2016;375:122–133.
44. Wald R, Adhikari NK, Smith OM, et al. Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury. *Kidney Int*. 2015;88:897–904.

This page intentionally left blank

Part Seven
Neurological Disorders

This page intentionally left blank

49

Disorders of consciousness

Hayden White, Balasubramanian Ventakesh

NEUROANATOMY AND PHYSIOLOGY OF WAKEFULNESS

A normal level of consciousness depends on the interaction between the cerebral hemispheres and the rostral reticular activating system (RAS) located in the upper brainstem. Although the RAS is a diffuse projection, the areas of RAS of particular importance to the maintenance of consciousness are those located between the rostral pons and the diencephalon. In contrast, however, consciousness is not focally represented in any of the cerebral hemispheres and is in many ways related to the mass of functioning cortex. Thus anatomical bilateral hemispheric lesions or brain stem lesions may result in an altered conscious state.[1] Large unilateral hemispheric lesions may produce impairment of consciousness by compression of the upper brainstem. In addition, metabolic processes may result in coma from the interruption of energy substrate delivery or alteration of neuronal excitability. Disorders of consciousness are characterised either by an alteration in the level or content of consciousness (Box 49.1). **These are also illustrated in Fig. 49.1.**[2]

The last three conditions described in Box 49.1 are a frequent source of confusion and require further discussion (Table 49.1). These neurological states are seen more frequently in modern day clinical practice, partly because of the advances in therapy of severe brain injury and in intensive care, which have led to the survival of many patients who would have otherwise died.

DIFFERENTIAL DIAGNOSIS OF COMA

Although the aetiology of coma is invariably multifactorial, the differential diagnosis of coma can be broadly grouped into three classes:

1. Diseases that produce focal or lateralising signs
2. Coma without focal or lateralising signs, but with signs of meningeal irritation
3. Coma without focal or lateralising signs or signs of meningeal irritation.

These are considered in greater detail in Table 49.2.

CLINICAL EXAMINATION OF THE COMATOSE PATIENT

The neurological examination of the comatose patient is of crucial importance to assess the depth of the coma and to locate the site of the lesion. Although the detailed neurological examination, which can be carried out in a conscious patient, is not possible in a comatose individual, useful information can be obtained by performing a thorough general examination and a neurological examination, particularly evaluating the level of consciousness, brainstem signs and motor responses in coma.

GENERAL EXAMINATION

General examination of the patient may point to the aetiology of coma. Skin changes may be seen in carbon monoxide poisoning (cherry red discolouration of skin), alcoholic liver disease (telangiectasia, clubbing), hypothyroidism (puffy facies) and hypopituitarism (sallow complexion). The presence of cutaneous petechiae or ecchymoses may point to meningococcemia, rickettsial infection or endocarditis as possible causes of coma. Needle puncture marks may suggest substance abuse. Bullous skin lesions are a feature of barbiturate overdose. An excessively dry skin may indicate diabetic ketoacidosis or anticholinergic overdose.

Periorbital haematomas (raccoon eyes) indicate an anterior basal skull fracture, particularly if there is associated cerebrospinal fluid rhinorrhoea. The other signs of a basal skull fracture include Battle's sign and cerebrospinal fluid otorrhoea. Nuchal rigidity may be seen in meningoencephalitis and subarachnoid haemorrhage (SAH), although this sign may not be present in the elderly and in patients in a deep coma.

The presence of hepatomegaly or stigmata of chronic liver disease may suggest hepatic encephalopathy. Bilateral enlarged kidneys may indicate polycystic kidney disease and should prompt one to consider SAH as a possible aetiology of coma. The breath may smell of alcohol or other poisons (organophosphates). The smell of ketones in the breath is an unreliable sign and hepatic and uraemic foetor are rare.

ABSTRACT

An altered level of consciousness is a common finding in the intensive care unit (ICU) population. Although often induced by clinicians to facilitate patient management, cerebral functioning is altered by a number of disease processes commonly found in the ICU, both brain specific (e.g. acute brain injury), or as a consequence of systemic disease (e.g. sepsis-induced encephalopathy). While significant progress has been made in understanding the impact of disease on the brain, many questions still remain. What is clear is that altered cerebral function has a significant impact on morbidity and mortality. This is evidenced by the poor outcomes demonstrated in patients suffering from delirium in the ICU, and has led to a number of attempts to increase clinician awareness of the impact of ICU management on the brain, and investigate more 'brain friendly' treatment options. It is hoped that as technology advances, monitoring of cerebral function will improve and lead to a better understanding of cerebral dysfunction in the ICU environment.

KEY WORDS

Acute brain injury
coma
altered consciousness
Glasgow Coma Scale
delirium
encephalopathy
traumatic brain injury
sepsis
intracranial pressure
cerebral oedema

Box 49.1 Disorders of consciousness

Consciousness	An awake individual demonstrates full awareness of self and environment
Confusion	Inability to think with customary speed and clarity, associated with inattentiveness, reduced awareness and disorientation
Delirium	Confusion with agitation and hallucination
Stupor	Unresponsiveness with arousal only by deep and repeated stimuli
Coma	Unarousable unresponsiveness
Locked-in syndrome	Total paralysis below third cranial nerve nuclei; normal or impaired mental function
Persistent vegetative state	Prolonged coma >1 month, some preservation of brainstem and motor reflexes
Akinetic mutism	Prolonged coma with apparent alertness and flaccid motor tone
Minimally conscious state	Preserved wakefulness, awareness and brainstem reflexes, but poorly responsive

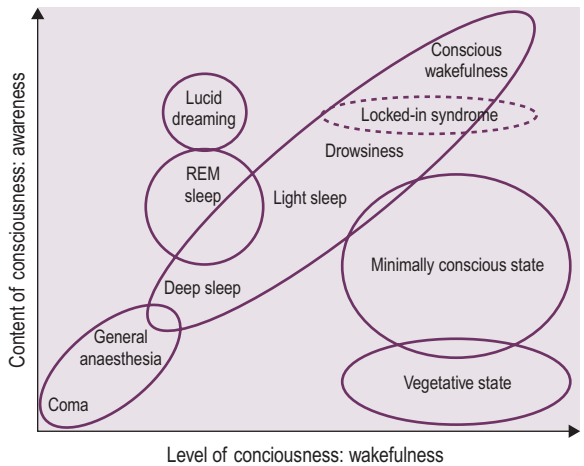


Figure 49.1 Disorders of consciousness are characterised by an alteration in either the level or content of consciousness. *REM*, Rapid eye movements. *With permission from Gosseries O, Vanhaudenhuyse A, Bruno MA, et al. Disorders of consciousness: coma, vegetative and minimally conscious states. In: Cvetkovic D, Cosic I, eds.* States of Consciousness: Experimental Insights into Meditation, Waking, Sleep and Dreams. *Berlin: Springer; 2011.*

LEVEL OF CONSCIOUSNESS

This is assessed by the Glasgow Coma Scale (GCS), which takes into account the patient's response to command and physical stimuli. The GCS (Box 49.2), which was originally developed to grade the severity of head injury and prognosticate outcome, has now been extended for all causes of impaired consciousness and coma. Whilst it is a simple clinical score easily performed by both medical and nursing staff by the bedside, there are a number of caveats:

Box 49.2 Glasgow coma scale

EYE OPENING	POINTS
Spontaneous	4
To speech	3
To pain	2
Nil	1
BEST VERBAL RESPONSE	
Oriented	5
Confused	4
Inappropriate	3
Incomprehensible	2
Nil	1
Intubated	T
BEST MOTOR RESPONSE	
Obeys commands	6
Localises to pain	5
Withdraws to pain	4
Abnormal flexion	3
Extensor response	2
Nil	1

1. The GCS should always be determined prior to administration of sedative drugs or endotracheal intubation
2. It should also be defined with regard to patient's vital signs, namely blood pressure, heart rate and temperature
3. The GCS must be interpreted in light of previous or concomitant drug therapy
4. The presence of alcohol in the breath or in the serum should always be documented
5. Because of the considerable interobserver variation in scoring, it is important to define the responses in descriptive terms rather than emphasising the numerical score associated with each response
6. The measurement of awareness by the GCS is limited. Subtle changes in brainstem reflexes are not adequately assessed by the GCS.

To overcome the limitations of the GCS in assessing brainstem activity, the FOUR (Full Outline of UnResponsiveness) score was proposed by Wijdicks et al.[8,9] The components of the FOUR score include eye movements, motor score, brainstem reflexes and respiration.

Table 49.1 Coma-like syndromes and related states

SYNDROME	FEATURES	SITE OF LESION	EEG	METABOLISM (% OF NORMAL)[3]	COMMENTS
Locked-in syndrome[4] (de-efferented state)	Alert and aware, vertical eye movements present, and able to blink. Quadriplegic, lower cranial nerve palsies, no speech, facial or pharyngeal movements	Bilateral anterior pontine lesion which transects all descending motor pathways, but spares ascending sensory and RAS systems	Normal	90%–100%	Similar state seen with severe polyneuropathies, myasthenia gravis and neuromuscular blocking agents
Persistent vegetative state (PVS)[5] (apallic syndrome, neo-cortical death)	Previously comatose, who now appear to be awake. Spontaneous limb movements, eye movements and yawning seen. However, patient inattentive, no speech, no awareness of environment and total inability to respond to commands	Extensive damage to both cerebral hemispheres with relative preservation of the brainstem	Polymorphic delta or theta waves, sometimes alpha	40%–60%	When vegetative state lasts longer than 4 weeks, it is termed persistent. PVS lasting for longer than 2 weeks implies a poor prognosis
Akinetic mutism[6] (coma vigile)	Partially or fully awake patient, immobile and silent	Lesion in bilateral frontal lobes or hydrocephalus or third ventricular masses	Diffuse slowing	40%–80%	Abulia is the term applied to milder forms of akinetic mutism
Catatonia	Awake patients, sometimes a fixed posture, muteness with decreased motor activity	Usually of psychiatric origin	Non-specific EEG patterns associated with associated medical conditions	Variable metabolic changes in prefrontal cortex	May be mimicked by frontal lobe disease and drugs
Minimally conscious state[7]	Globally impaired responsiveness, limited but discernible evidence of self and environment	Global neuronal damage	Theta & alpha waves	40%–60%	Differs from PVS in that patients diagnosed with minimally conscious state have some level of awareness

EEG, Electroencephalography; *RAS*, reticular-activating system.

Each subcomponent is scored out of a maximum of four and therefore the maximum score is 16. It does not include verbal response and may be more suitable in the intubated patient.

PUPILLARY RESPONSES IN COMA

The presence of normal pupils (2–5 mm and equal in size and demonstrate both direct and consensual light reflexes) confirms the integrity of the pupillary pathway (retina, optic nerve, optic chiasma and tracts, midbrain and third cranial nerve nuclei and nerves).[10]

The size of the pupil is a balance between the opposing influences of both sympathetic (causing dilatation) and parasympathetic (causing constriction) systems. Pupillary abnormalities have localising and diagnostic value in clinical neurology (Table 49.3). When the pupils are miosed, the light reaction is difficult to appreciate and may require a magnifying glass.

OPHTHALMOSCOPY IN COMA

The pupils *should never be dilated pharmacologically* without prior documentation of the pupillary size and

Table 49.2 Differential diagnosis of coma

CATEGORY	SPECIFIC DISORDER	FEATURES IN HISTORY AND EXAMINATION	INVESTIGATIONS	COMMENTS
COMA WITH FOCAL SIGNS	*Trauma* – extradural, subdural and parenchymal haemorrhage, concussions	History of trauma, findings of fracture base of skull, scalp haematoma, other associated body injuries	Usually an abnormal CT	Exclude coexisting drug or alcohol ingestion
	Vascular – Intracerebral haemorrhage	Sudden onset, history of headaches or hypertension, neck stiffness may be present	Abnormal CT scan	Consider causes of secondary hypertension in young hypertensives
	Vascular – thromboembolic	Sudden onset, atrial fibrillation, vascular bruits, endocarditis	An abnormal CT after a few days	Consider echocardiography to diagnose cardiac sources of emboli
	Brain abscess	Subacute onset, look for ENT and dental sources of infection	Abnormal CT and CSF	Consider infective endocarditis and suppurative lung disease as sources of sepsis
Coma without focal signs, but with meningeal irritation	Infection Meningitis, encephalitis	Onset of illness over a few hours to days, neck stiffness, rash of meningococcemia	Abnormal CSF	Consider underlying immunosuppressive states
	Subarachnoid haemorrhage	Onset usually sudden, subhyaloid haemorrhages on fundoscopy	Abnormal CT and CSF	Consider polycystic kidney disease in subarachnoid haemorrhage
Coma without focal signs and no meningeal irritation	Metabolic causes Hyponatraemia Hypoglycaemia, hyperglycaemia Hypoxia Hypercapnia Hypo- and hyperthermia Hyper- and hypo-osmolar states	History might point to the cause of metabolic disturbance, asterixis a feature of hypercapnia-induced coma	Abnormal blood results	Rapid correction of hyponatraemia and osmolality should be avoided
	Endocrine causes Myxoedema Adrenal insufficiency Hypopituitarism	Puffy facies, may be hypothermic	Abnormal electrolyte profile, hypoglycaemia	Multiple disorders may be present in the same patient
	Seizure disorders	History typical	Abnormal EEG, check anticonvulsant levels	CT scan to exclude an underlying space occupying lesion
	Organ failure Hepatic Renal	History of jaundice, chronic alcohol ingestion, stigmata of liver disease, asterixis	Abnormal hepatic and renal functions	Presence of A-V fistula may be a pointer to chronic renal failure
	Toxic/drug Sedatives Narcotics Alcohol Psychotropic Carbon monoxide Poisons	History, may be hypothermic at presentation except in psychotropic drug overdose	Metabolic screen is usually normal	Rapid improvement in conscious states with antidotes
	Behavioural Sleep deprivation Pseudocoma	No typical features	No specific diagnostic tests	Diagnosis of exclusion

A-V, Arteriovenous; *CSF*, cerebrospinal fluid; *CT*, computed tomography; *EEG*, electroencephalography; *ENT*, ear, nose and throat.

Table 49.3 Pupillary abnormalities in coma

ABNORMALITY	CAUSE	NEUROANATOMICAL BASIS
MIOSIS (<2 MM IN SIZE)		
Unilateral	Horner's syndrome	Sympathetic paralysis
	Local pathology	Trauma to sympathetics
Bilateral	Pontine lesions	
	Thalamic haemorrhage	Sympathetic paralysis
	Metabolic encephalopathy	
	Drug ingestion	
	Organophosphate	Cholinesterase inhibition
	Barbiturate	
	Narcotics	Central effect
MYDRIASIS (>5 MM IN SIZE)		
Unilateral fixed pupil	Midbrain lesion	Third nerve damage
	Uncal herniation	Stretch of third nerve against the petroclinoid ligament
Bilateral fixed pupils	Massive midbrain haemorrhage	Bilateral third nerve damage
	Hypoxic cerebral injury	Mesencephalic damage
	DRUGS	
	Atropine	Paralysis of parasympathetics
	Tricyclics	Prevent local reuptake of catecholamines by nerve endings
	Sympathomimetics	Stimulation of sympathetics

the light reflex. The presence of papilloedema suggests the presence of intracranial hypertension, but is frequently absent, when the lesion is acute. Subhyaloid and vitreous haemorrhages are seen in patients with SAH.[11]

EYE MOVEMENTS IN COMA[12]

Horizontal eye movements to the contralateral side are initiated in the ipsilateral frontal lobe and are closely coordinated with the corresponding centre in the contralateral pons. To facilitate conjugate eye movements, yoking of the third, fourth and sixth nerve nuclei is achieved by the medial longitudinal fasciculus.

To look to the left, the movement originates in the right frontal lobe and is coordinated by the left pontine region and vice versa. In contrast to horizontal gaze, vertical eye movements are under bilateral control of the cortex and upper midbrain.

The position and movements of the eyes are observed at rest. The presence of spontaneous roving eye movements excludes brainstem pathology as a cause of coma. In a paralytic frontal lobe pathology, the eyes will deviate towards the side of the lesion, while in pontine pathologies, the eyes will deviate away from the side of the lesion. Ocular bobbing, an intermittent downward jerking eye movement, is seen in pontine lesions due to loss of horizontal gaze and unopposed midbrain controlled vertical gaze activity.[13] Skew deviation (vertical separation of the ocular axes) occurs with pontine and cerebellar disorders.[14]

The presence of full and conjugate eye movements in response to oculocephalic and oculovestibular stimuli demonstrates the functional integrity of a large segment of the brainstem. Corneal reflexes are preserved until late in the coma. Upward rolling of the eyes after corneal stimulation (Bell's phenomenon) implies intact midbrain and pontine function.

LIMB MOVEMENTS AND POSTURAL CHANGES IN COMA

Restlessness, crossing of legs and spontaneous coughing, yawning, swallowing and localising movements suggest only a mild depression of the conscious state. Choreoathetotic or ballistic movements suggest a basal ganglion lesion. Myoclonic movements indicate a metabolic disorder usually of post anoxic origin. Asterixis is seen with metabolic encephalopathies. Hiccup is a non-specific sign and does not have any localising value.

Decerebrate rigidity is characterised by stiff extension of the limbs, internal rotation of the arms and plantar flexion of the ankles. With severe rigidity, opisthotonos and jaw clenching may be observed. These movements may be unilateral or bilateral, and spontaneous or in response to a noxious stimulus. Whilst animal studies suggest that the lesion is usually in the midbrain or caudal diencephalon (leading to exaggeration of antigravity reflexes), in humans such posturing may be seen in a variety of disease states: midbrain lesion, certain metabolic disorders (e.g. hypoglycaemia, anoxia, hepatic coma) and in drug intoxication.

Box 49.3 Disorders of respiratory rate and pattern in coma

ABNORMALITY	SIGNIFICANCE
Bradypnoea	Drug-induced coma, hypothyroid coma
Tachypnoea	Central neurogenic hyperventilation (midbrain lesion), metabolic encephalopathy
Cheyne Stokes respiration	Deep cerebral lesions, metabolic encephalopathy (hyperpnoea alternating regularly with apnoea)
Apneustic breathing (an inspiratory pause)	Pontine lesions
Ataxic breathing (ataxic breathing normally progresses to agonal gasps and terminal apnoea)	Medullary lesions

Decorticate posturing is characterised by the flexion of the elbows and wrists and extension of the lower limbs. The lesion is usually above the midbrain in the cerebral white matter.

RESPIRATORY SYSTEM[15]

Abnormal respiratory rate and patterns have been described in coma, but their precise localising value is uncertain. As a general rule, at lighter levels of impaired consciousness tachypnoea predominates, while respiratory depression increases with the depth of coma. Some of the commonly observed respiratory abnormalities are summarised in Box 49.3. Respiratory failure in comatose patients may result from hypoventilation, aspiration pneumonia and neurogenic pulmonary oedema, a sympathetic nervous-system-mediated syndrome seen in acute brain injury.

BODY TEMPERATURE IN COMA

The presence of altered core body temperature is a useful aid in the diagnosis of coma. Hypothermia (<35°C) is frequently observed with alcohol or barbiturate intoxication, sepsis with shock, drowning, hypoglycaemia, myxoedema coma and exposure to cold. Severe hyperthermia may be seen in pontine haemorrhage, intracranial infections, heat stroke and anticholinergic drug toxicity.

RECOGNITION OF BRAIN HERNIATION[16–18]

When patients with an impaired level of consciousness deteriorate, it is important to consider brain herniation as a possible cause of worsening. Several herniation syndromes have been described. Subfalcine herniation usually results from the lateral displacement of the brain and is identified by the horizontal shift of the pineal gland. Ischaemia of the medial aspect of the cerebral hemispheres can result from compression of the pericallosal and the marginal arteries. Transtentorial herniation results from the downward displacement of the upper brainstem (central herniation) with or without involvement of the uncus (lateral herniation). The clinical signs of a central herniation are progressive obtundation, Cheyne-Stokes respiration, small pupils followed by extensor posturing and medium-sized fixed dilated pupils. Uncal herniation differs from central herniation in that pupillary dilatation occurs early in the process because of third nerve compression. The traditional Cushing's response of hypertension and bradycardia is not always a feature of herniation and any heart rhythm may be present. Tonsillar herniation is the protrusion of the cerebellar tonsils through the foramen magnum resulting in caudal medullary compression and obstruction of the fourth ventricle.

DIFFERENTIATING TRUE COMA FROM PSEUDOCOMA

Patients feigning coma resist passive eye opening and may even hold their eyes tightly closed. They may blink in response to a threat and do not demonstrate spontaneous roving eye movements. In contrast, they move the eyes concomitantly with head rotation; with cold caloric testing, they may wake up or demonstrate preservation of the fast component of nystagmus. They also demonstrate avoidance of 'self-injury'. In addition, the pattern of clinical 'abnormalities' does not fit any specific neurological syndromes.

MANAGEMENT OF THE COMATOSE PATIENT

EMERGENT THERAPEUTIC MEASURES

Irrespective of the aetiology of coma, certain emergent therapeutic measures apply to the care of all patients. These take precedence over any diagnostic investigation.

1. Ensuring adequate airway and oxygenation
2. Securing intravenous access and maintain circulation
3. Administering 50% dextrose after drawing a sample of blood for serum glucose levels. Although there are theoretical concerns about augmentation of brain lactic acid production[19,20] in anoxic coma, the relatively good prognosis for hypoglycaemic coma when treated expeditiously far outweigh any potential risks of glucose administration

4. Thiamine must always be administered in conjunction with dextrose to prevent precipitation of Wernicke's encephalopathy
5. Consideration should be given to administering naloxone, when there is a suspicion of narcotic overdose with impending respiratory arrest
6. If hypertension, bradycardia and fixed dilated pupils are present at the time of the initial presentation, suggestive of marked intracranial hypertension and tentorial herniation, 20% mannitol at a dose 0.5–1 g/kg body weight should be administered. Consideration should be given to the emergency placement of an external ventricular drain
7. Treat suspected meningitis with antibiotics even if cerebrospinal fluid results are not available. A combination of penicillin and ceftriaxone is usually recommended for a community-acquired bacterial meningitis
8. Control of seizures must be achieved as outlined in the chapter on Status Epilepticus
9. Treat extreme body temperatures
10. Stabilisation of the cervical spine if trauma is suspected.

INVESTIGATIONS

The order of investigation depends on the clinical circumstance. In the majority of cases, history and examination will provide enough information to be able to perform specific cause-related investigation. In general, the investigations can be grouped as follows.

ROUTINE INVESTIGATIONS

Measurements of serum glucose, electrolytes, arterial blood gases, liver and renal function tests, osmolality, blood count and blood film are part of the routine investigations. When drug overdose is suspected, a toxicology screen for alcohol, paracetamol, salicylates, benzodiazepines and tricyclic antidepressants should be performed. A sample of serum should be stored for later analysis for uncommon drug ingestions.

NEUROIMAGING

COMPUTED TOMOGRAPHY SCAN

The most commonly used radiological investigation for evaluation of the comatose patient is computed tomography (CT) scan of the brain. This is useful for diagnosing central nervous system (CNS) trauma, SAH and intracerebral haemorrhage, haemorrhagic and non-haemorrhagic strokes, cerebral oedema, hydrocephalus and the presence of space-occupying lesion (SOL). Frequently, a CT is performed prior to a lumbar puncture (LP) to exclude rather than confirm the presence of severe cerebral oedema or a SOL. Its other advantages include lower cost, easy availability, short examination time and safety in the presence of pacemakers, surgical clips and other ferromagnetic substances. The advent of helical CT whereby multiple images are possible has reduced scanning times and is suitable for the uncooperative patient. The limitations of a CT scan include:

1. the need to transfer the patient to a site where resuscitation and monitoring facilities are limited
2. the need to sedate and possibly endotracheally intubate patients who are agitated
3. its low sensitivity to demonstrate an abnormality in the acute phase of a stroke
4. its low sensitivity for detecting brainstem lesions
5. the need to administer intravenous (IV) contrast agents. The two major side effects of IV contrast include anaphylaxis (with an approximate death rate of 1 in 40,000) and renal failure. The use of N-acetylcysteine, sodium bicarbonate and haemodialysis has been reported to reduce the incidence of contrast-induced nephropathy, although data in critically ill patients are minimal).[21]

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) scans provide superior contrast and resolution of the grey and white matter compared to CT scans, thus facilitating easy identification of the deep nuclear structures within the brain. MRI is more sensitive than CT for the detection of acute ischaemia, diffuse axonal injury and cerebral oedema, tumour and abscess. Brainstem and posterior fossa structures are better visualised. The other advantage of MRI is the use of non-ionising energy. The use of gadolinium, a paramagnetic agent as a contrast agent, permits sharp definition of lesions. Magnetic resonance coupled with angiography may enable the diagnosis of vascular lesions. However, MRI is limited by:

1. the need for special equipment
2. long imaging times
3. the need to transfer the patient to a site where resuscitation and monitoring facilities are limited
4. the need to sedate and possibly endotracheally intubate patients who are agitated
5. the risk of dislodgement of metal clips on blood vessels and the resetting of pacemakers.

POSITRON EMISSION TOMOGRAPHY AND SINGLE PHOTON EMISSION WITH COMPUTERISED TOMOGRAPHY SCANS

Newer nuclear medicine scans such as SPECT (single photon emission with computerised tomography) and PET (positron emission tomography) are useful for the assessment of cerebral blood flow and oxygenation and in the prognostication of neurotrauma, but have little role to play in the management of acute disorders of consciousness. In PET scans, positron emitting isotopes, such as ^{11}C, ^{18}F and ^{15}O, are incorporated into biologically active compounds, such as deoxyglucose or fluorodeoxyglucose, which are metabolised in the

body. By determining the concentration of the various tracers in the brain and constructing tomographic images, cerebral blood flow and metabolism can be measured by PET scanning.

SPECT scans use iodine containing isotopes incorporated into biologically active compounds and, like PET scans, their cranial distribution is determined after a dose of tracer. Information on cerebral blood flow and metabolism can be obtained from SPECT scans. The advantage of a PET scan is that it does not require a cyclotron for the generation of isotopes. Despite their many advantages, both these technologies continue to be research tools and are not routinely available in many medical centres.

OPTIC NERVE DIAMETER[22]

While the gold standard for detecting changes in intracranial pressure (ICP) involves the intracranial placement of a catheter, a non-invasive technique has emerged that may allow emergency non-invasive detection of intracranial hypertension. This involves the bedside measurement of optic nerve sheath diameter (ONSD) using ultrasonography. Various measures have been described. One technique is using a 7 MHz probe to measure the ONSD at 3 mm behind the optic nerve head. A recent study comparing ONSD with ICP demonstrated that the ONSD value of 5.205 mm was 95.8% sensitive and 80.4% specific in detecting raised ICP. An ONSD of 5.47 mm in the traumatic group yielded 94.4% sensitivity and 95.2% specificity. This information may help augment management of the comatose patient especially in regions where invasive ICP monitoring is not available.

TRANSCRANIAL DOPPLER[23]

Transcranial Doppler (TCD) is a non-invasive technique that can be used for both diagnostic and management purposes in the comatose patient. The technique involves using a 2 MHz probe to determine intracranial blood velocities and flow patterns via a number of 'cranial windows'. The commonest employed is the trans-temporal window where it may be possible to view the entire circle of Willis. By combining the flow velocities with certain indices it may be possible to detect a variety of pathological processes, including raised intracranial pressure, cerebral vasospasm, loss of cerebral autoregulation, cerebral embolism etc. Furthermore, TCD can be invaluable in detecting cerebral circulatory arrest in patients suspected of brain death. Although this cannot be used legally to determine brain death, it may direct the timing of further investigations, such as cerebral angiography.

LUMBAR PUNCTURE[24]

Cerebrospinal fluid is most commonly obtained by means of a LP. This should be performed after ensuring that raised ICP has been excluded clinically or radiologically. The major use of an LP is to diagnose an intracranial infection and to detect abnormal cytology in cases of suspected malignant meningeal infiltration. The advent of CT scans has diminished the role of LP in the diagnosis of SAH. Some of the commonly reported complications post-LP include post-puncture headache (12%–39%) and traumatic tap (15%–20%). Brain herniation is a rare potential complication seen with conditions associated with raised ICP due to an SOL.

Box 49.4 Usefulness of electroencephalography in coma

Identification of non-convulsive status epilepticus
Diagnosis of hepatic encephalopathy
- presence of paroxysmal triphasic waves

Assessing severity of hypoxic encephalopathy
- presence of theta activity
- diffuse slowing
- burst suppression (seen with more severe forms)
- alpha coma (seen with more severe forms)

Herpes encephalitis
- periodic sharp spikes

Monitoring of therapy (e.g. thiopentone infusion for status epilepticus)

ELECTROENCEPHALOGRAPHY IN COMA[25–27]

The usefulness of electroencephalography (EEG) in coma is summarised in Box 49.4. Continuous EEG monitoring in the ICU has been reported to be useful in the identification of acute cerebral ischaemia and non-convulsive seizures, and for monitoring therapy used in an induced coma, such as thiopentone infusion for refractory status, and to assess level of sedation.

EVOKED POTENTIALS

Visual, brainstem and somatosensory evoked potentials test the integrity of neuroanatomical pathways within the brain and the spinal cord. They may be used in the diagnosis of blindness in comatose patients and in the assessment of locked-in states. There are data to suggest that they have better prognostic value than clinical judgement in patients with anoxic coma.[28,29]

BIOCHEMICAL ABNORMALITIES[30–33]

A number of biomarkers of brain injury have been evaluated as predictors of the severity of the brain injury and to assess the progression of injury severity from traumatic and non-traumatic aetiologies. These include

neuron-specific enolase (cytoplasm of neurons), S-100B protein (astroglial cells), CK-BB fraction (astrocytes), glial fibrillary acidic protein (glial origin) calpain and caspase. Whilst early studies showed S-100B as a reliable marker of traumatic brain injury, concerns remain about their sensitivity and specificity for the assessment of severity and prediction of outcome.

CARE OF THE COMATOSE PATIENT

AIRWAY

As mentioned before, assessment of airway adequacy should take precedence over any diagnostic investigation in comatose patients. This is best done by assessing the patient's response to command and physical stimulation, and whether a gag reflex is present. Securing the airway will depend on the level of consciousness. This may entail simple manoeuvres, such as jaw thrust, chin lift, the use of oropharyngeal airways or – in the comatose patient – mandate endotracheal intubation. All of these patients are at risk of pulmonary aspiration and there must be a low threshold for establishing a definitive airway.

As a general rule, patients presenting with medical causes of coma may be nursed on their side (coma position, if the airway is adequate). However, all traumatised patients should be assumed to have a potential cervical spine injury and must be nursed with the cervical spine in the neutral position and/or with a rigid collar until an injury is excluded by definitive radiological views. All patients with disordered consciousness must receive supplemental oxygen.

VENTILATION

It is important to ensure optimal gas exchange and avoid hypoxia and hypercapnia. Generally a Pa_{O_2} of >10 kPa and P_{CO_2} of 4.7–5.3 kPa is desirable. If spontaneous ventilatory efforts are not adequate to achieve these levels of arterial blood gases, mechanical ventilatory support may be necessary.

CIRCULATION

Adequacy of circulation should be assessed by conventional clinical endpoints. The goals of circulatory therapy in coma include prompt restoration of appropriate mean arterial blood pressure, correction of dehydration and hypovolaemia, and urgent attention to life-threatening causes of shock.

SPECIFIC TREATMENT

This will depend on the underlying aetiology of the coma and is discussed in the relevant chapters. Avoidance of secondary insults is of paramount importance in the management of these patients.[34,35]

NURSING CARE

Meticulous eye and mouth care, regular changes in limb position, limb physiotherapy, bronchial toilet and psychological support are mandatory. Nosocomial infections and iatrogenic complications are associated with an increased mortality and morbidity in these patients and must be promptly diagnosed and treated. The rational use of daily investigations, invasive procedures and antibiotic prescription is essential.

OTHER THERAPY

Stress ulcer and deep vein thrombosis prophylaxis should be instituted. Early establishment of enteral feeding via a nasoenteric tube is preferable. It is important to exclude a basal skull fracture before the insertion of a nasoenteric tube.

ANOXIC COMA/ENCEPHALOPATHY

Cardiac arrest is the third leading cause of coma resulting in ICU admission after trauma and drug overdose. The symptomatology and clinical outcome of patients with anoxic brain damage depend on the severity and duration of oxygen deprivation to the brain. A number of criteria have been developed to prognosticate outcome in anoxic coma. Although a number of laboratory and imaging criteria contribute to the prognostic assessment, clinical signs still have major prognostic impact. The important clinical predictors of outcome are listed in Box 49.5. However, there are data to suggest that electrophysiological studies using evoked potential have far greater prognostic accuracy compared to clinical assessment.[32] It is important to note that the clinical criteria of poor prognosis were developed in the pre-hypothermia era. The optimal time for prognostication following hypothermia is unclear.[37]

Targeted temperature management (TTM) has proven a game changer in managing patients post-cardiac arrest. Although there exists controversy over whether patients should be cooled to 33°C or 36°C, it is clear that TTM is now the standard of care. As such, there is now some evidence that the original criteria published in 2006 by the American Academy of Neurology, which predicted poor outcome following cardiac arrest, may be less applicable in the post-TTM era.[38] By 2010, a series of isolated reports questioned the usefulness of a number of clinical and laboratory criteria previously employed in predicting poor outcomes. Reports of patients surviving with good outcomes despite absent motor responses on day 3, neuron-specific enolase levels above 33 µg/L and absent N20 evoked potentials, to name a few.[39] Furthermore, since a landmark study in 1994, the presence of myoclonic status epilepticus post-cardiac arrest was universally considered to predict dismal outcome. Many patients

Box 49.5 Clinical and laboratory predictors of unfavourable prognosis in anoxic coma

CLINICAL PREDICTOR	UNFAVOURABLE PROGNOSIS
Duration of anoxia (time interval between collapse and initiation of CPR)	8–10 min
Duration of CPR (time interval between initiation of CPR and ROSC)	>30 min
Duration of postanoxic coma	>72 h
Pupillary reaction	Absent on day 3
Motor response to pain (absent = a motor response worse than withdrawal)	Absent on day 3
Roving spontaneous eye movements	Absent on day 1
Elevated neuron specific enolase	>33 mcg/L
SSEP recording	Absent N20

CPR, Cardiopulmonary resuscitation; *ROSC*, return of spontaneous circulation; *SSEP*, somatosensory evoked potentials.
See references 23, 27, 36.

were given do-not-resuscitate orders based on this finding. However, in 2015, Seder et al. published a retrospective review of 2532 cardiac arrest survivors, 88% of which underwent TTM, and 471 exhibited myoclonus.[40] A good outcome at hospital discharge was found in 9% of patients with myoclonus, although they tended to be younger with shorter ischemic time and more witnessed arrests. Better evidence is therefore required before firm criteria indicating poor neurological outcome can be developed.

In the absence of strong evidence, Sandroni et al. suggest using the most robust predictors of outcome following 72 hours of absent motor responses first.[41] These include bilaterally absent pupillary reflexes for greater than 72 hours from return of spontaneous circulation and bilaterally absent SSEP N20 wave after rewarming. This may be combined with absent corneal reflexes. The predictors have a false positive rate of less than 5% and 95% confidence interval of less than 5% in patients treated with controlled temperature. They suggested using a prognostication strategy as outlined in Fig. 49.2.

THE CONFUSED/ENCEPHALOPATHIC PATIENT IN THE INTENSIVE CARE UNIT

Encephalopathy is a term used to describe the alteration in the level or content of consciousness due to a process extrinsic to the brain. Metabolic encephalopathy, particularly of septic aetiology, is the most common cause of altered mental status in the ICU setting.[3,42] A number of processes can lead to metabolic encephalopathy (Box 49.6). A number of features in the history and examination help to differentiate metabolic from structural causes of altered conscious states (Table 49.4).

Box 49.6 Aetiology of metabolic/toxic encephalopathy

Hepatic failure
Renal failure
Respiratory failure
Sepsis
Electrolyte abnormalities: Hyponatraemia, hypernatraemia, hypercalcaemia
Hypoglycaemia and hyperglycaemia
Acute pancreatitis
Endocrine – Addisonian crisis, myxoedema coma, thyroid storm
Drug withdrawal – Benzodiazepine, opiates
Hyperthermia
Toxins: Alcohols, glycols, tricyclic antidepressants
ICU syndrome
D-Lactic Acidosis

ICU, Intensive care unit.
See references 43–45.

Owing to their increased frequency in and exclusiveness to the critical care setting, two types of encephalopathy will be considered in detail: septic encephalopathy and ICU syndrome.

Sepsis associated encephalopathy (SAE) has been reported to occur in 8%–80% of patients with sepsis.[46] The criteria to diagnose SAE include the presence of impaired mental function, evidence of an extracranial infection and absence of other obvious aetiologies for the altered conscious state. Although the precise mechanism of damage to the brain has not been delineated, the pathogenesis of the encephalopathy is thought to be multifactorial: alteration in cerebral blood flow induced by mediators of inflammation, generation of free radicals by activated leucocytes resulting in erythrocyte sludging in the microcirculation, breakdown of the blood–brain barrier resulting in cerebral oedema, reduced brain oxygen consumption induced by endotoxin and cytokines, neuronal degeneration and increased neuronal apoptosis, increases in aromatic amino acids resulting in altered neurotransmitter function and increased GABA-mediated neurotransmission leading to general inhibition of the CNS. Hypotension may contribute to the encephalopathy.[47,48] The asterixis, tremor and myoclonus – features of other metabolic encephalopathies – are uncommon in sepsis. The presence of lateralising signs is extremely rare in SAE and warrant exclusion of other causes, such a stroke. The mortality of patients with SAE is higher than in those

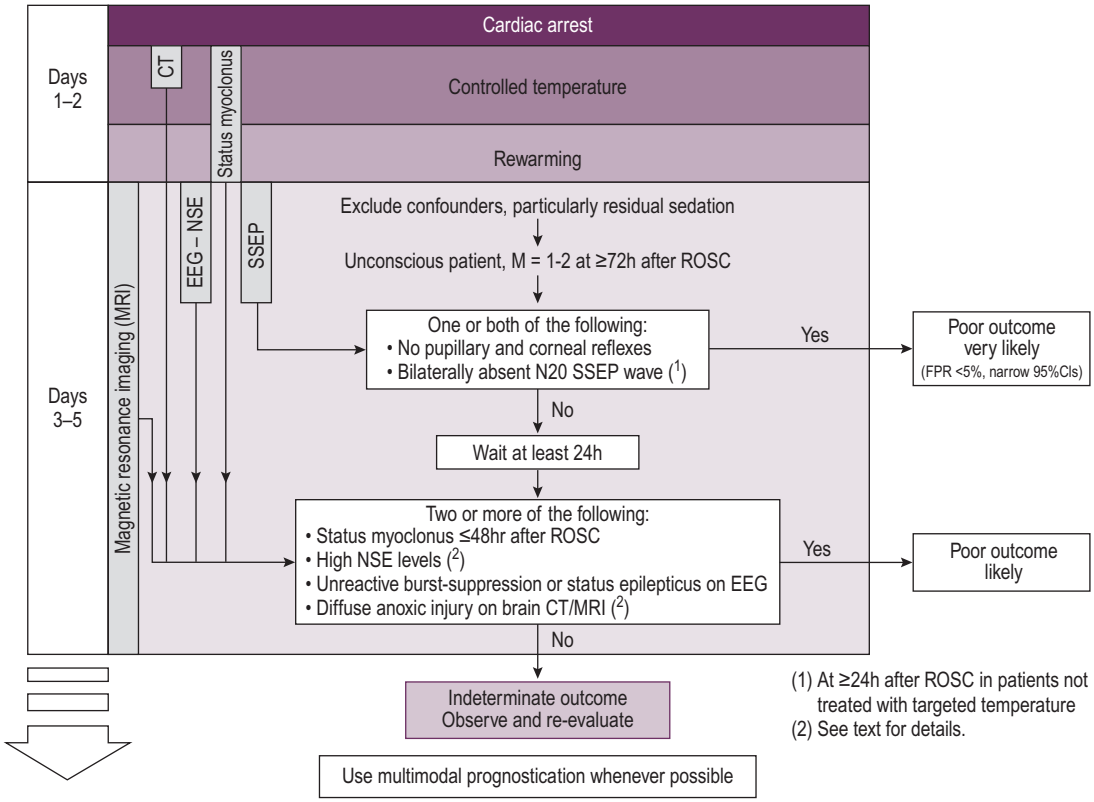


Figure 49.2 Suggested prognostication algorithm. The algorithm is entered ≥72 hours after ROSC if, after the exclusion of confounders (particularly residual sedation), the patient remains unconscious with a Glasgow Motor Score of 1 or 2. The absence of pupillary and corneal reflexes, and/or bilaterally absent N20 somatosensory evoked potentials (SSEP) wave indicates that a poor outcome is very likely. If neither of the features is present, wait at least 24 hours before reassessing. At this stage, two or more of the following indicate that a poor outcome is likely: status myoclonus ≤48 hours; high neuron-specific enolase values; unreactive EEG with burst suppression or status epilepticus; diffuse anoxic injury on brain CT and/or MRI. If none of these criteria is met, consider continuing to observe and re-evaluate. *CT*, Computed tomography; *EEG*, electroencephalography; *FPR*, false positive rate; *MRI*, magnetic resonance imaging; *NSE*, neuron specific enolase; *ROSC*, return of spontaneous circulation. *With permission from Sandroni C, Cariou A, Cavallaro F, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine.* Resuscitation. *2014;85:1779–1789.*

with sepsis without encephalopathy.[49] Therapy is largely directed at the underlying septic process.

INTENSIVE CARE UNIT ENCEPHALOPATHY OR INTENSIVE CARE UNIT SYNDROME[50,51]

This is a term used to describe behavioural disorders that develop in patients 5–7 days after admission to the ICU. Clinically, this may present as agitation, restlessness and frank delirium. The causes are multifactorial: prolonged ventilation sleep deprivation,[52,53] distortion of perception with loss of day–night cycles, immobilisation, noisy environment and monotony. These coupled with the administration of multiple sedatives and neurological consequences of the underlying disease can precipitate psychotic behaviour in the ICU. It is important to bear in mind that *this is a diagnosis of exclusion and that all other reversible causes are looked for (Table 49.4)* before this diagnostic label is applied. Tools to assess delirium, such as the CAM-ICU, have been developed and validated for the critical care setting.[54]

Abnormal behaviour can increase patient morbidity (self-extubation, ripping of catheters, soft tissue damage, etc.). Episodes of delirium in the ICU are also associated with increased mortality.[55] Postoperative delirium after cardiac surgery has also been associated with a significant decline in cognitive ability during the first year after cardiac surgery.[56] It is important to identify the underlying cause of the abnormal behaviour to institute appropriate therapy. Management of this condition may require the use of restraints, sedation

Table 49.4 Distinguishing features of structural and metabolic encephalopathy

FEATURE	STRUCTURAL	METABOLIC
State of consciousness	Usually fixed level of depressed conscious state, may deteriorate progressively	Milder alteration of conscious state, waxing and waning of altered sensorium
Fundoscopy	May be abnormal	Usually normal
Pupils	May be abnormal, either in size or response to light	Usually preserved light response (although pupil shape and reactivity affected in certain overdoses – see above)
Eye movements	May be affected	Usually preserved
Motor findings	Asymmetrical involvement	Abnormalities usually symmetrical
Involuntary movements	Not common	Asterixis, tremor, myoclonus frequently seen

Plum F. Sustained impairment of consciousness. In: Bennett C, ed. *Cecil Textbook of Medicine*. Philadelphia, PA: W.B. Saunders; 1996:1970–1978.

and major tranquilisers. Improvement of sleep quality (minimising interruption of nocturnal sleep, adjusting lighting in the ICU), reducing patient boredom by the use of television and music, and better communication with the patient may reduce the incidence and severity of this syndrome. Regular administration of haloperidol has not been shown to reduce the incidence of delirium coma.[57] However, dexmedetomidine has been advocated as an agent to minimise delirium in the critically ill patient.[58] More recent evidence suggests that the introduction of dexmedetomidine among patients with agitated delirium results in more ventilator-free hours at 7 days when compared with standard care.[59] Other evidence suggests that the introduction of ABCDE bundles may reduce delirium by up to 50%.[60] More work in this area is needed.

PROGNOSIS IN COMA

Drug-induced comas usually have a good prognosis unless hypoxia and hypotension have resulted in severe secondary insults. Coma following head injury has a statistically better outcome compared to non-traumatic coma (coma occurring during the course of a medical illness). In non-traumatic coma lasting for 6 hours or more, only 15% of the patients make a meaningful recovery to be able to return to their pre-morbid state of health.[61] The prognosis following anoxic coma has been described in a separate section. Within the non-traumatic coma category, coma resulting from infection, metabolic causes and multiple organ dysfunction syndrome have a better outcome compared to anoxic coma.[62] A number of outcome scales have been developed to assess neurological recovery following brain injury.[63] These include the Barthel index, Rankin scale and the Glasgow outcome scale (GOS). The GOS is widely used to assess recovery after traumatic brain injury. It has five broad categories: 1 = good recovery, 2 = moderate disability, 3 = severe disability, 4 = persistent vegetative state and 5 = death. It is simple, easy to administer and has been reported to have good inter-rater agreement.

TREATMENT OPTIONS IN DISORDERS OF CONSCIOUSNESS[64]

No effective standardised treatment exists for these patients. Currently, evaluated interventions can be divided into pharmacological and non-pharmacological measures. Pharmacological measures include the use of progesterone, levodopa and amantadine. Initial trials reported some recovery response in terms of reduction in spasticity and improved cognitive behaviour and communication, such as following simple commands. Giacino et al. found a significant improvement in the Disability Rating Scale following administration of amantadine in patients with traumatic brain injury who were in a vegetative or minimally conscious state.[65] However, the administration of progesterone was not associated with improved GOS following traumatic brain injury (TBI).[66,67] Zolpidem has also been trialled in patients with traumatic and anoxic aetiologies of reduced consciousness, and results have been variable. While some investigators report enhanced verbal, motor and cognitive functions, these have not been reproduced in other small trials. Moreover, the duration of the effects of zolpidem is short. Bromocriptine and intrathecal baclofen have also been tried, but no large-scale studies have been reported.

Non-pharmacological measures include deep brain stimulation, extradural cortical stimulation, spinal cord stimulation and median nerve stimulation. Thibaut et al. demonstrated that the application of left dorsolateral prefrontal cortex transcranial direct current stimulation transiently improved signs of consciousness in patients in a minimally conscious state, although the overall outcome did not change.[68] While reports of improved responsiveness have been published, the evidence is largely anecdotal, and data from large studies are lacking.

REFERENCES

1. Ropper A, Martin J. Coma and other disorders of consciousness. In: Harrison TR, Isselbacher KJ, eds. *Harrison's Principles of Internal Medicine*. 13th ed. New York, NY: McGraw-Hill; 1994:146–152.
2. Gosseries O, Vanhaudenhuyse A, Bruno MA. Disorders of consciousness: coma, vegetative and minimally consious states. In: Cvetkovic D, Cosic I, ed. *States of Consciousness*. Berlin: Springer-Verlag; 2011:29–55.
3. Stevens RD, Bhardwaj A. Approach to the comatose patient. *Crit Care Med*. 2006;34:31–41.
4. Nordgren RE, Markesbery WR, Fukuda K, et al. Seven cases of cerebromedullospinal disconnection: the 'locked-in' syndrome. *Neurology*. 1971; 21:1140–1148.
5. Jennett B, Plum F. Persistent vegetative state after brain damage. A syndrome in search of a name. *Lancet*. 1972;1:734–737.
6. Cairns H, Oldfield R, Pennybacker K. Akinetic mutism with an epidermoid cyst of the third ventricle. *Brain*. 1941;64:273.
7. Stevens RD, Pronovost PJ. The spectrum of encephalopathy in critical illness. *Semin Neurol*. 2006;26:440–451.
8. Wijdicks EF, Bamlet WR, Maramattom BV, et al. Validation of a new coma scale: the FOUR score. *Ann Neurol*. 2005;58:585–593.
9. Wijdicks EF, Rabinstein AA, Bamlet WR, et al. FOUR score and Glasgow Coma Scale in predicting outcome of comatose patients: a pooled analysis. *Neurology*. 2011;77:84–85.
10. Adams R, Victor M, Ropper A. *Coma and Related Disorders of Consciousness. Principles of Neurology*. New York, NY: McGraw Hill; 1997:344–366.
11. Keane JR. Retinal hemorrhages. Its significance in 100 patients with acute encephalopathy of unknown cause. *Arch Neurol*. 1979;36:691–694.
12. Keane J. Eye movements in coma. In: Jakbiec AA, ed. *Principles and Practice of Ophthalmology*. Philadelphia, PA: W.B. Saunders; 2000:4075–4083.
13. Fisher C. Ocular bobbing. *Arch Neurol*. 1964;11:543.
14. Keane JR. Ocular skew deviation. Analysis of 100 cases. *Arch Neurol*. 1975;32:185–190.
15. North JB, Jennett S. Abnormal breathing patterns associated with acute brain damage. *Arch Neurol*. 1974;31:338–344.
16. Kernohan J, Woltman H. Incisura of the crus due to contralateral brain tumour. *Arch Neurol Psych*. 1929;21:274.
17. McNealy D, Plum F. Brainstem dysfunction with supratentorial mass lesions. *Arch Neurol*. 1962;7:10.
18. Young GB. Impaired consciousness and herniation syndromes. *Neurol Clin*. 2011;29:765–772.
19. De Salles AA, Muizelaar JP, Young HF. Hyperglycemia, cerebrospinal fluid lactic acidosis, and cerebral blood flow in severely head-injured patients. *Neurosurgery*. 1987;21:45–50.
20. Penney DG. Hyperglycemia exacerbates brain damage in acute severe carbon monoxide poisoning. *Med Hypotheses*. 1988;27:241–244.
21. Perrin T, Descombes E, Cook S. Contrast-induced nephropathy in invasive cardiology. *Swiss Med Wkly*. 2012;142:w13608.
22. Raffiz M, Abdullah JM. Optic nerve sheath diameter measurement: a means of detecting raised ICP in adult traumatic and non-traumatic neurosurgical patients. *Am J Emerg Med*. 2017;35:150–153.
23. White H, Venkatesh B. Applications of transcranial Doppler in the ICU: a review. *Intensive Care Med*. 2006;32:981–994.
24. Venkatesh B, Scott P, Ziegenfuss M. Cerebrospinal fluid in critical illness. *Crit Care Resusc*. 2000;2: 42–54.
25. Bauer G. Coma and brain death. In: Da Silva F, ed. *Electroencephalogrpahy: Basic Principles, Clinical applications and Related Fields*. Baltimore, MD: Williams & Wilkins; 1999.
26. Nuwer MR. ICU monitoring. *Electroencephalogr Clin Neurophysiol Suppl*. 1999;49:322–324.
27. Friedman D, Claassen J, Hirsch LJ. Continuous electroencephalogram monitoring in the intensive care unit. *Anesth Analg*. 2009;109:506–523.
28. Zandbergen EG, de Haan RJ, Stoutenbeek CP, et al. Systematic review of early prediction of poor outcome in anoxic-ischaemic coma. *Lancet*. 1998;352: 1808–1812.
29. Guerit JM, Amantini A, Amodio P, et al. Consensus on the use of neurophysiological tests in the intensive care unit (ICU): electroencephalogram (EEG), evoked potentials (EP), and electroneuromyography (ENMG). *Neurophysiol Clin*. 2009;39:71–83.
30. Berger RP. The use of serum biomarkers to predict outcome after traumatic brain injury in adults and children. *J Head Trauma Rehabil*. 2006;21:315–333.
31. Berger RP, Adelson PD, Richichi R, et al. Serum biomarkers after traumatic and hypoxemic brain injuries: insight into the biochemical response of the pediatric brain to inflicted brain injury. *Dev Neurosci*. 2006;28:327–335.
32. Shinozaki K, Oda S, Sadahiro T, et al. Serum S-100B is superior to neuron-specific enolase as an early prognostic biomarker for neurological outcome following cardiopulmonary resuscitation. *Resuscitation*. 2009;80:870–875.
33. Shinozaki K, Oda S, Sadahiro T, et al. S-100B and neuron-specific enolase as predictors of neurological outcome in patients after cardiac arrest and return of spontaneous circulation: a systematic review. *Crit Care*. 2009;13:R121.
34. White H, Venkatesh B. Cerebral perfusion pressure in neurotrauma: a review. *Anesth Analg*. 2008;107: 979–988.
35. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma*. 1993;34: 216–222.
36. Levy DE, Caronna JJ, Singer BH, et al. Predicting outcome from hypoxic-ischemic coma. *JAMA*. 1985; 253:1420–1426.
37. Perman SM, Kirkpatrick JN, Reitsma AM, et al. Timing of neuroprognostication in postcardiac

arrest therapeutic hypothermia. *Crit Care Med*. 2012;40:719–724.
38. Dangayach NS, Mayer SA. Futility after cardiac arrest: another one bites the dust. *Crit Care Med*. 2015;43:1136–1138.
39. Rittenberger JC, Sangl J, Wheeler M, et al. Association between clinical examination and outcome after cardiac arrest. *Resuscitation*. 2010;81: 1128–1132.
40. Seder DB, Sunde K, Rubertsson S, et al. Neurologic outcomes and postresuscitation care of patients with myoclonus following cardiac arrest. *Crit Care Med*. 2015;43:965–972.
41. Sandroni C, Cariou A, Cavallaro F, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. *Resuscitation*. 2014;85: 1779–1789.
42. Stevens RD, Nyquist PA. Types of brain dysfunction in critical illness. *Neurol Clin*. 2008;26:469–486, ix.
43. Surtees R, Leonard JV. Acute metabolic encephalopathy: a review of causes, mechanisms and treatment. *J Inherit Metab Dis*. 1989;12(suppl 1):42–54.
44. Uribarri J, Oh MS, Carroll HJ. D-lactic acidosis. A review of clinical presentation, biochemical features, and pathophysiologic mechanisms. *Medicine (Baltimore)*. 1998;77:73–82.
45. Plum F. Sustained impairment of consciousness. In: Bennett C, ed. *Cecil Textbook of Medicine*. Philadelphia, PA: W.B. Saunders; 1996:1970–1978.
46. Wilson JX, Young GB. Progress in clinical neurosciences: sepsis-associated encephalopathy: evolving concepts. *Can J Neurol Sci*. 2003;30:98–105.
47. Flierl MA, Rittirsch D, Huber-Lang MS, et al. Pathophysiology of septic encephalopathy – an unsolved puzzle. *Crit Care*. 2010;14:165.
48. Polito A, Brouland JP, Porcher R, et al. Hyperglycaemia and apoptosis of microglial cells in human septic shock. *Crit Care*. 2011;15:R131.
49. Eidelman LA, Putterman D, Putterman C, et al. The spectrum of septic encephalopathy. Definitions, etiologies, and mortalities. *JAMA*. 1996;275: 470–473.
50. Jones SF, Pisani MA. ICU delirium: an update. *Curr Opin Crit Care*. 2012;18:146–151.
51. McGuire BE, Basten CJ, Ryan CJ, et al. Intensive care unit syndrome: a dangerous misnomer. *Arch Intern Med*. 2000;160:906–909.
52. Granberg A, Engberg IB, Lundberg D. Intensive care syndrome: a literature review. *Intensive Crit Care Nurs*. 1996;12:173–182.
53. Shilo L, Dagan Y, Smorjik Y, et al. Patients in the intensive care unit suffer from severe lack of sleep associated with loss of normal melatonin secretion pattern. *Am J Med Sci*. 1999;317:278–281.
54. Mitasova A, Kostalova M, Bednarik J, et al. Poststroke delirium incidence and outcomes: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med*. 2012;40:484–490.
55. Shehabi Y, Riker RR, Bokesch PM, et al. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. *Crit Care Med*. 2010;38:2311–2318.
56. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. *N Engl J Med*. 2012;367:30–39.
57. Page VJ, Ely EW, Gates S, et al. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med*. 2013;1:515–523.
58. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA*. 2009; 301:489–499.
59. Reade MC, Eastwood GM, Bellomo R, et al. Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: a randomized clinical trial. *JAMA*. 2016;315: 1460–1468.
60. Maas MB, Naidech AM. Critical care neurology perspective on delirium. *Semin Neurol*. 2016;36: 601–606.
61. Plum F, Levy DE. Outcome from severe neurological illness; should it influence medical decisions? *Ciba Found Symp*. 1979;267–277.
62. Levy DE, Bates D, Caronna JJ, et al. Prognosis in nontraumatic coma. *Ann Intern Med*. 1981;94: 293–301.
63. Kasner SE. Clinical interpretation and use of stroke scales. *Lancet Neurol*. 2006;5:603–612.
64. Georgiopoulos M, Katsakiori P, Kefalopoulou Z, et al. Vegetative state and minimally conscious state: a review of the therapeutic interventions. *Stereotact Funct Neurosurg*. 2010;88:199–207.
65. Giacino JT, Whyte J, Bagiella E, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. *N Engl J Med*. 2012;366:819–826.
66. Skolnick BE, Maas AI, Narayan RK, et al. A clinical trial of progesterone for severe traumatic brain injury. *N Engl J Med*. 2014;371:2467–2476.
67. Wright DW, Yeatts SD, Silbergleit R, et al. Very early administration of progesterone for acute traumatic brain injury. *N Engl J Med*. 2014;371:2457–2466.
68. Thibaut A, Bruno MA, Ledoux D, et al. tDCS in patients with disorders of consciousness: sham-controlled randomized double-blind study. *Neurology*. 2014;82:1112–1118.

50

Status epilepticus

Helen I Opdam

STATUS EPILEPTICUS

Status epilepticus (SE) is a neurological emergency involving prolonged seizure activity that requires prompt intervention to prevent the development of irreversible brain damage.

DEFINITION AND CLASSIFICATION

SE is continuous or recurrent clinical and/or electrographic seizure activity that lasts more than 5 minutes. Seizures of this duration are unlikely to remit spontaneously and require urgent treatment.[1,2]

An international taskforce on the classification of SE emphasised two time points: (1) when treatment should be initiated; and (2) after which there is a risk of long-term consequences including neuronal death (5 and 30 minutes, respectively, for convulsive status epilepticus [CSE]).[3]

Refractory SE (RSE) is defined as persistent seizures resistant to first-line and second-line anticonvulsant therapy, usually necessitating general anaesthesia.[4,5] RSE develops in about one in five patients with SE and is associated with a worse prognosis.[6,7]

Continuation or recurrence of SE beyond 24 hours of anaesthetic therapy has been termed super RSE.[8]

SE may be classified according to clinical presentation, aetiology, electroencephalography (EEG) and age.[3] Key clinical features include whether prominent motor symptoms are present and the degree of impaired consciousness. This chapter will focus on two forms of SE most commonly encountered in intensive care that involve the acutely ill patient with impaired mental status:

- CSE (also known as tonic-clonic SE), and
- non-convulsive status epilepticus (NCSE) with coma.

The incidence of SE is U-shaped, being greatest under 1 year and over 60 years of age.[9]

PATHOPHYSIOLOGY

Ongoing or recurrent seizures result from failure of normal seizure terminating mechanisms or the initiation of mechanisms causing seizures to persist.[3]

The major inhibitory mechanism in the brain is gamma-aminobutyric acid (GABA) receptor-mediated inhibition. With ongoing seizure activity, GABA receptors undergo cellular internalisation and subsequent degradation, leading to the loss of endogenous inhibition and the persistence of seizures. This reduction in synaptic GABA receptors explains the progressive pharmacoresistance to GABAergic anticonvulsants, such as benzodiazepines.[10]

Mechanisms that induce persistent seizures are predominantly excitatory via glutamine acting on *N*-methyl-D-aspartate (NMDA) receptors. NMDA receptors increase on synapses during ongoing epileptic activity, facilitating neuronal excitability and sustainability of seizures. This, in contrast, explains the efficacy of NMDA antagonists, even late in the course of SE.

The pathophysiological effects of seizures on the brain are thought to result from both direct excitotoxic neuronal injury and secondary injury due to systemic complications, such as hypotension, hypoxia and hyperthermia. Ongoing excitation leads to neuronal injury and death, predominantly through intracellular calcium influx and mitochondrial dysfunction. Experimental models and anecdotal human evidence also suggest that SE is epileptogenic.[10,11]

AETIOLOGY

SE may occur following acute or remote central nervous system (CNS) or systemic illness (approximately 60% of presentations) or less commonly in a previously diagnosed epileptic.[3,9] In the situation where RSE does not have a clear cause, more unusual conditions should be considered as their diagnosis may lead to a specific therapy. These include autoimmune conditions,

ABSTRACT

Status epilepticus (SE) is prolonged (>5 minutes) clinical and/or electrographic seizure activity that requires urgent treatment to prevent neuronal injury. The forms commonly encountered in acutely unwell patients requiring intensive care include convulsive SE (CSE) and non-convulsive SE (NCSE) with coma. CSE is the most serious form and treatment involves rapid termination of seizures using benzodiazepines, followed by loading with anticonvulsant medications and, if seizures persist (refractory SE), general anaesthesia. NCSE can evolve from CSE when motor manifestations subside and electrical seizures persist, or may arise de novo and be under-recognised in critically ill patients. Although NCSE also requires prompt treatment, attempts to control seizures whilst avoiding general anaesthesia may be warranted. Causes of SE include acute central nervous system pathology (e.g. infection, stroke), systemic illness (e.g. sepsis, organ failure, autoimmunity) or pre-existing epilepsy. Diagnosis of the precipitant is important as some causes require specific treatment.

KEYWORDS

Status epilepticus
seizures
epilepsy
convulsive
non-convulsive
refractory
intensive care
anticonvulsant
treatment

Box 50.1 Causes of status epilepticus in adults

Low antiepileptic drug levels – poor compliance, recent dose reduction or discontinuation (most common cause in patients with epilepsy)
Stroke – vascular occlusion or haemorrhage
Metabolic disturbances – electrolyte abnormalities (hyponatraemia, hypocalcaemia, hypomagnesaemia, hypophosphataemia), hyperglycaemia, hypoglycaemia
Organ failure – uraemia, hepatic encephalopathy
CNS infection – bacterial meningitis, viral encephalitis, cerebral toxoplasmosis, tuberculosis, other
Cerebral hypoxia/anoxia
Alcohol – withdrawal or intoxication
Head trauma
Drug toxicity – cephalosporins, isoniazid, tranexamic acid, tacrolimus, cyclosporine, tricyclic antidepressants, olanzapine, phenothiazines, theophylline, cocaine, amphetamine, antiepileptic drugs, other
CNS tumours – primary or secondary
Temporally remote causes (previous CNS injury) – stroke, trauma, tumour, meningitis
Cortical dysplasias
Hypertensive encephalopathy, eclampsia
Autoimmune disorders – paraneoplastic syndromes, Hashimoto's encephalopathy, anti-NMDA receptor encephalitis (may have associated ovarian tumour), anti-voltage-gated potassium channel receptor encephalitis, cerebral lupus, thrombotic thrombocytopenic purpura, multiple sclerosis, other
Mitochondrial diseases
Metabolic disorders – porphyria, ornithine transcarbamylase deficiency, other
Cryptogenic, including new-onset refractory status epilepticus (NORSE)

CNS, Central nervous system; *NMDA*, *N*-methyl-D-aspartate.
See references 3, 9, 12–14.

unusual infections and mitochondrial diseases.[12] The aetiologies of SE are given in Box 50.1.[3,9,12–14]

CONVULSIVE STATUS EPILEPTICUS

CSE is the most common and dangerous type of SE. There is impairment of consciousness and abnormal muscle contraction, which may be sustained (tonic) and/or interrupted (clonic). The seizures may be primary generalised or have a focal onset evolving into bilateral convulsive SE.

CLINICAL

Patients are unresponsive with rhythmic jerking movements. With time, the clinical manifestations may become subtle and patients have only small-amplitude twitching movements of the face, hands or feet, or nystagmoid jerking of the eyes (late or subtle CSE). Later still, some patients will have no observable motor activity and the detection of ongoing seizures requires EEG. Most authors classify these subtle or electrical forms as NCSE.[1–3,15] Such patients are still at risk of CNS injury and require prompt treatment.

Box 50.2 Physiological changes in convulsive status epilepticus

Hypoxia
Respiratory acidosis
Lactic acidosis
Hyperpyrexia
Hypertension (early)/hypotension (late)
Hyperglycaemia (early)/hypoglycaemia (late)
Tachycardia
Cardiac arrhythmias
Blood leucocytosis
CSF pleocytosis, increased CSF protein
Intracranial hypertension
Neurogenic pulmonary oedema
Aspiration pneumonitis
Rhabdomyolysis

CSF, Cerebrospinal fluid.
Walton NY. Systemic effects of generalized convulsive status epilepticus. *Epilepsia*. 1993;34(suppl 1):S54–S58.

ELECTROENCEPHALOGRAPHY CHANGES

Just as there is a progression from overt to increasingly subtle motor manifestations, there is also a predictable sequence of EEG changes during untreated CSE. Initially, discrete electrographic seizures merge to a waxing and waning pattern of seizure activity, followed by continuous monomorphic discharges, which become interspersed with increasing periods of electrographic silence and, eventually, periodic epileptiform discharges on a relatively flat background.[16] The presence of any of these EEG patterns should suggest the diagnosis of SE.

ENDOCRINE AND METABOLIC EFFECTS

Early in CSE there is a marked increase in plasma catecholamines, producing systemic physiological changes that resolve if SE is stopped early (Box 50.2). However, if seizures continue, many of these early physiological changes reverse, and the resultant hypotension and hypoglycaemia may exacerbate neurological injury.[17]

Hyperthermia is due to both muscle activity and central sympathetic drive, and thus may still occur when paralysing agents prevent motor activity. In early SE, both cerebral metabolic activity and cerebral blood flow (CBF) are increased. In late SE, although

Box 50.3 Features suggestive of pseudoseizures

Lack of stereotyped seizures, with behavioural manifestations varying from event to event
Lack of sustained convulsive activity – 'on-off' appearance
Increase in movement if restraint is applied
Degree of interaction or responsiveness, such as movements modifiable with suggestion
Resistance to eye opening and gaze aversion
Poor response to treatment, RSE
Absence of pupillary dilatation
Normal tendon reflexes and plantar responses immediately after convulsion
Lack of metabolic consequences despite some hours of apparent fitting

RSE, Refractory status epilepticus.
See references 18, 19.

Box 50.4 Investigations in status epilepticus

Initial studies
Blood glucose, electrolytes (sodium, potassium, calcium, magnesium), urea
Arterial blood gases
Anticonvulsant drug levels
Full blood count
Urinalysis
Further investigations after stabilisation
Liver function tests, lactate, creatine kinase
Toxicology screen
Lumbar puncture
Electroencephalogram
Brain imaging with computed tomography or magnetic resonance imaging

cerebral metabolic activity remains high, CBF may fall owing to hypotension and loss of cerebral autoregulation leading to cerebral ischaemia.

PSEUDOSEIZURES

An important differential diagnosis of convulsive epilepsy is pseudoseizures, also known as psychogenic non-epileptic seizures.[18,19] The vast majority are not deliberate and they can occur in patients with or without a history of epilepsy.

Clinical features suggestive of pseudoseizures are listed in Box 50.3. Distinction between the two may be extremely difficult, and pseudoseizures are best confirmed using EEG monitoring where there is an absence of ictal EEG changes with events. Pseudostatus, misdiagnosed as true SE, is often refractory to initial therapy and can lead to patients receiving general anaesthesia and mechanical ventilation.

NON-CONVULSIVE STATUS EPILEPTICUS WITH COMA

There is altered consciousness and EEG evidence of seizures with minimal or no convulsive movements. NCSE may evolve from CSE when electrical seizure activity continues with the loss of motor manifestations.

The diagnosis of NCSE should be considered in any patient with an unexplained altered conscious state, particularly those with CNS injury, metabolic disturbance, hepatic encephalopathy or sepsis. Its incidence is probably underestimated because of failure to recognise the condition. Series where EEG has been performed in critically ill patients with an unexplained depressed conscious state have found a high incidence of seizures (8%–18%).[20–22] Seizures will usually be detected within the first 30 minutes of EEG monitoring in such patients, although the presence of epileptiform discharges increases the likelihood of seizures being detected with more prolonged monitoring.[23]

NCSE may be mistaken for other conditions, such as persisting sedative effects, metabolic encephalopathy and post-ictal confusion. A high index of suspicion must therefore be present to trigger investigation with an EEG. EEG monitoring is required in patients with CSE who do not recover consciousness after resolution of overt convulsive activity; in one study more than 14% of such patients had NCSE.[15]

As NCSE includes a heterogeneous group of aetiologies, there is variable response to treatment. The outcome is largely determined by the underlying cause.[24–26]

EPILEPTIFORM ENCEPHALOPATHIES

In many advanced coma stages, the EEG exhibits continuous or periodic EEG abnormalities, but in such situations it is unclear whether the abnormal discharges are responsible for, or contribute to, the altered consciousness, or are merely a reflection of a severe cerebral insult.[27]

Some consider myoclonic SE that follows an anoxic insult as part of this category, rather than as a form of SE.[27]

INVESTIGATIONS

Not all of the investigations listed in Box 50.4 need to be performed in every patient, and they should be guided by the presentation.

NEUROIMAGING

Most patients with SE should have a computed tomography (CT) scan of the brain performed, although this

may not always be necessary if another episode of SE occurs in a patient with established epilepsy who has previously been thoroughly evaluated. Magnetic resonance imaging may occasionally reveal abnormalities not visualised on CT scans and should be considered for non-emergency imaging. Imaging should only be performed after patient stabilisation.[28]

LUMBAR PUNCTURE

In any patient, especially in young children with fever and SE, CNS infection and lumbar puncture along with blood cultures should be considered.[29] Meningitis is an uncommon cause of SE in adults, and brain imaging should usually be performed before a lumbar puncture. If meningitis is suspected and a lumbar puncture cannot be performed expediently, antibiotics should be administered immediately rather than delayed. Approximately 20% of patients have a modest CSF white cell count pleocytosis after SE, and treatment for meningitis should be given until the diagnosis is excluded.

MANAGEMENT

CONVULSIVE STATUS EPILEPTICUS

An accurate history should be obtained – with particular emphasis on eye-witness accounts of the onset and nature of the seizures – and a full physical examination performed. However, neither should delay the initial management. Rapid control of seizures is crucial to prevent brain injury and the development of RSE. There is evidence that the longer SE goes untreated the harder it is to control with drugs.[5,30,31]

Management of SE involves the termination of seizures, treating the precipitating causes and underlying conditions, and the prevention of complications and recurrence of seizures.

There are few controlled data to support the use of any particular agents and existing randomised, controlled trials (RCTs) have recently been reviewed.[32] One double-blind RCT for treatment of CSE found that lorazepam, phenobarbital or diazepam followed by phenytoin are all acceptable as an initial treatment, but that phenytoin alone was not as effective as lorazepam.[31]

There are few data to guide the treatment of RSE, for which anaesthetising agents, such as thiopental, propofol or midazolam infusions, are commonly used.[32] The only RCT in RSE, which compared propofol versus barbiturates, was terminated after 3 years with only 24 of the required 150 patients recruited.[6]

The EEG goal of treatment for RSE remains controversial as to whether seizure suppression is sufficient or therapy should be escalated to achieve burst suppression (periods of high-voltage electrical activity 'bursts' alternating with periods of suppression).[4,11]

There are various protocols for SE management including a recent evidence-based guideline issued by the American Epilepsy Society.[1,2,4,30,33] One approach is outlined in Box 50.5.

NON-CONVULSIVE STATUS EPILEPTICUS

There is considerable debate as to whether NCSE presents the same degree of risk of neurological injury as CSE. Prompt treatment is generally recommended and the use of additional non-anaesthetising anticonvulsants, such as valproate, levetiracetam and phenobarbital, has been suggested prior to embarking upon general anaesthesia.[1,26,34]

The side-effects of aggressive treatment (hypotension, immobility, immunosuppression) need to be balanced against the potential neurological morbidity of NCSE and so treatment tailored according to the aetiology.[35,36] Particularly in elderly patients, aggressive treatment may be associated with more risk than benefit and a worse outcome.[25,35,37]

DRUGS FOR STATUS EPILEPTICUS

BENZODIAZEPINES

Benzodiazepines are fast-acting antiseizure drugs and thus preferred as initial therapy. They act mainly by enhancing the neuroinhibitory effects of GABA. The efficacy of benzodiazepines diminishes with the duration of SE as prolonged seizures result in a reduction in synaptic GABA receptors.[10]

The choice of benzodiazepine will depend upon its efficacy, the setting and the available formulations.

Diazepam, as with other benzodiazepines, is highly lipid-soluble with rapid CNS penetration.

Diazepam, however, has a short redistribution half-life (1 hour) compared with midazolam (2 hours) and lorazepam (14 hours), and therefore a short duration of action.[32] It can be administered intravenously or by the rectal route, which is useful in the pre-hospital setting and when vascular access is delayed.

Intravenous lorazepam has a longer duration of action and appears better than diazepam in both stopping seizures and preventing recurrence.[32]

Midazolam can be administered via intramuscular, buccal and intranasal routes as well as intravenously. Intramuscular midazolam appears as safe and efficacious as intravenous lorazepam in both adults and children, and it can be administered more reliably in the pre-hospital setting.[38,39]

Midazolam, by bolus and infusion, may terminate seizures when other agents have failed, and it is used in RSE. Unlike other benzodiazepines, it does not accumulate with prolonged infusion.[40]

Clonazepam has a longer duration of action than diazepam, and early reports suggested superior

Box 50.5 Protocol for management of status epilepticus

1. Assess A, B, C, GCS.
2. Give O_2 and consider need for intubation/ventilation.
3. Monitor blood pressure, ECG, pulse oximetry.
4. Obtain IV access, perform bedside blood sugar level and draw blood for investigations.
5. If patient is hypoglycaemic give glucose:
   adults: give thiamine 100 mg IV and 50 mL of 50% glucose IV.
   children: give 2 mL/kg of 25% glucose IV.
6. Seizure control*:
   A. Give a benzodiazepine (first-line),† for example:
      diazepam: 0.2 mg/kg IV at 5 mg/min, max 10 mg/dose, may repeat once.
      lorazepam: 0.1 mg/kg IV at 2 mg/min, max 4 mg/dose, may repeat once.
      clonazepam: 0.015 mg/kg IV at 1 mg/min, may repeat up to 4 mg.
      If diazepam stops the seizures, phenytoin should be given next to prevent recurrence.
   B. If seizures persist, give a second-line agent,†† for example:
      phenytoin: 20 mg/kg IV (adults ≤50 mg/min; children ≤1 mg/kg/min) or fosphenytoin 20 phenytoin equivalents (PE) mg/kg IV (adults ≤150 mg/min; children ≤3 mg/kg/min). May give a further dose of 5 mg/kg IV for persistent seizures.
      valproate: 40 mg/kg IV single dose, max 3000 mg.
      levetiracetam: 60 mg/kg IV single dose, max 4500 mg.
   C. If seizures persist (RSE), intubate and ventilate patient. Give third-line therapy intravenously, either:
      propofol: slow bolus 1–2 mg/kg, repeat every 3–5 minutes until seizure control, followed by infusion 2–5 mg/kg/h§, *or*
      midazolam: slow bolus 0.1–0.2 mg/kg, repeat every 3–5 minutes until seizure control, followed by infusion 0.1–3 mg/kg/h, *or*
      thiopental: slow bolus 3–5 mg/kg, repeat 1 mg/kg every 3–5 minutes until seizure control, followed by infusion 1–5 mg/kg/h, *or*
      pentobarbital: slow bolus 5–15 mg/kg, repeat 5 mg/kg every 3–5 minutes until seizure control, followed by infusion 1–5 mg/kg/h.
      Titrate doses to achieve seizure control or until burst suppression pattern is achieved on EEG.
      A combination of agents (e.g. propofol and midazolam) may be required for seizure control.
   D. Insert nasogastric tube and administer maintenance doses of long acting anticonvulsant medication(s); continue after withdrawal of anaesthesia.
   E. Beware of ongoing unrecognised seizures.
      Use continuous EEG monitoring until seizures are controlled, during withdrawal of anaesthesia and preferably during the maintenance phase.
      Avoid muscle relaxants (use continuous EEG if giving repeated doses of muscle relaxants).
   F. Reduce anaesthesia 24–48 hours after seizure control using continuous EEG monitoring. If seizures recur, reinstate the infusion and repeat this step at 24-hour intervals or longer. Consider adjunctive therapies including ketamine (see text).
   In addition:
   Look for and treat underlying cause and precipitant.
   Look for and treat complications: hypotension, hyperthermia and rhabdomyolysis.

*First-line therapy should be initiated after 5 minutes of seizures, second-line therapy at the 20- to 40-minute time point and third-line within 40–60 minutes of onset of SE.

†If none of these three options are available, give IV phenobarbital 15–20 mg/kg, single dose. If IV access is not obtainable, consider rectal diazepam (0.2–0.5 mg/kg, single dose, max 20 mg), IM midazolam (10 mg for > 40 kg, 5 mg for 13–40 kg, single dose), buccal midazolam, intranasal midazolam, or IM fosphenytoin.

††If none of these three options are available, give IV phenobarbital 15–20 mg/kg, single dose, if not already given.

§High infusion rates for prolonged periods require caution.

A, Airway; *B*, breathing; *C*, circulation; *ECG*, electrocardiogram; *EEG*, electroencephalography; *GCS*, Glasgow Coma Scale; *IM*, intramuscular; *IV*, intravenous; *RSE*, refractory status epilepticus.

efficacy and fewer side effects though there are no published comparisons.

PHENYTOIN

Phenytoin is useful for maintaining a prolonged antiseizure effect after rapid termination of seizures with a benzodiazepine, or when benzodiazepines fail. It has lower efficacy than benzodiazepines when used alone as initial therapy.[31]

The recommended intravenous loading dose is 20 mg/kg. The common practice of giving a standard loading dose of 1000 mg may provide inadequate therapy for some adults.

When phenytoin is infused at the maximal adult recommended rate of 50 mg/min, hypotension occurs in up to 50% of patients, and cardiac rhythm disturbance occurs in 2%. These adverse effects are more common in older patients and those with cardiac disease, and are due to the phenytoin itself as well as the propylene glycol diluent. Blood pressure and the electrocardiogram (ECG) should be monitored and the infusion slowed or stopped if cardiovascular complications occur.

Intramuscular phenytoin is not recommended due to erratic absorption and local tissue reactions.

Fosphenytoin, a water-soluble prodrug of phenytoin, can be administered at rates up to 150 phenytoin

equivalents (PE) mg/min since it is not formulated with propylene glycol. Despite this, studies have not demonstrated a faster onset of action than phenytoin. Systemic side effects are similar, although infusion site reactions are less common. Fosphenytoin can be administered intramuscularly, which is useful when intravenous access is not possible.

VALPROATE

Intravenous valproate may be used in both CSE and NCSE in adults and children, and is the preferred second-line agent in children with primary generalised epilepsy.[2] It is non-sedating, appears as effective as phenytoin and may be better tolerated with few reports of hypotension or respiratory depression.[41]

LEVETIRACETAM

There is some evidence for the use of levetiracetam as second-line therapy and in situations where it is desirable to avoid intubation, such as in NCSE and treatment in the elderly.[5,34,42] Levetiracetam may have particular utility in controlling seizures after cerebral hypoxia.[5]

BARBITURATES

Phenobarbital is a potent anticonvulsant with a long duration of action. Although it has equal efficacy to benzodiazepines as first-line therapy, its slower rate of infusion makes it an alternate rather than preferred initial therapy.[33] It may also be used as second-line therapy but only if other recommended agents are unavailable due to it having higher adverse events.[33]

Thiopental is an intravenous anaesthetic agent used for RSE. Following intravenous bolus, the drug is rapidly redistributed into peripheral fat stores and an infusion is required for the ongoing suppression of seizures. Once lipid stores are saturated, the duration of action is prolonged and recovery may take hours to days. Side effects include hypotension, myocardial depression and immunosuppression with increased infection risk.

Pentobarbital (the first metabolite of thiopental) is available in the United States as the alternative to thiopental.

PROPOFOL

Propofol (2,6-diisopropylphenol) is an anaesthetic agent that has become increasingly popular for the treatment of RSE. Recommended infusion rates in RSE vary within 1–10 mg/kg/h.[4,40] High doses may be required to attain seizure control, although this increases the risk of refractory bradycardia/asystole, metabolic acidosis, rhabdomyolysis, lipaemia and death (propofol-related infusion syndrome).[43]

KETAMINE

Ketamine acts as an antagonist at the NMDA receptor and has a theoretical advantage over standard anaesthesia agents, which act on the GABA receptor and therefore may be less effective in prolonged RSE. Its reported use is mostly in super RSE, although it may be a promising alternative or adjunctive therapy used earlier in the treatment of RSE.[4] Suggested dose ranges include a loading intravenous bolus of 0.5–3 mg/kg followed by an infusion of 1–10 mg/kg/h.[4,8,44,45] Case series also report improvement in haemodynamic stability with reduced vasopressor requirement.[45] Ketamine may increase intracranial pressure (ICP) so caution is required in at-risk patients.

OTHER AGENTS OF POTENTIAL USE IN REFRACTORY STATUS EPILEPTICUS

Magnesium is the drug of choice in eclamptic seizures and is also effective in seizures due to hypomagnesaemia, but there is little evidence to support its use in other forms of SE. Nonetheless, given that infusing magnesium is relatively safe, it may be used as adjunctive treatment in super RSE.[8,40]

Lacosamide is a new anticonvulsant drug. Small case series have suggested utility as an adjunctive treatment in RSE when seizures persist after traditional second-line antiepileptic agents or with anaesthetic agents.[11]

Inhalational anaesthesia has been used in RSE. Limitations include difficulties with administration in intensive care, seizure recurrence with discontinuation and adverse effects (e.g. hypotension, ileus), including concerns about neurotoxicity.[11]

OTHER TREATMENTS FOR REFRACTORY STATUS EPILEPTICUS

Neuromuscular-blocking agents are indicated if uncontrolled fitting causes difficulty with providing adequate ventilation or severe lactic acidosis. Paralysis should be used only if EEG monitoring is available, as the clinical expression of seizure activity is abolished.

Hypothermia (32°C–35°C) is utilised for super RSE in several centres, although there are only a small number of case reports suggesting benefit.[40] Targeted temperature management with avoidance of fever as a general neuroprotective strategy has been recommended pending the results of large clinical trials.[4]

Immunotherapy (high-dose steroids, immunoglobulins and/or plasma exchange) has been used in super RSE arising from paraneoplastic aetiologies or autoimmune encephalitis.[4,11] Small case series have also suggested benefit in super RSE from unknown cause – cryptogenic or new-onset RSE (NORSE).[11,46,47]

A ketogenic diet has been reported to be useful in super RSE that is unresponsive to other therapies in

Box 50.6 Indications for electroencephalography monitoring

RSE, to aid the titration of anticonvulsant anaesthetic drugs (minimising dose and toxicity) and ensure suppression of seizure activity*
Patients receiving neuromuscular blockade*
Patients who continue to have a poor conscious state after apparent cessation of seizures
Suspected NCSE in a patient with an altered conscious state
Suspected pseudoseizures

*Continuous or regular intermittent EEG monitoring recommended.
NCSE, Non-convulsive status epilepticus; *RSE*, refractory status epilepticus.
See references 15, 50.

Box 50.7 Causes of status epilepticus in children

Febrile
Acute symptomatic – meningitis, encephalitis, cerebrovascular disease, trauma, metabolic derangement, hypoxia, sepsis, drug related
Remote symptomatic causes – previous traumatic brain injury or insult, CNS malformation, cerebral palsy
Progressive neurological conditions – tumours, degenerative, autoimmune diseases
Congenital and genetic disorders
Cryptogenic, including FIRES

CNS, Central nervous system; *FIRES*, febrile infection-related epilepsy syndrome.
See references 28, 29, 48.

children (mostly with febrile infection-related epilepsy syndrome [FIRES]) and in adults.[11,48]

Surgery has had some success in carefully selected cases of RSE. Techniques include focal cortical resection, multiple subpial transection, corpus callosotomy, hemispherectomy and vagus nerve stimulation.[8,49]

INTENSIVE CARE MONITORING

Pulse oximetry, capnography, intra-arterial and ECG monitoring should be used in patients at risk of cardiorespiratory compromise. Indications for EEG monitoring are listed in Box 50.6.[15,50] Cerebral function monitors are useful in titrating doses of anaesthetic agents to EEG background suppression, but may not be sufficiently sensitive to detect seizure activity. ICP monitoring should be considered if elevated ICP is present owing to the underlying brain pathology.

OUTCOME

The prognosis of patients with SE is related to age, aetiology, degree of impairment of consciousness at presentation and duration of SE.[9,14] RSE is associated with a worse prognosis and prolonged super RSE an even higher mortality. However, where no underlying irreversible brain damage is present, good recovery is possible even after weeks of SE.[8,30]

Children have a much lower mortality of 3%,[51] whereas those aged over 65 years have a mortality rate of 30%.[24,52]

SE precipitated by low antiepileptic drug levels, alcohol abuse or systemic infection has a very low mortality, whereas SE secondary to an acute CNS insult, such as stroke or infection, has a higher mortality.[9,52] SE associated with hypoxic brain injury is most often fatal. NCSE in comatose critically ill patients, despite recognition and treatment, has a poor outcome.[22,37]

The consequences of SE include brain damage resulting in permanent neurological deficits, and the development of focal epilepsy. Multiorgan failure and death can result from uncontrolled seizures, the underlying illness or complications of treatment.

STATUS EPILEPTICUS IN CHILDREN

Most paediatric SE is in very young children with 80% below 4 years of age.[51] The majority are convulsive and generalised.[28] The distribution of causes is highly age-dependent with febrile SE, which is usually self-limiting, and with that due to acute neurological disease (e.g. CNS infection) being more common in children under 4 years. Remote symptomatic causes and SE in a child with previously diagnosed epilepsy are more common in older children.[51] The most frequent aetiologies of SE in children are listed in Box 50.7.[28,29,48,51]

The likelihood of bacterial meningitis is much higher in febrile children presenting with a first-ever episode of SE (12%) as opposed to a brief seizure (1%).[51]

A rare, severe form of SE, called FIRES, usually occurs in school-age children who within weeks of a minor febrile illness develop RSE.[48] The syndrome possibly may have an inflammatory or autoimmune mechanism, and immune treatment and the ketogenic diet may help. The outcome is poor with most children left with significant cognitive disability and refractory epilepsy. Features are similar to NORSE in adults, and there may be a common pathophysiology.

Treatment of SE in children is essentially the same as in adults.[33,53] In addition, pyridoxine should be administered to young children presenting with SE, who may have an inborn error of metabolism of pyridoxine; in these patients lifelong supplementation is required. Pyridoxine-responsive super RSE has also been described in children in whom the genetic test was negative and who only needed immediate and not

ongoing treatment. Given the infusion is without significant side effects, it is now commonly recommended that pyridoxine be routinely given to young children with super RSE.[2,8,40]

The underlying cause is the main determinant of mortality, which is negligible for prolonged febrile seizures other than FIRES and 12%–16% for acute symptomatic causes.[54] Similarly, the risk of subsequent epilepsy is low in neurologically normal children, but is higher than 50% in those with acute or remote symptomatic causes.[54]

KEY REFERENCES

2. Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care*. 2012;17:3–23.
3. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia*. 2015;56:1515–1523.
8. Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain*. 2011;134(Pt 10):2802–2818.
11. Bayrlee A, Ganeshalingam N, Kurczewski L, et al. Treatment of super-refractory status epilepticus. *Curr Neurol Neurosci Rep*. 2015;15(10):66. doi:10.1007/s11910-015-0589-2.
12. Tan RY, Neligan A, Shorvon SD. The uncommon causes of status epilepticus: a systematic review. *Epilepsy Res*. 2010;91(2–3):111–122.
32. Prasad M, Krishnan PR, Sequeira R, et al. Anticonvulsant therapy for status epilepticus. *Cochrane Database Syst Rev*. 2014;(9):CD003723, doi:10.1002/14651858.CD003723.pub3.
33. Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr*. 2016;16(1):48–61.
53. Abend NS, Gutierrez-Colina AM, Dlugos DJ. Medical treatment of pediatric status epilepticus. *Semin Pediatr Neurol*. 2010;17(3):169–175.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Meierkord H, Boon P, Engelsen B, et al. EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol*. 2010;17(3):348–355.
2. Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care*. 2012;17:3–23.
3. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia*. 2015;56:1515–1523.
4. Legriel S, Oddo M, Brophy GM. What's new in refractory status epilepticus? *Intensive Care Med*. 2016;43(4):543–546. doi:10.1007/s00134-016-4501-6.
5. Holtkamp M. Treatment strategies for refractory status epilepticus. *Curr Opin Crit Care*. 2011;17(2): 94–100.
6. Rossetti AO, Milligan TA, Vulliemoz S, et al. A randomized trial for the treatment of refractory status epilepticus. *Neurocrit Care*. 2011;14(1):4–10.
7. Novy J, Logroscino G, Rossetti AO. Refractory status epilepticus: a prospective observational study. *Epilepsia*. 2010;51(2):251–256.
8. Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain*. 2011;134(Pt 10):2802–2818.
9. Neligan A, Shorvon SD. Frequency and prognosis of convulsive status epilepticus of different causes: a systematic review. *Arch Neurol*. 2010;67(8):931–940.
10. Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. *Lancet Neurol*. 2006;5(3):246–256.
11. Bayrlee A, Ganeshalingam N, Kurczewski L, et al. Treatment of super-refractory status epilepticus. *Curr Neurol Neurosci Rep*. 2015;15(10):66. doi:10.1007/s11910-015-0589-2.
12. Tan RY, Neligan A, Shorvon SD. The uncommon causes of status epilepticus: a systematic review. *Epilepsy Res*. 2010;91(2–3):111–122.
13. DeLorenzo RJ, Hauser WA, Towne AR, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. *Neurology*. 1996;46(4):1029–1035.
14. Legriel S, Azoulay E, Resche-Rigon M, et al. Functional outcome after convulsive status epilepticus. *Crit Care Med*. 2010;38(12):2295–2303.
15. DeLorenzo RJ, Waterhouse EJ, Towne AR, et al. Persistent nonconvulsive status epilepticus after the control of convulsive status epilepticus. *Epilepsia*. 1998;39(8):833–840.
16. Treiman DM. Electroclinical features of status epilepticus. *J Clin Neurophysiol*. 1995;12(4):343–362.
17. Walton NY. Systemic effects of generalized convulsive status epilepticus. *Epilepsia*. 1993;34(suppl 1): S54–S58.
18. Betts T. Pseudoseizures: seizures that are not epilepsy. *Lancet*. 1990;336(8708):163–164.
19. LaFrance WC Jr, Baker GA, Duncan R, et al. Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: a staged approach: a report from the International League Against Epilepsy Nonepileptic Seizures Task Force. *Epilepsia* 2013;54(11):2005–2018.
20. Towne AR, Waterhouse EJ, Boggs JG, et al. Prevalence of nonconvulsive status epilepticus in comatose patients. *Neurology*. 2000;54(2):340–345.
21. Claassen J, Mayer SA, Kowalski RG, et al. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. *Neurology*. 2004;62(10):1743–1748.
22. Pandian JD, Cascino GD, So EL, et al. Digital video-electroencephalographic monitoring in the neurological-neurosurgical intensive care unit: clinical features and outcome. *Arch Neurol*. 2004;61(7):1090–1094.
23. Westover MB, Shafi MM, Bianchi MT, et al. The probability of seizures during EEG monitoring in critically ill adults. *Clin Neurophysiol*. 2015;126(3): 463–471.
24. Rossetti AO, Hurwitz S, Logroscino G, et al. Prognosis of status epilepticus: role of aetiology, age, and consciousness impairment at presentation. *J Neurol Neurosurg Psychiatry*. 2006;77(5):611–615.
25. Meierkord H, Holtkamp M. Non-convulsive status epilepticus in adults: clinical forms and treatment. *Lancet Neurol*. 2007;6(4):329–339.
26. Kaplan PW. The clinical features, diagnosis, and prognosis of nonconvulsive status epilepticus. *Neurologist*. 2005;11(6):348–361.
27. Bauer G, Trinka E. Nonconvulsive status epilepticus and coma. *Epilepsia*. 2010;51(2):177–190.
28. Riviello JJ Jr, Ashwal S, Hirtz D, et al. Practice parameter: diagnostic assessment of the child with status epilepticus (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2006;67(9):1542–1550.
29. Freilich ER, Zelleke T, Gaillard WD. Identification and evaluation of the child in status epilepticus. *Semin Pediatr Neurol*. 2010;17(3):144–149.
30. Rossetti AO, Lowenstein DH. Management of refractory status epilepticus in adults: still more questions than answers. *Lancet Neurol*. 2011;10(10): 922–930.
31. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med*. 1998;339(12):792–798.
32. Prasad M, Krishnan PR, Sequeira R, et al. Anticonvulsant therapy for status epilepticus. *Cochrane Database Syst Rev*. 2014;(9):CD003723, doi:10.1002/14651858.CD003723.pub3.
33. Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr*. 2016;16(1):48–61.
34. Aiguabella M, Falip M, Villanueva V, et al. Efficacy of intravenous levetiracetam as an add-on treatment

in status epilepticus: a multicentric observational study. *Seizure*. 2011;20(1):60–64.
35. Walker MC. Status epilepticus on the intensive care unit. *J Neurol*. 2003;250(4):401–406.
36. Ferguson M, Bianchi MT, Sutter R, et al. Calculating the risk benefit equation for aggressive treatment of non-convulsive status epilepticus. *Neurocrit Care*. 2013;18:216–227.
37. Litt B, Wityk RJ, Hertz SH, et al. Nonconvulsive status epilepticus in the critically ill elderly. *Epilepsia*. 1998;39(11):1194–1202.
38. Silbergleit R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med*. 2012; 366(7):591–600.
39. Welch RD, Nicholas K, Durkalski-Mauldin VL, et al. Intramuscular midazolam versus intravenous lorazepam for the prehospital treatment of status epilepticus in the pediatric population. *Epilepsia*. 2015;56(2):254–262.
40. Ferlisi M, Shorvon S. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. *Brain*. 2012;135(Pt 8):2314–2328.
41. Agarwal P, Kumar N, Chandra R, et al. Randomized study of intravenous valproate and phenytoin in status epilepticus. *Seizure*. 2007;16(6):527–532.
42. Fattouch J, Di Bonaventura C, Casciato S, et al. Intravenous levetiracetam as first-line treatment of status epilepticus in the elderly. *Acta Neurol Scand*. 2010;121(6):418–421.
43. Iyer VN, Hoel R, Rabinstein AA. Propofol infusion syndrome in patients with refractory status epilepticus: an 11-year clinical experience. *Crit Care Med*. 2009;37:3024–3030.
44. Gaspard N, Foreman B, Judd LM, et al. Intravenous ketamine for the treatment of refractory status epilepticus: a retrospective multicenter study. *Epilepsia*. 2013;54:1498–1503.
45. Synowiec AS, Singh DS, Yenugadhati V, et al. Ketamine use in the treatment of refractory status epilepticus. *Epilepsy Res*. 2013;105(1–2):183–188.
46. Gall CR, Jumma O, Mohanraj R. Five cases of new onset refractory status epilepticus (NORSE) syndrome: outcomes with early immunotherapy. *Seizure*. 2013;22(3):217–220.
47. Li J, Saldivar C, Maganti RK. Plasma exchange in cryptogenic new onset refractory status epilepticus. *Seizure*. 2013;22(1):70–73.
48. Kramer U, Chi CS, Lin KL, et al. Febrile infection-related epilepsy syndrome (FIRES): pathogenesis, treatment, and outcome: a multicenter study on 77 children. *Epilepsia*. 2011;52(11):1956–1965.
49. Vendrame M, Loddenkemper T. Surgical treatment of refractory status epilepticus in children: candidate selection and outcome. *Semin Pediatr Neurol*. 2010;17(3):182–189.
50. Claassen J, Taccone FS, Horn P, et al. Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM. *Intensive Care Med*. 2013;39:1337–1351.
51. Chin RF, Neville BG, Peckham C, et al. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. *Lancet*. 2006;368(9531):222–229.
52. Logroscino G, Hesdorffer DC, Cascino G, et al. Short-term mortality after a first episode of status epilepticus. *Epilepsia*. 1997;38(12):1344–1349.
53. Abend NS, Gutierrez-Colina AM, Dlugos DJ. Medical treatment of pediatric status epilepticus. *Semin Pediatr Neurol*. 2010;17(3):169–175.
54. Raspall-Chaure M, Chin RF, Neville BG, et al. Outcome of paediatric convulsive status epilepticus: a systematic review. *Lancet Neurol*. 2006;5(9): 769–779.

51

Acute cerebrovascular complications

Thearina de Beer

Cerebrovascular disease is common and its acute manifestation – stroke – produces considerable morbidity and mortality. Stroke is defined as an acute focal neurological deficit caused by cerebrovascular disease, which lasts for more than 24 hours or causes death before 24 hours. Transient ischaemic attack (TIA) also causes focal neurology, but this resolves within 24 hours. Stroke is the fourth largest cause of death in the United Kingdom, the second largest worldwide and is the most common cause of physical disability in adults.[1] Stroke can be categorised as ischaemic or haemorrhagic (Table 51.1).

The main risk factors are increasing age, hypertension, ischaemic heart disease, atrial fibrillation, smoking, diabetes, obesity, some oral contraceptives and raised cholesterol or haematocrit.

PROGNOSIS IN ACUTE CEREBROVASCULAR DISEASE

Mortality after stroke averages 30% within a month, with more patients dying after subarachnoid haemorrhage (SAH) or intracerebral haemorrhage than after cerebral infarction, although survival to 1 year is slightly better in the haemorrhagic group. In all types of stroke, about 30% of survivors remain disabled to the point of being dependent on others. Risk of stroke increases with age and doubles every decade over the age of 55.[1] Thus stroke is often accompanied by significant age-related medical co-morbidity. In the past, this may have been partially responsible for a relatively non-aggressive approach to the treatment of stroke patients, so the gloomy prognosis of stroke becomes a self-fulfilling prophecy. The challenge for intensivists is to identify those patients who are most likely to survive, and not to offer aggressive therapy to those who are not. Stroke should be regarded as a medical emergency. Patients should initially be treated in a stroke unit as there is good evidence of reduction in both mortality and dependency compared with those treated in a general ward. The UK National Institute for Health and Clinical Excellence (NICE) has published guidelines aimed at ensuring early diagnosis and aggressive therapy.[2]

CEREBRAL INFARCTION

Infarction of cerebral tissue (ischaemic stroke) occurs as a result of inadequate perfusion from occlusion of cerebral blood vessels (large or small) in association with inadequate collateral circulation. It may occur due to cerebral thrombosis or embolism.

AETIOLOGY AND PATHOLOGY

CEREBRAL THROMBOSIS

Atherosclerosis is the major cause of major arterial occlusion and most often produces symptoms if it occurs at the bifurcation of the carotid artery or the carotid syphon. Progressive plaque formation causes narrowing and forms a nidus for platelet aggregation and thrombus formation. Ulceration and rupture of the plaque exposes its thrombogenic lipid core, activating the clotting cascade. Hypertension and diabetes mellitus are common causes of smaller arterial thrombosis. Rarer causes of thrombosis include any disease resulting in vasculitis, vertebral or carotid artery dissection (either spontaneous or post-traumatic) or carotid occlusion by strangulation or systemic hypotension after cardiac arrest. Cerebral venous thrombosis, responsible for less than 1% of strokes, may occur in hypercoagulable states, such as dehydration, polycythaemia, thrombocythaemia, some oral contraceptive pills, protein C or S deficiency, or antithrombin III deficiency or vessel occlusion by tumour or abscess. Cerebral infarction may also result from sustained systemic hypotension from any cause, particularly if associated with hypoxaemia.

CEREBRAL EMBOLISM

Embolism commonly occurs from thrombus or platelet aggregations overlying arterial atherosclerotic plaques, but 30% of cerebral emboli will arise from thrombus in the left atrium or ventricle of the heart. This is very likely in the presence of atrial fibrillation, left-sided valvular disease, recent myocardial infarction, chronic atrial enlargement or ventricular aneurysm. The

ABSTRACT

Stroke, whether it is ischaemic or haemorrhagic, is an acute medical emergency, and great strides have been made in its treatment in the last 10 years. It still remains a high-ranking cause of death worldwide, but outcomes have improved with the newer treatments. When a stroke is suspected, a computed tomography scan of the brain needs to be performed within an hour of presentation, and what type of stroke it is will determine further management. Stroke patients should be treated in hyperacute stroke centres with neurosurgical support. Subarachnoid haemorrhage patients should be in a neurosurgical centre with access to interventional neuroradiologists. With rehabilitation, the stroke survivors can make a significant recovery.

KEYWORDS

Stroke
ischaemic stroke
haemorrhagic stroke
intracerebral haemorrhage
intracerebral bleed
subarachnoid haemorrhage
endovascular coiling
mechanical thrombectomy

Table 51.1 Classification of stroke

ISCHAEMIC STROKE CAN BE DIVIDED INTO FIVE TYPES:	HAEMORRHAGIC STROKE CAN BE DIVIDED INTO TWO TYPES:
1. Large-artery atherosclerosis	1. Intracerebral haemorrhage (ICH)
2. Cardioembolism	2. Subarachnoid haemorrhage (SAH)
3. Small-vessel occlusion	
4. Stroke of other determined aetiologies	
5. Stroke of undetermined aetiology	

presence of a patent foramen ovale or septal defects allows paradoxical embolism to occur. Iatrogenic air embolism may occur during cardiopulmonary bypass, cardiac catheterisation or cerebral angiography. Embolisation may also occur as a complication of attempted coil embolisation of cerebral aneurysms or arteriovenous malformations (AVMs) after SAH.

CLINICAL PRESENTATION

In cerebral thrombosis, there is initially no loss of consciousness or headache, and the initial neurological deficit develops over several hours. Cerebral embolism may be characterised by sudden onset and rapid development of complete neurological deficit. No single clinical sign or symptom can reliably distinguish a thrombotic from an embolic event.

Where infarction occurs in a limited arterial territory the clinical signs are often characteristic. The commonest site involves the middle cerebral artery, which classically produces acute contralateral brachiofacial hemiparesis with sensory or motor deficits, depending on the precise area of infarction. Infarction of the middle cerebral territory leads to a dense contralateral hemiplegia, contralateral facial paralysis, contralateral hemianopia and ipsilateral eye deviation. Dominant left-hemisphere lesions result in language difficulties from aphasia, dysphasia, dysgraphia and dyscalculia. Non-dominant right hemispheric lesions cause the patient to neglect the left side, and failure to communicate with anyone approaching from that side. In strokes involving the posterior fossa, the precise pattern of symptoms depends on the arterial territories involved and the presence or absence of collaterals. The onset of symptoms, such as gait disturbance, headache, nausea, vomiting and loss of consciousness, may be very rapid. Venous thrombosis may occur, particularly in the cerebral veins, sagittal or transverse dural sinuses, causing headache, seizures, focal neurology and loss of consciousness. Other cognitive effects of stroke include memory impairment, anxiety, depression, emotional lability, aprosody and spatial impairment. Bilateral brainstem infarction after basilar artery thrombosis may produce deep coma and tetraparesis. Pontine stroke may produce the 'locked-in' syndrome. The precise clinical presentation depends on the size of the infarcted area and its position in the brain. Vascular lesions, such as carotid dissection, can present with ipsilateral Horner syndrome with facial pain, a painful Horner's from local stellate ganglion damage or if there is significant ischaemia from impaired flow or emboli, then with contralateral signs consistent with infarction.[3]

INVESTIGATIONS

A full history and examination of the patient will produce a differential diagnosis that will require specific investigations. The aim is to make the diagnosis, establish the nature, size and position of the pathology, so that correct treatment can target the effects of the primary injury, and prevent extension of the lesion or complications occurring.

BLOOD TESTS

A blood glucose test should be done to exclude diabetes and rule out hypoglycaemia as a cause for symptoms. A full blood count should be taken to look for polycythaemia, infection or thrombocythaemia. A raised erythrocyte sedimentation rate or C-reactive protein level may indicate vasculitis, infection or carcinoma, warranting further appropriate investigations. Cardiac enzymes and troponin should be taken after an electrocardiogram (ECG). Urea and electrolytes, as well as creatinine and liver function tests, should be taken to rule out a metabolic component. A coagulation screen should also be taken together with serum cholesterol, triglyceride and syphilis serology. Specific investigation for thrombophilia due to protein C, protein S, Leiden factor V and antithrombin III abnormalities should be undertaken in patients with venous thrombosis or patients with otherwise unexplained cerebral infarction or TIA. A pregnancy test should be performed on females under the age of 55.

ELECTROCARDIOGRAPHY

This may demonstrate atrial fibrillation, other arrhythmia or recent myocardial infarct.

ECHOCARDIOGRAPHY

Either transthoracic or transoesophageal echocardiography (TOE) may demonstrate mural or atrial appendage thrombus as a source of embolism. TOE is more effective in detecting patent foramen ovale, aortic arteriosclerosis or dissection. Base the decision to perform echocardiography on history, ECG or physical findings.[2]

IMAGING

New guidelines suggest a computed tomography (CT) brain scan within 1 hour of presentation with

a suspected stroke.[2] These techniques are used to distinguish infarction from haemorrhage. Tumour, abscess or subdural haematoma may also produce the symptoms and signs of stroke. Early scanning is vital if interventional treatment, such as thrombolysis, thrombectomy, anticoagulation, antiplatelet therapy or surgery, is planned.

The CT scan may be normal or show only minor loss of grey/white matter differentiation in the first 24 hours after ischaemic stroke, but haemorrhage is seen as areas of increased attenuation within minutes. After a couple of weeks, the CT appearances of an infarct or haemorrhage become very similar and it may be impossible to distinguish them if CT is delayed beyond this time. CT angiography (CTA) will often demonstrate vascular abnormalities and vasospasm but multimodal magnetic resonance imaging (MRI), a combination of diffusion and perfusion-weighted MRI and magnetic resonance angiography (MRA), is much more sensitive in demonstrating small areas of ischaemia. Timing from the onset of symptoms and the exclusion of intracranial haemorrhage (ICH) determines the suitability and benefit of thrombolysis.[4] Where cerebral infarction has occurred as a result of venous thrombosis, the best imaging technique is MRA. Any patient with a stroke or TIA in the internal carotid artery territory should have duplex Doppler ultrasonography, which may demonstrate stenosis, occlusion or dissection of the internal carotid. Where trauma is an aetiological factor reconstruction CT bone window views are required to demonstrate any site of fracture-associated vascular injury.

MANAGEMENT

There is strong evidence that admission to a specialised stroke care unit as soon as possible after the occurrence of a stroke provides a cost-effective reduction in long-term brain damage and disability.[2] In general, only those patients with a compromised airway due to a depressed level of consciousness or life-threatening cardiorespiratory disturbances require admission to medical or neurosurgical intensive care units (ICUs). In either case, attention to basic resuscitation, involving stabilisation of airway, breathing and circulation, is self-evident.

AIRWAY AND BREATHING

Patients with Glasgow Coma Scores (GCS) of 8 or less, or those with absent gag or defects of swallowing (both of which may occur at higher GCS), will require intubation to preserve their airway and to prevent aspiration. Where this requirement is likely to be prolonged, early tracheostomy should be considered. Adequate oxygenation and ventilation should be confirmed by arterial blood gas analysis, and supplemental oxygen prescribed if there is any evidence of hypoxia. If hypercarbia occurs then ventilatory support to achieve normocarbia is necessary to prevent exacerbation of cerebral oedema. A multicentre international study demonstrated that ICU mortality was 37% and hospital mortality was 45% for ventilated stroke patients; it also demonstrated a longer ventilation time and higher tracheostomy rate than non-neurological patients.[5]

CIRCULATORY SUPPORT

A large number of stroke patients will have raised blood pressure (BP) on admission, presumably as an attempt by the vasomotor centre to improve cerebral perfusion. Hypertensive patients may have impaired autoregulation and regional cerebral perfusion may be very dependent on BP. The patient's clinical condition and neurological status should determine treatment rather than an arbitrary level of BP. Current recommendations are that emergency administration of antihypertensive agents should be withheld unless the systolic pressure is >220 mm Hg or the diastolic pressure is >120 mm Hg. Aggressive lowering of BP is not without risk and may result in the progression of ischaemic stroke, so reduction should be monitored closely (not exceeding 15% of normal BP).[6] It would seem reasonable on physiological grounds to avoid drugs that cause cerebral vasodilatation in that they may aggravate cerebral oedema, although there is no hard evidence for this. Cardiac output should be maintained and any underlying cardiac pathology, such as failure, infarction and atrial fibrillation, treated appropriately.

METABOLIC SUPPORT

Both hypo- and hyperglycaemia have been shown to worsen prognosis after acute stroke; therefore blood sugar levels should be maintained in the normal range (<8.6 mmol/L).[7] In the long term, nutritional support must not be neglected, and early enteral feeding should be instituted by nasogastric intubation if needed. In the longer term, particularly where bulbar function is reduced, percutaneous endoscopic gastrostomy may be necessary.

ANTICOAGULATION

The routine use of prophylactic heparin in immobile stroke patients should be avoided as the risk of intracerebral bleeding is high. Intermittent pneumatic compression should be used for 30 days or until mobile.[2] Anticoagulation can only be recommended in individuals where there is a high risk of recurrence, such as in those patients with prosthetic heart valves, atrial fibrillation with thrombus or those with thrombophilic disorders. A CT scan must be obtained prior to commencing therapy to exclude haemorrhage, and careful monitoring used. In patients with large infarcts, there is always the risk of haemorrhage (haemorrhagic conversion) into the infarct and early heparinisation is best avoided. Aspirin 160–300 mg should be given within 48 hours after thrombolysis and continued for 2

weeks while antithrombotic therapy is commenced. If the patient is intolerant of aspirin, an alternative, such as clopidogrel, should be used.[2]

THROMBOLYSIS

Thrombolysis with intravenous recombinant tissue plasminogen activator (rtPA alteplase) is now an established treatment for acute ischaemic stroke.[8] There are specific inclusion and exclusion criteria. Inclusion criteria are a diagnosis of ischaemic stroke causing measurable neurological deficit, age over 18 with an onset of symptoms to treatment time of less than 3 hours. Patients should be excluded if there is a history of head trauma or stroke (ischaemic or haemorrhagic) in the previous 3 months, evidence of subarachnoid or ICH, intracranial neoplasma, AVM or aneurysm, recent intracranial or intraspinal surgery, arterial puncture in a non-compressible site in the past 7 days, any active bleeding or bleeding diathesis including platelet count less than 100,000/mm^3, heparin within 48 hours, current anticoagulant therapy, hypoglycaemia or multilobar infarction (more than one-third of a cerebral hemisphere) on CT scan. Relative contraindications include minor or rapidly improving stroke symptoms, seizure at time of stroke with residual postictal signs, serious trauma or major surgery in the past 14 days, gastrointestinal or urinary tract bleeding in the past 21 days, or myocardial infarction within the past 3 months or pregnancy.

There is some evidence for improved clinical outcome after rtPA use between 3 and 4.5 hours after symptom onset, although the degree of clinical benefit is less.[6] Patients must be in an environment where they can be monitored for potential complications, the most serious of which is ICH. The inclusion criteria must be adhered to, age <80 years, not having a history of diabetes AND stroke, not taking warfarin or other oral anticoagulant (National Institutes of Health Stroke Score, NIHSS), ≤25. This risk is reduced where there is strict adherence to the inclusion and exclusion criteria and the appropriate dose used.

ENDOVASCULAR THERAPY

Several studies have shown positive results with mechanical thrombectomy in immediate and 90-day functional outcome, specifically for patients with a large artery proximal occlusion in addition to thrombolysis and for patients who have contraindications to thrombolysis but not mechanical thrombectomy.[2,9,10] This procedure is available only in specialist neuroradiology departments, which have the support of a neurosurgical centre.

DECOMPRESSIVE CRANIECTOMY

Some patients with malignant middle cerebral artery infarction syndrome (MMCAS) (Fig. 51.1) may benefit from decompressive craniectomy, especially patients with large middle cerebral artery territory infarcts aged <60 years. Decompressive craniectomy must be done within 48 hours of symptom onset. The number needed to treat (NNT) for survival is 2 and for severe disability is 6. Untreated, MMCAS has a mortality of 80% and it is suggested craniectomy can reduce mortality to around 30%, but with residual neurological deficit. This procedure is limited to specialist centres. MMCAS development is predicted by middle cerebral artery (MCA) territory stroke of >50%, a perfusion deficit of >66% on CT, an infarct volume of >145 mL within 14 hours and >82 mL within 6 hours of onset. Electroencephalography (EEG) and tissue cerebral tissue oxygenation have been used to predict cerebral oedema; intracranial pressure (ICP) monitoring has not been proven to change the outcome. Craniectomy has to be large enough to extend past the margins of the infarct. This seems to be well tolerated even after thrombolysis. There is no difference in outcome whether dominant or non-dominant hemispheres are involved. The patients who survive after craniectomy have moderate to severe disability and may have a high incidence of psychological complications. A recent study has shown benefit in this procedure for patients over 60 years.[11] Whether this is acceptable to patients has not been studied.[12]

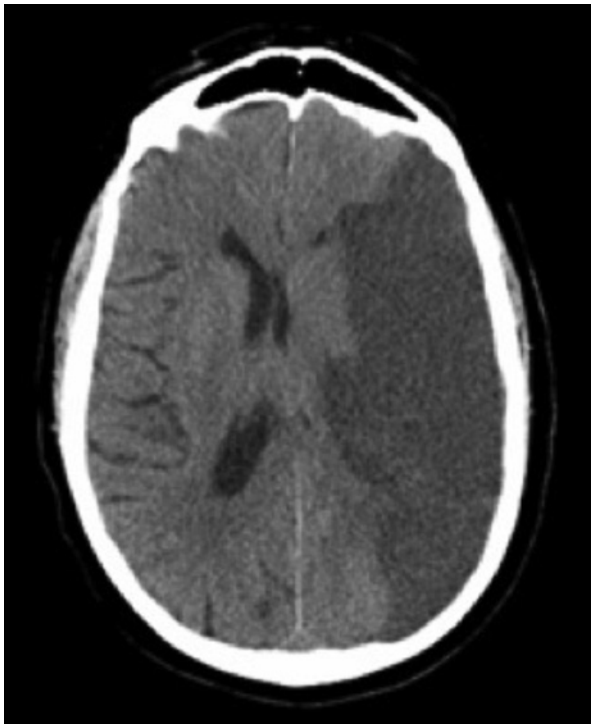


Figure 51.1 Malignant MCA infarct.

Other forms of surgical intervention proven to be effective in making more intracranial space and reducing ICP are drainage of secondary hydrocephalus by extraventricular drain (EVD) insertion or evacuation

of haemorrhage into infarcted areas, resulting in new compressive symptoms. This is especially useful in the posterior fossa where the room for expansion of mass lesions is limited by its anatomy.

COMPLICATIONS

Local complications include cerebral oedema, haemorrhage into infarcted areas or secondary hydrocephalus. General complications include bronchopneumonia, aspiration pneumonia, deep-vein thrombosis, urinary tract infections, pressure sores, contractures and depression. Stroke patients who are ventilated seem particularly susceptible to ventilator-acquired pneumonia.[13] A team approach of specialist nursing, physiotherapists, occupational and speech and language therapists is best able to avoid these complications.

SPONTANEOUS INTRACRANIAL HAEMORRHAGE

Spontaneous ICH producing stroke may occur from either intracerebral haemorrhage (10%) or SAH (5%).

INTRACEREBRAL HAEMORRHAGE

The incidence of intracerebral haemorrhage is about 9/100,000 of the population, mostly in the age range of 40–70 years, with an equal incidence in males and females.

AETIOLOGY AND PATHOLOGY

The commonest cause is the effect of chronic systemic hypertension. This results in degeneration of the walls of vessels or microaneurysms, by the process of lipohyalinosis, and these microaneurysms then suddenly rupture. This may also occur in malignant tumour neovasculature, vasculitis, mycotic aneurysms, amyloidosis, sarcoidosis, malignant hypertension, primary haemorrhagic disorders and over-anticoagulation.

Occasionally, cerebral aneurysms or AVMs may cause intracerebral haemorrhage without SAH. Where intracerebral haemorrhage occurs in young patients, the most likely cause is an underlying vascular abnormality. In some areas, this is also associated with the abuse of drugs with sympathomimetic activity, such as cocaine. The rupture of microaneurysms tends to occur at the bifurcation of small perforating arteries. Common sites of haemorrhage are the putamen (55%), cerebral cortex (15%), thalamus (10%), pons (10%) and cerebellum (10%). Haemorrhage is usually due to the rupture of a single vessel, and the size of the haemorrhage is influenced by the anatomical resistance of the site into which it occurs. The effect of the haemorrhage is determined by the area of brain tissue that it destroys. Cortical haemorrhages tend to be larger than pontine bleeds (Fig. 51.2), but the latter are much more destructive owing to the anatomical density of neural tracts and nuclei.

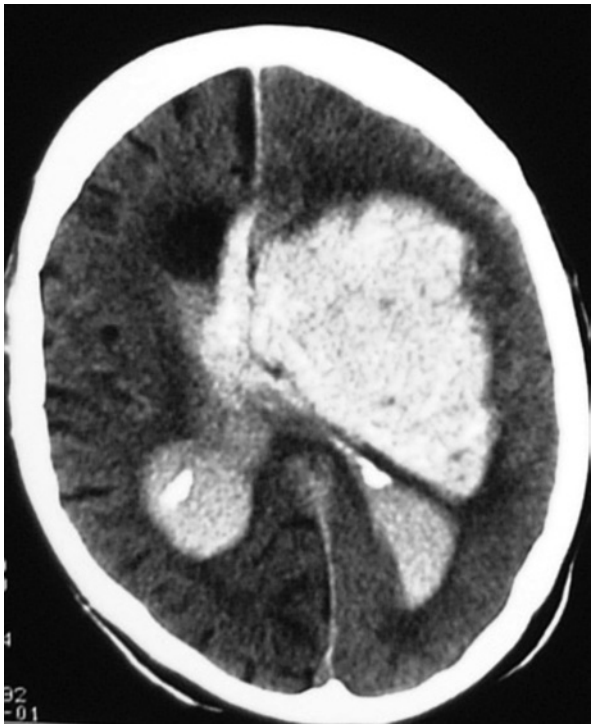


Figure 51.2 Devastating intracerebral haemorrhage.

CLINICAL PRESENTATION

Usually, there are no prodromal symptoms, and a sudden onset of focal neurology or depressed level of consciousness occurs. Headache and neck stiffness will occur in conscious patients if there is subarachnoid extension by haemorrhage into the ventricles. Where intraventricular extension occurs there may be a progressive fall in GCS as secondary hydrocephalus occurs, and this may be accompanied by ocular palsies, resulting in ‘sunset eyes’. Early deterioration is common in the first few hours after haemorrhagic stroke and more than 20% of patients will drop their GCS by two or more points between the initial onset of symptoms and arrival in the emergency department.[14] As with ischaemic stroke, focal neurology is determined by which area of the brain is involved. The only way to differentiate absolutely between ischaemic, intracerebral and SAH is by appropriate imaging. The symptoms relate to tissue destruction, compression and raised ICP, which, if progressive, will result in brainstem ischaemia and death.

INVESTIGATIONS

The general investigations are essentially those listed previously for ischaemic stroke, since it is difficult

to distinguish between the two in the early stages. Patients undergoing treatment with oral anticoagulants, particularly warfarin in atrial fibrillation, mean that anticoagulant-associated ICH is increasing in frequency and a full coagulation screen is essential.[14] CT and/or MRI should be performed at the earliest opportunity. The early deterioration seen in ICH relates to active bleeding and repeat imaging after 3 hours of symptom onset often shows significant enlargement of the initial haematoma. CTA/MRA or venography is very important to determine the cause of the haemorrhage such as AVM, aneurysm or tumour neovasculature. Lumbar puncture may be performed to exclude infection if mycotic aneurysm is suspected, but only after CT has excluded raised ICP or non-communicating hydrocephalus.

MANAGEMENT

The general management principles are identical to those for ischaemic stroke. There is, of course, no place for anticoagulation or thrombolysis, and reversal of any coagulation defect, either primary or secondary to therapeutic anticoagulation, must be undertaken as a matter of urgency. A full coagulation screen must be performed and the administration of vitamin K, fresh frozen plasma, cryoprecipitate, etc., directed by the results. Where emergency decompressive surgery is indicated, warfarin-induced coagulopathy should be corrected using prothrombin complex concentrate (Beriplex or Octaplex). Intraventricular extension occurs in around 45% of cases and the insertion of an EVD may increase the conscious level, particularly in the presence of secondary hydrocephalus. The EVD level should be set so that the cerebrospinal fluid (CSF) drains at around 10 mm Hg. The normal production of CSF should produce an hourly output and a sudden fall in output to zero should alert staff to the possibility that the drain has blocked. This is particularly likely if the CSF is heavily blood-stained. The meniscus of the CSF within the drain tubing should be examined for transmitted vascular pulsation or the level of the drain temporally lowered by a few centimetres to see if drainage occurs. If the drain is blocked, secondary hydrocephalus will recur. Because of the risk of introducing infection and causing ventriculitis, the drain must be unblocked in a sterile manner by the neurosurgeons. Blood in the CSF acts as a pyrogen, but the patient's high temperature should never be ascribed to this alone, and regular blood cultures and CSF samples are required as part of sepsis surveillance. Operative decompression of the haematoma should be undertaken only in neurosurgical centres, and safe transfer must be assured if this is considered. The administration of mannitol prior to transfer should be discussed with the neurosurgical unit. There is some evidence that patients with supratentorial intracerebral haemorrhage less than 1 cm from the cortical surface benefitted from surgery within 96 hours, although this finding did not reach statistical significance.[15] Current recommendations of the American Heart Association/American Stroke Association (AHA/ASA) are: 'Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible'.[14] The management of hypertension following spontaneous intracerebral haemorrhage may be difficult as too high a BP may provoke further bleeding, whereas too low a BP may result in ischaemia. Current recommendations of the AHA/ASA are: 'ICH patients presenting with SBP between 150 and 220 mm Hg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mm Hg is safe and can be effective for improving functional outcome'.[14] This should be done for 7 days.[2] The adoption of these guidelines may have significant resource implications regarding access to ICU beds to provide the required levels of monitoring. There is no place for steroids, and hyperventilation to $PaCO_2$ of 30 mm Hg (4 kPa) or less to control raised ICP will have detrimental effects on cerebral blood flow in other areas of the brain.

SUBARACHNOID HAEMORRHAGE

SAH refers to bleeding that occurs principally into the subarachnoid space and not into the brain parenchyma. The incidence of SAH is around 6/100,000; the apparent decrease, compared with earlier studies, is due to more frequent use of CT scanning, which allows exclusion of other types of haemorrhage. Risk factors are the same as for stroke, but SAH patients are usually younger, peaking in the sixth decade, with a female-to-male ratio of 1.24:1. The only modifiable risk factors for SAH are smoking, heavy drinking, the use of sympathomimetics (e.g. cocaine) and hypertension, which increase the risk odds ratio by 2 or 3. Overall mortality is 50%, of which 15% die before reaching hospital, with up to 30% of survivors having residual deficit-producing dependency. High-volume centres (>60 cases per year) have shown a much improved outcome over that of low-volume centres (<20 cases per year).[16]

AETIOLOGY AND PATHOLOGY

The majority of cases of SAH are caused by ruptured saccular (berry) aneurysms (85%), the remainder being caused by non-aneurysmal perimesencephalic haemorrhage (10%) and rarer causes, such as arterial dissection, cerebral or dural AVMs, mycotic aneurysm, pituitary apoplexy, vascular lesions at the top of the spinal cord and cocaine abuse. Saccular aneurysms are not congenital, almost never occur in neonates and young children and develop during later life. It is not

known why some adults develop aneurysms at arterial bifurcations in the circle of Willis and some do not. It was thought that there was a congenital weakness in the tunica media, but gaps in the arterial muscle wall are equally as common in patients with or without aneurysms and, once the aneurysm is formed, the weakness is found in the wall of the sac and not at its neck.[17] The association with smoking, hypertension and heavy drinking would suggest that degenerative processes are involved. Sudden hypertension plays a role in causing rupture, as shown by SAH in patients taking crack cocaine or, rarely, high doses of decongestants, such as pseudoephedrine.

CLINICAL PRESENTATION

Classically, there is a 'thunderclap' headache developing in seconds, with half of the patients describing its onset as instantaneous. This is followed by a period of depressed consciousness for less than 1 hour in 50% of patients, with focal neurology in about 30% of patients. About one-fifth of patients recall similar headaches and these may have been due to sentinel bleeds; this increases the chances of early rebleed 10-fold. The degree of depression of consciousness depends upon the site and extent of the haemorrhage. Meningism – neck stiffness, photophobia, vomiting and a positive Kernig's sign – is common in those patients with higher GCS. A high index of suspicion is needed for patients presenting with the classical headache; a non-contrast CT is recommended and, if negative, a lumbar puncture should be done 12 hours after ictus. If that is also negative, consider CTA.

The clinical severity of SAH is often described by a grade, the most widely used being that described by the World Federation of Neurological Surgeons (WFNS), which is summarised in Table 51.2. This grading, together with the extent of the haemorrhage and the age of the patient, gives some indication of the prognosis, in that the worse the grade the bigger the bleed, and the older the patient the less likely is a good prognosis. Another scale [Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage (PAASH) scale] has been validated for SAH prognosis, and has shown some benefits over WFNS; however WFNS is currently the most used and recommended scale.[18] Other poor prognostic signs are pre-existing severe medical illness, clinically symptomatic vasospasm, delayed multiple cerebral infarction, hyperglycaemia, fever, anaemia and medical complications, such as pneumonia and sepsis. Anatomical risk factors may increase periprocedural risk of complications. On the other hand, better outcomes seem to be associated with treatment in a high-volume neurosurgical centre.

COMPLICATIONS

The clinical status of the patient may be complicated by factors other than the physical effect of the initial bleed. Factors, such as acute hydrocephalus, early rebleeding, cerebral vasospasm, parenchymal haematoma, seizures and medical complications, must be considered.

Table 51.2 Clinical neurological classification of subarachnoid haemorrhage

GRADE	SIGNS
I	Conscious patient with or without meningism
II	Drowsy patient with no significant neurological deficit
III	Drowsy patient with neurological deficit – probably intracerebral clot
IV	Deteriorating patient with major neurological deficit (because of large intracerebral clot)
V	Moribund patient with extensor rigidity and failing vital centres

WFNS GRADE	*GCS*	*MOTOR DEFICIT*
I	15	Absent
II	14–13	Absent
III	14–13	Present
IV	12–7	Present or absent
V	3–6	Present or absent

GCS, Glasgow Coma Score; *WFNS*, World Federation of Neurological Surgeons.

REBLEEDING

This may occur within the first few hours after admission and 15% of patients may deteriorate from their admission status. They may require urgent intubation and resuscitation, but not all rebleeds are unsurvivable, and as such deterioration should be treated. The chance of rebleeding is dependent on the site of the aneurysm, the presence of the clot, the degree of vasospasm and the age and sex of the patient. Although most studies quote an incidence for rebleeding of 4% in the first 24 hours, more recent studies suggest an incidence of 9%–17% with most cases occurring within 6 hours. A few small studies have shown that antifibrinolytics, such as tranexamic acid, can be used early and short term (<72 hours) in patients who do not have a pre-existing high risk for thrombotic events, for the prevention of rebleeding while awaiting securing of the aneurysm. It is an off-licence use of antifibrinolytics.[16]

ACUTE HYDROCEPHALUS

This may occur within the first 24 hours post ictus and is often characterised by a drop in the GCS, sluggish pupillary responses and bilateral downward deviation of the eyes ('sunset eyes'). If these signs occur, a CT scan should be repeated and, if hydrocephalus is

confirmed or there is a large amount of intraventricular blood, then a ventricular drain may be inserted. This is recommended by the AHA/ASA.[19]

DELAYED CEREBRAL ISCHAEMIA

Vasospasm is the term used to describe the narrowing of the cerebral blood vessels in response to the SAH seen on angiography. It occurs in up to 70% of patients, but not all of these patients will have symptoms. Delayed cerebral ischaemia (DCI) refers to the onset of focal neurological deficit, a drop in GCS by 2 or more points, and/or cerebral infarction that occurs typically 4–12 days post SAH unrelated to aneurysm treatment or other causes of neurological deficit, such as hydrocephalus, cerebral oedema or metabolic disorder.[20] The use of transcranial Doppler (TCD) to estimate middle cerebral artery blood velocity has shown that a velocity of more than 120 cm/s correlates with angiographic evidence of vasospasm. This technology allows diagnosis in the ICU and provides a means of monitoring the success of treatment to reduce DCI, which is undertaken to reduce the severity of delayed neurological deficit secondary to vasospasm. The problem is that not all patients who have angiographic vasospasm or high Doppler velocities have symptoms. If there is evidence of a depressed level of consciousness in the absence of rebleeding, hydrocephalus or metabolic disturbances, but there is evidence of DCI clinically, on TCD or angiogram, then it would seem appropriate to initiate treatment. If vasospasm occurs at the time of angiography or coiling, then intravascular vasodilators, such as papaverine or nimodipine have been used. CTA is the imaging modality of choice unless intracerebral therapy is planned, then digital subtraction angiography (DSA) is recommended as first-line imaging.

PARENCHYMAL HAEMATOMA

This may occur in up to 30% of SAH following aneurysm rupture and has a much worse prognosis than SAH alone. If there is mass effect with compressive symptoms then evacuation of haematoma and simultaneous clipping of the aneurysm may improve outcome.

MEDICAL COMPLICATIONS

Medical complications will occur in 40% of SAH patients. The mortality due to medical complications is almost the same as that due to the combined effects of the initial bleed, rebleeds and DCI. The types of medical complication seen are shown in Table 51.3.

Table 51.3 Types of medical complication seen in patients with subarachnoid haemorrhage

MEDICAL COMPLICATION	INCIDENCE (%)
Arrhythmias	35
Liver dysfunction	24
Neurogenic pulmonary oedema	23
Pneumonia	22
ARDS and atelectasis	20
Renal dysfunction	5

ARDS, Acute respiratory distress syndrome.

INVESTIGATIONS

The general investigations for stroke should be performed, and early CT imaging is mandatory. Blood appears characteristically hyperdense on CT and the pattern of haemorrhage may enable localisation of the arterial territory involved (Fig. 51.3). Very rarely, a false-positive diagnosis may be made if there is severe generalised oedema resulting in venous congestion in the subarachnoid space. Small amounts of blood may not be detected, and the incidence of false-negative reports is around 2%.[19] It may be difficult to distinguish between post-traumatic SAH and primary aneurysmal SAH, which precipitates a fall in the level of consciousness that provokes an accident or fall. MR scanning is particularly effective for localising the bleed after 48

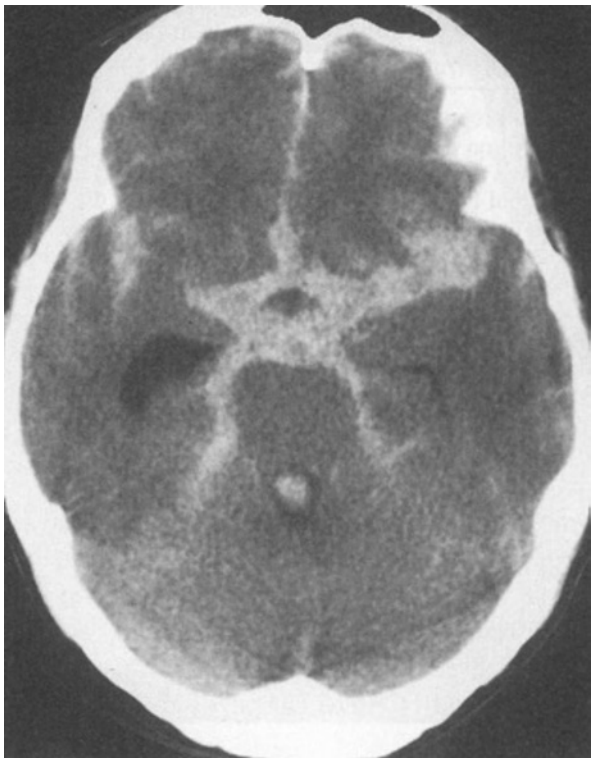


Figure 51.3 Subarachnoid haemorrhage on computed tomography scan of the head.

hours when extravasated blood is denatured, and provides a good signal on MRI.

Lumbar puncture is still necessary in those patients where the suspicion of SAH is high despite a negative CT, or there is a need to exclude infection. There must be no raised ICP and at least 12 hours should have passed to give time for the blood in the CSF to lyse, enabling xanthochromia to develop.

Angiography via arterial catheterisation is still the most commonly used investigation for localising the aneurysm or other vascular abnormality prior to surgery. It is generally performed on patients who remain, or become, conscious after SAH. It is not without risk and aneurysms may rupture during the procedure, and a meta-analysis has shown a complication rate of 1.8%. Other methods under investigation include CTA and MRA. DSA is the diagnostic tool of choice in cases where CTA is still inconclusive.[19]

ICP monitoring is of limited use in SAH patients except in those where hydrocephalus or parenchymal haematoma is present, and early detection of pressure increases may be the trigger for drainage or decompressive surgery.[21]

Multimodal monitoring: TCD studies may be useful in detecting vasospasm or those patients in whom autoregulation is impaired.[19] The technique is dependent on there being a 'window' of thin temporal bone allowing insonation of the Doppler signal along the middle cerebral artery. It is very user dependent and 15% of patients do not have an adequate bone window. Continuous EEG monitoring, cerebral blood flow monitoring, jugular venous oximetry, brain tissue oxygen oximetry and cerebral microdialysis have all been used to diagnose DCI.[22]

MANAGEMENT

The initial management of SAH is influenced by the grading, medical co-morbidity or complications, and the timing or need for surgery. Patients with decreased GCS may need early intubation and ventilation, simply for airway protection, whereas those with less severe symptoms require regular neurological observation, analgesia for headache and bed rest prior to investigation and surgery. Other management options are stress ulcer prophylaxis, deep-vein thrombosis prophylaxis using compression stockings or boots, and seizure control with phenytoin or barbiturates. If the patient is sedated and ventilated, the use of an analysing cerebral function monitor should be considered to detect subclinical seizure activity.

Hyponatraemia is a common finding and adequate fluid therapy with normal saline is required with electrolyte levels maintained in the normal range. Occasionally, as in other types of brain injury, excessive natriuresis occurs and may result in hyponatraemic dehydration – cerebral salt-wasting syndrome (CSWS).[23] Its aetiology is not known, but some suggest increased levels of atrial natriuretic peptide. It usually occurs within the first week after insult and resolves spontaneously in 2–4 weeks. Failure to distinguish CSWS from the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) could lead to inappropriate treatment by fluid restriction, which would have adverse effects on cerebral perfusion. Urine sodium concentrations are usually elevated in both SIADH and CSWS (>40 mmol/L) but urinary sodium excretion, urine sodium concentration [Na mmol/L] × urine volume [L/24 hours] is high in CSWS and normal in SIADH. If CSWS does not respond to fluid replacement with saline or is not self-limiting then fludrocortisone therapy may be useful. Euvolaemia is crucial to help prevent and not exacerbate DCI.

BLOOD PRESSURE CONTROL

Elevation of BP is commonly seen after SAH and there are no precise data on what constitutes an unacceptably high pressure that is likely to cause rebleeding. Equally, there are no precise data on a minimum level of pressure below which infarction is likely to occur, since this will depend on the patient's normal pressure, the degree of cerebral oedema and the presence or absence of intact autoregulation. One observational study has demonstrated reduced rebleeding, but higher rates of infarction, in newly treated compared with untreated post-SAH hypertensive patients. Although there are no precise data on specific BP controls, the AHA guidelines recommend that systolic BP is kept <160 mm Hg or mean arterial pressure of <110 mm Hg in a person with an unsecured aneurysmal SAH.[19] Beta-adrenergic blockers or calcium antagonists are the most widely used agents, since drugs producing cerebral vasodilation may increase ICP. The choice is less important than the titratability of the drug, as the balance between the increased risk of rebleed and cerebral perfusion needs to be maintained. If nimodipine causes severe hypotension, timing and dose need to be changed too (i.e. 30 mg 2-hourly instead of 60 mg 4-hourly). If nimodipine still remains a problem, consider omitting doses until the patient is more cardiovascularly stable while maintaining euvolaemia.

DELAYED CEREBRAL ISCHAEMIA

Angiographic demonstration of vasospasm may be seen in about 70% of SAH patients, but only about 30% develop cerebral symptoms related to vasospasm, hence the change of nomenclature.

Symptoms tend to occur between 4 and 14 days post-bleed, which is the period when cerebral blood flow is decreased after SAH.

PREVENTION

One method of pre-empting vasospasm is oral nimodipine at 60 mg given 4-hourly for 21 days, which has been shown to achieve a reduction in the risk of ischaemic stroke of 34%. Intravenous nimodipine should be used in the patients who are not absorbing enterally, but it must be titrated against BP to avoid hypotension. Aspirin, clazosentan, enoxaparin, erythropoietin, fludrocortisone, magnesium, methylprednisolone, nicardipine and statins have been in trials but have not been shown to prevent DCI.[22]

TREATMENT

Low cerebral blood flow is known to worsen outcome and this resulted in the development of prophylactic hypertensive hypervolaemic haemodilution – so-called triple-H therapy. This has been shown to cause harm. The focus now is on euvolaemia and, if this is indicated and the BP is not already raised, hypertension is induced with vasopressors. This needs to be done in a stepwise fashion with assessment of neurological function at each step.[22] Cerebral angioplasty or direct intracerebral vasodilators should be considered if induced hypertension is not reversing the DCI symptoms. Where symptoms develop it is important to exclude other causes, such as rebleeding, hydrocephalus or metabolic disorder. Poor-grade SAH patients who are sedated or have low GCS are clinically difficult to assess; multimodal monitoring is recommended to look for deterioration.[22]

SEIZURES

Seizure occurs in up to 26% of SAH sufferers. The evidence for prophylactic use of anticonvulsants is poor and not recommended. Some prognostic indicators for the development of seizures have been identified: increased intracerebral blood, poor-grade SAH, rebleeding infarction and MCA aneurysm. Patients should be observed for seizure activity and treated appropriately. A patient with poor-grade SAH who is not improving or is deteriorating neurologically, from an unknown cause, should have continuous EEG monitoring.[16]

SURGERY

Clipping of the aneurysm is the surgical treatment of choice, with wrapping, proximal ligation or bypass grafting being used if the aneurysm is inaccessible to Yasargil clipping. The timing of surgery remains debatable. Recommendations by the AHA are to secure the aneurysm within 48 hours of ictus or 48 hours of presentation. Large intracerebral haematomas associated with the SAH and middle cerebral artery aneurysms should be strongly considered for surgery. There is no good level-one evidence for the use of induced hypertension or hypothermia during clipping, but in certain patients it could be considered. What is clear is that hypotension and hyperglycaemia should be avoided.[19]

ENDOVASCULAR COILING

In patients with ruptured intracranial aneurysms suitable for both surgery and endovascular coiling treatments, endovascular coiling is more likely to result in independent survival at 1 year than neurosurgical clipping; the survival benefit continues for at least 7 years. The risk of late rebleeding is low, but is more common after endovascular coiling than after neurosurgical clipping as well as retreatment of up to 20%.[24] Additional complications of coiling include rupture during catheter placement in the aneurysm, coil embolisation and vasospasm. Not all aneurysms, particularly those with wide necks, multiple filling vessels or giant aneurysms, are suitable for coiling. Aneurysms that are amenable to either surgery or coiling should be coiled; if patients are elderly (>70 years) or have poor-grade SAH then coiling is preferred. Stenting of acute SAH carries a worse prognosis.[19]

THERAPY OF MEDICAL COMPLICATIONS

This is specific to the type of complication. Pneumonia may require continuous positive airway pressure or ventilatory support together with directed antimicrobial therapy; acute respiratory distress syndrome requires lung-protective/recruitment ventilatory strategies; and renal failure necessitates an appropriate means of renal replacement therapy. Arrhythmias require correction of trigger factors, such as hypovolaemia and electrolyte or acid-base disturbances prior to the appropriate antiarrhythmic drug or direct current cardioversion. Cardiac function should be evaluated in patients with cardiovascular deterioration, by means of serial enzymes and echocardiography. Cardiac output monitoring should be considered. Neurogenic pulmonary oedema may be associated with severe cardiogenic shock, which may require inotropic support or even temporary intra-aortic balloon counterpulsation. The cardiogenic shock is reversible and patients can make a good recovery despite the need for aggressive support.[25]

Hyper- and hyponatraemia are frequently seen, with hyponatraemia occurring in up to 30% of cases, and it is implicated in the development of DCI. The aim is for euvolaemia; if it cannot be achieved because of a persistent negative fluid balance as a result of CSWS, then fludrocortisone should be considered. Hyponatraemia should be corrected by no more than 0.5 mmol/L per hour with a maximum of 8 mmol/L per day (if it is chronic; i.e. of more than 48 hours' duration) during which 4-hourly sodium levels should be taken. This may be achieved by using intravenous fluid that has more sodium than the serum concentration of the patient. In patients who are resistant to vasopressors, hypothalamic dysfunction should be considered and

hydrocortisone should be administered, but no more than 300 mg/day.

Blood glucose should be kept at 4.4–11.1 mmol/L (80–200 mg/dL), as higher and lower levels of blood glucose have been shown to be detrimental to the outcome.

Fever should be controlled by antipyretics as the first-line treatment, especially when DCI is suspected. Cooling devices should be considered if first-line antipyretics have failed, but care should be taken to monitor for pressure ulcers and venous thrombotic events. Shivering needs to be addressed as this will be counterproductive to therapy by increasing oxygen consumption.

Deep-vein thrombosis prophylaxis should be instituted as soon as possible in the form of graduated compression devices; heparin (unfractionated or low molecular weight) should be started 24 hours after securing the aneurysm.[16]

Anaemia should be minimised by limiting the amount of blood taken for blood tests. A transfusion trigger of 8 g/dL in patients without DCI and 9–10 g/dL in patients with DCI has been recommended.[22]

REFERENCES

1. Stroke Association. *State of the Nation: Stroke Statistics*; 2015. https://www.stroke.org.uk/resources/state-nation-stroke-statistics.
2. 2016 National Clinical Guideline for Stroke. https://www.strokeaudit.org/Guideline/Guideline-Home.aspx/.
3. Gottesman RF, Sharma P, Robinson KA, et al. Clinical characteristics of symptomatic vertebral artery dissection. A systematic review. *Neurologist*. 2012;18(5):245–254.
4. Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl): e601S–e636S.
5. Pelosi P, Ferguson ND, Frutos-Vivar F, et al. Management and outcome of mechanically ventilated neurologic patients. *Crit Care Med*. 2011; 39(6):1482–1492.
6. Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke. *Stroke*. 2013. STR.0b013e318284056a.
7. Quinn TJ, Lees KR. Hyperglycaemia in acute stroke – to treat or not to treat. *Cerebrovasc Dis*. 2009;27(1): 148–155.
8. NICE. *Alteplase for treating acute ischaemic stroke*. Guidance and guidelines. Available from: https://www.nice.org.uk/guidance/ta264?unlid=838784222016926215536.
9. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387(10029):1723–1731.
10. Powers WJ, Derdeyn CP, Biller J, et al. 2015 AHA/ASA focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment. *Stroke*. 2015. STR.0000000000000074.
11. Jüttler E, Unterberg A, Woitzik J, et al *Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke*; 2014. http://dx.doi.org/10.1056/NEJMoa1311367. http://www.nejm.org/doi/full/10.1056/NEJMoa1311367.
12. Wartenberg KE. Malignant middle cerebral artery infarction. *Curr Opin Crit Care*. 2012;18(2): 152–163.
13. Kasuya Y, Hargett JL, Lenhardt R, et al. Ventilator-associated pneumonia in critically ill stroke patients: frequency, risk factors, and outcomes. *J Crit Care*. 2011;26(3):273–279. http://www.jccjournal.org/article/S0883-9441(10)00279-0/abstract.
14. Hemphill JC, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46(7):2032–2060.
15. Vespa PM, Martin N, Zuccarello M, et al. Surgical trials in intracerebral hemorrhage. *Stroke*. 2013;44 (6 suppl 1):S79–S82.
16. Diringer MN, Bleck TP, Claude Hemphill J, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the neurocritical care society's multidisciplinary consensus conference. *Neurocrit Care*. 2011;15(2):211–240.
17. Backes D, Rinkel GJE, Laban KG, et al. Patient- and aneurysm-specific risk factors for intracranial aneurysm growth. *Stroke*. 2016;47(4):951–957.
18. van Heuven AW, Mees SMD, Algra A, et al. Validation of a prognostic subarachnoid hemorrhage grading scale derived directly from the glasgow coma scale. *Stroke*. 2008;39(4):1347–1348.
19. Connolly ES, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. *Stroke*. 2012;43(6):1711–1737.
20. Washington CW, Zipfel GJ, Participants in the International Multi-disciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage. Detection and monitoring of vasospasm and delayed cerebral ischemia: a review and assessment of the literature. *Neurocrit Care*. 2011;15(2):312–317.
21. Cossu G, Messerer M, Stocchetti N, et al. Intracranial pressure and outcome in critically ill patients with aneurysmal subarachnoid hemorrhage: a systematic review. *Minerva Anestesiol*. 2016;82(6):684–696. https://www.researchgate.net/publication/299771292_Intracranial_pressure_and_outcome_in_critically_ill_patients_with_aneurysmal_subarachnoid_hemorrhage_A_systematic_review.

22. Francoeur CL, Mayer SA. Management of delayed cerebral ischemia after subarachnoid hemorrhage. *Crit Care*. 2016;20(1):277.
23. Mapa B, Taylor BES, Appelboom G, et al. Impact of hyponatremia on morbidity, mortality, and complications after aneurysmal subarachnoid hemorrhage: a systematic review. *World Neurosurg*. 2016;85:305–314.
24. Soize S, Gawlitza M, Raoult H, et al. Imaging follow-up of intracranial aneurysms treated by endovascular means. *Stroke*. 2016;47(5):1407–1412.
25. Kerro A, Woods T, Chang JJ. Neurogenic stunned myocardium in subarachnoid hemorrhage. *J Crit Care*. 2017;38:27–34.

52

Cerebral protection

Colin Andrew Eynon

'The chief function of the body is to carry the brain around.'

Thomas A. Edison

'The human brain has 100 billion neurons, each neuron connected to 10 thousand other neurons. Sitting on your shoulders is the most complicated object in the known universe.'

Michio Kaku

CEREBRAL PHYSIOLOGY AND ANATOMY

The brain receives around 15% of the cardiac output (50 mL/100 g/min) and utilises around 3–5 mL O_2/min per 100 g tissue and 5 mg glucose/min per 100 g tissue. The grey matter of the brain, which consists primarily of the neuronal cell bodies and synapses, has a higher blood flow compared with the white matter, which consists largely of fibre tracts. Critical cerebral blood flow (CBF) is around 20 mL/100 g/min, with the electroencephalogram (EEG) becoming isoelectric at 15 mL/100 g/min.

The anterior cerebral circulation is provided by the two internal carotid arteries which subdivide into the anterior and middle cerebral arteries. These provide around 70% of the cerebral circulation supplying the frontal, parietal and temporal lobes and the anterior diencephalon (basal ganglia and hypothalamus). The two vertebral arteries join to form the basilar artery which supplies the posterior circulation; the brainstem, cerebellum, occipital lobes and the posterior diencephalon (thalamus). The two circulations (anterior and posterior) are joined by communicating arteries to form the circle of Willis at the base of the brain. As the circle facilitates collateral flow, obstruction to one of the four principle arteries (right and left internal carotid, right and left vertebral) supplying the brain may be clinically insignificant. Damage to the intracerebral vessels, however, often results in significant damage due to the lack of anatomical reserve. The areas between those supplied by the principle cerebral arteries are supplied by the leptomeningeal arteries. These areas are potential watershed areas that are particularly at risk in conditions of low- or no-flow such as cardiac arrest, severe sepsis or following major trauma (Fig. 52.1).

CEREBRAL PERFUSION

Cerebral perfusion is controlled in part by the perfusion pressure across the brain (cerebral perfusion pressure or CPP). CPP is the difference between the cerebral arterial pressure and cerebral venous pressure. As these pressures are difficult to measure, systemic mean arterial pressure (MAP) and intracranial pressure (ICP) are used as surrogates.

$$CPP = MAP - ICP$$

MAP can be estimated as equal to diastolic blood pressure + 1/3 pulse pressure. In adults, the normal resting ICP is 0–10 mm Hg. ICP can rise to 50 mm Hg or higher during straining or sneezing with no impairment in cerebral function. It is not, therefore, an elevated ICP alone that is important in pathological conditions. CPP is around 60 mm Hg in the normal state.

CEREBRAL METABOLISM

The energy requirements of the brain are large, in order to maintain membrane integrity and to support the transmembrane ion gradients required for electrical activity and cell survival. Energy is also required for the synthesis, storage and release of neurotransmitters. Neurones produce adenosine triphosphate almost entirely by the oxidative metabolism of glucose and ketone bodies. Over 85% of the glucose used by the brain undergoes oxidative metabolism with brain tissue having only very limited ability for anaerobic metabolism. Consciousness is lost rapidly if the supply of either oxygen or glucose is restricted. Loss of consciousness will occur in less than 10 seconds following acute decompression at 50,000 ft, with the time delay resulting from the transit time of deoxygenated blood from the lungs to the brain.[1] Similarly, unconsciousness occurs swiftly following intravenous administration of high doses of insulin.[2]

ABSTRACT

The brain is arguably the most important organ in the body and also one of its most vulnerable. Primary brain injury may result from conditions such as trauma, stroke or intracerebral haemorrhage (ICH), or it may be secondarily injured most commonly due to circulatory or respiratory disease. Cerebral protection is the application of often simple, therapeutic interventions with the intention of limiting or preventing further neuronal injury and thus improving the patient's ultimate neurological outcome. The key to cerebral protection is early intervention, as neuronal damage can occur within minutes of an insult. Prevention of hypoxia, hyper- and hypocarbia, hyper- and hypoglycaemia, seizures and maintenance of adequate cerebral perfusion and osmolarity are all important. Although many therapeutic agents have been studied to try and reduce neuronal damage, very few have been successfully transferred into clinical practice.

KEYWORDS

Secondary insults
intracranial pressure
cerebral perfusion pressure
time-critical
specialist care

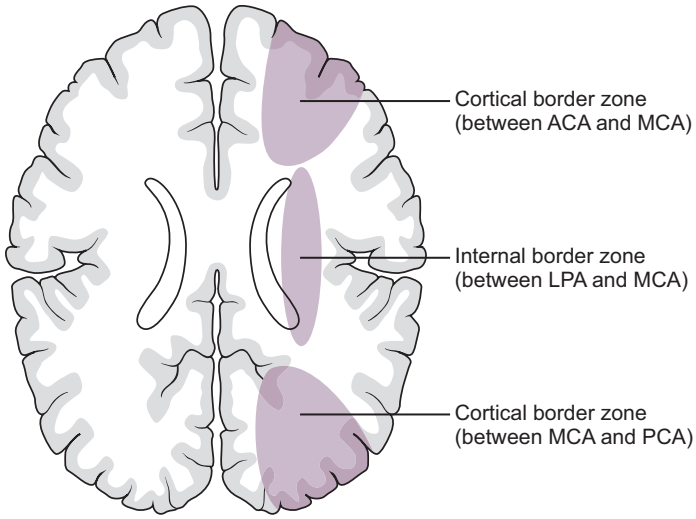


Figure 52.1 Axial view of the brain showing the major arterial territories. Watershed infarcts may occur at the border between the major cerebral arterial territories in conditions of low blood flow. These may be (a) cortical border zone infarcts (infarction of the cortex and neighbouring subcortical white matter at the border of the ACA and the MCA and/or the MCA and the PCA), or (b) internal border zone infarction of deep white matter (between the LPA and the deep cortical branches of the MCA or at the border zone of deep white matter branches of the MCA and the ACA). *ACA,* Anterior cerebral artery; *LPA,* lentriculostriate perforating arteries; *MCA,* middle cerebral artery; *PCA,* posterior cerebral artery.

LOCAL CONTROL OF CEREBRAL BLOOD FLOW

AUTOREGULATION (MYOGENIC REGULATION)

Autoregulation ensures that CBF remains constant between MAPs from 60 to 160 mm Hg. The stimulus for autoregulation is CPP. Autoregulation is thought to be a myogenic mechanism with reflex vasoconstriction of cerebral vessels occurring in response to increases in CPP and vascular wall tension, and vasodilatation occurring in response to decreases in CPP and reduction in wall tension.[3] Outside the values where autoregulation is effective, the relationship between CBF and MAP is linear and CBF is pressure dependent (Fig. 52.2). The range at which autoregulation can operate varies with age and in certain pathological conditions. The range is shifted to the left in early life and to the right in chronic hypertension. A rapid reduction in the blood pressure of a patient with chronic hypertension risks inadequate perfusion of the brain, heart and/or the kidneys. Autoregulation may be also impaired by hypoxia, ischaemia, hypercapnia, trauma and certain anaesthetic agents.

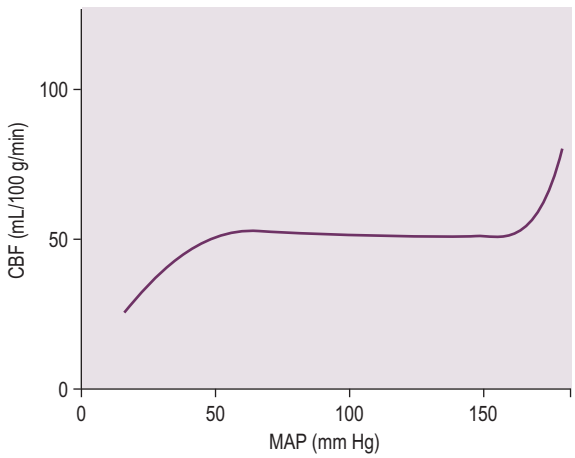


Figure 52.2 The relationship between mean arterial pressure *(MAP)* and cerebral blood flow *(CBF)* under normal circumstances, illustrating the range of autoregulation.

Rapid rises in systemic blood pressure are also poorly tolerated. Hypertensive emergencies occur in an estimated 1–2/100,000 patients per year and may be associated with retinopathy, papilloedema or encephalopathy. Hypertensive encephalopathy results from cerebral oedema due to increased hydrostatic pressures and can cause drowsiness, coma, seizures and ICH. Posterior reversible encephalopathy syndrome (PRES) may present with seizures, disturbed vision, headache and altered mental state.[4] It is strongly linked to conditions that co-exist in patients with renal disease, such as hypertension, vascular and autoimmune diseases, immunosuppression, and organ transplantation. More than 70% of patients are

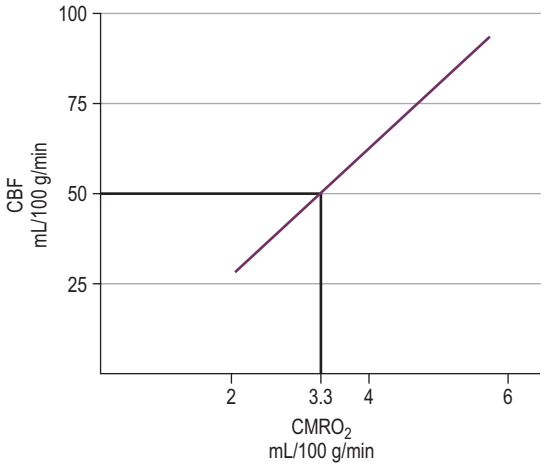


Figure 52.3 Flow-metabolism coupling. As the cerebral metabolic rate for oxygen *($CMRO_2$)* increases there is proportional increase in cerebral blood flow *(CBF)*. Normal CBF is around 50 mL/100 g/min.

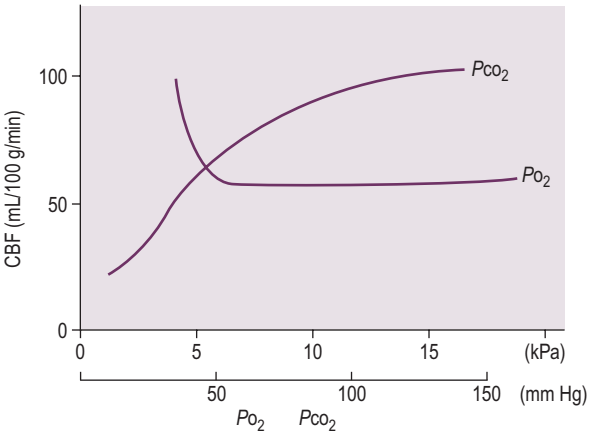


Figure 52.4 The relationship between the partial pressure of oxygen and carbon dioxide and cerebral blood flow *(CBF)*.

hypertensive. Typical magnetic resonance imaging (MRI) findings are of reversible, symmetrical, posterior subcortical vasogenic oedema.[5] If promptly treated and managed, symptoms often resolve within a few days to weeks.

FLOW–METABOLISM COUPLING

Flow–metabolism coupling is the direct relationship of the metabolic activity of the brain to CBF. Increases in metabolic demand are met rapidly by increases in CBF and delivery of substrates (Fig. 52.3). The exact mechanisms that control flow–metabolism coupling are unknown but may involve a variety of mediators such as neurokinin-A, nitric oxide and substance P. It is not clear how the diameter of cerebral vessels upstream to the area of activity can be altered so rapidly by metabolic products which are being washed downstream. It is thought that there may be control neurons that act on specific cerebral vessels that control local blood flow.[6] Regional variations in cerebral metabolism can now be visualised using techniques such as positron emission tomography scanning, although the hypothesis that such variations existed dates as far back as 1890.[7]

SYSTEMIC CONTROL OF CEREBRAL BLOOD FLOW

CARBON DIOXIDE

CBF increases by 3%–4% for each mm Hg increase in $PaCO_2$. A doubling of $PaCO_2$ doubles CBF and conversely a halving of $PaCO_2$ will halve CBF (Fig. 52.4). The responses to changes in $PaCO_2$ occur rapidly, within 30s, and are thought to relate to changes in extracellular or interstitial hydrogen ion concentrations. Tight control of $PaCO_2$ is essential if CPP is critical; increases in CO_2 cause vasodilatation and increased ICP, whereas decreases in $PaCO_2$ below 4 kPa have been shown to result in vasoconstriction sufficient to precipitate critical cerebral ischaemia.[8] Impaired CO_2 reactivity is associated with poor outcomes in patients with severe head injury.[9]

OXYGEN

CBF is not affected by changes in Pa_{O_2} within the normal range, but levels <50 mm Hg (6.65 kPa) result in cerebral vasodilatation and increases in CBF. Below 30 mm Hg (4 kPa), CBF is roughly doubled with a consequent increase in ICP (see Fig. 52.4).

TEMPERATURE

The cerebral metabolic rate for oxygen ($CMRO_2$) is reduced by around 8% for each degree Celsius reduction in temperature. Mild hypothermia remains recommended for the management of patients who are resuscitated from cardiac arrest.[10] More profound cooling enables patients to withstand prolonged periods of low CBF during cardiopulmonary bypass. Application of cooling to unselected patients with traumatic brain injury is now thought to be ineffective.[11] Avoidance of hyperthermia in cerebral injury remains important as $CMRO_2$ is increased by a similar amount for every degree Celsius increase in temperature.

CEREBRAL INJURY

Cerebral injury is commonly divided into primary and secondary. Primary injuries include traumatic,

ischaemic or hypoxic and may be focal or global. Secondary injuries may be initiated as a consequence of the primary injury and can contribute significantly to the ultimate outcome of the patient.

Primary traumatic brain injury may result in four main pathological conditions which can all co-exist: brain contusions, axial and extra-axial haematomas (subdural, extradural and intracerebral), traumatic subarachnoid haemorrhage (SAH) and diffuse axonal injury (DAI). DAI results from dynamic deformation of the brain with resultant shearing forces, affecting the blood vessels and axons. Areas commonly affected include axons in the brainstem, the parasagittal white matter near the cerebral cortex, and the corpus callosum.[12]

Focal hypoxic or ischaemic insults often occur acutely such as in acute stroke. If the area supplied by the affected artery has a good collateral supply, injury may be modest. If, however, the area is poorly supplied, cell death will occur within minutes without reperfusion. Around areas of infarction there is an ischaemic penumbra. Interventions to preserve function in the penumbral area are the key to optimising outcome.

Global hypoxic-ischaemic conditions are often secondary to respiratory or cardiovascular insufficiency, seen most severely in cardiorespiratory arrest. Recovery depends on rapid reversal of the primary cause. MRI examination of patients with persistent disorders of consciousness following resuscitation from cardiac arrest have shown regions of pathological white matter signals in the frontal and occipital lobes and in the periventricular regions.[13] The total volumes of the lesions have been associated with the severity of the patients' outcomes. These patterns demonstrate the different vulnerabilities of particular areas of the brain to ischaemia-hypoxia.

Secondary injury may be initiated as a consequence of the primary injury. The duration and severity of secondary insults can have a significant effect on patient outcome and present an opportunity for prevention or early clinical intervention.[14–17] Intracranial secondary injury may be caused by expansion of intracranial haematomas or the development of cerebral oedema causing pressure effects on more distant parts of the brain, distortion of blood supply or further axonal shearing. Shift of vital structures can ultimately lead to herniation of the brain. Secondary seizure activity can rapidly deplete the brain's supply of metabolites.

Systemic secondary insults include hypoxia, hypotension, hyper- or hypocarbia, hyperthermia, hyper- and hypoglycaemia, anaemia and electrolyte disturbances. Many studies have demonstrated the importance of the duration and severity of secondary insults on the outcome from traumatic brain injury (Table 52.1).

Table 52.1 Effects of secondary injuries on outcome from traumatic brain injury

INSULT	IMPACT ON MORTALITY	IMPACT ON GLASGOW OUTCOME SCORE
Duration of SBP <90 mm Hg	Yes	Yes
Duration of Sa_{O_2} <90%	Yes	No
Duration of temp >38°C	Yes	No
Duration of ICP >30 mm Hg	Yes	No
Duration of CPP <50 mm Hg	Yes	No

CPP, cerebral perfusion pressure; *ICP*, intracranial pressure; *SBP*, systolic blood pressure.

Although hyperventilation of patients with severe brain injury has previously been recommended as a short-term measure to manage elevated ICP before more definitive measures can be employed, there is now evidence of the effects of hypocarbia on cerebral vasculature with vasoconstriction and secondary ischaemia/hypoxia. Levels of $PaCO_2$ below 4 kpa should be avoided.[8]

Anaemia has been associated with poorer outcomes in traumatic brain injury (TBI), aneurysmal SAH, ICH and ischaemic stroke. Transfusion improves brain oxygenation in some patients with TBI.[18] Most critical care units now adopt a restrictive strategy to red cell transfusion using a trigger haemoglobin around 7–8 g/dL. In patients with TBI, neither administration of erythropoietin nor maintaining a haemoglobin concentration >10 g/dL have resulted in improvement in neurological outcome and the 10 g/dL threshold was associated with a greater incidence of adverse events.[19]

The brain is particularly vulnerable to disturbances of osmolality.[20,21] Under physiological conditions, brain osmolality is in equilibrium with extracellular fluid osmolality. When hyponatraemia occurs, the reduction in plasma osmolality causes water movement into the brain along the osmotic gradient, causing cerebral oedema. Cerebral volume increases by around 7% for every three milli-osmolar reduction in osmolality.

METABOLIC AND BIOCHEMICAL PROCESSES IN CEREBRAL INJURY

The pathophysiology of brain injury is complex (Fig. 52.5). Even brief disturbances in CBF and delivery of substrates can initiate a cascade of events leading to cellular death.[22] Different areas of brain have differing thresholds for damage, with the cell bodies (grey matter) being more resilient than the white matter (axons). Anaerobic metabolism results in intracerebral acidosis with accumulation of lactic acid and hydrogen ions. Loss of the normal homeostatic mechanisms responsible for the maintenance of ion gradients results in abnormal sodium, potassium, calcium and chloride movements and the failure of glutamate reuptake into

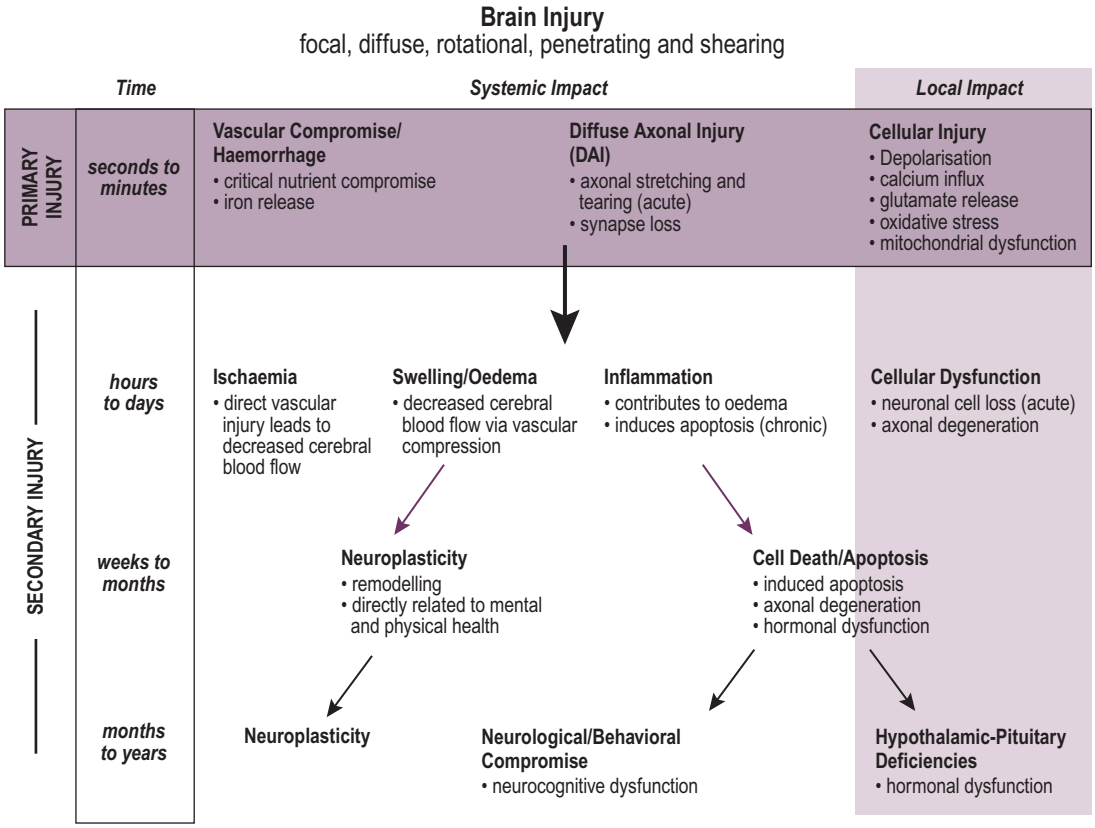


Figure 52.5 Hypothesised model for progression from primary to secondary injury after trauma to the central nervous system. *Modified from Reifschneider K, Auble BA, Rose SR. Update of endocrine dysfunction following paediatric traumatic brain injury.* J Clin Med. *2015;4(8):1536–1560 (with permission).*

cells. Glutamate and aspartate are the main excitatory neurotransmitters in the brain. When uptake mechanisms fail, toxic levels of glutamate can accumulate in the extracellular space, causing a surge of neuronal activity and membrane depolarisation. The increases in intracellular calcium and sodium activate pathways mediated by Ca^{2+} dependent enzymes. The restriction of oxygen and substrates to mitochondria induces a cellular metabolic crisis with disruption of cell membranes and organelles, activation of cellular apoptosis, activation of macrophages and platelet aggregation causing secondary disturbances of the microvasculature. Cytotoxic oedema occurs due to failure of ionic pumps with subsequent ion and fluid shifts. Vasogenic oedema is due to mediator release with damage to endothelium, basement membranes and glial cells with breakdown of the blood-brain barrier.

CEREBRAL PROTECTIVE STRATEGIES

For all patients, including those with brain injury, the priorities are the assessment and management of airway, breathing and circulation (ABC) over assessment of the neurological status (D – disability). For patients who have sustained major trauma, control of catastrophic haemorrhage is now included before ABC (C-ABC). Cerebral protective strategies must start pre-hospital to maximise the opportunities for a good neurological outcome.

AIRWAY

Recommendations regarding securing of the airway in patients with brain injury include those patients with the following[23]:

- Glasgow Coma Score ≤8, or with a significantly deteriorating conscious level (i.e. fall in motor score of ≥ two points)
- Loss of protective laryngeal reflexes
- Hypoxia (Pa_{O_2} <13 kPa on oxygen)
- Hypercarbia ($PaCO_2$ >6 kPa)
- Spontaneous hyperventilation causing $PaCO_2$ <4.0 kPa
- Bilateral fractured mandible or copious bleeding into the mouth (e.g. from skull base fracture)
- Seizures

The projected clinical course of the patient should also be considered. Those requiring transfer for definitive care or who are likely to require surgery for other conditions may require early intubation.

OXYGEN

The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report, 'Trauma: who cares?' published in 2007 found that administration of oxygen was only documented to have occurred in 78% of patients with neurological injury and that peripheral oxygen saturations of <95% occurred in 28% of patients pre-hospital.[24] In mechanically ventilated patients with TBI, avoidance of hypoxia may require application of positive end-expiratory pressure (PEEP) especially in patients with polytrauma. Although there is a theoretical risk that the increase in intrathoracic pressure can cause increased cerebral blood volume (CBV) and ICP, application of PEEP up to 15 cm H_2O has been used successfully in cases of refractory hypoxaemia.[25] National Institute for Health and Clinical Excellence (NICE) recommendations are that patients with acute stroke should have supplemental oxygen if the peripheral oxygen saturations fall below 95%.[26]

CARBON DIOXIDE

Tight control of $PaCO_2$ is required for all mechanically ventilated patients with acute cerebral injury. This can create difficulties in patients with co-existent lung disease or acute respiratory distress syndrome (ARDS) where a balance needs to be struck between the effects of a raised $PaCO_2$ on the brain and lung-protective strategies.[27–29] As detailed earlier, a target $PaCO_2$ of 4.5–5 kPa is usual in the acute stages of injury.

CEREBRAL PERFUSION (BLOOD PRESSURE TARGETS)

Cerebral perfusion depends on MAP and ICP. If the ICP is elevated due to the presence of intracranial haemorrhage or swelling, MAP must be increased to maintain CPP. Many patients with isolated acute intracranial injury have an initial period of arterial hypertension. Generally this will reduce spontaneously or with simple measures such as analgesia, relieving hypoxia or hypercarbia, and ensuring that the patient does not have other systemic disturbances such as urinary retention. There have been concerns that reducing the blood pressure acutely may risk the perfusion of penumbral areas and worsen the clinical outcome. Recent studies have shown benefit with intensive management of elevated blood pressure for patients with spontaneous ICH and in the early phase of management of SAH before the aneurysm is secured.[30] In patients with acute ischaemic stroke, the blood pressure needs to be less than 185/110 mm Hg prior to administration of thrombolytic therapy and controlled <180/105 mm Hg for the next 24 hours thereafter.

For patients who are unconscious following traumatic brain injury, it is generally recommended that the MAP target should be >80 mm Hg with the presumption that ICP is at least 20 mm Hg. This can present a challenge, especially with multiply injured patients. A patient who is hypotensive despite resuscitation should not be transported to specialist care until the cause has been identified and the patient stabilised. Persistent hypotension will significantly adversely affect the neurological outcome.

FLUIDS

Isotonic crystalloid and blood (if required) are the mainstays of fluid replacement in patients with cerebral injury; 0.9% saline is the only isotonic crystalloid solution that is commonly available. Gelatins, albumin, Ringer's lactate (compound sodium lactate), Ringer's acetate and Plasma-Lyte should be avoided as all are hypotonic when real osmolality (mosm/kg) is measured. The Brain Trauma Foundation (BTF) recommends that the sodium be kept >140 mmol/L for patients with TBI.[31] This avoids the risk of worsening cerebral oedema. Hyperosmolar therapy such as mannitol (2 mL/kg of a 20% solution) or hypertonic saline are often used when ICP is critically elevated. Despite clear effectiveness on measured ICP, there remains little evidence of improvement in clinical outcomes.[32]

POSITIONING 30 DEGREE HEAD UP (WITH SPINAL PRECAUTIONS)

Measures such as elevating the head of the bed by 30 degrees, ensuring the head is in a neutral position and in alignment with the body are important, simple steps that can reduce ICP. For patients with potential spinal injuries, the whole bed should be tilted.

TEMPERATURE CONTROL

Pyrexia is common following acute brain injury. Vigilance for possible infective sources, drug reactions or physical causes such as venous thromboembolism is essential. Central (neurogenic) fever can occur, thought due to disturbance of temperature regulation in the hypothalamus. It is uncommon and characterised by a constant fever which is often >40°C. As the normal regulatory point has been altered, patients characteristically have an absence of the measures normally taken to mitigate hyperthermia, such as sweating.[33] Maintenance of normothermia is common practice in specialist intensive care units (ICUs). Although therapeutic hypothermia has been shown to reduce ICP in patients with TBI, its widespread use has not been found to be beneficial in clinical trials.[11] Targeted temperature

management remains recommended for patients who remain unresponsive after resuscitation from cardiac arrest.[10]

SEDATION/ANALGESIA

Patients requiring intubation for cerebral protection are usually managed using a rapid sequence induction technique (with in-line stabilisation of the cervical spine for those with potential trauma). The use of an opiate is recommended to mitigate rises in ICP. The induction agent and dose used should be chosen to ensure maintenance of an adequate MAP. Commonly, barbiturates or propofol are used. Ketamine may be useful in haemodynamically unstable patients. The concerns regarding potential increases in ICP and cerebral metabolic rate with ketamine appear to be clinically unfounded.[34,35] Following intubation and ventilation, sedation in brain-injured patients is commonly maintained with continuous intravenous infusions of propofol or midazolam. Both reduce the cerebral metabolic rate for oxygen and CBF. High doses are often required to decrease the ICP. Use of continuous infusions of an opiate may help in reducing the amount of sedative required especially if there are concerns regarding propofol infusion syndrome.

SEIZURE CONTROL

Risk factors for early seizures following trauma (within 7 days of injury) include: Glasgow Coma Score (GCS) ≤10; immediate seizures, post-traumatic amnesia >30 minutes, linear or depressed skull fracture, penetrating head injury, subdural, epidural, or intracerebral haematoma, cerebral contusions, age ≤65 years, or chronic alcoholism.[31] Post-traumatic epilepsy is defined as recurrent seizures occurring more than 7 days following injury. The BTF recommends the use of phenytoin to decrease the incidence of early seizures when the overall benefit is felt to outweigh the potential complications associated with treatment.[31]

Seizures occur at the time of bleeding in around 7% of patients with SAH.[36] Another 10% will develop seizures over the first few weeks. Risk factors for early seizures include middle cerebral artery (MCA) aneurysm, thickness of acute subarachnoid clot, associated ICH, re-bleeds, cerebral infarction, poor neurological grade and mode of treatment with endovascular treatment having a lower risk of seizures.[36] The European Stroke Organisation recommends antiepileptic treatment only for those patients with overt seizures. The American Heart Association (AHA)/American Stroke Association guidance states that prophylactic anticonvulsants may be considered in the immediate post-haemorrhagic period.[37] Seizures occur in <16% of patient within 1 week after ICH. A cortical location of the ICH is the most important risk factor for early seizures. Prophylactic anticonvulsant medication has not been shown to be beneficial and the AHA recommends only treatment of clinical seizures.[38]

GLUCOSE CONTROL

Hyperglycaemia has been associated with poorer outcomes for a wide range of acute neurological conditions including TBI, SAH, ICH and acute ischaemic stroke.[39] Studies of tight glycaemic control have been disappointing and guidelines recommend the avoidance of both hyperglycaemia and hypoglycaemia.

SPECIFIC PHARMACOLOGICAL INTERVENTIONS

Although many potential neuroprotective agents have been tried, most clinical studies have failed to show outcome benefits.[22] Nimodipine is used to prevent cerebral vasospasm following aneurysmal SAH.[40] The lack of evidence regarding pharmacological interventions emphasises the importance of the adoption of simple protective measures and rapid access to specialist care.

SPECIALIST MONITORING

INTRACRANIAL PRESSURE

The major intracranial contents are the brain, blood (both arterial and venous), and cerebrospinal fluid (CSF). When a new intracranial mass is introduced (haemorrhage, hydrocephalus or cerebral oedema), a compensatory change in volume must occur through a reciprocal decrease in venous blood or CSF to maintain a constant total intracranial volume. This is the Monro-Kellie doctrine. In young children, with open fontanelles and whose sutures have not yet fused, the cranium can expand to physically accommodate extra volume. In the normal situation, changes in intracerebral volume produce little or no change in ICP and the compensatory reserve is good. If compensatory reserve is poor, any changes in intracerebral volume produce a rapid rise in ICP.

Although there is a lack of Class 1 evidence to support the measurement of ICP and the targeting of CPP in severe head injury, there is good evidence that measurement of these as part of a guideline of care on specialist units results in improvements in mortality and functional outcomes following brain injury.[31] Measurement of ICP may be of use in a number of other neurological conditions.[41] The value of ICP-based management for non-traumatic conditions is even less clear than in traumatic brain injury.

The devices commonly used to measure ICP are intraventricular and intraparenchymal catheter tip microtransducer catheters. Intraparenchymal monitors are most commonly placed by making a small incision in the scalp, screwing a bolt into the skull and then passing a spinal needle through the lumen of the bolt,

puncturing the dura. The monitor is then zeroed to atmospheric pressure before the transducer is passed through the bolt and into the brain parenchyma. The transducer is usually placed into the non-dominant frontal lobe or the dominant frontal lobe if the non-dominant lobe is the primary site of injury. The drift over time of modern intraparenchymal monitors is insignificant, the rates of infection are low and there is no need to routinely change the monitor. Pressure transducers in the subdural or subarachnoid space are now rarely used.

Intraventricular catheters are the gold standard for monitoring ICP and also allow drainage of CSF if the ICP is raised. External ventricular devices (EVDs) can be placed during craniotomy procedures or via a burr hole in similar manner to the intraparenchymal devices. If the ventricles are compressed, placement can be facilitated using ultrasound or stereotactic computed tomography (CT) guidance. The pressure monitor is zeroed to the level of the external auditory meatus. The risks from EVDs include a rate of <5% for placement-associated ICH (although the need for neurosurgical evacuation is far smaller) and <20% for catheter-related infections. Infection rates increase with the duration of placement and can be reduced by strict attention to asepsis during manipulation or use of antibiotic or silver-impregnated catheters.

Non-invasive methods of measuring ICP include transcranial Doppler (TCD), measurement of optic nerve sheath diameter and tympanic membrane displacement. Operator experience and reproducibility have limited the clinical applications of these techniques.

INTRACRANIAL PRESSURE IN NORMAL AND PATHOLOGICAL CONDITIONS

The normal ICP trace looks similar to an arterial trace (Fig. 52.6A). The three peaks are: P1 – the percussion wave caused by arterial pressure transmitted from the choroid plexus to the ventricle; P2 – the tidal wave thought to be due to brain compliance; and P3 – the dicrotic wave resulting from closure of the aortic valve. If the intracranial volume is increased, the ICP waveform shows an initial increase in amplitude, although the mean ICP remains largely unaltered. As the brain compliance reduces further, the P2 component of the wave exceeds P1 and the wave becomes broader (see Fig. 52.6B).

In 1960, Lundberg described fluctuations in ICP waves (Fig. 52.7).[42] Lundberg A waves or plateau waves are slow vasogenic waves seen in patients with critical cerebral perfusion. These waves can reach 50–100 mm Hg and last between 5–20 minutes before spontaneously subsiding. Plateau waves cause critical cerebral ischaemia within minutes and are thought to result from spontaneous reductions in MAP, resulting in cerebral vasodilatation. This results in increased ICP and further reduction in CPP until maximal cerebral vasodilatation occurs and the wave plateaus. Early termination of Lundberg A waves can occur if MAP is increased, thus restoring CPP. Plateau waves are always pathological and indicative of reduced cerebral compliance. Lundberg B waves are smaller changes in ICP that occur every 30 seconds to a few minutes and can be seen in normal individuals. ICP rises to levels 20–30 mm Hg above baseline before falling. Lundberg C waves are of little clinical importance. They are of low amplitude and occur with a frequency of 4–8/min and are associated with variations in blood pressure.

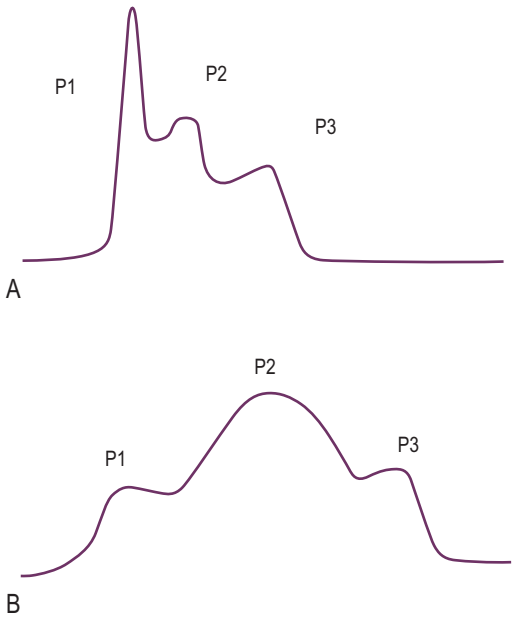


Figure 52.6 Intracranial pressure waveforms in (A) the normal state and (B) when brain compliance is reduced.

OTHER FORMS OF NEUROLOGICAL MONITORING

Patients with neurological illness can be monitored using a wide range of different techniques depending upon the condition and the institution where they are treated. In many specialist ICUs these techniques may be combined, often known as multimodality monitoring (MMM). Despite widespread use in specialist centres, there is limited evidence to support their effectiveness in improving outcomes.[43,44]

CEREBRAL OXYGENATION

Brain tissue oxygenation can be assessed using invasive or non-invasive methods. Intraparenchymal probes are available that measure brain oxygen content (Pbt_{O_2})

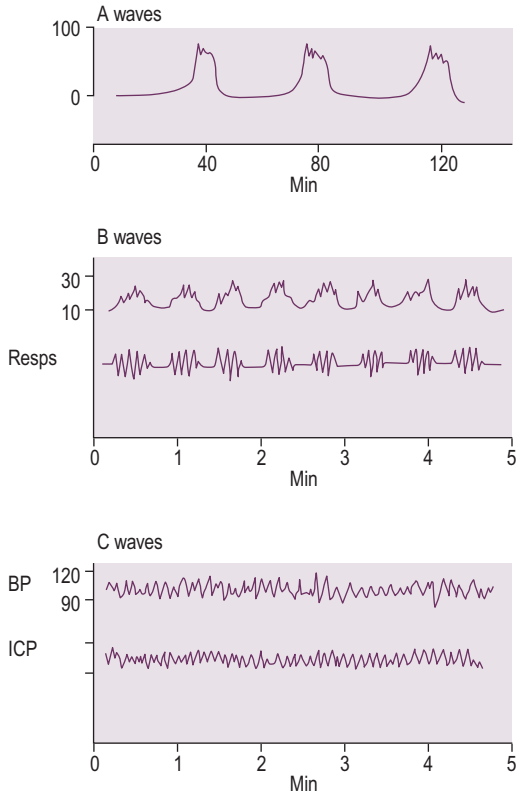


Figure 52.7 Lundberg waves. *A waves* are plateau waves of 50–100 mm Hg lasting 5–20 minutes that compromise CPP. *B waves* are smaller changes in ICP that occur every 30 seconds to a few minutes and may be associated with variations in partial pressure of oxygen and carbon dioxide due to changes in breathing patterns. *C waves* are of low amplitude, occur with a frequency of 4–8/min and are associated with variations in blood pressure. *BP*, blood pressure; *ICP*, intracranial pressure.

in the adjacent white matter. $P\text{bt}_{O_2}$ is the product of CBF and the arteriovenous tension of oxygen; brain oxygenation depends on both the adequate supply of oxygen and its extraction. The normal range of $P\text{bt}_{O_2}$ is 20–35 mm Hg. A level below 20 mm Hg has been suggested as the threshold for therapeutic intervention with increased morbidity and mortality associated with levels less than 10 mm Hg.

Jugular bulb venous oxygen saturation ($S\text{jv}_{O_2}$) provides information on the global utilisation of oxygen by the brain. A catheter is placed into the dominant internal jugular vein and advanced into the jugular bulb. Normal values for $S\text{jv}_{O_2}$ are between 55% and 75%. Low levels of $S\text{jv}_{O_2}$ are indicative of ischaemia resulting either from reduced oxygen delivery or increased demand. High levels of $S\text{jv}_{O_2}$ may indicate hyperaemia, reduced demand or tissue death.

Near-infrared spectroscopy (NIRS) measures regional cerebral oxygen saturation by measuring near-infrared light that is reflected from brain chromophores, the most commonly used of which is oxygenated haemoglobin. The changes in the concentration of near-infrared light are measured as it passes through these compounds and these allow calculation of their oxygenation status. Although NIRS has proved useful in vascular and cardiothoracic surgery, its value in the ICU has not been proven.

MICRODIALYSIS

Brain metabolism can be monitored using cerebral microdialysis probes. Dialysis fluid is passed through the catheter which has a semipermeable membrane. This allows molecules below the size of the membrane to equilibrate along the concentration gradient. The technique analyses substrates such as lactate, pyruvate, glucose, glutamate and glycerol in the extracellular fluid of subcortical white matter. Glutamate is an excitatory neurotransmitter that is associated with injury and inflammation. Glycerol is a lipid-rich component of neurons and is indicative of irreversible cell death when levels are elevated. Lactate, pyruvate and the lactate/pyruvate ratio are used as markers of hypoxia or ischaemia.

CEREBRAL BLOOD FLOW

Invasive measurement of regional CBF can be achieved using thermal diffusion probes or laser Doppler flowmetry. The thermal conductivity of brain tissue varies in proportion to CBF. The most commonly used CBF catheter introduces heat in subcortical white matter and calculates the rate of temperature dissipation at a set distance, allowing calculation of local CBF. Laser Doppler flowmetry involves placement of a small Doppler probe within the brain tissue. Doppler change of laser light is used to measure the movement of red cells within the cerebral microcirculation. Both techniques are limited to the assessment of a small area of cerebral tissue.

TCD ultrasound measures blood flow velocity in the major intracranial vessels. Although TCD measures velocity rather than flow, it can be used to assess relative changes in CBF. TCD is most widely used to assess vasospasm following SAH, high flow velocity being indicative of a reduction in vessel diameter. Comparison of the velocities in the MCA and the external carotid artery (the Lindegaard ratio) can help distinguish between vasospasm and hyperaemia.

ELECTROENCEPHALOGRAPHY

The EEG represents the summation of the brain's electrical activity as recorded from the scalp. It can be used to detect seizure activity, especially when there

is concern regarding non-convulsive status epilepticus, to monitor the response to antiepileptic therapy and to help to prognosticate in patients with persistent coma.[45] EEG monitoring is also useful in diagnosing pseudo-status epilepticus due to psychogenic problems, allowing rapid withdrawal of inappropriate drug therapies.

TIMELINESS OF SPECIALIST CARE

There is a wide body of evidence supporting the care of brain-injured patients in specialist facilities which are often distant to the hospital of first attendance.[46–50] Although many secondary preventive measures can be successfully applied pre-hospital or in a regional hospital prior to transfer to definitive care, rapid diagnosis and transfer is essential to optimise outcomes. The Society of British Neurosurgeons recommends the evacuation of acute extradural or subdural haemorrhages within 4 hours. Major trauma networks advocate direct transfer to specialist care if patients are within a certain time of the specialist centre. Automatic admission criteria have been developed to facilitate rapid transfer from other hospitals without waiting for 'permission' to transfer.[51]

The primary treatment of SAH is occlusion of any identifiable aneurysm that has ruptured. Up to 15% of patients re-bleed within a few hours of the initial bleed, often before definitive treatment can be undertaken. The European Stroke Organisation recommends that the aneurysm should be treated as early as possible to reduce the risk of re-bleeding, ideally within 72 hours of onset of first symptoms.[36] The volume of cases treated and the availability of endovascular services and neurological intensive care are also important determinants of outcome from SAH. The American Heart Association recommends that low-volume hospitals (<10 SAH cases per year) should consider early transfer of patients to high-volume centres (>35 SAH cases per year) with experienced neurovascular surgeons, endovascular specialists, and neuro-intensive care services.[37] Similarly, ICH is a medical emergency that needs to be diagnosed and managed swiftly. Expansion of the haematoma and clinical deterioration are common in the first few hours. Among patients undergoing head CT within 3 hours of ICH onset, up to 38% have expansion of more than one third of the initial haematoma volume on follow-up CT.[38] While awaiting transfer for specialist care, it is important to minimise the risk of haematoma expansion by fully reversing any prescription anticoagulants and reducing elevated blood pressure.[52]

In several countries, acute stroke care has also been centralised, creating specialist centres to which patients are taken rather than going to the nearest hospital.[53,54] This has increased access to specialist care and thrombolysis. With the advent of other time-critical therapies such as intra-arterial thrombectomy,[55] it is likely that there will be continued centralisation of care for acute stroke.

REHABILITATION

Early access to specialist rehabilitation that continues into the community is essential to maximise the recovery following neurological injury. Early mobilisation has been shown to enhance recovery and improve functional outcomes for patients in acute and intensive care settings including neurosciences ICU.[56] There is now a substantial body of evidence to support the effectiveness and cost-effectiveness of specialist rehabilitation.[57] Despite a longer length of stay, the cost of providing early specialist rehabilitation is offset by longer-term savings in the cost of community care.[58]

KEY REFERENCES

14. Andrews PJD, Piper IR, Dearden NM, et al. Secondary insults during intrahospital transport of head-injured patients. *Lancet*. 1990;335:327–330.
21. van der Jagt M. Fluid management of the neurological patient: a concise review. *Crit Care*. 2016;20:126.
31. *Brain Trauma Foundation*. Guidelines for the management of severe traumatic brain injury, 4th ed; 2016. https://www.braintrauma.org/.
36. Steiner T, Juvela S, Unterberg A, et al. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis*. 2013;35:93–112.
37. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid haemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2012;43:1711–1737.
46. Patel HC, Menon DK, Tebbs S, et al. Specialist neurocritical care and outcome from head injury. *Int Care Med*. 2002;28:547–553.
51. Dickinson P, Eynon CA. Improving the timeliness of time-critical transfers: removing 'referral and acceptance' from the transfer pathway. *JICS*. 2014;15:2–6.
54. Morris S, Hunter RM, Ramsay AIG, et al. Impact of centralising acute stroke services in English metropolitan areas on mortality and length of hospital stay: differences-in-differences analysis. *BMJ*. 2014;349:g4757.
58. Turner-Stokes L, Paul S, Williams H. Efficiency of specialist rehabilitation in reducing dependency and costs of continuing care for adults with complex acquired brain injuries. *J Neurol Neurosurg Psychiatr*. 2006;77:634–639.

Access the complete references list online at http://www.expertconsult.com.

REFERENCES

1. Lovelace WR, Gagge AP. Aero medical aspects of cabin pressurization for military and commercial aircraft. *J Aeronaut Sci*. 1946;13:143–150.
2. Jensen VFH, Bøgh IB, Lykkesfeldt J. Effect of insulin-induced hypoglycaemia on the central nervous system: evidence from experimental studies. *J Neuroend*. 2014;26:123–150.
3. Czosnyka M, Brady K, Reinhard M, et al. Monitoring of cerebrovascular autoregulation: facts, myths, and missing links. *Neurocrit Care*. 2009;10:373–386.
4. Fischer M, Schmutzhard E. Posterior reversible encephalopathy syndrome. *J Neurol*. 2017;264(8):1608–1616.
5. Bartynski W. Posterior reversible encephalopathy syndrome, part 1: fundamental imaging and clinical features. *AJNR Am J Neuroradiol*. 2008;29: 1036–1042.
6. Suzuki N, Hardebo JE, Kahrstrom J, et al. Effect on cortical blood flow of electrical stimulation of trigeminal cerebrovascular nerve fibres in the rat. *Acta Physiol Scand*. 1990;138:307–316.
7. Roy CS, Sherrington CS. On the regulation of the blood supply to the brain. *J Physiol*. 1890;11:85–108, 158.7–158.17.
8. Coles JP, Minhas PS, Fryer TD, et al. Effect of hyperventilation on cerebral blood flow in traumatic head injury: clinical relevance and monitoring correlates. *Crit Care Med*. 2002;30:1950–1959.
9. Lee JH, Kelly DF, Oertel M, et al. Carbon dioxide reactivity, pressure autoregulation, and metabolic suppression reactivity after head injury: a transcranial Doppler study. *J Neurosurg*. 2001;95:222–232.
10. Donnino MW, Andersen LW, Berg KM, et al. Temperature management after cardiac arrest. An advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. *Circulation*. 2015;132:2448–2456.
11. Andrews PJ, Sinclair HL, Rodriguez A, et al. Hypothermia for intracranial hypertension after traumatic brain injury. *NEJM*. 2015;373:2403–2412.
12. Adams H, Mitchell DE, Graham DI, et al. Diffuse brain damage of immediate impact type. Its relationship to 'primary brain-stem damage' in head injury. *Brain*. 1977;100:489–502.
13. Ammermann H, Kassubek J, Lotze M, et al. MRI brain lesion patterns in patients in anoxia-induced vegetative state. *J Neurol Sci*. 2007;260:65–70.
14. Andrews PJD, Piper IR, Dearden NM, et al. Secondary insults during intrahospital transport of head-injured patients. *Lancet*. 1990;335:327–330.
15. Jones PA, Andrews PJ, Midgley S, et al. Measuring the burden of secondary insults in head-injured patients during intensive care. *J Neurosurg Anesthesiol*. 1994;6:4–14.
16. Robertson CS, Valadka AB, Hannay HJ, et al. Prevention of secondary ischemic insults after severe head injury. *Crit Care Med*. 1999;27:2086–2095.
17. Signorini DF, Andrews PJD, Jones PA, et al. Adding insult to injury: the prognostic value of early secondary insults for survival after traumatic brain injury. *J Neurol Neurosurg Psychiatry*. 1999;66:26–31.
18. Zygun DA, Nortje J, Hutchinson PJ, et al. The effect of red blood cell transfusion on cerebral oxygenation and metabolism after severe traumatic brain injury. *Crit Care Med*. 2009;37:1074–1078.
19. Robertson CS, Hannay J, Yamal JM, et al. Effect of erythropoietin administration and transfusion threshold on neurological recovery after traumatic brain injury: a randomized clinical trial. *JAMA*. 2014;312:36–47.
20. Giuliani C, Peri A. Effects of hyponatraemia on the brain. *J Clin Med*. 2014;3:1163–1177.
21. van der Jagt M. Fluid management of the neurological patient: a concise review. *Crit Care*. 2016;20:126.
22. Quillinan N, Herson PS, Traystman RJ. Neuropathophysiology of brain injury. *Anaesthesiol Clin*. 2016;34:453–464.
23. *Association of Anaesthetists of Great Britain and Ireland*. Recommendations for the safe transfer of patients with brain injury; 2006. https://www.aagbi.org/sites/default/files/braininjury.pdf.
24. *National Confidential Enquiry into Patient Outcome and Death*. Trauma: who cares? 2007. http://www.ncepod.org.uk/2007t.html.
25. Nemer SN, Caldeira JB, Santos RG, et al. Effects of positive end-expiratory pressure on brain tissue oxygen pressure of severe traumatic brain injury patients with acute respiratory distress syndrome: a pilot study. *J Crit Care*. 2015;30:1263–1266.
26. *National Institute for Health and Clinical Excellence*. Stroke and transient ischaemic attack in over 16s: diagnosis and initial management; 2008. https://www.nice.org.uk/guidance/cg68/chapter/1-Guidance.
27. Nyquist P, Stevens RD, Mirski MA. Neurologic injury and mechanical ventilation. *Neurocrit Care*. 2008;9:400–408.
28. Mascia L. Acute lung injury in patients with severe brain injury: a double hit model. *Neurocrit Care*. 2009;11:417–426.
29. Young N, Rhodes JK, Mascia L, et al. Ventilatory strategies for patients with acute brain injury. *Curr Opin Crit Care*. 2010;16:45–52.
30. Carcel C, Sato S, Anderson CS. Blood pressure management in intracranial haemorrhage: current challenges and opportunities. *Curr Treat Options Cardio Med*. 2016;18:22.
31. *Brain Trauma Foundation*. Guidelines for the management of severe traumatic brain injury, 4th ed; 2016. https://www.braintrauma.org/.
32. Boone MD, Oren-Grinberg A, Robinson TM, et al. Mannitol or hypertonic slaine in the setting of traumatic brain injury: what have we learned? *Surg Neurol Int*. 2015;6:177.

33. Agrawal A, Timothy J, Thapa A. Neurogenic fever. *Singapore Med J*. 2007;4:492–494.
34. Zeiler FA, Teitelbaum J, West M, et al. The ketamine effect on intracranial pressure in nontraumatic neurological illness. *J Crit Care*. 2014;29:1096–1106.
35. Zeiler FA, Teitelbaum J, West M, et al. The ketamine effect on ICP in traumatic brain injury. *Neurocrit Care*. 2014;21:163–173.
36. Steiner T, Juvela S, Unterberg A, et al. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis*. 2013;35:93–112.
37. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid haemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2012;43:1711–1737.
38. Hemphill JC 3rd, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral haemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46:2032–2060.
39. Godoy DA, Behrouz R, Di Napoli M. Glucose control in acute brain injury: does it matter? *Curr Opin Crit Care*. 2016;22:120–127.
40. Pickard JD, Murray GD, Illingworth R, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. *BMJ*. 1989;298:636–642.
41. Helbok R, Olson DWM, Le Roux PD, et al. Intracranial pressure and cerebral perfusion pressure monitoring in non-TBI patients: special considerations. *Neurocrit Care*. 2014;21:S85–S94.
42. Lundberg N. Continuous recording and control of ventricular fluid pressure in neurosurgical practice. *Acta Psychiatr Scand Suppl*. 1960;36:1–193.
43. Le Roux P, Menon DK, Citerio G, et al. Consensus summary statement of the international multidisciplinary consensus conference on multimodality monitoring in neurocritical care. *Int Care Med*. 2014;40:1189–1209.
44. Roh D, Park S. Brain multimodality monitoring: updated perspectives. *Curr Neurol Neurosci Rep*. 2016;16:56.
45. Claassen J, Taccone FS, Horn P, et al. Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM. *Int Care Med*. 2013;39:1337–1351.
46. Patel HC, Menon DK, Tebbs S, et al. Specialist neurocritical care and outcome from head injury. *Int Care Med*. 2002;28:547–553.
47. Diringer MN, Edwards DF. Admission to a neurologic/neurosurgical intensive care unit is associated with reduced mortality rate after intracerebral haemorrhage. *Crit Care Med*. 2001;29:635–640.
48. Samuels O, Webb A, Culler S, et al. Impact of a dedicated neurocritical care team in treating patients with aneurysmal subarachnoid haemorrhage. *Neurocrit Care*. 2011;14:334–340.
49. Sadek AR, Eynon CA. The role of neurosciences intensive care in trauma and neurosurgical conditions. *Br J Hosp Med*. 2013;74:552–557.
50. Sadek AR, Damian M, Eynon CA. The role of neurosciences intensive care in neurological conditions. *Br J Hosp Med*. 2013;74:558–563.
51. Dickinson P, Eynon CA. Improving the timeliness of time-critical transfers: removing 'referral and acceptance' from the transfer pathway. *JICS*. 2014;15:2–6.
52. Kuramatsu JB, Gerner ST, Schellinger PD, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral haemorrhage. *JAMA*. 2015;313:824–836.
53. Weir NU, Buchan AM. A study of the workload and effectiveness of a comprehensive acute stroke service. *J Neurol Neurosurg Psychiatry*. 2005;76:863–865.
54. Morris S, Hunter RM, Ramsay AIG, et al. Impact of centralising acute stroke services in English metropolitan areas on mortality and length of hospital stay: differences-in-differences analysis. *BMJ*. 2014;349:g4757.
55. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723–1731.
56. Olkowski BF, Shah SO. Early mobilization in the Neuro-ICU: how far can we go? *Neurocrit Care*. 2017;27(1):141–150.
57. Turner-Stokes L, Pick A, Nair A, et al. Multi-disciplinary rehabilitation for acquired brain injury in adults of working age. *Cochrane Database Syst Rev*. 2015;(12):CD004170, doi:10.1002/14651858.CD004170.pub3.
58. Turner-Stokes L, Paul S, Williams H. Efficiency of specialist rehabilitation in reducing dependency and costs of continuing care for adults with complex acquired brain injuries. *J Neurol Neurosurg Psychiatr*. 2006;77:634–639.

53

Brain death

Martin Smith

Death has important medical, legal and societal implications, making it imperative that its determination is accurate, reliable and certain. It was historically defined only by confirmation of cessation of cardiorespiratory function, but the concept of brain death, now more accurately referred to as the determination of death by neurological criteria, was introduced into clinical practice almost 50 years ago. From a legal and scientific perspective, brain death is a definable event which is established as a legitimate definition of death in most countries in the world. Its confirmation provides a professional and legal framework for the withdrawal of life-sustaining therapies from an individual who can no longer derive benefit from them, and additionally allows the retrieval of organs for transplantation.

BRAIN DEATH EPIDEMIOLOGY AND PATHOPHYSIOLOGY

The incidence of brain death is related to several factors including national rates of catastrophic brain injury, access to intensive care and neurosurgical services, the presence of organ donation and transplantation systems, and patterns of professional practice. The true international incidence of brain death is unknown, although it is estimated to account for 1%–2% of all deaths in countries with advanced health care systems and 5%–10% of deaths in comatose patients admitted to intensive care units.[1] Rates of brain death are declining as the incidence of catastrophic brain injury reduces in some parts of the world, and brain injury management improves.

The principal causes of brain death in adults are severe traumatic and haemorrhagic brain injury and cerebral hypoxia–ischaemia. Brain death results from a sustained rise in intracranial pressure above systemic arterial pressure leading to the irreversible cessation of brain activity due to permanent loss of blood flow and oxygen supply to the brain. Brainstem reflexes are lost sequentially in a craniocaudal direction; this process may take several hours to complete but finally results in apnoea due to failure of the medulla oblongata. Because of the fundamental controlling role of the brainstem, cardiovascular and other systemic organ system functions deteriorate after the onset of brain death resulting in profound physiological instability and ultimately asystolic cardiac arrest.[2]

DEVELOPMENT OF BRAIN DEATH CRITERIA

A state of unconsciousness, brainstem areflexia and absence of spontaneous respiration in patients supported by mechanical ventilation was first reported in 1959 by Mollaret and Goulon who described this state as 'le coma dépasse' – literally, a state beyond coma. Almost 10 years later, in 1968, *ad hoc* Committee of the Harvard Medical School in the United States developed and published the first widely accepted standard for the definition and confirmation of brain death.[3] Because the brainstem is responsible for consciousness, breathing and circulatory regulation, and conduction of virtually all throughput to and from the brain, it is loss of brainstem function that is fundamental to the state of irreversible coma described in the Harvard criteria.[4] This concept was incorporated into the United Kingdom criteria for the diagnosis of brain (stem) death which was first published in 1976.[5] A 2008 update retains the key components of those original criteria and emphasises that a clinical diagnosis is sufficient for the determination of brainstem death subject to the fulfilment of essential preconditions and exclusion of reversible causes of coma and apnoea.[6]

Unlike in the United Kingdom, the 1981 Uniform Determination of Death Act (UDDA) defined brain death in the United States as the irreversible cessation of functions of the *entire* brain.[7] The UDDA specified that, like death determined by cessation of cardiorespiratory function, the determination of brain death should be made in accordance with accepted medical standards. The American Academy of Neurology published practice parameters in 1995, updated in 2010, which have become the accepted medical standards for the determination of brain death in the United States.[8]

WHOLE BRAIN AND BRAINSTEM DEATH

There is broad consensus, particularly in Western cultures, that human death is ultimately death of the brain and that this crucially involves the irreversible loss of

ABSTRACT

Death was historically defined only by confirmation of cessation of cardiorespiratory function, but the concept of brain death, now more accurately referred to as the determination of death by neurological criteria, was introduced into clinical practice almost 50 years ago. From a legal and scientific perspective, brain death is a definable event which is established as a legitimate definition of death in most countries in the world. Practice guidelines for the determination of brain death are widely available but there is large international variation in their content and application. Clinical determination is the gold standard for the diagnosis of brain death in many countries, but ancillary investigations are required in some. The clinical determination of brain death incorporates three sequential but interdependent steps – fulfilment of essential preconditions, exclusion of reversible causes of coma and apnoea, and confirmation of brainstem areflexia and apnoea.

KEYWORDS

Brain death
brainstem death
apnoea test
ancillary tests
organ donation

the capacity for consciousness combined with loss of the capacity to breathe. Taken together, these elements represent the most basic manner in which human beings can interact with their environment. Despite this consensus, debate continues over the extent of brain functions that must cease in order to satisfy a definition of brain death which, as outlined above, is defined in two different ways based on 'whole' brain and 'brainstem' formulations.

The determination of whole brain death requires confirmation, in theory at least, of the loss of *all* brain function, including, but not limited to, the brainstem. The diagnosis of brainstem death on the other hand requires confirmation of absence of brainstem function; it does not require that all other brain functions have ceased, only that any functions that might persist should not indicate any form of consciousness. The whole brain formulation is the standard for the determination of death by neurological criteria in many parts of the world, including the United States and most European countries, whereas the United Kingdom retains the brainstem formulation. The clinical determination of whole brain and brainstem death is identical, and highlighting differences between them is an unnecessary cause of confusion and controversy.[9]

Death is not a single event but a process that leads progressively to the failure of all functions that constitute the life of the human organism.[10] Once a threshold of irreversibility has been reached, and permanent cessation of cardiorespiratory function or brain death (however defined) marks such a point, it is not necessary to wait for the death of the whole organism for the inevitable consequence of its biological death to be certain. It is universally accepted that cessation of cardiorespiratory function marks the death of an individual, but nobody would claim that the whole human organism is dead at this point. The same is not yet the case for brain death. Reports of brain dead patients 'being kept alive on a ventilator' are familiar, and elements of the public continue to refuse to accept that brain dead patients are actually dead.[11] In a 2015 international survey, 57% of physician respondents also did not believe that brain death equates to death defined by cardiorespiratory criteria.[12] To minimise such confusion, it has been recommended that death should no longer be defined anatomically using terms such as cardiac or brain death, which inaccurately imply death of an individual organ, but functionally based on confirmation of permanent non-function of the brain subsequent to circulatory arrest or catastrophic brain injury.[1]

VARIABILITY IN BRAIN DEATH PRACTICES

Although confirmation of brain death is legally accepted as the death of an individual in the majority of countries, there are major differences between, and even within, countries in the procedures for its determination.[12] Some of these arise because of legal, religious and cultural differences, whereas others relate to different approaches to the clinical determination of brain death and variable requirements for ancillary investigations. In addition, there are well-documented failures to adhere to clinical practice guidelines for the determination of death by neurological criteria.[13,14] Another factor contributing to practice variability is that, unlike circulatory death which is relatively easily diagnosed, the determination of brain death is a much more complex process which requires expertise, familiarity and diligence.[7]

The variability in brain death practices risks adversely influencing public and professional trust, and an international standard for the diagnosis of brain death would reduce such variability and increase public and professional confidence in the credibility of the determination of death by neurological criteria.[10] While it is by no means certain that a true international consensus can ever be reached, there are fundamental components that are common to the determination of brain death in all countries (Box 53.1).[1]

Box 53.1 Areas of consistency in international guidelines for the determination of brain death

- Unresponsive coma with an established aetiology
- Absence of reversible conditions
- Absence of cortical or brainstem-mediated motor responses
- Absent brainstem reflexes
- Loss of the capacity to breathe

GENERAL PRINCIPLES FOR THE CLINICAL DETERMINATION OF BRAIN DEATH

The majority of countries have followed the lead of the United States and United Kingdom in specifying that a clinical diagnosis of brain death is sufficient for the determination of death in adults. Three sequential but interdependent steps form the diagnostic criteria – fulfilment of essential preconditions, exclusion of reversible causes of coma and apnoea, and clinical confirmation of brainstem areflexia and apnoea (Fig. 53.1). While the third step, the clinical examination, demonstrates the absence of brainstem function, it is the first two that determine irreversibility and which require a greater degree of expertise to interpret.[15]

PRECONDITIONS

The patient's comatose condition and apnoea must be due to irreversible brain damage of known aetiology. This is established by clinical examination and cranial imaging that confirms a catastrophic brain injury.

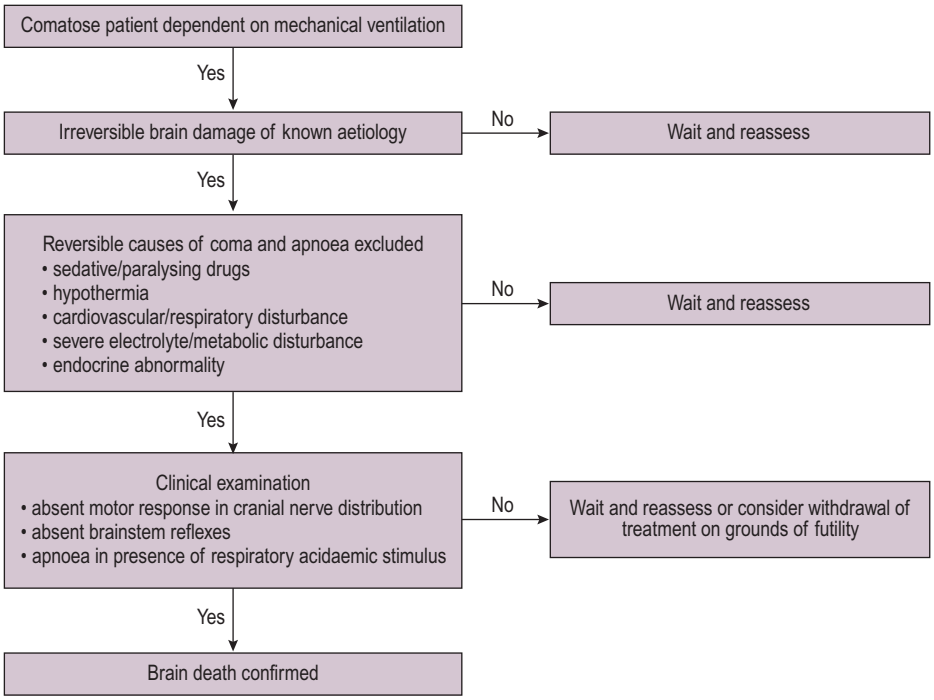


Figure 53.1 The three sequential but interdependent steps that form the criteria for the clinical determination of death by neurological criteria.

Irreversibility might be obvious within a relatively short period of time after severe traumatic brain injury or intracranial haemorrhage, but it may take longer to establish the diagnosis and be confident of prognosis in patients with hypoxic-ischaemic brain injury.

EXCLUSION OF POTENTIALLY REVERSIBLE CAUSES OF COMA AND APNOEA

Following confirmation of a diagnosis that is compatible with brain death, potentially reversible causes of coma and apnoea must be excluded (Table 53.1). The confounding effects of hypothermia, depressant drugs and severe electrolyte abnormalities are consistently cited in all clinical guidelines, but the thresholds vary between them.[12,16]

DRUG EFFECTS

The effects of sedative and paralysing drugs must be excluded as a cause of the patient's unresponsive state. Sufficient time must be allowed for sedative drugs to be metabolised and excreted; five half-lives in the presence of normal hepatic and renal function are usually considered appropriate. However, the presence of hypothermia as well as hepatic or renal dysfunction brings significant confounders to the confident exclusion of residual drug effects. The serum concentration of some sedatives can be measured, but be difficult to interpret because of the unpredictable effects on consciousness of a given drug concentration in a critically ill brain-injured patient. Administration of specific antagonists to exclude opioid or benzodiazepine effects can also be considered. Ancillary investigations may be used to confirm the diagnosis of brain death in some jurisdictions when sedation drug effects cannot be excluded. Residual pharmacological paralysis should be excluded by 'train-of-four' stimulation to confirm the absence of neuromuscular blockade.

HYPOTHERMIA

Although brainstem reflexes are likely to be absent only if body temperature falls below 28°C, temperatures between 32°C and 34°C have occasionally been associated with impaired consciousness. Most guidelines recommend that core temperature should be at or near normal at the time of the clinical examination.[12,16]

ELECTROLYTE AND ENDOCRINE DISTURBANCE

All guidelines require that there should be no evidence of severe electrolyte or endocrine disturbance, but 'severe' is rarely defined. Diabetes insipidus-related hypernatraemia is a common consequence of brain death and a particular problem. Many guidelines recommend a target plasma sodium concentration, while others acknowledge that delay in clinical testing because of strict adherence to a predetermined plasma sodium concentration is inappropriate in the

Table 53.1 Exclusion of potentially reversible causes of coma and apnoea during the determination of death by neurological criteria

VARIABLE	REQUIREMENTS

Drugs	• No residual sedative drug effects
	  • serum drug levels should be measured where assays are available
	  • no consensus regarding the minimal concentration at which brain death can be diagnosed
	  • consider specific opioid or benzodiazepine antagonists
	• No residual effects of neuromuscular-blocking drugs
	  • presence of deep tendon reflexes
	  • train-of-four present on peripheral nerve stimulation

Hypothermia	• Temperature at or near normal
Cardiorespiratory	• Systolic blood pressure consistently >100 mm Hg • SpO_2 >95%
Electrolytes	• Sodium –120 to 160 mmol/L (guidelines vary) • Normoglycaemia
Endocrine	• Hormonal assays if suspicion of myxoedema or Addisonian crisis

presence of other stigmata of brain death and when the hypernatraemia can be confidently excluded as a cause (rather than a result) of the clinical state. Blood glucose concentration should be normalised prior to and during the clinical examination(s).

Several endocrine abnormalities can be associated with impaired consciousness or present as acute coma, but are rare and unlikely to co-exist in the presence of known primary intracranial pathology. Hormone assays are generally only recommended if there is any clinical suspicion of endocrine disturbance.

CARDIORESPIRATORY DISTURBANCES

The onset of brain death is accompanied by intense circulatory and respiratory disturbance. Oxygen saturation should be maintained greater than 95% and systolic blood pressure above 100 mm Hg before and throughout the clinical examination.

CLINICAL EXAMINATION

The clinical examination is designed to confirm the absence of brainstem reflexes and presence of persistent apnoea, and should be performed only after preconditions have been met and reversible causes of coma excluded.

Box 53.2 Components of the cranial nerve examination to confirm brain death

- Pupils non-reactive to bright light
  - absent pupillary response to sharp changes in the intensity of incident light
  - pupils do not need to be maximally dilated, simply unresponsive
- Corneal reflexes absent
- Oculovestibular reflexes absent
  - no eye movements during or following slow injection of 50 mL ice-cold water over 1 min into each external auditory meatus
  - clear access to tympanic membrane must be confirmed by direct inspection prior to testing
  - head at 30 degrees to the horizontal unless contraindicated by unstable spine injury
- Oculocephalic reflexes absent
  - not required in all jurisdictions
  - eyes remain in mid-position during brisk turning of the head from side to side ('doll's eyes')
  - tested only if cervical-spine integrity ensured
- No facial movement to adequate stimulation in the trigeminal areas
  - usually firm pressure over the supraorbital area or temporomandibular joint
- No facial movement to noxious stimuli in all four limbs
  - spinal reflex limb responses are permissible
- Cough reflex absent
  - no response to tracheal suctioning
- Gag reflex absent
  - no response to stimulation (under direct vision) of the posterior pharynx

Apnoea test

- Absence of respiratory effort observed for >5 min despite a respiratory acidaemia
- $PaCO_2$ must rise to specified target (guidelines vary – most require that $PaCO_2$ should be greater than 8.0 kPa or have increased more than 0.5–2.5 kPa above a baseline of 6.0 kPa > 6.5 kPa)
- SpO_2 >95% throughout
- cardiovascular stability during the test (systolic blood pressure >100 mm Hg)

CRANIAL NERVE EXAMINATION

Assessment of brainstem reflexes is common to all guidelines for the clinical confirmation of brain death (Box 53.2). In most jurisdictions the diagnosis is not invalidated if pupil response, corneal reflex and oculovestibular reflex are not assessable on one side because of injury or disease. Ancillary investigations should be considered if bilateral assessment is impossible. Absence of the oculocephalic reflex ('doll's-eye' movements) is a required component of the clinical diagnosis of brain death in some countries. It can also be used

as a 'screening' test; the presence of eye movements indicates that brainstem function persists.

APNOEA TEST

Confirmation of apnoea is fundamental to the determination of brain death in all guidelines, although end-points differ.[12] While the overall aim is to produce an acidaemic respiratory stimulus, fewer than 60% of jurisdictions specify a $PaCO_2$ target for the end-point of the apnoea test.[16] In others there is no guidance whatsoever or only a stipulation that the ventilator should be disconnected for a defined period of time. The apnoea test should be performed only after brainstem areflexia has been confirmed, and using a technique that minimises the risk of significant hypoxaemia, excessive hypercarbia or changes in mean arterial blood pressure.

The UK guidance provides a structured approach for conduct of the apnoea test which maintains physiological stability and allows successful completion in most circumstances. The patient should be preoxygenated with 100% oxygen for at least 10 minutes, and arterial blood gases measured to correlate $PaCO_2$ with end-tidal carbon dioxide ($ETCO_2$). The ventilation rate is then reduced to allow a slow rise in $ETCO_2$. When $ETCO_2$ rises above 6.0 kPa, arterial blood gases are checked to confirm that $PaCO_2$ is at least 6.0 kPa and pH less than 7.40. In patients with chronic CO_2 retention, $PaCO_2$ can be allowed to rise above 6.5 kPa to generate a pH less than 7.40. The patient is then disconnected from the ventilator, oxygen insufflated at 5 L/min via an endotracheal catheter, and the patient observed for respiratory effort. The ventilator should always be disconnected during the apnoea test because autocycling can incorrectly suggest the presence of spontaneous respirations. Apnoea is confirmed following visual inspection for at least 5 minutes, and after documentation of the absence of spontaneous respiratory activity in the presence of $PaCO_2$ that has increased to the target level. This varies between jurisdictions; most require that it should be greater than 8.0 kPa or have increased by more than 0.5–2.5 kPa above a baseline of 6.0 kPa. The ventilator is then reconnected and minute volume adjusted to allow a gradual return of arterial blood gases to pre-test levels. SpO_2 should be maintained above 95% and systolic blood pressure above 100 mm Hg throughout the apnoea test. If adequate oxygenation proves difficult, a prior recruitment manoeuvre and continuous positive airway pressure via an appropriate circuit (e.g. Mapleson B) minimises the risk of desaturation during the test.

TIMING AND REPETITION OF CLINICAL TESTS

There is no evidence to define a minimum period of observation between the onset of apnoeic coma and clinical examination to ensure irreversibility. Some countries recommend a minimum of 6 hours in all cases, whereas no minimum time is stipulated in others.[16] A period of observation of at least 24 hours is usually required in coma related to hypoxic-ischaemic brain injury.

Two clinical examinations are required to confirm brain death in many jurisdictions, although there is no evidence that a second examination is necessary. A large study of brain dead adults showed that the second examination added nothing to the first, delayed the declaration of death, and reduced organ donation rates.[17] The clinical diagnosis of brain death using standard criteria is robust,[8] and there is an increasing trend towards a requirement for only a single examination. Where two examinations are required, there is often no specified time interval between them. In the United Kingdom, for example, the second examination can be undertaken as soon as arterial blood gases have returned to baseline after the first apnoea test. The legal time for certification of death is usually at the initial confirmation of brain death but, in Australia, the time of death is that of the second confirmatory examination.

The number of doctors required to determine brain death also varies. In most jurisdictions a single doctor is sufficient, but in the United Kingdom, Australia and some states in the United States at least two medical practitioners are required. The base specialty of doctors confirming brain death is stipulated in some countries whereas, in others, relevant competencies are defined.[12] To avoid any conflict of interest, the determination of brain death should not be made by a physician involved with organ transplantation.

ANCILLARY TESTS

Clinical determination is the gold standard for the diagnosis of brain death in many countries, but ancillary investigations are mandatory in some.[18] They are also useful if only a limited clinical examination is possible or when confounding or special conditions are present.[19] Ancillary investigations fall into two main categories assessing brain blood flow or electrophysiological activity, but there are limited data to confirm the applicability and reliability of any ancillary test for any particular circumstance.[20]

ASSESSMENT OF CEREBRAL BLOOD FLOW

Absence of blood flow to the brain is widely accepted to be consistent with brain death. Methods to confirm the absence of cerebral blood flow are less affected by confounding factors such as residual sedation, metabolic disturbance or hypothermia than electrophysiological methods, and are preferred.

CEREBRAL ANGIOGRAPHY

Four-vessel digital subtraction cerebral angiograph (DSA) is the gold-standard confirmatory test for brain

death in some jurisdictions.[18] Following bilateral injection of contrast into vertebral and carotid arteries, absence of flow beyond the foramen magnum in the posterior circulation and beyond the petrosal portion of the carotid artery in the anterior circulation is accepted to be indicative of brain death. DSA is reliable and easy to interpret, but invasive, time-consuming and often available only in neuroscience units. It also requires administration of contrast agents which may adversely affect graft function in donated kidneys.

Non-invasive vascular techniques such as computed tomography (CT) cerebral angiography (CTA) are increasingly employed. CTA has high sensitivity for the confirmation of brain death in individuals who fulfil clinical diagnostic criteria but there is insufficient evidence to support its use as a screening tool.[21] A significant proportion of patients meeting clinical criteria for brain death retain some evidence of contrast in the proximal intracranial arteries with all angiographic techniques. False-negative results occur, particularly after decompressive craniectomy and in the presence of cerebrospinal fluid drains or low arterial blood pressure. Systolic blood pressure should be maintained above 100 mm Hg during blood flow confirmation of brain death.[18]

PERFUSION IMAGING

Contrast-enhanced CT cerebral perfusion techniques are widely available, although there is little evidence of advantages over CTA. Positron emission tomography measures regional cerebral metabolic rate for glucose in addition to regional blood flow. It has theoretical advantages as an ancillary investigation in the diagnosis of brain death but there are currently no data to support its use in this situation. Nuclear imaging techniques are also able to confirm absent cerebral perfusion; an 'empty skull' appearance in which no intracranial contrast is visible is indicative of brain death.[18] False positives are rare, and no contrast agent is required.

TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

Transcranial Doppler (TCD) is a non-invasive bedside investigation that can be used as a confirmatory test during the diagnosis of brain death.[22] When intracranial pressure exceeds mean arterial blood pressure, TCD assessment of blood flow velocity in basal cerebral vessels reveals systolic spikes with reversal of diastolic flow. Absence of a TCD waveform should never be taken as confirmation of absent cerebral blood flow because at least 10% of patients have no acoustic bone window. TCD examination has high sensitivity (86%) and specificity (98%) for the diagnosis of brain death when compared to clinical examination, with very few false-positive cases reported in the literature.[18] There is significant operator dependence, and previous surgery or open ventricular drains make TCD waveform interpretation difficult.

ELECTROPHYSIOLOGY

Electroencephalography (EEG) remains widely used in the diagnosis of brain death despite substantial disadvantages and a requirement for specialist interpretation. The absence of cortical electrical activity during high-sensitivity recordings from 16 or 18 channels over 30 minutes is often taken as confirmatory evidence of brain death. However, an isoelectric cortical EEG does not exclude activity in the brainstem or other deep structures, and electrical activity in some cortical cells does not confirm that the whole brain is functioning.[18] EEG examination is a mandatory part of a brain death diagnosis in many European countries and strongly recommended in some states in the United States where loss of whole brain function must be confirmed. However, EEG is affected by hypothermia and sedation, and therefore of limited value in circumstances where a confirmatory investigation might be required. Some experts argue that the substantial disadvantages of EEG mean that it should no longer be used as an ancillary test for the diagnosis of brain death.[20]

Evoked potentials (EPs) monitor the integrity of discrete sensory pathways and are able to assess components of brainstem function. EP monitoring is feasible in the setting of hypothermia and sedation but, like EEG, requires specialist expertise for interpretation. Because EPs rely on the integrity of the whole sensory pathway, a lesion affecting any point of the monitored pathway can result in an absent EP and false-positive result.[18] EPs can also be transiently absent after a hypoxic/ischaemic insult making them unreliable as an ancillary test for brain death.

DIAGNOSING BRAIN DEATH IN SPECIAL CIRCUMSTANCES

Although there are no published reports of recovery of neurological function after a clinical diagnosis of brain death using standard criteria, there are numerous case reports highlighting situations or conditions that may mimic brain death and lead to erroneous conclusions if unrecognised.[23] Such diagnostic errors invariably involve failure to identify preconditions and exclude reversible factors.

HYPOTHERMIA AND SEDATIVE DRUGS AND HYPOTHERMIA

The effects of high-dose sedative or opioid infusions may persist for several days after discontinuation, particularly in the presence of hypothermia. In one report of misdiagnosed brain death, the potential confounding effects of a very high cumulative dose of fentanyl in a patient with renal and hepatic impairment who had been treated with therapeutic hypothermia after a cardiac arrest appear to have been dismissed.[24] This

case illustrates the crucial importance of adherence to a sequential approach to the clinical determination of brain death, with confident exclusion of confounding factors before proceeding to the clinical examination. As noted earlier, ancillary tests may have a role if the clinical diagnosis of brain death is complicated by the effects of prolonged sedation, particularly in the context of hypothermia.

INABILITY TO COMPLETE THE APNOEA TEST

In patients with high spinal cord injury, the possibility that apnoea might be related to the cord injury can bring some uncertainty to the diagnosis of brain death. The degree of any cord injury should be quantified clinically, structurally and functionally by meticulous clinical examination, magnetic resonance imaging and electrophysiological investigation prior to consideration of a brain death diagnosis. In other situations, such as after polytrauma, it may not be possible to attempt or complete the apnoea test because of haemodynamic instability or poor oxygenation. However, in the vast majority of cases the apnoea test can be safely completed using an oxygen diffusion technique as described earlier.[25] Most guidelines consider the apnoea test to be a fundamental component of the clinical determination of death by neurological criteria, although in Australia and New Zealand brain death can be confirmed by demonstration of absent intracranial blood flow if the apnoea test cannot be completed.

OTHER CONDITIONS

Other brain death 'mimics', including baclofen and valproic acid overdose, organophosphate intoxication and some neurological conditions such as fulminant Guillain-Barré syndrome or Miller-Fisher variant, have been reported.[23] Importantly, the preconditions for the diagnosis of brain death are not met in any of these conditions which should therefore never be mistaken for brain death.[7]

EXTRACORPOREAL MEMBRANE OXYGENATION

There are a few case reports of patients who are clinically brain dead while supported on extracorporeal membrane oxygenation (ECMO). Because use of this technology will increase and up to 20% of patients on ECMO may become brain dead, protocols for conduct of the apnoea test in this situation are required.[7]

CHILDREN

The clinical determination of brain death in infants and children can be more problematic than in adults because of difficulties performing the clinical examination and the relative immaturity of some brainstem reflexes.[26] The majority of countries have separate guidelines for the determination of brain death in infants and children, but clinical examination remains paramount in all.[27] In those over 2 months of age, the general criteria are the same as for adults but the period of observation is often longer and ancillary investigations are required in some countries. A higher $PaCO_2$ target is also recommended during the apnoea test. As in adults, the clinical confirmation of brain death must be undertaken by two competent physicians but, in the case of young children, one should be a paediatrician and the other not directly involved in the child's clinical care. Two clinical examinations, separated by an observation period that varies with age, are required to establish brain death in children in most countries.[27]

BRAIN DEATH AND ORGAN DONATION

Development of the original Harvard brain death criteria was driven in part by advances in organ transplantation and the associated importance of determining death prior to organ retrieval. Recent calls for an international standard for brain death determination are also based as much on a need to improve the availability of organs for transplantation as they are on a desire to establish a consensus for its determination. Transplantation networks increasingly operate across national borders, arguing for consistency in the determination of death in potential donors. Despite the inescapable link between brain death and organ donation and transplantation policies, it is vitally important that, in the clinical setting, there is an inviolable separation between brain death and organ donation. The primary reason for confirming brain death is to ensure professional, legal and societal acceptability for the withdrawal of treatment, including mechanical ventilation, from a patient who can no longer derive benefit from it, and to bring closure for family and friends. Confirmation of brain death is therefore in an individual's best interests irrespective of any subsequent potential for organ donation.[9] After brain death has been confirmed, donation should of course be considered in all appropriate patients.[2]

SUMMARY

From a legal and scientific perspective brain death, more accurately referred to as the determination of death by neurological criteria, is a definable event which is established as a legitimate definition of death in most countries in the world. Practice guidelines for the determination of brain death are widely available. Although there is large international variation in their content and application, there are fundamental components that are common to the determination of brain

death in all jurisdictions. A clinical diagnosis of brain death is sufficient for the determination of death in adults in many countries, although ancillary investigations are required in some.

REFERENCES

1. Shemie SD, Baker A. Uniformity in brain death criteria. *Semin Neurol*. 2015;35:162–168.
2. Citerio G, Cypel M, Dobb GJ, et al. Organ donation in adults: a critical care perspective. *Intensive Care Med*. 2016;42:305–315.
3. A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. *JAMA*. 1968; 205:337–340.
4. Mohandas A, Chou SN. Brain death. A clinical and pathological study. *J Neurosurg*. 1971;35:211–218.
5. Diagnosis of brain death. Statement issued by the honorary secretary of the Conference of Medical Royal Colleges and their Faculties in the United Kingdom on 11 October 1976. *Br Med J*. 1976;2: 1187–1188.
6. Academy of Medical Royal Colleges. *A code of practice for the diagnosis and confirmation of death*. London, UK: Academy of the Medical Royal Colleges; 2008.
7. Varelas PN, Lewis A. Modern approach to brain death. *Semin Neurol*. 2016;36:625–630.
8. Wijdicks EF, Varelas PN, Gronseth GS, et al. Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2010;74:1911–1918.
9. Smith M. Brain death: time for an international consensus. *Br J Anaesth*. 2012;108(suppl 1):i6–i9.
10. Shemie SD, Hornby L, Baker A, et al. International guideline development for the determination of death. *Intensive Care Med*. 2014;40:788–797.
11. Magnus DC, Wilfond BS, Caplan AL. Accepting brain death. *N Engl J Med*. 2014;370:891–894.
12. Wahlster S, Wijdicks EF, Patel PV, et al. Brain death declaration: practices and perceptions worldwide. *Neurology*. 2015;84:1870–1879.
13. Greer DM, Wang HH, Robinson JD, et al. Variability of brain death policies in the United States. *JAMA Neurol*. 2016;73:213–218.
14. Shappell CN, Frank JI, Husari K, et al. Practice variability in brain death determination: a call to action. *Neurology*. 2013;81:2009–2014.
15. Smith M. Brain death: the United Kingdom perspective. *Semin Neurol*. 2015;35:145–151.
16. Wijdicks EF. Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. *Neurology*. 2002;58:20–25.
17. Lustbader D, O'Hara D, Wijdicks EF, et al. Second brain death examination may negatively affect organ donation. *Neurology*. 2011;76:119–124.
18. Kramer AH. Ancillary testing in brain death. *Semin Neurol*. 2015;35:125–138.
19. Bernat JL. Controversies in defining and determining death in critical care. *Nat Rev Neurol*. 2013;9: 164–173.
20. Wijdicks EF. The case against confirmatory tests for determining brain death in adults. *Neurology*. 2010;75:77–83.
21. Brasil S, Bor-Seng-Shu E, de Lima-Oliveira M, et al. Role of computed tomography angiography and perfusion tomography in diagnosing brain death: a systematic review. *J Neuroradiol*. 2016;43:133–140.
22. Sharma D, Souter MJ, Moore AE, et al. Clinical experience with transcranial Doppler ultrasonography as a confirmatory test for brain death: a retrospective analysis. *Neurocrit Care*. 2011; 14:370–376.
23. Busl KM, Greer DM. Pitfalls in the diagnosis of brain death. *Neurocrit Care*. 2009;11:276–287.
24. Webb AC, Samuels OB. Reversible brain death after cardiopulmonary arrest and induced hypothermia. *Crit Care Med*. 2011;39:1538–1542.
25. Datar S, Fugate J, Rabinstein A, et al. Completing the apnea test: decline in complications. *Neurocrit Care*. 2014;21:392–396.
26. Shemie SD, Pollack MM, Morioka M, et al. Diagnosis of brain death in children. *Lancet Neurol*. 2007;6:87–92.
27. Mathur M, Ashwal S. Pediatric brain death determination. *Semin Neurol*. 2015;35:116–124.

54

Meningitis and encephalomyelitis

Michel Toledano, Nicholas WS Davies

INTRODUCTION

Infections of the cranial contents can be divided into those affecting the meninges (meningitis; empyema) and those affecting the brain parenchyma (encephalitis; abscess). Involvement of the spinal cord is termed myelitis. Chronic, insidious or rare infections are beyond the scope of this chapter, which will focus on acute bacterial and viral causes of meningitis, encephalomyelitis, and abscess/empyema in adults.

The crucial diagnostic questions to be considered for an individual patient with a neurological infection are to determine why this individual, in this place, has developed this disease at this time.[1]

All patients presenting with symptoms or signs suggestive of meningitis or encephalitis warrant immediate testing for human immunodeficiency virus (HIV) infection.

DEFINITIONS

- *Meningitis:* is inflammation of the meninges and subarachnoid space, which may be caused by infection. Infection can be caused by viruses, bacteria, fungi or protozoa. Meningeal inflammation may also be caused by subarachnoid haemorrhage, vaccination or be a manifestation of other multiorgan diseases such as systemic lupus erythematosus, sarcoidosis, lymphoma or meningeal micrometastases from a disseminated carcinoma.
- *Aseptic meningitis:* is a generic term for cases of meningitis in which bacteria cannot be isolated from the cerebrospinal fluid (CSF). The differential diagnosis includes: (1) viral meningitis, (2) partially treated bacterial meningitis, (3) tuberculosis (TB) meningitis, (4) fungal meningitis, (5) lymphoma, (6) sarcoidosis, (7) drug-induced meningitis, and (8) other collagen vascular diseases. The most common causes of aseptic meningitis are viral infections.
- *Encephalitis:* is inflammation of the brain parenchyma, which can be due to infection or immune-mediated processes. Patients may have a history of focal symptoms including preceding seizures together with cognitive or behavioural symptoms.
- *Tuberculous meningitis:* causes subacute lymphocytic meningitis. Patients may have a non-specific prodromal phase, including symptoms such as headache, vomiting and fever.
- *Subdural empyema:* a suppurative process in the space between the pia and dura maters.
- *Brain abscess:* a collection of pus within the brain tissue.

BACTERIAL MENINGITIS

Bacterial meningitis is an inflammatory response to infection of the leptomeninges and subarachnoid space. This is characterised by the clinical syndrome of fever, headache, neck stiffness and CSF pleocytosis. Despite antibiotic therapy, some patients continue to suffer significant morbidity and mortality.

Bacterial organisms are usually not confined to the brain and meninges and frequently cause systemic illness, for example severe sepsis, shock, acute respiratory distress syndrome, and bleeding disorders such as disseminated intravascular coagulation (DIC).[2,3]

A variety of other pathogens cause meningeal inflammation, resulting in very similar clinical presentations. Bacterial infections must be treated urgently and appropriately to limit ongoing central nervous system (CNS) damage. It is also important to treat the complications of meningitis such as seizures and raised intracranial pressure (ICP).

Where possible, spinal fluid examination following a lumbar puncture is required in order to confirm the diagnosis and establish the pathogenic organism responsible.[4] A CSF examination may be contraindicated if there are signs of raised ICP including:

- papilloedema
- focal neurological signs
- seizures
- Glasgow Coma Scale (GCS) ≤12

These features raise the possibility of an undiagnosed cerebral mass lesion or malignant cerebral oedema, which could cause cerebral herniation should lumbar puncture be performed. A computed tomography (CT) brain scan is required prior to

ABSTRACT

Infections of the central nervous system can be divided into those that affect the meninges (meningitis and empyema) and those that affect the brain parenchyma (encephalitis and abscess). Here we focus on the diagnosis and treatment of common viral, bacterial and fungal acute meningeal and brain infections, as well as on the management of common complications.

KEYWORDS

Meningitis
encephalitis
brain abscess
subdural empyema
epidural infection

CSF examination in order to rule out this possibility and lessen, but not obviate, the risk of cerebral herniation. Even if the CT brain scan is normal, ICP may be raised. The importance of performing a safe CSF examination must be balanced against the need to commence immediate treatment in each individual patient.[4–6]

PATHOGENESIS

All three main causes of bacterial meningitis (see later) are spread by droplet infection or exchange of saliva. Bacterial meningitis may occur when pathogenic organisms colonise the nasopharynx and reach the blood–brain barrier. It can also occur as a consequence of infection in the middle ear, sinus or teeth leading to secondary meningeal infection. Most bacteria obtain entry into the CNS via the haematogenous route. As the organisms multiply, exponentially, they release cell wall products and lipopolysaccharide, which can generate a local inflammatory reaction that itself also releases inflammatory mediators. The net result of the release of cytokines, tumour necrosis factor and other factors is associated with a significant inflammatory response. Vasculitis of CNS vessels, thrombosis, cell damage and exudative material all contribute to vasogenic and cytotoxic oedema, altered blood flow and cerebral perfusion pressure. Later on, infarction and raised ICP occur.[4,7]

The inflammatory events seen with infection are summarised in Fig. 54.1.

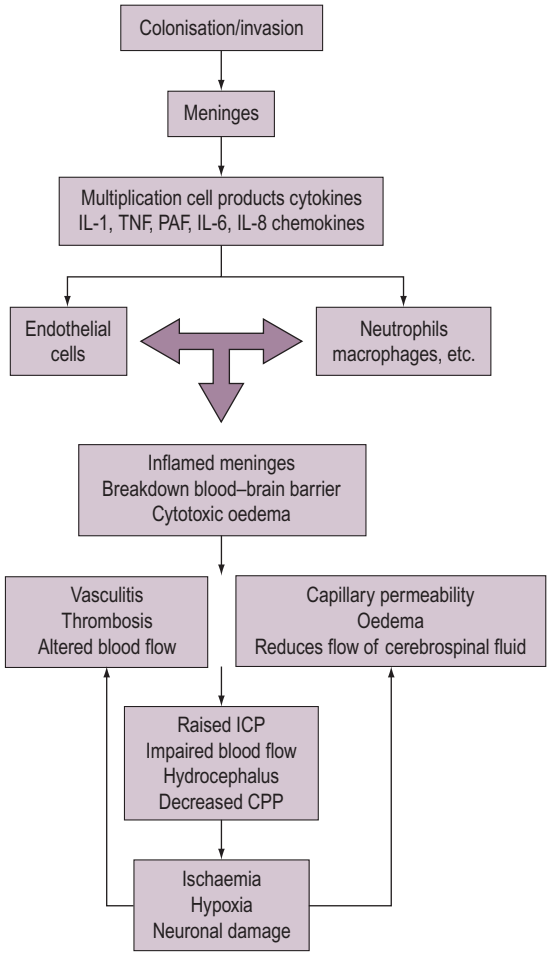


Figure 54.1 Cascade of events in meningitis. *CPP*, Cerebral perfusion pressure; *ICP*, intracranial pressure; *IL*, interleukin; *PAF*, platelet-activating factor; *TNF*, tumour necrosis factor.

AETIOLOGIES

Acute bacterial meningitis can be caused by many species of bacteria, although two organisms are commonly reported in resource-rich settings:

- *Streptococcus pneumoniae*
- *Neisseria meningitidis*

Until the advent of the meningitis vaccination programme, *Haemophilus influenzae* type B was the most common cause of bacterial meningitis. *S. pneumoniae* and *N. meningitidis* remain the most common causes of bacterial meningitis in adults worldwide.[4] *Listeria monocytogenes* can occur in the elderly, immunocompromised, or those with chronic illnesses such as alcohol dependency, diabetes, or malignancy. The emergence of pneumococcal strains resistant to penicillin has also influenced the epidemiology of meningitis.[8]

NOSOCOMIAL INFECTIONS

Common systemic nosocomial pathogens such as *Staphylococcus* species (spp.) *Escherichia coli*, *Pseudomonas* spp., *Klebsiella* and *Acinetobacter* spp. account for a high percentage of nosocomial infections of the meninges.

IMMUNOCOMPROMISED HOSTS

In the immunocompromised patient with meningitis (e.g. HIV or organ transplanted patients), fungal (cryptococcal), viral (cytomegalovirus [CMV]) and mycobacterial meningitis should be considered.[9]

NEUROSURGERY AND TRAUMA

Infections following skull trauma are frequently caused by *Staphylococcus aureus* and *Staphylococcus epidermis*, which should be considered in those with shunts or other intracranial devices.

CLINICAL PRESENTATION

The history may reveal evidence of trauma or infection. Meningitis usually presents with an acute onset of:

Table 54.1 Cerebrospinal fluid changes in meningitis

	NORMAL	BACTERIAL	VIRAL
Appearance	Clear	Turbid/purulent	Clear/turbid
White cell count	<5 per mm^3 mononuclear	200–10,000 per mm^3 predominantly polymorphonuclear	<500 per mm^3 mainly lymphocytes
Protein	0.2–0.4 g/L	0.5–2.0 g/L	0.4–0.8 g/L
CSF: blood glucose ratio	0.6	Normal or ≤0.6	Usually normal
CSF Lactate	<3.5 mmol/L	>3.5 mmol/L	<3.5 mmol/L

CSF, Cerebrospinal fluid.

- fever
- headache
- neck stiffness
- photophobia
- altered level of consciousness
- irritability
- seizures (paediatric).

However, in the immunocompromised, elderly or infant patient, non-specific features such as a low-grade fever or mild behavioural change may be all that is apparent. Many of the classic symptoms are late manifestations of meningitis and are preceded by early symptoms such as leg pain or cold hands, which may not immediately suggest the more serious underlying diagnosis.

If the presenting symptoms are highly suggestive of pyogenic bacterial meningitis, empirical administration of a third-generation cephalosporin such as cefotaxime or ceftriaxone should be given.

It is important to identify from the history any reports of preceding trauma, upper respiratory tract infection or ear infection. Symptoms may develop over hours or days. Specific infections relate partly to an individual's age.

Neurological signs can be present with meningitis, but signs such as nuchal rigidity, stiffness and a positive Kernig's sign (pain and hamstring spasm resulting from attempts to straighten, e.g. with the hip flexed) are not always present; a number of studies have shown that the classic triad of signs were present in less than 50% of cases. There may be focal neurological signs. Systemic signs occur most often in meningococcal disease where a haemorrhagic, petechial or purpuric rash may be observed. Digital gangrene or skin necrosis may occur. Some patients present severely septic with acute respiratory distress syndrome and DIC.

Approximately 25% of patients have a seizure during the course of the illness. Differential diagnoses include subarachnoid haemorrhage, migraine, encephalitis and tumour.

INVESTIGATIONS

The patient with suspected bacterial meningitis requires immediate blood cultures and collection of ethylenediaminetetraacetic acid (EDTA) blood sample for diagnostic polymerase chain reaction (PCR) studies.[4] Thereafter they should be given empirical intravenous (IV) antibiotics if there is likely to be any delay in further assessment (Table 54.1).

CEREBROSPINAL FLUID FINDINGS

A CSF examination is a vitally important investigation that will definitively confirm the diagnosis of bacterial meningitis. Its value should, in this regard, not be dismissed. Concern about the risks of coning following lumbar puncture should be considered in the context of patients' symptoms where the presence of coma, seizures, focal neurological signs and papilloedema may suggest raised ICP. Neuroimaging may not always predict whether it is safe to lumbar puncture a patient, although it may provide some level of reassurance that it is safe to proceed. A young patient who is alert, orientated, immune competent and without focal signs can safely have a lumbar puncture without prior imaging.

Bacterial meningitis is suggested when there is:

- polymorphic leucocytosis
- low CSF glucose relative to the plasma value
- raised CSF protein concentration
- elevated CSF lactate (>3.5 mmol/L).

An urgent Gram stain and microbiological culture are mandatory. The Gram stain is positive in approximately 50%–60% of cases. A CSF examination shortly after empirical antibiotics may, but does not necessarily, decrease the diagnostic sensitivity of CSF culture. Bacterial latex agglutination tests applied to CSF have no greater sensitivity than Gram stain and may give non-specific results; care should be taken with their interpretation and they should not be used alone to limit the spectrum of antimicrobial cover. PCR techniques can now be used to detect the presence of different organisms. A throat swab should be routinely taken. The clinical decision-making process to determine whether a patient does or does not have bacterial meningitis cannot be modelled easily and is reliant on both clinical and laboratory findings as well as patient observations over time.

Table 54.2 Empirical antibiotics for meningitis

INDICATION	ANTIBIOTIC	DOSE
<60 years	Ceftriaxone *or* cefotaxime	2 g IV 12-hourly, 2 g IV 6-hourly
>60 years or impaired cell immunity	Ceftriaxone *or* cefotaxime AND Ampicillin *or* amoxicillin	2 g IV 12-hourly, 2 g IV 6-hourly 2 g IV 4-hourly
Drug-resistant *Streptococcus pneumoniae**	Ceftriaxone AND Vancomycin *or* Rifampicin	2 g IV 12-hourly 15–20 IV mg/kg 12-hourly 600 mg IV or po 12-hourly
Neurosurgery shunt infection	Vancomycin AND Meropenem	15–20 IV mg/kg 12-hourly 2 g IV 6-hourly

*Add in IV vancomycin or rifampicin if penicillin resistance is suspected such as if the patient has travelled in the preceding 6 months to a country with high prevalence of penicillin-resistant pneumococci.
IV, Intravenous.

As spread is haematogenous, blood cultures comprise an important investigation in meningitis, and a number of sets of cultures should be sent. It is advisable to routinely check a full blood count, clotting profile (to exclude DIC) and biochemistry including blood glucose level. A chest radiograph and blood gases should be performed to identify systemic involvement. Relevant areas such as infected sinuses or ears should be examined if there is any indication they are implicated.

MANAGEMENT

Broad-spectrum antibiotics should be started as early as possible and continued until bacterial identification is made (Table 54.2). Antibiotic selection is influenced by the clinical situation in conjunction with known allergies or local patterns of antibiotic resistance and the CSF findings. The patient's travel history, exposure risks and level of immunocompetence are key to determining empirical antibiotic treatment. Delay in administering antibiotics is a significant risk factor for a poor prognosis. Adults with suspected meningitis should receive empirical treatment with ceftriaxone 2 g IV every 12 hours *or* 2 g cefotaxime IV every 6 hours (Table 54.3).[4]

If the patient has within the last 6 months been to a country where resistant pneumococci are present, IV vancomycin 15–20 mg/kg should be added (*or* 600 mg rifampicin 12-hourly IV or orally). Up-to-date information regarding antibiotic resistance in travellers can be obtained from the World Health Organization (http://bit.ly/1rOb3cx and http://bit.ly/1rOb3cx).

Those aged over 60 or immunocompromised (including diabetics and those with a history of alcohol misuse) should receive 2 g IV ampicillin *or* amoxicillin *in addition* to a cephalosporin.

Table 54.3 Alternative antibiotic choices for empirical treatment of meningitis

ORGANISM	ANTIBIOTIC	DOSE
<60 years	Chloramphenicol	25 mg/kg 6-hourly
>60 years or impaired cell immunity	Chloramphenicol AND Co-trimoxazole 10–20 mg/kg (of the trimethoprim component)	25 mg/kg 6-hourly In four divided daily doses

Always check local sensitivity as resistance patterns are variable.

It is more difficult to select an appropriate empirical antibiotic in the immunocompromised patient. Discussion with local microbiology services is recommended. When the organism has been identified and sensitivity results are available, it will probably be necessary either to change or to rationalise the antibiotics being given.[10] Meningitis caused by Gram-negative organisms is rare but multidrug resistance amongst enterobacteriaceae is increasing.[4] If there is a high suspicion that an extended spectrum beta lactamase organism might be present then meropenem 2 g IV 8-hourly should be given (instead of cephalosporin with or without amoxicillin/ampicillin).

In all cases, it is important to monitor the clinical response; antibiotics should be reviewed and appropriately altered once antibiotic sensitivities are known or if a patient is not improving. A repeat CSF

examination should be performed if there is concern about antibiotic sensitivity or selection. In those with penicillin-resistant pneumococcal meningitis, a CSF examination 48 hours after presentation is recommended to ensure bacteriological improvement. Antibiotics should be given for 5 days for *N. meningitidis*; 10–14 days for fully sensitive *S. pneumonia*; and 21 days for *L. monocytogenes*. Intrathecal antibiotics are not recommended.[4]

STEROID ADMINISTRATION

The benefit of steroid administration in adult meningitis has been debated, but clear guidance is now available to support its routine use as the Cochrane Database of 4121 adults and children demonstrated significantly lower rates of hearing loss and neurological sequelae in those treated with corticosteroids.[11] Decreased mortality was only observed in those with pneumococcal meningitis. Concern remains that corticosteroids may reduce CSF penetration of antibiotics, although this has not been demonstrated in studies conducted in humans. For reasons that remain unclear, these effects are only observed in high-income countries with multiple studies showing no benefit to adjunctive corticosteroid therapy in low-income settings.

RECOMMENDATIONS IN ADULTS

Dexamethasone 10 mg is an adjuvant treatment and should be given in adults IV shortly before or with the first of antibiotics and continued 6-hourly for 4 days. Dexamethasone should be halted if a microbiological cause for meningitis other than *S. pneumoniae* is identified.[4]

ANTICONVULSANTS

Focal or generalised seizures should be treated immediately with IV benzodiazepines to stop the seizures, with subsequent IV loading with phenytoin or levetiracetam. The possibility of the following should be considered:

- raised ICP
- cerebritis
- cerebral abscess
- septic venous thrombosis.

The development of seizures may be indicative of a poor prognosis.

INTRACRANIAL PRESSURE

Intracranial hypertension is a common complication of meningitis. ICP monitoring may be required and standard measures such as hyperventilation, mannitol infusion or CSF drainage should be considered. Depending upon the particular circumstance, serial lumbar punctures or external ventricular drainage should be implemented.

GENERAL MANAGEMENT CONSIDERATIONS

CRITICAL CARE

Intensive care teams should be involved early in patients with rapidly evolving rash, evidence of limb ischaemia, cardiovascular instability, acid/base disturbance, hypoxia, respiratory compromise, frequent seizures or altered mental state. Patients with a rapidly evolving rash, GCS ≤12 (or a drop of >2 points), those requiring monitoring or specific organ support, or those with uncontrolled seizures should be transferred to critical care facilities.[4]

Normal haemodynamics should be maintained. Inappropriate antidiuretic hormone secretion may occur in meningitis. Those with severe shock or profound coma may require a secure airway and respiratory support. Intubation should be strongly considered in those with GCS less than 12. Attention should be paid to management of the unconscious patient with appropriate mouth and eye care. Physiotherapy will be required in order to prevent the onset of pressure sores. Surgical evaluation may be needed for skin necrosis.[12,13]

PUBLIC HEALTH

Meningitis prophylaxis is recommended for close (kissing contacts) associates and for those medical personnel with close contact in cases of probable or confirmed meningococcal meningitis only. Ciprofloxacin 500 mg po stat should be given to adults (alternative rifampicin 600 mg twice-daily for 2 days).[4] Meningococcal vaccination may also be considered. Procedures should be in place to alert the infectious disease team and public health authorities. In many countries the latter is a statutory obligation for the treating physician.

PROGNOSIS

Untreated bacterial meningitis is usually fatal. Appropriate therapy significantly reduces the mortality rate but studies still show that the overall mortality is approximately 18%. Mortality is slightly higher in those who have seizures, when there have been delays introducing treatment, and if the patient is either elderly or very young (see Table 54.3).[13,14]

CRYPTOCOCCAL MENINGITIS

Cryptococcus neoformans is a yeast that can cause a chronic meningitis that is clinically similar to tuberculous meningitis. It is most frequently found in those who are immunocompromised, such as with HIV infection. A lumbar puncture should be obtained if the diagnosis is suspected and the opening pressure should be measured. India ink evaluation and cryptococcal

antigen testing can help establish the diagnosis, but culturing the organism from the spinal fluid remains the gold standard. Serum cryptococcal antigen testing is useful for evaluation of patients with HIV infection, although a negative result cannot be used to rule out cryptococcal meningoencephalitis. Initial treatment is with amphotericin B and 5-fluorocytosine followed by consolidation therapy with fluconazole. Management of the raised ICP may necessitate daily lumbar punctures or CSF diversion.

VIRAL MENINGITIS

The majority of cases of viral meningitis are benign, usually self-limiting conditions that are often caused by enteroviruses (which include Coxsackie viruses), herpes simplex virus (HSV) type 2 and varicella zoster virus (VZV). In endemic regions, some are caused by arthropod-borne viruses (arboviruses), such as West Nile virus. The same viruses that produce meningitis can also cause encephalitis. HSV type 1 usually produces encephalitis but rarely causes meningitis. Other viruses causing CNS infections include echoviruses, mumps, Toscana virus and HIV (particularly at the time of seroconversion). Patients with migrainous headaches often receive a lumbar puncture to rule out viral meningitis, which paradoxically may prolong their hospital stay with a post-lumbar-puncture headache and migraine.

CLINICAL PRESENTATION

Patients usually present with symptoms of meningeal irritation, fever, headache, neck stiffness, retrobulbar pain, photophobia, vertigo, nausea and vomiting that are less severe than those with bacterial meningitis. The presence of intellectual impairment, focal neurological symptoms or seizures suggests that the brain parenchyma is involved often due to meningoencephalitis. A detailed travel history should be obtained, as this may alter the differential diagnosis in terms of the likely organism. True viral meningitis develops over hours to days but rarely lasts longer than 7–10 days. Occasionally it can have a thunderclap presentation. A variety of associated symptoms, such as nausea, vomiting and generalised malaise, may accompany this condition.[15]

INVESTIGATIONS

A CSF examination is important and usually shows:

- a mild to moderate lymphocytic pleocytosis (can be neutrophilic initially)
- a mildly elevated CSF protein concentration
- normal glucose concentration
- normal CSF lactate.

Staining for microorganisms, including bacteria, *Mycobacterium tuberculosis* and cryptococci is necessary. Sites for viral culture include the mucous membranes, throat, skin and rectum.

MANAGEMENT

Acute viral meningitis is usually a self-limiting condition and only supportive therapy is required with analgesia and bedrest. Viral meningitis caused by HSV or VZV may require IV acyclovir, especially where it occurs in the immunosuppressed. Acute HIV infection causing meningitis responds to antiretroviral therapy.

ENCEPHALITIS

Encephalitis refers to inflammation of the brain. When secondary to an infectious organism, it can be caused by direct infection or by post-infectious, immune-mediated mechanisms. Autoimmune encephalitis can also occur independent of infection. HSV type 1, the most common and serious cause of focal encephalitis, usually affects the temporal and frontal lobes. There are a large number of arboviruses that cause epidemics of encephalitis. Encephalitis acts as a sentinel for new and emerging infections, including Japanese encephalitis, Nipah virus, Hendra virus, a variety of bat-associated viruses as well as West Nile and some tick-borne encephalitides such as Murray Valley encephalitis.

West Nile virus is now the most common cause of epidemic viral encephalitis in some countries. Although, on neuroimaging, changes in the basal ganglia may suggest the diagnosis, a CSF pleocytosis may be a more obvious diagnostic finding. Specific CSF antibodies can be sent for West Nile virus. There are also a variety of antibody-mediated encephalitides that target synaptic proteins. These include *N*-methyl-D-aspartate receptor (NMDAR) antibodies and voltage-gated K^+ channel antibodies.[16] Occasionally the former can be a sequela of HSV encephalitis.

CLINICAL PRESENTATION

The key clinical pointer to encephalitis is the presence of focal neurological symptoms indicating involvement of brain parenchyma. In particular, the presence of speech disturbance, seizures, altered cognition and disturbance of conscious level suggest this.

Diagnosis can be difficult.

- Abnormalities on cranial imaging such as T2-weighted magnetic resonance imaging (MRI) may support this diagnosis (Fig. 54.2).
- Electroencephalogram (EEG) studies may show slow-wave activity or epileptiform discharges in the temporal lobe. The presence of extreme delta brush pattern is specific for NMDAR encephalitis. EEG may also exclude non-convulsive status epilepticus that can mimic or be a complication of encephalitis.

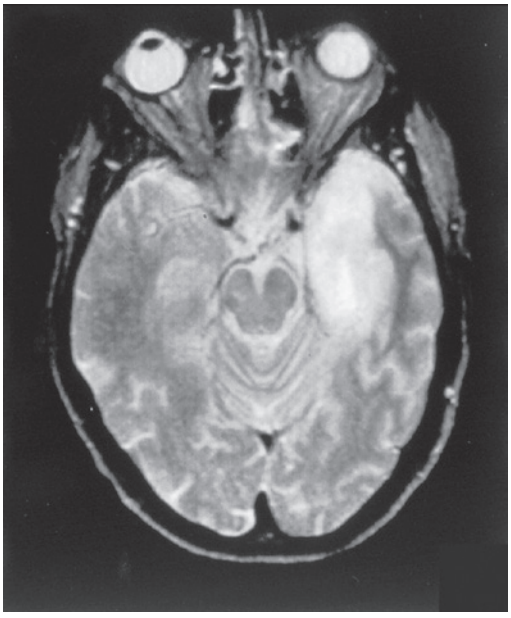


Figure 54.2 Temporal lobe following herpes simplex encephalitis.

- PCR examination of the CSF examination may confirm the virus.

A systematic approach to the investigation of those with encephalitis has been proposed and national guidelines developed to reduce the proportion of unidentified cases.[17]

TREATMENT

Understanding, and if at all possible identifying, the specific aetiological cause of an individual's encephalitis may ultimately have the greatest influence on the successful management of individual patients.[18]

Specific treatment for HSV encephalitis requires IV aciclovir at a dose of 30 mg/kg per day in three divided doses for at least 14 days; some recommend repeating the lumbar puncture, ensuring that the CSF is HSV DNA negative before halting aciclovir.[17] Untreated, the mortality of HSV encephalitis is approximately 70% but there is still 10%–20% mortality in patients treated with optimal therapy, and patients can be left with significant disability due to cognitive dysfunction or seizures. Most patients with significant cerebral oedema receive empirical steroids, although there are no clinical trials to support this therapy. Aciclovir can cause renal impairment and the patient should be hydrated intravenously and renal function monitored.[19] Aggressive treatment of seizures is important.

CMV infection requires antiviral therapy with ganciclovir or valganciclovir. CMV can cause a ganglionitis and polyradiculitis, which may suggest this diagnosis clinically in an immunocompromised patient.

Most CNS viruses cause neuronal damage but chronic John Cunningham (JC) virus infection in oligodendrocytes causes the syndrome of progressive multifocal leucoencephalopathy (PML). This condition presents with a subacute onset of confusion, weakness and visual symptoms, usually in an immunosuppressed individual. The MRI scan is usually suggestive but CSF examination with PCR amplification of the JC virus particles may be required. Currently, no specific therapy for PML exists. Initiation of combined antiretroviral therapy in HIV patients with associated PML significantly improves survival but can be associated with paradoxical clinical worsening due to transient inflammation, a phenomenon known as immune reconstitution inflammatory syndrome (IRIS).[20]

Viral infection with HIV, measles and rubella can also cause chronic CNS infection leading to chronic encephalitides. *Mycoplasma* infection can give rise to post-infectious encephalitis.

A number of systemic neurological conditions (e.g. lymphoma, Lyme disease, sarcoidosis and vasculitides such as Behçet disease) may present with aseptic meningitis. It is therefore important to consider these systemic conditions in those presenting with viral meningitis or encephalitis.

TUBERCULOUS MENINGITIS

Meningitis caused by *M. tuberculosis* (TBM) has a variable natural history with a range of different clinical presentations. It typically affects adolescents and young persons but is not restricted to these age groups. It is more frequent in the immunosuppressed. This and the lack of specific and sensitive tests hinder the diagnosis of this condition. Approximately 10% of individuals with TB develop meningeal involvement. A variety of risk factors such as HIV, diabetes mellitus and recent use of steroids increases the risk of tuberculous meningitis.[21]

CLINICAL FEATURES

TBM has a very varied clinical presentation. Often, it is heralded by a non-specific prodromal phase, frequently but not necessarily including headache, vomiting and fever. Of one case series that included those admitted to an intensive care unit, only 65% had fever, 52% had focal neurology and 88% had signs of meningism. A variety of cranial nerve palsies can occur, but other presentations include those seen with stroke, hydrocephalus and tuberculoma.

DIAGNOSIS

An investigation of the differential diagnosis of TBM is important. A minimum of three serial lumbar punctures should be performed to increase the sensitivity of acid-fast bacilli smear and mycobacterial culture.

The use of PCR amplification of mycobacterial DNA can increase sensitivity further, and some of the newer assays such as the Xpert MTB/RIF, can provide information regarding antibiotic resistance.[22] CSF analysis shows an elevated protein, lymphocytic pleocytosis and hypoglycorrhachia. Those who are immunosuppressed can have an atypical CSF appearance, including normal CSF examinations in occasional HIV individuals. TB culture from CSF is required but may take up to 6 weeks before a positive culture result is available. Imaging studies may show a basal meningitis and hydrocephalus but these features are non-specific.[23]

Current advice suggests that in adults the first 2 months of treatment should comprise quadruple therapy:

- Isoniazid oral/IV 300 mg daily
- Rifampicin oral/IV 450 mg (<50 kg) and 600 mg (≥50 kg)
- Pyrazinamide oral 1.5 g (<50 kg) and 2 g (≥50 kg)
- Ethambutol oral 15 mg/kg

Fluoroquinolones (moxifloxacin or levofloxacin) may represent an effective fourth agent. Streptomycin is used rarely. Agent toxicity must be monitored in terms of renal and liver function and the effect on other organs, such as the eye. It is strongly recommended that advice is sought from local experts or networks with experience in management of TB.

Corticosteroids are recommended in HIV seronegative patients with TBM. The initial steroid dose is guided by the patient's GCS and is tapered over 4–6 weeks.[24,25] There is increasing multidrug-resistant tuberculous meningitis, especially in the HIV-positive population, reiterating the importance of culturing *M. tuberculosis* from clinical specimens in order to obtain sensitivities. Patients with TB meningitis frequently deteriorate over the weeks following initiation of appropriate chemotherapy and steroid regimens. Neurosurgical intervention for the treatment of hydrocephalus is sometimes required.

SUBDURAL EMPYEMA

This is a collection of pus between the dural and arachnoid space and usually is a consequence of middle ear or sinus disease. It may follow cranial osteomyelitis related to previous neurosurgery. Head trauma can also be responsible.

Individuals present acutely with headache, fever, neck stiffness, seizures and focal neurological symptoms. Meningeal signs and evidence of hemispheric dysfunction with sinusitis should suggest the diagnosis.

DIAGNOSIS

CT and MRI are both effective in demonstrating a fluid collection.

Surgical intervention, drainage and appropriate antibiotic regimens are required. Both Gram-positive (*S. aureus* and *Streptococcus* species), and Gram-negative organisms may be implicated. Initial broad-spectrum (Ceftriaxone 2 g IV 12-hourly and Metronidazole 500 mg IV 8-hourly) cover should be narrowed to targeted treatment when the organism or organisms are known.

PROGNOSIS

This condition if left untreated is invariably fatal. With treatment, mortality is in the order of 20% but neurological sequelae are common.

EPIDURAL INFECTION

Cranial and spinal epidural abscess is an infection between skull or spinal column and dura often as a consequence of osteomyelitis or malignancy. There is an occasional incidence following epidural anesthesia. It is similar to subdural empyema. The organism involved where a catheter or drain is implicated is often the same as that found at the skin; hence, *S. aureus* is frequently responsible.

PRESENTATION

Inflammation is commonly (but not always) present on the back, and is usually generalised to the area of the back involved. There may be local tenderness over the site associated with redness of the catheter insertion site. Fever is common. Initially mild neurological deficit may rapidly progress leading to para/quadriparesis.

Blood cultures may be positive and may indicate the organism.

DIAGNOSIS

CT and MRI are both effective in diagnosis.

Spinal decompression and drainage are urgently required. This is usually a nosocomial infection and therefore resistant organisms are commonly found. Antibiotics should be specific for the organisms involved and may need to be continued for prolonged periods, often weeks, to eradicate the infection.

Where there have been neurological symptoms and signs prior to surgery, residual deficit is common. In one series, the recovery rate for patients with paresis/plegia after lumbar epidural abscess was 50%, whereas no patients with paresis/plegia following a thoracic abscess recovered. The majority of long-term survivors had severe neurological deficits.

CEREBRAL VENOUS AND SAGITTAL SINUS THROMBOSIS

Venous and sinus thrombosis may occur in the context of infection – in particular meningitis, and epidural or

subdural abscess. It may also be secondary to facial or dental infection. It may have no septic aetiology but can occur either as an isolated event or in association with prothrombotic problems such as diabetic ketoacidosis, 3,4-methlenedioxy-methamphetamine (MDMA) (ecstasy) abuse, oral contraceptives and hereditary prothrombotic conditions in pregnancy.[26]

Clinical signs at presentation include:

- headache
- focal neurological deficits in particular cranial nerves
- seizures
- papilloedema.

The diagnostic sensitivity of CT, MRI and digital subtract angiography are 59%, 86% and 100%, respectively, but MRI with magnetic resonance angiography or CT venography reaches 96% (Fig. 54.3).

TREATMENT

- Treat the primary infection if present.
- Anticoagulants are the mainstay of treatment. Paradoxically there are often areas of intracerebral haemorrhage in patients with sinus thrombosis. The presence of such haemorrhages is not a contraindication to anticoagulation.

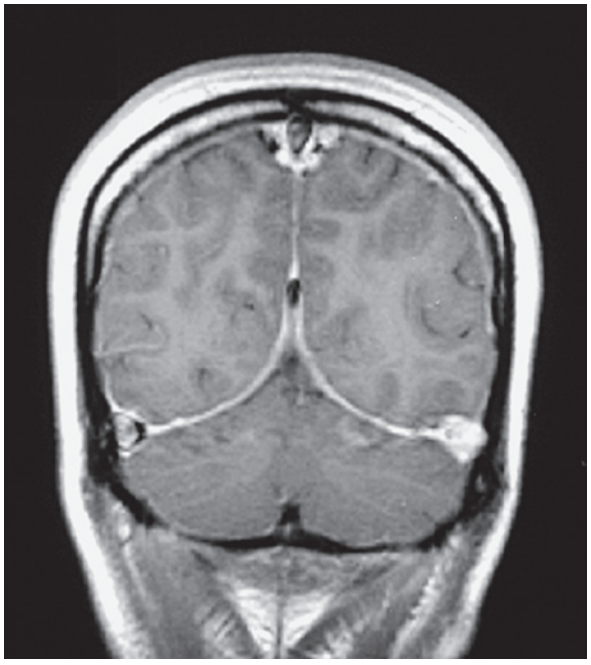


Figure 54.3 Magnetic resonance imaging (MRI) of superior sagittal sinus thrombosis: coronal T1-weighted post-contrast MRI; patient developed a sinus thrombosis following protracted labour and delivery.

BRAIN ABSCESS

AETIOLOGY

Direct spread from bone or dura or may be via haematogenous spread. Predisposition includes cranial trauma, neurosurgery, chronic ear or sinus disease, suppurative lung disease, congenital heart disease and recurrent sepsis. Immunological compromise may predispose to more exotic organisms, but more common organisms include *S. aureus* (associated with local and haematogenous) spread; and *Streptococcus* spp., *Bacteroides fragilis* and Gram-negative bacteria, which are common with lung disease or recurrent sepsis.

PRESENTATION

Severe headache, vomiting, obtundation, seizures and focal neurological signs. Neck stiffness is often absent. Clinical sepsis may not be obvious.

DIAGNOSIS

- An obvious primary source of infection
- Evidence of raised ICP
- Focal cerebral or cerebellar signs.

INVESTIGATIONS

- Lumbar puncture is low yield and potentially dangerous if there is significant mass effect
- CT scan – contrast will usually show a ring-enhancing lesion (Fig. 54.4)
- MRI
- Assessment of the patient's immune status
- Blood cultures
- Echocardiogram – where infective endocarditis suspected
- Specific blood tests such as HIV and toxoplasma serology.

TREATMENT

Indications for surgery include large single lesions, relief of raised ICP and the need for tissue diagnosis.

Antibiotics are the mainstay of therapy. If the organism is known, then the treatment should be specific. In the absence of a definitive organism, ceftriaxone 2 g IV 12-hourly *or* cefotaxime 2 g IV 6-hourly *with* metronidazole 500 mg IV 8-hourly. If there is a recent history of trauma or neurosurgery, then a regimen that will cover *Staphylococcus* should be used. Antibiotics should be continued for 3–6 weeks.

Supportive therapy limits morbidity, which is nevertheless high. Mortality from cerebral abscesses is still 10%–20%.[27]

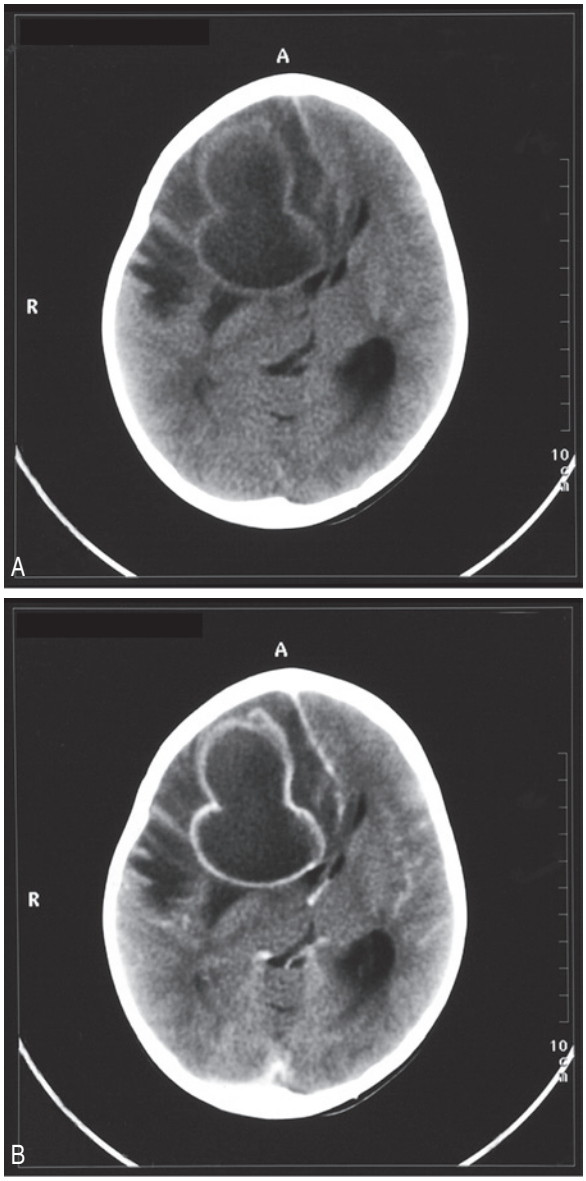


Figure 54.4 Abscess: (a) pre-contrast and (b) post-contrast.

LYME DISEASE

This is a tick-borne multisystem disease with dermatological, cardiological, rheumatological and neurological effects caused by the spirochaete *Borrelia burgdorferi*.

A history of potential exposure should be sought but is not always found. The disease may present in a variable fashion neurologically including as a cranial neuropathy (commonly a facial palsy) or as meningoencephalitis or radiculopathy. It may also cause lymphocytic meningitis and may have been diagnosed as 'viral' meningitis in the past. A variety of longer-term neurological sequelae have been described.[28]

INVESTIGATIONS

CEREBROSPINAL FLUID

White cell count is equivocal but may be raised. Protein is normal or marginally raised and sugar is normal or marginally low. Demonstration of intrathecal production of antibodies against *B. burgdorferi* establishes the diagnosis. PCR has very low sensitivity, as well as low positive and negative predictive value.

TREATMENT

Practice parameters for the treatment of nervous system Lyme disease state that nervous system infection responds favourably to penicillin, ceftriaxone, cefotaxime and doxycycline. The optimal duration of treatment is not known, but 10–21 days is recommended.[29] Prolonged treatment with antibiotic appears to have no benefit in preventing post-Lyme syndrome.

OTHER DISEASES

There are several other diseases that may have an encephalopathic component. Cerebral malaria is dealt with elsewhere. *Legionella* may lead to subclinical or clinical neurological manifestations, ranging from headache to coma or encephalopathy usually seen in conjunction with pneumonia, in addition to possible renal impairment. Similarly, *Mycoplasma* has been associated with an encephalitic picture characterised by impaired consciousness and seizures, and by normal or non-specific neuroradiological findings. Occasionally, symmetrical lesions in the putamen and its external surrounding areas have been seen.

SEPTIC ENCEPHALOPATHY

Septic encephalopathy has been described as a common complication in the critically ill, presenting in a panoply of ways, from the agitated confused state seen in acute sepsis through to profound loss of consciousness. The aetiology is almost certainly multifactorial involving changes in cerebral blood flow, alteration in oxygen extraction, cerebral oedema, disruption of the blood–brain barrier, the presence and effects of diverse inflammatory mediators and abnormal neurotransmitter activity; deranged liver and renal function contribute. It is a syndrome of exclusion based on observation and circumstantial evidence. The EEG is usually abnormal with decreased fast activity and an increase of slow-wave activity, but the findings are not pathognomonic. There are no specific treatments. In general terms, outcome appears to correlate with the management of the underlying sepsis.[30]

REFERENCES

1. Davies N, Thwaites G. Infections of the nervous system. *Pract Neurol*. 2011;11(2):121–131.
2. Isenberg H. Bacterial meningitis: signs and symptoms. *Antibiot Chemother*. 1992;45:79–95.
3. Spach DH, Jackson LA. Bacterial meningitis. *Neurol Clin*. 1999;17(4):711–735.
4. McGill F, Heyderman RS, Michael BD, et al. The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocomptent adults. *J Infect*. 2016;72:405–438.
5. Roos KL. Acute bacterial meningitis. *Semin Neurol*. 2000;20(3):293–306.
6. Anderson M. Management of cerebral infection. *J Neurol Neurosurg Psychiatry*. 1993;56(12):1243–1258.
7. Pfister HW, Fontana A, Tauber MG, et al. Mechanisms of brain injury in bacterial meningitis: workshop summary. *Clin Infect Dis*. 1994;19(3): 463–479.
8. Kasanmoentalib ES, Brouwer MC, van de Beek D. Update on bacterial meningitis: epidemiology, trials and genetic association studies. *Curr Opin Neurol*. 2013;26(3):282–288.
9. Gottfredsson M, Perfect JR. Fungal meningitis. *Semin Neurol*. 2000;20(3):307–322.
10. Vandecasteele SJ, Knockaert D, Verhaegen J, et al. The antibiotic and anti-inflammatory treatment of bacterial meningitis in adults: do we have to change our strategies in an era of increasing antibiotic resistance? *Acta Clin Belg*. 2001;56(4):225–233.
11. Brouwer MC, McIntyre P, Prasad K, et al. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev*. 2015;(9):CD004405.
12. Hussein AS, Shafran SD. Acute bacterial meningitis in adults. A 12-year review. *Medicine (Baltimore)*. 2000; 79(6):360–368.
13. Durand ML, Calderwood SB, Weber DJ, et al. Acute bacterial meningitis in adults. A review of 493 episodes. *N Engl J Med*. 1993;328(1):21–28.
14. Pfister HW, Feiden W, Einhaupl KM. Spectrum of complications during bacterial meningitis in adults. Results of a prospective clinical study. *Arch Neurol*. 1993;50(6):575–581.
15. Rotbart HA. Viral meningitis. *Semin Neurol*. 2000; 20(3):277–292.
16. Linnoila JJ, Rosenfeld MR, Dalmau J. Neuronal surface antibody-mediated autoimmune encephalitis. *Semin Neurol*. 2014;34(4):458–466.
17. Solomon T, Michael BD, Smith PE, et al. Management of suspected viral encephalitis in adults – Association of British Neurologists and British Infection Association National Guidelines. *J Infect*. 2012; 64(4):347–373.
18. Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis*. 2010;10(12):835–844.
19. Schmutzhard E. Viral infections of the CNS with special emphasis on herpes simplex infections. *J Neurol*. 2001;248(6):469–477.
20. Brew BJ, Davies NW, Cinque P, et al. Progressive multifocal leukoencephalopathy and other forms of JC virus disease. *Nat Rev Neurol*. 2010;6(12):667–679.
21. Thwaites GE, Tran TH. Tuberculous meningitis: many questions, too few answers. *Lancet Neurol*. 2005; 4(3):160–170.
22. Denkinger CM, Schumacher SG, Boehme CC, et al. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *Eur Respir J*. 2014;44(2):435–446.
23. Roos KL. *Mycobacterium tuberculosis* meningitis and other etiologies of the aseptic meningitis syndrome. *Semin Neurol*. 2000;20(3):329–335.
24. Thwaites G, Fisher M, Hemingway C, et al. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. *J Infect*. 2009;59(3): 167–187.
25. Prasad K, Singh MB, Ryan H. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev*. 2016;(4):CD002244.
26. de Bruijn SF, Stam J, Koopman MM, et al. Case-control study of risk of cerebral sinus thrombosis in oral contraceptive users and in carriers of hereditary prothrombotic conditions. The Cerebral Venous Sinus Thrombosis Study Group. *BMJ*. 1998;316(7131):589–592.
27. Yildizhan A, Pasaoglu A, Ozkul MH, et al. Clinical analysis and results of operative treatment of 41 brain abscesses. *Neurosurg Rev*. 1991;14(4):279–282.
28. Halperin JJ. Nervous system Lyme disease. *Infect Dis Clin North Am*. 2015;29(2):241–253.
29. Marques AR. Lyme neuroborreliosis. *Continuum (Minneap Minn)*. 2015;21(6 Neuroinfectious Disease): 1729–1744.
30. Papadopoulos MC, Davies DC, Moss RF, et al. Pathophysiology of septic encephalopathy: a review. *Crit Care Med*. 2000;28(8):3019–3024.

55

Tetanus

Jeffrey Lipman

Tetanus is a preventable, often Third-World disease frequently requiring expensive First-World technology to treat. It is an acute, often fatal disease caused by exotoxins produced by *Clostridium tetani,* and is characterised by generalised muscle rigidity, autonomic instability and sometimes convulsions.

EPIDEMIOLOGY

Recently, tetanus has become a disease of the elderly and debilitated in developed countries, as younger people are likely to have been immunised.[1,2] In the United States, its incidence decreased from 0.23 per 100,000 in 1955 to 0.04 per 100,000 in 1975, and remained stable thereafter.[1] In England and Wales, the annual incidence has been reported as 0.2 per million population, with the highest incidence in patients older than 64 years.[2] It is reported that 1 million people annually are afflicted with tetanus, signifying a global incidence of about 18 per 100,000 population, with an estimated world mortality of more than 200,000 per year.[2,3] It is geographically prevalent in rural areas with poor hygiene and medical services. Thus, tetanus remains a significant public health problem in the developing world, primarily because of poor access to immunisation programmes. In addition, modern management requires intensive care unit (ICU) facilities, which are rarely available in the most severely afflicted populations[4]; therefore, tetanus will continue to afflict developing populations in the foreseeable future.

PATHOGENESIS

C. tetani is an obligate anaerobic, spore-bearing, Gram-positive bacillus. Spores exist ubiquitously in soil and in animal and human faeces. After gaining access to devitalised tissue, spores proliferate in the vegetative form, producing the toxins tetanospasmin and tetanolysin. Tetanospasmin is extremely potent; an estimated 240 g could kill the entire world population,[5] with 0.01 mg being lethal for an average human. Tetanolysin is of little clinical importance.

C. tetani is non-invasive. Hence, tetanus occurs only when the spores gain access to tissues to produce vegetative forms. The usual mode of entry is through a puncture wound or laceration, although tetanus may follow surgery, burns, gangrene, chronic ulcers, dog bites, injections such as with drug users, dental infection, abortion and childbirth. Tetanus neonatorum usually follows infection of the umbilical stump. The injury itself may be trivial, and in 10%–20% of cases there is no history or evidence of a wound.[1,2] Germination of spores occurs in oxygen-poor media (e.g. in necrotic tissue), with foreign bodies, and with infections. *C. tetani* cannot grow in healthy tissue.[2] *C. tetani* infection remains localised, but the exotoxin tetanospasmin is distributed widely via the bloodstream, taken up into motor nerve endings, and transported into the nervous system. Here, it affects motor neuron end-plates in skeletal muscle (to decrease release of acetylcholine), the spinal cord (with dysfunction of polysynaptic reflexes) and the brain (with seizures, inhibition of cortical activity and autonomic dysfunction). Tetanus is not communicable from person to person.

The symptoms of tetanus appear only after tetanospasmin has diffused from the cell body through the extracellular space, and gained access to the presynaptic terminals of adjacent neurons.[1,2] Tetanospasmin spreads to all local neurons, but is preferentially bound by inhibitory interneurons – that is, glycinergic terminals in the spinal cord, and γ-aminobutyric acid (GABA) terminals in the brain.[4] Its principal effect is to block these inhibitory pathways. Hence, stimuli to and from the central nervous system (CNS) are not 'damped down'.

ACTIVE IMMUNOPROPHYLAXIS[1–3,5]

Natural immunity to tetanus does not occur. Tetanus may both relapse and recur. Victims of tetanus must be *actively immunised*. Tetanus toxoid is a cheap and effective vaccine that is thermally stable.[5] It is a non-toxic derivative of the toxin that, nevertheless, elicits and reacts with antitoxic antibody. By consensus, an

ABSTRACT

Tetanus is a preventable disease caused by *Clostridium tetani*, an obligatory anaerobic, spore–bearing, Gram-positive bacillus. Spores produce an exotoxin tetanospasmin which, within the central nervous system, inhibits inhibitory pathways. Tetanus is characterised by generalised muscle rigidity, in severe cases autonomic instability and occasionally convulsions. Without expensive intensive care treatment, the disease is often fatal.

Good wound care with extensive debridement and metronidazole will eradicate the organism and prevent spores releasing tetanospasmin. Human rich tetanus antitoxin neutralises circulating toxin. Trismus is often the presenting symptom and airway control can be lifesaving. The goal of therapy is to block the tetanospasmin's central nervous system effects of overactivity (benzodiazepines, morphine, magnesium, blood pressure management and muscle relaxants in severe cases). Symptomatic intensive care management and prevention of complications allows >90% survival rates. As the disease does not produce immunity, active immunisation with antitetanus toxin must follow.

KEYWORDS

Tetanus
Clostridium tetani
human rich antitetanus immunoglobulin
trismus
muscle spasms
autonomic dysfunction
supportive care
active immunisation

antibody titre of 0.01 U/mL serum is protective,[2,6] but this thinking comes from very old data.[2] In a damped-down form, tetanus has been reported in a few victims with much higher serum antibody titres.[2]

In adults, a full immunisation course consists of three toxoid doses, given at an optimal interval of 6–12 weeks between the first and second doses, and 6–12 months between the second and third doses. A single dose will offer no immediate protection in the unimmunised, but a full course should never be repeated. Neonates have immunity from maternal antibodies. Children over 3 months should be actively immunised, and need four doses in total. Two or more doses to child-bearing females over 14 years will protect any child produced within the next 5 years. Pregnant females who are not immunised should thus be given two spaced-out doses 2 weeks to 2 months before delivery. Booster doses should be given routinely every 10 years.

Side effects of tetanus toxoid are uncommon and not life threatening. They are associated with excessive levels of antibody due to indiscriminate use.[7] Common reactions include urticaria, angio-oedema and diffuse, indurated swelling at the site of injection.

CLINICAL PRESENTATION[1–3,6,8]

The incubation period (i.e. time from injury to onset of symptoms) varies from 2 to 60 days. The period of onset (i.e. from first symptom to first spasm) similarly varies. Nearly all cases (90%), however, present within 15 days of infection.[8] The incubation period and the period of onset are of prognostic importance, with shorter times signifying more severe disease.

Presenting symptoms are pain and stiffness. Stiffness gives way to rigidity, and there is difficulty in mouth opening – trismus or lockjaw. Most (75%) non-neonatal generalised tetanus cases present with trismus.[8] Rigidity becomes generalised, and facial muscles produce a characteristic clenched-teeth expression called risus sardonicus. The disease progresses in a descending fashion. Typical spasms, with flexion and adduction of the arms, extension of the legs and opisthotonos, are very painful and may be so intense that fractures and tendon separations occur.[1,2] Spasms are caused by external stimuli (e.g. noise and pressure). As the disease worsens, even minimal stimuli produce more intense and longer-lasting spasms. Spasms are life threatening when they involve the larynx and/or diaphragm.

Neonatal tetanus presents most often on day 7 of life,[6] with a short (1-day) history of failure of the infant to feed. The neonate displays typical spasms that can be easily misdiagnosed as convulsions of another aetiology. In addition, because these infants vomit (as a result of the increased intra-abdominal pressure) and are dehydrated (because of their inability to swallow), meningitis and sepsis are often considered first.

Autonomic dysfunction occurs in severe cases,[8–10] and begins a few days after the muscle spasms. (The toxin has further to diffuse to reach the lateral horns of the spinal cord.) There is increased basal sympathetic tone, manifesting as tachycardia and bladder and bowel dysfunction. Also, episodes of marked sympathetic overactivity involving both α- and β-receptors occur. Vascular resistance, central venous pressure and, usually, cardiac output are increased, manifesting clinically as labile hypertension, pyrexia, sweating and pallor and cyanosis of the digits.[9] These episodes are usually of short duration and may occur without any provocation. They are caused by reduced inhibition of postsynaptic sympathetic fibres in the intermediolateral cell column, as evidenced by very high circulating norepinephrine (noradrenaline) concentrations.[1,10] Other postulated causes of this variable sympathetic overactivity include loss of inhibition of the adrenal medulla with increased epinephrine (adrenaline) secretion, direct inhibition by tetanospasmin of the release of endogenous opiates, and increased release of thyroid hormone.[1,4]

The role of the parasympathetic nervous system is debatable. Episodes of bradycardia, low peripheral vascular resistance, low central venous pressure and profound hypotension are seen, and are frequently preterminal.[9] Sudden and repeated cardiac arrests occur, particularly in intravenous drug abusers.[10] These events have been attributed to total withdrawal of sympathetic tone, since it is unresponsive to atropine.[11] However, they may be caused by catecholamine-induced myocardial damage[10,12] or direct brainstem damage.[10] Whatever the mechanism, patients afflicted with the autonomic dysfunction of tetanus are at risk of sudden death.

Local tetanus is an uncommon mild form of tetanus with a mortality of 1%. The signs and symptoms are confined to a limb or muscle, and may be the result of immunisation. *Cephalic tetanus* is also rare. It results from head and neck injuries, eye infections and otitis media. The cranial nerves, especially the seventh, are frequently involved and the prognosis is poor. This form may progress to a more generalised form. Tetanus in heroin addicts seems to be severe, with a high mortality, but numbers are small.[10,13]

DIAGNOSIS

The diagnosis is clinical and often straightforward. Examination and special investigations often exclude other diseases. There are no laboratory tests specific to tetanus. *C. tetani* is cultured from the wound in only a third of cases. The most common differential diagnosis is dystonic reaction to tricyclics. Other differential diagnoses include strychnine poisoning, local

temporomandibular disease, local oral disease, convulsions, tetany, intracranial infections or haemorrhage and psychiatric disorders.

MANAGEMENT

Initial objectives of treatment are to neutralise circulating toxin (i.e. passive immunisation) and prevent it from entering peripheral nerves (i.e. wound care), as well as eradicating the source of the toxin (i.e. extensive surgery, hygiene, wound care and antibiotics). Treatment then aims to minimise the effect of toxin already bound in the nervous system, and to provide general supportive care.

PASSIVE IMMUNISATION[1,3,14]

Human antitetanus immunoglobulin (HIG) has now largely replaced antitetanus serum (ATS) of horse origin, as it is less antigenic. HIG will at best neutralise only circulating toxin, but does not affect toxins already fixed in the CNS (i.e. it does not ameliorate symptoms already present).

Current recommendations for HIG in tetanus are 500 IU.[3] It has been suggested that unimmunised patients or those whose immunisation status is unknown should be given HIG on presentation with contaminated wounds. No controlled study has shown this to be more effective than wound toilet and penicillin administration.

Intrathecal administration of antitetanus toxin is still controversial,[15–17] with the most recent meta-analysis reporting some benefit.[18] Moreover, suitable intrathecal preparations are not widely available. Side effects of human antitetanus toxin include fever, shivering and chest or back pains. Cardiovascular parameters need to be monitored, and the infusion may need to be stopped temporarily if significant tachycardia and hypotension are present.[1,7,14] If HIG is not available, equine ATS can be used after testing and desensitisation.[1]

ERADICATION OF THE ORGANISM

WOUND CARE

Once HIG has been given, the infected site should be thoroughly cleaned and all necrotic tissue extensively debrided.

ANTIBIOTICS

Tetanus spores are destroyed by antibiotics. The vegetative form (bacillus) is sensitive to antibiotics in vitro. However, in vivo efficacy depends on the antibiotic concentration at the wound site, and large doses may be required. Recommended antibiotic regimens include:

- *metronidazole 500 mg intravenous (IV) 6–8-hourly for 10 days:* the drug has a spectrum of activity against anaerobes, is able to penetrate necrotic tissue, and has been shown to be more effective than penicillin in this situation[17,19]
- *penicillin G 1–3 Mu IV 6-hourly for 10 days:* penicillin is a GABA antagonist in the CNS,[20] and may aggravate the spasms; nevertheless, it is still often used in this situation.

Nowadays, metronidazole is probably the drug of choice.[17]

SUPPRESSION OF EFFECTS OF TETANOSPASMIN

CONTROLLING MUSCLE SPASMS

In the early stages of tetanus, the patient is most at risk from laryngeal and other respiratory muscle spasm. Therefore, if muscle spasms are present, the airway should be urgently secured by endotracheal intubation or tracheostomy. If respiratory muscles are affected, mechanical ventilation should be instituted. In severe tetanus, spasms usually preclude effective ventilation, and muscle relaxants may be required. Any muscle relaxant can be used.[21] Heavy sedation alone may prevent muscle spasms and improve autonomic dysfunction (see below).

MANAGEMENT OF AUTONOMIC DYSFUNCTION

Autonomic dysfunction manifests in increased basal sympathetic activity[22] and episodic massive outpourings of catecholamines.[22–24] During these episodes, norepinephrine and epinephrine may be up to 10 times basal levels.[22,23] The clinical picture is variable.[24] Hypertension, tachycardia and sweating do not always occur concurrently.

Traditionally, a combination of α- and β-adrenergic blockers has been used to treat sympathetic overactivity. Phenoxybenzamine, phentolamine, bethanidine and chlorpromazine have been used as α-receptor blockers. Ganglion blockers and nitroprusside have occasionally been used, but with the safety profile of newer agents, all these drugs are probably outdated.[17] Propranolol and labetalol have had limited success.[25–27] However, unopposed β-adrenergic blockade cannot be advised. Deaths from acute congestive cardiac failure have resulted.[24,25] Removal of β-mediated vasodilatation in limb muscle causes a rise in systemic vascular resistance, and β-blocked myocardium may not be able to maintain adequate cardiac output. Also, with β blockade, hypotension follows when sympathetic overactivity abates. Esmolol, a very short-acting β-adrenergic blocker given IV, has been reported to

be useful.[28] However, although sympathetic crises can be controlled by esmolol, catecholamine levels remain raised.[24] This raises concern because excessive catecholamine secretion is associated with myocardial damage.[12]

From the above, it appears more logical to decrease catecholamine output. This can be done with sedatives. Benzodiazepines and morphine are successfully used.[23] Morphine and diazepam act centrally to minimise the effects of tetanospasmin. Morphine probably acts by replacing deficient endogenous opioids.[1] Benzodiazepines increase the affinity and efficacy of GABA.[1,17] Very large doses of these agents (e.g. diazepam 3400 mg/day[23] and morphine 235 mg/day[29]) may be required, and are well tolerated, although they may cause a metabolic acidosis due to the preservative propylene glycol within benzodiazipines.[17]

Magnesium has been used as an adjunct to sedation,[23,30] now confirmed by a large trial.[31] Magnesium sulphate infusions to keep serum concentrations between 2.5 and 4.0 mmol/L have decreased systemic vascular resistance and pulse rate, with a small decrease in cardiac output.[23,30] In animal studies, magnesium inhibits release of epinephrine and norepinephrine, and reduces the sensitivity of receptors to these neurotransmitters. Magnesium also has a marked neuromuscular-blocking effect, and may reduce the intensity of muscle spasms. Nevertheless, it could not be shown to decrease the need for mechanical ventilation.[31] However, magnesium sulphate can't be used alone and must be used with other sedatives,[17,23] and calcium supplements may be needed when it is infused. Anecdotally, clonidine, a central α_2-stimulant, has successfully produced sedation with control of autonomic dysfunction.[32] It seems sensible to attempt to make use of the central nervous system effects of an α_2-adrenergic agonist, namely sedation and vasodilatation.[33] Intrathecal baclofen has produced similar beneficial results in a series of cases, but significant respiratory depression occurred in a third.[34] When given intrathecally, baclofen can diminish spasms and spasticity, allowing for a reduction in sedative and paralysis requirements.[17,35]

SUPPORTIVE TREATMENT

Steps should be taken to prevent contractures, nosocomial pneumonias and deep-vein thrombosis. The patient (including the mother if a neonate is afflicted) must be actively immunised. Where possible, supportive psychotherapy should be offered to both patient and family.

COMPLICATIONS[1,2,6,8,12,36]

Muscle spasms disappear after 1–3 weeks, but residual stiffness may persist. Although most survivors recover completely by 6 weeks, cardiovascular complications, including cardiac failure, arrhythmias, pulmonary oedema and hypertensive crises, can be fatal. No obvious cause of death can be found at autopsy in up to 20% of deaths. Other complications include those associated with factors shown in Box 55.1.

Box 55.1 Factors contributing to death in tetanus

- Hypoxia
- Complications of mechanical ventilation
- Myoglobinuria and its attendant problems
- Sepsis, particularly pneumonia
- Fluid and electrolyte problems (including inappropriate antidiuretic hormone secretion)
- Deep-vein thrombosis and embolic phenomena
- Bed sores
- Bony fractures

OUTCOME

Recovery from tetanus is thought to be complete. However, in 25 non-neonatal patients followed for up to 11 years,[37] 15 were reported to have one or more abnormal neurological features such as intellectual or emotional changes, fits and myoclonic jerks, sleep disturbance and decreased libido. Of the 10 apparently normal survivors, 6 had electroencephalogram changes. Some of these symptoms resolved within 2 years.

Mortality figures depend on the availability of intensive care. In neonates, the mortality from African countries with no ICU facilities can be up to 80% of cases, but falls to about 10% when artificial ventilation is used. In the USA, mortality in non-neonates relates directly to age, with rates from 0% in patients under 30 years rising to 50% in those 60 years or older. An average of 10% mortality would seem to be reasonable for most ICUs. However, as this disease is easily and completely preventable, loss of life is unacceptable.

KEY REFERENCES

1. Bleck TP. Tetanus: pathophysiology, management and prophylaxis. *Dis Mon*. 1991;37(9):556–603.
2. Afshar M, Raju M, Ansell D, et al. Narrative review: tetanus – a health threat after natural disasters in developing countries. *Ann Intern Med*. 2011;154:329–335.
8. Kerr JH, Corbett JL, Prys-Roberts C, et al. Involvement of the sympathetic nervous system in tetanus. *Lancet*. 1968;2:236–241.
15. Miranda-Filho Dde B, Ximenes RA, Barone AA, et al. Randomised controlled trial of tetanus treatment with antitetanus immunoglobulin by the intrathecal or intramuscular route. *Br Med J*. 2004;328:615–617.

16. Kabura L, Ilibagiza D, Menten J, et al. Intrathecal vs. intramuscular administration of human antitetanus immunoglobulin or equine tetanus antitoxin in the treatment of tetanus: a meta-analysis. *Trop Med Int Health*. 2006;11:1075–1081.
17. Ahmadsyah I, Salim A. Treatment of tetanus: an open study to compare the efficacy of procaine penicillin and metronidazole. *Br Med J*. 1985;291:648–650.
23. Buchanan N, Smit L, Cane RD, et al. Sympathetic overactivity in tetanus: Fatality associated with propanolol. *Br Med J*. 1978;2:254–255.
27. Rocke DA, Wesley AG, Pather M, et al. Morphine in tetanus – the management of sympathetic nervous system overactivity. *S Afr Med J*. 1986;70:666–668.
29. Thwaites CL, Yen LM, Loan HT, et al. Magnesium sulphate for treatment of severe tetanus: a randomised controlled trial. *Lancet*. 2006;368:1436–1443.

Access the complete references list online at http://www.expertconsult.com.

REFERENCES

1. Bleck TP. Tetanus: pathophysiology, management and prophylaxis. *Dis Mon*. 1991;37(9):556–603.
2. Ergonul O, Egeli D, Kahyaoglu B, et al. An unexpected tetanus case. *Lancet Infect Dis*. 2016;16: 746–752.
3. Afshar M, Raju M, Ansell D, et al. Narrative review: tetanus – a health threat after natural disasters in developing countries. *Ann Intern Med*. 2011;154:329–335.
4. Ackerman AD. Immunology and infections in the pediatric intensive care unit. Part B: infectious diseases of particular importance to the pediatric intensivist. In: Rogers MC, ed. *Textbook of Pediatric Intensive Care*. Baltimore, MD: Williams and Wilkins; 1987:866–875.
5. Prevention of neonatal tetanus. *Lancet*. 1983;1:1253–1254.
6. Stoll BJ. Tetanus. *Pediatr Clin North Am*. 1979;26: 415–431.
7. Reactions to tetanus toxoid. *Br Med J*. 1974;1:48.
8. Alfery DD, Rauscher LA. Tetanus: a review. *Crit Care Med*. 1979;7:176–181.
9. Kerr JH, Corbett JL, Prys-Roberts C, et al. Involvement of the sympathetic nervous system in tetanus. *Lancet*. 1968;2:236–241.
10. Tsueda K, Oliver PB, Richter RW. Cardiovascular manifestations of tetanus. *Anesthesiology*. 1974;40: 588–592.
11. Kerr J. Current topics in tetanus. *Intensive Care Med*. 1979;5:105–110.
12. Rose AG. Catecholamine-induced myocardial damage associated with phaeochromocytomas and tetanus. *S Afr Med J*. 1974;48:1285–1289.
13. Sun KO, Chan YW, Cheung RT, et al. Management of tetanus: a review of 18 cases. *J R Soc Med*. 1994;87:135–137.
14. Antitoxin in treatment of tetanus. *Lancet*. 1976;1:944.
15. Abrutyn E, Berlin JA. Intrathecal therapy in tetanus: a meta-analysis. *JAMA*. 1991;266:2262–2267.
16. Miranda-Filho Dde B, Ximenes RA, Barone AA, et al. Randomised controlled trial of tetanus treatment with antitetanus immunoglobulin by the intrathecal or intramuscular route. *Br Med J*. 2004;328:615–617.
17. Rodrigo C, Fernando D, Rajapakse S. Pharmacological management of tetanus: an evidence-based review. *Crit Care*. 2014;18:217.
18. Kabura L, Ilibagiza D, Menten J, et al. Intrathecal vs. intramuscular administration of human antitetanus immunoglobulin or equine tetanus antitoxin in the treatment of tetanus: a meta-analysis. *Trop Med Int Health*. 2006;11:1075–1081.
19. Ahmadsyah I, Salim A. Treatment of tetanus: an open study to compare the efficacy of procaine penicillin and metronidazole. *Br Med J*. 1985;291:648–650.
20. Clarke G, Hill RG. Effects of a focal penicillin lesion on responses of rabbit cortical neurones to putative neurotransmitters. *Br J Pharmacol*. 1972;44: 435–441.
21. Spelman D, Newton-John H. Continuous pancuronium infusion in severe tetanus. *Med J Aust*. 1980;1:676.
22. Domenighetti GM, Savary G, Stricker H. Hyperadrenergic syndrome in severe tetanus: extreme rise in catecholamines responsive to labetalol. *Br Med J*. 1984;288:1483–1484.
23. Lipman J, James MFM, Erskine J, et al. Autonomic dysfunction in severe tetanus: magnesium sulphate as an adjunct to deep sedation. *Crit Care Med*. 1987;15:987–988.
24. Beards SC, Lipman J, Bothma PA, et al. Esmolol in a case of severe tetanus: adequate haemodynamic control despite markedly elevated catecholamine levels. *S Afr J Surg*. 1994;32:33–35.
25. Buchanan N, Smit L, Cane RD, et al. Sympathetic overactivity in tetanus: fatality associated with propanolol. *Br Med J*. 1978;2:254–255.
26. Wesley AG, Hariparsad D, Pather M, et al. Labetalol in tetanus. The treatment of sympathetic nervous system overactivity. *Anaesthesia*. 1983;38:243–249.
27. Edmondson RS, Flowers MW. Intensive care in tetanus: management, complications and mortality in 100 cases. *Br Med J*. 1979;1:1401–1404.
28. King WW, Cave DR. Use of esmolol to control autonomic instability of tetanus. *Am J Med*. 1991;91:425–428.
29. Rocke DA, Wesley AG, Pather M, et al. Morphine in tetanus – the management of sympathetic nervous system overactivity. *S Afr Med J*. 1986;70:666–668.
30. James MFM, Manson EDM. The use of magnesium sulphate infusions in the management of very severe tetanus. *Intensive Care Med*. 1985;11:5–12.
31. Thwaites CL, Yen LM, Loan HT, et al. Magnesium sulphate for treatment of severe tetanus: a randomised controlled trial. *Lancet*. 2006;368:1436–1443.
32. Sutton DN, Tremlett MR, Woodcock TE, et al. Management of autonomic dysfunction in severe tetanus: the use of magnesium sulphate and clonidine. *Intensive Care Med*. 1990;16:75–80.
33. Kamibayashi T, Maze M. Clinical uses of alpha2-adrenergic agonists. *Anesthesiology*. 2000;93:1345–1349.
34. Saissy JM, Demaziere J, Vitris M, et al. Treatment of severe tetanus by intrathecal injections of baclofen without artificial ventilation. *Intensive Care Med*. 1992;18:241–244.
35. Boots RJ, Lipman J, O'Callaghan J, et al. The treatment of tetanus with intrathecal baclofen. *Anaesth Intensive Care*. 2000;28:438–442.
36. Potgieter PD. Inappropriate ADH secretion in tetanus. *Crit Care Med*. 1983;11:417–418.
37. Illis LS, Taylor FM. Neurological and electroencephalographic sequelae of tetanus. *Lancet*. 1971; 1:826–830.

56

Delirium

Marcela Paola Vizcaychipi, Mena Farag, Edward Watson

Delirium is an acute confusional state common in critically ill patients, particularly those who require ventilation. It is an independent predictor of death and long-term cognitive decline. Prompt identification and treatment of delirium in patients aims to improve outcomes, reduce length of stay (LOS), mechanical ventilator days, morbidity and mortality, as well as the associated financial costs in the intensive care unit (ICU).

DEFINITION

Delirium, as defined by the American Psychiatric Association (APA) in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), is a disturbance in attention, awareness and cognition that develops over a short period of time, fluctuates and is associated with perceptual changes, such as hallucinations (Box 56.1).[1] New to the DSM-5 is the withdrawal of the use of the term 'consciousness' in the revised classification of delirium. Furthermore, it explicitly necessitates that such disturbances are not applicable in the context of a reduced level of arousal (e.g. a comatose state). Omitting consciousness and shifting focus towards attention and awareness is likely a reflection of the challenges encountered in the objective assessment of consciousness.

Three clinical subtypes of delirium are recognised: (1) hypoactive; (2) hyperactive and (3) mixed, each distinguishable by arousal and psychomotor behaviour observed in hospitalised patients. Hypoactive delirium, which is the most common subtype, is often unrecognised or misdiagnosed as depression or sedation. Patients will appear cooperative and docile but will show signs of inattention and be unable to organise thoughts. Pure hyperactive delirium, in contrast, is much less common but more familiar and recognisable to the clinician. Patients can be aggressive and agitated, combative and uncooperative. Patients with hyperactive delirium are more likely to have hallucinations. Mixed delirium exists when patients fluctuate between hypoactive and hyperactive subtypes.

Subsyndromal delirium (SSD) has recently emerged as a distinct yet clinically relevant condition from delirium. SSD has been defined by the presence of one or more symptoms of delirium, but that does not meet the threshold for, nor progress to, delirium.[2,3] Some patients will not present with or progress to full-blown delirium but do have altered mental status. For instance, patients may be able to attend to a conversation whilst experiencing hallucinations. SSD delirium can be diagnosed using the Intensive Care Delirium Screening Checklist (ICDSC).[4] Of note, the presence of a single SSD symptom has been attributed to a significant increase in hospital LOS and functional decline (i.e. it infers a prognostic value).[2] Whilst SSD has been associated with reduced outcomes, prognosis is still better than for those demonstrating the full clinical syndrome.

Delirium tremens (DT) is a subtype of delirium that falls under the clinical spectrum of alcohol withdrawal syndrome. DT onset emerges 48–72 hours following cessation of heavy drinking and is characterised by psychomotor agitation, similar to hyperactive delirium, with symptoms of global confusion, hallucinations and sympathetic nervous system arousal.

HISTORICAL PERSPECTIVE

The first records of delirium are from the 5th century BC by Hippocrates, who described delirium in an acutely confused patient using the terms phrenitis (frenzy) and lethargus. This terminology reflected the belief that the diaphragm governed the 'seat of consciousness' and thus phrenitis – inflammation of the diaphragm – was the underlying pathogenic process.[5] Da Medicina, a 1st century BC treatise by Aulus Cornelius Celsus, used well into the 15th century as a source of medical wisdom, has the first written entry of delirium to describe the acutely confused state. The word delirium is derived from the latin *de* away from + *lira* furrow in a field, hence literally meaning *going away from the ploughed track*. Until relatively recently, those ICU patients who were recognised as delirious were described as either having acute brain failure, ICU psychosis or subacute befuddlement.[6] As per APA recommendations, the term 'delirium' is now uniformly employed in clinical practice to describe this condition of brain dysfunction.

ABSTRACT

Delirium is an acute confusional state that is frequently observed in intensive care unit (ICU) patients. It is characterised by transitory changes in attention, awareness and cognition that develops over a short period of time. ICU delirium is an independent predictor of a longer hospital stay and mortality. Patients who develop this disorder are also at risk of long-term cognitive decline and early dementia. Identification of ICU delirium is feasible through the effective and routine use of delirium screening in daily ICU culture. Regular assessment of cognitive function and sedation will enable early detection of the delirious patient, triggering subsequent prompt intervention and management.

KEYWORDS

Delirium
hyperactive
hypoactive
mixed
postoperative delirium
critical care
intensive care

Box 56.1 DSM-5 classification of delirium

A Disturbance in attention (i.e. reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
B The disturbance develops over a short period of time (usually hours to a few days), represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
C An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability or perception).
D The disturbances in criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal such as coma.
E There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple aetiologies.

INTENSIVE CARE UNIT INCIDENCE, PREVALENCE AND RELEVANCE

ICU patients have the highest incidence of delirium of all clinical areas in the hospital, including orthopaedic/care of the elderly wards. Delirium can occur in up to 69% of ventilated patients in the United Kingdom (UK).[7] Prevalence rates in the ICU have been reported in prospective observational studies varying from 48% in non-ventilated medical ICU patients to 67% and 73% in ventilated (greater than 24 hours) trauma and surgical ICU patients, respectively.[8,9] Peterson et al.[10] examined delirium subtypes in a cohort of 614 critically ill patients admitted to the ICU. Mixed delirium was the most common subtype detected (54.9%), followed by hypoactive delirium (43.5%) and hyperactive delirium (1.6%).[10] In this study, delirium mainly occurred within the first 48 hours of active monitoring, which justifies and reinforces the importance of monitoring for delirium as part of routine clinical care and practice in the ICU.

ICU delirium is an independent predictor of a longer hospital stay and mortality.[8,11] Compared with case-matched critically ill patients without delirium, those with delirium have a 6-month mortality that is three times greater, following ICU admission.[11] Each day spent in a delirious state has been associated with a 10% increase in risk of death.[8,11] ICU delirium is known to be associated with long-term cognitive decline and early dementia. It results in a threefold increase in the risk of discharge into long-term care.[12] and a ninefold increase in the likelihood of experiencing a degree of cognitive impairment following discharge, compared with non-delirious ICU patients.[11] In specific conditions such as Alzheimer disease, the development of delirium has been shown to accelerate cognitive decline.

While the association between delirium and poor outcome is clear, a causal relationship has yet to be proven. Clearly, delirium has implications for quality of life and the independence of patients and their relatives. Patients with delirium have longer ICU and hospital stays.[8] Furthermore, associated costs are increased for both ICU (1.4 fold) and overall hospital (1.3 fold) stays.[13]

PATHOPHYSIOLOGY

The pathophysiology of delirium is ill-defined, but there are a number of theories regarding the pathological changes in the brain that result in and from delirium. Studies supporting the hypotheses reviewed in this subsection were conducted in populations of non-ICU patients and thus further research is required in order to characterise the intricate interplay between critical illness and delirium in the ICU setting. These hypotheses range from neuroinflammation with tumour necrosis factor-alpha (TNF-α) activation of microglia, impaired oxidative metabolism, altered cerebral blood flow, increased blood–brain barrier permeability, thalamic dysfunction and aberrant levels of large neutral amino acids.[14,15]

It is likely that several mechanisms contribute to the development of delirium, which then results in a common pathway of neurotransmitter imbalance and resultant cholinergic hypoactivity.[16,17] There is then, inevitably, a state of relative dopamine excess, which can also cause deterioration in attention or consciousness. The interlinking role of acetylcholine and dopamine makes it difficult to ascertain which of these imbalances is primarily responsible for delirium.

Other theories relate to the availability of tryptophan, a metabolic precursor of serotonin, which may play a role since both increased and decreased levels of serotonin are seen in delirium. It is also possible that there is a genetic component for developing delirium. Apolipoprotein E4 (Apoε4) genotype, wild-type Apoε3, is a susceptibility factor for Alzheimer disease possibly by being less able to suppress cerebral inflammation than the other isoforms. In all of these mechanisms of the cause of delirium, the data are conflicting.[18,19]

RISK FACTORS

The numerous risk factors for delirium fall into two main categories: predisposing (non-modifiable) and precipitating (both modifiable and non-modifiable) (Box 56.2). It is important to realise that the risk of delirium increases with the number of risk factors to which the patient is exposed,[20] and a frail, elderly

Box 56.2 Risk factors for developing delirium in intensive care

Precipitating	Predisposing
infection	age (especially over 65)
anticholinergic drugs	cognitive impairment
opiates	dementia
pain	depression
immobility	genetic factors
dehydration or constipation	institutionalised residence
sedative drugs	liver impairment
sensory impairment	
hyponatraemia	
hypoxia	
hypercarbia	
acidosis	
polypharmacy	
sleep disturbance	
use of physical restraints	
use of bladder catheter	

patient with many predisposing factors may develop delirium from only a minor precipitating factor.

The PRE-DELIRIC (PREdiction of DELIRium in ICu patients) model described by van den Boogaard et al.[21,22] has been developed to help predict the likelihood that a patient admitted to the ICU will develop delirium based on risk factors. It uses various parameters readily available during the first 24 hours of admission, for example the Acute Physiology and Chronic Health Evaluation score (APACHE-II), metabolic acidosis, urea concentration, use of sedatives, etc. Using this model, the risk factors that confer the highest risk of developing delirium in the ICU are coma (from any cause), infection and sedatives.

Utility of the PRE-DELIRIC model, however, is limited given that it only reliably predicts delirium using data acquired after 24 hours in the ICU. Indeed, patients can develop delirium within the first 24 hours following admission to the ICU,[11] which reinforced the need for a validated model capable of immediately predicting the development of delirium at the time of admission to the ICU. This formed the rationale underlying the multinational prospective cohort study by Wassenaar et al.,[23] which led to the development and validity of the early prediction E-PRE-DELIRIC model. Variables that form the E-PRE-DELIRIC model are consistent with established risk factors for delirium,[24–27] including candidate predictors derived from the original PRE-DELIRIC model.[21,22] This model incorporates the following predictors assessed and readily available at the time of ICU admission: age, cognitive impairment, alcohol abuse, admission category (medical, surgical, trauma, neurology/neurosurgery), urgent admission, mean arterial blood pressure, corticosteroid use, respiratory failure and blood urea nitrogen.[23]

DIAGNOSIS AND SCREENING

Diagnosis of delirium is challenging and difficult, particularly without the use of a diagnostic tool and especially when a patient with delirium presents with hypoactive symptoms. Unfortunately, in practice there is converging evidence to suggest that delirium is under-diagnosed and under-recognised. In one study, nurses detected daily delirium in only 34.8% of cases with doctors detecting delirium in only 28%.[28] In another study that used a semi-structured interview to explore current awareness and practice related to delirium in the ICU setting, only 26.8% of ICU healthcare professionals were found to screen for delirium on a routine basis.[29] The notable disparity between the clinical recognition and the actual disease burden of ICU delirium reinforces the importance of employing recently published clinical practice guidelines from the American College of Critical Care Medicine (ACCM) and Society of Critical Care Medicine (SCCM).[30] These guidelines, which are based on available evidence, emphasise and strongly recommend routine monitoring for the presence of delirium in adult ICU patients.[30]

To date, the American Psychiatric Association recommends the use of observational assessment tools in screening for delirium, yet few of them have been validated for use in ICU with intubated patients. The most widely used screening tools in critical care are the Confusion Assessment Method for ICU (CAM-ICU) (Fig. 56.1)[20] and the ICDSC.[4] These tools are designed for clinical use to identify delirium in a critically ill patient and have been validated for intubated patients. They are non-verbal, simple to use and require minimal training. CAM-ICU is a point-in-time assessment, whereas ICDSC uses information gathered over a nursing shift providing information on delirium occurrence.

These screening tools aim to detect the key features of delirium, which are inattention, disorganised thinking, altered level of arousal (with or without hallucinations) and altered sleep pattern in the case of ICDSC. Specificity and sensitivity for each of these tools in critically ill patients are 81% and 96%, respectively (CAM-ICU)[31] and 99% and 66% (ICDSC).[4] However, a cautionary note was sounded by van Eijk et al., who discovered in a multicentre trial that routine daily use of CAM-ICU by nursing staff has a specificity of 98% but a sensitivity of only 47%.[32] Such differences in sensitivity reporting may be secondary to assessor knowledge and implementation processes, which calls for further research to ascertain whether teaching and training can influence delirium detection rates in the clinical setting.

The ACCM and SCCM guidelines advocate both the CAM-ICU and ICDSC as the most valid and reliable screening tools for detecting and monitoring delirium in adult ICU patients.[30] These tools have

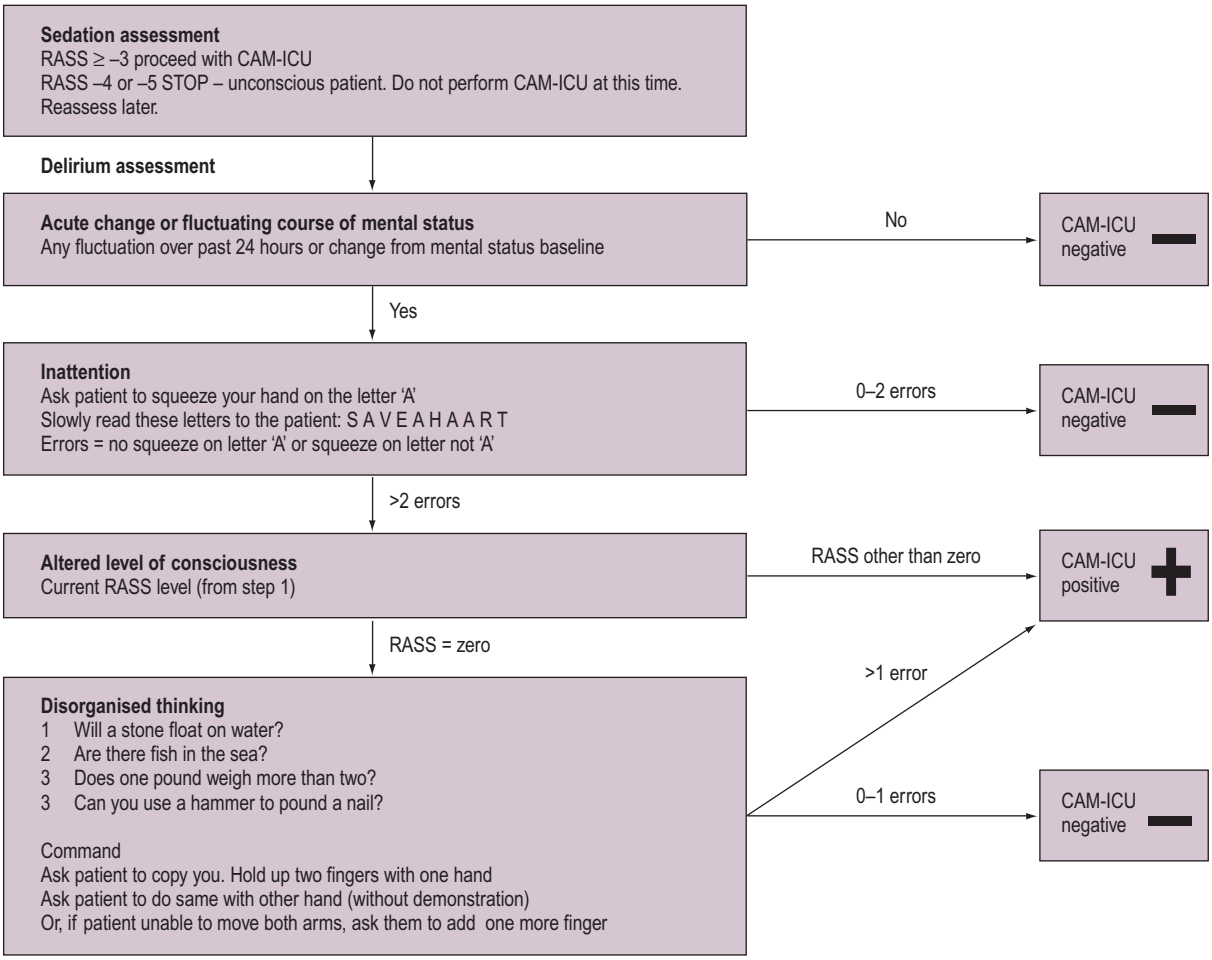


Figure 56.1 Confusion assessment method for intensive care unit *(CAM-ICU)* flow chart. *RASS*, Richmond Agitation–Sedation Scale. *Reproduced with permission from E Wesley Ely, MD MPH.*

high sensitivity, specificity and inter-rater reliability. Identification of ICU delirium is feasible if effective and routine delirium screening is integrated into daily ICU culture, for example, as part of the standard ICU admission clerking.

MANAGEMENT OF DELIRIUM

GENERAL MANAGEMENT

Initial management should aim at correcting the cause of delirium. If a medical condition has triggered delirium, it is likely that the patient will continue to be delirious, with all the associated neuroinflammation, neurotransmitter imbalance and alterations in cerebral blood flow, until the medical condition has successfully been treated. Reversal of the underlying cause is important and necessary examination and investigations should be undertaken, taking into account that there may, of course, be more than one precipitating cause. Management strategies should not only aim to reverse and reduce the duration of ICU delirium, but emphasis should be placed on the prevention. Approaches to prevent the occurrence of ICU delirium can be divided into non-pharmacological and pharmacological interventions.

NON-PHARMACOLOGICAL INTERVENTIONS

There are a multitude of simple, non-pharmacological measures, free from adverse effects, that can be employed with the aim of reducing the severity or preventing delirium.[33] These include clear and firm communication with frequent verbal orientation cues (e.g. date, time and location). Involvement of relatives provides the patient with a sense of control, familiarity and security. It can also provide the clinician with vital collateral information regarding the patient's premorbid mental and functional status. Other factors include

minimising environmental noise and correcting audio and visual sensory impairments.

Reduced sleep quality and interruptions in rapid eye movement (REM) sleep is a postulated contributory factor to the development of ICU delirium.[34] Minimising sleep deprivation and its associated impact on delirium can be achieved through pragmatic steps. Promotion of a normal sleep-wake cycle is important and can be facilitated by reducing night-time disturbances, for example the mindful timing of interventions.

Early mobilisation of critically ill patients has been demonstrated to decrease delirium and improves outcomes.[35] On the basis of a moderate quality of evidence (+1B), the ACCM and SCCM guidelines explicitly promote early mobilisation as a strategy to reduce the duration and incidence of ICU delirium.[30] Physical restraints, rarely used in the United Kingdom, are known to increase the risk of delirium. Use of physical restraints should be avoided. Medical restraints, for example lines, leads and catheters, can also impact the mobility of patients and should be removed as early as is prudent.

Other measures such as controlling febrile episodes, correcting electrolyte and metabolic derangements, setting patient-appropriate blood pressure and oxygenation targets represent essential non-pharmacological strategies to prevent the onset and reduce the duration of delirium in the ICU.

PHARMACOLOGICAL INTERVENTIONS

Sedation is a common and unfortunately requisite element of ICU therapy. All sedative drugs, including fentanyl and propofol, are likely to precipitate delirium. It is essential to have a sedation protocol with routine sedation scoring, sedation targets and daily sedation holds where appropriate.[36] The pharmacological class and dose of the sedative, and patient susceptibility factors, are all important considerations when prescribing and administering central nervous system (CNS) depressants. Daily sedation holds and spontaneous breathing trials, as the patient clinical condition allows, have been shown to decrease mortality.[37] Deep sedation (e.g. RASS –3 [Richmond Agitation–Sedation Scale]) in the first 48 hours of sedation and ventilation in the ICU has been associated with increased time to extubation and mortality.[38] Unless there is a clinical reason to keep a patient sedated, for example in cases of severe or life-threatening asthma, it is suggested that a daily sedation target of RASS 0 to –1 is appropriate.

Pain control in critical care is important. Although opioids can be deliriogenic, higher doses of opiates are associated with a significantly lower risk of delirium in the population of intensive care burns patients.[39] Weighing the risk of opioid-induced delirium against suffering and pain-induced delirium is a difficult balancing act. Pain management can be optimised, however, through routine pain monitoring, for example using structured tools such as the Behavioural Pain Scale (BPS) and the Critical-Care Pain Observation Tool (CPOT), as recommended in the ACCM and SCCM guidelines.[30] Although self-reporting is the gold standard for assessment of pain, the BPS and CPOT are reliable and valid tools that enable assessment of pain in adult ICU patients who are reluctant or unable to self-report.

Pharmacological treatment primarily involves the use of dopamine antagonists – typical and atypical antipsychotics. Clinical trials have attempted to address the question whether antipsychotics can be used to prevent delirium.[40,41] Although these have shown positive effects on delirium, reducing either duration or severity, this has not been translated to an improvement in outcome. Thus, there is currently insufficient robust scientific evidence to recommend the use of prophylactic antipsychotics. In fact, the ACCM and SCCM guidelines openly recommend against pharmacological prophylaxis in view of the low quality of evidence (–2C).[30]

HALOPERIDOL

Haloperidol is a butyrophenone with partial selectivity for dopamine $D\text{-}_2$ receptors. Its licensing is variable in different countries; for example, intravenous (IV) haloperidol is not licensed in the United States. However, in the United Kingdom it is commonly used in monitored, critically ill patients when enteral absorption is impaired.

Side effects include sedation, autonomic effects and, more importantly, extrapyramidal symptoms (e.g. dystonia, excessive salivation). Akathisia, an unpleasant sensation of restlessness, may be mistaken for continuing agitation. Haloperidol should not be given to patients with Parkinson disease or patients with a family history of dystonia.

More serious side effects include neuroleptic malignant syndrome and Torsades de pointes, both potentially life threatening. QT_c prolongation increases the risk of Torsades de pointes; monitoring should be carried out prior to starting haloperidol and daily whilst the patient is receiving the drug. Haloperidol can be used with caution with a QT_c greater than 450 ms and should not be used if greater than 500 ms.

Doses of haloperidol used clinically range from 0.5–10 mg, although 2.5–5 mg is more common; the maximum dose in 24 hours is 18 mg.

OLANZAPINE, QUETIAPINE, RISPERIDONE

Other antipsychotics have lower incidence of extrapyramidal side effects. Olanzapine can be given both intramuscularly and intravenously. It is as effective as haloperidol in critically ill patients[41] and is a useful alternative if haloperidol is contraindicated.[42] The starting dose is usually 5 mg, up to 20 mg daily (10 mg in renal failure). For patients with dementia who are

agitated, quetiapine and risperidone are recommended. Quetiapine has been shown to decrease delirium in a placebo-controlled trial[43] and risperidone was seen to be as effective as olanzapine in managing delirium.[44]

CLONIDINE, DEXMEDETOMIDINE

α_2 adrenergic receptor agonists have a sedative effect without gamma-aminobutyric acid-ergic (GABAergic) activity, potentially reducing the requirements of sedation, which itself can be deliriogenic.

Clonidine is favoured by some clinicians if a patient is requiring large doses of sedatives due to agitation. A starting dose would be 1 μg/kg enterally or diluted with saline and given slowly intravenously. Dexmedetomidine is a more highly selective α_2 agonist and may be beneficial in terms of length of time at targeted level of sedation and less agitated delirium.[45] Of note, the ACCM and SCCM guidelines comment that dexmedetomidine infusions administered for sedation may be associated with a lower prevalence of delirium in mechanically ventilated patients (compared to benzodiazpine sedation) and thus may represent a preferable sedation strategy to adopt in practice.[30]

ANTICHOLINESTERASES

The use of anticholinesterases, including rivastigmine, for treatment of delirium in critically ill patients is not recommended and may be harmful.[46]

BENZODIAZEPINES

Benzodiazepines should be used only for the treatment of delirium tremens resulting from alcohol withdrawal. A Cochrane review of benzodiazepines in delirium treatment concluded that their use is not indicated in non–alcohol-withdrawal agitated delirium.[47] Indeed, a study in critically ill burns patients revealed benzodiazepine exposure to be an independent risk factor, with these patients approximately seven times more likely to develop delirium.[39] However, if agitation is severe and is putting the patient at risk, a *stat* dose of a benzodiazepine might be indicated for rapid control of the incident. Up to 2 mg IV of lorazepam every 4 hours may be of benefit. It has rapid onset, short duration of action and low risk of accumulation. A reduced dose should be prescribed when administering to elderly patients and those with hepatic disease.

PERSISTENT DELIRIUM

Elderly patients may be left with persistent delirium, lasting beyond three months. The use of antipsychotics may be considered in individual cases, although generally care-of-the-elderly physicians avoid antipsychotics in their practice, relying on non-pharmacological interventions.

A possible ICU management protocol is outlined in Fig. 56.2.

REMEMBER THE RELATIVES

ICU admission is already a distressing time for relatives and friends of patients and this is exacerbated by witnessing their loved ones suffering from delirium. Thus, it is good practice to emphasise awareness that mental status changes in the ICU are common and inform them that, although delirium can lead to cognitive impairment, generally any acute psychosis is transient. It is often useful to provide a delirium information leaflet for relatives and reassure them that clinicians are conscientiously vigilant to seek and address underlying treatable causes.

Furthermore, it is prudent to continue to counsel and support the patient after recovery. This may involve affording time to listen to the patient talk about their experience, in particular any vivid hallucinations endured during the delirious episode. Patient diaries have been shown to help fill gaps in memory and rationalise traumatic hallucinations.[48]

SUMMARY

Delirium is commonly encountered in the ICU, is associated with longer ICU and hospital stays, increased mortality and with a long-term cognitive deficit and early dementia. Regular assessment of cognitive function and sedation will enable early detection of the delirious patient, triggering subsequent prompt intervention and management. Delirium primarily requires correction of likely causes (medical or drug related) and minimising known risk factors. First-line treatment of agitated delirium consists of antipsychotics, usually IV haloperidol; olanzapine or quetiapine are useful second-line treatments and the use of benzodiazepines is strongly advised against. Keep friends and relatives, and, whenever possible, the patient informed.

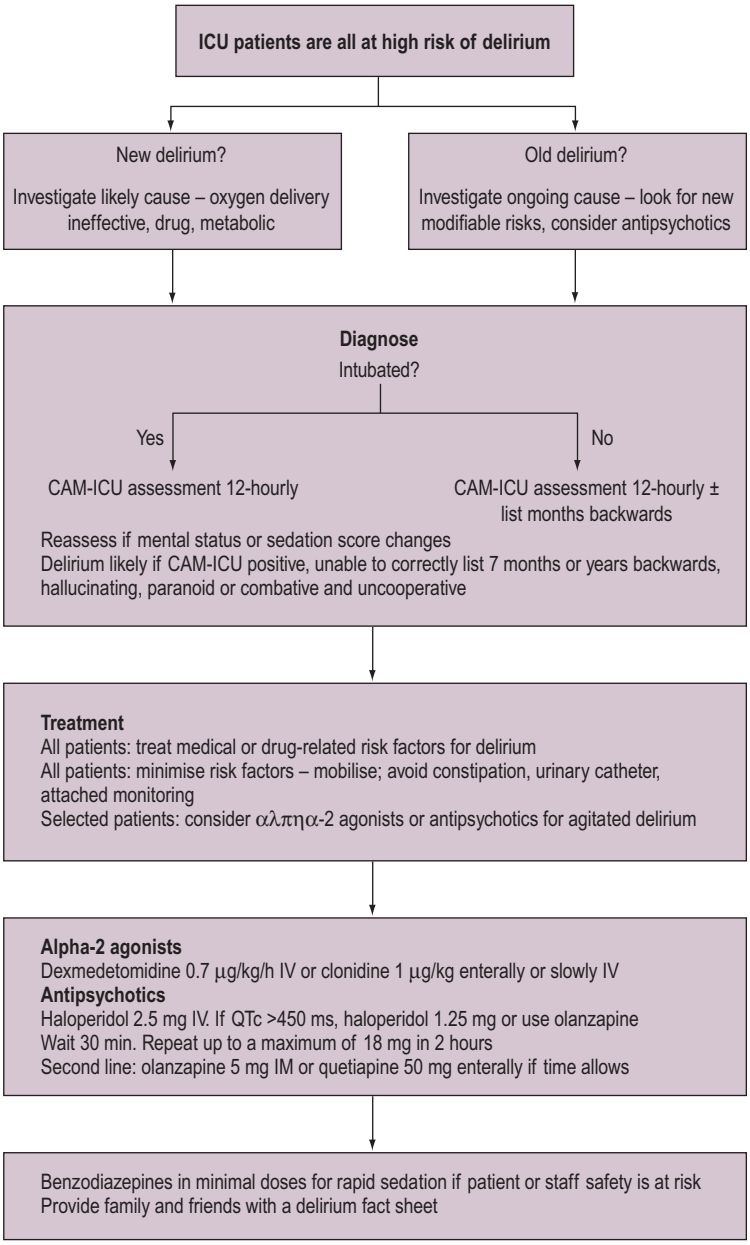


Figure 56.2 Critical care unit guideline for treatment of delirium. *CAM-ICU*, Confusion assessment method for intensive care unit; *IM*, intramuscular; *IV*, intravenous.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.
2. Shim J, DePalma G, Sands LP, et al. Prognostic significance of postoperative subsyndromal delirium. *Psychosomatics*. 2015;56(6):644–651. doi: 10.1016/j.psym.2015.05.002.
3. Cole MG, Ciampi A, Belzile E, et al. Subsyndromal delirium in older people: a systematic review of frequency, risk factors, course and outcomes. *Int J Geriatr Psychiatry*. 2013;28(8):771–780. doi:10.1002/gps.3891.
4. Bergeron N, Dubois MJ, Dumont M, et al. Intensive care delirium screening checklist: evaluation of a new screening tool. *Intensive Care Med*. 2001;27:859–864.

5. Lipowski AJ. *Delirium: Acute Confusional States*. New York: Oxford University Press; 1990.
6. Liston EH. Delirium in the aged. *Psychiatr Clin North Am*. 1982;5(1):49–66.
7. Page VJ, Navarange S, Gama S, et al. Routine delirium monitoring in a UK intensive care unit. *Crit Care*. 2009;13:R16.
8. Thomason JW, Shintani A, Peterson JF, et al. Intensive care unit delirium is an independent predictor of longer hospital stay: a prospective analysis of 261 non-ventilated patients. *Crit Care*. 2005;9(4):R375–R381.
9. Pandharipande P, Cotton BA, Shintani A, et al. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *J Trauma*. 2008;65(1):34–41. doi:10.1097/TA.0b013e31814b2c4d.
10. Peterson JF, Pun BT, Dittus RS, et al. Delirium and its motoric subtypes: a study of 614 critically ill patients. *J Am Geriatr Soc*. 2006;54(3):479–484.
11. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*. 2004;291(14):1753–1762.
12. McCusker J, Cole MG, Voyer P, et al. Prevalence and incidence of delirium in long-term care. *Int J Geriatr Psychiatry*. 2011;26(11):1152–1161. doi:10.1002/gps.2654.
13. Milbrandt EB, Deppen S, Harrison PL, et al. Costs associated with delirium in mechanically ventilated patients. *Crit Care Med*. 2004;32(4):955–962.
14. Lemstra AW, Groen in't Woud JC, Hoozemans JJ, et al. Microglia activation in sepsis: a case-control study. *J Neuroinflammation*. 2007;4:4.
15. Maclullich AM, Ferguson KJ, Miller T, et al. Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. *J Psychosom Res*. 2008;65(3):229–238. doi:10.1016/j.jpsychores.2008.05.019.
16. Field RH, Gossen A, Cunningham C. Prior pathology in the basal forebrain cholinergic system predisposes to inflammation-induced working memory deficits: reconciling inflammatory and cholinergic hypotheses of delirium. *J Neurosci*. 2012;32(18):6288–6294. doi:10.1523/JNEUROSCI.4673-11.2012.
17. Trzepacz PT. Update on the neuropathogenesis of delirium. *Dement Geriatr Cogn Disord*. 1999;10(5):330–334.
18. Leung JM, Sands LP, Wang Y, et al. Apolipoprotein E e4 allele increases the risk of early postoperative delirium in older patients undergoing noncardiac surgery. *Anesthesiology*. 2007;107(3):406–411.
19. Abelha FJ, Fernandes V, Botelho M, et al. Apolipoprotein E e4 allele does not increase the risk of early postoperative delirium after major surgery. *J Anesth*. 2012;26:412–421.
20. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med*. 2001;29(7):1370–1379.
21. van den Boogaard M, Pickkers P, Slooter AJ, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. *BMJ*. 2012;344:e420. doi:10.1136/bmj.e420.
22. van den Boogaard M, Schoonhoven L, Maseda E, et al. Recalibration of the delirium prediction model for ICU patients (PRE-DELIRIC): a multinational observational study. *Intensive Care Med*. 2014;40(3):361–369. doi:10.1007/s00134-013-3202-7.
23. Wassenaar A, van den Boogaard M, van Achterberg T, et al. Multinational development and validation of an early prediction model for delirium in ICU patients. *Intensive Care Med*. 2015;41(6):1048–1056. doi:10.1007/s00134-015-3777-2.
24. Van Rompaey B, Schuurmans MJ, Shortridge-Baggett LM, et al. Risk factors for intensive care delirium: a systematic review. *Intensive Crit Care Nurs*. 2008;24(2):98–107.
25. Van Rompaey B, Elseviers MM, Schuurmans MJ, et al. Risk factors for delirium in intensive care patients: a prospective cohort study. *Crit Care*. 2009;13(3):R77. doi:10.1186/cc7892.
26. Huai J, Ye X. A meta-analysis of critically ill patients reveals several potential risk factors for delirium. *Gen Hosp Psychiatry*. 2014;36(5):488–496. doi:10.1016/j.genhosppsych.2014.05.002.
27. Zaal IJ, Devlin JW, Peelen LM, et al. A systematic review of risk factors for delirium in the ICU. *Crit Care Med*. 2015;43(1):40–47. doi:10.1097/CCM.0000000000000625.
28. Spronk PE, Riekerk B, Hofhuis J, et al. Occurrence of delirium is severely underestimated in the ICU during daily care. *Intensive Care Med*. 2009;35(7):1276–1280. doi:10.1007/s00134-009-1466-8.
29. Selim AA, Wesley Ely E. Delirium the under-recognised syndrome: survey of health care professionals' awareness and practice in the intensive care units. *J Clin Nurs*. 2016;doi:10.1111/jocn.13517.
30. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41(1):263–306. doi:10.1097/CCM.0b013e3182783b72.
31. Luetz A, Heymann A, Radtke FM, et al. Different assessment tools for intensive care unit delirium: which score to use? *Crit Care Med*. 2010;38(2):409–418. doi:10.1097/CCM.0b013e3181cabb42.
32. van Eijk MM, van den Boogaard M, van Marum RJ, et al. Routine use of the confusion assessment method for the intensive care unit: a multicenter study. *Am J Respir Crit Care Med*. 2011;184(3):340–344. doi:10.1164/rccm.201101-0065OC.
33. Inouye SK, Bogardus ST Jr, Charpentier PA, et al. A multicomponent intervention to prevent

delirium in hospitalised older patients. *N Engl J Med*. 1999;340(9):669–676.
34. Trompeo AC, Vidi Y, Locane MD, et al. Sleep disturbances in the critically ill patients: role of delirium and sedative agents. *Minerva Anestesiol*. 2011;77(6):604–612.
35. Naughton BJ, Saltzman S, Ramadan F, et al. A multifactorial intervention to reduce prevalence of delirium and shorten hospital length of stay. *J Am Geriatr Soc*. 2005;53(1):18–23.
36. Skrobik Y, Ahern S, Leblanc M, et al. Protocolised intensive care unit management of analgesia, sedation, and delirium improves analgesia and subsyndromal delirium rates. *Anesth Analg*. 2010;111(2): 451–463. doi:10.1213/ANE.0b013e3181d7e1b8.
37. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371(9607):126–134. doi:10.1016/S0140-6736(08)60105-1.
38. Shehabi Y, Bellomo R, Reade MC, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. *Am J Respir Crit Care Med*. 2012;186(8):724–731. doi:10.1164/rccm.201203-0522OC.
39. Agarwal V, O'Neill PJ, Cotton BA, et al. Prevalence and risk factors for development of delirium in burn intensive care unit patients. *J Burn Care Res*. 2010;31(5):706–715. doi:10.1097/BCR.0b013e3181eebee9.
40. Wang W, Li HL, Wang DX, et al. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomised controlled trial. *Crit Care Med*. 2012;40(3):731–739. doi:10.1097/CCM.0b013e3182376e4f.
41. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomised placebo-controlled study. *J Am Geriatr Soc*. 2005;53(10): 1658–1666.
42. Skrobik YK, Bergeron N, Dumont M, et al. Olanzapine vs haloperidol: treating delirium in a critical care setting. *Intensive Care Med*. 2004; 30(3):444–449.
43. Devlin JW, Roberts RJ, Fong JJ, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomised, double-blind, placebo-controlled pilot study. *Crit Care Med*. 2010;38(2):419–427. doi:10.1097/CCM.0b013e3181b9e302.
44. Kim SW, Yoo JA, Lee SY, et al. Risperidone versus olanzapine for the treatment of delirium. *Hum Psychopharmacol*. 2010;25(4):298–302. doi:10.1002/hup.1117.
45. Hoy SM, Keating GM. Dexmedetomidine: a review of its use for sedation in mechanically ventilated patients in an intensive care setting and for procedural sedation. *Drugs*. 2011;71(11):1481–1501. doi:10.2165/11207190-000000000-00000.
46. van Eijk MM, Roes KC, Honing ML, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. *Lancet*. 2010;376(9755):1829–1837. doi:10.1016/S0140-6736(10)61855-7.
47. Lonergan E, Luxenberg J, Areosa Sastre A. Benzodiazepines for delirium. *Cochrane Database Syst Rev*. 2009;(4):CD006379.
48. Ewens B, Chapman R, Tulloch A, et al. ICU survivors' utilisation of diaries post discharge: a qualitative descriptive study. *Aust Crit Care*. 2014;27(1):28–35. doi:10.1016/j.aucc.2013.07.001.

WEBSITES

http://www.hospitalelderlylifeprogram.org
www.icudelirium.co.uk
www.icudelirium.org

57

Intensive care unit-acquired weakness

Zudin Puthucheary

The loss of flesh and strength is striking
William Osler 1882

DEFINITION

Intensive care unit-acquired weakness (ICU-AW), first recognised in 1977, is an encompassing functional description of post-critical-illness weakness of all causes (once primary neuromuscular diseases have been excluded). Over time, more than 20 different terms have been used[1] until a definition framework was proposed[1] and later accepted[2] as part of clinical practice guidelines.

We currently consider all generalised new weakness with no alternative explanation to be ICU-AW. In those with documented polyneuropathy and/or myopathy, subcategories exist of:

Critical illness polyneuropathy (CIP): Those with electrophysiological evidence of distal axonal polyneuropathy

Critical illness myopathy (CIM): those with electrophysiological and/or histological evidence of myopathy

Critical illness neuromyopathy (CINM): those with electrophysiological and/or histological evidence of CIM and CIP.

At this current point in time, subcategory diagnoses are not relevant in the acute phase, as no treatments are available. In the setting of long-term follow-up survivor outpatient clinics, these diagnoses may have an important role and implications.

CLINICAL FEATURES

The classical features are that of a symmetrical flaccid weakness, with absent reflexes. Proximal muscle wasting is a hallmark of ICU-AW.[3] The facial muscles are often spared. The presence of distal muscle weakness predominance suggests either an alternative diagnosis or the presence of axonal damage (CIP or overlap).[4]

DIAGNOSTIC CRITERIA

PHYSICAL EXAMINATION

ICU-AW is diagnosed on physical examination using the Medical Research Council (MRC) Sum Score. The MRC sum score was first described in 60 patients with Guillain-Barré syndrome as an assessment tool, as part of the Dutch gamma globulin trial.[5,6] A 90% inter-rater agreement (defined as <10% change in score) was seen in measurements between blinded observers. In 2002, this technique was deployed in a multicentred observational study of 95 critically ill patients following 7 days of mechanical ventilation.[3] Patients were expected to respond appropriately to three of five questions, on two consecutive evaluations with a 6-hour interval, to be considered appropriate for manual muscle testing.

Each limb is scored using the MRC strength scale of 0-5 for proximal and distal muscle groups in regards to the ability to exert force against resistance (5-4), overcome gravity (3), to move once gravity is eliminated (2) or if only fasciculation (1) or no movement (0) is observed (Table 57.1; the score for each limb is then added up to a maximum of 60). An arbitrary cut-off of 48 is used to distinguish weak patients.

Several concerns exist as regards its clinical utility. Whilst excellent inter-rater reliability has been seen in healthy subjects and critical illness survivors, this worsens considerably in the ICU setting.[7,8] Furthermore, 30%–60% of patients have been unable to perform manual muscle testing when assessed.[3,8] Proximal muscle wasting is extremely common[3] and of initial substantial functional importance, but is underrepresented in the MRC Sum Score (Fig. 57.1). Finally, MRC Sum score assessment can detect weakness once it occurs, but is unable to identify those *at risk*.

ELECTROPHYSIOLOGICAL STUDIES

Nerve conduction abnormalities have been demonstrated repeatedly in the critically ill patient, and were first described by Bolton in 1984.[9] Emerging hypotheses for the pathophysiology include acquired channelopathies of voltage-gated sodium channels,

ABSTRACT

Intensive care unit-acquired weakness (ICU-AW), first recognised in 1977, is an encompassing functional description of post-critical-illness weakness of all causes (once primary neuromuscular diseases have been excluded).

KEYWORDS

Intensive care acquired weakness
muscle
protein homeostasis
functional outcomes

Table 57.1 Medical Research Council Sum Score

RIGHT	SCORE	LEFT	SCORE
Shoulder abduction	(0–5)	Shoulder abduction	(0–5)
Elbow flexion	(0–5)	Elbow flexion	(0–5)
Wrist extension	(0–5)	Wrist extension	(0–5)
Hip flexion	(0–5)	Hip flexion	(0–5)
Knee extension	(0–5)	Knee extension	(0–5)
Ankle dorsiflexion	(0–5)	Ankle dorsiflexion	(0–5)
TOTAL	(0–30)	TOTAL	(0–30)

MRC SS = TOTAL of RIGHT AND LEFT SCORES
MRC SS ≤ 48 = ICU-AW

Strength is scored as ability to exert force against resistance (5-4), overcome gravity (3), to move once gravity is eliminated (2), or only fasciculation (1) or no movement (0) is observed.
ICU-AW, Intensive care unit-acquired weakness; *MRC SS*, Medical Research Council sum score.

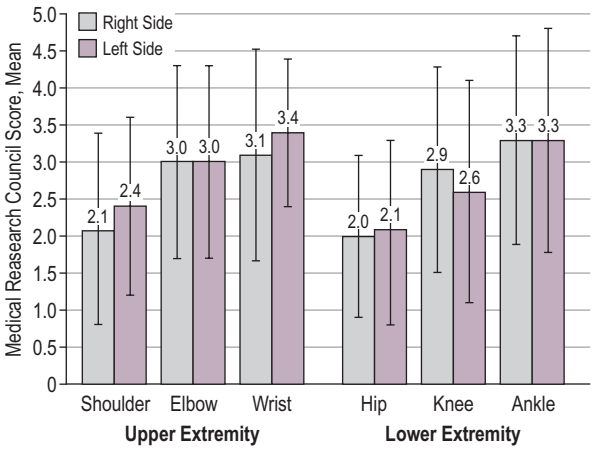


Figure 57.1 Medical Research Score distribution in awake critically ill patients, demonstrating proximal muscle wasting. *From De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit: a prospective multicenter study*. JAMA. *2002;288(22): 2859–2867*.

localising the defect to the muscle membrane.[10–12] In addition, neuronal tissue architecture disruption has been seen in peripheral nerve biopsies.[13] Quantification and description of these functional defects is done by nerve conduction studies (NCS) and electromyography (EMG).[14] Aside from the technical difficulties of performing and interpreting EMG in the critical care setting, their use in assessing the aetiology or severity of muscle weakness is limited by two factors. Firstly, EMG and NCS abnormalities appear universal in ICU patients and correlate poorly with the severity of muscle function loss.[3,14–17] Secondly, lack of patient cooperation (for instance, due to sedation or pharmacological paralysis) prevents early detection of neuromuscular abnormalities and thus risk of weakness.[1] Whilst severe neuropathy is debilitating, critical illness neuropathy is much less common than *CIM*[3,18,19] and, again, correlates poorly with symptoms of weakness.

Electrophysiological studies are rarely performed in the acute setting. However, neurophysiology is essential for the diagnosis of peripheral nerve injury – both foot drop and entrapment syndromes are common and, if untreated, can lead to functional disability. Further, it can be used to distinguish other less common causes of weakness that are unmasked by critical illness (e.g. motor neurone disease).

Criteria for subcategories of ICU-AW described by Stevens[1] are as follows:

CIP:
- Compound muscle action potential amplitudes are decreased to less than 80% of lower limit of normal in ≥2 nerves
- Sensory nerve action potential amplitudes are decreased to less than 80% of lower limit of normal in ≥2 nerves
- Normal or near-normal nerve conduction velocities without conduction block
- Absence of a decremented response on repetitive nerve stimulation

CIM:
- Sensory nerve action potential amplitudes are greater than 80% of the lower limit of normal in ≥2 nerves
- Needle electromyogram in ≥2 muscle groups demonstrates short-duration, low-amplitude motor unit potentials with early or normal full recruitment with or without fibrillation potentials
- Direct muscle stimulation demonstrates reduced excitability (muscle/nerve ratio >0.5) in ≥2 muscle groups

INCIDENCE

ICU-AW is the most common secondary complication of critical illness. Weakness at awakening can be detected in up to 65% of patients following 5–7 days of ventilation.[3,20–22] This is unsurprising given that a 10% change in muscle mass has significant functional implications[23] and critically ill patients in multiorgan failure waste away at rates between 2% and 3% per day.[24]

Understanding the incidence of CIP, CIM and CINM is less easy as electrophysiological abnormalities are almost universally present in the acute critical illness phase[16] and bear an unclear relationship with the eventual clinical phenotype. Furthermore, the variation in diagnostic methodology and timings vary widely in the literature.[25] In a longitudinal study of 92

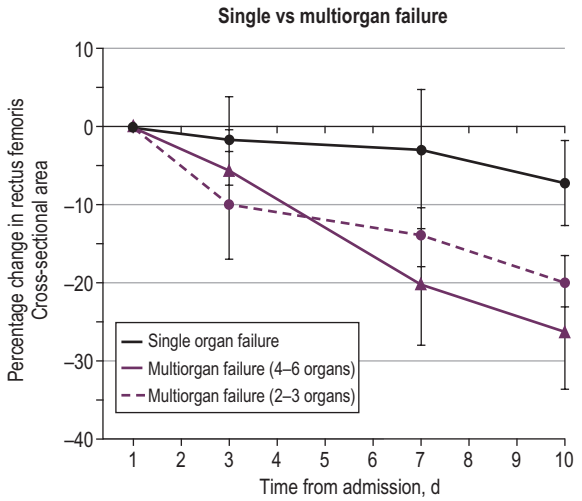


Figure 57.2 Rates of skeletal muscle wasting by organ failure. Organ failure defined as cumulative sequential organ failure assessment scores. *d*, day. *From Puthucheary ZA, Rawal J, McPhail M, et al. Acute skeletal muscle wasting in critical illness.* JAMA. *2013;310(15): 1591–1600.*

patients, 6.5% had CIM, 4.3% CIP and 5.4% CINM[26] on ICU discharge.

PATHOPHYSIOLOGY

LOSS OF MUSCLE MASS

Acute muscle wasting occurs rapidly and early in critical illness. Detectable muscle loss can occur within the first 72 hours. Several studies have suggested that wasting occurs at rates of 2%–3% per day of critical illness.[27] The severity of muscle wasting is directly related to the degree of illness severity; as more organs fail (sequential organ failure assessment [SOFA] score >2 within an organ system), more muscle is lost (Fig. 57.2).[24]

Clinical drivers of muscle wasting have been noted to be the Pa_{O_2} to Fi_{O_2} ratio, and the degrees of acidosis and inflammation. In the only direct study comparing nutritional delivery to change in muscle mass, no interactions were seen with calories delivered, and increased protein delivery was associated with increased muscle wasting.[24] Whilst controversial and should be seen as hypothesis generating currently, the ability of nutritional delivery to affect muscle mass remains contentious (see later).

ALTERED PROTEIN HOMEOSTASIS

Skeletal muscle mass in all vertebral organisms is governed by the principles of protein homeostasis: a balance of muscle protein synthesis (MPS) and muscle protein breakdown (MPB).[28] The two processes are

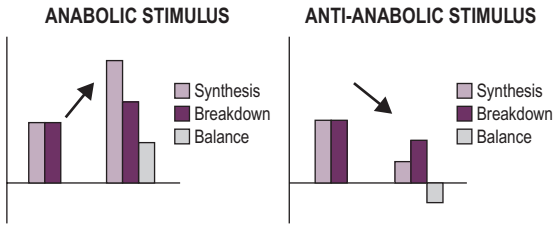


Figure 57.3 Schematic of the protein homeostatic response in humans to anabolic and anti-anabolic stimuli.

linked. In humans (in a completely different fashion from rodents), MPS has been repeatedly shown to be facilitative (the initial responsive process to a physiological stimulus) and MPB *adaptive* (responds to the change in MPS) by decreasing or increasing (but to a lesser amount) alongside MPS (Fig. 57.3).[29a]

Within the critical care environment, patients are exposed to a variety of stimuli that affect this balance (Fig. 57.4).

Muscle protein homeostasis in the critically ill seems to be determined by the time course of illness. Whilst several studies have conflicted as to the altered balance, a longitudinal study demonstrated suppressed MPS on the initial day of critical illness, with variable recovery over the first week.[24] This decrease in MPS resulted in a greater MPB than MPS, resulting in a net catabolic state that was mirrored by activity of the intracellular signalling pathways governing muscle protein homeostasis.[24] This same alteration in protein homeostasis was recently seen in patients ventilated for greater than 10 days, though it was noted that with increasing time, MPS recovered but MPB rose.[29b]

BIOENERGETIC IMPAIRMENT

MPS is a highly energy-dependent process and its depression may be the result of altered metabolism. Mitochondrial numbers[30] and function[31–33] reductions have been described, and intramuscular adenosine triphosphate (ATP) declines during critical illness irrespective of nutritional delivery.[34] This is mirrored by decreases in phosphorylated and total creatine, likely contributed to by the observed myonecrosis (see later). Beta-oxidation additionally declines, rendering fatty acid delivered as part of nutrition or sedation (propofol) relatively inert bioenergetically. Insulin resistance is well described in critical illness, and is in part the result of impaired GLUT-4 translocation, worsening the bioenergetic impairment.[35]

SKELETAL MUSCLE INFLAMMATION

Inflammation is well described as a suppressant of MPS[36] and intramuscular inflammation occurs in critically ill patients, related to altered protein homeostasis.[34] Additionally, this may impede recovery from myonecrosis by affecting macrophage function.

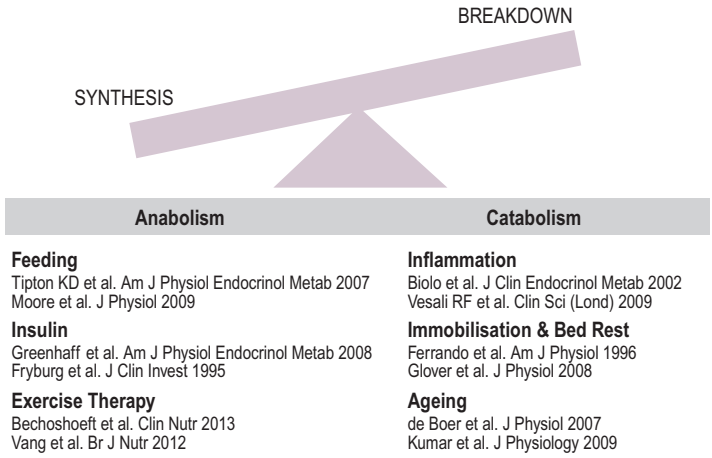


Figure 57.4 Factors affecting muscle protein homeostasis in critically ill patients.

IMPAIRED MUSCLE MEMBRANE EXCITABILITY

ICU-AW was originally described as a distal, axonal neuropathy[9] before observational data revealed the far greater prevalence of muscle wasting.[3,24] However, inflammation in experimental settings has been shown to affect muscle membrane excitability.[12] This is likely to be the result of inactivation of the voltage-gated muscle membrane sodium channels.[37] Additionally, sepsis models have suggested altered contractility secondary to deranged intracellular calcium homeostasis.[38]

In critically ill patients, this was elegantly demonstrated to be clinically relevant by the ability of the compound muscle action potential after direct muscle stimulation to be decreased in critical illness and to be highly predictive of subsequent ICU-AW (Fig. 57.5).[39]

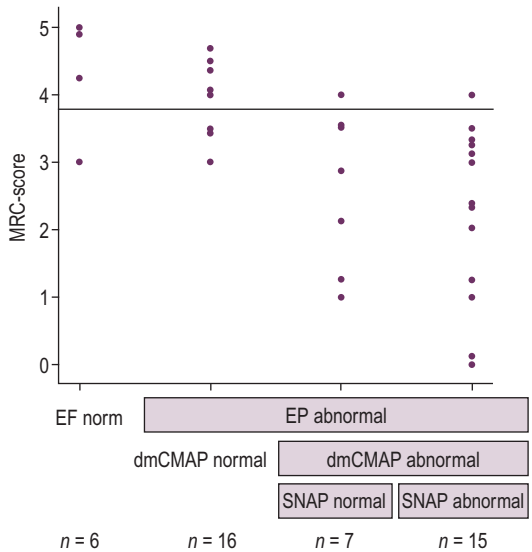


Figure 57.5 Medical Research Council score in the lower limb stratified by abnormal electrophysiology. *dmCMAP*, Direct muscle stimulation; *EP*, electrophysiology; *MRC*, Medical Research Council; *SNAP*, sensory nerve action potentials. (*From Weber-Carstens S, Koch S, Spuler S, et al. Nonexcitable muscle membrane predicts intensive care unit-acquired paresis in mechanically ventilated, sedated patients.* Crit Care Med. *2009;37:2632–2637.*)

LOSS OF MUSCLE QUALITY

In addition to muscle mass loss, loss of muscle quality is seen. Over 40% of patients develop patchy myonecrosis, detectable non-invasively by muscle ultrasound (Fig. 57.6). This necrosis is accompanied by a macrophagic infiltrate, and a fasciitis.[40] The pathological relevance of the macrophages remains unclear, though their presence may reflect clearance of dead tissue in preparation for regeneration.

Regeneration may not, however, be straightforward – a small human study suggests aberrant expression of regenerative genes[41] which may result in a mass/strength mismatch[42] (i.e. larger mass not being associated with greater strength).

AXONAL DEGENERATION

Neuropathies remain poorly understood, given the intrinsic difficulties in tissue analysis. Axonal degeneration may occur secondary to endoneurium microvascular changes,[43] with either neurotoxicity or oedema leading to axonal destruction.[44] Hyperglycaemia may also contribute to axonal damage.[45]

RISK FACTORS

These can be divided into pre-existing and in-ICU risk factors. The pre-existing risk factors of low muscle

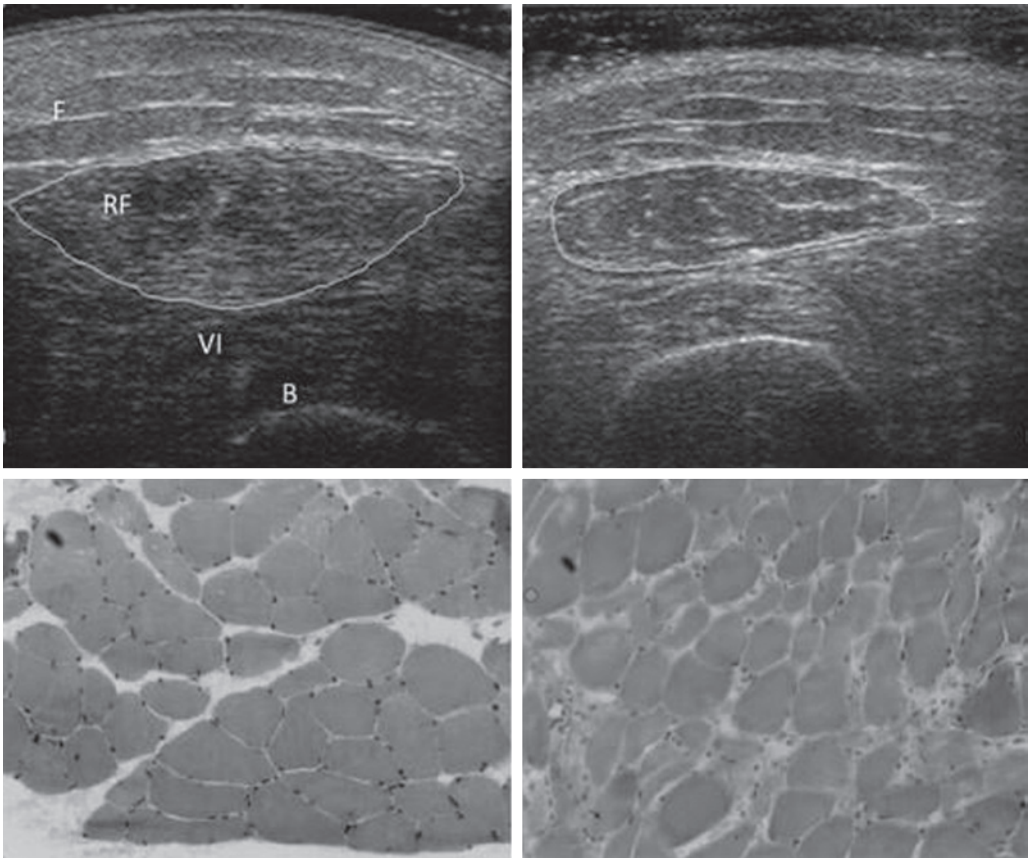


Figure 57.6 Paired ultrasound and haematoxylin and eosin stained sections of a patient on day 1 and day 10, demonstrating the reduction in rectus femoris (RF) cross-sectional area, an increase in RF echogenicity and the presence of myofibre necrosis with cellular infiltrate on day 10. *B*, Femoral bone; *F*, fascial layer; *VI*, vastus intermedius. *Reproduced from Puthucheary ZA, Phadke R, Rawal J, et al. Qualitative ultrasound in acute critical illness muscle wasting.* Crit Care Med. *2015;43(8):1603–1611.*

mass, age and presence of chronic disease have significant overlap, and relative contributions are often hard to dissect, which has led to the translation of the concept of frailty into critical care.

BASELINE MUSCLE MASS

Whilst few studies exist specifically relating baseline muscle mass with subsequent muscle wasting and functional disability, low muscle mass is clearly associated with poor functional status across the spectrum of health and disease. In health, muscle mass is directly related to muscle strength. The loss of further muscle from critical illness can only exacerbate this. Indirect evidence exists within the Nutrition Risk in Critically Ill (NUTRIC) score data where a low body mass index (BMI) is a predictor of mortality.[46] Within the critical illness literature, low skeletal muscle mass[47] and quality[48] are predictors of mortality. The diagnosis of ICU-AW is an independent predictor of mortality too,[3,21] and the combination of these observations allows confidence in the role of low pre-existing muscle mass in subsequent ICU-AW and functional disability.

PRE-EXISTING CHRONIC DISEASE

The presence or absence of chronic disease as a risk factor for ICU-AW is not clear. What is clear is that chronic co-morbidities lead to decreased muscle mass, and decreased function and physical activity post intensive care (compared to those without). A differential response to exercise rehabilitation also exists (Fig. 57.7). Separating the specific contribution of chronic disease states from disuse muscle atrophy is not currently possible. The presence of a chronic

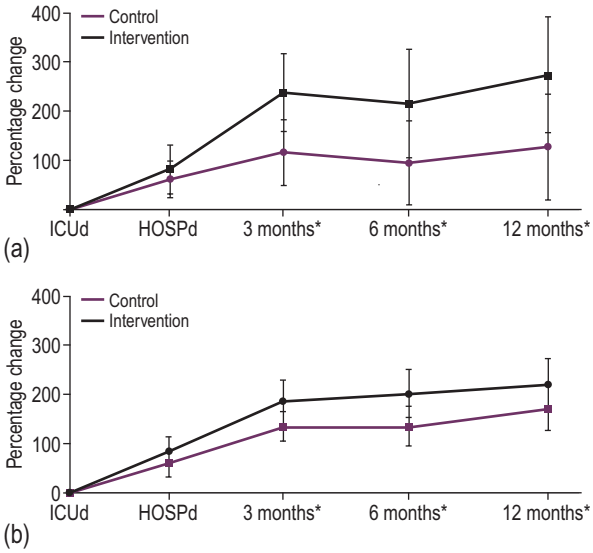


Figure 57.7 (a) Change in 6-minute walk test from intensive care unit discharge in patients with no pre-existing chronic disease and (b) those with pre-existing chronic disease. *Broken lines* represent control groups, and *solid lines* those undergoing exercise rehabilitation. *ICUd*, Intensive care discharge; *HOSPd*, hospital discharge. *represents significant change from baseline, $p < 0.05$. *From Puthucheary ZA, Denehy L. Exercise interventions in critical illness survivors: understanding inclusion and stratification criteria.* Am J Respir Crit Care Med. *2015;191(12):1464–1467.*

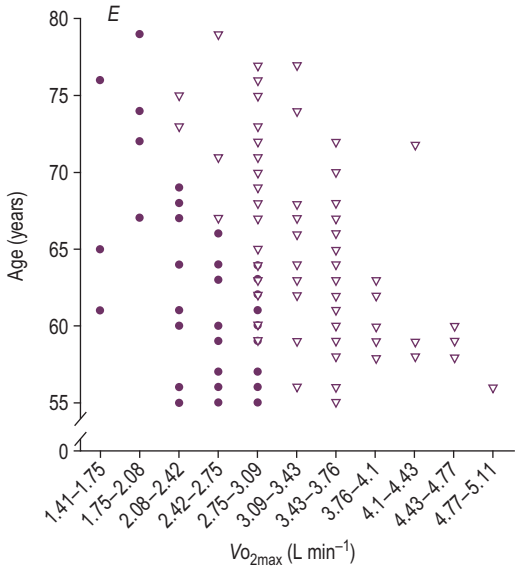


Figure 57.8 VO_{2max} in healthy master athletes demonstrating poorer than expected correlation between numerical age and cardiopulmonary physiology. *From Lazarus NR, Harridge SD. Declining performance of master athletes: silhouettes of the trajectory of healthy human ageing?* J Physiol. *2017;595(9):2941–2948.*

disease state should prompt a detailed functional history to be taken.

AGE

The vast majority of data informing this field is observational, and the effect of age *per se* separated from accompanying chronic diseases and sarcopaenia is difficult to dissect. The use of numerical age alone as a risk factor is controversial but may have a role: anabolic resistance (the inability of MPS in response to resistance exercise and nutrition) is well described in the elderly.[49,50] However, it may be that high-functioning elderly patients are different – research into master athletes clearly demonstrated the dissociation between numerical age and physiology except at the extremes of age (Fig. 57.8).[51]

There exist several large observational studies suggesting that age does matter. For example, contrasting studies of critically ill patients in their 40s[52] and 50s[53] show very different outcome trajectories, with the latter having only 9% alive without functional dependence in one study. In an 8-year follow-up study, older patients had a higher rate of new functional limitations compared to younger patients and a higher decrement in function.

Batt et al.[54] summarise this complex issue of baseline health with '…there appears to be a clear prognostic signal in the elderly in terms of the importance of physiological reserve, burden of chronic organ dysfunction, and nature of the health trajectory before the critical illness for prognostication for survival, function, and Health Related Quality of Life. An emphasis on physiological rather than chronologic age and by inference the degree of fitness and muscle reserve may provide valuable insight into projected outcome.' These interactions hold true in observational studies where age[55] and/or chronic disease[56] were used to stratify functional outcomes.

FRAILTY

The construct of frailty was first described in the geriatric literature,[57] and is defined as *a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes* (Fig. 57.9). This is therefore separate from disability and chronic disease, though these conditions, as stated above, overlap considerably.

Several forms of assessment for frailty exist. The Clinical Frailty Score has been used repeatedly in observational studies to both assess and grade frailty, and has good construct validity with objective functional measures.[56] Frail patients are highly likely to have low muscle mass, given that a fundamental of the frailty

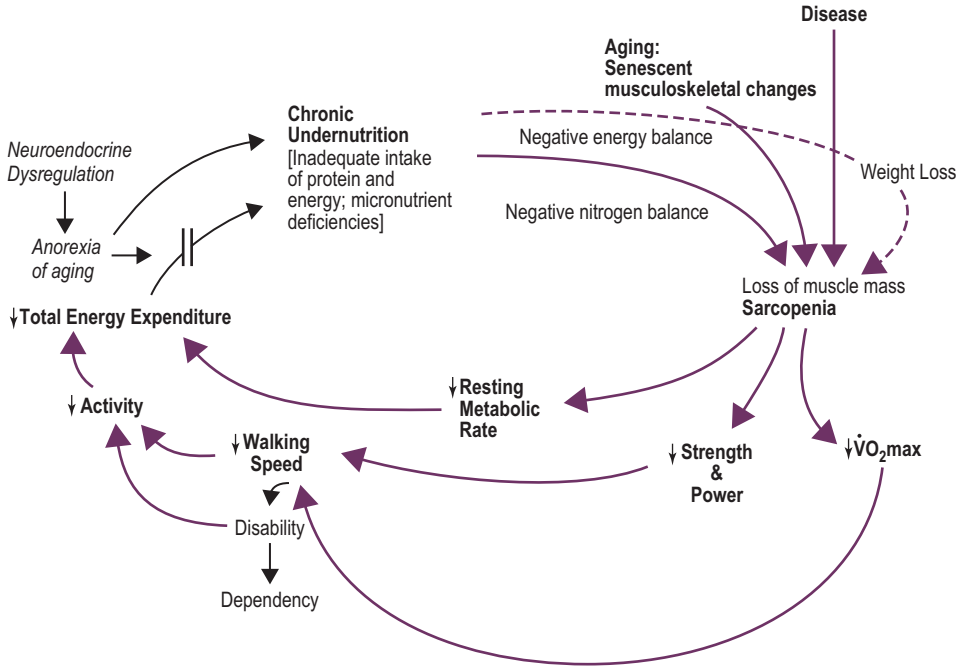


Figure 57.9 The cycle of frailty. *From Fried LP, Tangen CM, Walston J, et al. Frailty in older adults.* J Gerontol A Biol Sci Med Sci. *2001;56(3):M146–M157.*

diagnosis is altered physical function. What is key here is that frailty is a spiral: not only do these patients have low muscle mass, they are unable to increase this, with their default being to continue to lose muscle.

ILLNESS SEVERITY AND LENGTH OF STAY

Muscle wasting is related to severity of illness: patients in single-organ failure seem to lose no appreciable muscle in the first 10 days of critical illness, whilst those in 2–3 organ failure (defined using SOFA scoring) lose 20% in the first 10 days on average, and those in 4–6 organ failure lose more, averaging 26% lost in the same time period (see Fig. 57.2).[26]

INTENSIVE CARE UNIT LENGTH OF STAY

With muscle wasting occurring at rates of 2%–3% per day, it is perhaps unsurprising that the greater the length of stay, the greater the muscle mass lost. Length of stay is also a risk factor for subsequent functional disability as a result.[57]

GLYCAEMIC CONTROL

Insulin resistance secondary to impaired GLUT-4 translocation is well recognised in critically ill patients.[35] Hyperglycaemia results in mitochondrial damage[58,59] and strict glycaemic control improves mitochondrial function.[60] Insulin itself decreased MPB,[61,62] and separating glucose/insulin interactions is difficult.

IMMOBILISATION AND SEDATION

The effects on muscle protein homeostasis and muscle mass of immobilisation have been long established. Whilst bed rest alone results in detectable muscle wasting within 10 days[63] as a result of decreased MPS,[64] immobilisation in critical illness may be worse, given the metabolic effects of bed rest – insulin resistance, decreased aerobic capacity and anabolic resistance.[65]

Sedation remains an unquantified risk factor given the dependent relationship with immobilisation. Direct pharmacological effects of propofol and benzodiazepines on post-synaptic skeletal muscle receptors may attenuate neurotrophic stimulation of muscle mass.[65]

INFLAMMATION

Systemic inflammation is a common feature of critical illness. In human endotoxin experiments, inflammation suppresses MPS.[36] C-reactive protein concentrations are associated with loss of muscle mass[24] and intramuscular pro-inflammatory cytokine concentrations are strongly related to impaired anabolic signalling.[34]

Tumour necrosis factor alpha (TNFα) and its superfamily are the most studied of the pro-inflammatory

cytokines. Circulating levels and TNF receptor activation promotes muscle atrophy via nuclear factor kappa beta pathways. Additionally, apoptosis may be triggered by TNF receptor activation, leading to decreases in mitochondrial density and therefore energy availability,[34] and potentially necrosis.[40]

UNPROVEN RISK FACTORS

Neuromuscular blocking agents (NMBAs) have repeatedly been examined as a risk factor for ICU-AW. An important distinction is that ICU-AW is not prolonged neuromuscular blockade – this being the result of decreased drug clearance.[66] There is a clear lack of associative evidence,[18] and examining the historical context of the association reveals the far greater likelihood that the observed association was the result of concomitant high-dose steroids, use of ventilators without synchronised or spontaneous modes, or both.[67]

The only randomised controlled trial was performed in acute respiratory distress syndrome (ARDS) research and no increase in incidence of ICU-AW was noted with 48-hour infusions of cisatracurium,[68] even in the sub-cohort that received corticosteroids.[69] Importantly, there was a reduction in systemic inflammation[70] – if any conclusion were to be drawn, it might be that NMBAs reduce inflammation and therefore are protective in muscle wasting.

CLINICAL RELEVANCE

Survival and functional disability are rarely discussed acutely on admission to intensive care. However, this is of increasing relevance to patients and families, in the face of a significant year-on-year decrease in mortality worldwide. This survival is not without cost. The facts surrounding survival need to be clearly communicated to patients and families: muscle wasting occurs at rates of 2%–3% per day,[24] and a 10% loss of muscle mass is considered sufficient to affect physical function.[23] This is likely to affect patient and families in four domains.

LONG-TERM FUNCTIONAL DISABILITY

Herridge's landmark observational study in 2003[52] demonstrated the significant functional disability that these survivors suffer from and these findings have been confirmed repeatedly. We now know that although 75% of patients are discharged,[71] long-term impairment of physical function and quality of life are common: substantial functional limitations occur in 70% at 6–12 months, and 30% are carer-dependent.[52,72] One-third of working-age patients never work again.[52] Patients,[73] the National Institute of Clinical Excellence (UK)[71] and researchers[52] recognise muscle wasting and weakness as a major contributor to this functional deficit which may persist for up to 5 years (Fig. 57.10)[74] and in the setting of older age and co-morbidities, worsen[75] over time.

DISCHARGE PLANNING

Functional disability is now accepted as a major consequence of ICU-AW,[76] and often compounded by cognitive impairment,[77] which may recover eventually.[74] Critically ill patients lose muscle mass rapidly, and prolonged stays often result in discharges to intermediate care centres as opposed to home.[78] The elderly and those with pre-existing co-morbidity are often worse affected and less likely to return home. Discharge destination can be predicted by functional outcome assessment by scoring systems such as the Chelsea Critical Care Physical Assessment Tool,[79] which is well used internationally (Fig. 57.11).[80] Interestingly (likely due to the contribution from pre-illness muscle mass and co-morbidities), discharge destination can be predicted very early in the course of critical illness[81] and the likely destination should be communicated early.

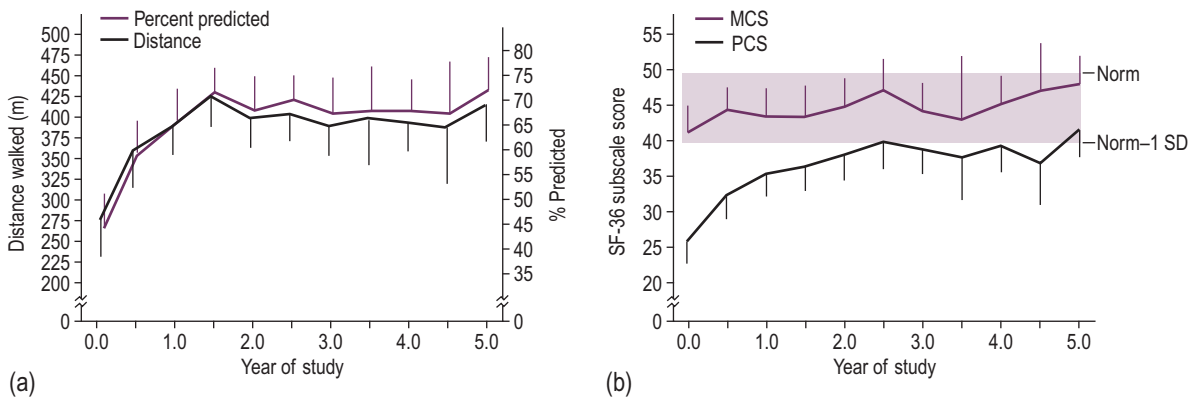


Figure 57.10 Trajectories of recovery from critical illness over 5 years. *MCS*, Mental component score; *PCS*, physical component score; *SF-36*, short Form 36. *From Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome.* New Engl J Med. *2011;364(14):1293–1304.*

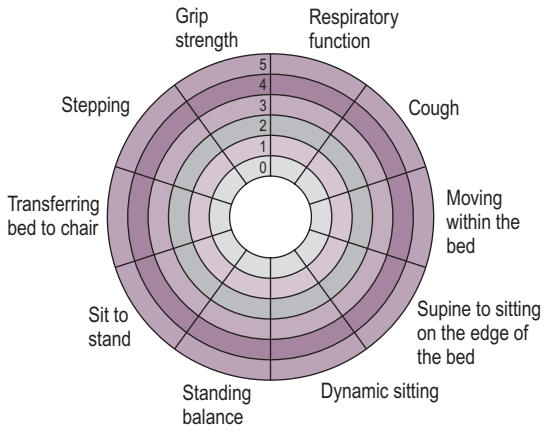


Figure 57.11 Chelsea Critical Care Physical Assessment Tool. *From Corner EJ, Handy JM, Brett SJ. eLearning to facilitate the education and implementation of the Chelsea Critical Care Physical Assessment: a novel measure of function in critical illness.* BMJ Open. *2016;6(4):e010614.*

LENGTH OF STAY AND VENTILATION

Observational studies have repeatedly demonstrated the association between muscle weakness and increased ICU length of stay, using various methods such as muscle ultrasound,[24] hand-grip strength[21] and the MRC Sum Score.[3] The effect on ventilator dependence has also been demonstrated, with one study seeing 9 days on average longer duration of ventilation, specifically post awakening,[82] which has significant implications for tracheostomy planning and avoidance of complications related to longer critical care (e.g. delirium, sleep deprivation, secondary infections and rehabilitation).

LONG-TERM MORTALITY

Short-term mortality rates from critical illness continue to fall. However, late mortality[53,83–92] remains high: 5-year mortality was 61% amongst 439 survivors of severe sepsis[93] and 58% amongst 300 mixed ICU survivors,[85] data similar to those reported by others.[74,94–97] In studies with careful matching and control for confounding, pneumonia,[7] sepsis,[8] and all-cause critical illness have each been found to increase survivors' risk for late mortality, independent of age and baseline health status. Overall, increased risk of death over 5 years (relative risk 3.4 when compared to the general population)[97] may extend to 15 years or more after discharge.[95] Death from the diseases that led to ICU admission[98–100] or from significant chronic disease pre-dating ICU admission[101,102] tends to occur in the first 6–12 months. Thereafter, for reasons, which are unexplained, malignancy and chronic cardiovascular diseases dominate as causes of death.[98–100] In a study of 156 ARDS survivors,[103] muscle weakness at hospital discharge was independently associated with 5-year mortality regardless of trajectory of recovery (i.e. those with persistent weakness had the same mortality as those with resolving weakness). Swallowing dysfunction,[18] decreased nutritional intake,[18] increased aspiration,[18] and decreased physical activity[19] are all sequelae of muscle weakness. Decreased physical activity may in turn increase risk for cardiovascular events and malignancy. Individually or in combination, these factors may impair MPS, leading to a vicious cycle of maintained cachexia increasing mortality.[20]

With these consequences of surviving critical illness in mind, clinicians need to ascertain physiological reserve, burden of chronic organ dysfunction, and nature of the health trajectory before the critical illness for prognostication for survival, function, and health related quality of life. These facts need to be communicated to families and, whenever possible, the patient.

PREVENTION AND TREATMENT

Nutrition: As a result of our incomplete understanding of the pathophysiology of ICU-AW, to date, trials of additional substrate delivery[104–110] have yet to preserve muscle mass and improve outcomes. Recent pathophysiological data on bioenergetics impairment may explain why conflict exists between data from observational studies demonstrating a clinical benefit from increased nutrition over the *entire* ICU stay[46,111,112] and the lack of benefit seen with *early* targeted nutrition,[104–107] when ATP turnover is impaired.

Glucose control: In a meta-analysis of two large randomised controlled trials of tight glucose control, intensive insulin therapy resulted in a decrease in electrophysiological abnormalities in patients ventilated greater than 1 week.[113] However, the impracticalities of such treatment were demonstrated in the NICE-SUGAR trial where an unacceptable incidence of hypoglycaemia and mortality was noted.[114] Current best practice is to avoid hyperglycaemia.

Neuromuscular electrical stimulation: Multiple trials in the acute setting have failed to demonstrate a benefit on muscle mass.[115–119] Statistically positive trials exist with methodological issues related to mass measurement techniques, which have not been reproduced by the same investigators.

Physiologically electrical stimulation is unlikely to have a beneficial effect in the acute setting in the presence of an impaired anabolic response.[24] Further, resistance exercise is needed for an anabolic stimulus, as opposed to simple muscle contraction. Lastly, non-excitability is predictive of ICU-AW, and by definition, is unaffected by electrical stimulation.[39] There is a high chance for harm – muscle necrosis is common,[40] (see Fig. 57.6) and electrical stimulation results in direct muscle damage.[120] It may be that a more focused approach using functional electrical stimulation will be

successful in maintenance of muscle mass,[121] and trials are ongoing.[122]

ABCDEF: Preventing muscle wasting and subsequent functional disability are intertwined goals. It is unlikely that a single intervention will manage this. The ABCDEF[123] bundle represents the best intervention available, and has been demonstrated to additionally decrease mortality significantly in a cost-neutral fashion. The bundle components are:

ABBREVIATION	INTERVENTION
A	Awakening trials[124]
B	Spontaneous breathing[125]
C	Coordination of care[125]
D	Delirium assessment
E	Early mobilisation[126]
F	Family engagement

Technically the evidence for each of these is related to mortality or ICU/hospital length of stay rather than treating ICU-AW *per se*. However, the evidence includes or requires increases in physical functioning, which, all things being equal, can only be achieved by addressing muscle mass and function. The muscle-specific intervention of early mobilisation is impractical without other aspects of the bundle.

Despite the neutral cost and significant patient and institutional gains from bundle implementation, the ABCDEF bundle has yet to become a standard of care, as a result of workplace cultural issues centred on early mobilisation and coordination of care.[127,128]

POST-DISCHARGE MANAGEMENT

Rehabilitation: As yet no evidence exists that post-discharge rehabilitation leads to increases in physical function or quality of life in critical care survivors, despite a number of high-quality multicentre randomised controlled trials.[129–133] This may be a result of trial methodology[134] and/or a failure to account for baseline function (Fig. 57.7).[56] Nevertheless, physical and exercise rehabilitation remains a recommendation in survivors.[71]

Bone health: Survivors of critical illness have an increased fracture risk.[135,136] This is the result of a combination of pre-existing osteopaenia, and the acute effects of critical illness on bone mineral density and structure.[137] In the setting of low muscle mass and decreased mobility, these patients represent a high falls-and-fracture risk. A comprehensive falls assessment is needed, as is staging of osteopaenia.

Nutrition: Ingestion of protein is mandatory for MPS to occur, preferably following resistance exercise. There is some evidence of poor appetite among critical illness survivors. This couples with functional disability that may limit shopping; financial constraints following loss of income and hospital costs may lead to poor dietary habits, and into the spiral of continued muscle wasting and functional decline.

Small fibre neuropathy: Two studies have described loss of small fibres, resulting in neuropathic pain and non-dermatomal sensory loss.[138,139] These symptoms may be difficult to control, and if non-responsive to first-line neuropathic pain treatments (e.g. gabapentin or amitriptyline), expert advice should be sought and formal diagnosis criteria checked.[140]

Nerve entrapment: Focal compression neuropathies with normal electro-diagnostic testing may occur.[141] In a 1-year follow-up series, this was noted in 7% of patients.[52] Whilst foot drop (a common compression neuropathy) is often recognised and treated by physiotherapists, uncommon compression neuropathies may need specialist neurological diagnostic input.

Patients, families and healthcare professionals need to be made aware of the sequelae of surviving critical illness rather than a pure focus on immediate mortality. Non-intensivists need to be made aware, as this has profound ramifications for their own discussions with patients regarding subsequent/ongoing treatment of complex conditions such as neoplastic disease (chemotherapy having a pre-requisite of good performance status) and complex surgery (recovery of muscle mass and rehabilitation not occurring in the short term). Only in this fashion can patients and families weigh the cost/benefit ratio of intensive care treatment versus subsequent quality of life.

REFERENCES

1. Stevens RD, Marshall SA, Cornblath DR, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. *Crit Care Med*. 2009;37(10 suppl):S299–S308.
2. Fan E, Cheek F, Chlan L, et al. An official American Thoracic Society Clinical Practice guideline: the diagnosis of intensive care unit-acquired weakness in adults. *Am J Respir Crit Care Med*. 2014;190(12):1437–1446.
3. De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA*. 2002;288(22):2859–2867.
4. Latronico N, Shehu I, Seghelini E. Neuromuscular sequelae of critical illness. *Curr Opin Crit Care*. 2005;11(4):381–390.
5. Kleyweg RP, van der Meche FG, Meulstee J. Treatment of Guillain-Barre syndrome with high-dose gammaglobulin. *Neurology*. 1988;38(10):1639–1641.
6. Kleyweg RP, van der Meche FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barre syndrome. *Muscle Nerve*. 1991;14(11):1103–1109.

7. Fan E, Ciesla N, Truong A, et al. Inter-rater reliability of manual muscle strength testing in ICU survivors and simulated patients. *Intensive Care Med*. 2010;36:1038–1043.
8. Hough C, Lieu B, Caldwell E. Manual muscle strength testing of critically ill patients: feasibility and interobserver agreement. *Crit Care*. 2011; 15(1):R43.
9. Bolton CF, Gilbert JJ, Hahn AF, et al. Polyneuropathy in critically ill patients. *J Neurol Neurosurg Psychiatry*. 1984;47(11):1223–1231.
10. Allen DC, Arunachalam R, Mills KR. Critical illness myopathy: further evidence from muscle-fiber excitability studies of an acquired channelopathy. *Muscle Nerve*. 2008;37(1):14–22.
11. Novak KR, Nardelli P, Cope TC, et al. Inactivation of sodium channels underlies reversible neuropathy during critical illness in rats. *J Clin Invest*. 2009; 119(5):1150–1158.
12. Teener J, Rich M. Dysregulation of sodium channel gating in critical illness myopathy. *J Muscle Res Cell Motil*. 2006;27(5):291–296.
13. Kerbaul F, Brousse M, Collart F, et al. Combination of histopathological and electromyographic patterns can help to evaluate functional outcome of critical ill patients with neuromuscular weakness syndromes. *Crit Care*. 2004;8(6):R358–R366.
14. Griffiths RD, Hall JB. Intensive care unit-acquired weakness. *Crit Care Med*. 2010;38(3):779–787. doi:10.1097/CCM.1090b1013e3181cc1094b1053.
15. Berek K, Margreiter J, Willeit J, et al. Polyneuropathies in critically ill patients: a prospective evaluation. *Intensive Care Med*. 1996;22(9): 849–855.
16. Coakley JH, Nagendran K, Honavar M, et al. Preliminary observations on the neuromuscular abnormalities in patients with organ failure and sepsis. *Intensive Care Med*. 1993;19(6):323–328.
17. Tennila A, Salmi T, Pettila V, et al. Early signs of critical illness polyneuropathy in ICU patients with systemic inflammatory response syndrome or sepsis. *Intensive Care Med*. 2000;26(9):1360–1363.
18. Stevens RD, Dowdy DW, Michaels RK, et al. Neuromuscular dysfunction acquired in critical illness: a systematic review. *Intensive Care Med*. 2007;33(11):1876–1891.
19. Bednarik J, Lukas Z, Vondracek P. Critical illness polyneuromyopathy: the electrophysiological components of a complex entity. *Intensive Care Med*. 2003;29:1505–1514.
20. Sharshar T, Bastuji-Garin S, Stevens RD, et al. Presence and severity of intensive care unit-acquired paresis at time of awakening are associated with increased intensive care unit and hospital mortality. *Crit Care Med*. 2009;37(12):3047–3053.
21. Ali NA, O'Brien JM Jr, Hoffmann SP, et al. Acquired weakness, handgrip strength, and mortality in critically ill patients. *Am J Respir Crit Care Med*. 2008;178(3):261–268.
22. Bercker S, Weber-Carstens S, Deja M, et al. Critical illness polyneuropathy and myopathy in patients with acute respiratory distress syndrome. *Crit Care Med*. 2005;33:711–715.
23. Seymour JM, Spruit MA, Hopkinson NS, et al. The prevalence of quadriceps weakness in COPD and the relationship with disease severity. *Eur Respir J*. 2010;36(1):81–88.
24. Puthucheary ZA, Rawal J, McPhail M, et al. Acute skeletal muscle wasting in critical illness. *JAMA*. 2013;310(15):1591–1600.
25. Latronico N, Bolton CF. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. *Lancet Neurol*. 2011; 10(10):931–941.
26. Guarneri B, Bertolini G, Latronico N. Long-term outcome in patients with critical illness myopathy or neuropathy: the Italian multicentre CRIMYNE study. *J Neurol Neurosurg Psychiatry*. 2008;79(7): 838–841.
27. Parry SM, El-Ansary D, Cartwright MS, et al. Ultrasonography in the intensive care setting can be used to detect changes in the quality and quantity of muscle and is related to muscle strength and function. *J Crit Care*. 2015;30(5):1151.e9–1151.e14.
28. Millward D. *Protein Turnover in Cardiac and Skeletal Muscle During Normal Growth and Hypertrophy*. Amsterdam: Elsevier/North Holland; 1980.

29a. Phillips SM, Glover EI, Rennie MJ. Alterations of protein turnover underlying disuse atrophy in human skeletal muscle. *J Appl Physiol*. 2009;107(3): 645–654.

29b. Gamrin-Gripenberg L, Sundström-Rehal M, Olsson D, et al. An attenuated rate of leg muscle protein depletion and leg free amino acid efflux over time is seen in ICU long-stayers. *Crit Care*. 2018;22:13.

30. Carre JE, Orban JC, Re L, et al. Survival in critical illness is associated with early activation of mitochondrial biogenesis. *Am J Respir Crit Care Med*. 2010;182(6):745–751.
31. Brealey D, Brand M, Hargreaves I, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. *Lancet*. 2002; 360(9328):219–223.
32. Fredriksson K, Hammarqvist F, Strigard K, et al. Derangements in mitochondrial metabolism in intercostal and leg muscle of critically ill patients with sepsis-induced multiple organ failure. *Am J Physiol Endocrinol Metab*. 2006;291(5):E1044–E1050.
33. Jiroutkova K, Krajcova A, Ziak J, et al. Mitochondrial function in skeletal muscle of patients with protracted critical illness and ICU-acquired weakness. *Crit Care*. 2015;19:448.
34. Puthucheary Z. *Alterations in skeletal muscle metabolism in early critical illnesss*; 2017.
35. Weber-Carstens S, Schneider J, Wollersheim T, et al. Critical illness myopathy and GLUT4 – significance of insulin and muscle contraction. *Am J Respir Crit Care Med*. 2013;187(4):387–396.
36. Vesali RF, Cibicek N, Jakobsson T, et al. Protein metabolism in leg muscle following an endotoxin

injection in healthy volunteers. *Clin Sci*. 2009; 118(6):421–427.
37. Rich MM, Pinter MJ. Sodium channel inactivation in an animal model of acute quadriplegic myopathy. *Ann Neurol*. 2001;50(1):26–33.
38. Zink W, Kaess M, Hofer S, et al. Alterations in intracellular Ca^{2+}-homeostasis of skeletal muscle fibers during sepsis. *Crit Care Med*. 2008;36(5): 1559–1563.
39. Weber-Carstens S, Koch S, Spuler S, et al. Nonexcitable muscle membrane predicts intensive care unit-acquired paresis in mechanically ventilated, sedated patients. *Crit Care Med*. 2009;37: 2632–2637.
40. Puthucheary ZA, Phadke R, Rawal J, et al. Qualitative ultrasound in acute critical illness muscle wasting. *Crit Care Med*. 2015;43(8): 1603–1611.
41. Walsh CJ, Batt J, Herridge MS, et al. Transcriptomic analysis reveals abnormal muscle repair and remodeling in survivors of critical illness with sustained weakness. *Sci Rep*. 2016;6:29334.
42. Dos Santos C, Hussain SN, Mathur S, et al. Mechanisms of chronic muscle wasting and dysfunction after an intensive care unit stay. A pilot study. *Am J Respir Crit Care Med*. 2016; 194(7):821–830.
43. Fenzi F, Latronico N, Refatti N, et al. Enhanced expression of E-selectin on the vascular endothelium of peripheral nerve in critically ill patients with neuromuscular disorders. *Acta Neuropathol*. 2003;106(1):75–82.
44. Bolton CF. Neuromuscular abnormalities in critically ill patients. *Intensive Care Med*. 1993; 19:309–310.
45. Sharma R, Buras E, Terashima T, et al. Hyperglycemia induces oxidative stress and impairs axonal transport rates in mice. *PLoS ONE*. 2010;5(10):e13463.
46. Heyland DK, Dhaliwal R, Jiang X, et al. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. *Crit Care*. 2011;15(6):R268.
47. Weijs PJ, Looijaard WG, Dekker IM, et al. Low skeletal muscle area is a risk factor for mortality in mechanically ventilated critically ill patients. *Crit Care*. 2014;18(1):R12.
48. Looijaard WG, Dekker IM, Stapel SN, et al. Skeletal muscle quality as assessed by CT-derived skeletal muscle density is associated with 6-month mortality in mechanically ventilated critically ill patients. *Crit Care*. 2016;20(1):386.
49. Cuthbertson D, Smith K, Babraj J, et al. Anabolic signaling deficits underlie amino acid resistance of wasting, aging muscle. *FASEB J*. 2005;19(3): 422–424.
50. Rennie MJ. Anabolic resistance: the effects of aging, sexual dimorphism, and immobilization on human muscle protein turnover. *Appl Physiol Nutr Metab*. 2009;34(3):377–381.
51. Lazarus NR, Harridge SD. Declining performance of master athletes: silhouettes of the trajectory of healthy human ageing? *J Physiol*. 2017;595(9): 2941–2948.
52. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med*. 2003;348(8):683–693.
53. Unroe M, Kahn JM, Carson SS, et al. One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. *Ann Intern Med*. 2010;153(3):167–175.
54. Batt J, dos Santos CC, Cameron JI, et al. Intensive care unit-acquired weakness: clinical phenotypes and molecular mechanisms. *Am J Respir Crit Care Med*. 2013;187(3):238–246.
55. Herridge MS, Chu LM, Matte A, et al. The RECOVER Program: Disability Risk Groups and 1-Year Outcome after 7 or More Days of Mechanical Ventilation. *Am J Respir Crit Care Med*. 2016;194(7):831–844.
56. McNelly AS, Rawal J, Shrikrishna D, et al. An exploratory study of long-term outcome measures in critical illness survivors: construct validity of physical activity, frailty, and health-related quality of life measures. *Crit Care Med*. 2016;44(6): e362–e369.
57. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146–M157.
58. Vanhorebeek I, Gunst J, Ellger B, et al. Hyperglycemic kidney damage in an animal model of prolonged critical illness. *Kidney Int*. 2009; 76(5):512–520.
59. Vanhorebeek I, Ellger B, De Vos R, et al. Tissue-specific glucose toxicity induces mitochondrial damage in a burn injury model of critical illness. *Crit Care Med*. 2009;37(4):1355–1364.
60. Fram RY, Cree MG, Wolfe RR, et al. Intensive insulin therapy improves insulin sensitivity and mitochondrial function in severely burned children. *Crit Care Med*. 2010;38(6):1475–1483.
61. Gelfand RA, Barrett EJ. Effect of physiologic hyperinsulinemia on skeletal muscle protein synthesis and breakdown in man. *J Clin Invest*. 1987;80(1):1–6.
62. Tessari P, Trevisan R, Inchiostro S, et al. Dose-response curves of effects of insulin on leucine kinetics in humans. *Am J Physiol*. 1986;251(3 Pt 1):E334–E342.
63. Kortebein P, Ferrando A, Lombeida J, et al. Effect of 10 days of bed rest on skeletal muscle in healthy older adults. *JAMA*. 2007;297(16):1772–1774.
64. Gibson JN, Halliday D, Morrison WL, et al. Decrease in human quadriceps muscle protein turnover consequent upon leg immobilization. *Clin Sci*. 1987;72(4):503–509.
65. Parry SM, Puthucheary ZA. The impact of extended bed rest on the musculoskeletal system in the critical care environment. *Extrem Physiol Med*. 2015;4:16.

66. Murray MJ, Cowen J, DeBlock H, et al. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Crit Care Med*. 2002;30(1):142–156.
67. Puthucheary Z, Rawal J, Ratnayake G, et al. Neuromuscular blockade and skeletal muscle weakness in critically ill patients: time to rethink the evidence? *Am J Respir Crit Care Med*. 2012;185(9): 911–917.
68. Papazian L, Forel J-M, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010; 363(12):1107–1116.
69. Puthucheary Z, Hart N, Montgomery H. Neuromuscular blockers and ARDS. *N Engl J Med*. 2010;363(26):2563.
70. Forel JM, Roch A, Marin V, et al. Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. *Crit Care Med*. 2006;34(11): 2749–2757.
71. NICE. *CG83 Critical illness rehabilitation: NICE guideline*; 2009.
72. Hayes JA, Black NA, Jenkinson C, et al. Outcome measures for adult critical care: a systematic review. *Health Technol Assess*. 2000;4(24):1–111.
73. ICUSTEPS. http://www.icusteps.org/.
74. Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364(14): 1293–1304.
75. Pfoh ER, Wozniak AW, Colantuoni E, et al. Physical declines occurring after hospital discharge in ARDS survivors: a 5-year longitudinal study. *Intensive Care Med*. 2016;42(10):1557–1566.
76. Parry SM, El-Ansary D, Cartwright MS, et al. Ultrasonography in the intensive care setting can be used to detect changes in the quality and quantity of muscle and is related to muscle strength and function. *J Crit Care*. 2015;30(5): 1151.e9–1151.e14.
77. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med*. 2013;369(14):1306–1316.
78. Kahn JM, Benson NM, Appleby D, et al. Long-term acute care hospital utilization after critical illness. *JAMA*. 2010;303(22):2253–2259.
79. Corner EJ, Soni N, Handy JM, et al. Construct validity of the Chelsea critical care physical assessment tool: an observational study of recovery from critical illness. *Crit Care*. 2014;18(2): R55.
80. Corner EJ, Handy JM, Brett SJ. eLearning to facilitate the education and implementation of the Chelsea Critical Care Physical Assessment: a novel measure of function in critical illness. *BMJ Open*. 2016;6(4):e010614.
81. Holland DE, Rhudy LM, Vanderboom CE, et al. Feasibility of discharge planning in intensive care units: a pilot study. *Am J Crit Care*. 2012;21(4): e94–e101.
82. De Jonghe B, Bastuji-Garin S, Durand MC, et al. Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. *Crit Care Med*. 2007;39(9):2007–2015.
83. Chelluri L, Im KA, Belle SH, et al. Long-term mortality and quality of life after prolonged mechanical ventilation. *Crit Care Med*. 2004;32(1): 61–69.
84. Cheung AM, Tansey CM, Tomlinson G, et al. Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2006;174(5):538–544.
85. Cuthbertson B, Roughton S, Jenkinson D, et al. Quality of life in the five years after intensive care: a cohort study. *Crit Care*. 2013;14(1):R6.
86. Niskanen M, Kari A, Halonen P. Five-year survival after intensive care – comparison of 12,180 patients with the general population. Finnish ICU Study Group. *Crit Care Med*. 1996;24(12): 1962–1967.
87. Oeyen SG, Vandijck DM, Benoit DD, et al. Quality of life after intensive care: a systematic review of the literature. *Crit Care Med*. 2010;38(12):2386–2400. doi:10.1097/CCM.2380b2013e3181f2383dec2385.
88. Winters BD, Eberlein M, Leung J, et al. Long-term mortality and quality of life in sepsis: a systematic review. *Crit Care Med*. 2010;38(5):1276–1283.
89. Wunsch H, Guerra C, Barnato AE, et al. Three-year outcomes for Medicare beneficiaries who survive intensive care. *JAMA*. 2010;303(9):849–856.
90. Waterer GW, Kessler LA, Wunderink RG. Medium-term survival after hospitalization with community-acquired pneumonia. *Am J Respir Crit Care Med*. 2004;169(8):910–914.
91. Yende S, Angus DC, Ali IS, et al. Influence of comorbid conditions on long-term mortality after pneumonia in older people. *J Am Geriatr Soc*. 2007; 55(4):518–525.
92. Quartin AA, Schein RM, Kett DH, et al. Magnitude and duration of the effect of sepsis on survival. Department of Veterans Affairs Systemic Sepsis Cooperative Studies Group. *JAMA*. 1997;277(13):1058–1063.
93. Cuthbertson BH, Elders A, Hall S, et al. Mortality and quality of life in the five years after severe sepsis. *Crit Care*. 2013;17(2):R70.
94. Cuthbertson BH, Scott J, Strachan M, et al. Quality of life before and after intensive care. *Anaesthesia*. 2005;60(4):332–339.
95. Williams TA, Dobb GJ, Finn JC, et al. Determinants of long-term survival after intensive care. *Crit Care Med*. 2008;36(5):1523–1530.
96. Graf J, Wagner J, Graf C, et al. Five-year survival, quality of life, and individual costs of 303 consecutive medical intensive care patients – a cost-utility analysis. *Crit Care Med*. 2005;33(3): 547–555.
97. Wright JC, Plenderleith L, Ridley SA. Long-term survival following intensive care: subgroup analysis and comparison with the general population. *Anaesthesia*. 2003;58(7):637–642.

98. Ridley S, Purdie J. Cause of death after critical illness. *Anaesthesia*. 1992;47(2):116–119.
99. Mayr VD, Dunser MW, Greil V, et al. Causes of death and determinants of outcome in critically ill patients. *Crit Care*. 2006;10(6):R154.
100. Hicks PR, Mackle DM. Cause of death in intensive care patients within 2 years of discharge from hospital. *Crit Care Resusc*. 2010;12(2):78–82.
101. Bagshaw SM. The long-term outcome after acute renal failure. *Curr Opin Crit Care*. 2006;12(6): 561–566.
102. Bagshaw SM, Laupland KB, Doig CJ, et al. Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. *Crit Care*. 2005;9(6):R700–R709.
103. Dinglas VD, Aronson Friedman L, Colantuoni E, et al. Muscle weakness and 5-year survival in acute respiratory distress syndrome survivors. *Crit Care Med*. 2017;45(3):446–453.
104. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med*. 2011;365(6):506–517.
105. Casaer MP, Wilmer A, Van den Berghe G. Supplemental parenteral nutrition in critically ill patients. *Lancet*. 2013;381(9879):1715.
106. Heidegger CP, Berger MM, Graf S, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. *Lancet*. 2013;381(9864):385–393.
107. National Heart, Lung, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Netwrok, Rice TW, Wheeler AP, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA*. 2012;307(8):795–803.
108. Doig GS, Simpson F, Finfer S, et al. Effects of evidence based feeding guidelines on mortality of critically ill patients. A cluster randomized controlled trial. *JAMA*. 2008;300:2731–2741.
109. Doig GS, Simpson F, Sweetman EA, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. *JAMA*. 2013;309(20):2130–2138.
110. Arabi YM, Aldawood AS, Haddad SH, et al. Permissive underfeeding or standard enteral feeding in critically ill adults. *N Engl J Med*. 2015; 372(25):2398–2408.
111. Heyland DK, Cahill N, Day AG. Optimal amount of calories for critically ill patients: depends on how you slice the cake! *Crit Care Med*. 2011;39(12): 2619–2626.
112. Rahman A, Hasan RM, Agarwala R, et al. Identifying critically-ill patients who will benefit most from nutritional therapy: further validation of the 'modified NUTRIC' nutritional risk assessment tool. *Clin Nutr*. 2016;35(1):158–162.
113. Hermans G, De Jonghe B, Bruyninckx F, et al. Interventions for preventing critical illness polyneuropathy and critical illness myopathy. *Cochrane Database Syst Rev*. 2014;(1):CD006832.
114. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283–1297.
115. Gerovasili V, Stefanidis K, Vitzilaios K, et al. Electrical muscle stimulation preserves the muscle mass of critically ill patients: a randomized study. *Crit Care*. 2009;13(5):R161.
116. Gerovasili V, Tripodaki E, Karatzanos E, et al. Short-term systemic effect of electrical muscle stimulation in critically ill patients. *Chest*. 2009; 136(5):1249–1256.
117. Gruther W, Kainberger F, Fialka-Moser V, et al. Effects of neuromuscular electrical stimulation on muscle layer thickness of knee extensor muscles in intensive care unit patients: a pilot study. *J Rehabil Med*. 2010;42(6):593–597.
118. Poulsen JB, Møller K, Jensen CV, et al. Effect of transcutaneous electrical muscle stimulation on muscle volume in patients with septic shock*. *Crit Care Med*. 2011;39(3):456–461. doi:10.1097/CCM.1090b1013e318205c318207bc.
119. Routsi C, Gerovasili V, Vasileiadis I, et al. Electrical muscle stimulation prevents critical illness polyneuromyopathy: a randomized parallel intervention trial. *Crit Care*. 2010;14(2):R74.
120. Mackey AL, Bojsen-Moller J, Qvortrup K, et al. Evidence of skeletal muscle damage following electrically stimulated isometric muscle contractions in humans. *J Appl Physiol*. 2008;105(5):1620–1627.
121. Parry SM, Berney S, Warrillow S, et al. Functional electrical stimulation with cycling in the critically ill: a pilot case-matched control study. *J Crit Care*. 2014;29(4):695.e1–695.e7.
122. Parry SM, Berney S, Koopman R, et al. Early rehabilitation in critical care (eRiCC): functional electrical stimulation with cycling protocol for a randomised controlled trial. *BMJ Open*. 2012;2(5):e001891.
123. Balas MC, Burke WJ, Gannon D, et al. Implementing the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle into everyday care: opportunities, challenges, and lessons learned for implementing the ICU Pain, Agitation, and Delirium Guidelines. *Crit Care Med*. 2013;41(9 suppl 1):S116–S127.
124. Kress JP. Daily interruption of sedative infusions in critically ill patients. *N Engl J Med*. 2000;343(11): 814–815.
125. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371(9607):126–134.
126. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational

therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. 2009;373(9678):1874–1882.
127. Parry SM, Knight LD, Connolly B, et al. Factors influencing physical activity and rehabilitation in survivors of critical illness: a systematic review of quantitative and qualitative studies. *Intensive Care Med*. 2017;43(4):531–542.
128. Parry SM, Remedios L, Denehy L, et al. What factors affect implementation of early rehabilitation into intensive care unit practice? A qualitative study with clinicians. *J Crit Care*. 2017;38:137–143.
129. Denehy L, Skinner EH, Edbrooke L, et al. Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. *Crit Care*. 2013;17(4):R156.
130. Elliott D, McKinley S, Alison J, et al. Health-related quality of life and physical recovery after a critical illness: a multi-centre randomised controlled trial of a home-based physical rehabilitation program. *Crit Care*. 2011;15(3):R142.
131. Morris PE, Berry MJ, Files DC, et al. Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure: a randomized clinical trial. *JAMA*. 2016;315(24):2694–2702.
132. Moss M, Nordon-Craft A, Malone D, et al. A randomized trial of an intensive physical therapy program for patients with acute respiratory failure. *Am J Respir Crit Care Med*. 2016;193(10):1101–1110.
133. Walsh TS, Salisbury LG, Merriweather JL, et al. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge. The RECOVER Randomized Clinical Trial. *JAMA Intern Med*. 2015;175(6):901–910.
134. Puthucheary ZA, Denehy L. Exercise interventions in critical illness survivors: understanding inclusion and stratification criteria. *Am J Respir Crit Care Med*. 2015;191(12):1464–1467.
135. Orford NR, Saunders K, Merriman E, et al. Skeletal morbidity among survivors of critical illness. *Crit Care Med*. 2011;39(6):1295–1300.
136. Orford NR, Lane SE, Bailey M, et al. Changes in bone mineral density in the year after critical illness. *Am J Respir Crit Care Med*. 2016;193(7):736–744.
137. Rawal J, McPhail MJ, Ratnayake G, et al. A pilot study of change in fracture risk in patients with acute respiratory distress syndrome. *Crit Care*. 2015;19(1):165.
138. Latronico N, Filosto M, Fagoni N, et al. Small nerve fiber pathology in critical illness. *PLoS ONE*. 2013;8(9):e75696.
139. Skorna M, Kopacik R, Vlckova E, et al. Small-nerve-fiber pathology in critical illness documented by serial skin biopsies. *Muscle Nerve*. 2015;52(1):28–33.
140. Devigili G, Tugnoli V, Penza P, et al. The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology. *Brain*. 2008; 131(Pt 7):1912–1925.
141. Angel MJ, Bril V, Shannon P, et al. Neuromuscular function in survivors of the acute respiratory distress syndrome. *Can J Neurol Sci*. 2007;34(4): 427–432.

58

Neuromuscular disorders

Manoj K Saxena

A number of peripheral nerve disorders producing weakness can require admission to the intensive care unit (ICU). These may involve:

- spinal anterior horn cells: motor neuron (or neurone) disease, poliomyelitis
- peripheral nerve conduction: Guillain–Barré syndrome (GBS) and related disorders
- the neuromuscular junction: myasthenia gravis (MG), botulism
- muscle contraction: myopathies, periodic paralysis

Weakness that results from peripheral nerve or muscle lesions as a complication of critical illness ('Intensive Care Unit Acquired Weakness') is covered in Chapter 57.

Box 58.1 lists a differential diagnosis of muscle weakness in critically ill patients.

GUILLAIN–BARRÉ SYNDROME AND RELATED DISORDERS

In 1834, James Wardrop reported a case of ascending sensory loss and weakness in a 35-year-old man, leading to almost complete quadriparesis over 10 days, and complete recovery over several months.[1] In 1859, Landry described an acute ascending paralysis occurring in 10 patients, 2 of whom died. Guillain, Barré and Strohl in 1916 reported two cases of motor weakness, paraesthesiae and muscle tenderness in association with increased protein in the cerebrospinal fluid (CSF)[2]; lumbar puncture for CSF examination was first described in the 1890s.

The many variants of this syndrome and the lack of specific diagnostic criteria have previously resulted in confusion in nomenclature. More recently, clinical, electrical and laboratory criteria for the three predominant variants have been described – acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN).[3,4] GBS is usually preceded by an infection or other immune stimulation that induces an aberrant immune reaction to peripheral nerves and their spine roots. It is probably best regarded as a heterogeneous group of immunologically mediated disorders of peripheral nerve function.

INCIDENCE

Since the incidence of poliomyelitis has markedly declined due to mass immunisation programmes, GBS has become the major cause of rapid-onset flaccid paralysis in previously healthy people, with an incidence of approximately 1.7 per 100,000.[5] The disorder is commoner in males, and up to four times commoner in the elderly. No consistent seasonal or racial predilection has been demonstrated, and it now appears unlikely that GBS occurs after vaccination.[6,7]

AETIOLOGY

Most recent evidence supports the proposition that the AMAN and AMSAN variants of GBS are caused by immunological antibody-mediated nerve injury.[8,9] This antibody-mediated injury is driven by accidental molecular mimicry between surface gangliosides[10,11] on the nerve and an antecedent microbial antigen, such as *Campylobacter jejuni*.[12,13] However, it is important to note that unwanted autoimmunity does not arise in the majority of individuals exposed to *C. jejuni* infection.[14] The immune mechanism underlying AIDP is less well elucidated and this may be because of a greater heterogeneity in antecedent microbial infections or immune stimulation.

Two-thirds of cases are preceded by symptoms suggestive of respiratory or gastrointestinal infection. *C. jejuni* gastroenteritis now appears to be the most common predisposing infection and may be associated with a more severe clinical course; 26%–41% of GBS patients show evidence of recent *C. jejuni* infection. Cytomegalovirus infection accounts for a further 10%–22% of cases.[15] Other infective agents implicated include influenza A, hepatitis E,[16] parainfluenza, *haemophilus*,[17] varicella-zoster, Epstein–Barr, chickenpox, mumps, human immunodeficiency virus,[18] measles virus and *Mycoplasma*. Immunisations against viral infections, tuberculosis, tetanus and typhoid have all been reported to be associated with the onset of GBS, but most of these reports are anecdotal and of

ABSTRACT

Weakness due to disorders of peripheral nerve, the neuromuscular junction and muscle are a small, but important subset of neurological admissions to intensive care units. Several disorders including Guillain-Barré syndrome, myasthaenia gravis and motor neurone disease are discussed in this chapter summarising the epidemiology, pathogenesis, clinical features and management of these conditions. Recent advances include the identification of an increasing number of autoantibodies in Guillain–Barré syndrome and myasthaenia gravis, the consolidation of immunotherapy in the management of these two conditions and the confirmation of the benefit of thymectomy in the management of the latter, particularly for early onset disease. The prognosis of both disorders remains good. Motor neurone disease remains a disease with a poor prognosis and short life expectancy following diagnosis, although early multidisciplinary involvement and the use of noninvasive ventilation, assisted feeding and riluzole may modestly slow the progression of the disease.

KEYWORDS

Intensive care
critical illness
Guillain-Barré syndrome
myasthaenia gravis and motor neurone disease

Box 58.1 Differential diagnosis of muscle weakness in critically ill patients

Brainstem
Lower pontine haemorrhage or infarction (locked-in state)
Spinal cord
Transverse myelitis
Compression by tumour, abscess or haemorrhage
Carcinomatous or lymphomatous meningitis
Peripheral nerve
Intensive care unit acquired neuropathy/neuromyopathy
Phrenic nerve injury during thoracic surgery
Guillain–Barré syndrome
Ingested toxins, including arsenic, thallium, cyanide
Neuromuscular junction
Delayed reversal of neuromuscular blockade
Myasthaenia gravis
Lambert–Eaton syndrome
Botulism
Pesticide poisoning
Skeletal muscle
Acute necrotising myopathy
Steroid myopathy
Severe hypokalaemia, hypophosphataemia, and/or hypomagnesaemia
Acute alcoholic myopathy
Polymyositis or dermatomyositis
Toxic myopathy (colchicine, lovastatin, cocaine, bumetanide, amiodarone and others)
Intensive care unit acquired myopathy/neuromyopathy

questionable aetiological significance.[7] Surveillance data following the 2009 H1N1 influenza epidemic suggested that the risk of GBS following immunisation was only marginally increased over baseline.[6]

PATHOGENESIS

The peripheral nerves of patients who have died of GBS show infiltration of the endoneurium by mononuclear cells, in a predominantly perivenular distribution. The inflammatory process may be distributed throughout the length of the nerves, but with more marked focal changes in the nerve roots, spinal nerves and major plexuses. Electron micrographs show macrophages actively stripping myelin from the bodies of Schwann cells and axons. In some cases, Wallerian degeneration of axons is also seen, and failure of regeneration in these cases may correspond with a poor clinical outcome.[8,9]

Patients with recent *C. jejuni* infection have a high incidence of antibodies to the gangliosides GM1 and GD1a on the axonal surface (AMAN). Antibodies to the ganglioside GQ1b, which is enriched in the extraocular muscles, are described in the Miller-Fisher variant.[11] The basis of the effectiveness of plasma exchange and immunoglobulin therapy is likely to be by blocking or removing these autoantibodies.[19]

CLINICAL PRESENTATION

Most patients describe a minor illness in the 8 weeks prior to presentation, with a peak incidence 2 weeks beforehand. Approximately half the patients initially experience paraesthesiae, typically beginning in the hands and feet. Motor weakness proceeds to flaccid paralysis, which becomes the predominant problem. Objective loss of power and reduction or loss of tendon reflexes usually commence distally and ascend, but a more haphazard spread may occur. Muscle and/or neuropathic pain can be a prominent early feature. Cranial nerves are involved in 45% of cases, most commonly the facial nerve, followed by the glossopharyngeal and vagus nerves. One-third of patients require ventilatory support.

In typical GBS, sensory loss is generally mild, with paraesthesiae or loss of vibration and proprioception, but occasionally sensory loss, pain or hyperaesthesia can be prominent features. Autonomic dysfunction is common, and a major contributor to morbidity and mortality in ventilator-dependent cases. Orthostatic or persistent hypotension, paroxysmal hypertension and bradycardia are all described, as are fatal ventricular tachyarrhythmias. Sinus tachycardia is seen in 30% of cases. Paralytic ileus, urinary retention and abnormalities of sweating are also commonly seen. Progression of symptoms occurs up to 4 weeks after onset and rarely can be longer. Approximately 20%–30% of patients during the progressive phase require mechanical ventilation.

One subgroup of patients presents with a primarily axonal neuropathy (AMAN or AMSAN). In these cases, motor (and sensory) axons appear to be the primary targets of immune attack, rather than myelin. These patients have a more fulminant and severe course, and there is again a strong association with *C. jejuni* infection and anti-GM1 and -GD1a antibodies.

In the Miller–Fisher syndrome, a variant of GBS, cranial nerve abnormalities predominate, with ataxia, areflexia and ophthalmoplegia as the main features.[20] This is strongly associated with recent *C. jejuni* infection and with the presence of GQ1b antibodies.

DIFFERENTIAL DIAGNOSIS

Most of the important alternative diagnoses are listed in Box 58.2. In patients with prolonged illness, the possibility of chronic inflammatory demyelinating polyradiculopathy should be considered.[21] In this condition, preceding viral infection is uncommon, the onset is more insidious and the course is one of slow worsening or stepwise relapses. Corticosteroids and plasma

Box 58.2 Diagnostic criteria for typical Guillain–Barré syndrome

Features required for diagnosis
Progressive weakness in both arms and both legs
Areflexia
Features strongly supportive of the diagnosis
Progression over days to 4 weeks
Relative symmetry of symptoms
Mild sensory symptoms or signs
Cranial nerve involvement, especially bilateral weakness of facial muscles
Recovery beginning 2–4 weeks after progression ceases
Autonomic dysfunction
Pain
High concentration of protein in cerebrospinal fluid protein, with fewer than 10×10^6 cells/L
Typical electrodiagnostic features
Features that should raise doubt about the diagnosis of Guillain-Barré syndrome
Mononuclear cell count in CSF >50 cells per μL
Presence of fever at onset
Severe pulmonary pathology with minimal limb weakness at onset
Persistent bladder or bowel dysfunction
Sharp spinal cord sensory level
Persistent asymmetry of weakness
Slow progression of weakness without respiratory involvement
Purely sensory syndrome, without weakness

Feasby T, Hahn A, Brown W, et al. Severe axonal degeneration in acute Guillain-Barre syndrome: evidence of two different mechanisms? *J Neurol Sci.* 1993;116(2):185–192.

exchange are possibly effective in this disorder, but adequate studies of immunosuppressive drugs have not been carried out.

An intermediate *subacute* polyneuropathy as well as a recurrent form of GBS are also described, and these variants may be part of the spectrum of a single condition.

A purely motor axonal neuropathy (AMAN), which causes seasonal childhood epidemics mimicking classical GBS in China and elsewhere,[22] appears to be a distinct entity. Once again, this is strongly associated with *C. jejuni* infection.

INVESTIGATIONS

In over 90% of patients, CSF protein is increased (greater than 0.4 g/L) within 2 weeks of onset of symptoms. The level does not correlate with the clinical findings. A pleocytosis with lymphocytes and monocytes in the CSF may be seen in a small proportion of patients (<15%), especially later in the disease. Nerve conduction studies may be normal early in the disease and are most useful around 2 weeks after the onset of weakness. Nerve conduction studies can help differentiate between the demyelinating (AIDP) and axonal (AMAN and AMSAN) subtypes and this differentiation may relate to prognosis.

MANAGEMENT

Although the management of the patient with severe and protracted GBS provides a major challenge, the prognosis is generally good if complications can be treated early or avoided.

SPECIFIC THERAPY

Plasma exchange (plasmapheresis) is of value in GBS, and in two trials a reduction in patients requiring mechanical ventilation, reduced duration of mechanical ventilation for those who required it, reduced time to motor recovery and time to walking without assistance were demonstrated.[23,24] Mortality, however, was not altered. Plasma exchange was most effective when carried out within 7 days of onset of symptoms. The currently recommended plasma exchange schedules consist of four exchanges of 1–2 plasma volumes each, over 1–2 weeks.[25] Adverse events are common, and some relate to the disease itself[26]; Fresh frozen plasma is reported to have more side effects than albumin as the replacement fluid.

Immunoglobulin therapy was as effective as plasmapheresis[27] and previous concerns of higher recurrence rates are probably unfounded. Because of its ease of use, many authorities now advocate immunoglobulin as the treatment of choice.[28] A total dose of 2 g/kg body weight intravenously, over 2–5 days, is reasonable.[29]

About 10% of patients relapse after initial treatment with either plasmapheresis or immunoglobulin; most respond well to a further course. There appears to be no benefit in combining plasmapheresis and immunoglobulin treatments, or in crossing over from one to the other.[27]

Low- or high-dose corticosteroids are of no value, and may even slow recovery.[30]

SUPPORTIVE CARE

RESPIRATORY

In the spontaneously breathing patient, chest physiotherapy and careful monitoring of respiratory function are of paramount importance. Regular measurement of vital capacity is probably the best way to predict respiratory failure, and is more reliable than arterial blood gases.[31] Any patient with a vital capacity less than 15 mL/kg or 30% of the predicted level, or a rising arterial $PaCO_2$ (a late sign of respiratory failure) is likely to require mechanical ventilation.

Bulbar involvement should be carefully sought, as there is a significant risk of aspiration of upper airway secretions, gastric contents or ingested food. The cough

reflex may be inadequate, and airway protection by tracheal intubation or tracheostomy is then required. Oral feeding should be stopped in any patient in whom bulbar involvement is suspected.

Mechanical ventilation is mandatory if coughing is inadequate, pulmonary collapse or consolidation develop, arterial blood gases are significantly abnormal, vital capacity is less than predicted tidal volume (approximately 15 mL/kg), or the patient is dyspnoeic, tachypnoeic or appears exhausted. Mechanical ventilation, if necessary, will probably be required for several weeks (although there is wide variation), and early tracheostomy should be considered.

CARDIOVASCULAR

Cardiac rhythm and blood pressure should be monitored. Sinus tachycardia is the commonest autonomic manifestation of GBS and usually requires no active treatment. Induction of anaesthesia appears particularly likely to induce serious arrhythmias. Use of suxamethonium may contribute significantly to this and, as with many other neuromuscular disorders, should be avoided.[32] Endotracheal suctioning has also been associated with serious arrhythmias. Cardiovascular instability may also be exacerbated by several drugs (Box 58.3). These, likewise, should be avoided or used with great care.

Mild hypotension and bradycardia may require no treatment, particularly if renal and cerebral functions are maintained. However, blood volume expansion or inotropic drugs may be required in some cases. Hypertension is often transient, but occasionally requires appropriate drug therapy. Hypoxia, hypercarbia, pain and visceral distension should be excluded as causes.

Box 58.3 Drugs associated with cardiovascular instability in Guillain–Barré syndrome

Exaggerated hypotensive response
Phentolamine
Nitroglycerin
Edrophonium
Thiopentone
Morphine
Furosemide

Exaggerated hypertensive response
Phenylephrine
Ephedrine
Dopamine
Isoprenaline

Arrhythmias
Suxamethonium

Cardiac arrest
General anaesthesia

FLUIDS, ELECTROLYTES AND NUTRITION

Paralytic ileus is not uncommon, especially immediately following the institution of mechanical ventilation, and a period of parenteral nutrition may be required. However, where possible, nasoenteric feeding should be instituted because of its significantly greater safety. Energy and fluid requirements are considerably reduced in these patients.

SEDATION AND ANALGESIA

In non-ventilated patients, sedation should be avoided because of the potential for worsening respiratory and upper airway function. In ventilated patients, sedation becomes less necessary as the patient becomes accustomed to the ventilator, but night sedation may help to preserve diurnal rhythms. Limb pain, particularly with passive movement, is very common and often quite severe. Quinine, non-steroidal analgesics and antidepressant drugs may all be tried, but the pain can be difficult to control and opioids are often required. Methadone, transdermal fentanyl, gabapentin and tramadol have all been advocated.

GENERAL AND NURSING CARE

A comprehensive programme of physiotherapy should be implemented by nurses and physiotherapists, with careful attention to pressure area care, the maintenance of joint mobility and pulmonary function. Nosocomial infection should be actively sought. Sites of vascular access should be inspected frequently, and changed whenever necessary. It may be possible to manage stable long-term patients without venous access. Care should be taken to prevent corneal ulceration and faecal impaction.

Prophylaxis against venous thromboembolism should be given, and enterally administered low-dose warfarin may be preferable to twice-daily heparin injections in long-stay patients. Psychological problems, especially depression, are common, and some patients are helped by antidepressant drugs. Good communication and rapport between the patient and staff, involvement of allied health practitioners, the provision of television, radio and reading aids and, where possible, occasional trips out of the ICU often have great value.

PROGNOSIS

The nadir of the disease is reached within 2–4 weeks, and gradual resolution follows over weeks to months. Of those who survive the acute illness, 70% have recovered to functional independence within 1 year, and a further 20% are left with minor limitations. Poor prognostic features[33] include age over 60 years, rapid progression to quadriparesis in less than 7 days, the need for mechanical ventilation (except for children), and a preceding diarrhoeal illness. Even in patients ventilated for more than 2 months, gradual improvement

may continue for 18 months to 2 years. These severely affected patients require a protracted period of rehabilitation. A substantial proportion of patients have residual pain and fatigue that may be attributed to persistent axonal loss. Many patients adapt their work or daily activities even after substantial recovery.

Overall mortality in well-resourced settings is 5%–8% and is usually due to respiratory complications or because of autonomic instability.

MYASTHAENIA GRAVIS

MG is an autoimmune disorder of skeletal muscle caused by antibodies directed against acetylcholine (ACh) receptors or functionally related molecules in the post-synaptic membrane at the neuromuscular junction.[34] Despite its relative rarity, it is the most studied and best understood clinical disorder of neuroreceptor function, and arguably the best understood organ-specific autoimmune disease. It is characterised clinically by ocular and skeletal muscle weakness and exaggerated fatigability on sustained effort. Intensive care is most commonly required because of severe involvement of the bulbar or respiratory muscles, which may be the result of a spontaneous exacerbation of the disease, a complication of drug therapy, intercurrent illness or surgery, or following surgical thymectomy – a component of treatment for some patients. The diagnosis of MG is based on the combination of symptoms, signs and a positive test for specific autoantibodies, although seronegative forms are recognised.

INCIDENCE

The incidence of MG is approximately 8–10 per million. There is no racial or geographic predilection. Although MG can occur at any age, it is very rare in the first 2 years of life, and the peak incidence is in young adult females. Overall, females are affected about twice as often as males. This gender predilection decreases with increasing age, and there is a smaller, second incidence peak in elderly males.

AETIOLOGY AND PATHOPHYSIOLOGY

In 70% of cases, there is histological evidence of thymic abnormality. Thymic hyperplasia is present in most patients, particularly early onset (<50 years old). Approximately 10% have a thymoma and this is more common in the older age group.

The precise role of the thymus is uncertain, but ACh receptors (AChR) are present in the myoid cells of the normal thymus, and there is evidence that anti-AChR antibody production is mediated by both B and T lymphocytes of thymic origin.

Other organ-specific autoimmune disorders, most commonly thyroid disease[35] but also rheumatoid arthritis and lupus erythematosus, are significantly associated with MG; autoantibodies to other organs may be seen in MG patients without evidence of disease. Other associations include myocarditis and lymphoma.

Children born to mothers with MG demonstrate transient weakness ('neonatal MG') in about 15% of cases.

A number of congenital myasthaenic syndromes exist, in which symptoms develop in infancy, without evidence of autoantibody production.[36] A familial tendency is more common in this group, and structural changes at the neuromuscular junction have been demonstrated.

The stimulus to autoantibody production is not known, but these can be detected in about 90% of patients with generalised myasthaenia. The antibodies may interfere with neuromuscular transmission by competitively blocking receptor sites, by initiating immune-mediated destruction of receptors, or by binding to portions of the receptor molecule that are not part of the AChR site but nevertheless are important in allowing ACh to bind.

CLINICAL PRESENTATION

Ptosis and diplopia are the most common initial symptoms and in 20% of cases the disorder remains confined to the eye muscles (ocular MG); ocular signs are usually asymmetrical. Bulbar muscle weakness is common and may result in nasal regurgitation, dysarthria and dysphagia.[33] Limb and trunk weakness can occur with varying distribution, and is usually symmetrical.

Some patients complain of fatigue rather than weakness and may be misdiagnosed as having psychiatric problems. However, weakness can be elicited by sustained effort of an involved muscle group (e.g. sustained upward gaze is often worse at the end of the day and improves with rest).

Early onset disease tends to be associated with thymic hyperplasia, whereas late onset disease is often associated with thymic atrophy.

INVESTIGATIONS

Impairment of neuromuscular transmission may be confirmed by a positive edrophonium ('Tensilon') test. However, this traditional test has waned in popularity as it has high sensitivity but rather poor specificity. Atropine 0.6 mg is given IV to prevent muscarinic side effects, and this is followed by 1 mg edrophonium. If there is no obvious improvement within 1–2 minutes, a further 5 mg may be given. Some authors recommend the use of a saline placebo injection, and the presence of a second doctor as a 'blinded' observer.

Resuscitation facilities should be available as profound weakness may ensue, especially in patients already receiving anticholinesterase drugs.

The presence of autoantibodies against nicotinic AChR is quite specific, but false positives may occur in patients with penicillamine-treated rheumatoid disease, other autoimmune diseases and in some first-degree relatives of myasthaenic patients.[37] Other antibodies associated with myasthaenia include muscle-specific kinase and lipoprotein receptor related protein antibodies; the former appears to be associated with more severe, treatment-resistant disease. About 15% of patients are seronegative.

Electromyography shows characteristic changes in 90% of patients with generalised MG and also in many patients with ocular symptoms only.

A syndrome of myasthaenic weakness occurs in association with malignancy and other autoimmune diseases (Eaton–Lambert syndrome). Although fatigability is present, the pelvic and thigh muscles are predominantly affected, whereas ocular and bulbar involvement is rare. Tendon reflexes are reduced or absent, and there are specific electromyographic changes.

MANAGEMENT

1. *Symptomatic treatment* is provided by anticholinesterase drugs, which potentiate the action of ACh at receptor sites. Pyridostigmine (Mestinon) is the most commonly used, and is usually commenced at a dose of 60 mg orally three to four times daily. Considerable adjustment of dosage may be required based on symptom relief and side effects (diarrhoea, abdominal pain, cramps, urinary urgency and increased flatus, salivation and sweating).
2. Expert consensus and limited controlled trial data suggest that most patients require immunosuppression with a combination of *Corticosteroids and/or azathioprine*.[38–40] High doses of corticosteroids (e.g. prednisolone 50–100 mg/day) are used initially and may be introduced gradually, before being carefully reduced to the minimal dose (10–40 mg/day) for symptom control. Transient exacerbation upon commencement of steroids is very common, and severely affected patients are often hospitalised for the initiation of therapy with gradually increasing doses. Older patients are more likely to respond, but an average of 4 months' treatment is required to achieve clinical stability and the majority will require continuing treatment indefinitely.[41] *Azathioprine and mycophenolate* are both effective adjuncts to corticosteroid therapy because a combination of corticosteroid with either agent allows a reduced dose of steroid, minimising side effects of steroid therapy and achieving a better functional outcome overall. Azathioprine and mycophenolate are purine synthesis antagonists and have effects on T and B lymphocytes. Thiopurine methyltransferase activity should ideally be tested before treatment with azathioprine because low activity increases the risk of toxic side effects.[42,43] Overall, 80% of patients are improved with a combination of steroid and either azathioprine or mycophenolate, but this may be seen only after some months. A few patients may achieve complete remission.
3. *Ciclosporin (cyclosporine), mycophenolate, tacrolimus and rituximab* are all supported by limited evidence in MG and are occasionally used.[44–46]
4. *Thymectomy* offers the prospect of long-term, drug-free remission and has long been advocated as a mainstay of MG treatment. Thymectomy should be performed in patients with MG and a thymoma. Historical studies suggested that total thymectomy also benefited patients with MG without a thymoma.[47] Recently, this has been confirmed in a clinical trial supporting early total thymectomy for patients with generalised disease, duration of disease of less than 3–5 years and age of less than 65.[48] Thymectomy was associated with symptom reduction, less immunosuppressive drug treatment and fewer exacerbations during the 3-year follow up.

   Preoperative optimisation of neuromuscular function is essential, using anticholinesterase drugs and steroids, supplemented by plasma exchange or immunoglobulin if necessary. Though anticholinesterase requirements are usually reduced in the immediate postoperative period to about three-quarters of the preoperative dose, sustained improvement following thymectomy may not be seen for months or even years. A thoracoscopic approach may achieve equivalent results with less short-term morbidity, but the traditional sternotomy approach continues to be commonly used.
5. *Plasma exchange and intravenous immunoglobulin* are equally effective in producing short-term clinical improvement.[35,49,50] Either approach may be used in myasthaenic crisis or to improve severely affected patients before thymectomy. For *plasma exchange*, five exchanges of 3–4 L each are performed over a 2-week period, and this results in improvement within days. However, the benefits are short-lived, lasting only weeks. *Intravenous immunoglobulin* can be used at a total dose of 1–2 g/kg given over 1–2 days, and occasional patients derive long-term benefit. Interestingly, immunoglobulin has no consistent effect on AChR antibody concentrations, and its mechanism of action is poorly understood.

MYASTHAENIC AND CHOLINERGIC CRISIS

Patients with known MG may undergo life-threatening episodes of acute deterioration affecting bulbar and respiratory muscle function. These may occur spontaneously, or may follow intercurrent infection, pregnancy, surgery, the administration of various drugs (Box 58.4) or attempts to reduce the level of immunosuppression.

Box 58.4 Drugs that may exacerbate myasthaenia gravis

Antibiotics	**Local anaesthetics**
Streptomycin	Procaine
Kanamycin	Lidocaine
Tobramycin	**General anaesthetics**
Gentamicin	Ether
Polymyxin group	**Muscle relaxants**
Tetracycline	Curare
Antiarrhythmics	Suxamethonium
Quinidine	**Analgesics**
Quinine	Morphine
Procainamide	Pethidine

Such episodes, known as myasthaenic crises, usually resolve over several weeks, but occasionally last for months. The incidence of myasthaenic crisis increases markedly with age.

Rarely, a patient may deteriorate due to excessive dosage of anticholinesterase drugs ('cholinergic crisis'). Abdominal cramps, diarrhoea, excessive pulmonary secretions, sweating, salivation and bradycardia may be present, but these can also occur in patients with myasthaenic crisis on high doses of pyridostigmine. Though the two situations may be difficult to distinguish, myasthaenic crisis is far more likely unless extremely large doses of pyridostigmine (at least 120 mg every 3 hours) have been administered.

A Tensilon test is now considered an unreliable method of distinguishing between these two possibilities, may be hazardous, and is generally not recommended.

Patients with myasthaenic crisis should be admitted directly to the ICU, as there is a significant risk of pulmonary aspiration due to bulbar involvement, bacterial pneumonia due to stasis, acute respiratory failure or cardiorespiratory arrest. After initial stabilisation and resuscitation, every effort should be made to identify and correct reversible causes, especially respiratory infections and electrolyte disturbances.

Frequent estimations of vital capacity and maximum inspiratory force should be made and recorded. Tracheal intubation and mechanical ventilation should be considered in patients with significant bulbar involvement or clinical evidence of worsening respiratory failure. As with other neuromuscular disorders, deterioration of blood gases may occur late, and is an unreliable sign of progressive respiratory failure.[31] Aggressive chest physiotherapy, urinary drainage and nasogastric feeding may be required. Hypokalaemia, hypocalcaemia and hypermagnesaemia should be avoided, as all may exacerbate muscle weakness.

If the patient's clinical status cannot be rapidly improved by the adjustment of anticholinesterase dosage, immunosuppressive therapy and aggressive treatment of intercurrent illness, high-dose corticosteroids and plasma exchange or immunoglobulin should be commenced simultaneously, and may produce some benefit within as little as 24 hours.

PERIOPERATIVE MANAGEMENT

MG patients often require intensive care in relation to surgery for intercurrent illness or prior to thymectomy. Unstable patients should be admitted to hospital some days in advance for stabilisation. In severely affected patients, preoperative high-dose corticosteroids and/or plasma exchange may be used to improve the patient's fitness for surgery. It may be prudent to omit premedication, and an anaesthetic technique that avoids the use of non-depolarising muscle relaxants is usually advocated, though vecuronium and atracurium are probably safe in reduced dosage.[51,52] Suxamethonium can be used safely in normal dosage.[53]

Up to one-third of patients require continuing mechanical ventilation postoperatively following thymectomy. Predictive factors include a long preoperative duration of myasthaenia, coexistent chronic respiratory disease, high anticholinesterase requirements (e.g. pyridostigmine >750 mg/day) and a preoperative vital capacity of less than 2.9 L.[54] In those cases requiring mechanical ventilation, some authors advocate temporary cessation of anticholinesterase drugs to reduce respiratory secretions, but generally they should be continued, though dosage requirements must be reassessed carefully and repeatedly.

MOTOR NEURON DISEASE (AMYOTROPHIC LATERAL SCLEROSIS, LOU GEHRIG'S DISEASE)

Motor neuron disease is a heterogeneous progressive, paralytic disorder characterised by gradual generalised degeneration of all types of motor neurons.[55,56] This leads to increasing physical disability and there is now a recognised association with impaired cognition (frontotemporal dementia). There is often a delay in initial diagnosis and death occurs 3–5 years after diagnosis due to respiratory failure.

PATHOGENESIS

The key pathological finding is mixed upper and lower motor neurone death in the motor cortex and spinal cord, accompanied by inflammation and proliferation of astrocytes, microglia and oligodendrocytes. A common finding is aggregation of cytoplasmic proteins in motor neurones. The cerebral cortex as well as the anterior horns of the spinal cord are involved, with shrinkage, degenerative pigmentation and, eventually, disappearance of the affected cells accompanied by gliosis of the lateral columns ('lateral sclerosis'). As

muscles are denervated, there is progressive atrophy of muscle fibres ('amyotrophy'), but sensory neurons as well as those concerned with autonomic function and coordination are all spared.

Over 120 genetic variants of motor neurone disease have been identified and approximately 10% of cases are familial and 90% are sporadic. The disease may arise because of the interplay between genetic and environmental factors, although it is possible that the disease occurs because of mainly complex genetic factors.

CLINICAL PRESENTATION

There are four main clinical phenotypes of motor neurone disease.

- Amyotropic lateral sclerosis (ALS) is the dominant phenotype (70%) and presents with mixed upper and lower motor neurone signs affecting the limbs. This is the most malignant form of the disease and median life expectancy is about 3 years. In North America the term ALS is often used more generically, essentially equivalent to the broader term motor neurone disease.
- Isolated bulbar palsy (4%–8%) presents initially with progressive speech and swallowing difficulty prior to the development of more generalised disease. Median life expectancy is around 4 years.
- Progressive muscular atrophy (5%) presents with pure lower motor neurone signs affecting the limbs. The prognosis may be slightly better than for classic ALS.
- Primary lateral sclerosis presents with pure upper motor neurone signs affecting the lower limbs mainly, with patients having a much slower disease progression and in some cases a normal life expectancy.

As motor neurone disease becomes more generalized, a mixed pattern of upper and lower motor neurone signs affecting limb skeletal muscle evolves (i.e. spasticity and hyperreflexia in addition to gross wasting) with bulbar and respiratory muscles also affected.

Awareness and intellect were previously thought to be preserved, but it is now recognised that up to half the patients have evidence of cognitive dysfunction, manifest as language difficulties and frontal symptoms. Motor neurone disease and frontotemporal dementia are now recognised to be part of a continuum in which pure motor neurone disease and pure frontotemporal dementia form the ends of a clinical and pathological spectrum.

Death occurs in 50% of cases within 3–5 years, usually due to respiratory infection, aspiration or ventilatory failure from profound weakness. However, there is wide variability, and a few patients may survive for many years.

DIAGNOSIS

There are no specific investigations, and the diagnosis must be made on clinical grounds together with electromyogram evidence of generalised denervation. The most important differential diagnosis is multifocal motor neuropathy. The distinction is of clinical importance, as the latter is amenable to treatment. Poliomyelitis can also result in a syndrome of progressive weakness, wasting and fasciculation, beginning many years after the initial illness (the post-polio syndrome), and leading occasionally to respiratory failure and death.[57]

MANAGEMENT

Treatment is essentially symptomatic and supportive. Current evidence suggests that treatment within a multidisciplinary team may improve both quality of life and life expectancy by 7–24 months. Non-invasive ventilation improves both quality of life and survival in patients who do not have severe bulbar dysfunction.[58,59] Regular assessment and management of nutrition status is important and interventions such as nasoenteral feeding tubes or gastrostomy may have a role.[60] Riluzole, a centrally acting glutamate antagonist that also modifies sodium channel activity, has been shown to slow slightly the progression of ALS by 3–6 months.[61–63]

Admission to the ICU is sometimes requested when these patients present with an acute deterioration or intercurrent illness. The intensivist may also be asked to assist with ambulatory or home respiratory support for gradually worsening chronic respiratory failure.

Respiratory support may be given by face mask, nasal mask or, rarely, by tracheostomy using simple, compact ventilators. Some patients require only intermittent support, particularly at night or during periods of acute deterioration due to intercurrent illness. Although home-based non-invasive ventilation has become routine, long-term invasive respiratory support outside the ICU is a major undertaking, requiring specific equipment and extensive liaison with the patient, the family and numerous specialised support services.

RARE CAUSES OF ACUTE WEAKNESS IN THE INTENSIVE CARE UNIT

PERIODIC PARALYSIS[64]

This term describes a group of rare primary disorders, mostly inherited as autosomal dominant traits, producing episodic weakness. They must be distinguished from other causes of intermittent weakness, including electrolyte abnormalities, MG and transient ischaemic attacks. The inherited types are now grouped together with the various forms of myotonia

and susceptibility to malignant hyperthermia. All are classified as congenital defects of skeletal muscle ion channels and there is an association with long QT syndrome and other cardiac channelopathies. Symptoms begin early in life (before age 25), and follow rest or sleep rather than exertion. Alertness during attacks is completely preserved, and muscle strength between attacks is normal. Treatment is usually successful in preventing both the attacks and the chronic weakness, which can develop after many years in untreated patients.

The *hypokalaemic* form of periodic paralysis is predominantly inherited, but can also present sporadically in association with thyrotoxicosis. Involvement of bulbar or respiratory muscles occurs rarely. The degree of hypokalaemia during attacks is mild, but patients rapidly respond to potassium administration. Effective prophylaxis is conferred by acetazolamide, with potassium replacement. Many patients eventually develop established myopathy. Depolarising muscle relaxants should be avoided in these patients.

The *hyperkalaemic* form is milder, almost always inherited and rarely requires intensive care. The serum potassium is modestly elevated at the beginning of attacks, but may be normal at other times. Creatine kinase levels may be elevated during attacks. Attacks respond to carbohydrate administration, sympathomimetics (which activate the sodium/potassium pump) and acetazolamide. Thiazide diuretics or acetazolamide provide effective prophylaxis. Non-depolarising muscle relaxants should be avoided in these patients.

A *normokalaemic* form and several eponymously named congenital syndromes are also included in this group of disorders.

BOTULISM[65]

Botulism is a widespread but very uncommon potentially lethal disease caused by exotoxins produced by *Clostridium botulinum* – an anaerobic, spore-forming Gram-positive bacillus. The vast majority of botulism is *foodborne* and outbreaks are largely due to home-preserved vegetables (type A toxin), meat (type B) or fish (type E), but high-risk foods also include low-acid fruit and condiments. Signs and symptoms are caused by toxin produced in vitro and then ingested.

The first recorded outbreak occurred in Germany in 1817, from ingestion of improperly preserved blood sausage (*Botulus* [Latin] = 'sausage').

Wound botulism arises rarely, when wounds (typically open fractures) are contaminated by soil containing type A or B organisms. Intravenous drug abusers are an increasing source of this condition through infected injection sites.

Infantile botulism arises in infants under 6 months of age, and is due to the active production of toxin by organisms in the gut rather than the direct ingestion of toxin.

Hidden botulism describes the adult equivalent of infantile botulism, and is a rare complication of various gastrointestinal abnormalities.

Inadvertent botulism is the most recently described form, and occurs as a complication of the medical or cosmetic use of botulinum toxin (BoNT).

Inhalational botulism is the form that would occur as a result of aerosolised toxin released in the context of bioterrorism. BoNT is the most potent known neurotoxin, and it has been estimated that as little as 1 g of aerosolised BoNT could lead to the death of over 1.5 million people.

In most cases, exogenously produced exotoxin is absorbed (primarily in the upper small intestine), and carried by the bloodstream to cholinergic nerves at the neuromuscular junction, postganglionic parasympathetic nerve endings and autonomic ganglia, to which it irreversibly binds. The toxin enters the nerve endings to interfere with ACh release.

Most patients become ill about 3 days after ingestion of toxin, with gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhoea or constipation), dryness of the eyes and mouth, dysphagia and generalised weakness, which progresses in a symmetrical, descending fashion, with ventilatory failure in severe cases. Cranial nerve dysfunction is a prominent early feature, manifested by ptosis and diplopia, facial weakness and impaired upper airway reflexes. The pupils may be fixed and dilated in severe cases. Patients are usually afebrile and have no sensory involvement.

The differential diagnosis includes food poisoning from other causes, MG and GBS. Botulism can be confirmed by the presence of toxin (either in the patient's serum or stool, or in contaminated food) in about two-thirds of cases. Contact tracing, in the case of food-borne botulism, is of great importance.

Treatment is mainly supportive, with airway protection and mechanical ventilation when required. Mean duration of mechanical ventilation, when required, is 7 weeks. Clearance of toxin from the bowel with enemas and cathartics has been advocated. Guanidine hydrochloride, which enhances the release of ACh from nerve terminals, has been reported to improve muscle strength, especially in ocular muscles, and may be useful in milder cases. Antibiotics have not been clearly shown to be useful. Equine antitoxins are available, but side effects are common and their efficacy is limited. A human-derived antitoxin has been shown to be effective in *infantile botulism*, and the United States Defense Department has a pentavalent antitoxin, which is not available for public use. Antitoxin must be given before the onset of paralysis in order to be effective. In *wound botulism*, antibiotics (penicillin or metronidazole) and aggressive debridement are recommended.

Most patients begin to improve after a week or so, but hospitalisation is usually required for 1–3 months. The mortality is low (5%–8%) with good supportive

care, including mechanical ventilation. Mild weakness and constipation may persist for many months.

KEY REFERENCES

5. Sejvar JJ, Baughman AL, Wise M, et al. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. *Neuroepidemiology*. 2011;36(2):123–133.
9. Willison HJ, Jacobs BC, Van Doorn PA. Guillain-Barré syndrome. *Lancet*. 2016;388(10045):717–727.
28. Patwa H, Chaudhry V, Katzberg H, et al. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2012;78(13):1009–1015.
29. Hughes RA, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. *Cochrane Database Syst Rev*. 2014;(9):CD002063.
34. Gilhus NE. Myasthenia gravis. *N Engl J Med*. 2016; 375(26):2570–2581.
38. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: executive summary. *Neurology*. 2016;87(4): 419–425.
40. Hart IK, Sathasivam S, Sharshar T. Immunosuppressive agents for myasthenia gravis. *Cochrane Database Syst Rev*. 2007;(4):CD005224.
48. Wolfe GI, Kaminski HJ, Aban IB, et al. Randomized trial of thymectomy in myasthenia gravis. *N Engl J Med*. 2016;375(6):511–522.
50. Barth D, Nouri MN, Ng E, et al. Comparison of IVIg and PLEX in patients with myasthenia gravis. *Neurology*. 2011;76(23):2017–2023.
55. Dharmadasa T, Henderson RD, Talman PS, et al. Motor neurone disease: progress and challenges. *Med J Aust*. 2017;206(8):357–362.
56. Brown RH, Al-Chalabi A. Amyotrophic lateral sclerosis. *N Engl J Med*. 2017;377(2):162–172.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Wardrop J. Clinical observations on various diseases. *Lancet*. 1834;1:380–382.
2. Guillain G. Sur un syndrome de radiculonevrite avec hyperalbuminose due liquide cephalo-rachidien sans reaction cellulaire. Remarque sur les caracteres clinique et graphiques des reflezes tendinuex. *Bull Mem Soc Med Hop Paris*. 1916; 40:1462.
3. Feasby T, Hahn A, Brown W, et al. Severe axonal degeneration in acute Guillain-Barre syndrome: evidence of two different mechanisms? *J Neurol Sci*. 1993;116(2):185–192.
4. Asbury AK. Criteria for diagnosis of Guillain-Barré syndrome. *Ann Neurol*. 1978;3:565.
5. Sejvar JJ, Baughman AL, Wise M, et al. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. *Neuroepidemiology*. 2011; 36(2):123–133.
6. Salmon DA, Proschan M, Forshee R, et al. Association between Guillain-Barré syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta-analysis. *Lancet*. 2013; 381(9876):1461–1468.
7. Kuitwaard K, Bos-Eyssen ME, Blomkwist-Markens PH, et al. Recurrences, vaccinations and long-term symptoms in GBS and CIDP. *J Peripher Nerv Syst*. 2009;14(4):310–315.
8. van Doorn PA, Ruts L, Jacobs BC. Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome. *Lancet Neurol*. 2008;7(10):939–950.
9. Willison HJ, Jacobs BC, Van Doorn PA. Guillain-Barré syndrome. *Lancet*. 2016;388(10045):717–727.
10. Susuki K, Yuki N, Schafer DP, et al. Dysfunction of nodes of Ranvier: a mechanism for anti-ganglioside antibody-mediated neuropathies. *Exp Neurol*. 2012;233(1):534–542.
11. Liu J-X, Willison HJ, Pedrosa-Domellöf F. Immunolocalization of GQ1b and related gangliosides in human extraocular neuromuscular junctions and muscle spindles. *Invest Ophthalmol Vis Sci*. 2009; 50(7):3226–3232.
12. Islam Z, Jacobs B, van Belkum A, et al. Axonal variant of Guillain-Barre syndrome associated with Campylobacter infection in Bangladesh. *Neurology*. 2010;74(7):581–587.
13. Rees JH, Soudain SE, Gregson NA, et al. Campylobacter jejuni infection and Guillain–Barré syndrome. *N Engl J Med*. 1995;333(21):1374–1379.
14. Huizinga R, Van Den Berg B, Van Rijs W, et al. Innate immunity to Campylobacter jejuni in Guillain-Barré syndrome. *Ann Neurol*. 2015;78(3): 343–354.
15. Visser L, Van der Meché F, Meulstee J, et al. Cytomegalovirus infection and Guillain-Barre syndrome: the clinical, electrophysiologic, and prognostic features. *Neurology*. 1996;47(3):668–673.
16. van den Berg B, van der Eijk AA, Pas SD, et al. Guillain-Barré syndrome associated with preceding hepatitis E virus infection. *Neurology*. 2014;82(6): 491–497.
17. Mori M, Kuwabara S, Miyake M, et al. Haemophilus influenzae infection and Guillain–Barré syndrome. *Brain*. 2000;123(10):2171–2178.
18. Simpson D, Olney R. Peripheral neuropathies associated with human immunodeficiency virus infection. *Neurol Clin*. 1992;10(3):685–711.
19. Sater RA, Rostami A. Treatment of Guillain-Barré syndrome with intravenous immunoglobulin. *Neurology*. 1998;51(6 suppl 5):S9–S15.
20. Fisher M. An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia). *N Engl J Med*. 1956;255(2):57–65.
21. Hughes R. The spectrum of acquired demyelinating polyradiculoneuropathy. *Acta Neurol Belg*. 1994; 94(2):128–132.
22. McKhann G, Cornblath D, Griffin J, et al. Acute motor axonal neuropathy: a frequent cause of acute flaccid paralysis in China. *Ann Neurol*. 1993;33(4):333–342.
23. Efficiency of plasma exchange in Guillain-Barré syndrome: role of replacement fluids. French Cooperative Group on Plasma Exchange in Guillain-Barré syndrome. *Ann Neurol*. 1987;22:753–761.
24. Raphaël JC, Chevret S, Hughes RA, et al. Plasma exchange for Guillain-Barré syndrome. *Cochrane Database Syst Rev*. 2012;(7):CD001798, 7.
25. Hughes RA, Swan AV, Raphaël J-C, et al. Immunotherapy for Guillain-Barré syndrome: a systematic review. *Brain*. 2007;130(9):2245–2257.
26. Bouget J, Chevret S, Chastang C, et al. Plasma exchange morbidity in Guillain-Barre syndrome: results from the French prospective, double-blind, randomized, multicenter study. *Crit Care Med*. 1993;21(5):651–658.
27. Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome. *Lancet*. 1997;349(9047):225–230.
28. Patwa H, Chaudhry V, Katzberg H, et al. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2012;78(13):1009–1015.
29. Hughes RA, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. *Cochrane Database Syst Rev*. 2014;(9):CD002063.
30. Hughes RA, Brassington R, Gunn AA, et al. Corticosteroids for Guillain-Barré syndrome. *Cochrane Database Syst Rev*. 2016;(10):CD001446.
31. Harrison B, Collins J, Brown K, et al. Respiratory failure in neuromuscular diseases. *Thorax*. 1971;26(5): 579–584.
32. Fergusson R, Wright D, Willey R, et al. Suxamethonium is dangerous in polyneuropathy. *Br Med J (Clin Res Ed)*. 1981;282(6260):298.
33. Sharp H, Degrip A, Mitchell D, et al. Bulbar presentations of myasthenia gravis in the elderly patient. *J Laryngol Otol*. 2001;115(1):1–3.
34. Gilhus NE. Myasthenia gravis. *N Engl J Med*. 2016; 375(26):2570–2581.

35. Gajdos P, Chevret S, Clair B, et al. Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. *Ann Neurol*. 1997;41(6):789–796.
36. Engel AG, Ohno K, Sine SM. Congenital myasthenic syndromes: progress over the past decade. *Muscle Nerve*. 2003;27(1):4–25.
37. Vincent A. Acetylcholine receptor antibody as a diagnostic test for myasthenia gravis: results in 153 validated cases and 2967 diagnostic assays. *J Neurol Neurosurg Psychiatry*. 2012;83(3):237–238.
38. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: executive summary. *Neurology*. 2016;87(4): 419–425.
39. Skeie G, Apostolski S, Evoli A, et al. Guidelines for treatment of autoimmune neuromuscular transmission disorders. *Eur J Neurol*. 2010;17(7): 893–902.
40. Hart IK, Sathasivam S, Sharshar T. Immunosuppressive agents for myasthenia gravis. *Cochrane Database Syst Rev*. 2007;(4):CD005224.
41. Sghirlanzoni A, Peluchetti D, Mantegazza R, et al. Myasthenia gravis prolonged treatment with steroids. *Neurology*. 1984;34(2):170–174.
42. Sanderson JD. TPMT testing before starting azathioprine or mercaptopurine: surely just do it? *Gastroenterology*. 2015;149(4):850–853.
43. Rae W, Burke G, Pinto A. A study of the utility of azathioprine metabolite testing in myasthenia gravis. *J Neuroimmunol*. 2016;293:82–85.
44. Tindall RS, Phillips JT, Rollins JA, et al. A clinical therapeutic trial of cyclosporine in myasthenia gravis. *Ann N Y Acad Sci*. 1993;681(1):539–551.
45. Pasnoor M, He J, Herbelin L, et al. A randomized controlled trial of methotrexate for patients with generalized myasthenia gravis. *Neurology*. 2016;87(1):57–64.
46. Yoshikawa H, Kiuchi T, Saida T, et al. Randomised, double-blind, placebo-controlled study of tacrolimus in myasthenia gravis. *J Neurol Neurosurg Psychiatry*. 2011;82(9):970–977.
47. Gronseth GS, Barohn RJ. Practice parameter: thymectomy for autoimmune myasthenia gravis (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55(1):7–15.
48. Wolfe GI, Kaminski HJ, Aban IB, et al. Randomized trial of thymectomy in myasthenia gravis. *N Engl J Med*. 2016;375(6):511–522.
49. Gajdos P, Chevret S, Toyka KV. Intravenous immunoglobulin for myasthenia gravis. *Cochrane Database Syst Rev*. 2012;(12):CD002277.
50. Barth D, Nouri MN, Ng E, et al. Comparison of IVIg and PLEX in patients with myasthenia gravis. *Neurology*. 2011;76(23):2017–2023.
51. Bell C, Florence A, Hunter J, et al. Atracurium in the myasthenic patient. *Anaesthesia*. 1984;39(10): 961–968.
52. Eisenkraft JB, Book WJ, Papatestas AE. Sensitivity to vecuronium in myasthenia gravis: a dose-response study. *Can J Anaesth*. 1990;37(3):301–306.
53. Wainwright A, Brodrick P. Suxamethonium in myasthenia gravis. *Anaesthesia*. 1987;42(9):950–957.
54. Eisenkraft JB, Papatestas AE, Kahn CH, et al. Predicting the need for postoperative mechanical ventilation in myasthenia gravis. *Anesthesiology*. 1986;65(1):79–81.
55. Dharmadasa T, Henderson RD, Talman PS, et al. Motor neurone disease: progress and challenges. *Med J Aust*. 2017;206(8):357–362.
56. Brown RH, Al-Chalabi A. Amyotrophic lateral sclerosis. *N Engl J Med*. 2017;377(2):162–172.
57. Fischer DA. Poliomyelitis: late respiratory complications and management. *Orthopedics*. 1985; 8(7):891–894.
58. Kleopa KA, Sherman M, Neal B, et al. Bipap improves survival and rate of pulmonary function decline in patients with ALS. *J Neurol Sci*. 1999;164(1): 82–88.
59. Berlowitz DJ, Howard ME, Fiore JF, et al. Identifying who will benefit from non-invasive ventilation in amyotrophic lateral sclerosis/motor neurone disease in a clinical cohort. *J Neurol Neurosurg Psychiatry*. 2015;jnnp-2014-310055.
60. Desport J, Preux P, Truong T, et al. Nutritional status is a prognostic factor for survival in ALS patients. *Neurology*. 1999;53(5):1059–1063.
61. Zoing MC, Burke D, Pamphlett R, et al. Riluzole therapy for motor neurone disease: an early Australian experience (1996–2002). *J Clin Neurosci*. 2006;13(1):78–83.
62. Miller RG, Mitchell J, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database Syst Rev*. 2012;(3): CD001447.
63. Zoccolella S, Beghi E, Palagano G, et al. Riluzole and amyotrophic lateral sclerosis survival: a population-based study in southern Italy. *Eur J Neurol*. 2007;14(3):262–268.
64. Lehmann-Horn F, Jurkat-Rott K, Rüdel R. Diagnostics and therapy of muscle channelopathies–Guidelines of the Ulm Muscle Centre. *Acta Myol*. 2008;27(3):98.
65. Zhang J-C, Sun L, Nie Q-H. Botulism, where are we now? *Clin Toxicol*. 2010;48(9):867–879.

Part Eight
Endocrine Disorders

This page intentionally left blank

59

Diabetic emergencies

Ayush Sinha

INTRODUCTION

Diabetes, with a global prevalence of 8.5% in adult population, is rising in prevalence as are its associated emergencies. In 2014 approximately 422 million adults were living with diabetes globally,[1] and this is expected to rise to 552 million by 2030.[2] Diabetic emergencies can either be hyperglycaemic or hypoglycaemic. Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) are the two most common hyperglycaemic acute complications of diabetes resulting from absolute or relative insulin deficiency. Its overtreatment – usually with insulin – leads to hypoglycaemia. Both hyperglycaemia or hypoglycaemia are associated with immediate and long-term adverse clinical outcomes and significant economic burden on healthcare. In the United States, the annual cost of managing DKA as estimated by the reimbursements is $2.4 billion.[3,4] DKA, more prevalent in the younger population, has an annual incidence of 14 episodes per thousand patients with diabetes. The hospital admissions in the last decade have gone up by 30%, most likely due to an increase in ketosis-prone type 2 diabetics. HHS represents approximately 1% of primary admissions to hospital with diabetes as compared with DKA. Up to 20% of HHS patients can die, whereas it is observed that mortality in DKA is less than 1% (but remains high in the elderly).[5] However, a recent Scottish study conducted over a 5-year period determining the readmission rates for DKA patients treated in intensive care units revealed that mortality after intensive care unit admission was 8%, 18% and 35% at 1 month, 1 year and 5 years, respectively.[6]

PATHOPHYSIOLOGY

Normal carbohydrate metabolism depends upon the presence of insulin; both DKA and HHS result from a reduction in the effect of insulin, relative or absolute. A concomitant rise of counter-regulatory hormones like glucagon, catecholamines, cortisol and growth hormone results in hormonal imbalance leading to hyperglycaemia.

Hyperglycaemia occurs as a consequence of increased gluconeogenesis, increased glycogenolysis and reduced peripheral glucose utilisation. The increase in glucose production occurs in both the liver and the kidneys as there is high availability of gluconeogenic precursors such as amino acids (protein turnover shifts from balanced synthesis and degradation to reduced synthesis and increased degradation). Lactate and glycerol also become available owing to an increase in skeletal muscle glycogenolysis and an increase in adipose tissue lipolysis, respectively. Lactate, converted to pyruvate in the liver via the Cori cycle, is used to generate glucose. Gluconeogenic enzyme activity, especially phosphoenol pyruvate carboxykinase (PEPCK) is further enhanced by stress hormones. The resultant hyperglycaemia leads to glycosuria, osmotic diuresis and dehydration. The resultant reduction in renal perfusion leads to a progressive decline in glomerular filtration rate and worsens hyperglycaemia.

Insulin deficiency and increased epinephrine levels activate hormone sensitive lipase in adipose tissue, which leads to breakdown of triglycerides into glycerol and free fatty acids (FFA). Increased concentrations of glucagon promote oxidation of FFAs to ketone bodies in the liver. Acetyl–CoA carboxylase is inhibited by glucagon with resultant reduction in synthesis of malonyl-CoA. Decreased levels of malonyl-CoA stimulates ketogenesis by stimulating carnitine O-palmitoyltransferase 1, liver isoform (CPT1-L), thus promoting transesterification of fatty acyl carnitine and oxidation of FFA to ketone bodies.[7] Both cortisol and growth hormone are capable of increasing FFA and ketone levels and experiments conducted on pancreatectomised patients suggest that glucagon is not essential for the development of ketoacidosis but that it may accelerate the onset of ketonaemia and hyperglycaemia in insulin deficiency.[8] In DKA states, the metabolism and clearance of ketone bodies are decreased, leading to a further rise in ketone levels.[9] As ketone bodies are strong acids, a large hydrogen ion load is produced as it dissociates at physiological pH. The need to buffer hydrogen ions depletes the body's alkali reserves and ketone anions accumulate, accounting for the elevated

ABSTRACT

Diabetic emergencies can be either hyperglycaemic or hypoglycaemic. Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) are the two most common hyperglycaemic acute complications of diabetes. Its overtreatment – usually with insulin – leads to hypoglycaemia. Both hyperglycaemic or hypoglycaemic emergencies are associated with immediate and long-term adverse clinical outcomes and can be fatal if not recognised and treated timely. DKA is more common than HHS; however, 20% of patients with HHS can die. The incidence of 'hospital-acquired DKA' is high and a cause for concern. Five-year mortality after an episode of DKA can be as high as 35%. Hypoglycaemia is the most common and frequently underreported sequel to insulin and oral hypoglycaemic agents. Hypoglycaemia in hospitalised patients is seen both in diabetic and non-diabetic patients. There is approximately 66% increased risk of death within 1 year and about 3 days longer stay in patients who experience hypoglycaemia compared to those who don't.

KEYWORDS

Diabetic ketoacidosis
hyperglycaemic hyperosmolar state
hypoglycaemia
ketogenesis
SGLT2 inhibitors
euglycaemic DKA
inpatient hypoglycaemia

plasma anion gap. High levels of ketone bodies also contribute to osmotic diuresis.

In contrast to DKA, higher levels of basal and stimulated C-peptide in HHS suggest there is enough insulin present in HHS to prevent lipolysis but not enough to promote peripheral glucose utilisation.[10] Albeit in experimental animals, hyperosmolarity has been shown to directly inhibit lipolysis and FFA release from adipose tissue.[11] Ketogenesis, consequently, is usually absent in HHS. Moreover, patients with HHS have reduced levels of FFA, glucagon, cortisol and growth hormone as compared to patients with DKA.

HHS, as compared to DKA, has slower onset and hyperosmolarity, which is a prominent feature, and is caused by the prolonged effect of osmotic diuresis with impaired ability to take adequate fluids; even when well, patients who have suffered from HHS have impaired thirst reflexes. However, the hyperosmolarity seen in about one-third of patients with DKA results from a shorter osmotic diuresis and to variable fluid intake due to nausea and vomiting, which is often ascribed to the brainstem effects of ketones.

Hyperglycaemia is a proinflammatory state with a direct correlation between high blood glucose and increased mortality.[12] Both in DKA and non-ketotic hyperglycaemia, there is a significant rise of pro-inflammatory cytokines, C-reactive protein, reactive oxygen species, cortisol, growth hormone and FFAs which resolves within 24 hours of insulin therapy.[13] Insulin therapy, in diabetic and non-diabetic critically ill patients, has shown to improve clinical outcomes owing to its powerful anti-inflammatory effect.[14,15]

The inflammatory milieu in hyperglycaemic emergencies predisposes to a prothrombotic state. There is diffuse vascular injury and abnormalities of coagulation cascade, platelet activation, blood flow and vascular reactivity. This may result in thrombotic events like deep vein thrombosis, ischaemic stroke and other thrombotic complications.[16]

CLINICAL PRESENTATION AND DIAGNOSIS

DKA and HHS represent the two extreme metabolic complications of insulin deficiency. It should be suspected in every clinically unwell, hyperglycaemic patient presenting to the emergency department or in hospital under treatment. HHS develops insidiously over days to weeks, whereas the development of DKA is more acute with a prodrome lasting only hours to days (Table 59.1). DKA and HHS co-exist in up to 30% of cases.[10] In both DKA and HHS, polyuria, polydipsia, weakness and weight loss are experienced for variable periods prior to admission. In DKA, nausea, vomiting and abdominal pain is present in the majority of patients. Abdominal pain, more common in children, could either be the manifestation or precipitant of DKA and needs further investigations if it fails to resolve with the correction of dehydration and metabolic acidosis.[3] Dehydration presents with loss of skin turgor, dry mucous membrane, tachycardia and hypotension. Mental obtundation occurs more frequently in HHS than DKA as more patients, by definition, are hyperosmolar and the presence of stupor or coma in patients who are not hyperosmolar requires consideration of other potential causes for mental illness.[17] Despite infection being a common precipitant in both DKA and HHS, most patients are either normothermic or hypothermic. Hypothermia could be a precipitant or due to vasodilatation and lack of substrate for cellular heat production,[18] with its extent correlating with the severity of the disease. Leucocytosis is a common feature in both DKA and HHS.

Table 59.1 Comparison of diabetic ketoacidosis and hyperosmolar hyperglycaemic state

PRESENTATION	DKA	HHS
Prodromal illness	Days	Weeks
Coma	+	+++
Blood glucose	++	+++
Ketones	+++	0 or +
Acidaemia	+++	0 or +
Anion gap	++	0 or +
Osmolality	++	+++

DKA, diabetic ketoacidosis; *HHS*, hyperosmolar hyperglycaemic state.

DIABETIC KETOACIDOSIS

It is a serious acute metabolic complication of type 1 diabetes and ketosis-prone type 2 diabetes. The classic triad of DKA comprises hyperglycaemia, ketonaemia and metabolic acidosis; however, the absence of hyperglycaemia or ketonaemia does not always preclude the diagnosis of DKA. Compensatory hyperventilation with deep and laboured breathing pattern (Kussmaul breathing) may be present, as may the breath odour of acetone. The biochemical diagnostic criteria for DKA are[19]:

- Ketonaemia >3.0 mmol/L **or** significant ketonuria (more than 2+ on standard urine sticks)
- Blood glucose >11 mmol/L **or** known diabetes mellitus
- Bicarbonate (HCO_3^-) <15 mmol/L **and/or** venous pH < 7.3.

Blood glucose per se is not a determinant of severity; however, deteriorating consciousness, worsening anion gap and extent of metabolic acidosis are. To aid clinical management, DKA can be classified into mild (pH 7.25–7.3), moderate (pH 7.0–7.24) and severe (pH <7.0) forms.[20] The anion gap is more than 10 in

mild DKA whereas it is more than 12 in moderate and severe forms.

Poor compliance to insulin treatment and infection are the most common precipitants in developed nations, whereas infection and poor access to healthcare are the leading precipitants in developing countries.[9] A recent UK survey identified infection as the precipitant in 44.1% followed by non-compliance in 18.7% patients, whereas as many as 7.8% patients developed DKA during their hospital stay.[21] Patients developing DKA as inpatients, otherwise called 'hospital-acquired DKA,' assume particular significance as this may reflect the quality of care, and is preventable. Underlying medical illness like myocardial infarction, pancreatitis and drugs affecting carbohydrate metabolism can also precipitate DKA. Sodium-glucose co-transport 2 (SGLT2) inhibitors, in type 1 and type 2 diabetic patients, in the presence of risk factors like intercurrent illness, reduced oral intake and reduced insulin doses, have been linked with development of serious, life-threatening DKA.[22] In addition, numerous cases of fatal and nearfatal DKA have also been reported in patients on atypical antipsychotics.[23]

EUGLYCAEMIC DIABETIC KETOACIDOSIS

Described first in 1973 by Munro, euglycaemic DKA (EuDKA) presents with severe ketoacidosis with only mildly elevated plasma glucose levels. Inhibition of gluconeogenesis in conjunction with reduced insulin facilitated by carbohydrate restriction, partially treated DKA, or alcohol and in patients with liver failure can result in EuDKA. SGLT2 inhibitors, by inducing rapid excretion of urinary glucose, can cause EuDKA in type 2 diabetics.[22]

HYPEROSMOLAR HYPERGLYCAEMIC SYNDROME

HHS is commonly seen in elderly type 2 diabetes patients; however, younger presentations, often as an initial presentation of type 2 diabetes, are observed these days.[11] Infection, in particular, pneumonia and urinary tract infections,[24] are the most common precipitants. Inadequate dose of insulin or oral anti-hyperglycaemic agents and certain drugs including diuretics, corticosteroids, β-blockers, phenytoin and diazoxide are the other common triggers.

Characteristic features of patients with HHS are[25]:

- Hypovolaemia
- Marked hyperglycaemia (>30 mmol/L) without significant hyperketonaemia (<3.0 mmol/L) or acidosis (pH >7.3, bicarbonate >15 mmol/L)
- Serum osmolality >320 mOsmol/kg.

Neurological symptoms like mental obtundation, confusion, or seizures may correlate with severity of hyperosmolality.

MANAGEMENT

DKA and HHS are severe, life-threatening complications of diabetes and these patients are at increased risk of death. Presentation with altered mental status, cardiovascular instability, acute abdominal symptoms or severe metabolic acidosis will necessitate high dependency care or intensive care unit admission for treatment (Table 59.2). The aims of treatment are fluid resuscitation, termination of ketogenesis, restoration of biochemical milieu with insulin and electrolytes, and prompt attention to an underlying precipitant. Moreover, prevention of potentially fatal thrombotic events and aspiration pneumonitis necessitates deep vein thrombosis prophylaxis and insertion of a nasogastric tube, especially in patients with reduced consciousness state.

FLUIDS

Fluid replacement followed by insulin is the most vital step in the initial management of DKA and HHS. The objectives of fluid therapy are to restore the circulatory volume, improve tissue perfusion and correct hyperosmolality. The total osmolar load on the kidney in DKA

Table 59.2 Patients who may require high-dependency unit or intensive care unit admission

DKA	HHS
Blood ketones >6 mmol/L	Osmolality >350 mOsmol/kg
Bicarbonate <5 mmol/L	Sodium >160 mmol/L
K^+ <3.5 mmol/L	K^+ <3.5.0 mmol/L or >6.0 mmol/L
Venous/arterial pH <7.0	Venous/arterial pH <7.1
GCS <12 or abnormal AVPU	GCS <12 or abnormal AVPU
Oxygen saturation <92%, SBP <90 mm Hg, heart rate <60 or >100	Oxygen saturation <92%, SBP <90 mm Hg, heart rate <60 or >100
Anion gap >16	Urine output <0.5 mL/kg/h, Serum creatinine >200 µmol/L Hypothermia Macrovascular event like myocardial infarction or stroke Other serious co-morbidities

AVPU, Alert, voice, pain, unresponsive; *DKA*, diabetic ketoacidosis; *GCS*, Glasgow Coma Scale; *HHS*, hyperosmolar hyperglycaemic state; *SBP*, systolic blood pressure.

Adapted from Joint British Diabetes Societies Inpatient Group (see references 19 and 25).

can be as much as 2000 mOsm/day.[26] Fluid loss from osmotic diuresis is worsened by poor reabsorption of salt, water and phosphate in the kidney – a direct effect attributable to lack of insulin. Water deficits in HHS are about twice as much as in DKA and can be estimated by the formula:

$$\text{Free water deficit} = 0.6 \times \text{weight (kg)} \times (\text{Current sodium} - 1)/140$$

Fluid alone will reduce levels of glucose and counter-regulatory hormones and reduce insulin peripheral resistance. Insulin therapy drives extracellular water into the intracellular space and can exacerbate hypovolaemia and hypernatraemia as true sodium in hyperglycaemia is higher than the measured sodium. Rapid fluctuations in sodium concentration could result in pontine or extrapontine myelinolysis. This is why it is critically important to initiate fluid therapy early. However, overaggressive fluid replacement, especially in children and in those with cardiac and renal dysfunction, could lead to cerebral oedema, thus worsening the outcome. Hyperosmolality should be corrected cautiously at a rate no faster than 3 mOsm/kg H_2O/h. Crystalloids, isotonic 0.9% saline[19] or balanced crystalloids like Hartmann's should be used for fluid replacement, as there is a consensus that colloids can potentially increase the risk of mortality and morbidity.[27] Use of balanced crystalloids can reduce the incidence of resuscitation-associated hyperchloraemia.[28] Hyperchloraemic metabolic acidosis with its vasoconstrictive effect on renal arterioles may delay the resolution of acidosis. Infusion of 15–20 mL/kg of crystalloids in the first hour and subsequent fluid guided by vital signs like heart rate, blood pressure, laboratory values and clinical examination should correct the fluid deficits in first 24 hours.[3] Ten per cent dextrose is added to the replacement fluid once blood sugar falls below 14 mmol/L to avoid hypoglycaemia and allow the continuation of insulin infusion to suppress ketogenesis.

INSULIN THERAPY

Low-dose, physiological insulin replacement resolves the biochemical abnormalities as quickly as higher doses without running the risk of hypoglycaemia and hypokalaemia, and gradual correction of hyperglycaemia is associated with a lower mortality.[29] In addition to correction of hyperglycaemia, insulin acts to suppress ketogenesis and lipolysis. In DKA, a bolus dose of insulin (0.1 Unit/kg) at the initiation of therapy could risk hypoglycaemia and is not routinely recommended unless there is a delay in commencing the weight-based fixed rate intravenous insulin infusion (FRIII) at 0.1 Unit/kg per hour. In HHS, FRIII at 0.05 Unit/kg per hour is recommended once the initial fluid resuscitation has taken place. Glucose decrement is the same irrespective of the route chosen; however, for critically ill patients (see Table 59.2), intravenous infusion of regular human insulin should be used. Metabolic targets like increasing bicarbonate concentration by 3 mmol/L per hour, reducing the blood glucose concentration by 3 mmol/L per hour and reducing the blood ketone concentration by 0.5 mmol/L per hour whilst maintaining normal potassium levels are essential in guiding insulin therapy. Studies have suggested that FRIII at 0.1 Unit/kg per hour will bring the blood sugar down by 50%–60% in the first 4 hours. If the glucose levels fail to reduce appropriately, it may indicate insufficient fluid resuscitation. Severe insulin resistance occurs in 10% of cases and will necessitate the use of higher doses. The insulin infusion rate should be reduced to 0.02–0.05 Unit/kg per hour when the glucose levels fall below 12 mmol/L in DKA and below 15 mmol/L in HHS. Along with insulin infusion, subcutaneous long-acting insulin analogues should be continued. This is to avoid hypoglycaemia at the cessation of insulin infusion.[30] In DKA, FRIII should be continued until the resolution of ketoacidosis as evidenced by blood ketone levels of less than 0.6 mmol/L, venous pH over 7.3 and/or venous bicarbonate over 18 mmol/L.[19] In HHS, however, insulin infusion should only cease with the correction of mental obtundation and normalisation of serum osmolality.[9]

ELECTROLYTE THERAPY

POTASSIUM

Hyperosmolality and acidosis cause a shift of potassium from intracellular to extracellular compartment. This potassium is lost as a result of osmotic diuresis. Renal losses are augmented by secondary hyperaldosteronism and ketoanion excretion as potassium salts. Despite total body deficits (Table 59.3), the measured potassium is usually normal or high and replacement should not commence until the potassium is less than 5.5 mmol/L. DKA patients may rarely present with very low potassium (less than 3.3 mmol/L). This represents profound potassium depletion (600–800 mmol) and replacement at 10–20 mmol/h should commence

Table 59.3 Typical deficits in diabetic ketoacidosis and hyperosmolar hyperglycaemic state

	DKA	HHS
Water	100 mL/kg	100–220 mL/kg
Sodium	7–10 mmol/kg	5–13 mmol/kg
Potassium	3–5 mmol/kg	4–6 mmol/kg
Chloride	3–5 mmol/kg	5–15 mmol/kg

DKA, diabetic ketoacidosis; *HHS*, hyperosmolar hyperglycaemic state.

immediately with fluid therapy. Insulin therapy is initiated only when potassium level is more than 3.3 mmol/L. In most patients, 20–30 mmol of potassium in every litre of crystalloid generally maintains serum potassium within normal range.

PHOSPHATE

In DKA, typical total body phosphate deficit is about 1 mmol/kg but serum phosphate is usually normal at presentation. Routine phosphate replacement has not been shown to be beneficial in DKA,[31] but correction of severely low levels (<0.4 mmol/L) may be necessary as this may lead to muscle weakness, impaired cardiac systolic performance and haemolytic anaemia. Excessive phosphate replacement may cause hypocalcaemia and calcium should be monitored.

MAGNESIUM

A chronic magnesium deficiency may be present in type 1 or 2 diabetes and may be exacerbated by renal impairment. The benefits of magnesium replacement have not been demonstrated in diabetic emergencies, but the principles of magnesium supplementation are similar to other critical care situations.

BICARBONATE

Use of bicarbonate for correction of acidosis in DKA is controversial and is not routinely recommended. Side effects like paradoxical intracellular acidosis, hypokalaemia, volume overload and altered tissue oxygenation may overshadow any potential benefits. In the context of DKA, sodium bicarbonate also delays the clearance of ketones and may enhance further hepatic production even when insulin and glucose are being delivered.[32] At pH >7.0 insulin will block lipolysis and ketoacidosis production; however, when pH is between 6.9 and 7.1 it remains uncertain whether bicarbonate is beneficial or otherwise. Most authorities agree to the use of bicarbonate below pH 6.9 to partially correct the pH. The threshold for correction is debatable (between pH 6.9 and 7.15), but life-threatening hyperkalaemia is an undisputed indication for bicarbonate therapy.

MONITORING

The recognition that blood glucose is only a surrogate of the metabolic derangement in DKA has shifted the focus of management to ketonaemia. Ketonuria may persist up to 2 days after the correction of acidosis due to the presence of acetone. Moreover, urine ketone strips, being semiquantitative, may not truly reflect the condition. There is a significant correlation between serum and capillary beta-hydroxybutyrate (β-OHB) and glucose.[33] This makes point of care (POC) blood tests for ketones and glucose and near bedside electrolytes, bicarbonate and pH measurement the cornerstone of management of DKA. POC meters allow for not only rapid and accurate diagnosis but monitoring as well. Accurate measurement of β-OHB, the main ketoacid in DKA, with blood ketone meters has been one of the biggest advancements in the management of DKA.

In HHS, serum osmolality can be measured with an osmometer or estimated osmolarity. Regular monitoring of neurological status includes Glasgow Coma Scale and computed tomography (CT) scans as indicated for persistent coma or worsening neurological status.

DKA is considered to be resolved when pH >7.3 units; bicarbonate greater than 15.0 mmol/L; and blood ketone level less than 0.6 mmol/L (rather than <0.3 mmol/L). This is to prevent the rebound rise of ketones upon discontinuation of insulin infusion.[19]

The resolution of HHS is indicated by return to normal plasma osmolality and recovery from mental obtundation.

COMPLICATIONS OF DIABETIC KETOACIDOSIS AND HYPEROSMOLAR HYPERGLYCAEMIC STATE

Hypoglycaemia and hypokalaemia – Hypoglycaemia and hypokalaemia are the most frequently occurring serious complications during the management of DKA, usually due to overtreatment with insulin and inadequate replacement of potassium. Recent UK data suggested that over a quarter of these patients can develop hypoglycaemia whereas the incidence of hypokalaemia was 55%.[21]

Cerebral oedema – Clinically apparent cerebral oedema is a rare (0.5%–1%) but an extremely serious complication of DKA occurring predominantly in children; the mortality is high (25%), with a quarter of survivors being left with some permanent neurological sequelae. Studies have suggested a subclinical incidence approaching 50%.[34] Risk factors for developing cerebral oedema include degree of hypocapnia and dehydration, the failure of serum sodium to rise with treatment and the use of sodium bicarbonate.[35] It also occurs in young adults and may be associated with rapid deterioration in consciousness level with or without seizures. If progressive signs of brainstem herniation are present, the mortality is high, with only 7%–14% likely to make a complete recovery. The risks of brain herniation are related to the degree of acidosis and the volume of initial fluid resuscitation. Oedema formation most likely occurs due to a vasogenic mechanism[36] and cerebral hyperaemia with loss of autoregulation evident; this can take up to 36 hours to resolve.[37,38] Some degree of brain dysfunction is apparent even in those patients who are not comatose but who have severe DKA as measured by sensory evoked potentials. This reverts to normal with correction of the ketoacidosis.

Other – Pulmonary oedema is usually iatrogenic, and myocardial infarction can occur, particularly in the elderly. In HHS various neurological complications including reversible tetraplegia, amnesia and optic atrophy have been described.

PREVENTION OF HYPERGLYCAEMIC EMERGENCIES

Patient information and education programmes on home monitoring of glucose and ketones and recognition of early signs of hyperglycaemic emergencies could prevent emergency department and hospital admissions.

HYPOGLYCAEMIA

Hypoglycaemia is the most common and frequently underreported sequel to insulin and oral hypoglycaemic agents. The self-treated form is classified as 'mild' whereas it is 'severe' if external help is required for recovery. Any blood glucose of less than 4 mmol/L should be treated. Hypoglycaemia may lead to an impaired counter-regulatory system and, hence, non-specific and relatively insensitive neuroglycopaenic symptoms[39] and hypoglycaemia unawareness. The incidence therefore is difficult to quantify; however, patients with type 1 diabetes experience about two episodes of symptomatic hypoglycaemia per week and 1.0–1.7 episodes/patient per year of severe hypoglycaemia.[40] The UK hypoglycaemia study showed that the incidence of hypoglycaemia in type 2 diabetes can be as high as 25% as the disease approaches the insulin-deficient end of the spectrum.[41] Although more frequently seen in type 1 diabetes, the incidence matched for duration of insulin therapy is similar in both type 1 and 2 diabetes.[42]

Risk factors to developing hypoglycaemia include elderly patients, alcohol, early pregnancy, renal and hepatic impairment, strict glycaemic control, previous history of severe hypoglycaemia,[43] sulfonylureas, administration of wrong insulin product, and abrupt reduction in food intake.[44]

The adverse effects of hypoglycaemia range from autonomic symptoms (sweating, palpitations, shaking) to transient impairment in the level of consciousness to permanent neurological damage and increased risk of death even at 1 year after discharge.[45] It can cause seizures, hemiparesis, coma, arrhythmias, prolonged QT interval[46] and contributes to increased cardiovascular morbidity and mortality. Much of these effects result from brain neuronal glucose deprivation and hypoglycaemia-induced sympathoadrenal activation.

IN-PATIENT HYPOGLYCAEMIA

Hypoglycaemia in hospitalised patients is seen both in diabetic and non-diabetic patients. Hypoglycaemia not triggered by glycaemic lowering agents (spontaneous hypoglycaemia) may be a manifestation of severe illness. Attempts should be made to diagnose the underlying disease, as hypoglycaemia is an independent risk factor in increased length of hospital stay and mortality. One study quoted 66% increased risk of death within 1 year and about 3 days longer stay in patients who experienced hypoglycaemia compared to those who didn't.[45] Five to thirty-two percent of in-patients treated with insulin could suffer from episodes of severe hypoglycaemia.[47] Over 29% of DKA patients treated with FRIII suffered from hypoglycaemic episodes.[21] Episodes of severe hypoglycaemia are more prevalent in type 1 diabetic patients and nocturnal episodes seemed to be the commonest ones.

Potential causes of in-patient hypoglycaemia are summarised (Box 59.1). Insulin prescription errors are one of the most common causes.

Box 59.1 Potential causes of in-patient hypoglycaemia

1. Errors in insulin and OHA administration – inappropriate use of 'stat' or 'PRN' rapid/short-acting insulin, incorrect type or inappropriately timed insulin or OHA administration, IV insulin infusion without glucose infusion, inadequate mixing of mixed insulin
2. Missed meals or inadequate carbohydrate intake
3. Acute discontinuation of long-term steroid therapy
4. Severe illness
5. Prolonged starvation times (i.e. 'nil by mouth')
6. Drug interactions – concomitant administration of hypoglycaemic agents with warfarin, quinine, salicylates, MAO inhibitors, NSAIDs
7. Endocrinal disorders (hypothyroidism, hypopituitarism, Addison's disease) leading to loss of counter-regulatory hormone production

IV, Intravenous; *MAO*, monoamine oxidase; *NSAIDs*, non-steroidal anti-inflammatory drugs; *OHA*, oral hypoglycaemic agents.

From *Joint British Diabetes Societies*. The hospital management of hypoglycaemia in adults with diabetes mellitus. <https://www.diabetes.org.uk/Documents/About%20Us/Our%20views/Care%20recs/JBDS%20hypoglycaemia%20position%20(2013).pdf>; 2013.

MANAGEMENT OF HYPOGLYCAEMIA

The majority of hypoglycaemic episodes are preventable. In type 1 diabetics, both avoidance of strict glycaemic targets and patient education are effective.[48] Meticulous attention to factors mentioned in Box 59.1 will help to mitigate the incidence of hypoglycaemia. For type 1 diabetic patients with frequent disabling or severe hypoglycaemia whilst being on multiple daily injections (MDI), adoption of continuous subcutaneous insulin infusion (CSII) has shown to reduce the incidence of hypoglycaemia. During treatment in DKA patients, administration of 100 mL

10% glucose solution and 100 mL 20% glucose solution at blood glucose levels less than 14 mmol/L and 6 mmol/L, respectively, can reduce the incidence of hypoglycaemia.[49]

In patients experiencing hypoglycaemia, Diabetes UK's policy to 'make four the floor' recommends 4 mmol/L as the threshold of treatment in diabetic patients. Nevertheless, adults experiencing hypoglycaemic symptoms with blood glucose levels of more than 4 mmol/L should receive prompt treatment as well. Strategies to treat hypoglycaemia vary with the level of consciousness. It is generally agreed that 15–20 g of quick-acting carbohydrate is the initial treatment of choice for patients who are alert and orientated.

For confused, disorientated or uncooperative patients, glucagon 1 mg IM is an effective option, whereas 75–100 mL 20% dextrose (or 150–200 mL 10% dextrose) intravenous (IV) is the initial treatment for unconscious patients or those having seizures due to hypoglycaemia.

The key steps following initial treatment are-

1. Repeat capillary blood glucose in 10–15 minutes
2. Repeat initial steps if blood sugar is less than 4 mmol/L. Glucagon, however, should only be administered once and non-responders should receive IV dextrose.
3. Administer long-acting carbohydrate once blood sugar is more than 4 mmol/L
4. Insulin, if due, should not be omitted. The regimen, however, may need to be reviewed.

KEY REFERENCES

3. Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care*. 2009;32(7):1335–1343.
6. Ramaesh A. Incidence and long-term outcomes of adult patients with diabetic ketoacidosis admitted to intensive care: a retrospective cohort study. *J Intensive Care Soc*. 2016;17(3):222–233.
19. Joint British Diabetes Societies Inpatient Care Group. *Management of Diabetic Ketoacidosis in Adults*. 2nd ed. Online. Available: https://www.diabetes.org.uk/Documents/About%20Us/What%20we%20say/Management-of-DKA-241013.pdf; 2013.
22. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable and preventable safety concern with SGLT2 inhibitors. *Diabetes Care*. 2015;38(9):1638–1642.
23. Ely SF, Neitzel AR, Gill JR. Fatal diabetic ketoacidosis and antipsychotic medications. *J Forensic Sci*. 2013;58(2):398–403.
30. Hsia E, Seggelke S, Gibbs J, et al. Subcutaneous administration of glargine to diabetic patients receiving insulin infusion prevents rebound hyperglycemia. *J Clin Endocrinol Metab*. 2012;97(9):3132–3137.
33. Voulgari C, Tentolouris N. The performance of a glucose-ketone meter in the diagnosis of diabetic ketoacidosis in patients with type 2 diabetes in the emergency room. *Diabetes Technol Ther*. 2010;12(7):529–535.
43. Joint British Diabetes Societies. *The Hospital Management of Hypoglycaemia in Adults with Diabetes Mellitus*. Online. Available: https://www.diabetes.org.uk/Documents/About%20Us/Our%20views/Care%20recs/JBDS%20hypoglycaemia%20position%20(2013).pdf; 2013.
47. Farrokhi F, Smiley D, Umpierrez GE. Hypoglycemia in the hospital setting. *Diabetic Hypoglycemia*. 2012;5(2):3–8.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. World Health Organization. *Global report on diabetes*. 2016.
2. IDF Diabetes Atlas. *International Diabetes Federation*. 5th ed. Brussels, Belgium: International Diabetes Federation; 2011. http://www.idf.org/diabetesatlas.
3. Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care*. 2009;32(7):1335–1343.
4. Sunny K. Burden of hospitalizations primarily due to uncontrolled diabetes. *Diabetes Care*. 2007;30(5):1281–1282.
5. Nyenwe E, Kitabchi A. Evidence-based management of hyperglycaemic emergencies in diabetes mellitus. *Diabetes Res Clin Pract*. 2011;94:340–351.
6. Ramaesh A. Incidence and long-term outcomes of adult patients with diabetic ketoacidosis admitted to intensive care: a retrospective cohort study. *J Intensive Care Soc*. 2016;17(3):222–233.
7. McGarry JD, Woeltje KF, Kuwajima M, et al. Regulation of ketogenesis and the renaissance of carnitine palmitoyltransferase. *Diabetes Metab Rev*. 1989;5(3):271–284.
8. Barnes AJ, Bloom SR, Alberti GM, et al. Ketoacidosis in pancreatectomized man. *N Engl J Med*. 1977;296:1250–1253.
9. Umpierrez G, Korytkowski M. Diabetic emergencies–ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. *Nat Rev Endocrinol*. 2016;12(4):222–232.
10. Magee MF, Bhatt BA. Management of decompensated diabetes. Diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome. *Crit Care Clin*. 2001;17(1):75–106.
11. Ekpebegh CO, Longo-Mbenza B, Akinrinmade A, et al. Hyperglycemic crisis in Eastern Cape province of South Africa: high mortality and association of hyperosmolar ketoacidosis with a new diagnosis of diabetes. *S Afr Med J*. 2010;100(12):822–826.
12. Finney SJ, Zekveld C, Elia A, et al. Glucose control and mortality in critically ill patients. *JAMA*. 2003;290(15):2041–2047.
13. Stenz FB, Umpierrez GE, Cuervo R, et al. Proinflammatory cytokines, markers of cardiovascular risks, oxidative stress, and lipid peroxidation in patients with hyperglycemic crisis. *Diabetes*. 2004;53(8):2079–2086.
14. Van der Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359–1367.
15. Hansen TK, Thiel S, Wouters PJ, et al. Intensive insulin therapy exerts antiinflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. *J Clin Endocrinol Metab*. 2003;88(3):1082–1088.
16. Foster JR, Morrison G, Fraser DD. Diabetic ketoacidosis-associated stroke in children and youth. *Stroke Res Treat*. 2011;2011:219706.
17. Umpierrez GE, Khajavi M, Kitabchi AE. Review: diabetic detoacidosis and hyperglycemic hyperosmolar nonketotic syndrome. *Am J Med Sci*. 1996;311(5):225–233.
18. Matz R. Hypothermia in diabetic acidosis. *Hormones*. 1972;3(1):36–45.
19. Joint British Diabetes Societies Inpatient Care Group. *Management of diabetic ketoacidosis in adults*. 2nd ed. https://www.diabetes.org.uk/Documents/About%20Us/What%20we%20say/Management-of-DKA-241013.pdf; 2013.
20. American Diabetes Association. Hyperglycemic crises in diabetes. *Diabetes Care*. 2004;27(1):94–102.
21. Dhatariya KK, Nunney I, Higgins K, et al. National survey of the management of diabetic ketoacidosis (DKA) in the UK in 2014. *Diabet Med*. 2016;33:252–260.
22. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable and preventable safety concern with SGLT2 inhibitors. *Diabetes Care*. 2015;38(9):1638–1642.
23. Ely SF, Neitzel AR, Gill JR. Fatal diabetic ketoacidosis and antipsychotic medications. *J Forensic Sci*. 2013;58(2):398–403.
24. Wachtel TJ. The diabetic hyperosmolar state. *Clin Geriatr Med*. 1990;6(4):797–806.
25. Joint British Diabetes Societies Inpatient Group. *The management of hyperosmolar hyperglycaemic state (HHS) in adults with diabetes*. https://www.diabetes.org.uk/Documents/Position%20statements/JBDS-IP-HHS-Adults.pdf; 2012.
26. DeFronzo RA, Goldberg M, Agus ZS. The effects of glucose and insulin on renal electrolyte transport. *J Clin Invest*. 1976;58(1):83–90.
27. Reinhart K, Perner A, Sprung CL, et al. Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. *Intensive Care Med*. 2013;38(3):368–383.
28. Mahler S, Conrad S, Wang H, et al. Resuscitation with balanced electrolyte solution prevents hyperchloremic metabolic acidosis in patients with diabetic ketoacidosis. *Am J Emerg Med*. 2011;29(6):670–674.
29. Wagner A, Risse A, Brill HL, et al. Therapy of severe diabetic ketoacidosis. Zero-mortality under very-low-dose insulin application. *Diabetes Care*. 1999;22(5):674–677.
30. Hsia E, Seggelke S, Gibbs J, et al. Subcutaneous administration of glargine to diabetic patients receiving insulin infusion prevents rebound hyperglycemia. *J Clin Endocrinol Metab*. 2012;97(9):3132–3137.
31. Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. *J Clin Endocrinol Metab*. 1983;57(1):177–180.
32. Okuda Y, Androgue HJ, Field JB, et al. Counterproductive effects of sodium bicarbonate in diabetic ketoacidosis. *J Clin Endocrinol Metab*. 1996;81:314–320.
33. Voulgari C, Tentolouris N. The performance of a glucose-ketone meter in the diagnosis of diabetic ketoacidosis in patients with type 2 diabetes in the

emergency room. *Diabetes Technol Ther*. 2010;12(7): 529–535.
34. Glaser N, Wootton-Gorges SL, Buonocore MH, et al. Frequency of sub-clinical cerebral edema in children with diabetic ketoacidosis. *Pediatr Diabetes*. 2006;7:75–80.
35. Glaser N, Barnett P, McCaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. *N Engl J Med*. 2001;344: 264–269.
36. Figueroa RE, Hoffman WH, Momin Z, et al. Study of subclinical cerebral edema in diabetic ketoacidosis by magnetic resonance imaging T2 relaxometry and apparent diffusion coefficient maps. *Endocr Res*. 2005;31:345–355.
37. Roberts JS, Vavilala MS, Schenkman KA, et al. Cerebral hyperemia and impaired cerebral autoregulation associated with diabetic ketoacidosis in critically ill children. *Crit Care Med*. 2006;34:2217–2223.
38. American Diabetes Association. Hyperglycemic crises in patients with diabetes mellitus. *Diabetes Care*. 2001;24(1):154–161.
39. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. *Diabetes Care*. 2003;26(6):1902–1912.
40. Frier BM. The incidence and impact of hypoglycemia in type 1 and type 2 diabetes. *International Diabetes Monitor*. 2009;21:210–218.
41. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia*. 2007;50(6):1140–1147.
42. Hepburn DA, MacLeod KM, Pell AC, et al. Frequency and symptoms of hypoglycaemia experienced by patients with type 2 diabetes treated with insulin. *Diabet Med*. 1993;10:231–237.
43. Joint British Diabetes Societies. *The hospital management of hypoglycaemia in adults with diabetes mellitus*. https://www.diabetes.org.uk/Documents/About%20Us/Our%20views/Care%20recs/JBDS%20hypoglycaemia%20position%20(2013).pdf; 2013.
44. Geller AL, Shehab N, Lovegrove MC, et al. National estimates of insulin-related hypoglycaemia and errors leading to emergency department visits and hospitalizations. *JAMA Intern Med*. 2014; 174(5):678–686.
45. Turchin A, Matheny ME, Shubina M, et al. Hypoglycemia and clinical outcomes in patients with diabetes hospitalized in the general ward. *Diabetes Care*. 2009;32(7):1153–1157.
46. Tsujimoto T, Yamamoto-Honda R, Kajio H, et al. Vital signs, QT prolongation, and newly diagnosed cardiovascular disease in severe hypoglycemia in type 1 and type 2 diabetic patients. *Diabetes Care*. 2014;37(1):217–225.
47. Farrokhi F, Smiley D, Umpierrez GE. Hypoglycemia in the hospital setting. *Diabetic Hypoglycemia*. 2012; 5(2):3–8.
48. Yeoh E, Choudhary P, Nwokolo M, et al. Interventions that restore awareness of hypoglycemia in adults with type 1 diabetes: asystemic review and meta-analysis. *Diabetes Care*. 2015;38(8): 1592–1609.
49. Sidana JK, Phillips C, Sinha A, et al. Therapeutic challenges in the management of diabetic ketoacidosis. *J Intensive Care Soc*. 2016;17(4):353–355.

60

Diabetes insipidus and other polyuric syndromes

Alaistair Craig Carr

Diabetes insipidus (DI) refers to a syndrome of pathological polyuria, excessive thirst and polydipsia. Polyuria is defined as urinary output greater than 3 L/day in an adult of normal mass and greater than 2 L/m^2 in children. The urine in DI is inappropriately dilute, having low specific gravity (<1.005) and low osmolality (<200 mOsmol/kg) in the face of high (>285 mOsmol/kg) or normal plasma osmolality.

Three subtypes of DI are recognised:

1. **nephrogenic DI** (NDI) – caused by insensitivity of the kidney to antidiuretic hormone (ADH)
2. **cranial/central/hypothalamic/neurogenic DI** (CDI) – caused by reduced or absent production of ADH
3. **gestational DI** – caused by increased placental vasopressinase production or as a variant of central or NDI developing during pregnancy.

A separate disorder is occasionally classified as a type of DI; **primary polydipsia** (also called psychogenic or neurogenic polydipsia or polydipsic DI). This is caused by excessive water ingestion secondary to psychological disturbance or rarely a hypothalamic lesion. In hospital in-patients, a similar iatrogenic condition results from overenthusiastic administration of intravenous solutions of dextrose 5% or hypotonic saline. Although water overload reduces plasma osmolality and thereby the ability of the kidney to maximally concentrate urine, the hypo-osmolar diuresis seen with water overload is physiological, as the body attempts to lose free water and restore normal plasma osmolality.

In critically ill patients, polyuria may be the sole part of the DI syndrome apparent to the clinician. Patients are seldom in control of their own fluid intake or able to report thirst. Failure to recognise and treat the syndrome appropriately may result in severe dehydration, hyperosmolality and an increased risk of morbidity and mortality. As there are many causes of polyuria in the critically ill (Box 60.1), it is important to adopt a systematic approach to its clinical assessment, investigation and diagnosis.

The classification as a solute or water diuresis is not always absolute; the table provides a convenient structure but a diuresis should be considered in terms of the individual patient together with physical and biochemical assessments. A diuresis frequently represents the clearance of both excess water and solute (e.g. following the resolution of septic shock with multiorgan failure).

BACKGROUND PHYSIOLOGY AND ANATOMY

OSMOLALITY

Osmolality is the measure of osmoles of solute per kilogram of solvent and includes both permeant (e.g. urea) and impermeant (e.g. sodium) solutes. It may change with either water or permeant solute movement. Osmolarity is the measure of osmoles per litre of solute and, unlike osmolality, is temperature dependent. Normal plasma osmolality is in the range of 275–295 mOsmol/kg. Plasma osmolality can be estimated from several equations.[2] The formula of Worthley[3] below is simple and correlates well with measured values.[4]

$$\text{Plasma osmolality (mOsmol/kg)} = 2[Na^+] + [\text{Urea}] + [\text{Glucose}]$$

All units of solute are mmol/L.

Where a patient is markedly uraemic, a value of 8 mmol/L is substituted for the actual urea. Actual osmolality may differ markedly from estimated osmolality in the presence of unmeasured, osmotically active solutes such as mannitol, ethanol, bicarbonate, lactate and amino acids. Whenever concern exists that a patient may be hyper- or hypo-osmolal, osmolality should be measured by assessing the freezing point depression of the plasma or urine. Increasing the osmolality results in depression of the freezing point.

The osmolal gap is the difference between the calculated and measured osmolality in plasma or urine. The normal osmolal gap is less than 10 mOsmol/kg. An increased osmolal gap indicates the presence of an unmeasured osmotically active solute.

TONICITY

Tonicity describes the ability of a solution of impermeant solute (such as sodium) to cause the movement of water between itself and another fluid compartment.

ABSTRACT

Polyuria is a common finding amongst critically ill patients. It may be physiological or pathological and represent a solute, a water or a combined diuresis. It is essential that the intensive care physician understands, monitors and appropriately manages pathological diureses, as untreated, in the absence of normal autonomous control of drinking, profound volume and solute disturbances can arise, leading to long-term morbidity and mortality.

This chapter presents an overview of the central, peripheral and renal physiological control mechanisms of plasma osmolality and volume before describing pathologies that upset these, resulting in a diuresis. Normal values of plasma and urine osmolality, and plasma antidiuretic hormone concentrations are offered. An investigative approach to differentiating cranial, nephrogenic, gestational and polydipsic diabetes insipidus as well as a normal physiological diuresis is outlined. Treatment strategies are suggested.

KEYWORDS

Diabetes insipidus
polyuria
osmolality
osmolarity
tonicity
water deprivation test
polydipsia
ADH/antidiuretic hormone
osmoreceptors
urinary concentration

Box 60.1 Causes of polyuria

1. Water Diuresis:
   a. Pathological
      Diabetes insipidus: cranial, nephrogenic, gestational
   b. Physiological
      Psychogenic polydipsia (excess drinking is pathological but the diuresis is not)
      Iatrogenic – excessive administration of hypotonic solutions e.g.
      5% dextrose solution,
      0.45% saline,
      0.18% saline 4% dextrose solutions
2. Solute Diuresis:
   a. Pathological
      Hyperglycaemia
      Azotaemia (uraemia[1])
      Cerebral salt wasting
      Fanconi's syndrome
      Renal tubular acidosis
      Glomerulonephritis
      Hyperaldosteronism
      Addison's disease
      Anorexia nervosa
      Migraines
      Paroxysmal tachycardia (via increased atrial natriuretic peptide release)
      Poisons/drugs:
         Ethanol
         Methanol
         Ethylene glycol
         Mannitol
         Loop diuretics
         Thiazide diuretics
   b. Physiological
      Resolving sepsis (redistribution of fluid into the vascular compartment from the third space)
      Iatrogenic – excessive administration of isotonic or hypertonic solutions e.g.
         0.9% saline
         hypertonic saline
         Hartmann's solution
         Gelofusin

It may be considered an index of the water concentration rather than the solute concentration, as the solute is impermeant. The tonicity of plasma is largely determined by sodium, the main solute in extracellular fluid that cannot cross freely into the intracellular space. This characteristic facilitates the control of extracellular fluid volume through the regulation of sodium balance.

It is possible for a solution to be both hypotonic and iso-osmolar. An example of this is 5% dextrose solution; the solution contains no impermeant solute (assuming no absence of insulin, glucose freely enters the cell) but is iso-osmolar with the intracellular milieu.

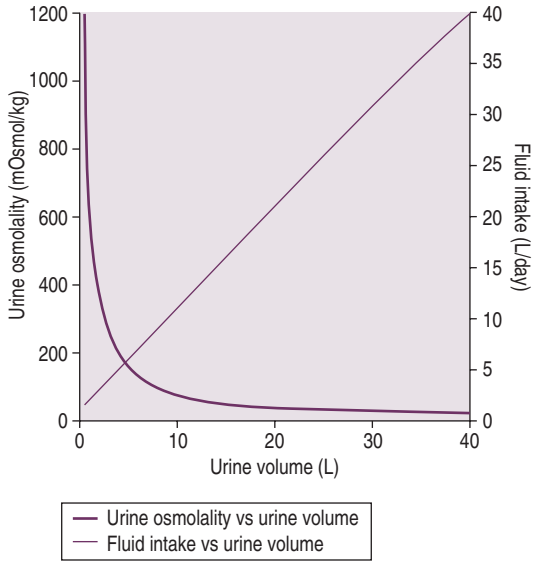


Figure 60.1 Urine output rises and urine osmolality falls in health as a function of increasing water intake. Assuming normal solute ingestion, normal solute excretion (around 800 mmol/day) is preserved between water intakes of 1.5 and 32 L/day.

SOLUTE AND WATER INTAKE AND LOSSES

In order to understand disorders of osmolality, tonicity, fluid balance and urine output, it is necessary to be aware of the physiological mechanisms which maintain normal fluid and osmolal balance in health. Assuming a normal diet, a 75 kg man has daily obligatory losses of around 800 mmol of solute, approximately 300 mmol of urea and 500 mmol of cations and anions. The maximum concentrating ability of the healthy kidney is around 1200 mOsmol/kg; consequently, minimum daily urine production of 666 mL is required to excrete osmotically active solutes. Additionally, insensible water losses approximate 10 mL/kg per day and rise markedly with fever and hot dry climates. Minimum daily obligatory water losses due to insensible losses and solute excretion therefore total around 1.5 L.

NORMAL URINARY OSMOLALITY

In health, urinary osmolality is usually maintained between 500 and 700 mOsmol/kg. As the obligatory solute load to be excreted is relatively constant, urine osmolality will fall in response to increased free water intake and rise in response to dehydration or water restriction (Fig. 60.1). The minimum urine osmolality achievable in man is around 25 mOsmol/kg. Diuresis refers to urine output greater than 1.5 mL/kg per hour and may be transient or persistent, physiological or pathological. Water diuresis occurs when total daily urinary solute excretion is within the normal range

but urine osmolality is low. Osmotic or solute diuresis occurs when the total daily solute excretion is higher than normal; the urine passed is usually iso-osmolar to plasma if the extracellular fluid volume is expanded or hyperosmolar if the patient is hypo- or euvolaemic.

PLASMA OSMOLALITY AND PLASMA VOLUME REGULATION

Changes in plasma osmolality and volume can occur in tandem or independently of one another. Whilst normal plasma osmolality lies in a population range of 275–295 mOsmol/kg (265–285 mOsmol/kg in pregnancy), individuals usually vary less than ±1% around their set value.

The body regulates osmolality and volume by separate mechanisms. Water balance and osmolality are maintained via osmoreceptors which mediate their control via control of thirst and ADH production. Control of the plasma volume is maintained via volume receptors and sodium receptors which mediate their actions through the sympathetic nervous and renin-angiotensin-aldosterone systems. Additionally, volume receptors have inputs to the hypothalamus via which they too can mediate ADH release and the sensation of thirst. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), predominantly released from atrial and ventricular myocytes, respectively, inhibit the release of renin, aldosterone, vasopressin and endothelin, leading to both a natriuresis and a diuresis.[5]

THIRST

In health, fluid intake is determined by the sensation of thirst and subsequent fluid ingestion. Plasma osmolality greater than 290 mOsmol/kg, elevated angiotensin II (AII) concentrations, sympathetic nervous system activation and circulating volume depletion of 5%–10% are all associated with the onset of thirst. Fluid and solute excretion are largely regulated through the kidney, although some solutes such as ethanol and glucose are largely cleared through metabolism rather than excretion.

In the intensive care unit (ICU), patients lose control over their fluid and solute intake and frequently have impaired excretory mechanisms. Thus both volume and solute homeostasis may become dependent upon the skills of attending clinicians.

OSMORECEPTORS AND OTHER INPUTS TO THE SUPRAOPTIC AND PARAVENTRICULAR NUCLEI

Osmolality is mainly detected at osmo- (Na^+) receptors around the anterior aspect of the third ventricle of the brain. These sense both plasma osmolality and cerebrospinal fluid sodium concentration. Hypertonic saline is a more potent stimulus than equi-isotonic equi-isoosmolar solutions of other solutes.[6] These osmoreceptors link to the cells of the paraventricular nuclei (PVN) and supraoptic nuclei (SON), the sites of ADH synthesis. Axons of PVN and SON cells form part of the pituitary stalk linking the hypothalamus to the pituitary gland, where they terminate. A proportion of the axons terminate in the median eminence where they release ADH and oxytocin. These are transported to the anterior lobe of the pituitary by portal vessels and stimulate release of adrenocorticotrophic hormone (ACTH) and prolactin, respectively; the ADH acts synergistically with corticotropin releasing factor (CRF), but has ACTH secretagogue properties in its own right.[7,8]

Direct sympathetic nervous system inputs to the PVN and SON stimulate ADH release via α-adrenoreceptors. Other central osmoreceptors directly contact plasma outwith the blood–brain barrier in the subfornical organ (SFO). ANP and AII[9] are believed to act via these receptors to inhibit or elicit ADH synthesis and/or release and to modify the sensation of thirst. Osmoreceptors in the mouth, stomach and liver play roles in the anticipation of an osmolal load following ingestion of food and may preemptively stimulate hypothalamic ADH synthesis.

Baroreceptor and osmoreceptor inputs to the PVN and SON are distinct; it is therefore possible to lose the normal ADH response to hyperosmolality but maintain a normal ADH response to hypovolaemia.[10] In animal experiments, when hypotension increases the basal plasma ADH concentration, there is simultaneous resetting of the osmomolality-plasma ADH response curve to preserve osmoregulatory function from the new higher baseline.[11] Without this, the ADH response to hypotension would lead to hypo-osmolality in addition to vasoconstriction.

The normal response of osmoreceptors to changing plasma osmolality in terms of ADH is illustrated in Fig. 60.2. At plasma osmolalities of less than 275 mOsmol/kg, the osmoreceptors remain hyperpolarised and virtually no ADH release occurs via them. At osmolalities greater than 295 mOsmol/kg, the osmoreceptors are maximally depolarised and plasma concentrations of ADH of greater than 5 pg/mL are attained. Other inputs and influences upon ADH release are summarised in Fig. 60.3 and Box 60.2.

ANTIDIURETIC HORMONE/ ARGININE VASOPRESSIN

ADH (8-arginine vasopressin [AVP]) is a nine amino-acid peptide differing from oxytocin at only two residues but sharing the disulfide bond between the first and sixth ones. This similar structure and conformation results in some functional and receptor cross-reactivity.[12] It is synthesised in the SON and PVN, bound to neurophysin, transferred down axons to the posterior pituitary and stored in granules prior to release. Synthesis and replacement of released stores is

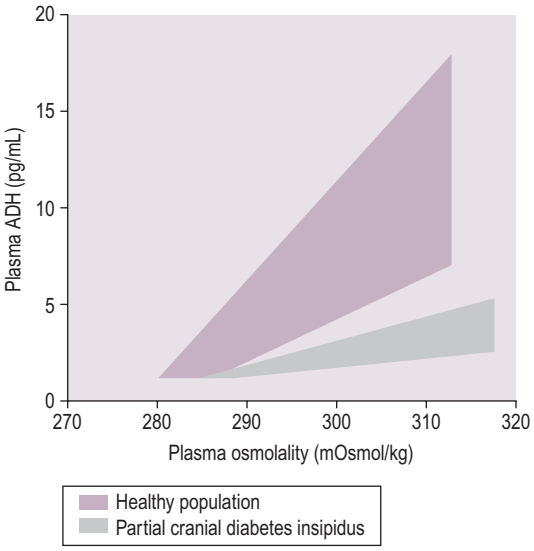


Figure 60.2 Plasma antidiuretic hormone (ADH) and plasma osmolality in health and partial cranial diabetes insipidus.

Box 60.2 Factors influencing antidiuretic hormone release

Increased ADH release with	Decreased ADH release with
Hyperosmolality	Elevated ANP, BNP
Hypovolaemia	Hypo-osmolality
Hypotension	Hypervolaemia
Hypoxia	Hypertension
Hypothyroidism	Ethanol
Hyperthermia	Cranial DI
Positive-pressure ventilation	
Pain	
Emotional stress	
Exercise	
Nausea	
Nicotine	
Trauma/surgery	

ADH, antidiuretic hormone; *ANP*, atrial natriuretic peptide; *BNP*, brain natriuretic peptide; *DI*, diabetes insipidus.

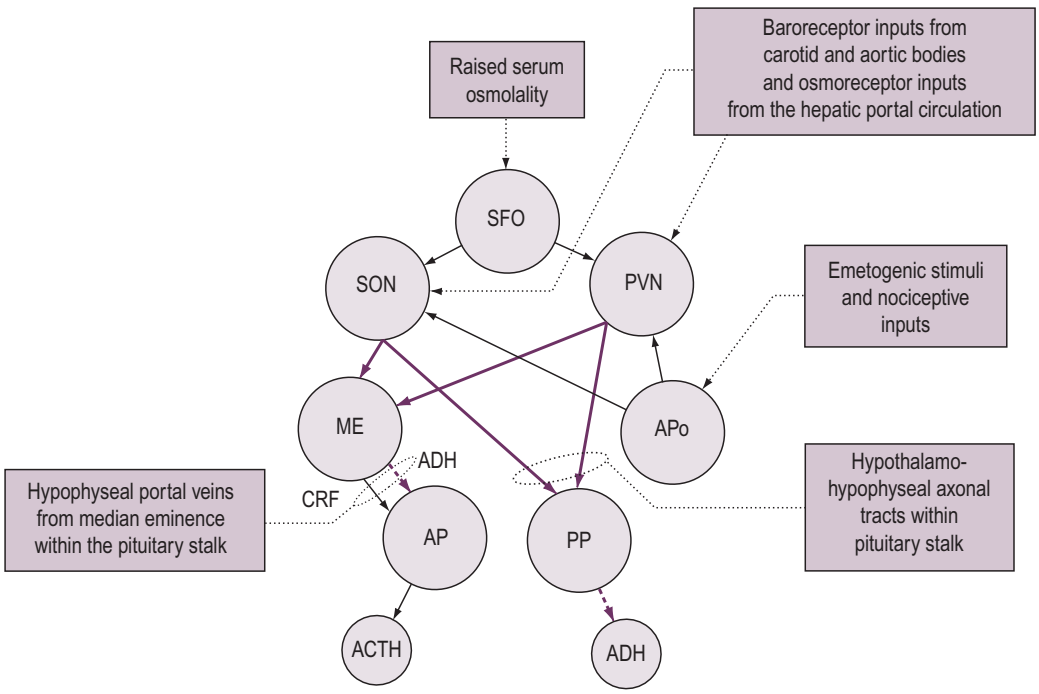


Figure 60.3 A schematic representation of anatomical and physiological connections of the supraoptic and paraventricular nuclei (SON and PVN), the principal sites of antidiuretic hormone (ADH) synthesis within the hypothalamus. *Blue arrows* represent the transport of ADH or its precursor between anatomically distinct sites. Baroreceptor inputs into these nuclei travel via the vagus nerve to reach the central nervous system. Whereas the majority of ADH produced in the SON and PVN is transported to the posterior pituitary (PP) for storage, some is transported to the median eminence (ME) then onwards to the anterior pituitary (AP), where it acts synergistically as a secretagogue for adrenocorticotropic hormone (ACTH). *APo*, Area postrema; *CRF*, corticotropin-releasing factor; *SFO*, subfornical organ.

a rapid process (1–2 hours) and patients with damage to the pituitary can achieve near normal plasma osmoregulatory concentrations (1–8 pg/mL) of ADH via release of newly synthesised ADH via axons terminating in the median eminence. However, the higher plasma concentrations associated with hypovolaemia (up to 40 pg/mL) under the influence of the sympathetic nervous system, baroreceptor responses and AII cannot be achieved.

Once released from the pituitary, ADH has a plasma half-life of around 10–35 minutes.[13] It is metabolised by hepatic, renal and placental vasopressinases with around 10% being excreted unchanged in the urine.

ACTIONS OF ANTIDIURETIC HORMONE

Through V_1, V_2 and V_3 receptors, ADH has antidiuretic, vasopressor, haemostatic and ACTH secretagogue actions. Additionally, it has roles in memory, water permeability of the blood–brain barrier, nociception, splenic contraction and thermoregulation. It also has actions on the uterus and mammary tissue mediated through oxytocin receptors. Cardiac inotropic (positive and negative) effects are reported through purinergic P_2 receptors but this remains controversial.[14,15]

Antidiuresis

ADH activates V_2 receptors on the principal cell basal membranes of the collecting duct and distal tubule. This induces cyclic adenosine monophosphate (cAMP) production which in turn activates protein kinases effecting the integration of vesicles containing aquaporin-2 highly selective water channels into the luminal membrane. Prostaglandin E_2 (PGE_2) synthesis, which inhibits cAMP production, is stimulated by the action of ADH on V_1 receptors on the luminal membrane of the collecting duct.[16] Thus, a form of autoregulatory limitation of the antidiuretic effect of ADH may exist. Hypokalaemia, lithium and hypercalcaemia also antagonise the renal actions of ADH.

ADH also increases renal urinary concentrating ability by increasing expression of urea transport proteins in the collecting duct and reducing renal medullary blood flow (V_1-mediated), thereby increasing medullary interstitial hypertonicity. Hypertonicity additionally depends upon intact ascending loop of Henle function with sodium and chloride reabsorption without simultaneous absorption of water. Dysfunction reduces the osmolal gradient between the collecting duct and the interstitium and reduces water absorption even in the presence of ADH and functioning aquaporin-2.

Exogenous ADH administration may paradoxically induce diuresis in patients with septic shock.[17] Increased renal perfusion pressure and thereby glomerular filtration rate (GFR) may be responsible.

Vasoconstriction

At higher concentrations, ADH activates V_1 as well as V_2 receptors, causing preferential vasoconstriction in muscle, skin and fat with relative sparing of coronary, cerebral and mesenteric circulations. These relative sparing effects are controversial.[18–21] Activation of V_1 receptors activates phospholipase C, increasing inositol trisphosphate and ultimately intracellular free calcium. This leads to smooth muscle constriction in the blood vessel wall.

Following brainstem death, reducing ADH may cause both hypotension and CDI with disturbances of osmolality and organ function. Treatment with α-adrenoreceptor agonists may restore organ perfusion pressure but also cause ischaemic damage. Low-dose ADH infusions (0.5–3 U/h) titrated against urine output reduces the need for catecholamine support and reduces perturbations in plasma osmolality and fluid balance. 1-deamino-8-O-arginine vasopressin (DDAVP) has similar benefits but causes less vasoconstriction. It is preferred for the treatment of CDI associated with brainstem death where hypotension is not a concomitant feature.

Coagulation

ADH increases circulating levels of tissue plasminogen activator, factor VIII and von Willebrand factor.[22] These effects are possibly mediated by V_2 receptors. At high physiological concentrations, it also acts via V_1 receptors as a platelet aggregating agent.[23–25] ADH and DDAVP are used as first-line treatments in patients with von Willebrand's disease, and may be used in bleeding associated with uraemic platelet dysfunction.

ACTH secretion

ADH transported from the median eminence to the anterior pituitary acts upon V_3 receptors to directly stimulate ACTH release and increase plasma cortisol. The ADH also increases the efficacy of CRF in releasing ACTH. In septic shock, ADH insufficiency may contribute to the relative adrenal insufficiency noted in certain patients. The relative importance and potency of ADH compared with CRF in stimulating ACTH release in humans is unclear.

Volume receptors

Volume homeostasis takes precedence over sodium homeostasis with rises and falls in sodium occurring in order to preserve correct circulating volume. In euvolaemia, sodium homeostasis is maintained. Sodium concentration is detected by SFO osmoreceptors outside the blood–brain barrier and by the juxtaglomerular apparatus which secretes renin in response to both reduced GFR and reduced tubular sodium load.[26]

High pressure baroreceptors in the pulmonary veins, left atrium, carotid sinus and aortic arch are the predominant determinants of sodium balance.[27] Reduced stretch increases sympathetic nervous system activity, activates the renin-angiotensin-aldosterone system, reduces sodium excretion (via reduced GFR)

and increases reabsorption of sodium in the proximal and distal convoluted tubules. Additionally, release of ADH is stimulated, resulting in concomitant water retention. Conversely, stretch of the baroreceptors reduces sodium retention through reduced activity of these systems and through release of ANP/BNP with reduced sodium reabsorption in the distal convoluted tubule and collecting duct. ADH release is reduced by the fall in sympathetic nervous tone from the baroreceptors and by the action of ANP on cerebral osmoreceptors lying outside the blood–brain barrier.[28]

The role of low-pressure baroreceptors in the systemic venous circulation and right atrium is less clearly defined. Venodilatation occurs in both sepsis and reduced cardiac output states. Simultaneous reduced baroreceptor signalling in the high-pressure system results in sodium and water retention. This expands the extracellular fluid compartment, potentially causing tissue oedema. As sepsis resolves, venous tone is restored, capillary leak reduces, and an increase in the loading of the high-pressure baroreceptors results and a natriuresis takes place. Patients may become transiently polyuric as they clear the excess salt and water accumulated whilst shocked. During this physiological diuresis, plasma osmolality remains tightly within the normal range provided that renal concentrating mechanisms have not been injured during the septic episode or by drug administration.

CRANIAL DIABETES INSIPIDUS

CONGENITAL CRANIAL DIABETES INSIPIDUS

Congenital cranial diabetes insipidus (CDI) is rare and usually inherited as an autosomal dominant characteristic due to mutations of the gene encoding the ADH precursor pre-provasopressin neurophysin II.[29] Onset may occur anywhere between 1 year of age and middle adult life and is associated with the eventual destruction of ADH-producing cells due to abnormal ADH precursor accumulation.[30] Until destruction of SON and PVN cells is complete, ADH secretion (facilitated by expression of the normal gene) and regulation of plasma osmolality are often unaffected.

ACQUIRED CRANIAL DIABETES INSIPIDUS

Acquired CDI may be transient or permanent with either an absolute (complete) or relative (incomplete) lack of ADH. If non-traumatic, it is usually associated with abnormality of the inferior hypophyseal arterial system[31] or autoimmune reactivity against ADH-producing cells.[32] Complete CDI is usually associated with lesions above the median eminence level in the supraoptic or paraventricular nuclei or of the neurohypophyseal stalk, whereby the production of ADH in the hypothalamus is terminated.[33] Permanent central DI tends to be associated with transecting, obliterating or chronic inflammatory lesions and transient DI with acute inflammatory or oedematous lesions with gradual recovery of ADH secretion occurring as the inflammation or oedema resolves. An exception is the transient DI seen following posterior pituitary excision or destruction; ADH produced in the hypothalamus can still be released into the systemic circulation from capillaries in the median eminence.

If normal ADH release into the circulation in response to rising plasma osmolality is reduced or absent, inappropriately high urine volumes of inappropriately low osmolality are passed. With absolute ADH deficiency, over 20 L/day of very dilute urine (25–200 mOsomol/kg) may be produced. If unable to drink freely or if thirst mechanisms are impaired, profound dehydration rapidly follows unless appropriate interventions are made.

Where ADH deficiency is relative/partial, urinary osmolalities of 500–800 mOsmol/kg and volumes as low as 3 L/day are not atypical. These osmolalities are inappropriately low relative to the plasma osmolality and the urine volumes inappropriately high when assessed in terms of the minimum required for the solute excretion. The diagnosis of partial CDI may not be obvious; there are many other causes of diuresis of this magnitude. Additionally, extrinsic stimulants of ADH release (see Box 60.2) may have an antidiuretic effect, further complicating the diagnosis.

Plasma osmolality in CDI is usually in the high normal or slightly supranormal range but remains remarkably constant in those with free access to water and intact thirst mechanisms. They will drink huge quantities of water to regulate and maintain their water balance. Hyperosmolality or hypernatraemia suggest impaired sensation of thirst or inability to access water (see water deprivation test later) and is also seen if patients are administered large quantities of isotonic saline or Hartmann's solution to replace their hypotonic urine losses. If unrecognised and untreated, hyperosmolality and hypernatraemia may result in death.

CDI is usually associated with reduced production of ADH or impaired release mechanisms of ADH. However, dysfunction of osmoreceptors or intracellular signalling pathways with normal ADH production and storage has been described. It is possible to have normal release of ADH in response to hypotensive baroreceptor activation but subnormal release in response to hyperosmolality. This has been described in association with chronic hypernatraemia.[34]

The main recognised causes of CDI are listed in Box 60.3. Traumatic or post-surgical brain injury are common causes of CDI in the ICU. Transsphenoidal surgical treatment of suprasellar tumours results in DI in 10%–70% of patients; the frequency parallels the magnitude of the tumour removed. Transcranial surgery may also cause CDI in the absence of a fall in plasma ADH; it is postulated release of a

Box 60.3 Causes of cranial diabetes insipidus

Acquired:

1. idiopathic
2. autoimmune[29]
3. tumours (especially suprasellar, lung, breast, lymphoma and leukaemia)
4. surgery (especially transsphenoidal surgery)
5. traumatic head injury (strongly associated with base of skull fracture)[35]
6. hypoxic brain injury
7. brainstem death
8. electrolyte disturbance – profound hyponatraemia
9. radiotherapy
10. drugs – amiodarone, lithium (Li more likely to cause nephrogenic DI)
11. inflammatory/infectious diseases
    - sickle cell disease
    - TB
    - abscesses
    - encephalitis
    - meningitis
    - sarcoidosis (may also cause nephrogenic DI)
    - Wegener's granulomatosis
    - histiocytosis X
12. vascular disease
    - ischaemic or haemorrhagic strokes
    - aneurysmal bleeds (especially anterior communicating artery SAH [subarachnoid haemorrhage])
    - Sheehan's syndrome
    - pituitary apoplexy

Congenital (1%–2% of all cases)

1. autosomal dominant mutations of ADH expression (despite the dominant expression of the gene, the onset of clinical DI may take up to 30 years to develop)[36]
2. Wolfram syndrome – autosomal recessive condition characterised by DI, diabetes mellitus, optic atrophy and deafness

ADH, antidiuretic hormone; *DI*, diabetes insipidus.

hypothalamic ADH precursor acting as a competitive antagonist of both ADH and synthetic analogues. The presence of a competitive antagonist creates an endocrinological picture similar to NDI with normal or high plasma ADH but an inappropriate diuresis of dilute urine.

Following surgery or traumatic brain injury, different patterns of polyuria may arise. Immediate polyuria is common and may be transient or permanent. Occasionally it is preceded by a period of oliguria due to an initial surge of ADH release. Additionally, a classical triphasic pattern of urine output may be observed with:

1. transient polyuria due to transient impairment of the release of ADH (0–5 days in duration), then
2. a phase of normal or reduced urine output; the ADH previously stored in the pituitary gland is gradually released into the circulation as the cells storing it involute (3–6 days in duration)
3. persistent polyuria as the pituitary stores exhaust and no replacement hormone from the hypothalamus is produced.

During the second phase of this pattern, administration of fluids may result in volume overload and hyponatraemia as the ADH release is not under feedback control from osmoreceptors but occurring in an uncontrolled manner as a result of pituitary degeneration. Effectively, there is a transient syndrome of inappropriate ADH (SIADH) secretion. The triphasic pattern is usually associated with sudden severe damage to the hypothalamus or pituitary from trauma, surgery or intracranial bleed. Careful, regular clinical and biochemical assessments are essential to ensure normal water balance and osmolality during this transition from DI to SIADH and back to DI again.

The exact urinary pattern seen in DI is relatively unimportant and gradual resolution may occur over several months in those with transient DI. In all instances, avoidance of unnecessary fluid and solute imbalances that worsen morbidity or mortality require meticulous, regular assessments of the patient and their plasma and urinary biochemistry and fluid inputs and outputs. Imaging the hypothalamus and pituitary with T1 magnetic resonance imaging (MRI) may provide prognostic information as to whether recovery is likely or not; hypothalamic lesions have a poorer prognosis than pituitary ones.[37]

A high level of suspicion of DI is recommended in anyone suffering from pituitary disease or with past pituitary injury; the symptoms may have gradual and insidious onset. Anterior pituitary failure can lessen the impact of CDI as deficiencies of ACTH and cortisol reduce GFR and free water loss. Additionally, loss of feedback inhibition may increase ADH release from the median eminence. Thus, in Sheehan's syndrome and pituitary apoplexy, presenting symptoms tend not to be those of DI with polyuria. However, once corticosteroid therapy is commenced, polyuria indicating DI may become apparent or exacerbated. Conversely, patients with persistent idiopathic CDI require long-term endocrine follow-up as a proportion develop tumours of the pituitary several years following initial diagnosis of DI.[38,39]

TREATMENT OF CRANIAL DIABETES INSIPIDUS

Four separate problems have to be addressed when treating CDI:

1. associated anterior pituitary dysfunction should be considered and managed if present

2. hypernatraemia must be recognised and meticulously managed
3. any deficit of total body water must be recognised and corrected
4. the underlying ADH deficiency must be addressed.

In all ICU patients with DI, hourly urine volumes, fluid losses and fluid inputs and at least twice-daily urine and plasma osmolalities are recommended. In shocked patients and those with hypernatraemia, hourly monitoring of plasma sodium is recommended to avoid worsening hyperosmolality or over-rapid correction of hypernatraemia.

ANTERIOR PITUITARY DYSFUNCTION

If present, this requires recognition and treatment. In the emergent situation with a shocked patient, hydrocortisone 100 mg can be administered as an intravenous (IV) bolus, and steroid replacement continued if required. Steroids may worsen the diuresis but will improve cardiovascular stability in patients with pituitary ablation.

HYPERNATRAEMIA

Restricted access to fluids or replacement of dilute urine with equal volumes of isotonic (to plasma) intravenous fluids in CDI with on-going water diuresis will lead to hyperosmolality/hypertonicity. In order to counteract cellular dehydration in chronic (>24 hours) hypernatraemic states, the brain accumulates intracellular organic osmolytes such as amino acids, taurine and sorbitol.[40–42] Any sudden reduction in plasma tonicity may then result in cerebral oedema, pontine myelonecrosis and permanent neurological damage as water moves into brain cells down an osmotic gradient.

When a euvolaemic state is present, AVP or DDAVP may be administered to reduce urine output. Simultaneous fluid restriction and replacement of the previous hour's urine output with an appropriate fluid to avoid falls in plasma sodium concentration greater than 0.5 mmol/h[43] is then introduced. Absolute safety data determining the ideal reduction rate of plasma sodium are unavailable. However, in hypernatraemia of greater than 48 hours duration, reductions greater than 8 mmol/L in any 24-hour period should be avoided.[44] Formulae exist to guide fluid replacement whilst controlling the rate of plasma sodium concentration reduction. Nonetheless, close monitoring with hourly plasma sodium measurement more reliably avoids sudden unexpected changes in tonicity.[45]

DEHYDRATION AND HYPOVOLAEMIA

Hypovolaemia associated with shock requires rapid resuscitation. If hypernatraemia is also present, extreme caution is required during resuscitation. Isotonic saline should be used and frequent reassessments of plasma sodium, cardiovascular and neurological states are recommended. With hypernatraemia greater than 155 mmol/L, a combination of isotonic (0.9%) and hypertonic saline should be considered to reduce the rate of sodium reduction. In the face of plasma hypertonicity, cells reduce their chloride and potassium conductance in addition to synthesising intracellular osmolytes. If 0.9% saline (effective osmolality 290 mOsmol/kg when diluted by plasma proteins) is infused rapidly into hypertonic plasma with a sodium of 160 mmol/L (effective osmolality 330 mOsmol/kg), a rapid drop in plasma osmolality may cause cerebral and other organ oedema, seizures and death. Gradual reduction of plasma osmolality facilitates downregulation of intracellular osmolyte synthesis and increased potassium and chloride conductance with reduced swelling as plasma tonicity falls.

CORRECTION OF POLYURIA AND ADH DEFICIENCY

During mild polyuria (2–3 mL/kg per hour) where resolution is expected, replacement of the previous hour's urine output with appropriate fluid (usually IV 5% dextrose, IV 0.18% saline/4% dextrose or nasogastric water in ICU) whilst closely monitoring plasma and urinary osmolality and electrolytes may suffice. Overadministration of dextrose solutions may cause hyperglycaemia, hyperosmolality and osmotic diuresis.

Severe (>3 mL/kg per hour) or persistent polyuria merits ADH/AVP or DDAVP administration. DDAVP is a selective V_2 receptor agonist and is therefore less likely to cause hypertension. Resistant to breakdown by vasopressinases, DDAVP is long-acting. Daily dose rates of 1–4 micrograms in a single or divided dose by intravenous, intramuscular or subcutaneous administration are usual. Oral and intranasal formulations also exist. ADH may be administered subcutaneously or by intravenous infusion. In the acute situation, an ADH infusion (0.1–3 U/h) can be conveniently titrated against urine output and facilitates re-establishment of the hypertonic renal medullary interstitium before conversion to longer-acting DDAVP. ADH and DDAVP dose requirements are often higher during the acute onset of CDI – this may reflect loss of medullary interstitial hypertonicity, competitive antagonism at V_2 renal receptors by biologically inactive ADH precursors released from the damaged hypothalamic-pituitary tract, or both.

The dose of ADH or DDAVP used is the minimum dose required to achieve acceptable control of urine output. Excessive administration may cause water retention and hypo-osmolal syndromes.

Other drugs may also reduce the polyuria of CDI. Provided there is some residual ADH synthesis, chlorpropamide, clofibrate and carbamazepine are all reported to both enhance ADH release and renal responsiveness to ADH. However, in modern ICU

management of CDI, DDAVP and ADH have better efficacy, better safety profiles and are more easily titrated to effect than the alternatives whose role is now largely confined to treatment of NDI (see later).

NEPHROGENIC DIABETES INSIPIDUS

Nephrogenic diabetes insipidus (NDI) may be congenital or acquired (Box 60.4). As the majority of congenital cases present in the first week of life, the majority of cases seen in the adult ICU are acquired, the commonest causes being lithium toxicity due to long-term drug treatment, hypercalcaemia and post-obstructive uropathy following relief of urinary tract obstruction.

CONGENITAL NEPHROGENIC DIABETES INSIPIDUS

Eighty to ninety percent of patients presenting with congenital NDI are male with x-linked recessive abnormalities of the *AVPR*$_2$ gene coding for the V_2-receptor.[29,46] The majority of the mutations result in intracellular trapping of the V_2-receptor, preventing integration into the collecting duct membrane. Drugs that facilitate receptor integration into the membrane, restoring some of the urine concentrating abilities of ADH, are being investigated.[47] Female children also present but usually with less severe polyuria and polydipsia due to part-expression of the recessive gene.

Approximately 10% of cases of congenital NDI have mutations of the *AQP*$_2$ (aquaporin 2) gene which codes for the AQP_2 channel and are not x-linked. Over 40 autosomal dominant and recessive mutations have been described to date.

The remaining congenital NDI cases arise from failure to generate renal medullary interstitial hypertonicity, with inability to reabsorb water even with normal V_2 receptor and AQP_2 channels.

Absence of the Kidd (blood group) antigen prevents urinary concentration greater than 800 mOsmol/kg even with water deprivation and exogenous ADH administration.[48] The antigen is also normally expressed in the collecting duct epithelium, facilitating transport of urea (urea transport B protein) from urine into the medullary interstitium contributing to the osmolal gradients required to facilitate water reabsorption. Patients with mutations in chloride channel, potassium channel or the sodium-potassium-chloride co-transporter genes resulting in the Bartter syndrome are even less able to generate medullary interstitial hypertonicity and urine can rarely be concentrated greater than 350 mOsol/kg.[49]

With congenital NDI, early diagnosis and management is essential as avoidance of hypernatraemia and dehydration facilitates the achievement of normal developmental milestones and avoids the cerebral damage once commonly accepted as an inevitable association of NDI.

Box 60.4 Causes of nephrogenic diabetes insipidus

Acquired
1. lithium toxicity
2. post-obstructive diuresis
3. hypercalcaemia
4. hypokalaemia
5. hypoproteinaemia
6. Sjogren's syndrome
7. amyloid
8. multiple myeloma
9. sickle cell disease
10. polycystic kidney disease
11. pyelonephritis
12. renal transplantation
13. other drugs: amiodarone, amphotericin B, clozapine, colchicine, demeclocycline, foscarnet, gentamicin, loop diuretics, rifampicin

Congenital
1. x-linked recessive – *AVPR*$_2$ gene mutations
2. autosomal recessive or dominant – *AQP*$_2$ gene mutations
3. Bartter's syndrome
4. Gitelman's syndrome
5. Urea Transport Protein B (Kidd Ag) deficiency/absence

ACQUIRED NEPHROGENIC DIABETES INSIPIDUS

Lithium-associated nephrotoxicity is the commonest cause of acquired NDI; greater than 20% of patients on chronic lithium therapy develop polyuria. Lithium enters collecting duct principal cells via sodium channels and inhibits intracellular adenylate cyclase antagonising the effects of ADH. It also reduces medullary interstitial hypertonicity, possibly through reducing urea transport protein B expression. Some reversal of both polyuria and lithium-mediated toxicity is possible in early lithium-related NDI following amiloride administration. Amiloride's natriuretic action occurs through closure of the collecting duct luminal sodium channels through which lithium enters the cells.[50] Indomethacin increases intracellular cAMP, counteracting the diminution of this and AQP_2 caused by lithium, markedly reducing urine output. However, care is required as non-steroidal anti-inflammatory drugs (NSAIDs) may worsen renal failure, reducing GFR and lithium excretion, and thereby worsening toxicity.

Hypercalcaemia, hypokalaemia, relief of urinary tract obstruction and hypoproteinaemia are also recognised as causing NDI and are associated with reduced expression of AQP_2 channels, urea transport proteins and a loss of interstitial hypertonicity. These defects normally cause milder polyuria than that associated with lithium toxicity. Aging also reduces urinary concentrating ability, probably due to a combination of pathophysiological changes characteristic of both NDI

and CDI with relative reductions of both AQP_2 and AVP production.[51]

TREATMENT OF NEPHROGENIC DIABETES INSIPIDUS

The treatment of NDI aims to remove the underlying cause wherever possible and to minimise the occurrence of hypernatraemia and hypovolaemia.

1. Correct reversible causes
   a. Stop any drugs suspected in the aetiology
   b. Correct hypokalaemia, hypercalcaemia and hypoproteinaemia
2. Reduce solute load. If maximum urine concentration is 250 mOsmol/kg, a solute intake of 750 mOsmol/day requires production of greater than 3 L of urine to clear the solute. If intake is reduced to 500 mOsmol/day, 2 L of urine will suffice. In the ICU, reduction of solute intake is difficult as drugs and diluents have high solute loads and catabolic patients have high protein requirements. Rather than restricting solute intake, close monitoring of fluid balance and adequate, appropriate replacement of urinary losses may be preferred.
   a. Salt intake restriction (aiming <100 mmol/day)
   b. Protein intake reduction aiming to meet minimum daily requirements including essential amino acids requires specialist dietetic advice and supervision to avoid protein malnutrition. Protein restriction in children is inappropriate as it may adversely affect normal growth and development.
3. Diuretics – thiazides and amiloride
   a. Thiazides – In DI, water losses exceed solute ones causing plasma hyperosmolality and intracellular dehydration to maintain the intravascular volume. Thiazide diuretics cause solute loss in excess of water and reduce intravascular volume. This causes activation of the sympathetic nervous and renin-angiotensin-aldosterone systems and reductions in GFR and ANP. Thiazides also increase expression of AQP_2 channels in the collecting duct.[52] These neuroendocrine changes facilitate increased proximal tubular reabsorption of sodium and water and increased ADH release. Less ultrafiltrate reaches the collecting duct and urine volumes can fall by up to 30%. Combined with a solute reduced diet, urine output may reduce up to 50%.
   b. Amiloride may prove a useful adjunct to thiazides, causing further slight reduction in urine output and combatting thiazide-associated hypokalaemia. It may have benefit in its own right in lithium-associated nephrotoxicity as noted earlier. If administered before damage becomes irreversible, it can both reduce cellular damage and reverse the antagonism of lithium on the actions of ADH.

   Loop diuretics are not effective in reducing the diuresis of NDI. Whilst they reduce intravascular volume and stimulate the sympathetic nervous system similarly to thiazides, they also reduce interstitial medullary sodium concentrations and hypertonicity, thus reducing water reabsorption by the collecting duct rather than enhancing it.
4. ADH
   In partial NDI (most acquired cases), supplementing endogenous ADH to create supraphysiological concentrations can reduce urine production by up to 25%. This may occur through greater V_2 receptor occupation or antagonism of any endogenous antagonists present. Care is required with long-term use as hypertension may result.
5. NSAIDs
   PGE_2 increases GFR and urine flow and decreases intracellular cAMP and thereby aquaporin expression. NSAIDs reduce the formation of renal PGE_2 and when used alone may reduce urine output by up to 50%.[53] Greatest efficacy is cited for indomethacin.[54] Combination with low solute diet and a thiazide diuretic may provide additional antidiuretic benefit.[55] However, the risks of NSAIDs are magnified in the ICU population who already bear increased risk of renal impairment and gastric erosions.
6. Chlorpropamide
   This enhances both ADH release and the sensitivity of the kidney to it. It is suggested to act via increasing renal medullary hypertonicity. Doses of 250 mg od or bd are prescribed but may cause hypoglycaemia[56] and use is reserved for severe refractory partial NDI.
7. Clofibrate
   This oral lipid-lowering agent is reported to enhance ADH release and increase the renal sensitivity to ADH.[57] Its use in CDI has largely been superseded by the introduction of safer, more efficacious DDAVP therapy. Its use in treatment of DI has been associated with myopathy.[58] If considered for treatment of partial NDI, biochemical markers of myopathy should be measured regularly.
8. Carbamazepine
   Although more effective in treating partial CDI, carbamazepine in doses three times those effective in epilepsy may reduce urine output in partial NDI. The high dose rate limits its utility.
9. Molecular chaperones
   Novel 'molecular chaperones' are being developed to treat NDI where functional V_2 receptors are confined intracellularly, unable to integrate into the principal cell basolateral membranes.[59] These membrane-permeable V_2 receptor antagonists cause receptor refolding into forms that allow membrane integration.[60] Animal models of congenital NDI, in vitro human V_2R mutations testing and early studies in humans report some

successes.[61] Unfortunately, a Relcovaptan (SR49059) study, whilst showing promising clinical results, had to be discontinued owing to cytochrome P450 pathway interference. Nonetheless, other chaperone molecules are currently being explored for human testing.[62,63]

GESTATIONAL DIABETES INSIPIDUS

In pregnancy, possibly under the influence of increased hCG,[64] the central osmostat resets,[65,66] thirst develops at osmolalities around 10 mOsmol/kg lower than in the non-pregnant state, the normal range of plasma osmolality falls to 265–285 mOsmol/kg and plasma sodium to 130–145 mmol/L. Reduced baroreceptor stimulation stimulates retention of water and sodium.[67]

During pregnancy, placental vasopressinases (cysteine-aminopeptidases) increase ADH metabolism up to fourfold and placental relaxin contributes to a 50% increase in GFR and venodilatation.[68] Aldosterone concentrations rise up to fivefold. Daily urinary production increases as a result of an increased solute load (including urinary proteins, glucose and amino acids), increased drinking and a raised GFR. Increased solute excretion means that small reductions in urine concentrating ability may cause unexpectedly large increases in urine volume. The diagnosis of gestational diabetes insipidus (GDI) – see Box 60.5 – requires careful differentiation from physiological polyuria and other pathological polyurias (e.g. gestational diabetes).

GDI occurs in around 1:30,000 pregnancies and can result from:

1. Increased ADH destruction by overexpressed placental vasopressinases[69] (especially gemellar pregnancies) or reduced de-activation of vasopressinases (e.g. in acute fatty liver of pregnancy),[70] pre-eclampsia or haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome. Exogenous ADH is also rapidly metabolised and may prove ineffective. DDAVP, the preferred treatment, is resistant to degradation by placental vasopressinase.
2. Relative ADH insufficiency, with barely sufficient reserves in the non-pregnant state, maybe unmasked by increased vasopressinase activity in pregnancy that cannot be compensated for by increased secretion.[71] This condition responds to treatment with ADH/DDAVP and is indicative of latent, subclinical DI that pre-dated pregnancy. Investigation and follow-up following pregnancy is warranted as a proportion of patients in this category will later develop hypothalamo-pituitary axis pathologies such as tumours or autoimmune hypophysitis.
3. Central DI is associated with Sheehan's syndrome and pituitary apoplexy. Sheehan's syndrome is commonest, and is usually preceded by major bleeding or hypotension at the time of delivery. Pituitary apoplexy has been described antenatally, too.[72]
4. Gestational NDI of unknown aetiology that is resistant to both ADH and DDAVP, with resolution in the post-natal period, has also been described.[73]

Box 60.5 Causes of gestational diabetes insipidus

1. Sheehan's syndrome
2. Pituitary apoplexy
3. Hepatic dysfunction:
   a. Acute fatty liver of pregnancy
   b. Pre-eclampsia
   c. HELLP syndrome
4. Vasopressinase release by placenta
5. Idiopathic gestational nephrogenic diabetes insipidus (resolves post-partum)

HELLP, haemolysis, elevated liver enzymes, low platelets.

The treatment of GDI varies depending on the underlying cause. In all cases, it is important not to allow the patient to become hypernatraemic and hyperosmolal, as this is likely to have adverse effects on both mother and child. Where hypernatraemia and hyperosmolality do occur, careful correction is required in a closely monitored, very gradual, step-wise fashion. A lowering of sodium by as little as 10 mmol/L per day has been associated with pontine myelinolysis.[74]

The associations between acute fatty liver of pregnancy, HELLP, pre-eclampsia and DI are well recognised, if not fully understood. It has been suggested that liver dysfunction results in reduced clearance of the vasopressinases released by the placenta and thus increased clearance of maternal ADH.[75,76] It is important to bear these associations in mind, as the polyuria of DI may mask the hypertension and fluid overload of pre-eclampsia and HELLP leading to later diagnosis, delayed management and poorer outcome.[77]

POLYDIPSIA (PSYCHOGENIC/NEUROGENIC/PRIMARY)

Polydipsia may result from:

1. a psychiatric disorder or disturbance[78]
2. drugs causing xerostomia[79] or drying of airways (e.g. oxygen therapy, phenothiazines, anticholinergics)
3. hypothalamic lesions which directly disturb the thirst centre[80] (e.g. sarcoidosis)

In all three causes outlined above, excessive drinking causes production of large quantities of urine of appropriate osmolality. If ingested fluids are hypotonic, the urine will be hypo-osomolal secondary to a fall in ADH secretion. If ingested fluids are hypertonic, the urine will have high osmolality but remain of high volume because of the combination of low ADH production and high ANP production causing a solute diuresis.

Polydipsia may also result from the appropriate detection by osmoreceptors of a raised plasma osmolality due to raised glucose, alcohol or sodium. The glycosuria itself will cause an osmotic diuresis and plasma osmolality may be normal or raised, depending on the severity of the hyperglycaemia and any accompanying ketoacidosis and dehydration.

Excessive drinking of hypotonic fluids leads to hyponatraemia and may progress to water intoxication with cerebral oedema, confusion, impaired consciousness, seizures and death. It has also been postulated that long-term polydipsia may lead to the development of dysregulation of ADH secretion and cranial DI.[81] These are important considerations in patients presenting with reduced consciousness and polyuria; water intoxication (more usually associated with SIADH) and DI may co-exist.

SOLUTE DIURESIS

Failure to reabsorb water in DI results in polyuria. Failure to reabsorb solute results in an osmotic load in the tubules and collecting duct that opposes water absorption and may also cause polyuria. Common causes include glycosuria, diuretic drugs, high protein feeds (increased urea load), supra-normal sodium and other solute intake (through fluids, feeds and drugs) and tubular inability to reabsorb solute (recovering ATN or drug toxicity).

Differentiation of solute from water diuresis is best facilitated by measuring 24-hour urinary solute excretion. Normally, 600–900 mOsmol/day of solute is excreted. Values greater than 900 mOsmol/day indicate a solute diuresis. Spot urine osmolalities greater than 300 mOsmol/kg are also suggestive but not diagnostic. In critically ill patients, simultaneous impairment of both water reabsorption and increased solute elimination are common and total solute excretion greater than 900 mOsmol/day via hypo-osmolal urine may be seen.

THE DIAGNOSIS OF POLYURIC SYNDROMES

MEASURE AND CALCULATE PLASMA OSMOLALITY AND URINE OSMOLALITY

High urine osmolality in the presence of high plasma osmolality is appropriate. When plasma osmolalities are greater than 295 mOsmol/L, urine osmolalities should reach 1000–1200 mOsmol/kg. Urine osmolalities less than 1000 mOsmol/kg imply a concentrating defect. Considerations include the causes of DI and medications that might reduce renal interstitial hypertonicity (e.g. loop diuretics). Urine osmolalities of less than 150 mOsmol/kg in this circumstance are sufficient to make the diagnosis of DI.

Polyuria with high plasma osmolalities and urine osmolalities greater than 1000 mOsmol/kg indicate an osmotic diuresis. The diuresis may be inappropriate inasmuch as it leads to dehydration but appropriate in that the kidneys are maximally retaining water whilst excreting a large solute load. An osmolal gap greater than 10 mOsmol/kg should prompt testing for unmeasured solutes (e.g. ethanol, mannitol, ethylene glycol, sorbitol or methanol).

When plasma osmolalities are less than 280 mOsmol/kg, urine osmolalities should also be less than 280 mOsmol/kg as the body attempts to clear free water. This picture implies water overload. Low plasma osmolality with high urine osmolality implies SIADH and would not normally be associated with polyuria. Cerebral/renal salt wasting should be considered if plasma osmolality and sodium are low/low-normal, intravascular volume depletion is present, there is a diuresis and urinary sodium is greater than 40 mmol/L. Urine may be iso-, hyper- or hypo-osmolal to plasma.

WATER DEPRIVATION AND ANTIDIURETIC HORMONE TESTS

In health, water deprivation rapidly causes increased plasma osmolality, ADH release and increased urine osmolality to 1000–1200 mOsmol/kg to preserve water and restore normal plasma osmolality. In the absence of pre-existing dehydration, a water deprivation test may be useful to determine the cause of persistent polyuria of unknown aetiology. The test is potentially dangerous as dehydration and hyperosmolality can develop rapidly, causing permanent cerebral damage and cardiovascular collapse; it should be conducted under close, expert supervision during daylight hours.

The limitations of the test should also be appreciated:

1. in acute CDI, release of ADH precursors from injured brain tissue may cross-react with ADH assays, rendering their interpretation unreliable
2. at high concentrations of ADH, the urine concentrations achieved in partial NDI and primary polydipsia may be similar
3. patients with partial CDI occasionally become hypersensitive to small rises in ADH such as those induced by the rise in osmolality associated with water deprivation and thus maximally concentrate urine once osmolality is raised, leading to an erroneous diagnosis of primary polydipsia[82]
4. in patients with chronic hypernatraemia and CDI secondary to osmoreceptor dysfunction, hypovolaemia with water deprivation may cause sufficient baroreceptor stimulus to release ADH and suggest normal urine concentrating abilities.[83]

Conducting the water deprivation test:

Step 1. Plasma and urine osmolalities and plasma ADH are measured at time zero and access to IV/oral fluids is denied.

Step 2. Plasma and urine osmolalities are measured hourly until either three consecutive urine osmolalities are within 50 mOsmol/kg of one another

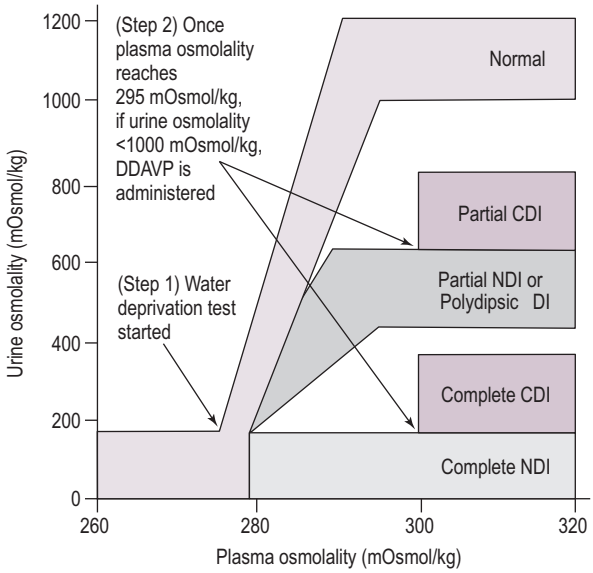


Figure 60.4 Urine versus plasma osmolality during water deprivation testing. *CDI*, Cranial diabetes insipidus; *DDAVP*, 1-deamino-8-0-arginine vasopressin; *NDI*, nephrogenic diabetes insipidus. *Adapted from Sands JM, Bichet DG. Nephrogenic diabetes insipidus.* Ann Intern Med. *2006;144:186–189.*

or plasma osmolality is greater than 295 mOsmol/kg. At this time, plasma ADH is measured again.

Step 3. If plasma osmolality is greater than 295 mOsmol/kg and urine osmolality is less than 1000 mOsmol/kg, 4 µg DDAVP s/c is administered to the patient and urine osmolality is measured hourly for three hours (this time is necessary to allow time for at least partial recovery of the medullary interstitial hypertonic gradient in patients with primary polydipsia). (DDAVP is preferred to AVP as it avoids misinterpretation of results in the presence of vasopressinases which would rapidly metabolise AVP and suggest a diagnosis of NDI rather than CDI. Although neither is the correct diagnosis if vasopressinases are present, the treatment is as for CDI [i.e. the administration of DDAVP].)

Step 4. Urine osmolality is then plotted against plasma osmolality (Fig. 60.4)

Step 5. Plasma and urine osmolalities are plotted against plasma ADH concentrations (Fig. 60.5)

INTERPRETATION OF THE TESTS (see Figs 60.4 and 60.5)

In complete DI, plasma osmolality will rise but urine osmolality will not rise above 300 mOsmol/kg. Upon administration of ADH, patients with complete CDI will raise their urine osmolality to 500 mOsmol/kg or higher, whereas there will be no rise in urine osmolality in complete NDI.

In complete CDI, the original plasma ADH measurement will be zero, whereas in complete NDI, the initial ADH measurement will be normal or high, dependent upon the corresponding plasma osmolality at the time of measurement.

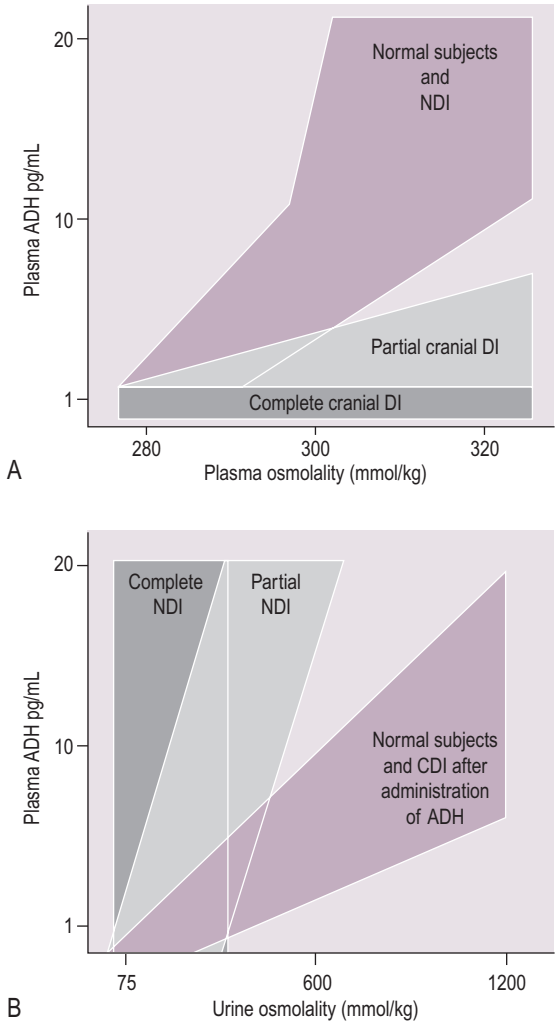


Figure 60.5 (a) As plasma osmolality increases as a result of water deprivation or hypertonic saline infusion, the measured concentration of antidiuretic hormone (ADH) should rise. Failure to do so suggests cranial diabetes insipidus. (b) At a given value of plasma ADH, whether endogenous or exogenous in origin, urine osmolality is expected to lie within a corresponding range of osmolality. However, the range of expected osmolalities is high as osmoreceptors adjust regulation around the basal level of ADH, which is also partly determined by volume receptors. In nephrogenic diabetes insipidus (NDI), the urine osmolality remains low even when high plasma ADH concentrations are measured. *CDI*, Cranial diabetes insipidus.

In partial DI, plasma osmolality will rise and urine osmolality will also increase but usually plateaus between 400 and 800 mOsmol/kg. In partial CDI, the ADH will initially be normal or low and will rise with increasing plasma osmolality but is unlikely to rise above 4–5 pg/mL. In partial NDI, the ADH will initially be normal or high and will increase with plasma osmolality to greater than 8 pg/mL but without achieving a correspondingly appropriate rise in urine concentration.

Following administration of ADH or DDAVP, urine osmolality is expected to increase greater than 100% in complete CDI, remain unchanged in complete NDI and rise by 10%–50% in partial CDI or NDI. In partial CDI, urine osmolality normally rises above plasma osmolality, whereas in partial NDI it tends to remain hypo- or iso-osmolal to plasma following ADH/DDAVP administration.

Contraindications to water deprivation tests include infancy, pre-existing hypovolaemia and hyperosmolality. Treatment of the fluid deficit and/or hyperosmolality should precede further investigations.

HYPERTONIC SALINE INFUSION

In patients with equivocal results from a water deprivation test and those at high risk of dehydration/hypovolaemia from water deprivation (e.g. infants), a hypertonic saline infusion test may be undertaken to establish the cause of a water diuresis. Interpretation of the test is as for the water deprivation test with clearer demarcation between partial CDI and primary polydipsia and the reduced risk of missing a diagnosis of CDI secondary to osmoreceptor dysfunction.[84]

Hypertonic saline is available in multiple different concentrations. Care is required in calculating the appropriate infusion rate to use for the test, as this varies with the concentration of the hypertonic preparation stocked. 0.0425 mmol/kg per minute of hypertonic sodium chloride solution is infused for up to three hours or until a plasma osmolality of 300 mOsmol/kg is achieved.

Blood samples are taken 30 minutes before and at 30-minute intervals throughout the test and plasma sodium, osmolality and ADH measured. Urine samples are collected before and where possible at 60-minute intervals throughout the test period and measurements of osmolality and sodium performed. Thirst and blood pressure are recorded at 30-minute intervals.

MAGNETIC RESONANCE IMAGING T1-WEIGHTED IMAGING OF THE NEUROHYPOPHYSEAL TRACT

Imaging may helpful in differentiating partial CDI from psychogenic polydipsia where results of a water deprivation test and the history make the differentiation uncertain. In CDI, the normal bright spot (stored ADH) seen in the posterior pituitary is usually reduced or absent, whereas in psychogenic polydipsia it is usually present or even enhanced (Fig. 60.6).

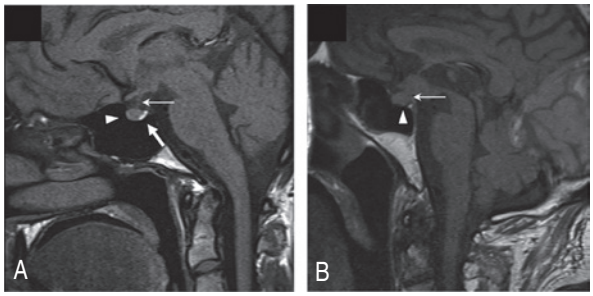


Figure 60.6 Sagittal T1-weighted magnetic resonance imaging scans of the hypothalamic-pituitary region in a patient with posterior pituitary (a) and a patient with cranial diabetes insipidus (CDI) (b). (a) A normal anterior pituitary *(arrowhead)* and pituitary stalk *(thin white arrow)* and hyperintensity of the posterior pituitary *(thick white arrow)*. (b) Sagittal T1-weighted scan obtained in a patient with CDI due to lymphoma shows a massively thickened pituitary stalk *(thin white arrow)* and an absent hyperintense signal in the posterior pituitary gland *(arrowhead)*. *Reproduced with permission from Fenske W, Allolio B. Clinical review: current state and future perspectives in the diagnosis of diabetes insipidus.* J Clin Endocrinol Metab. *2012;97(10):3426–3437.*

Although rapid and less labour-intensive than a hypertonic saline infusion test, the results of the MRI are not yet held to be entirely specific or sensitive. It is reported that the signal is often reduced in NDI (possibly due to ADH store depletion secondary to oversecretion) and in up to 30% of elderly subjects without any clinical symptoms of DI. Additionally, the signal intensity may change bi-directionally over time, even in young subjects. MRI-derived diagnostic information should be considered indicative rather than conclusive.

OTHER TESTS

Other tests have been explored for possible utility in suspected DI. Non-osmotic stimuli of ADH release such as nicotine and hypotension have been found unreliable. More promisingly, the biochemically stable C-terminal glycoprotein cleaved from the ADH-prohormone at the time of activation is relatively easy to measure and correlates well with plasma ADH concentrations; this copeptin may offer a simpler alternative to ADH measurement during water deprivation and hypertonic saline tests.

REFERENCES

1. Lindner G, Schwarz C, Funk G. Osmotic diuresis due to urea as the cause of hypernatraemia in critically ill patients. *Nephrol Dial Transpl*. 2012;27: 962–967.

2. Dorwart WV, Chalmers L. Comparison of methods for calculating serum osmolality from chemical concentrations and the prognostic value of such calculations. *Clin Chem*. 1975;21(2):190–194.
3. Worthley LI, Guerin M, Pain RW. For calculating osmolality, the simplest formula is the best. *Anaesth Intensive Care*. 1987;15(2):199–202.
4. Rasouli M, Kalantair KR. Comparison of methods for calculating serum osmolality: multivariate linear regression analysis. *Clin Chem Lab Med*. 2005;43(6): 635–640.
5. Lee CY, Burnett JC Jr. Natriuretic peptides and therapeutic applications. *Heart Fail Rev*. 2007;12(2): 131–142.
6. McKinely MJ, Denton DA, Weisinger RS. Sensors for antidiuresis and thirst – osmoreceptors or CSF sodium detectors? *Brain Res*. 1978;141:89–103.
7. Keller-Wood M. ACTH responses to CRF and AVP in pregnant and non-pregnant ewes. *Am J Physiol*. 1998;274:1762–1768.
8. Kalogeras KT, Nieman LK, Friedman TC, et al. Inferior petrosal sinus sampling in healthy human subjects reveals a unilateral corticotropin-releasing hormone-induced arginine vasopressin release associated with ipsilateral adrenocorticotropin secretion. *J Clin Invest*. 1996;97(9):2045–2050.
9. Stricker EM, Sved AF. Thirst. *Nutrition*. 2000;16: 821–826.
10. Halter JB, Goldberg AP, Robertson GL, et al. Selective osmoreceptor dysfunction in the syndrome of chronic hypernatraemia. *J Clin Endocrinol Metab*. 1977;44:609–616.
11. Holmes CL, Patel BM, Russell JA, et al. Physiology of vasopressin relevant to management of septic shock. *Chest*. 2001;120:989–1002.
12. Antunes-Rodrigues J, de Castro M, Elias LLK, et al. Neuroednocrine control of body fluid metabolism. *Physiol Rev*. 2004;84:169–208.
13. Czaczkes JW. Physiologic studies of antidiuretic hormone by its direct measurement in human plasma. *J Clin Invest*. 1964;43:1625–1640.
14. Holmes CL, Landry DW, Granton JT. Science review: vasopressin and the cardiovascular system parts 1 and 2. *Crit Care*. 2003;7:427–434 and 2004;8: 15–23.
15. Hantash BM, Thomas AP, Reeves JP. Regulation of the cardiac L-type calcium channel in L6 cells by arginine-vasopressin. *Biochem J*. 2006;400(Pt 3): 411–419.
16. Bankir L. Antidiuretic action of vasopressin: quantitative aspects and interaction between V_{1a} and V_2 receptor mediated effects. *Cardiovasc Res*. 2001;51:372–390.
17. Landry DW, Levin HR, Gallant EM, et al. Vasopressin pressor hypersensitivity in vasodilatory septic shock. *Crit Care Med*. 1997;95:1122–1125.
18. Maturi MF, Martin SE, Markle D, et al. Coronary vasoconstriction induced by vasopressin. Production of myocardial ischaemia in dogs by constriction of non-diseased small vessels. *Circulation*. 1991;83:2111–2121.
19. Vanhoutte PM, Katusic ZS, Shepherd JT. Vasopressin induces endothelium-dependent relaxations of cerebral and coronary but not of systemic arteries. *J Hypertens Suppl*. 1984;2:S421–S422.
20. Okamurat T, Ayajiki K, Fujiokah H, et al. Mechanisms underlying arginine vasopressin induced relaxation in isolated monkey coronary arteries. *J Hypertens*. 1999;17(5):673–678.
21. Sellke FW, Quillen JE. Altered effects of vasopressin on the coronary circulation after ischaemia. *J Thorac Cardiovasc Surg*. 1992;104:357–363.
22. Nussey SS, Bevaqn DH, Ang VT, et al. Effects of arginine vasopressin (AVP) infusions on circulating concentrations of platelet AVP, factor VIII:C and von Willebrand factor. *Thromb Haemost*. 1986;55(1):34–36.
23. Haslam RJ, Rosson GM. Aggregation of human blood platelets by vasopressin. *Am J Physiol*. 1972;223: 958–967.
24. Wun T, Paglieroni T, Lanchant NA. Physiological concentrations of arginine vasopressin activate human platelets in vitro. *Br J Haematol*. 1996;92: 968–972.
25. Filep J, Rosenkranz B. Mechanisms of vasopressin induced platelet aggregation. *Thromb Res*. 1987;45: 7–15.
26. Vander AJ. *Renal Physiology*. 5th ed. New York: McGraw Hill Inc; 1995:116–144.
27. Schrier RW. Water and sodium retention in edematous disorders: role of vasopressin and aldosterone. *Am J Med*. 2006;119(7A):S47–S53.
28. Richard D, Bourque CW. Atrial natriuretic peptide modulates synaptic transmission from osmoreceptor afferents to the supraoptic nucleus. *J Neurosc*. 1996;16(23):7526–7532.
29. Babey M, Kopp P, Robertson GL. Familial forms of diabetes insipidus: clinical and molecular characteristics. *Nat Rev Endocrinol*. 2011;7:701–714.
30. Hedrich CM, Zachurzok-Buczynska A, Gawlik A, et al. Autosomal dominant neurohypophyseal diabetes insipidus in two families. Molecular analysis of the vasopressin-neurophysin II gene and functional studies of three missense mutations. *Horm Res*. 2009;71(2):111–119.
31. Maghnie M, Altobelli M, di Iorgi N, et al. Idiopathic central diabetes insipidus is associated with abnormal blood supply to the posterior pituitary gland caused by vascular impairment of the inferior hypophyseal artery system. *J Endocrinol Metab*. 2004;89:1891–1896.
32. Pivonello R, De Bellis A, Faggiano A, et al. Central diabetes insipidus and autoimmunity: Relationship between the occurrence of antibodies to arginine vasopressin-secreting cells and clinical, immunological and radiological features in a large cohort of patients with central diabetes insipidus of unknown etiology. *J Clin Endocrinol Metab*. 2003;88: 1629–1636.
33. Shucart WA, Jackson I. Management of diabetes insipidus in neurosurgical patients. *J Neurosurg*. 1976;44:65–71.

34. Halter JB, Goldberg AP, Robertson GL, et al. Selective osmoreceptor dysfunction in the syndrome of chronic hypernatraemia. *J Clin Endocrinol Metab*. 1977;44:609–616.
35. Doczi T, Tarjanyi J, Kiss J. Syndrome of inappropriate antidiuretic syndrome after head injury. *Neurosurgery*. 1982;10:685–688.
36. Repaske DR, Medlej R, Gulteken EK, et al. Heterogeneity in clinical manifestation of autosomal dominant neurohypophyseal diabetes insipidus caused by a mutation encoding Ala^{-1}-Val in the signal peptide of the arginine vasopressin/neurophysinII/copeptin precursor. *J Clin Endocrinol Metab*. 1997;82:51–56.
37. Makaryus AN, McFarlane SI. Diabetes insipidus: diagnosis and treatment of a complex disease. *Clev Clin J Med*. 2006;73(1):65–71.
38. Charmandari E, Brook CG. 20 years of experience in idiopathic central diabetes insipidus. *Lancet*. 1999;353:2212–2213.
39. Sudha LM, Anthony JB, Grumbach MM, et al. Idiopathic hypothalamic diabets insipidus, pituitary stalk thickening and the occult intracranial germinoma in children and adolescents. *J Clin Endocrinol Metab*. 1997;82:1362–1367.
40. Arieff AI, Kleeman CR. Studies on mechanisms of cerebral edema in diabetic comas. Effects of hyperglycemia and rapid lowering of plasma glucose in normal rabbits. *J Clin Invest*. 1973;52(3):571–583.
41. Kreis R, Ross BD. Cerebral metabolic disturbances in patients with subacute and chronic diabetes mellitus: detection with proton MR spectroscopy. *Radiology*. 1992;184(1):123–130.
42. Lee JH, Arcinue E, Ross BD. Organic osmolytes in the brain of an infant with hypernatremia. *N Engl J Med*. 1994;331:439–442.
43. Blum D, Brasser D, Kahn A, et al. Safe oral rehydration of hypertonic dehydration. *J Pediatric Gastroenterol Nutr*. 1986;5:232–235.
44. Lindner G, Funk G. Hypernatraemia in critically ill patients. *J Crit Care*. 2013;28(2):216.e11–216.e20.
45. Lindner G, Schwarz C, Kneidinger N, et al. Can we really predict the changes in serum sodium levels? An analysis of currently proposed formulae in hypernatraemic patients. *Nephr Dial Tranplan*. 2008;23:3501–3508.
46. Spanakis E, Milord E, Gragnoli C. AVPR2 variants and mutations in nephrogenic diabetes insipidus: review and missense mutation significance. *J Cell Physiol*. 2008;217:605–617.
47. Robben JH, Sze M, Knoers NV, et al. Functional rescue of vasopressin V2 receptor mutants in MDCK cells by pharmacochaperones: relevance to therapy of nephrogenic diabetes insipidus. *Am J Physiol Renal Physiol*. 2007;292:F253–F260.
48. Sands JM, Gargus JJ, Fröhlich O, et al. Urinary concentrating ability in patients with Jk(a-b-) blood type who lack carrier-mediated urea transport. *J Am Soc Nephrol*. 1992;2:1689–1696.
49. Reinalter SC, Jeck N, Brochhausen C, et al. Role of cyclooxygenase-2 in hyperprostaglandin E syndrome/antenatal Bartter syndrome. *Kidney Int*. 2002;62(1):253–260.
50. Battle DC, von riotte AB, Gaviria M, et al. Amelioration of polyuria by amiloride in patients receiving long-term lithium therapy. *N Engl J Med*. 1985;312:408–414.
51. Sands JM, Bichet DG. Nephrogenic diabetes insipidus. *Ann Intern Med*. 2006;144:186–194.
52. Kim GH, Lee JW, Oh YK, et al. Nephrogenic diabetes insipidus is associated with up-regulation of aquaporin-2, Na-Cl cotransporter and epithelieal sodium channel. *J Am Soc Nephrol*. 2004;15:2836–2843.
53. Lam SS, Kjellstrand C. Emergency treatment of lithium-induced diabetes insipidus with nonsteroidal anti-inflammatory drugs. *Ren Fail*. 1997;19:183–188.
54. Libber S, Harrison H, Spector D. Treatment of nephrogenic diabetes insipidus with prostaglandin synthesis inhibitors. *J Pediatr*. 1986;108:305–311.
55. Hochberg Z, Even L, Danon A. Amelioration of polyuria in nephrogenic diabetes insipidus due to aquaporin-2 deficiency. *Clin Endocrinol*. 1998;49:39–44.
56. Thompson P Jr, Erll JM, Schaaf M. Comparison of clofibrate and chlorpropamide in vasopressin responsive diabetes insipidus. *Metabolism*. 1977;26:749–762.
57. Moses AM, Howanitz J, vanGemert M, et al. Clofibrate-induced antidiuresis. *J Clin Invest*. 1973;52:535–542.
58. Matsukura S, Matsumoto J, Chihara K, et al. Clofibrate-induced myopathy in patients with diabetes insipidus. *Endocrinol Jpn*. 1980;27:401–403.
59. Robben JH, Kortenoeven ML, Sze M, et al. Intracellular activation of vasopressin V2 receptor mutants in nephrogenic diabetes insipidus by nonpeptide agonists. *Proc Natl Acad Sci USA*. 2009;106(29):12195–12200.
60. Wuller S, Wiesner B, Loffler A, et al. Pharmacochaperones post-translationally enhance cell surface expression by increasing conformational stability of wild type and mutant vasopressin V_2 receptors. *J Biol Chem*. 2004;279(45):47254–47263.
61. Bernier V, Morello JP, Zarruk A, et al. Pharmacologic chaperones as a potential treatment for x-linked nephrogenic diabetes insipidus. *J Am Soc Nephrol*. 2006;17:232–243.
62. Los EL, Deen PM, Robben JH. Potential of nonpeptide (ant)agonists to rescue vasopressin V2 receptor mutants for the treatment of X-linked nephrogenic diabetes insipidus. *J Neuroendocrinol*. 2010;22(5):393–399.
63. Procino G, Milano S, Carmosino M, et al. Hereditary nephrogenic diabetes insipidus: molecular basis of the defect and potential novel strategies for treatment. *J Genet Syndr Gene Ther*. 2014;5:225.
64. Davison JM, Shiells EA, Philips PR, et al. Serial evaluation of vasopressin release and thirst in human pregnancy. Role of human chorionic gonadotrophin in the osmoregulatory changes of gestation. *J Clin Invest*. 1988;81(3):798–806.

65. Durr JA, Stamoutsos B, Lindheimer MD. Osmoregulation during pregnancy in the rat. Evidence for resetting of the threshold for vasopressin secretion during gestation. *J Clin Invest*. 1998;68: 337–346.
66. Lindheimer MD, Davison JM. Osmoregulation, the secretion of arginine vasopressin and its metabolism during pregnancy. *Eur J Endocrinol*. 1995;132: 133–143.
67. Schrier RW, Durr J. Pregnancy: an overfill or underfill state. *Am J Kidney Dis*. 1987;9:284–289.
68. Dschietzig T, Stangl K. Relaxin: a pregnancy hormone as central player of body fluid and circulation homeostasis. *Cell Molec Life Sci*. 2003; 60(4):688–700.
69. Durr JA, Haggard JG, Hunt JM, et al. Diabetes insipidus in pregnancy associated with abnormally high circulating vasopressin activity. *N Engl J Med*. 1987;316:1070–1074.
70. Cammu H, Velkeniers B, Charels K, et al. Idiopathic acute fatty liver of pregnancy associated with transient diabetes insipidus. *Br J Obstet Gynaecol*. 1987;94:173–178.
71. Iwasaki Y, Osio Y, Kondo K, et al. Aggravation of subclinical diabetes insipidus during pregnancy. *N Engl J Med*. 1991;324:522–526.
72. de Heide LJM, van Tol KM, Doorenbos B. Pituitary apoplexy presenting during pregnancy. *Netherl J Med*. 2004;62(10):393–396.
73. Jin-no Y, Kamiya Y, Okado M, et al. Pregnant woman with transient diabetes insipidus resistant to 1-desamino-8-D-arginine vasopressin. *Endocrin J*. 1998;45:693–696.
74. Hoashi S, Margey R, Haroum A, et al. Gestational diabetes insipidus, severe hypernatraemia and hyperemesis gravidarum in a primigravid pregnancy. *Endoc Abstr*. 2004;7:297.
75. Krege J, Katz VL, Bowes WA. Transient diabetes insipidus of pregnancy. *Obstet Gynecol Surv*. 1989;44:789–795.
76. Barbey F, Bonny O, Rothuizen L, et al. A pregnant woman with de novo polyuria-polydipsia and elevated liver enzymes. *Nephrol Dial Transplant*. 2003;18(10):2193–2196.
77. Aleksandrov N, Audibert F, Bedard MJ, et al. Gestational diabetes insipidus: a review of an underdiagnosed condition. *J Obstet Gynaecol Can*. 2010;32(3):225–231.
78. de Leon J. Polydipsia: a study in a long-term psychiatric unit. *Eur Arch Psychiatry Clin Neurosci*. 2003;253:37–39.
79. Rao KJ, Miller M, Moses A. Water intoxication and thioridazine. *Ann Intern Med*. 1975;82:61–65.
80. Martin JB, Riskind PN. Neurologic manifestations of hypothalamic disease. *Prog Brain Res*. 1992;93: 31–40.
81. Dundas B, Harris M, Narasimhan M. Psychogenic polydipsia review: etiology, differential, and treatment. *Curr Psychiatry Rep*. 2007;9(3):236–241.
82. Zerbe RL, Robertson GL. A comparison of plasma vasopressin measurements with a standard indirect test in the differential diagnosis of polyuria. *N Engl J Med*. 1981;305:1539–1546.
83. Bayliss PH, Robertson GL. Osmoregulation of vasopressin secretion in health and disease. *Clin Endocrinol*. 1988;29:549–576.
84. Mohn N, Acerini CL, Cheetham TD, et al. Hypertonic saline test for the investigation of posterior pituitary function. *Arch Dis Child*. 1998;79: 431–434.

61

Thyroid emergencies

Jonathan M Handy, Alex Li

INTRODUCTION

Thyroid emergencies are a rare cause for admission to critical care. However, mortality is high unless specific treatment is provided in an expeditious manner. Abnormal thyroid function tests (TFTs) are commonly encountered during critical illness; numerous factors must be considered before interpreting these findings as indicating thyroid disease.

BASIC PHYSIOLOGY

Thyroid hormones affect the function of virtually every organ system and must be constantly available for these functions to continue. The two biologically active hormones are tetraiodothyronine (thyroxine or T_4) and triiodothyronine (T_3). These are synthesised by incorporating iodine into tyrosine residues, a process which occurs in thyroglobulin contained within the lumena of the thyroid gland (Fig. 61.1). Stimulation of hormone release by thyroid stimulating hormone (TSH) results in endocytosis of thyroglobulin from the lumen into the follicular cells, followed by hydrolysis to form T_4 and T_3, which is released into the circulation.[1]

Both T_4 and T_3 contain two iodine atoms on their inner (tyrosine) ring. They differ in that T_4 contains two further iodine atoms on its outer (phenol) ring, whereas T_3 contains only one, resulting in a comparatively longer plasma half-life for T_4 of 5–7 days compared with that of 10 hours for T_3. T_4 is produced solely by the thyroid gland, whereas the majority of T_3 is synthesised peripherally by the removal of one iodine atom (de-iodination) from the outer ring of T_4. If de-iodination of an inner ring iodine atom occurs, the metabolically inert reverse-T_3 (rT_3) is formed. This is produced in preference to T_3 during starvation and many non-thyroidal illnesses, and the ratio of inactive (rT_3) to active T_3 synthesis appears to play an important role in the control of metabolism.[2] Numerous factors can affect the peripheral de-iodination process (Box 61.1). Both T_4 and T_3 are highly protein bound in the serum, predominantly to thyroid binding globulin but to a lesser extent to albumin and prealbumin. Changes in concentration of these serum binding proteins have a large effect on total T_4 and T_3 serum concentrations. Such protein changes do not, however, affect the concentration of free hormone or their rates of metabolism. The serum binding proteins act as both a store and a buffer to allow an immediate supply of the metabolically active free-T_4 (fT_4) and free-T_3 (fT_3). In addition, protein binding reduces the glomerular filtration and renal excretion of the hormones.

On reaching the target organs, fT_4 and fT_3 enter the cells predominantly by diffusion. Here, microsomal enzymes de-iodinate the fT_4 to form fT_3. This varies in differing tissues, the majority occurring in the liver, kidneys and muscles. The fT_3 subsequently diffuses into the nucleus, where it binds nuclear receptors and exerts its effect through stimulation of messenger RNA with subsequent synthesis of polypeptides including hormones and enzymes. The role of thyroid hormones in development and homeostasis are widespread and profound: the most obvious effects are to stimulate basal metabolic rate and sensitivity of the cardiovascular and nervous systems to catecholamines.

The regulation of thyroid function is predominantly determined by three main mechanisms, the latter two providing physiological control. Firstly, availability of iodine is crucial for the synthesis of the thyroid hormones. Dietary iodide is absorbed and rapidly distributed in the extracellular fluid, which also contains iodide released from the thyroid gland and from peripheral de-iodination processes. This becomes trapped within thyroid follicular cells, from which it is actively transported into the lumen to be oxidised into iodine and subsequently combined with tyrosine.[3] Other ions such as perchlorate and pertechnetate share this follicular cell active transport mechanism and thus act as competitive inhibitors for the process.

Secondly, thyroid hormone release is controlled by close feedback loop with the anterior pituitary. Diminished levels of circulating hormones trigger secretion of TSH, which acts on the follicular cells of the thyroid gland causing them to release thyroglobulin-rich colloid from the lumena. This thyroglobulin is hydrolysed to form T_4 and T_3 for systemic release. Increased levels of T_4 and T_3 cause diminished TSH secretion, resulting in the follicular cells becoming flat and

ABSTRACT

This chapter will focus on the biochemistry, clinical presentation, and management of critically ill patients presenting with thyroid endocrine emergencies. An understanding of the synthesis, storage, release and conversion of thyroid hormones allows better comprehension of the pathological processes underlying thyroid disease. This is therefore reviewed in advance of the clinical aspects of care.

Clinical diagnosis of thyroid disease in critically ill patients can be challenging due to the varied presentations; biochemical assay of thyroid function is needed to provide diagnostic confirmation. Treatment is aimed at supportive care and symptom management while correcting the underlying endocrine abnormalities.

Critically ill patients can develop abnormalities in thyroid function tests for numerous reasons. Not all require treatment and the causes and interpretation of abnormal thyroid function tests are discussed.

KEYWORDS

Thyrotoxicosis
hypothyroidism
thyroid storm
myxoedema coma
critical care
thyroid emergencies

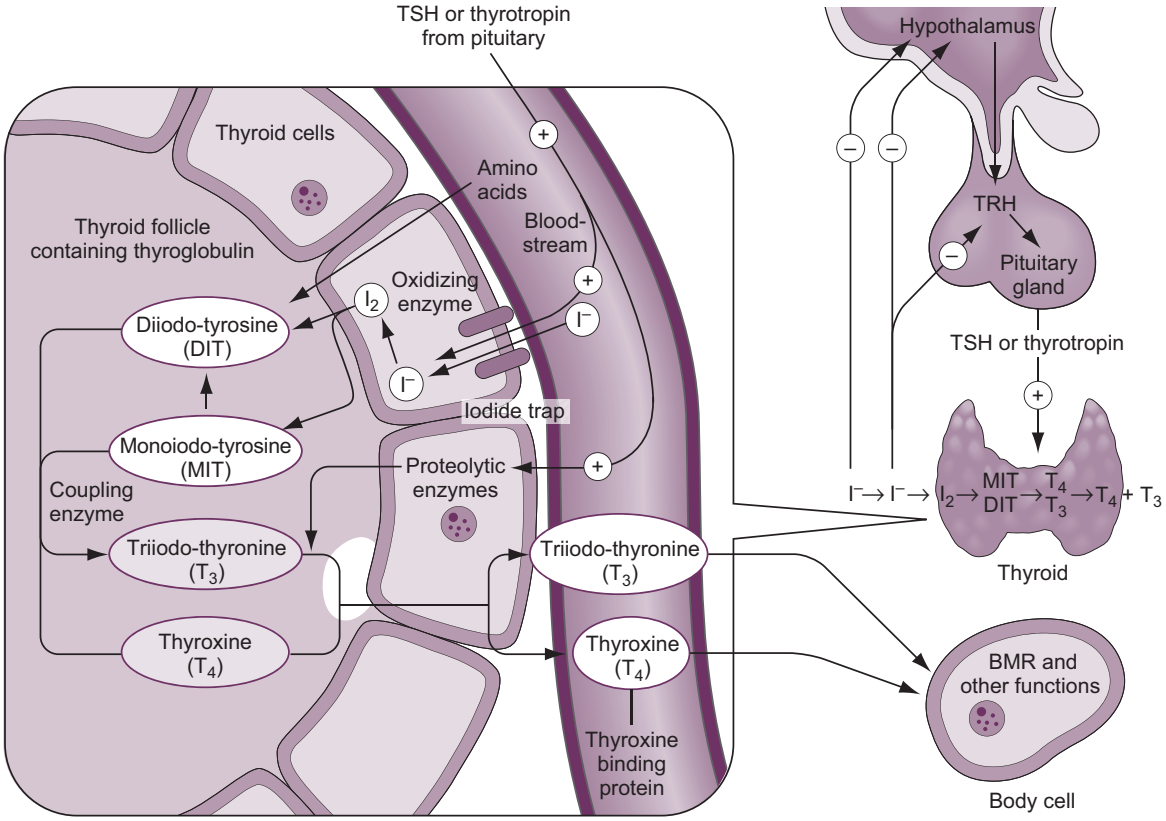


Figure 61.1 Synthesis of tetraiodothyronine (T_4) and triiodothyronine (T_3). Stimulation of hormone release by thyroid stimulating hormone (TSH) produced in the pituitary gland results in endocytosis of thyroglobulin from the lumen into the follicular cells, followed by hydrolysis to form T_4 and T_3 which is released into the circulation. *BMR*, Basal metabolic rate; *TRF*, thyrotropin-releasing factor; *TRH*, thyrotropin-releasing hormone.

Box 61.1 States associated with decreased de-iodination of T_4 to T_3

- Systemic illness
- Fasting
- Malnutrition
- Postoperative state
- Trauma
- Drugs: propylthiouracil; glucocorticoids; propranolol; amiodarone
- Radiographic contrast agents (ipodate, iopanoate)

allowing increased capacity for colloid storage. As a result, less thyroglobulin is mobilised and hydrolysed with less T_4 and T_3 release. The degree to which TSH is secreted in response to changes in circulating thyroid hormones is dependent on the hypothalamic hormone thyrotropin-releasing hormone (TRH), which is itself modulated by feedback from the thyroid hormones (see Fig. 61.1). TRH secretion is inhibited by dopamine, glucocorticoids and somatostatin.

Lastly, further regulation occurs during the enzyme-dependent peripheral conversion of fT_4 to fT_3. It is this latter stage that provides the rapid and fine control of local fT_3 availability. All of these mechanisms may be altered by drugs and in pathological states.

THYROID CRISIS (THYROID STORM)

Thyrotoxic storm is arguably the most serious complication of hyperthyroidism with reported mortality ranging from 10% to 75% in hospitalised patients.[4,5] Crisis most commonly occurs as a result of unrecognised or poorly controlled Grave's disease; however, other underlying diseases may be the cause.[6,7] Females outnumber males. Laboratory findings are inconsistent due to acute disruption of the normal steady state of the circulating hormones and there is no definitive value that separates thyrotoxicosis from thyroid storm. The latter is a clinical diagnosis and a scoring system has been proposed to guide the likelihood of the diagnosis (Table 61.1).[8] Precipitating factors are not always present, though many have been identified (Box 61.2).

Table 61.1 Severity assessment in thyroid crisis

TEMP (°C)	PULSE	CARDIAC FAILURE	CNS EFFECTS	GI SYMPTOMS	SCORE
Normal	<90	Absent	Normal	Normal	**0**
37.2–37.7	90–109	Pedal oedema	—	—	**5**
37.8–38.2	110–119	Bibasal crepitations Atrial fibrillation	Agitation	Diarrhoea Nausea Vomiting Abdominal pain	**10**
38.3–38.8	120–129	Pulmonary oedema	—	—	**15**
38.9–39.2	130–139	—	Delirium	Unexplained jaundice	**20**
39.3–39.9	>140	—	—	—	**25**
>40	—	—	Seizure Coma	—	**30**

Calculations:

- Add the scores for each of the five clinically observed parameters
- Add a further **10 points** if **atrial fibrillation** is present
- Add a further **10 points** if an identifiable **precipitating factor** is present
- Total score of **45** or greater is highly suggestive of thyroid storm
- Total score of **25–44** supports impending crisis
- Total score of less than **25** makes thyroid storm unlikely

CNS, Central nervous system; *GI*, gastrointestinal.

Adapted from Tietgens ST, Leinung MC. Thyroid storm. *Med Clin North Am*. 1995;79(1):169–184.

Box 61.2 Factors associated with precipitating thyroid storm

- Infection; sepsis
- Withdrawal of antithyroid treatment
- Surgery; trauma
- Parturition
- Diabetic ketoacidosis
- Radioactive iodine therapy
- Iodinated contrast dyes
- Hypoglycaemia
- Excessive palpation of the thyroid gland
- Emotional stress
- Burn injury
- Pulmonary thromboembolism
- Cerebrovascular accident; seizure disorder (including eclampsia)
- Thyroid hormone overdose

Box 61.3 Clinical features of hyperthyroidism/ thyroid crisis

- Fever
- Cardiovascular
  - Tachycardia, atrial fibrillation, ventricular arrhythmias
  - Heart failure
  - Hypertension (early), hypotension (late)
- Neuromuscular
  - Tremor
  - Encephalopathy, coma
  - Weakness
- Gastrointestinal
  - Diarrhoea, nausea and vomiting
- Respiratory
  - Dyspnoea
  - Increased oxygen consumption and carbon dioxide production
- Goitre (possible airway compromise)
- Laboratory abnormalities

CLINICAL PRESENTATION

The classic signs of thyroid crisis include fever, tachycardia, tremor, diarrhoea, nausea and vomiting (Box 61.3).[9] However, presentation is extremely variable and may range from apathetic hyperthyroidism (apathy, depression, hyporeflexia and myopathy)[10] to multiple organ dysfunction.[11,12] Differential diagnosis includes sepsis and other causes of hyperpyrexia such as adrenergic and anticholinergic syndromes.

FEVER

This is the most characteristic feature. Temperature may rise above 41°C. There have been suggestions that pyrexia is present in all cases of thyroid storm,[13] although normothermia has been reported.[11] Pyrexia is rare in uncomplicated thyrotoxicosis and should always raise suspicion of thyroid storm. It is not clear whether

this febrile response is due to alteration of central thermoregulation, or elevation of basal metabolic thermogenesis beyond the body's ability to lose heat.

CARDIOVASCULAR FEATURES

Dehydration with electrolyte imbalance is common and fluid requirements may be substantial in some patients; conversely, diuresis may be required in those with severe cardiac congestion. Cardiac decompensation can occur in young patients with no known antecedent cardiac disease. Systolic hypertension with widened pulse pressure is common initially; however, hypotension may supervene later. Shock with vascular collapse is a pre-terminal sign.[14]

NEUROMUSCULAR FEATURES

Tremor and hyperreflexia are common early signs, but as 'storm' progresses central nervous dysfunction evolves with progression from agitation and anxiety to encephalopathy or even coma.[15] Thyroid storm has been reported in association with status epilepticus and cerebrovascular accident.[16] Weakness may be a feature, particularly with apathetic thyrotoxicosis.[11] Thyrotoxic myopathy and rhabdomyolysis may be present[11,17]; the latter being differentiated from the former by its association with markedly elevated creatine phosphokinase levels. A number of other syndromes of neuromuscular weakness have been described including hypokalaemic periodic paralysis[18,19] and myasthaenia gravis.[20]

GASTROINTESTINAL FEATURES

Diarrhoea, nausea and vomiting are common, though the patient may present with symptoms of an acute abdomen.[21] Severe abdominal tenderness should raise the possibility of an abdominal emergency. Liver function tests may be abnormal due to congestion or necrosis and tenderness over the hepatic area may be present. Hepatosplenomegaly may be present. The presence of jaundice is a poor prognostic sign.[14]

RESPIRATORY CONSIDERATIONS

Dyspnoea at rest or on exertion may be present for a number of reasons. Oxygen consumption and carbon dioxide production are increased with subsequent increase in the respiratory burden. This may be exacerbated by pulmonary oedema, respiratory muscle weakness and tracheal obstruction from enlarged goitre (rare).

LABORATORY FINDINGS

Numerous abnormalities may be found

- fT_4 and fT_3 are usually increased, though this does not correlate with clinical severity: TSH is often undetectable
- Hyperglycaemia in non-diabetics
- Leucocytosis with a left shift, even in the absence of infection (leucopenia may be present in patients with Grave's disease)
- Abnormal liver function tests and hyperbilirubinaemia
- Hypercalcaemia due to haemoconcentration and the effect of thyroid hormones on bone resorption.
- Hypokalaemia and hypomagnesaemia (particularly in apathetic thyrotoxicosis)
- Serum cortisol should be elevated. If low values are found, adrenal insufficiency should be considered and treated. Adrenal reserve in thyrotoxic patients is often exceeded in the absence of absolute adrenal insufficiency.

MANAGEMENT

Patients with thyroid storm or an impending crisis should be treated in the intensive care or high-dependency unit. This permits close monitoring and treatment of cardiac and neurological dysfunction and correction of accompanying dehydration and electrolyte imbalances.

Treatment is aimed at:

- Control and relief of adrenergic symptoms
- Correction of thyroid hormone abnormalities
- Resolving the precipitating cause
- Investigation and treatment of the underlying thyroid disease
- Supportive measures

β-ADRENERGIC BLOCKADE

This is the mainstay of controlling adrenergic symptoms.[22] Intravenous propranolol titrated in 0.5–1 mg increments while monitoring cardiovascular response diminishes the systemic hypersensitivity to catecholamines. In addition, it inhibits peripheral conversion of T_4 to T_3.[23] Concurrent administration of enteral propranolol is the norm, with doses as high as 60–120 mg 4–6 hourly often being necessary due to enhanced elimination during thyroid crisis.[24] An alternative regimen uses intravenous esmolol with a loading dose of 250–500 μg/kg followed by infusion at 50–100 μg/kg per minute. This allows rapid titration of β-blockade while minimising adverse reactions.[25] Patients with contraindications to β-blockade or who exhibit resistance to this treatment may be successfully treated with reserpine or guanethidine though their onset of action is slow and side effects may be significant.

DIGOXIN

Control of heart rate and rhythm may result in significant improvement in cardiac performance. Electrolyte imbalance, particularly hypokalaemia and hypomagnesaemia, should be corrected prior to drug therapy. Relative resistance to digoxin may occur due to increased renal clearance[26] and increased Na/K ATPase units in

cardiac muscle.[27] Arterial thromboembolic phenomena are common (10%–40%) in thyrotoxicosis-related atrial fibrillation. This may be due to a procoagulant state or an increased incidence of mitral valve prolapse. Anticoagulation is controversial, given the increased sensitivity to warfarin and potential for bleeding; however, it should be considered in the management of these patients.

AMIODARONE

Amiodarone has theoretical benefits in thyrotoxicosis as it inhibits peripheral conversion of T_4 to T_3 and reduces the concentration of T_3-induced adrenoceptors in cardiac myocytes.[28] It does, however, cause profound (and sometimes physiologically irrelevant) changes to thyroid function tests and should not therefore be used as the first-line agent.

THIONAMIDES

These drugs block de novo synthesis of thyroid hormones within 1–2 hours of administration, but have no effect on the release of preformed glandular stores of thyroid hormones. Transient leucopenia is common (20%) and agranulocytosis can rarely occur with carbimazole use.

Propylthiouracil

This is usually considered the drug of choice in thyroid storm due to its ability to partially block peripheral conversion of T_4 to T_3. Its main mechanism of action is to block the iodination of tyrosine. Only enteral preparations are available and absorption may be unpredictable during thyroid crisis. Rectal administration has been reported. The initial dose is 200 mg every 4 hours.

Methimazole

Methimazole lacks peripheral effects, but has a long duration of action making administration easier and more reliable. It may be used in combination with drugs that block peripheral T_4-to-T_3 conversion (such as iopanoate or ipodate). Only enteral preparations are available, though rectal administration has been reported. The initial dose is 20 mg every 6 hours.

Carbimazole

This is metabolised to methimazole and is rarely associated with agranulocytosis. Only enteral preparations are available.

IODINE

The release of preformed glandular thyroid hormones is inhibited by administering either inorganic iodine or lithium. Enterally administered iodides include Lugol's solution and sodium or potassium iodide. Intravenous infusion of sterile sodium iodide may be used at a dose of 1 g 12 hourly; however, this is not always available commercially. If not, it may be prepared by the hospital pharmacy. Iodine therapy should not commence without prior thionamide administration. Used alone, it will enrich hormone stores within the thyroid gland and exacerbate thyrotoxicosis.

Iodine-containing contrast media (e.g. ipodate and iopanoate) may be used instead of the simple iodides, the former blocking T_4-to-T_3 conversion and inhibiting the cardiac effects of thyroxine. Ipodate is administered orally as a loading dose of 3 g followed by 1 g daily. As with the iodides, treatment should always be preceded by thionamide administration.

LITHIUM

Lithium carbonate has a similar, though weaker action to iodine and can be used in patients with iodine allergy. An initial dose regime of 300 mg 8-hourly has been used with subsequent dosage adjusted to maintain serum drug levels at about 1 mmol/L.[29] Renal and neurological toxicity tend to limit its use.

STEROIDS

Glucocorticoids reduce T_4-to-T_3 conversion and may modulate any autoimmune process underlying the thyroid crisis (e.g. Grave's disease). In addition, relative glucocorticoid deficiency may be a feature of the crisis. An adrenocorticotropic hormone (ACTH) stimulation test is desirable prior to administration of hydrocortisone (100 mg 6–8-hourly); alternatively, dexamethasone (4 mg 6-hourly) can be administered until the test has been performed. Combination therapy with iodides can produce rapid results. Glucocorticoids are the most effective treatment for type-2 amiodarone-induced thyrotoxicosis.[30]

OTHER THERAPIES

Plasmapheresis, charcoal haemoperfusion and dantrolene have all been used as novel therapies in thyroid storm; however, their use is not established or proven.

SUPPORTIVE THERAPY

Fluid management

Fluid management may be extremely difficult in patients suffering from thyroid storm, particularly the elderly. Fluid losses may be profound due to diarrhoea, vomiting, pyrexia and reduced intake. However, congestive cardiac failure may also develop as a result of the high cardiac demand. Echocardiography and cardiac output monitoring may be invaluable in guiding therapy for such patients.

Temperature control

Usually this can be achieved via passive cooling, but refractory hyperpyrexia has been successively treated with active measures such as endovascular cooling.[31]

Nutrition

Thyrotoxic patients have high energy expenditure and may present with a significant energy, vitamin and

nitrogen deficit. Nutritional requirements should take account of any deficit and the ongoing hypercatabolic state. Thiamine is usually supplemented.

Drug therapy

Consideration should be given to the enhanced metabolism and elimination of drugs that occurs in thyrotoxic patients. Salicylates and furosemide should be avoided, as they both displace thyroid hormones from their binding proteins and can rapidly exacerbate systemic symptoms.

Precipitating factors

Both the precipitating factors and the disease process underlying the thyroid crisis should be sought and treated aggressively. Infection is the leading precipitant of crisis; thus, early microbiological cultures and antibiotic therapy should be considered.

MYXOEDEMA COMA

Myxoedema coma is the extreme manifestation of hypothyroidism which, although rare, carries a mortality ranging from 30% to 60%. The term is a misnomer in that the majority of patients present with neither the non-pitting oedema known as myxoedema nor coma.[32] The condition should be considered in any patient presenting with reduced level of consciousness and hypothermia. The crisis occurs most commonly in elderly women with long-standing undiagnosed or undertreated hypothyroidism in whom an additional significant stress is experienced. Numerous precipitating factors have been identified (Box 61.4).

Box 61.4 Factors precipitating myxoedema coma

- Infection
- Cold environmental temperatures/hypothermia
- Burns
- Stroke
- Surgery
- Trauma
- Congestive heart failure
- Carbon dioxide retention
- Gastrointestinal haemorrhage
- Hypoglycaemia
- Medications
  - Amiodarone
  - Anaesthetic agents
  - Analgesics/narcotics
  - Beta blockers
  - Diuretics
  - Lithium
  - Phenytoin
  - Rifampicin
  - Sedatives/tranquilisers

CLINICAL PRESENTATION

Myxoedema coma can be defined when decreased mental status, hypothermia and clinical features of hypothyroidism are present (Box 61.5). When these features are present, diagnosis is straightforward; however, asymptomatic or atypical presentation (e.g. decreased mobility) may occur.[33] The presence of hypotension and bradycardia at presentation, a need for mechanical ventilation, hypothermia unresponsive to treatment, sepsis, intake of sedative drugs, lower Glasgow Coma Scale (GCS), high APACHE II score, and high SOFA score have been associated with an increased predicted mortality.[34]

NEUROMUSCULAR

Alteration of conscious or mental state is present in all patients. This can range from personality changes to coma with about 25% of patients experiencing seizures prior to the onset of coma. Electroencephalogram usually reveals non-specific changes. Weakness is common and skeletal muscle dysfunction may develop secondary to increased membrane permeability. The latter can lead to a rise in creatine phosphokinase. Hyponatraemia is present in up to 50% of patients and may contribute to alterations in conscious level. Lumbar puncture often reveals elevated protein levels and a high opening pressure.

HYPOTHERMIA

Hypothermia represents the decrease in thermogenesis that accompanies reduced metabolism and is exacerbated by low ambient temperatures. Mortality is proportional to the degree of hypothermia. A low-reading thermometer should be used during assessment.

CARDIOVASCULAR FEATURES

Diastolic hypertension is due to increased systemic vascular resistance and blood volume reduction[35]; however, myxoedema is associated with bradycardia and impaired myocardial contractility, with reduced cardiac output and hypotension a common feature. While pericardial effusions may occur, tamponade is uncommon. Creatine phosphokinase may be elevated, though this more commonly originates from skeletal rather than cardiac muscle. Acute coronary syndrome must nevertheless be excluded as a precipitant of the crisis. Electrocardiography (ECG) changes include bradycardia, decreased voltage, non-specific ST and T changes, varying types of block and prolonged QT interval. All of the cardiovascular abnormalities are reversible with thyroid hormone treatment.[36]

Box 61.5 Clinical features of myxoedema coma

- Neuromuscular
  - Abnormal conscious level
  - Psychiatric alterations
  - Weakness
  - Slow relaxing reflexes
  - Fatigue
- Hypothermia
- Cardiovascular
  - Diastolic hypertension
  - Bradycardia
  - Low cardiac output
  - Pericardial effusions
  - Electrocardiography alterations
- Respiratory
  - Diminished central response to hypoxia and hypercapnia
  - Respiratory alkalosis
  - Respiratory muscle weakness
  - Increased sensitivity to sedative drugs
  - Pleural effusions
  - Sleep apnoea
- Airway
  - Deep voice, goitre, vocal cord oedema, macroglossia
- Gastrointestinal
  - Gastric atony, distension, paralytic ileus, faecal impaction and megacolon (late)
  - Weight gain
  - Malabsorption
  - Ascites (rare)
- Bladder distension, urinary retention
- Cold intolerance
- Coarse hair
- Dry, pale, cool skin
- Laboratory abnormalities
  - Hyponatraemia
  - Hypoglycaemia

RESPIRATORY FEATURES

Hypothyroidism causes numerous respiratory alterations (see Box 61.5). There is a propensity to respiratory alkalosis, particularly during artificial ventilation. This is due to low metabolic rate which may be compounded by iatrogenic hyperventilation.[37] Diaphragmatic weakness may occur due to abnormalities of the phrenic nerve; as a result, exercise tolerance may be significantly reduced. These abnormalities improve with thyroid hormone replacement, though full recovery can take several months.

LABORATORY FINDINGS

TFTs will reveal low T_4 and T_3; TSH is raised in primary and low in secondary and tertiary hypothyroidism.

Hyponatraemia is common and usually develops due to free water retention resulting from excess vasopressin secretion or impaired renal function.[38] It may be severe and can contribute to diminished mental function. Although total body water is increased, intravascular volume is usually decreased.

Hypoglycaemia may result from hypothyroidism alone, or as a result of concurrent adrenal insufficiency (Schmidt's syndrome). The mechanism is probably reduced gluconeogenesis, but infection and starvation may contribute.

Azotaemia and hypophosphataemia are common; renal function may be severely abnormal due to low cardiac output and vasoconstriction. Mild leucopenia and normocytic anaemia are frequently present, though macrocytic and pernicious anaemia due to autoimmune dysfunction may occur.

Arterial blood gases often reveal respiratory acidosis, hypoxia and hypercapnia.

MANAGEMENT

The mainstay of therapy consists of thyroid hormone replacement, steroid replacement and supportive measures. Once clinical diagnosis has been made or is suspected, blood should be collected for thyroid function and plasma cortisol tests. This should be followed by thyroid hormone treatment, which should not be delayed to await laboratory results. Consideration should be given to identifying and treating precipitating factors and complications of the crisis.

THYROID HORMONE THERAPY

All patients with suspected myxoedema coma should receive presumptive treatment with thyroid hormone. The optimum speed, type, route and dose of thyroid hormone replacement in myxoedema coma are unknown due to the rarity of the condition and paucity of trials. The severity of clinical presentation does not correlate with the doses of replacement hormone that are required. Rapid replacement can result in life-threatening myocardial ischaemia or arrhythmias; delayed therapy exposes patients to prolonged risk of complications from the crisis. Both scenarios are associated with increased mortality.

Some experts favour administration of T_3, as it is biologically more active, has more rapid onset of action, and bypasses the impaired de-iodination of T_4 to T_3 which occurs in hypothyroidism and non-thyroidal illness. High serum T_3 concentration has, however, been associated with increased mortality[39] and T_3 is expensive and may be difficult to obtain. T_3 may be administered orally or intravenously and has been combined with T_4 therapy.[40,41] In one study of 23 successive patients suffering from myxoedema coma, those who received oral L-thyroxine had no difference in outcome from those receiving intravenous (IV) thyroxine.[34]

Most authorities recommend use of T_4 alone,[39,41,42] as the delayed conversion to T_3 allows more gradual

replacement of the deficient hormone. Bioavailability of orally administered T_4 is unpredictable given the high incidence of gastrointestinal dysfunction; therefore, intravenous administration is more frequently used. A loading dose of intravenous levothyroxine 100–500 µg is recommended,[41] as this saturates the binding proteins. This should be followed by 50–100 µg daily until conversion to the bioequivalent oral formulation is possible. The doses must be adjusted to allow for patient age, weight and their cardiovascular risk factors; the lower doses should be administered to patients who are elderly, frail or have co-morbidities (particularly cardiovascular disease).

CORTICOSTEROIDS

Corticosteroids are an important part of treatment, as relative or absolute hypoadrenalism may occur concurrently with hypothyroid disease. A random serum cortisol level should be collected prior to commencing hydrocortisone therapy at 100 mg 8-hourly. If ACTH stimulation test is warranted, dexamethasone 4 mg 6-hourly should be commenced with conversion to hydrocortisone or cessation of treatment once the results are known. If random serum cortisol levels return at normal levels, steroid treatment can be discontinued.

SUPPORTIVE THERAPY

Hypothermia should be treated by passive re-warming where possible but active measures may be required. Appropriate cardiovascular, temperature gradient, electrolyte and acid-base monitoring should be provided during the re-warming phase in order to prevent haemodynamic and metabolic compromise.

Numerous alterations in respiratory physiology occur, including hypoventilation and altered response to arterial oxygen and carbon dioxide tensions. In addition, anatomical changes to the airway, delayed gastric emptying and increased sensitivity to sedative drugs may be present. These changes should be considered when mechanical ventilation is required, particularly during intubation and the weaning process.[37]

Patients usually present with intravascular fluid depletion despite peripheral oedema. Cardiac output monitoring may help guide fluid resuscitation and therapy. Echocardiography is useful in identifying cardiac dysfunction, pericardial effusions and assisting in assessment of intravascular volume status. Cardiac monitoring should be used to alert to the presence of arrhythmias. Inotropes and vasopressors should be avoided where possible due to their potential to precipitate cardiac arrhythmias. Where inotropes are required, increased dosage may be necessary as reduction in β-adrenoceptors is common. α-Adrenoceptor function is usually preserved.

Hyponatraemia is reversible with thyroid hormone treatment, but severe abnormalities contributing to neurological dysfunction may require more expeditious correction. Free water intake should be restricted and hypertonic saline solutions may be required. Hypotonic fluid therapy should be avoided. If glucose therapy is required, hypertonic solutions (20%–50%) should be infused via a central venous catheter.

Precipitating factors must be considered. As with all critically ill patients, microbial cultures should be collected and antibiotic therapy commenced unless cultures are negative. Prophylaxis against venous thromboembolism and peptic ulceration should be considered. Enteral feeding should be attempted but may be unsuccessful if gastrointestinal dysfunction and stasis is present.

NON-THYROIDAL ILLNESS

Non-thyroidal illness describes the phenomenon of starved or systemically unwell patients with abnormal serum TFTs but with no apparent thyroidal illness. Low T_3, T_4 and TSH are commonly found, the degree of abnormality correlating with the severity of illness. Variants of these hormone levels are well described. Low serum T_3 is a frequent finding and occurs due to down-regulation of the monodeiodinase enzyme that converts T_4 to T_3, while rT_3 may increase due to increased activity of the T_4-to-rT_3 monodeiodinase.[43]

Serum T_4 is also commonly low in the critically ill. This is due to a decrease in the concentration of thyroid hormone binding proteins and the presence of inhibitors that reduce T_4 binding to these proteins. There is also suggestion that T_4 entry into cells may be impaired.[44] Free T_4 levels should be normal in less severe illness; however, in severe illness, the level may be low due to inadequate correction during the fT_4 assay.[45]

Low serum TSH levels were previously thought to be associated with the euthyroid state; however, more recent work suggests that acquired transient central hypothyroidism is present in these patients.[46] Cytokines such as tumour necrosis factor-α are known to inhibit TSH secretion. Such phenomena are probably evolutionary adaptations to conserve protein and energy during severe illness. Elevated TSH may also occur in nonthyroidal illness, but few of these patients prove to have hypothyroidism following recovery from their acute illness.

Changes in TFT are well described during starvation, sepsis, bone marrow transplantation, surgery, myocardial infarction, coronary artery bypass surgery, and probably any critical illness. However, replacement of thyroid hormone in these patients is of no benefit and may be harmful[47]; hence, thyroid function should not be assessed in critically ill patients unless there is a strong clinical indication to do so. A number of specific nonthyroidal illnesses are associated with abnormal TFTs. These include some psychiatric illnesses, hepatic disease, nephritic syndrome, acromegaly,

Table 61.2 Changes in thyroid hormone concentrations

	FT_4	T_3	TSH
Euthyroid	N	N	N
Hyperthyroid	↑	↑	↓
Hypothyroid	↓	↓ N	↑
Non-thyroidal illness	↑ N ↓	↓	N ↓

↑, Increased; ↓, decreased; *FT_4*, free tetraiodothyronine; *N*, normal; *T_3*, triiodothyronine; *TSH*, thyroid-stimulating hormone.

acute intermittent porphyria and Cushing's syndrome. Where assays are performed, TSH should not be interpreted in isolation as low values will not discriminate between true thyroid versus nonthyroidal disease. If low T_4 is also present, nonthyroidal illness is likely. If T_4 is elevated, then hyperthyroidism is the likely diagnosis, though elevated T_4 has been documented in nonthyroidal illness.

Given the alterations in these hormones and difficulties with their assay during critical illness, thyroid hormone replacement should not be undertaken on the strength of TFT results alone; additional laboratory and clinical indications must also be present (Table 61.2).

REFERENCES

1. Kopp P. Thyroid hormone synthesis. In: Braverman LE, Utiger RD, eds. *The Thyroid: Fundamental and Clinical Text*. 9th ed. Philadelphia: Lippincott Williams and Wilkins; 2005:52.
2. Marshall W, Bangert S. The thyroid gland. In: Marshall W, Bangert S, eds. *Clinical Chemistry*. 5th ed. Mosby: Elsevier; 2004:161–175.
3. Spitzweg C, Heufelder AE, Morris JC. Thyroid iodine transport. *Thyroid*. 2000;10(4):321–330.
4. Dillmann WH. Thyroid storm. *Curr Ther Endocrinol Metab*. 1997;6:81–85.
5. Tietgens ST, Leinung MC. Thyroid storm. *Med Clin North Am*. 1995;79(1):169–184.
6. Naito Y, Sone T, Kataoka K, et al. Thyroid storm due to functioning metastatic thyroid carcinoma in a burn patient. *Anesthesiology*. 1997;87(2):433–435.
7. Tewari K, Balderston KD, Carpenter SE, et al. Papillary thyroid carcinoma manifesting as thyroid storm of pregnancy: case report. *Am J Obstet Gynecol*. 1998;179(3 Pt 1):818–819.
8. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. *Endocrinol Metab Clin North Am*. 1993;22(2):263–277.
9. Waldstein SS, Slodki SJ, Kaganiec GI. A clinical study of thyroid storm. *Ann Intern Med*. 1960;52:626–642.
10. Yi-Sun Y, Chong-Jen Y, Fen-Yu T. Apathetic hypothyroidism associated with thyroid storm. *Geriatrics Gerontol Int*. 2004;4(4):255–258.
11. Jiang YZ, Hutchinson KA, Bartelloni P, et al. Thyroid storm presenting as multiple organ dysfunction syndrome. *Chest*. 2000;118(3):877–879.
12. Rufener S, Arunachalam V, Ajluni R, et al. Thyroid storm precipitated by infection. *Endocrinologist*. 2005;15(2):111–114.
13. Mazzaferri EL, Skillman TG. Thyroid storm. A review of 22 episodes with special emphasis on the use of guanethidine. *Arch Intern Med*. 1969;124(6):684–690.
14. Wartofsky L. Thyroid storm. In: Wass JAH, Shalet SM, Gale E, et al, eds. *Oxford Textbook of Endocrinology and Diabetes*. Oxford: Oxford University Press; 2002:481–485.
15. Aiello DP, DuPlessis AJ, Pattishall EG 3rd, et al. Thyroid storm. Presenting with coma and seizures. In a 3-year-old girl. *Clin Pediatr (Phila)*. 1989;28(12):571–574.
16. Lee TG, Ha CK, Lim BH. Thyroid storm presenting as status epilepticus and stroke. *Postgrad Med J*. 1997;73(855):61.
17. Lichstein DM, Arteaga RB. Rhabdomyolysis associated with hyperthyroidism. *Am J Med Sci*. 2006;332:103–105.
18. Ko GT, Chow CC, Yeung VT, et al. Thyrotoxic periodic paralysis in a Chinese population. *QJM*. 1996;89(6):463–468.
19. Dias Da Silva MR, Cerutti JM, Arnaldi LA, et al. A mutation in the KCNE3 potassium channel gene is associated with susceptibility to thyrotoxic hypokalemic periodic paralysis. *J Clin Endocrinol Metab*. 2002;87(11):4881–4884.
20. Marino M, Ricciardi R, Pinchera A, et al. Mild clinical expression of myasthenia gravis associated with autoimmune thyroid diseases. *J Clin Endocrinol Metab*. 1997;82(2):438–443.
21. Bhattacharyya A, Wiles PG. Thyrotoxic crisis presenting as acute abdomen. *J R Soc Med*. 1997;90(12):681–682.
22. Das G, Kreiger M. Treatment of thyrotoxic storm with intravenous administration of propranolol. *Ann Intern Med*. 1969;70:985.
23. Perrild H, Hansen JM, Skovsted L, et al. Different effects of propranolol, alprenolol, sotalol, atenolol and metoprolol on serum T3 and serum rT3 in hyperthyroidism. *Clin Endocrinol (Oxf)*. 1983;18(2):139–142.
24. Feely J, Forrest A, Gunn A, et al. Propranolol dosage in thyrotoxicosis. *J Clin Endocrinol Metab*. 1980;51(3):658–661.
25. Brunette DD, Rothong C. Emergency department management of thyrotoxic crisis with esmolol. *Am J Emerg Med*. 1991;9(3):232–234.
26. Shenfield GM, Thompson J, Horn DB. Plasma and urinary digoxin in thyroid dysfunction. *Eur J Clin Pharmacol*. 1977;12(6):437–443.
27. Chaudhury S, Ismail-Beigi F, Gick GG, et al. Effect of thyroid hormone on the abundance of Na,K-adenosine triphosphatase alpha-subunit messenger ribonucleic acid. *Mol Endocrinol*. 1987;1(1):83–89.
28. Perret G, Yin YL, Nicolas P, et al. Amiodarone decreases cardiac beta-adrenoceptors through an antagonistic effect on 3,5,3′ triiodothyronine. *J Cardiovasc Pharmacol*. 1992;19(4):473–478.

29. Boehm TM, Burman KD, Barnes S, et al. Lithium and iodine combination therapy for thyrotoxicosis. *Acta Endocrinol (Copenh)*. 1980;94(2):174–183.
30. Bartalena L, Brogioni S, Grasso L, et al. Treatment of amiodarone-induced thyrotoxicosis, a difficult challenge: results of a prospective study. *J Clin Endocrinol Metab*. 1996;81(8):2930–2933.
31. Qu A, He H, Xu Z, et al. Endovascular cooling combined with plasmapheresis to treat thyroid crisis patient: a case report. *Int J Clin Exp Med*. 2016;9(8):16812–16816.
32. Nicoloff JT, LoPresti JS. Myxedema coma. A form of decompensated hypothyroidism. *Endocrinol Metab Clin North Am*. 1993;22(2):279–290.
33. Mintzer MJ. Hypothyroidism and hyperthyroidism in the elderly. *J Fla Med Assoc*. 1992;79(4):231–235.
34. Dutta P, Bhansali A, Masoodi SR, et al. Predictors of outcome in myxoedema coma: a study from a tertiary care centre. *Crit Care*. 2008;12(1):R1.
35. Streeten DH, Anderson GH Jr, Howland T, et al. Effects of thyroid function on blood pressure. Recognition of hypothyroid hypertension. *Hypertension*. 1988;11(1):78–83.
36. Shenoy MM, Goldman JM. Hypothyroid cardiomyopathy: echocardiographic documentation of reversibility. *Am J Med Sci*. 1987;294(1):1–9.
37. Behnia M, Clay AS, Farber MO. Management of myxedematous respiratory failure: review of ventilation and weaning principles. *Am J Med Sci*. 2000;320(6):368–373.
38. Iwasaki Y, Oiso Y, Yamauchi K, et al. Osmoregulation of plasma vasopressin in myxedema. *J Clin Endocrinol Metab*. 1990;70(2):534–539.
39. Hylander B, Rosenqvist U. Treatment of myxoedema coma—factors associated with fatal outcome. *Acta Endocrinol (Copenh)*. 1985;108(1):65–71.
40. Wartofsky L. Myxedema coma. In: Braverman LE, Utiger RD, eds. *The Thyroid*. Phiadelphia: Lippincott-Raven; 1996:871.
41. Rodriguez I, Fluiters E, Perez-Mendez LF, et al. Factors associated with mortality of patients with myxoedema coma: prospective study in 11 cases treated in a single institution. *J Endocrinol*. 2004; 180(2):347–350.
42. Smallridge RC. Metabolic and anatomic thyroid emergencies: a review. *Crit Care Med*. 1992;20(2): 276–291.
43. Peeters RP, Wouters PJ, Kaptein E, et al. Reduced activation and increased inactivation of thyroid hormone in tissues of critically ill patients. *J Clin Endocrinol Metab*. 2003;88(7):3202–3211.
44. De Groot LJ. Dangerous dogmas in medicine: the nonthyroidal illness syndrome. *J Clin Endocrinol Metab*. 1999;84(1):151–164.
45. Chopra IJ, Solomon DH, Hepner GW, et al. Misleadingly low free thyroxine index and usefulness of reverse triiodothyronine measurement in nonthyroidal illnesses. *Ann Intern Med*. 1979;90(6): 905–912.
46. Chopra IJ. Clinical review 86: euthyroid sick syndrome: is it a misnomer? *J Clin Endocrinol Metab*. 1997;82(2):329–334.
47. Utiger RD. Altered thyroid function in nonthyroidal illness and surgery. To treat or not to treat? *N Engl J Med*. 1995;333(23):1562–1563.

62

Adrenocortical insufficiency in critical illness

Balasubramanian Venkatesh, Jeremy Cohen

The adrenal glands form an essential part of the organism's response to stress. Hence, in intensive care, an adequate adrenal response is considered to be of prime importance. Whilst primary adrenal insufficiency (AI) is a well-recognised but rare condition in intensive care, secondary, or relative AI is thought to be more prevalent. Adrenocortical insufficiency may present as an insidious, occult disorder, unmasked by conditions of stress, or as a catastrophic syndrome that may result in death.

PHYSIOLOGY

The adrenal glands are functionally divided into medulla and cortex; the latter is responsible for the secretion of three major classes of hormones: glucocorticoids (GCs), mineralocorticoids and sex hormones. The major pathogenic effects of disease result from cortisol and aldosterone deficiency.

Cortisol, the major GC synthesised by the adrenal cortex, plays a pivotal role in normal metabolism. It is necessary for the synthesis of adrenergic receptors, normal immune function, wound healing, and vascular tone. These actions are mediated by the GC receptor, a member of the nuclear hormone receptor superfamily. The activated receptor migrates to the nucleus and binds to specific recognition sequences within target genes, but also interacts with numerous transcription factors and cytosolic proteins. Numerous isoforms of the GCs receptor have now been described; the alpha subtype, a 777 amino acid polypeptide chain, was initially felt to be the primary mediator of GC action. In contrast, the beta isoform, a 742 amino acid chain, was felt to have no physiological activity. More recently it appears that the beta subtype has a negative effect on alpha–mediated gene transactivation, the physiological relevance of which remains controversial. Furthermore, additional isoforms have now been described, suggesting that GC receptor diversity may be an important factor in understanding the complex effects of corticosteroid action.[1]

Under normal circumstances, cortisol is secreted in pulses, and in a diurnal pattern.[2] The normal basal output of cortisol is estimated to be 15–30 mg/day, producing a peak plasma cortisol concentration of 110–520 nmol/L (4–19 μg/dL) at 8–9 a.m., and a minimal cortisol level of less than 140 nmol/L (<5 μg/dL) after midnight. The daily output of aldosterone is estimated to be 100–150 μg/day.

Secretion is under the control of the hypothalamic-pituitary axis. There are a variety of stimuli to secretion, including stress, tissue damage, cytokine release, hypoxia, hypotension and hypoglycaemia. These factors act upon the hypothalamus to favour the release of corticotropin releasing hormone (CRH) and vasopressin. CRH is synthesised in the hypothalamus and carried to the anterior pituitary in portal blood, where it stimulates the secretion of adrenocorticotropic hormone (ACTH), which in turn stimulates the release of cortisol, mineralocorticoids (principally aldosterone) and androgens from the adrenal cortex. CRH is the major (but not the only) regulator of ACTH release and is secreted in response to a normal hypothalamic circadian regulation and various forms of 'stress'. Vasopressin, oxytocin, angiotensin II and β-adrenergic agents also stimulate ACTH release while somatostatin, β-endorphin and enkephalin reduce it. Cortisol has a negative feedback on the hypothalamus and pituitary, inhibiting hypothalamic CRH release induced by stress, and pituitary ACTH release induced by CRH. During periods of stress, trauma or infection, there is an increase in CRH and ACTH secretion and a reduction in the negative feedback effect, resulting in increased cortisol levels, in amounts roughly proportional to the severity of the illness.[3–5]

Cortisol is transported in the blood to the tissues in three fractions; approximately 80% is closely bound to corticosteroid binding globulin (CBG), 10%–15% loosely bound to albumin, and 5%–8% as a free fraction. At normal levels of total plasma cortisol (e.g. 375 nmol/L or 13.5 μg/dL), less than 5% exists as free cortisol in the plasma; however, it is this free fraction that is biologically active. Circulating CBG concentrations are approximately 700 nmol/L. In normal subjects CBG can bind approximately 700 nmol/L (i.e. 25 μg/dL).[6] At levels greater than this, the increase in plasma cortisol is largely in the unbound fraction. The affinity of CBG for synthetic corticosteroids, with the exception of prednisolone, is negligible. CBG is a

ABSTRACT

Dysfunction of the hypothalamo-pituitary adrenal axis has become a central feature in descriptions of the pathophysiology of sepsis and critical illness. Changes in glucocorticoid secretion and responsiveness, protein binding, and activity have been reported. These changes have been described by the terms 'relative adrenal insufficiency', or 'critical illness related corticosteroid insufficiency', and form part of the rationale for trials of glucocorticoid treatment in septic shock. However, despite hundreds of published articles, including literature reviews and consensus statements, controversy still exists regarding the fundamental nature of the disorder and its relevance to clinical management. The role of steroid supplementation in critical illness continues to be debated. This chapter attempts to establish a critical reappraisal of the evidence for adrenal dysfunction in critical illness, and explores the indications for corticosteroid supplementation in the management of a number of critical illnesses with special emphasis on sepsis and septic shock.

KEYWORDS

Adrenal
corticosteroid
corticosteroid – head injury
corticosteroid – spinal injury
corticosteroid – sepsis
corticosteroid – pneumonia
corticosteroid – septic shock
relative adrenal insufficiency (RAI)
critical illness related corticosteroid insufficiency (CIRCI)

substrate for elastase, a polymorphonuclear enzyme that cleaves CBG, markedly decreasing its affinity for cortisol.[7] This enzymatic cleavage results in the liberation of free cortisol at sites of inflammation. CBG levels have been documented to fall during critical illness,[8–10] and these changes are postulated to increase the amount of circulating free cortisol.

Cortisol is lipophilic and diffuses into the cell freely. However, once inside the cell the concentrations of cortisol are profoundly affected by the activity of the 11β-Hydroxysteroid dehydrogenase 1 & 2 (11β-HSD 1 & 2) enzyme system.[11–14] 11β-HSD1 acts in vivo primarily as a reductase, generating active cortisol from inactive cortisone. By contrast, 11β-HSD2 has dehydrogenase action, inactivating cortisol by conversion to cortisone. 11β-HSD2 is found primarily in mineralocorticoid target tissues such as kidney, sweat glands and colonic mucosa, where it prevents illicit activation of the mineralocorticoid receptor by cortisol. 11β-HSD1 has a wide distribution including liver, adipose and vascular tissues, and whilst its primary action is reductase, there is some evidence its directionality may be tissue specific.[15] The system is able to regulate intracellular GC concentration irrespective of circulation concentration, thus rendering circulating levels highly problematic as indicators of tissue GC activity. Altered HSD status has been reported in critical illness.[16,17]

Cortisol has a half-life of 70–120 minutes. It is eliminated primarily by hepatic metabolism and glomerular filtration. The excretion of free cortisol through the kidney represents 1% of the total secretion rate. Currently, available routine assays measure only total cortisol levels, bound and free.

The metabolic effects of cortisol are complex and varied. In the liver, cortisol stimulates glycogen deposition by increasing glycogen synthase and inhibiting the glycogen-mobilising enzyme glycogen phosphorylase.[18] Hepatic gluconeogenesis is stimulated, leading to increased blood glucose levels. Concurrently, glucose uptake by peripheral tissues is inhibited.[19] Free fatty acid release into the circulation is increased, and triglyceride levels rise.

In the circulatory system, cortisol increases blood pressure both by direct actions upon smooth muscle and via renal mechanisms. The actions of pressor agents such as catecholamines are potentiated, whilst nitric oxide-mediated vasodilation is reduced.[20,21] Renal effects include both an increase in glomerular filtration rate, sodium transport in the proximal tubule, and sodium retention and potassium loss in the distal tubule.[22]

The primary effects of cortisol upon the immune system are anti-inflammatory and immunosuppressive. Lymphocyte cell counts decrease, whilst neutrophil counts rise.[22] Accumulation of immunologically active cells at inflammatory sites is decreased. The production of cytokines is inhibited, an effect that is mediated via nuclear factor kappa B (NF-kB). This occurs both by induction of NF-kB inhibitor, or by direct binding of cortisol to NF-kB, thus preventing its translocation to the nucleus. Whilst the well-defined effects of cortisol upon the immune system are primarily inhibitory, it is also suggested that normal host defense function requires some cortisol secretion. Cortisol has been described to have a positive effect upon immunoglobulin synthesis, potentiation of the acute phase response, wound healing, and opsonisation.[23]

CLASSIFICATION

AI may be considered to be primary, secondary or relative. Primary AI, otherwise known as Addison's disease, results from hypofunction of the adrenal cortex. Secondary AI occurs when there is suppression or absence of ACTH secretion from the anterior pituitary. In the setting of critical illness, a further classification has been proposed – that of critical illness related corticosteroid insufficiency (CIRCI). CIRCI represents a situation of disturbed GC metabolism which may result in an inadequate response to the physiological stress of severe illness.

PRIMARY ADRENAL INSUFFICIENCY

Primary AI or Addison's disease is a rare disorder. In the Western world its estimated prevalence is 120 per million.[24] In adulthood, the commonest cause is autoimmune, but in the intensive care setting, consideration should be given to other causes of adrenal gland destruction (Box 62.1). These include infection, haemorrhage and infiltration. Tuberculosis is the commonest

Box 62.1 Causes of primary adrenal insufficiency

- Infections
  - Tuberculosis
  - Histoplasmosis
  - Coccidiomycosis
  - Cytomegalovirus
- Autoimmune mediated
- Haemorrhagic
  - Sepsis (especially meningococcal)
  - Antiphospholipid syndrome
  - Trauma
  - Surgery
  - Coagulation disorders
- Infiltrative
  - Tumour
  - Amyloid
  - Sarcoidosis
  - Haemochromatosis
- Drug related
  - Etomidate
  - Fluconazole
  - Ketoconazole
  - Metyrapone
  - Suramin
  - Rifampicin
  - Phenytoin
- Congenital
  - Adrenal dysgenesis
  - Adrenoleucodystrophy
  - Impaired steroidogenesis
- Cytokine mediated

infective cause worldwide, but rarer infections such as histoplasmosis, coccidiomycosis and cytomegalovirus (CMV) (especially in patients with human immunodeficiency virus [HIV]) have also been implicated. Haemorrhage into the glands is associated with septicaemias, particularly meningococcal (Waterhouse-Friderichsen syndrome). Asplenia and the antiphospholipid syndrome may also be associated with adrenal haemorrhage. Adrenal gland destruction may also be secondary to infiltration with tumour, or amyloid.

Drugs may impair adrenal function either by inhibiting cortisol synthesis (etomidate, ketoconazole) or by inducing hepatic cortisol metabolism (rifampicin, phenytoin). High levels of circulating cytokines are also reported to have a suppressive effect upon ACTH release.[25]

PRESENTATION (BOX 62.2)

The disease is often unrecognised in its early stages, as the presenting features are ill-defined. Symptoms include tiredness and fatigue, vomiting, weight loss, anorexia and postural hypotension. Hyperpigmentation is seen in non-exposed areas (such as palmar skin creases) and is due to the hypersecretion of melatonin, a breakdown product from the ACTH precursor pro-opiomelanocortin.

Presentation to an intensive care physician is likely to be in the form of adrenal crisis. This may be precipitated by concurrent illness or surgery, or by failure to take replacement medication. Classically adrenal crisis will present as refractory shock with a poor response to inotropic or pressor agents. Abdominal or flank pain is often present and may lead to an erroneous diagnosis of an acute surgical abdomen.

Treatment should consist of immediate supportive measures, fluid resuscitation, and high-dose intravenous GC therapy. *A standard dose would be 100 mg of hydrocortisone 6-hourly, or as an infusion.* At these doses, separate mineralocorticoid replacement is not required.[26]

Box 62.2 Clinical features of Addison's disease

Symptoms	**Signs**
Muscular weakness	Hyperpigmentation – skin creases, buccal mucosa
Fatigue	Postural hypotension
Abdominal pain	Associated vitiligo
Vomiting	Decreased axillary and pubic hair
Diarrhoea	Auricular calcification
Salt craving	Vasodilated shock (in crisis)
Weight loss	
Arthralgia and myalgia	
Mood change	
Headache	
Sweating	
Syncope	

Adrenal crisis should be suspected in cases of undifferentiated shock not responding to standard management. Suggestive features would include a history of symptomatology consistent with the diagnosis, hyperpigmentation on examination, and demonstration of hyponatraemia, hyperkalaemia, and peripheral blood eosinophilia. A random plasma total cortisol taken during a crisis will be low (below 80 nmol/L) and in the acute phase ACTH stimulation testing is not required.

SECONDARY ADRENAL INSUFFICIENCY

The commonest cause of ACTH deficiency is sudden cessation of exogenous GC treatment. Patients who have been taking more than 30 mg/day of hydrocortisone or equivalent for more than 3 weeks are at risk of adrenal suppression.[22] Other causes include pituitary surgery, pituitary infarction (Sheehan's syndrome), or pituitary tumour.

Presentation is similar to that of primary AI. The major distinguishing characteristics are a lack of hyperpigmentation, and the absence of mineralocorticoid deficiency; hence, hyperkalaemia is not a feature of secondary AI, although hyponatraemia may still be present due to increased vasopressin levels.

INVESTIGATION OF ADRENAL INSUFFICIENCY

In a stable patient, suspected AI is routinely investigated by an ACTH stimulation test. The test is performed by administering 250 µg of a synthetic ACTH molecule comprising of the first 24 amino acids: tetracosactrin (Synacthen). Plasma total cortisol is measured at 0 and 30 minutes after administration, and a normal response is defined as a peak cortisol measurement over 525 nmol/L.[27] However, it should be noted that current immunoassays exhibit a significant degree of variability, and thus local laboratory reference ranges should be used.[28] The test cannot be performed if the patient is currently being prescribed hydrocortisone as this will cross react with the assays; *an alternative replacement therapy such as dexamethasone should be used in these cases.*

Secondary AI may be differentiated from primary by a prolonged ACTH test. This is performed by the use of a depot preparation or an intravenous infusion of tetracosactrin for 24–48 hours. Patients with secondary hypoadrenalism show a greater plasma cortisol response at 24 hours than at 4 hours; alternatively, measurement of a baseline ACTH level may be used. In patients with primary AI this will be elevated.

Other biochemical tests that may be used in investigation of AI include the insulin hypoglycaemia test, the overnight metyrapone test, and the CRH stimulation test. These investigations are not normally necessary in uncomplicated cases. In addition, the use of the low-dose ACTH stimulation test has been advocated in which only 1 µg of tetracosactrin is used. This approach has not yet gained widespread acceptance.

Critical illness related corticosteroid insufficiency

Substantial alterations in GC metabolism occur in response to critical illness.

Annane et al. prospectively studied 189 patients with septic shock and detailed a three-level classification system based upon the basal cortisol level and response to ACTH.[29] Mortality was found to be highest in those patients with a basal cortisol level above 34 μg/dL (938 nmol/L) and response to ACTH of less than 9 μg/dL (248 nmol/L). Patients with a basal cortisol above 34 μg/dL but a cortisol response greater than 9 μg/dL did better, whilst the best prognosis was seen in the group with a lower basal cortisol level and high response to ACTH. A similar pattern has been observed in numerous other studies of patients with both septic and non-septic critical illness. The significance of this observation, however, is not clear. It has been suggested to either represent a partially suppressed adrenal axis, implying a role for cortisol replacement therapy, or alternatively as indicating an 'overstressed' axis, in which case steroid treatment would be inappropriate. Treatment of septic patients fulfilling CIRCI criteria with hydrocortisone has been shown to improve outcome only in one study,[30] but these results have not been widely accepted. Alternative diagnostic criteria, relying on baseline plasma cortisol levels without ACTH stimulation, have been proposed,[31] but the lack of a consistently observed relationship between cortisol levels and mortality means that the optimal diagnostic criteria for CIRCI remain controversial (Box 62.3). Possible explanations for the difficulties in assessing adrenal function in this patient group include spontaneous fluctuations in the measured cortisol values,[32] increased variability of assays,[28] and changes in CBG levels affecting free cortisol values.[10,33] Measurement of the free cortisol fraction, representing the bioavailable active hormone, has been the focus of recent research interest, with some evidence suggesting it may give a more accurate representation of adrenal function.[10,33] However, the superiority of free cortisol estimations is by no means clear[16,34,35] and the limited availability of the assay means the test is not in general clinical use.

An alternative hypothesis put forward to explain the constellation of adrenocortical changes in critical illness is a sick euadrenal syndrome analogous to the sick euthyroid state,[36] in which changes in the free cortisol fraction, intracellular cortisol:cortisone interconversion, GC receptor density and gene transcription may all act to affect adrenal function at a tissue level. The complexity of this system suggests that simple measurement of total plasma cortisol levels may only give a partial insight into the true functioning of the 'stress response' in the critically ill. Recent evidence indicates that tissue sensitivity to the action of GCs in patients with septic shock is highly variable, and cannot be accurately assessed using plasma cortisol concentrations.[37]

Box 62.3 Controversies in the diagnosis of adrenal insufficiency in the critically ill

1. Limitations of a random cortisol
   a. In the critically ill there is a marked fluctuation in plasma cortisol concentration limiting the utility of a random cortisol[32]
   b. The 'normal' range of cortisol in critical illness is not defined
   c. There is no consensus 'cut-off' value below which adrenal insufficiency is present
2. Limitations of total cortisol
   a. Free cortisol is the bio-active fraction of cortisol
   b. There is large variation in total cortisol assay results when the same specimen is tested in different laboratories and using different assays[28]
   c. Peripheral tissue-specific glucocorticoid resistance is not tested
3. Limitations of the conventional Synacthen test
   a. The HDSST results in plasma Synacthen concentrations that are supraphysiological
   b. Published data may have overestimated the incidence of adrenal insufficiency, as many studies have not excluded patients who received etomidate
   c. The low-dose SST may be a better predictor of outcome

HDSST, High dose short Synacthen test; *SST,* short Synacthen test.

Box 62.4 Proven role for steroids in critical illness

1. Addisonian crisis
2. Anaphylaxis
3. Asthma
4. Bacterial meningitis
5. Chronic obstructive pulmonary disease (COPD) with acute respiratory failure
6. Croup
7. Hypercalcaemia
8. Fulminant vasculitis
9. Idiopathic thrombocytopenic purpura
10. Myasthaenic crisis
11. Myxoedema coma
12. Organ transplantation
13. Pneumocystis carinii pneumonia
14. Thyroid storm

STEROID THERAPY IN CRITICAL ILLNESS

Steroids have an established role in the management of a number of critical illnesses as outlined in Box 62.4. However, their use in other conditions has not been without controversy.

SPINAL INJURY

High-dose methylprednisolone has been advocated in the management of patients with spinal cord injury

following the publication of the National Acute Spinal Cord Injury Study (NASCIS) II and III trials. The major criticism of these studies is the lack of a demonstrable improvement in the primary outcome measures. For a more detailed review of the use of steroids in spinal cord injury, the reader is referred to Chapter 80.

HEAD INJURY

The role of steroids in the management of cerebral oedema secondary to tumours is well documented and accepted. However, their role in the management of head injury has been the subject of intense debate. Several prospective studies have not been able to prove any benefit with steroids in head trauma. However, these studies were not adequately powered to detect a difference. The recent Corticosteroid Randomisation After Significant Head Injury (CRASH) trial with nearly 10,000 patients clearly demonstrated the lack of any benefit with steroids in head injury.[38]

However, a more recent study of multiple trauma suggested that patients fulfilling criteria for CIRCI had a lower rate of development of ventilator-associated pneumonia when treated with hydrocortisone[39]; these findings were more marked in patients with head injury. A replication study, however, failed to confirm this finding.[40]

ACUTE RESPIRATORY DISTRESS SYNDROME

The acute respiratory distress syndrome (ARDS) clinical trial network published the results of its multicentre study where corticosteroids were administered to patients with ARDS persisting beyond 7 days. Although steroid use was associated with earlier ventilatory wean, improved arterial oxygenation and increased respiratory compliance, there was a higher rate of return to assisted ventilation and neuromuscular weakness.[41] No overall mortality difference was demonstrable between steroid and placebo groups. Commencement of steroids more than 2 weeks after onset of ARDS led to almost a fourfold increase in mortality as compared to the placebo group. Consequently, steroids cannot be routinely recommended for persistent ARDS and may be harmful in late-stage ARDS. Although one randomised controlled trial demonstrated some benefit in early ARDS, trial design issues preclude widespread application of these results.[42] Steroids were also not found to be of benefit in ARDS associated with severe H1N1 pneumonia.[43]

SEPTIC SHOCK

Since the first reported use of steroids in sepsis in 1951, therapy with this drug has undergone several transformations from 'steroid success' in sepsis and malaria in the 70s and early 80s to 'steroid excess' (30 mg/kg methylprednisolone) in severe sepsis in the mid to late 80s to total abandonment in early 90s and finally a resurgence of its use in the new millennium. The results of the only prospective randomised trial of steroids in septic shock by Annane[30] which found a beneficial effect have not been widely accepted owing to problems of randomisation, change of protocol and the use of etomidate (an adrenal suppressant drug) in the study. A European multicentre randomised trial of steroids in septic shock (CORTICUS)[44] did not demonstrate a mortality difference between steroids and placebo. Neither the CORTICUS trial ($N = 499$) nor the French study ($N = 299$) had adequate statistical power to demonstrate a clinically significant reduction in mortality. A recent meta-analysis[45] of 17 trials with 2138 patients reported reduced mortality in patients with septic shock treated with hydrocortisone. These conflicting data mean that the role of GC treatment in the management of septic shock is still uncertain. The most recent iteration of the Surviving Sepsis Campaign Guidelines suggests not using intravenous hydrocortisone if fluid resuscitation and vasopressor therapy are able to restore haemodynamic stability, and advised against the use of the ACTH test.[46] Subsequent to the publication of these guidelines, other studies have provided some further information in this field. A trial comparing vasopressin and noradrenalin either with or without hydrocortisone[47] (vasopressin vs norepinephrine as initial therapy in septic shock [VANISH]) found no beneficial effect of the hydrocortisone, contradicting a subgroup finding from a previous study.[48] The hydrocortisone for prevention of septic shock (HYPRESS) study[49] found no effect of hydrocortisone on the prevention of the development of shock in unshocked patients with severe sepsis. The role of fludrocortisone in septic shock also remains controversial. The study by Annane et al., quoted above, included a dose of 50 µg of fludrocortisone administered orally.[30] It has been argued, however, that doses of cortisol above 50 mg a day provide sufficient mineralocorticoid cover, and thus separate supplementation is unnecessary.[26] Furthermore, the oral route of administration is unreliable in critically ill patients. A study comparing fludrocortisone plus hydrocortisone versus hydrocortisone alone in septic patients failed to demonstrate a difference in outcome.[50]

The results of two large trials are awaited. An ANZICS CTG (Australia and New Zealand Intensive Care Society Clinical Trials Group) driven large multicentre randomised controlled trial (adjunctive corticosteroid treatment in critically ill patients with septic shock [ADRENAL]) of hydrocortisone in septic shock is underway (NCT01448109). This 3800 patient study is due to report its findings in 2017. Additionally, the APROCCHS (activated protein C and corticosteroids for human septic shock) trial (NCT00625209,

$N = 1200$), initially designed as a randomised factorial trial comparing activated protein C with hydrocortisone and fludrocortisone or placebo and converted to a randomised controlled trial to investigate the benefit to risk ratio of corticosteroids, completed enrolment in July 2016 and is due to report its findings soon.

CARDIAC ARREST

Little data exist on the role of GCs in post cardiac arrest patients with shock. Similarities between the post arrest shock state and septic shock have led some advocacy for the use of steroid therapy in this condition. A recent blinded randomised controlled trial, however, found no effect of hydrocortisone as compared with placebo on rate of shock reversal or mortality in vasopressor-dependent patients following cardiac arrest.[51]

PNEUMONIA

Adjunctive treatment with glucocorticoids has been advocated in the management of pneumonia as a strategy to reduce systemic effects of locally produced pulmonary cytokines. Results from these studies have been conflicting. A pilot study reported an improvement in oxygenation and mortality in patients with severe pneumonia treated with 7 days of hydrocortisone.[52] A larger trial in community-acquired pneumonia reported a reduced length of stay in patients receiving a 4-day course of dexamethasone; however, only 5% of these patients required intensive care unit (ICU) care.[53] Conversely, a trial of 7 days of prednisolone treatment in patients with community-acquired pneumonia showed no evidence of efficacy in either cure rate or length of stay[54] and a recent observational study of 316 patients with ICU acquired pneumonia suggested that systemic steroid treatment was associated with an increase in mortality.[55] More recent blinded randomised trials have observed a shorter time to clinical stability in hospitalised patients with pneumonia treated for 7 days with prednisolone,[56] as well as a reduced incidence of treatment failure.[57] A 2015 systematic review and meta-analysis suggested systemic corticosteroid therapy in this group reduced mortality by 3%, and need for mechanical ventilation by 5%.[58] At present GC treatment is not routinely recommended for critically ill patients with pneumonia; an exception would be for the case of *Pneumocystis jirovecii* infection in patients suffering from HIV.[59]

MENINGITIS

Randomised controlled trials have demonstrated the benefit of early steroid therapy in paediatric meningitis, particularly with *H. influenzae* infections. There is also evidence of benefit in adult patients with meningitis, particularly with pneumococcal infections. However, in cryptococcal meningitis associated with HIV infection there is evidence of harm (for more detail refer to Chapter 54).[60]

Box 62.5 Side effects of corticosteroid therapy

Adrenal suppression	Hypertension
Hypokalaemia	Osteoporosis
Glucose intolerance	Peptic ulcer disease
Truncal obesity	Glaucoma
Myopathy	Hyperlipidaemia
Mood alterations including psychosis	Aseptic necrosis of femoral/humeral head

SIDE EFFECTS OF STEROID THERAPY

Steroid therapy is associated with numerous side effects. Those that would be of particular relevance to intensive care are discussed below. A full list is given in Box 62.5.

1. Suppression of the adrenal axis (discussed above). Patients who have been receiving steroid treatment for less than a week are unlikely to be affected.
2. Hyperglycaemia – this may be associated with adverse outcomes in critically ill patients.[61]
3. Myopathy – steroid therapy is known to be associated with muscle weakness and also shown to be an independent risk factor for developing ICU acquired muscle paresis. This has significant clinical implications for weaning patients from mechanical ventilation.
4. Hypokalaemia.
5. Leucocytosis: Corticosteroids increase the neutrophil count by a shift from the marginating to the circulating pool. This effect may lead to concerns that the patient has developed an occult infection.
6. Poor wound healing.
7. Immunosuppression.
8. Pancreatitis.

REFERENCES

1. Yudt MR, Cidlowski JA. The glucocorticoid receptor: coding a diversity of proteins and responses through a single gene. *Mol Endocrinol*. 2002;16:1719–1726.
2. Weitzman ED, Fukushima D, Nogeire C, et al. Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. *J Clin Endocrinol Metab*. 1971;33:14–22.
3. Esteban NV, Loughlin T, Yergey AL, et al. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. *J Clin Endocrinol Metab*. 1991;72:39–45.
4. Barton RN, Stoner HB, Watson SM. Relationships among plasma cortisol, adrenocorticotrophin, and severity of injury in recently injured patients. *J Trauma*. 1987;27:384–392.
5. Chernow B, Alexander HR, Smallridge RC, et al. Hormonal responses to graded surgical stress. *Arch Intern Med*. 1987;147:1273–1278.
6. Williams G, Dluhy R. Disorders of the adrenal cortex. In: Braunwald E, Fauci A, Kasper D, et al,

eds. *Harrison's Principles of Internal Medicine*. New York: McGraw-Hill; 2001:2001–2084.
7. Pemberton PA, Stein PE, Pepys MB, et al. Hormone binding globulins undergo serpin conformational change in inflammation. *Nature*. 1988;336:257–258.
8. Beishuizen A, Thijs LG, Vermes I. Patterns of corticosteroid-binding globulin and the free cortisol index during septic shock and multitrauma. *Intensive Care Med*. 2001;27:1584–1591.
9. le Roux CW, Chapman GA, Kong WM, et al. Free cortisol index is better than serum total cortisol in determining hypothalamic-pituitary-adrenal status in patients undergoing surgery. *J Clin Endocrinol Metab*. 2003;88:2045–2048.
10. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. *N Engl J Med*. 2004;350: 1629–1638.
11. Ferrari P, Lovati E, Frey FJ. The role of the 11beta-hydroxysteroid dehydrogenase type 2 in human hypertension. *J Hypertens*. 2000;18:241–248.
12. Tomlinson JW, Stewart PM. Cortisol metabolism and the role of 11beta-hydroxysteroid dehydrogenase. *Best Pract Res Clin Endocrinol Metab*. 2001;15: 61–78.
13. Walker EA, Stewart PM. 11beta-hydroxysteroid dehydrogenase: unexpected connections. *Trends Endocrinol Metab*. 2003;14:334–339.
14. White PC, Mune T, Agarwal AK. 11 beta-Hydroxysteroid dehydrogenase and the syndrome of apparent mineralocorticoid excess. *Endocr Rev*. 1997;18:135–156.
15. Morris DJ, Brem AS, Ge R, et al. The functional roles of 11 beta-HSD1: vascular tissue, testis and brain. *Mol Cell Endocrinol*. 2003;203:1–12.
16. Cohen J, Smith ML, Deans RV, et al. Serial changes in plasma total cortisol, plasma free cortisol, and tissue cortisol activity in patients with septic shock: an observational study. *Shock*. 2012;37:28–33.
17. Venkatesh B, Cohen J, Hickman I, et al. Evidence of altered cortisol metabolism in critically ill patients: a prospective study. *Intensive Care Med*. 2007;33: 1746–1753.
18. Stalmans W, Laloux M. Glucocorticoids and hepatic glycogen metabolism. In: Baxter JD, Rousseau GG, eds. *Glucocorticoid Hormone Action*. New York: Springer-Verlag; 1979:518–533.
19. Olefsky JM. Effect of dexamethasone on insulin binding, glucose transport, and glucose oxidation of isolated rat adipocytes. *J Clin Invest*. 1975;56: 1499–1508.
20. Grunfeld JP, Eloy L. Glucocorticoids modulate vascular reactivity in the rat. *Hypertension*. 1987;10: 608–618.
21. Saruta T, Suzuki H, Handa M, et al. Multiple factors contribute to the pathogenesis of hypertension in Cushing's syndrome. *J Clin Endocrinol Metab*. 1986;62:275–279.
22. Larsen P, Kronenburg H, Melmed S, et al. *Williams Textbook of Endocrinology*. Philadelphia: W.B. Saunders Company; 2003.
23. Burchard K. A review of the adrenal cortex and severe inflammation: quest of the 'eucorticoid' state. *J Trauma*. 2001;51:800–814.
24. Willis AC, Vince FP. The prevalence of Addison's disease in Coventry, UK. *Postgrad Med J*. 1997;73: 286–288.
25. Bateman A, Singh A, Kral T, et al. The immune-hypothalamic-pituitary-adrenal axis. *Endocr Rev*. 1989;10:92–112.
26. Shenker Y, Skatrud JB. Adrenal insufficiency in critically ill patients. *Am J Respir Crit Care Med*. 2001; 163:1520–1523.
27. Clark PM, Neylon I, Raggatt PR, et al. Defining the normal cortisol response to the short Synacthen test: implications for the investigation of hypothalamic-pituitary disorders. *Clin Endocrinol (Oxf)*. 1998;49:287–292.
28. Cohen J, Ward G, Prins J, et al. Variability of cortisol assays can confound the diagnosis of adrenal insufficiency in the critically ill population. *Intensive Care Med*. 2006;32:1901–1905.
29. Annane D, Sebille V, Troche G, et al. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *JAMA*. 2000;283:1038–1045.
30. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002;288:862–871.
31. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med*. 2003;348: 727–734.
32. Venkatesh B, Mortimer RH, Couchman B, et al. Evaluation of random plasma cortisol and the low dose corticotropin test as indicators of adrenal secretory capacity in critically ill patients: a prospective study. *Anaesth Intensive Care*. 2005; 33:201–209.
33. Ho JT, Al-Musalhi H, Chapman MJ, et al. Septic shock and sepsis: a comparison of total and free plasma cortisol levels. *J Clin Endocrinol Metab*. 2006; 91:105–114.
34. Molenaar N, Groeneveld J, Dijstelbloem H, et al. Assessing adrenal insufficiency of corticosteroid secretion using free versus total cortisol levels in critical illness. *Intensive Care Med*. 2011;37(12): 1986–1993.
35. Venkatesh B, Imeson L, Kruger P, et al. Elevated plasma free cortisol concentrations and ratios are associated with increased mortality even in the presence of statin therapy in patients with severe sepsis. *Crit Care Med*. 2015;43(3):630–635.
36. Venkatesh B, Cohen J. Adrenocortical (dys)function in septic shock – a sick euadrenal state. *Best Pract Res Clin Endocrinol Metab*. 2011;25:719–733.
37. Cohen J, Pretorius CJ, Ungerer JP, et al. Glucocorticoid sensitivity is highly variable in critically ill patients with septic shock and is associated with disease severity. *Crit Care Med*. 2016; 44:1034–1041.

38. Roberts I, Yates D, Sandercock P, et al. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet*. 2004;364:1321–1328.
39. Roquilly A, Mahe PJ, Seguin P, et al. Hydrocortisone therapy for patients with multiple trauma: the randomized controlled HYPOLYTE study. *JAMA*. 2011;305:1201–1209.
40. Asehnoune K, Seguin P, Allary J, et al. Hydrocortisone and fludrocortisone for prevention of hospital-acquired pneumonia in patients with severe traumatic brain injury (Corti-TC): a double-blind, multicentre phase 3, randomised placebo-controlled trial. *Lancet Respir Med*. 2014;2: 706–716.
41. Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med*. 2006;354:1671–1684.
42. Meduri G, Golden E, Freire AX, et al. Methylprednisolone infusion in early severe ARDS: results of a randomised controlled trial. *Chest*. 2007; 131:954–963.
43. Brun-Bruisson C, Richard J, Mercat A, et al. Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2011;183:1200–1206.
44. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358:111–124.
45. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. *JAMA*. 2009;301:2362–2375.
46. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*. 2013;39:165–228.
47. Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: the VANISH randomized clinical trial. *JAMA*. 2016;316: 509–518.
48. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358:877–887.
49. Keh D, Trips E, Marx G, et al. Effect of hydrocortisone on development of shock among patients with severe sepsis: the HYPRESS randomized clinical trial. *JAMA*. 2016;316:1775–1785.
50. Annane D, Cariou A, Maxime V, et al. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. *JAMA*. 2010;303:341–348.
51. Donnino MW, Andersen LW, Berg KM, et al. Corticosteroid therapy in refractory shock following cardiac arrest: a randomized, double-blind, placebo-controlled, trial. *Crit Care*. 2016;20:82.
52. Confalonieri M, Urbino R, Potena A, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med*. 2005;171: 242–248.
53. Meijvis S, Hardeman H, Remmelts H, et al. Dexamethasone and length of hospital stay in patients with community acquired pneumonia: a randomised double-blind placebo-controlled trial. *Lancet*. 2011;377:2023–2030.
54. Snijders D, Daniels J, de Graff C, et al. Efficacy of corticosteroids in community acquired pneumonia: a randomized double blinded clinical trial. *Am J Respir Crit Care Med*. 2010;181:975–982.
55. Ranzani O, Ferrer M, Esperatti M, et al. Association between systemic corticosteroids and outcomes of intensive care unit acquired pneumonia. *Crit Care Med*. 2012;40(9):2552–2561.
56. Blum CA, Nigro N, Briel M, et al. Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet*. 2015; 385:1511–1518.
57. Torres A, Sibila O, Ferrer M, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA*. 2015; 313:677–686.
58. Siemieniuk RA, Meade MO, Alonso-Coello P, et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: a systematic review and meta-analysis. *Ann Intern Med*. 2015;163: 519–528.
59. Bozetti S, Sattler F, Chiu J, et al. A controlled trial of early adjunctive treatment with corticosteroids for pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. *N Engl J Med*. 1990; 323:1451–1457.
60. Beardsley J, Wolbers M, Kibengo FM, et al. Adjunctive dexamethasone in HIV-associated cryptococcal meningitis. *N Engl J Med*. 2016;374: 542–554.
61. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. 2001;345:1359–1367.

63

Acute calcium disorders

Balasubramanian Venkatesh, Priya Nair

Calcium is an important cation and one of the principal electrolytes of the body. A total of 1–2 kg is present in the average adult, of which 99% is found in the bone. Of the remaining 1%, nine tenths is present in the cells and only a tenth in the extracellular fluid (ECF). In the plasma, 50% of the calcium is ionised, 40% bound to plasma proteins mainly to albumin and the remaining 10% is chelated to anions such as citrate, bicarbonate, lactate, sulphate phosphate and ketones. The chelated fraction is usually of little clinical importance, but is increased in conditions where some of these anionic concentrations might be elevated, as in renal failure. Whilst most calcium inside the cell is in the form of insoluble complexes, the concentration of intracellular ionised calcium is about 0.1 mmol/L, creating a gradient of 10,000:1 between plasma and intracellular fluid (ICF) levels of ionised calcium.[1] A schematic illustration of calcium distribution within the various body compartments is shown in Fig. 63.1.

Because ionised calcium is the biologically active component of ECF calcium with respect to physiological functions (Box 63.1) and is also the reference variable for endocrine regulation of calcium homeostasis, its measurement is recognised as being one of prime importance in the management of disorders of calcium homeostasis.

HORMONAL REGULATION OF CALCIUM HOMEOSTASIS

The concentration of ionised calcium in the plasma is subject to tight hormonal control,[3,4] particularly by parathyroid hormone (PTH). A G-protein coupled calcium receptor plays a significant role in the maintenance of calcium homeostasis. This receptor, responsible for sensing extracellular calcium concentration, is present on the cell membrane of the chief cells of the parathyroid and in bone, gut and the kidney. In response to ionised hypocalcaemia, PTH secretion is stimulated, which in turns serves to restore serum calcium levels back to normal by increasing osteoclastic activity in the bone and renal reabsorption of calcium and stimulating renal synthesis of 1,25 dihydroxy D (calcitriol – the active metabolite of Vitamin D). Calcitriol production is stimulated by hypocalcaemia, and inhibited by hypercalcaemia. Calcitriol increases serum calcium by largely promoting gut absorption, and to a lesser extent renal reabsorption of calcium.

Calcitonin, a hypocalcaemic peptide hormone produced by the thyroid, acts as a physiological antagonist to PTH. Although calcitonin has been shown to reduce serum calcium levels in animals by increasing renal clearance of calcium and inhibiting bone resorption, its role in humans is less clear. Despite extreme variations in calcitonin levels, for example, total lack in patients who have undergone total thyroidectomy, or excess plasma levels as seen in patients with medullary carcinoma of the thyroid gland, no significant changes in calcium and phosphate metabolism are seen. Calcitonin is useful as a pharmacological agent in the management of hypercalcaemia.

METABOLIC FACTORS INFLUENCING CALCIUM HOMEOSTASIS

Alterations in serum protein, pH, serum phosphate and magnesium closely impact on serum calcium concentrations. Total plasma calcium levels vary with alterations in plasma protein concentration. Several equations have been put forward for the adjustment of serum calcium in the face of alterations in serum protein concentrations. The validity of these equations are dependent upon the patient population, the methodology used for assessment of serum calcium and the reference intervals.[5] Clinicians often use simple rules of thumb – a correction is made for hypoalbuminaemia by adding 0.2 mmol/L to the measured serum calcium concentration for every 10 g/L decrease in serum albumin concentration below normal (40 g/L). The corresponding correction factor for globulins is 0.04 mmol/L of serum calcium for every 10 g/L rise in serum globulin.

Changes in pH alter protein binding of calcium. As the relationship between ionised calcium and changes in pH is well defined, iCa concentrations can be predicted for a given pH using the following formula:

ABSTRACT

Calcium is an important cation and one of the principal electrolytes of the body. Calcium is essential for a wide variety of physiological functions, ranging from muscle contractility, electrical conduction, cell growth, and neurotransmitter release. Disorders of calcium homeostasis are observed in critically ill patients, hypocalcaemia more common than hypercalcaemia. Over the past decade there has been considerable research into vitamin D supplementation in the critically ill patient, although the existing data are insufficient to make an evidence-based recommendation regarding its potential benefit in the intensive care unit. Newer drugs receptor activator of nuclear factor κB ligand (RANKL) are emerging for the management of hypercalcaemia in malignancy and they may have a role to play in the management of hypercalcaemia in critically ill patients. Debate also continues about the utility of ionised calcium measurements and the significance of ionised hypocalcaemia in critically ill patients. A randomised controlled trial of ionised calcium measurement and supplementation will inform clinical practice and guide therapy.

KEYWORDS

calcium, total and ionised
calcium chloride
calcium gluconate
hypercalcaemia
hypocalcaemia
RANKL
vitamin D

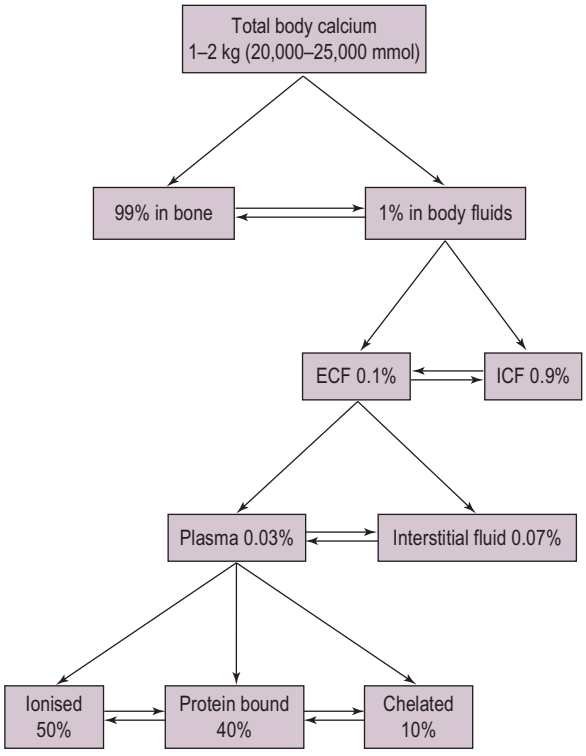


Figure 63.1 Distribution of body calcium. *ECF*, Extracellular fluid; *ICF*, intracellular fluid.

Box 63.1 Functions of calcium

Excitation – contraction coupling in cardiac, skeletal and smooth muscle
Cardiac action potentials and pacemaker activity
Release of neurotransmitters
Coagulation of blood
Bone formation and metabolism
Hormone release
Ciliary motility
Catecholamine responsiveness at the receptor site[2]
Role as a strong cation
Regulation of cell growth and apoptosis

Zaloga GP. Hypocalcemia in critically ill patients. *Crit Care Med*. 1992;20:251–262; Lind L, Ljunghall S. Critical care hypercalcemia – a hyperparathyroid state. *Exp Clin Endocrinol*. 1992;100:148–151.

$$\text{corrected iCa at pH 7.4} = \text{measured iCa} \times [1 - (0.53 \times (7.40 - \text{measured pH}))]^{5}$$

Another rule of thumb is that an increase in pH by 0.1 pH units results in a decrease in ionised calcium by approximately 0.1 mmol/L.[6]

Table 63.1 Daily calcium balance

GASTROINTESTINAL TRACT	
Diet	600–1200 mg/day
Absorbed	200–400 mg/day
Secreted	150–800 mg/day
RENAL	
Filtered	11 000 mg/day
Reabsorbed (97% in the proximal convoluted tubule)	10 800 mg/day
Urinary calcium	200 mg/day
BONE	
Turnover	600–800 mg/day

Calcium and phosphate are closely linked by the following reaction in the ECF: $HPO_4^{2-} + Ca^{2+} = CaHPO_4$. Increases in serum phosphate shift the reaction to the right. When the calcium phosphate solubility product exceeds the critical value of 5 mmol/L, calcium deposition occurs in the tissues, resulting in a fall in serum calcium concentration and a secondary increase in PTH secretion. Reductions in phosphate concentration lead to corresponding changes in the opposite direction.

As magnesium is required for PTH secretion and end-organ responsiveness, alterations in serum magnesium have an impact on serum calcium concentration.

Turnover of calcium in the bone is predominantly under control of PTH and calcitriol, although prostaglandins and some of the cytokines also play a role. Bone resorption is mediated by osteoclasts, while osteoblasts are involved in bone formation. The daily calcium balance is summarised in Table 63.1.

MEASUREMENT OF SERUM CALCIUM

Most hospital laboratories measure total serum calcium. The normal plasma concentration is 2.2–2.6 mmol/L. However, the ionised form (1.1–1.3 mmol/L) is the active fraction and its measurement is not routine in many laboratories, although most contemporary blood gas analysers can measure serum ionised calcium concentrations. Estimation of ionised calcium from total serum calcium concentration using mathematical algorithms is unreliable in critically ill patients.[2,7,8] Heparin forms complexes with calcium and decreases ionised calcium.[9] A heparin concentration of less than 15 units/mL of whole blood is therefore recommended for the measurement of ionised calcium.[10] Anaerobic collection of the specimen is recommended, as CO_2 loss from the specimen may result in alkalosis and reduction in ionised calcium concentration. Calcium levels are also reduced by a concomitant lactic acidosis

owing to chelation by lactate ion.[11] Free fatty acids (FFAs) increase calcium binding to albumin and may form a portion of the calcium binding site.[12] Increases in FFAs may be seen in relation to stress, use of steroids, catecholamines and heparin. The impact of pH on calcium measurements has been described above. The normal reference levels of serum calcium are reduced in pregnancy and in the early neonatal period.[13]

HYPERCALCAEMIA IN CRITICALLY ILL PATIENTS

The frequency of hypercalcaemia in critically ill patients is not well established, although it is not as common as hypocalcaemia. Depending on the patient population, the reported incidence ranges from 3% to 5% to as high as 32%.[14,15] Admission to the intensive care unit (ICU) with a primary diagnosis of a hypercalcaemic crisis is uncommon. Although a number of aetiologies have been described (Box 63.2) in the critical care setting, it is usually due to malignancy-related hypercalcaemia, immobilisation, renal failure or posthypocalcaemic hypercalcaemia.[28] Before undertaking a work up for hypercalcaemia, it is important to exclude false positive measurements. This is usually the result of inadvertent haemoconcentration during venipuncture and elevation in serum protein, although ionised calcium levels are not reported to be affected by haemoconcentration.[29] *Pseudohypercalcaemia* has also been described in the setting of essential thrombocythaemia. The erroneous result is thought to be due to in vitro release of calcium from platelets analogous to the pseudohyperkalaemia seen in the same condition.[23]

Box 63.2 Causes of hypercalcaemia

Common causes of hypercalcaemia in the critically ill patient

Complication of malignancy
- Bony metastases
- Humoral hypercalcaemia of malignancy

Posthypocalcaemic hypercalcaemia
- Recovery from pancreatitis[15]
- Recovery from acute renal failure following rhabdomyolysis[16–20]

Primary hyperparathyroidism
Adrenal insufficiency[21,22]
Prolonged immobilisation[23–26]
Disorders of magnesium metabolism
Use of total parenteral nutrition (TPN)[27]
Hypovolaemia
Iatrogenic calcium administration

Less common causes of hypercalcaemia in the critically ill patient

Granulomatous diseases – sarcoidosis, tuberculosis, berylliosis
Vitamin A & D intoxication
Multiple myeloma
Endocrine:
- Thyrotoxicosis
- Acromegaly
- Phaeochromocytoma

Lithium – chronic therapy
Tamoxifen
Thiazides
Rare association between drugs and hypercalcaemia
Theophylline, omeprazole and growth hormone therapy

MECHANISMS OF HYPERCALCAEMIA

From a pathophysiological standpoint, hypercalcaemia may be due to an elevation in PTH, in which case the homeostatic regulatory and feedback mechanisms are preserved, and this is termed *equilibrium hypercalcaemia*. Alternatively, it could be a non-parathyroid mediated hypercalcaemia with associated breakdown of homeostatic mechanisms, and this situation is termed *disequilibrium hypercalcaemia*.

Malignancy-related hypercalcaemia might arise from bony metastases or humoral hypercalcaemia of malignancy. In the latter (seen with bronchogenic carcinoma and hypernephroma), tumour osteolysis of bone resulting from the release of PTH-like substances (these cross react with PTH in the radioimmunoassay, but are not identical to PTH), calcitriol, osteoclast activating factor and prostaglandins is thought to be the major underlying mechanism. Aggravating factors include dehydration, immobilisation and renal failure.

Posthypocalcaemic hypercalcaemia is a transient phenomenon seen in patients following a period of hypocalcaemia.[28] This has been attributed to parathyroid hyperplasia which develops during the period of hypocalcaemia, which results in a rebound hypercalcaemia following resolution of the underlying hypocalcaemic disorder.

Immobilisation hypercalcaemia results from an alteration in balance between bone formation and resorption.[24–26,30] This leads to loss of bone minerals, hypercalcaemia, hypercalciuria and increased risk of renal failure. In patients with normal bone turnover, immobilisation rarely causes significant hypercalcaemia. However, in patients with rapid turnover of bone (children, post fracture patients, hyperparathyroidism, Paget disease, spinal injuries and Guillain-Barré syndrome), this may result in severe hypercalcaemia.

Intravascular volume depletion reduces renal calcium excretion by a combination of reduced glomerular filtration and increased tubular reabsorption of calcium. Hypercalcaemia further compounds this problem by causing a concentrating defect in the renal tubules, thus creating a polyuria and further aggravating the hypovolaemia.

Extrarenal production of calcitriol by lymphocytes in granulomata is thought to be the predominant

mechanism of hypercalcaemia in granulomatous diseases.[21,22]

Only 10%–20% of patients with adrenal insufficiency develop hypercalcaemia.[31,32] The aetiology of this is thought to be multifactorial: intravascular volume depletion, haemoconcentration of plasma proteins and the loss of anti-vitamin D effects of glucocorticoids.

Hypercalcaemia can be associated with the use of certain medications – vitamin D toxicity, loop diuretics, thiazide diuretics and lithium. For rarer causes of hypercalcaemia, the reader is referred to reviews by Jacobs and Kallas.[21,33]

MANIFESTATIONS OF HYPERCALCAEMIA

The clinical manifestations of hypercalcaemia (commonly encountered when total serum calcium exceeds 3 mmol/L) are outlined in Box 63.3. *Hypercalcaemic crisis* is defined as severe hypercalcaemia (total serum Ca >3.5 mmol/L) associated with acute symptoms and signs.

INVESTIGATIONS

A detailed diagnostic algorithm is outside of the scope of this chapter. The basic work up should include serum calcium, phosphorus and alkaline phosphatase estimation, PTH assay, renal function assessment and a skeletal survey.

Box 63.3 Clinical manifestations of hypercalcaemia

Cardiovascular
Hypertension
Arrhythmias
Digitalis sensitivity
Catecholamine resistance
Urinary system
Nephrocalcinosis
Nephrolithiasis
Tubular dysfunction
Renal failure
Gastrointestinal
Anorexia/nausea/vomiting
Constipation
Peptic ulcer
Pancreatitis
Neuromuscular
Weakness
Neuropsychiatric
Depression
Disorientation
Psychosis
Coma
Seizures

Ectopic calcification is usually seen with chronic hypercalcaemia.

THERAPY OF HYPERCALCAEMIA AND HYPERCALCAEMIC CRISIS

Mild asymptomatic hypercalcaemia does not require emergent treatment. Therapy is usually directed at the underlying cause.

The management of hypercalcaemic crisis consists of two principal components:

1. Increasing urinary excretion of calcium
2. Reducing bone resorption.

INCREASING URINARY EXCRETION OF CALCIUM

As almost all patients with hypercalcaemia are volume depleted, the initial therapy consists of rehydration with normal saline followed by diuresis with furosemide. Rehydration with normal saline improves intravascular volume, reduces serum calcium by extracellular dilution and saliuresis promotes calcium loss in the urine. Volume expansion should be titrated to clinical endpoints and central venous pressure (CVP) monitoring. A urine output of 4–5 L should be aimed for in these patients to promote calciuresis. In many patients, these measures would achieve a reduction in serum calcium by about 0.4–0.5 mmol/L. Hypokalaemia, hypomagnesaemia and calcium stone formation in the urine are potential side effects of this mode of treatment.

In patients with established renal failure in whom forced diuresis cannot be instituted, dialysis against a dialysate with zero or low calcium concentrations should be the treatment of choice.

REDUCTION OF BONE RESORPTION

Measures to increase urinary excretion of calcium should be followed up with administration of agents minimising bone resorption. A number of agents are available and these are listed in Table 63.2.

Disodium ethylenediaminetetraacetic acid (EDTA) at a dose of 15–50 mg/kg intravenously (IV) rapidly lowers serum calcium. However, its propensity to rapidly reduce serum calcium coupled with its nephrotoxic effects limits its usefulness to life-threatening hypercalcaemia. Other therapeutic modalities include the use of non-steroidal anti-inflammatory drugs (NSAIDs) and parathyroidectomy. Calcimimetics are agents which increase the activation of the calcium receptor, thus reducing serum PTH concentrations. Cinacalcet is a first-generation calcimimetic which has shown promise in early randomised trials for the management of hypercalcaemia. It has also been shown to be effective in the management of primary hyperparathyroidism across a wide spectrum of disease severity.[35] However, the role of calcimimetics in the management of acute hypercalcaemia[36] is limited.

At the present time, several newer and more potent bisphosphonates are under development. Their efficacy, combined with a relative lack of side effects, make them the agents of choice for the treatment of malignancy-related hypercalcaemia.

Table 63.2 Therapeutic agents for reducing bone resorption

THERAPY	INDICATIONS	DOSE	ONSET TIME/ DURATION	LIMITATIONS	MECHANISM OF ACTION	COMMENTS
Bi-phosphonates* Etidronate (first generation) Pamidronate (second generation)	Malignancy-related hypercalcaemia	5 mg/kg/day 90 mg as an infusion every 4 weeks	1–2 days, lasts 5–7 days 1–2 days, lasts 10–14 days	Hyperphosphataemia, short duration of action Hypophosphataemia, fever and hypomagnesaemia	Inhibit osteoclast activity, may have some effect on osteoblasts	High potency group. Pamidronate lowers Ca levels more rapidly than etidronate
Calcitonin	Hypercalcaemia Pagets disease	Initial IV dose 3–4 U/kg followed by 4 U/kg subcutaneously (SC) 12th hourly	Hours, lasts 2–3 days	Nausea, abdominal pain, flushing, tachyphylaxis, limited efficacy	Inhibit osteoclast activity, reduces renal tubular reabsorption of calcium	Tachyphylaxis minimised by concomitant steroid therapy
Glucocorticoids	Vit D toxicity, Myeloma, lymphoma, Granulomata	IV hydrocortisone 200–400 mg/day	Days, lasts days to weeks	Glucocorticoid side effects	Inhibit inflammatory cell production of calcitriol, reduce gut absorption of calcium	Improve the efficacy of calcitonin
Gallium nitrate	Malignancy-related hypercalcaemia	100–200 mg/m^2/day for 5–7 days	5–6 days, lasts 7–10 days	Nephrotoxic	Inhibits bone resorption and alters bone crystal structure	Recent Phase II data suggest equivalent efficacy with pamidronate[34]
Plicamycin	Malignancy-related hypercalcaemia	25 µg/kg IV	Rapid onset, lasts for a few days	Hepatotoxic, nephrotoxic and thrombocytopoenia	Inhibits cellular RNA synthesis	Side-effect profile limits the use of this drug
Intravenous phosphates	Limited clinical role	10–15 mmol as an infusion repeated at regular intervals	Hours, lasts 24–48 h after cessation	Ectopic calcification, severe hypocalcaemia	Ectopic calcification, reduce gut absorption, inhibition of bone resorption	Use superseded by the other modalities described.

*Other biphosphonates include ibandronate, risedronate and zoledronate. As compared to pamidronate, zoledronate has the advantage of simplicity of administration and better control of hypercalcaemia.

IV, Intravenous.

Other drugs that have been used in the management of hypercalcaemia include prostaglandin inhibitors for cancer-related hypercalcaemia, ketoconazole, and chloroquine (for sarcoid-induced hypercalcaemia)[22] and glucocorticoids for granulomatous disease-related hypercalcaemia.

ADJUNCT MEASURES IN THE MANAGEMENT OF HYPERCALCAEMIA

Monitoring of cardio-respiratory function and biochemical status is mandatory during therapy of hypercalcaemia. Thiazide diuretics, Vitamin D and absorbable antacids should be avoided. Hypercalcaemia potentiates digitalis effect and dosage should be adjusted accordingly. Endocrinologists should be consulted for further management.

HYPOCALCAEMIA

Hypocalcaemia is more common than hypercalcaemia in critically ill patients with an estimated incidence of around 70%–90%.[28] As the ionised calcium is the biologically active moiety, it is important to look at ionised hypocalcaemia. The frequency of this is far more varied, ranging from 15 to 70.[28,37,38] *Spurious hypocalcaemia* is seen with poor storage of specimens prior to analysis, resulting in CO_2 loss from the specimen, use of EDTA or large doses of heparin as anticoagulants in the syringe. Gadodiamide used in association with magnetic resonance imaging (MRI) as a contrast medium can interfere with the colorimetric assay and cause spurious hypocalcaemia.[39]

AETIOLOGIES

The aetiology of ionised hypocalcaemia based on the predominant pathophysiological mechanism is listed in Box 63.4. The other contributory mechanisms of hypocalcaemia in each of the conditions are shown in brackets.

Although a long list of causes exists for hypocalcaemia, calcium chelation and hypoparathyroidism constitute the common mechanisms of ionised hypocalcaemia in intensive care. The increasing prevalence of citrate anticoagulation used for renal replacement therapy, if not accompanied by appropriate metabolic monitoring, could emerge as another cause of hypocalcaemia in critically ill patients. Frequently, hypocalcaemia is accompanied by a number of other biochemical abnormalities, thus a pattern recognition approach towards the cause of hypocalcaemia will point to its aetiology and save a considerable amount of investigations for the patient. Common diagnostic patterns are listed in Table 63.3.

Whilst alkalosis is frequently associated with ionised hypocalcaemia, the presence of a metabolic acidosis in the face of low serum ionised calcium narrows the differential diagnosis even further (Box 63.5).

Box 63.4 Aetiology of ionised hypocalcaemia

Calcium chelation
Alkalosis (increased binding of calcium by albumin)
Citrate toxicity (calcium chelation)
Massive blood transfusion (citrate leading to calcium chelation)
Hyperphosphataemia (calcium chelation, ectopic calcification, reduced vitamin D3 activity)
Pancreatitis (calcium soap formation, reduced parathyroid secretion)
Tumour lysis syndrome (hyperphosphataemia)
Rhabdomyolysis (hyperphosphataemia and reduced levels of calcitriol)
Hypoparathyroidism
Hypo- and hypermagnesaemia
Sepsis (decreased parathyroid hormone [PTH] secretion, end-organ resistance to PTH, reduced calcitriol production, intracellular shift of calcium, hypomagnesaemia and actions of inflammatory cytokines on the parathyroid glands, kidneys and bone)
Burns (decrease in PTH secretion)
Neck surgery (removal of parathyroid gland, calcitonin release during thyroid surgery and hungry bone syndrome post-parathyroidectomy)
Hypovitaminosis D
Inadequate sun exposure
Inadequate intake
Malabsorption
Liver disease (impaired 25-hydroxylation of cholecalciferol)
Renal failure (impaired 1-hydroxylation of cholecalciferol, hyperphosphataemia)
Medications-phenytoin (inhibition of active calcium transport by intestinal epithelial cells), steroids (increased 24-hydroxylase activity)
Reduced bone turnover
Osteoporosis
Elderly
Cachexia
Drug induced
Bisphosphonates (see under hypercalcaemia)
Propofol
EDTA (calcium chelation)
Ethylene glycol (formation of calcium oxalate crystals in the urine)
Cis-platinum (renal tubular damage leading to hypermagnesuria)
Foscarnet (calcium chelation)
Protamine
Gentamicin (hypermagnesuria leading to hypomagnesaemia and therefore hypocalcaemia)

EDTA, ethylenediaminetetraacetic acid.

CLINICAL MANIFESTATIONS OF HYPOCALCAEMIA

Mild degrees of hypocalcaemia are usually asymptomatic. Ionised calcium levels less than 0.8 mmol/L may cause neuromuscular irritability and result in

Table 63.3 Pattern recognition in the diagnosis of common causes of hypocalcaemia

AETIOLOGY OF HYPOCALCAEMIA	CLINICAL/BIOCHEMICAL PATTERNS
Low serum albumin	Reduced total calcium, normal ionised calcium
Alkalosis	Normal total calcium, reduced ionised calcium
Hypomagnesaemia	Reduced ionised calcium and hypokalaemia
Pancreatitis	Hypocalcaemia, elevated serum lipase and glucose
Renal failure	Elevated blood urea nitrogen, elevated phosphate
Rhabdomyolysis	Hypocalcaemia, elevated phosphate, creatine kinase (CK) and urinary myoglobin
Tumour lysis syndrome	Hypocalcaemia, elevated phosphate, potassium and urate
Citrate toxicity	Low ionised calcium with high total calcium

Box 63.5 Hypocalcaemia with metabolic acidosis

Acute renal failure
Tumour lysis
Rhabdomyolysis
Pancreatitis
Ethylene glycol poisoning
Hydrofluoric acid intoxication

clinical symptoms. The clinical manifestations of hypocalcaemia are summarised in Box 63.6. The manifestations listed in the table below are by no means a comprehensive list of all the clinical features, but include the ones most commonly seen in the critical care setting.

When eliciting tetany, Trousseau's sign (carpopedal spasm) is more specific for hypocalcaemia than Chvostek's sign (facial twitch in response to facial nerve stimulus – present in 10%–30% of the normal population). Electrocardiographic (ECG) changes do not correlate well with the degree of hypocalcaemia. The symptoms of hypocalcaemia are exacerbated by a co-existing hypokalaemia and a hypomagnesaemia.

The laboratory work up should include serum calcium, phosphorus, magnesium and alkaline phosphatase, PTH and vitamin D assays and renal function assessment.

Box 63.6 Clinical manifestations of hypocalcaemia

Central nervous system
Circumoral and peripheral paraesthesia
Muscle cramps
Tetany
Seizures
Extrapyramidal manifestations: tremor, ataxia, dystonia
Proximal myopathy
Depression, anxiety, psychosis
Cardiovascular
Arrhythmias
Hypotension, inotrope unresponsiveness
Prolonged QT intervals, T-wave inversion
Loss of digitalis effect
Respiratory
Apnoea
Laryngospasm
Bronchospasm

APPROACH TO THE TREATMENT OF ASYMPTOMATIC AND SYMPTOMATIC HYPOCALCAEMIA

ARGUMENTS FOR AND AGAINST CORRECTION OF ASYMPTOMATIC HYPOCALCAEMIA

As stated before, it is not clear if asymptomatic hypocalcaemia needs correction. Based on published data which suggest that critical care hypocalcaemia is associated with a higher mortality and increased length of stay in intensive care,[40–42] it is advocated that ionised hypocalcaemia be corrected routinely irrespective of the level. However, arguments exist against the routine correction of asymptomatic ionised hypocalcaemia. Increases in cytosolic calcium lead to disruption of intracellular processes, activation of proteases and can lead to ischaemia and reperfusion injury.[43] Also, there are data suggesting that ionised calcium is an important participant in the pathogenesis of coronary and cerebral vasospasm.[16] In rodent models of endotoxic shock, there are also data demonstrating an increased mortality when these rats were administered intravenous calcium.[17] Most clinicians agree that an ionised calcium level of less than 0.8 mmol/L needs correction even if asymptomatic.

MANAGEMENT OF ACUTE SYMPTOMATIC HYPOCALCAEMIA

Acute symptomatic hypocalcaemia is a medical emergency that requires immediate therapy. In addition to treatment of underlying cause and support of airway, breathing and circulation, the definitive treatment includes administration of intravenous calcium. Intravenous calcium is available as a calcium salt of chloride or gluconate or acetate. The main difference between these formulations is the amount of elemental

Table 63.4 Commonly used intravenous calcium preparations

PREPARATION	DOSAGE	ELEMENTAL CALCIUM/GRAM
Calcium gluconate	10 mL	93 mg (2.3 mmol)
Calcium chloride	10 mL	272 mg (6.8 mmol)
Calcium acetate		253 mg (6.35 mmol)

Box 63.7 Indications for calcium administration

Absolute
Symptomatic hypocalcaemia
Ionised Ca <0.8 mmol/L
Hyperkalaemia
Ca channel blocker overdose
Relative
Beta-blocker overdose
Hypermagnesaemia
Hypocalcaemia in the face of high inotrope requirement
Massive blood transfusion post cardiopulmonary bypass to augment cardiac contractility

calcium available at equivalent volumes of drug (Table 63.4). The dose of calcium required should be based on the elemental calcium.[18] Intravenous calcium can be administered as a bolus or as an infusion. Rapid administration of calcium may cause nausea, flushing, headache and arrhythmias. Digitalis toxicity may be precipitated. Extravasation of calcium may lead to tissue irritation, particularly with the chloride salt. Calcium chloride may be better than calcium gluconate for the management of hypocalcaemia, if there is concomitant alkalosis. Following an initial bolus, an infusion may be commenced at a rate of 1–2 mg/kg/h of elemental calcium to maintain target levels of ionised calcium. With correction of the underlying disorder and restoration of calcium to normal levels, the infusion can be tapered and stopped. Adequacy of calcium therapy can be monitored clinically and by performing serial determinations of ionised calcium. Failure of ionised calcium to increase after commencement of IV calcium may indicate an underlying magnesium deficiency. This can be corrected by administration of 10 mmol of intravenous magnesium over 20 minutes. Administration of calcium in the setting of hyperphosphataemia may result in calcium precipitation in the tissues. In these situations, a phosphate binder may be administered. Calcium salts should not be administered with bicarbonate since the two precipitate. The other indications for calcium administration are listed in Box 63.7. Other therapy for hypocalcaemia consists of oral calcium supplements and calcitriol administration, although these are usually used in the management of chronic hypocalcaemia.

ASSOCIATION BETWEEN IONISED CALCIUM CONCENTRATION AND OUTCOME IN CRITICAL ILLNESS

A recent retrospective study examined the association between serum ionised calcium and mortality in a heterogeneous cohort of critically ill patients.[19] Data from greater than 7000 patients generating greater than 175,000 iCa measurements were analysed. The investigators concluded that within a broad range of values, ionised calcium concentration has no independent association with hospital or ICU mortality. However, from multivariate logistic regression analysis, an ionised calcium less than 0.8 mmol/L or an ionised calcium greater than 1.4 mmol/L were independently associated with ICU and hospital mortality. In patients requiring massive blood transfusion, another study reported a concentration dependent effect of hypocalcaemia on mortality.[20]

DIRECTIONS FOR FUTURE RESEARCH

VITAMIN D SUPPLEMENTATION IN CRITICAL ILLNESS

The traditional role of vitamin D has been thought to be the maintenance of adequate serum calcium and phosphate levels, for bone mineralisation and optimal cardiac and skeletal muscle function. Over the past decade, data from biochemical and molecular genetic studies indicate that vitamin D has a much wider range of effects than this traditional role. This is due to the activation to 1,25-dihydroxy-vitamin D in many tissues (in addition to the known activation in the kidneys) by tissue 1-alpha-hydroxylase and the action of this activated form on target tissue mediated by binding to vitamin D binding receptors, which are now known to exist on a myriad of tissues. These non-skeletal effects, termed pleiotropic, include potentiation of antimicrobial action, modification of inflammation, cardioprotective effects and immunomodulatory effects. Several large observational studies have demonstrated an association between increased morbidity and mortality and lower vitamin D levels as measured by serum 25-hydroxy-vitamin D in critically ill patients. On the other hand, there are data to suggest that a single measurement of vitamin D may not be reflective of the 24 hours profile in critically ill patients owing to the marked variability.[27,44] Moreover, there are also data to suggest that 1,25 dihydroxy-vitamin D levels may be increased during the inflammatory response. Both enteral and parenteral supplementation in critically ill patients are feasible and safe.[45] Currently, the existing data are insufficient to make an evidence-based recommendation regarding its potential benefit in the ICU.[34] A single-centre randomised trial of supplementation vitamin D deficient patients did not show a difference in the primary end point (hospital length of stay) but did report a significantly reduced mortality in severely

deficient patients.[46] Results from large prospective randomised controlled trials are lacking.

NEWER DRUGS FOR THE MANAGEMENT OF HYPERCALCAEMIA

Denosumab, a monoclonal antibody that binds to the receptor activator of nuclear factor κB ligand (RANKL), is used to prevent bone resorption in patients with skeletal metastases. Early studies show promise in the management of malignancy-related hypercalcaemia, refractory to bisphosphonates.[47] These agents may have utility in the management of hypercalcaemia in critically ill patients.

ELUCIDATING THE ROLE OF IONISED CALCIUM MEASUREMENTS IN THE INTENSIVE CARE UNIT

Perturbations of ionised calcium are common in critically ill patients. These are often thought to be an adaptive response to critical illness. Although measurement is routine on most contemporary blood gas analysers, utility is unproven. A randomised controlled trial of ionised calcium measurement and supplementation will inform clinical practice and guide therapy.

REFERENCES

1. Zaloga GP. Hypocalcemia in critically ill patients. *Crit Care Med*. 1992;20:251–262.
2. Vincent JL, Jankowski S. Why should ionized calcium be determined in acutely ill patients? *Acta Anaesthesiol Scand Suppl*. 1995;107:281–286.
3. Bourdeau J, Attie M. Calcium metabolism. In: Narins R, ed. *Clinical Disorders of Fluid and Electrolyte Metabolism*. 5th ed. New York: McGraw-Hill; 1994: 243–250.
4. Holick M, Krane S, Potts J. Calcium, phosphorus and bone metabolism: calcium-regulating hormones. In: Fauci AS, ed. *Principles of Internal Medicine*. New York: McGraw Hill; 1998.
5. Baird GS. Ionized calcium. *Clin Chim Acta*. 2011;412: 696–701.
6. Watchko J, Bifano EM, Bergstrom WH. Effect of hyperventilation on total calcium, ionized calcium, and serum phosphorus in neonates. *Crit Care Med*. 1984;12:1055–1056.
7. Zaloga GP, Chernow B, Cook D, et al. Assessment of calcium homeostasis in the critically ill surgical patient. The diagnostic pitfalls of the McLean-Hastings nomogram. *Ann Surg*. 1985;202: 587–594.
8. Toffaletti J. Physiology and regulation. Ionized calcium, magnesium and lactate measurements in critical care settings. *Am J Clin Pathol*. 1995;104: S88–S94.
9. Landt M, Hortin GL, Smith CH, et al. Interference in ionized calcium measurements by heparin salts. *Clin Chem*. 1994;40:565–570.
10. Sachs C, Rabouine P, Chaneac M, et al. In vitro evaluation of a heparinized blood sampler for ionized calcium measurement. *Ann Clin Biochem*. 1991;28:240–244.
11. Toffaletti J, Abrams B. Effects of in vivo and in vitro production of lactic acid on ionized, protein-bound, and complex-bound calcium in blood. *Clin Chem*. 1989;35:935–938.
12. Zaloga GP, Willey S, Tomasic P, et al. Free fatty acids alter calcium binding: a cause for misinterpretation of serum calcium values and hypocalcemia in critical illness. *J Clin Endocrinol Metab*. 1987;64:1010–1014.
13. Aggarwal R, Upadhyay M, Deorari AK, et al. Hypocalcemia in the newborn. *Indian J Pediatr*. 2001;68:973–975.
14. Forster J, Querusio L, Burchard KW, et al. Hypercalcemia in critically ill surgical patients. *Ann Surg*. 1985;202:512–518.
15. Lind L, Ljunghall S. Critical care hypercalcemia – a hyperparathyroid state. *Exp Clin Endocrinol*. 1992; 100:148–151.
16. Lemmer JH Jr, Kirsh MM. Coronary artery spasm following coronary artery surgery. *Ann Thorac Surg*. 1988;46:108–115.
17. Zaloga GP, Sager A, Black KW, et al. Low dose calcium administration increases mortality during septic peritonitis in rats. *Circ Shock*. 1992;37:226–229.
18. Stratta P, Soragna G, Morellini V, et al. The patient whose hypocalcaemia worsened after prompt intravenous calcium replacement therapy. *Lancet*. 2006;367:273.
19. Egi M, Kim I, Nichol A, et al. Ionized calcium concentration and outcome in critical illness. *Crit Care Med*. 2011;39:314–321.
20. Ho KM, Leonard AD. Concentration-dependent effect of hypocalcaemia on mortality of patients with critical bleeding requiring massive transfusion: a cohort study. *Anaesth Intensive Care*. 2011;39: 46–54.
21. Kallas M, Green F, Hewison M, et al. Rare causes of calcitriol-mediated hypercalcemia: a case report and literature review. *J Clin Endocrinol Metab*. 2010; 95:3111–3117.
22. Sharma OP. Hypercalcemia in granulomatous disorders: a clinical review. *Curr Opin Pulm Med*. 2000; 6:442–447.
23. Howard MR, Ashwell S, Bond LR, et al. Artefactual serum hyperkalaemia and hypercalcaemia in essential thrombocythaemia. *J Clin Pathol*. 2000;53: 105–109.
24. Massagli TL, Cardenas DD. Immobilization hypercalcemia treatment with pamidronate disodium after spinal cord injury. *Arch Phys Med Rehabil*. 1999;80:998–1000.
25. Sato Y, Fujimatsu Y, Kikuyama M, et al. Influence of immobilization on bone mass and bone metabolism in hemiplegic elderly patients with a long-standing stroke. *J Neurol Sci*. 1998;156:205–210.
26. Kedlaya D, Brandstater ME, Lee JK. Immobilization hypercalcemia in incomplete paraplegia: successful treatment with pamidronate. *Arch Phys Med Rehabil*. 1998;79:222–225.
27. Venkatesh B, Davidson B, Robinson K, et al. Do random estimations of vitamin D3 and parathyroid

hormone reflect the 24-h profile in the critically ill? *Intensive Care Med*. 2012;38:177–179.
28. Zaloga GP. Calcium homeostasis in the critically ill patient. *Magnesium*. 1989;8:190–200.
29. McMullan AD, Burns J, Paterson CR. Venepuncture for calcium assays: should we still avoid the tourniquet? *Postgrad Med J*. 1990;66:547–548.
30. Sam R, Vaseemuddin M, Siddique A, et al. Hypercalcemia in patients in the burn intensive care unit. *J Burn Care Res*. 2007;28:742–746.
31. Miell J, Wassif W, McGregor A, et al. Life-threatening hypercalcaemia in association with Addisonian crisis. *Postgrad Med J*. 1991;67:770–772.
32. Vasikaran SD, Tallis GA, Braund WJ. Secondary hypoadrenalism presenting with hypercalcaemia. *Clin Endocrinol (Oxf)*. 1994;41:261–264.
33. Jacobs TP, Bilezikian JP. Clinical review: rare causes of hypercalcemia. *J Clin Endocrinol Metab*. 2005; 90:6316–6322.
34. Amrein K, Venkatesh B. Vitamin D and the critically ill patient. *Curr Opin Clin Nutr Metab Care*. 2012;15:188–193.
35. Peacock M, Bilezikian JP, Bolognese MA, et al. Cinacalcet HCl reduces hypercalcemia in primary hyperparathyroidism across a wide spectrum of disease severity. *J Clin Endocrinol Metab*. 2011;96: E9–E18.
36. Steddon SJ, Cunningham J. Calcimimetics and calcilytics – fooling the calcium receptor. *Lancet*. 2005;365:2237–2239.
37. Zaloga GP, Chernow B. The multifactorial basis for hypocalcemia during sepsis. Studies of the parathyroid hormone-vitamin D axis. *Ann Intern Med*. 1987;107:36–41.
38. Desai TK, Carlson RW, Geheb MA. Prevalence and clinical implications of hypocalcemia in acutely ill patients in a medical intensive care setting. *Am J Med*. 1988;84:209–214.
39. Brown JJ, Hynes MR, Wible JH Jr. Measurement of serum calcium concentration after administration of four gadolinium-based contrast agents to human volunteers. *AJR Am J Roentgenol*. 2007;189: 1539–1544.
40. Chernow B. Calcium: does it have a therapeutic role in sepsis? *Crit Care Med*. 1990;18:895–896.
41. Desai TK, Carlson RW, Thill-Baharozian M, et al. A direct relationship between ionized calcium and arterial pressure among patients in an intensive care unit. *Crit Care Med*. 1988;16:578–582.
42. Broner CW, Stidham GL, Westenkirchner DF, et al. Hypermagnesemia and hypocalcemia as predictors of high mortality in critically ill pediatric patients. *Crit Care Med*. 1990;18:921–928.
43. Cheung JY, Bonventre JV, Malis CD, et al. Calcium and ischemic injury. *N Engl J Med*. 1986;314:1670–1676.
44. Krishnan A, Ochola J, Mundy J, et al. Acute fluid shifts influence the assessment of serum vitamin D status in critically ill patients. *Crit Care*. 2010;14:R216.
45. Nair P, Venkatesh B, Lee P, et al. A randomized study of a single dose of intramuscular cholecalciferol in critically ill adults. *Crit Care Med*. 2015; 43(11):2313–2320.
46. Amrein K, Schnedl C, Holl A, et al. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. *JAMA*. 2014;312(15):1520–1530.
47. Diel IJ, Body JJ, Stopeck AT, et al. The role of denosumab in the prevention of hypercalcaemia of malignancy in cancer patients with metastatic bone disease. *Eur J Cancer*. 2015;51(11):1467–1475.

Part Nine
Obstetric Emergencies

This page intentionally left blank

64

Pre-eclampsia and eclampsia

Joey Ka Ming Wai, Tony Gin

Pre-eclampsia was defined previously as new onset of hypertension after 20 weeks' gestation, associated with proteinuria. However, the diagnosis can now be made without proteinuria, if there is evidence of maternal organ dysfunction, or uteroplacental dysfunction resulting in foetal growth restriction (Table 64.1).[1] Eclampsia describes the occurrence of seizures in a pre-eclamptic woman not attributable to other causes.

Pre-eclampsia presents with a spectrum of signs and symptoms, and it can quickly progress to a serious disease (now termed pre-eclampsia with severe features). Patients may be referred to the intensive care unit (ICU) for poorly controlled hypertension, management of complications such as convulsions, stroke, pulmonary oedema, hepatic failure, haemorrhage and coagulopathy, and for postpartum monitoring and care.

The worldwide estimates for pre-eclampsia and eclampsia are 4.6% and 1.4% respectively, with wide variation across regions, and highest in less resourced countries.[2] Although maternal mortality from pre-eclampsia is low and considered avoidable in developed countries, hypertensive diseases are still often one of the leading causes of maternal death. Mothers have nearly four times the odds of dying and eight times the odds of severe outcomes if they have pre-eclampsia, and over 40 times the odds of dying if they have eclampsia.[3] This translates to worldwide estimates of 50,000 maternal deaths per year from pre-eclampsia and eclampsia, as well as substantial foetal growth restriction, and perinatal morbidity and mortality.[4,5] Although pre-eclampsia resolves after delivery of the placenta, women will subsequently have approximately two to four times the risk for ischaemic heart disease and stroke, as well as renal disease, metabolic disorders and death.[6–8]

Many organisations have issued guidelines for the prevention, diagnosis and treatment of pre-eclampsia and other hypertensive disorders in pregnancy.[9–13]

AETIOLOGY

The exact cause of pre-eclampsia is unknown, although the placenta is necessary for the disease, and delivery of the placenta is curative. There are many risk factors for pre-eclampsia, including previous or family history of pre-eclampsia, primigravidae, multiple gestation, advanced maternal age, and pre-existing medical conditions (e.g. diabetes, obesity, renal disease, hypertension and autoimmune disorders).[14]

Although there is a genetic predisposition, no single gene has been implicated in the majority of women. Pre-eclampsia may be a result of cumulative effects of variants at multiple genes, both foetal and maternal.[15,16] Some investigators differentiate early onset (before 34 weeks' gestation) and late onset pre-eclampsia (at or after 34 weeks) because of differences in clinical features, biomarkers and outcomes.[17]

There have been many attempts to predict pre-eclampsia from risk factors, symptoms, signs and investigations, but none of the prediction models have been very accurate or widely validated.[18] Low-dose aspirin therapy is often given to slightly reduce the risk of developing the disease and other adverse pregnancy outcomes in those with one or two risk factors. Biomarkers may have some diagnostic or predictive value but this is still debated.[19,20] In the United States and United Kingdom, regular blood pressure monitoring is still the standard screening test for pre-eclampsia.

PATHOGENESIS

Pre-eclampsia is a systemic disease that affects most organ systems. Many theories of pathogenesis have been proposed, and the current predominant concept is that of a two-stage disease with an initial stage of abnormal placentation and placental ischaemia, followed by a second stage of clinical disease.[8] Initially, the normal endovascular invasion of foetal trophoblast into the maternal uterine spiral arteries is inadequate, with reduced remodelling and dilatation of the arteries, leading to placental hypoperfusion and hypoxia that becomes more severe as pregnancy progresses. This acts as a precipitating factor that leads to an imbalance of angiogenic and antiangiogenic factors and a generalised inflammatory response. The exact link between placental triggering and the systemic response is unknown, but there is placental release of inflammatory cytokines and circulating antiangiogenic factors such as soluble Fms-like tyrosine kinase-1 (sFlt1) and soluble endoglin (sEng), along with reduced concentrations of angiogenic factors such as vascular endothelial growth factor (VEGF) and placental

ABSTRACT

Pre-eclampsia is now defined as new onset hypertension after 20 weeks' gestation with either proteinuria, maternal organ dysfunction, or foetal growth restriction. Pre-eclampsia with severe features requires rapid control of hypertension, prophylaxis against seizures with magnesium, and organ support as required before urgent delivery. Major complications include eclampsia, intracranial haemorrhage, stroke, pulmonary oedema, hepatic failure and coagulation abnormalities. Echocardiography is useful for cardiovascular and fluid management. If premature delivery is necessary, corticosteroids are given to promote foetal lung maturation. Complications may still occur after delivery and patients should be actively monitored and managed for at least another 24 hours. Although pre-eclampsia resolves after delivery of the placenta, women will subsequently have approximately two to four times the risk for ischaemic heart disease and stroke, as well as diabetes and death.

KEYWORDS

Pre-eclampsia
eclampsia
pregnancy
hypertension
proteinuria
placenta
magnesium
haemolysis
HELLP
postpartum

Table 64.1 Basic diagnostic criteria for pre-eclampsia

Hypertension (after 20 weeks' gestation)	Systolic arterial pressure >140 mm Hg *or* Diastolic arterial pressure >90 mm Hg
And one or more of the following new-onset conditions	
1. Proteinuria	Protein ≥300 mg in a 24-hour collection Protein/creatinine ratio ≥30 mg/mmol spot urine or positive dipstick 1+
2. Any maternal organ dysfunction	
Renal	Creatinine ≥0.09 mmol/L
Hepatic	Severe epigastric or right-upper-quadrant pain Elevated transaminases
Neurological	Convulsions (eclampsia) Altered mental state Persistent severe headaches Visual disturbances, blindness, papilloedema Hyperreflexia and clonus
Haematological	Thrombocytopenia Disseminated intravascular coagulation Haemolysis
Cardiorespiratory	Pulmonary oedema
3. Uteroplacental dysfunction	Fetal growth restriction

growth factor (PIGF). All this leads to diffuse endothelial dysfunction with an increase in sensitivity to vasoactive substances, a decrease in endothelial synthesis of vasodilator substances such as prostaglandin and nitric oxide, activation of platelets and coagulation, and an increase in capillary permeability. This then causes widespread vasoconstriction, fluid extravasation, proteinuria, decreased intravascular volume, haemoconcentration and decreased organ perfusion. PIGF and sFlt are being evaluated as diagnostic and prognostic biomarkers, and one experimental therapeutic strategy is to restore the balance of these angiogenic and antiangiogenic factors.

CLINICAL PRESENTATION

Pre-eclampsia is a syndrome with a spectrum of presentations. Although hypertension is the cardinal sign, some women present with convulsions, headache or abdominal pain, and there may be severe features without a marked increase in blood pressure. Rarely, cocaine intoxication and phaeochromocytoma may be confused with pre-eclampsia.

Haemodynamic changes of pre-eclampsia are hypertension, increased systemic vascular resistance and decreased intravascular volume. Cardiac output is often decreased, usually secondary to changes in preload and afterload rather than contractility.[21] Sympathetic activation occurs, and this may account for observations of increased cardiac output in the early stage.[22] Early onset and late onset pre-eclampsia appear to have different patterns of cardiovascular change.[23] Common echocardiographic findings are increased left ventricular mass, increased peripheral resistance, diastolic dysfunction and variable change in cardiac output.[24]

Pulmonary oedema may occur, especially after delivery, because of iatrogenic fluid overload, decreased left ventricular function, increased capillary permeability and narrowing of the colloid osmotic–pulmonary capillary wedge pressure (PCWP) gradient. Sudden ventricular tachycardia may occur during hypertensive crises.

Neurological symptoms include headache, visual changes, hyperreflexia, eclamptic convulsions, cerebral oedema and stroke. Intracranial haemorrhage is an important cause of death. Posterior reversible encephalopathy syndrome has been recognized as a primary event in eclampsia.[25]

Renal changes include reduced glomerular filtration rate due to reduced renal plasma flow and filtration coefficient. These features, together with proteinuria, are associated with the characteristic lesion of glomeruloendotheliosis. Hyperuricaemia is associated with increased prenatal risk, particularly if serum uric acid concentration rises rapidly.

Haemostatic abnormalities include thrombocytopenia, which may be associated with decreased platelet function. Associated coagulation abnormalities may occur but are unlikely unless the platelet count is less than $100{,}000 \times 10^9$/L.[26,27]

Hepatic complications include liver oedema, hepatocellular necrosis, periportal and subcapsular haemorrhage, hepatic infarcts and rupture. Patients with HELLP syndrome (see later in the chapter) are particularly at risk.

The leading causes of maternal death in pre-eclampsia/eclampsia are intracranial haemorrhage, pulmonary oedema and hepatic complications. Foetal morbidity results from placental insufficiency, prematurity and abruptio placentae.

MANAGEMENT OF PRE-ECLAMPSIA

The definitive curative treatment of pre-eclampsia is delivery of the placenta and foetus.

Table 64.2 Management in pre-eclampsia

General measures	Keep patient in lateral position Stress ulcer prophylaxis Deep vein thrombosis (DVT) prophylaxis
Maternal monitoring	Intra-arterial blood pressure monitoring in severe cases Sp_{O_2}, urine output, intake-output chart Consider central venous catheter or cardiac output monitoring
Investigations	Complete blood count, renal function and electrolytes Urate Liver function test Clotting profile Blood group matching Urinalysis
Foetal monitoring	Continuous foetal heart monitoring Other options as assessed by obstetricians: ultrasound, amniotic fluid index (AFI), umbilical artery Doppler
Magnesium sulphate	
Prophylaxis and treatment of eclampsia	Intravenous: Loading dose 4–6 g over 10–15 min Maintenance 1–2 g/h Intramuscular: 4 g every 4 h
For recurrent eclampsia	A further intravenous loading dose of 2–4 g over 10 min May increase maintenance up to 2 g/h
Antihypertensive therapy	Acute treatment if systolic blood pressure (SBP) > 160 mm Hg or diastolic blood pressure (DBP) > 110 mm Hg Control of blood pressure should be gradual and sustained while preserving maternal organ perfusion and placental perfusion
Liaison with obstetricians regarding timing of delivery	Antenatal steroid if gestation <34 weeks

The principles of management include:

- Timely delivery of the placenta and foetus.
- Supportive care before delivery, and during the immediate postpartum period, focusing on:
  - control of blood pressure,
  - prevention of seizures with magnesium sulphate,
  - maintenance of placental perfusion,
  - prevention of complications
  - monitoring of foetal well-being.

The management for pre-eclampsia is summarized in Table 64.2.

The main factors affecting timing of delivery are gestational age and severity of disease at time of diagnosis. In general, delivery is indicated when pre-eclampsia with severe features is diagnosed after 34 weeks of gestation. Before 34 weeks' gestation, prematurity is a major cause of neonatal morbidity, and expectant management with corticosteroid to promote foetal lung maturation may be decided. After delivery, severe cases should preferably be managed in an ICU for 24–72 hours.

ANTIHYPERTENSIVE THERAPY

The aim of antihypertensive therapy is to prevent maternal complications (intracerebral haemorrhage, cardiac failure and abruptio placentae) while maintaining placental blood flow. Hypertension is a marker and not a causal factor in pre-eclampsia. Controlling hypertension reduces the risk of complications, but it does not ameliorate the underlying pathological process. Acute treatment is indicated when blood pressure is greater than 160 mm Hg systolic or 105–110 mm Hg diastolic.[28] Reduction of systolic pressure is important for the prevention of stroke.[29] Initially, systolic blood pressure should be reduced by about 20–30 mm Hg and diastolic pressure by 10–15 mm Hg while monitoring the foetus, with the goal of achieving an initial range of 140–150/90–100 mm Hg. Concomitant plasma expansion reduces the risk of sudden hypotension when vasodilators are used. Recommended antihypertensive drugs for acute treatment are summarised in Table 64.3. The most commonly used drugs are labetalol intravenous (IV), hydralazine IV and oral nifedipine; insufficient data are available to show which of these is superior.[30]

If hypertension is refractory to conventional treatment, sodium nitroprusside (initial dose 0.25 µg/kg per minute, maximum dose 5 µg/kg per minute) can be used to reduce blood pressure rapidly in a hypertensive emergency but care should be taken in patients with depleted intravascular volume and duration

Table 64.3 Emergency drug treatment of hypertension in pre-eclampsia

DRUG	DOSAGE GUIDE	MECHANISM OF ACTION	NOTES
Labetalol	Bolus 20–40 mg IV every 10–15 min to maximum dose of 300 mg Infusion 1–2 mg/min, reducing to 0.5 mg/min or less after blood pressure is controlled	Non selective beta-adrenergic receptor block with alpha$_1$-blocking effect	Reduces blood pressure without decrease in uteroplacental flow[29] Crosses placenta, but neonatal hypoglycaemia and bradycardia is rarely seen Need foetal heart monitoring Should not be given to patients with asthma or myocardial dysfunction
Hydralazine	Bolus 5 mg IV followed with 5–10 mg every 20 min to maximum of 20 mg	Direct arteriolar vasodilator	Slow onset of action of 10–20 min but may cause sudden hypotension Consider concomitant fluid bolus (<250 mL) Adverse effects include headache, tachycardia, tremor, nausea, rarely neonatal thrombocytopenia
Nifedipine	Oral route is preferred, 10 mg, repeat after 20 min as required (sublingual route may cause sudden hypotension)	Calcium channel blocker	Cause uterine muscle relaxation that may increase risk of postpartum haemorrhage Potentiation of neuromuscular block in patient receiving magnesium sulphate

should be limited to less than 4 hours to avoid foetal cyanide poisoning. Nitroglycerine infusion (initial dose 5 µg/min, maximum dose 100 µg/min) may be useful in cases complicated by pulmonary oedema.

ANTICONVULSANT THERAPY

Anticonvulsants are used to prevent recurrent convulsions in eclampsia or to prevent initial convulsions in pre-eclampsia. Magnesium sulphate should be used as first-line treatment for prophylaxis and treatment of eclamptic seizures, and for prophylaxis of seizures in severe pre-eclampsia. The Magpie trial conducted in 33 countries showed that women in the magnesium group had a 58% (95% confidence interval [CI], 40%–71%) lower risk of eclampsia and probably lower maternal mortality.[31] Magnesium was more cost-effective in developing countries where pre-eclampsia is a more significant problem.[32] However, the benefits of using magnesium in mild pre-eclampsia are still debated, especially in developed countries.

The mechanism of action of magnesium for preventing eclamptic seizures is uncertain. Although abnormal electroencephalograms are frequent in pre-eclampsia and eclampsia, they are not altered by magnesium sulphate. Magnesium may reduce cerebral vasospasm via antagonism of calcium at membrane channels or intracellular sites. Magnesium amplifies release of prostacyclin by vascular endothelium, and this may inhibit platelet aggregation and vasoconstriction. Doppler ultrasonography suggests that magnesium vasodilates smaller-diameter intracranial blood vessels, and some of its effects may be from relieving cerebral ischaemia. The anticonvulsant activity of magnesium may be mediated by blockade or suppression of *N*-methyl-D-aspartate (NMDA) receptors. Magnesium has tocolytic effects, mild general vasodilator and antihypertensive actions, and increases renal and uterine blood flow.

Guidelines for administration of magnesium sulphate are summarised in Table 64.2. The kidney rapidly excretes magnesium. The half-life in patients with normal renal function is 4 hours and 90% of the dose is excreted by 24 hours after the infusion.[33] When there is renal impairment or oliguria, the dose should be reduced and serum concentration should be monitored. Suggested target serum concentration for severe pre-eclampsia is 2–3.5 mmol/L (4–7 mEq/L or 4.8–8.4 mg/dL). Magnesium toxicity is associated with muscle weakness and may lead to respiratory paralysis (>7.5 mmol/L). Increased conduction time with increased PR and QT intervals and QRS duration can lead to sinoatrial and atrioventricular block (>7.5 mmol/L) and cardiac arrest in diastole (>12.5 mmol/L). Toxicity is unlikely when deep tendon reflexes are present (the upper limb should be used during epidural analgesia). Magnesium toxicity can be treated with small IV doses of calcium gluconate and enhanced clearance with renal replacement therapy when it is associated with renal failure. Other reported adverse effects of magnesium include death from overdose, increased bleeding, slowed cervical dilatation and increased risk of pulmonary oedema. Magnesium crosses the placenta and can cause neonatal flaccidity and respiratory depression.

If repeated seizures occur despite therapeutic levels of magnesium, conventional anticonvulsants can be considered, but it is important to exclude other causes of convulsions. Although benzodiazepines and phenytoin are inferior to magnesium for preventing eclamptic seizures, these agents may be considered when magnesium

sulphate is contraindicated (e.g. renal failure, muscle weakness, allergy). Diazepam 5–10 mg IV, lorazepam 2–4 mg IV, and midazolam 1–2 mg IV have all been used depending on the desired duration of effect. Phenytoin is given as an initial IV loading dose of 10 mg/kg followed 2 hours later by 5 mg/kg. Doses are diluted in normal saline and given no faster than 50 mg/min. Electrocardiogram and arterial pressure should be monitored. Maintenance doses of 200 mg orally or intravenously are started 12 hours after the second bolus and given 8-hourly. However, there is no consensus on the optimal dosing regimen. Monitoring of phenytoin level is necessary to avoid toxicity.

ECLAMPSIA

With modern obstetric care, eclampsia may present without marked preceding hypertension or proteinuria, and up to 40% of cases occur postpartum, often more than 48 hours after delivery.[34,35] Priorities in the management of eclamptic seizures are airway protection, oxygenation, and termination and prevention of seizures. Delivery of the foetus should be arranged after maternal stabilisation. Patients should be placed in the left lateral position and given oxygen. Magnesium should be given if not already started. A further loading dose of $MgSO_4$ 2 g can be given if patient is already on magnesium therapy (see Table 64.2). Approximately 10% of eclamptic patients will have a recurrent seizure despite receiving magnesium. Prolonged seizures can be terminated by diazepam 5–10 mg intravenously. If seizures are refractory, thiopental and suxamethonium should be given and the airway secured. Eclampsia is not the only cause of seizure during pregnancy. Recurrent convulsions or prolonged unconsciousness may indicate additional cerebral pathology (e.g. cerebral oedema, intracerebral haemorrhage, cerebral venous thrombosis) and an urgent computed tomographic (CT) scan should be done whenever possible.

FLUID BALANCE

Pre-eclamptic patients usually have reduced circulating intravascular volume. There may also be a significant decrease in blood pressure upon initiation of antihypertensive therapy, particularly with hydralazine. However, the effectiveness of fluid loading is uncertain,[36] and there is a risk of pulmonary oedema so restrictive management is recommended. Oliguria is common in patients with pre-eclampsia, but this does not necessarily imply volume depletion. Fluid challenge should be considered for treatment of oliguria only when there are other signs of hypovolaemia. Renal failure in pre-eclampsia is uncommon. Some patients may require a period of continuous renal replacement therapy but the majority of cases recover. The risk of irreversible renal damage is greater when there is associated abruptio placentae, disseminated intravascular coagulation (DIC), hypotensive shock or sepsis.

Low-dose dopamine (3 μg/kg per minute) infusions have not been shown to improve renal outcome and are no longer recommended.[37] Furosemide should not be used to treat oliguria without pulmonary oedema because this may exacerbate the fluid-depleted state.

Pulmonary oedema is managed with oxygen therapy, positive end-expiratory pressure with or without ventilation, inotropes, vasodilators, morphine or diuretics as required.

CARDIOVASCULAR MONITORING

There is controversy over the effectiveness of central venous pressure (CVP) and PCWP for assisting fluid management. Optimal CVP and PCWP values are unknown, but the response to fluid challenge may be useful. Pulmonary artery catheterisation placement carries inherent risks and should only be considered when there are clear indications (e.g. refractory hypertension, pulmonary oedema, severe cardiac disease and refractory oliguria), and the obtained data will be used to guide decision making.[38]

Echocardiography has been increasingly recognised as a non-invasive tool to assess ventricular function and fluid responsiveness. Pregnant women already have an increased cardiac output, reduced peripheral vascular resistance and increased heart rate. In women with untreated pre-eclampsia, diastolic dysfunction with preserved ventricular systolic function is a common finding.[24] Although doctors may not feel confident about interpreting findings in pregnant and pre-eclamptic women, the usual focused assessments of ventricular dilatation, ejection fraction, and left-ventricular end-diastolic pressure can still be used to assist in the diagnosis and management of pulmonary oedema, heart failure and chest pain.[39] The response to straight leg raising may also be used to guide fluid responsiveness.

POSTPARTUM CARE

Patients are frequently referred to an ICU for postpartum care, particularly after caesarean delivery. Pre-eclampsia may persist or even develop postpartum.[40] The risk of pulmonary oedema is greatest after delivery. After delivery, there may be an initial improvement with a relapse in the first 24 hours. Magnesium should be continued for 24 hours after delivery or the last seizure. Antihypertensive drugs may be reduced according to the blood pressure. Psychological support is important, especially if there has been an adverse neonatal outcome. Full recovery from the organ dysfunction of pre-eclampsia is normally expected within 6 weeks. However, patients are more likely to develop pre-eclampsia in subsequent pregnancies, and have double the risk of early cardiovascular disease and mortality.[6–8]

HELLP SYNDROME AND HEPATIC COMPLICATIONS

HELLP is a syndrome characterised by *h*aemolysis (microangiopathic haemolytic anaemia), *e*levated *l*iver enzymes and *l*ow *p*latelets, although exact criteria vary and there is debate over whether it is a severe form of pre-eclampsia or a separate disorder.[41] The pathogenesis of HELLP is similar to that of early onset pre-eclampsia, but biomarker derangements are more severe.[42] Typically, HELLP syndrome presents at early gestational ages and is more common in white and multiparous women. In about 30% of cases, it first presents in the postpartum period, sometimes with no evidence of pre-eclampsia before delivery.

Many patients have non-specific signs such as right-upper-quadrant or epigastric pain, nausea, malaise or headache. Although most patients will have hypertension and proteinuria, these can be mild or absent. Important differential diagnoses include idiopathic thrombocytopenic purpura, systemic lupus erythematosus, thrombotic thrombocytopenic purpura, haemolytic–uraemic syndrome, and acute fatty liver of pregnancy. Complications of HELLP syndrome include DIC, abruptio placentae, acute renal failure, pulmonary oedema, severe ascites, pleural effusion, acute respiratory distress syndrome (ARDS), sepsis and stroke. Hepatic complications include segmental hepatic infarction, parenchymal haemorrhage, and subcapsular haematoma with or without rupture. If these are suspected, urgent CT scan should be performed. Hepatic artery embolisation has been successful in stable patients, but hepatic rupture is a surgical emergency requiring operative treatment ranging from packing to transplantation.

Patients with HELLP are treated aggressively, similarly to pre-eclampsia, with an emphasis on stabilisation and rapid delivery.[43] Dexamethasone is not usually given for maternal reasons because there is no difference in maternal or perinatal death, and no evidence of significant maternal benefit.[44] Platelet transfusions may be required for active bleeding or before caesarean delivery.

After delivery, patients usually show a continuing deterioration in platelet count and liver enzymes, with a peak in severity 24–48 hours after delivery followed by gradual resolution and complete recovery if complications are avoided.

ANAESTHESIA AND ANALGESIA

Platelet count and coagulation tests should be checked before regional anaesthesia. Epidural analgesia in labour reduces fluctuations in arterial pressure and improves placental blood flow.[45] For caesarean delivery, regional anaesthesia avoids the risks of aspiration, difficult intubation from airway oedema, exaggerated hypertensive response to intubation and magnesium-induced sensitivity to muscle relaxants associated with general anaesthesia.

If general anaesthesia is required, smaller-size endotracheal tubes may be required. The hypertensive response to intubation should be attenuated with drugs such as fentanyl (2.5 µg/kg), alfentanil (10 µg/kg), magnesium sulphate (40 mg/kg), a combination of alfentanil (7.5 µg/kg) with magnesium sulphate (30 mg/kg), or remifentanil (1 µg/kg). Occasionally, awake intubation under topical anaesthesia may be necessary when there is airway obstruction.

REFERENCES

1. Tranquilli AL, Dekker G, Magee L, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. *Pregnancy Hypertens*. 2014; 4(2):97–104.
2. Abalos E, Cuesta C, Grosso AL, et al. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol*. 2013;170(1):1–7.
3. Abalos E, Cuesta C, Carroli G, et al. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on maternal and newborn health. *BJOG*. 2014; 121(suppl 1):14–24.
4. Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol*. 2009;33:130–137.
5. Ghulmiyyah L, Sibai B. Maternal mortality from preeclampsia/eclampsia. *Semin Perinatol*. 2012;36: 56–59.
6. Wu P, Haththotuwa R, Kwok CS, et al. Pre-eclampsia and future cardiovascular health: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2017;10(2):pii:e003497.
7. Thellen LH, Fraser A, Hollimgshaus MS, et al. All-cause and cause-specific mortality after hypertensive disease of pregnancy. *Obstet Gynecol*. 2016;128(2): 238–244.
8. Jim B, Karumanchi SA. Pathogenesis, prevention and long-term complications. *Semin Nephrol*. 2017;37(4): 386–397.
9. World Health Organization. *WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia*. 2011. http://apps.who.int/iris/bitstream/10665/44703/1/9789241548335_eng.pdf.
10. International Federation of Gynecology and Obstetrics (FIGO). *The FIGO textbook of pregnancy hypertension – An evidence-based guide to monitoring, prevention and management*. 2016. http://www.glowm.com/pdf/NEW-Pregnancy_Hypertension-Final.pdf.
11. National Institute for Health and Clinical Excellence (NICE). *Hypertension in pregnancy: diagnosis and management. Clinical Guideline 107*. August 2010, updated January 2011. https://www.nice.org.uk/guidance/cg107.

12. American College of Obstetricians and Gynecologists. *Hypertensive disorders of pregnancy*. 2013. https://www.acog.org/Resources-And-Publications/Task-Force-and-Work-Group-Reports/Hypertension-in-Pregnancy.
13. Society of Obstetric Medicine of Australia and New Zealand. *The SOMANZ guideline for the management of hypertensive disorders of pregnancy*. 2014. https://www.somanz.org/documents/HTPregnancyGuidelineJuly2014.pdf.
14. Bartsch E, Medcalf KE, Park AL, et al. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. *BMJ*. 2016;353:i1753.
15. Staines-Urias E, Paez MC, Doyle P, et al. Genetic association studies in pre-eclampsia: systematic meta-analyses and filed synopsis. *Int J Epidemiol*. 2012;41:1764–1765.
16. Haram K, Mortensen JH, Nagy B. Genetic aspects of preeclampsia and the HELLP syndrome. *J Pregnancy*. 2014;2014:910751.
17. Raymond D, Peterson E. A critical review of early-onset and late-onset preeclampsia. *Obstet Gynecol Surv*. 2011;66:497–506.
18. Mol BW, Roberts CT, Thangaratinam S, et al. Pre-eclampsia. *Lancet*. 2016;387(10022):999–1011.
19. Nissaisorakarn P, Sharif S, Jim B. Hypertension in pregnancy: defining blood pressure goals and the value of biomarkers for preeclampsia. *Curr Cardiol Rep*. 2016;18:131.
20. Herraiz I, Llurba E, Verlohren S, et al. Update on the diagnosis and prognosis of preeclampsia with the aid of the sFlt-1/PlGF Ratio in singleton pregnancies. *Fetal Diagn Ther*. 2017;doi:10.1159/000477903.
21. Lang RM, Pridjian G, Feldman T, et al. Left ventricular mechanics in preeclampsia. *Am Heart J*. 1991;121:1768–1775.
22. Easterling TR. The maternal hemodynamics of preeclampsia. *Clin Obstet Gynecol*. 1992;35:375–386.
23. Valensise H, Vasapollo B, Gagliardi G, et al. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. *Hypertension*. 2008;52:873–880.
24. Castleman JS, Ganapathy R, Taki F, et al. Echocardiographic structure and function in hypertensive disorders of pregnancy. A systematic review. *Circ Cardiovasc Imaging*. 2016;9:e004888.
25. Postma IR, Slager S, Kremer HP, et al. Long-term consequences of the posterior reversible encephalopathy syndrome in eclampsia and preeclampsia: a review of the obstetric and nonobstetric literature. *Obstet Gynecol Surv*. 2014;69:287–300.
26. Leduc L, Wheeler JM, Kirshon B, et al. Coagulation profile in severe preeclampsia. *Obstet Gynecol*. 1992;79:14–18.
27. Sharma SK, Philip J, Whitten CW, et al. Assessment of changes in coagulation in parturients with preeclampsia using thromboelastography. *Anesthesiology*. 1999;90:385–390.
28. American College of Obstetricians and Gynecologists. Committee Opinion No. 692. 2017 Apr. Emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period. *Obstet Gynecol*. 2017;129:e90–e95.
29. Crovetto F, Somigliana E, Peguero A, et al. Stroke during pregnancy and pre-eclampsia. *Curr Opin Obstet Gynecol*. 2013;25(6):425–432.
30. Duley L, Meher S, Jones L. Drugs for treatment of very high blood pressure during pregnancy. *Cochrane Database Syst Rev*. 2013;(7):CD001449.
31. Magpie Trial Collaborative Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet*. 2002;359:1877–1890.
32. Simon J, Gray A, Duley L, et al. Cost-effectiveness of prophylactic magnesium sulphate for 9996 women with pre-eclampsia from 33 countries: economic evaluation of the Magpie Trial. *Br J Obstet Gynaecol*. 2006;113:144–151.
33. Lu JF, Nightingale CH. Magnesium sulfate in eclampsia and pre-eclampsia: pharmacokinetic principles. *Clin Pharmacokinet*. 2000;38:305–314.
34. Chames MC, Livingston JC, Ivester TS, et al. Late postpartum eclampsia: a preventable disease? *Am J Obstet Gynecol*. 2002;186:1174–1177.
35. Sibai BM. Diagnosis, prevention, and management of eclampsia. *Obstet Gynecol*. 2005;105:402–410.
36. Duley L, Williams J, Henderson-Smart DJ. Plasma volume expansion for treatment of pre-eclampsia. *Cochrane Database Syst Rev*. 2000;(2):CD001805.
37. Steyn DW, Steyn P. Low-dose dopamine for women with severe pre-eclampsia. *Cochrane Database Syst Rev*. 2007;(1):CD003515.
38. Clark SL, Cotton DB. Clinical indications for pulmonary artery catheterization in the patient with severe preeclampsia. *Am J Obstet Gynecol*. 1988;158:453–458.
39. Dennis AT. Transthoracic echocardiography in women with preeclampsia. *Curr Opin Anesthesiol*. 2015;28:254–260.
40. Sibai BM. Etiology and management of postpartum hypertension-preeclampsia. *Am J Ostet Gynecol*. 2012;206:470–475.
41. Aloizos S, Seretis C, Liakos N, et al. HELLP syndrome: understanding and management of a pregnancy-specific disease. *J Obstet Gynaecol*. 2013;34(4):331–337.
42. Abildgaard U, Heimdal K. Pathogenesis of the syndrome of hemolysis, elevated liver enzymes, and low platelet count (HELLP): a review. *Eur J Obstet Gynecol Reprod Biol*. 2013;166(2):117–123.
43. Haram K, Svendsen E, Abildgaard U. The HELLP syndrome: clinical issues and management. A review. *BMC Pregnancy Childbirth*. 2009;9:8.
44. Woudstra DM, Chandra S, Hofmeyr GJ, et al. Corticosteroids for HELLP. *Cochrane Database Syst Rev*. 2010;(9):CD008148.
45. Jouppila P, Jouppila R, Hollmén A, et al. Lumbar epidural analgesia to improve intervillous blood flow during labor in severe preeclampsia. *Obstet Gynecol*. 1982;59:158–161.

65

Obstetric emergencies

Winnie TP Wan, Tony Gin

The intensive care unit (ICU) will receive obstetric patients with the usual range of medical and surgical emergencies, and provide supportive care for patients who suffer specific obstetric complications. The pattern of admission varies widely among countries with different standards of obstetric care. A prospective cohort study in the Netherlands reported the incidence of ICU admission to be 2.4 per 1000 deliveries.[1] The most common reasons for admission were major obstetric haemorrhage, hypertensive disorders of pregnancy and sepsis. In Maryland in the United States, from 1999 to 2009 the ICU utilisation was 4.2 per 1000 deliveries, with hypertensive disorders, haemorrhage and cardiac diseases being the most common.[2] The recent Confidential Enquiries report from 2009 to 2014 in the United Kingdom reported an overall maternal mortality rate of 8.5 per 100,000 maternities, with the commonest cause of direct death being thrombosis and thromboembolism, and of indirect death being cardiovascular disease.[3] Over half of the mothers that die will spend some time in an ICU, and many die there. Overall, however, maternal outcomes are better than expected, and severity of illness scoring systems such as Acute Physiology and Chronic Health Evaluation (APACHE) II and Simplified Acute Physiology Score (SAPS) II overestimate mortality. The Mortality Prediction Model (MPM) II may be useful as it relies less on physiological and laboratory variables that are altered by pregnancy.[4]

The Confidential Enquiries report highlighted the need for early consultation by obstetricians to intensivists. Several obstetric early warning scores are in development to improve patient management and triage.[5] As serious emergencies are rare, and management can be different from non-pregnant patients, it is also useful to conduct simulation training for obstetric, emergency room, resuscitation, operating theatre, anaesthetic and critical care staff with a special focus on emergencies in pregnant patients.

PATHOPHYSIOLOGY[6]

Two important points to recognise in treating obstetric patients are:

1. During pregnancy, the normal ranges for physiological variables change (Table 65.1). This may modify the presentation of the problem, variables used to guide treatment, and the response to treatment. The majority of physiological changes revert to normal several days after delivery.
2. Both mother and foetus are affected by the pathology and subsequent treatment.

AIRWAY AND VENTILATION[7,8]

Several factors may complicate tracheal intubation in pregnancy:

- altered anatomy in pregnancy predisposes to a potentially difficult airway
- oedematous tissues
- delayed gastric emptying
- increased oxygen consumption.

Intensivists must be familiar with the difficult airway algorithm in obstetrics and the use of the laryngeal mask airway. Avoidance of intubation and the use of non-invasive ventilation may be a good option. Lung protective ventilation with low tidal volumes, and positive end-expiratory pressure are applicable in pregnant patients, but airway pressures may need to be higher because of decreased compliance, and permissive hypercapnia more limited ($PaCO_2$ <45 mm Hg) to prevent foetal acidosis.

CIRCULATION

Tachycardia, low blood pressure, increased cardiac output and warm peripheries are normal in late pregnancy. After 20 weeks' gestation, aortocaval compression by the gravid uterus can decrease uterine perfusion and venous return to the heart. This is best prevented by using the full left-lateral position, but a left-lateral tilt or manual displacement of the uterus may be more practicable.

Haemodynamic support should start with good hydration, and assessment should take into account the altered cardiovascular variables in pregnancy. Transthoracic echocardiography is especially useful for diagnosis and monitoring.[9] The uterine vascular

ABSTRACT

The management of obstetric emergencies is influenced by the need to consider that both the mother and foetus are affected by the emergency and the subsequent treatment. During pregnancy, maternal physiological variables change, and this can affect endpoints used to guide therapy. Transthoracic echocardiography is often very useful for diagnosis and monitoring of cardiac function and fluid status. Cardiopulmonary resuscitation should prioritize adequate chest compression, and preparation for emergency caesarean delivery if there is no return of circulation within 4 minutes. In acute respiratory failure, lung protective ventilation strategies are modified because hypercapnia is detrimental to the foetus. In severe postpartum haemorrhage, tranexamic acid should be given as early as possible and a Massive Transfusion Protocol in place to guide therapy. All staff involved in obstetric emergencies should have simulation training to prepare them for these diverse but infrequent emergencies where timely appropriate management is essential.

KEYWORDS

Pregnancy
cardiopulmonary resuscitation
trauma
burns
sepsis
venous thromboembolism
amniotic fluid embolism
acute respiratory failure
ovarian hyperstimulation syndrome

Table 65.1 Changes in physiological variables during pregnancy

PARAMETER	NON-PREGNANT	FIRST TRIMESTER	SECOND TRIMESTER	THIRD TRIMESTER
CARDIOVASCULAR				
SBP (mm Hg)	110 (14.63 kPa)		100 (–8%)	105 (–5%)
MAP (mm Hg)	90 (11.97 kPa)			85 (–5%)
DAP (mm Hg)	60 (7.98 kPa)		50 (–12%)	50 (–12%)
CVP (mm Hg)	4 (0.53 kPa)			4 (no change)
PCWP (mm Hg)	6 (0.8 kPa)			6 (no change)
HR (b.p.m.)	75	82 (+10%)	82 (+10%)	90 (+25%)
SV (mL)	65	80 (+20%)	85 (+30%)	82 (25%)
CO (L)	5	6.5 (+30%)	7 (+50%)	7 (+50%)
SVR (dyn cm/s^{-5})	1530			1210 (–20%)
PVR (dyn cm/s^{-5})	119			78 (–30%)
Total blood vol (L)	3.2	3.5 (+10%)	4.1 (+30%)	4.6 (+45%)
Haematocrit				–33%
Plasma albumin (g/L)	35			30
Oncotic pressure (mm Hg)	28 (3.72 kPa)			25 (–3–0.4 kPa)
RESPIRATORY				
pH	7.40	7.44	7.44	7.44
$PaCO_2$ (mm Hg)	40 (5.32 kPa)	30	30	30
Pa_{O_2} (mm Hg)	100 (13.3 kPa)	107	105	103
HCO_3 (mmol/L)	24	21	20	20
TV (mL)	500			700 (+40%)
RR (breath/min)	15			17 (+15%)
MV (mL/min)	7500			10,500 (+40%)
FRC (mL)	2800			2300 (–20%)
VC (mL)	3500			3500 (no change)
IC (mL)	2200			2500 (+15%)
ERV (mL)	1300			1100 (–20%)
RV (mL)	1500			1200 (–20%)
TLC (mL)	5000			4800 (–5%)
O_2 consumption (mL/min)	250			300 (+20%)

CO, Cardiac output; *CVP*, central venous pressure; *DBP*, diastolic arterial pressure; *ERV*, expiratory reserve volume; *FRC*, functional residual capacity; *HR*, heart rate; *IC*, inspiratory capacity; *MAP*, mean arterial pressure; *MV*, minute volume; *PCWP*, pulmonary capillary wedge pressure; *PVR*, pulmonary vascular resistance; *RR*, respiratory rate; *RV*, residual volume; *SBP*, systolic arterial pressure; *SV*, stroke volume; *SVR*, systemic vascular resistance; *TLC*, total lung capacity; *TV*, tidal volume; *VC*, vital capacity.

bed is considered maximally dilated but is still responsive to stimuli that cause vasoconstriction, such as circulating catecholamines. Ephedrine has traditionally been the vasoconstrictor used in obstetrics because it was thought to preserve uterine blood flow better than pure alpha agonists. However, alpha agonists, such as phenylephrine, are more effective and not associated with foetal acidosis when used to manage hypotension during caesarean delivery.[10] There is no evidence favouring any particular inotrope.

COAGULATION

Pregnancy is associated with at least a fivefold increase in thromboembolism, and patients should be given thromboembolic prophylaxis, typically with unfractionated heparin or low-molecular-weight heparin (LMWH) and elastic compression stockings.

MOTHER AND FOETUS

In the critically ill it is important to monitor the foetus because of the problems associated with:

- premature labour
- the placental transfer of drugs
- maintenance of placental perfusion and oxygenation.

An obstetric opinion should be sought as soon as possible regarding cardiotocography, ultrasound examination and timing of delivery. Foetal heart rate is usually a good indicator of placental perfusion. Nutrition is very important for the foetus and adequate maternal feeding should be started as soon as possible. Perineal and breast nursing care should not be neglected.

CARDIOPULMONARY RESUSCITATION[11,12]

Despite being younger than the usual cardiac arrest patients, pregnant patients have a poor survival rate. The obstetrician and neonatologist should be notified when the cardiac arrest call is activated, and preparations be made for perimortem caesarean delivery.

MODIFICATION OF CARDIOPULMONARY RESUSCITATION

Updated guidelines emphasise the importance of good-quality chest compression, and suggest rescuers consider starting cardiopulmonary resuscitation (CPR) with chest compression rather than ventilations (the sequence changes from 'ABC' to 'CAB').

After about 20 weeks' gestation, the gravid uterus can compress the inferior vena cava and impede venous return and cardiac output from CPR. Positioning for obstetric CPR should aim at relieving aortocaval compression and optimising the quality of chest compression. It can be done by manual left uterine displacement in the supine position first, either at the patient's left side with a two-handed technique, or at the patient's right side with a one-handed technique. Chest compression should be performed with a slightly higher hand position (slightly above the centre of the sternum). Airway management in pregnant patients is more difficult. Bag-mask ventilation with high-flow oxygen before intubation is especially important. Early tracheal intubation after cricoid pressure will facilitate ventilation and decrease the risk of acid aspiration. During advanced life support (ALS), drugs are given and defibrillation performed according to the normal protocols. Apical placement of the paddle may be difficult because of the position and breast enlargement, and adhesive defibrillation pads are preferred. Foetal or uterine monitors should be removed before defibrillation.

Both maternal and foetal survival from cardiac arrest depend on prompt caesarean delivery to relieve the effects of aortocaval compression. Resuscitation team leaders should activate the protocol for an emergency caesarean delivery as soon as cardiac arrest is identified in a pregnant woman with an obviously gravid uterus. Emergency caesarean section may be considered at 4 minutes after onset of maternal cardiac arrest if there is no return of spontaneous circulation.

POST-RESUSCITATION CARE

Therapeutic hypothermia has been shown to improve outcome in post-arrest adult patients. According to the ACLS 2015 guideline, targeted temperature management (32°C–34°C) should be considered in pregnant patients. The targeted temperature should follow the protocol for non-pregnant patients. Foetal monitoring should be continued during targeted temperature management.

TRAUMA[13,14]

The epidemiology of trauma in pregnant women varies considerably among countries.[15,16] Trauma complicates approximately 7% of pregnancies, but maternal morbidity and mortality are higher than similar injuries in non-pregnant women. Most injuries occur as the result of motor vehicle accidents, and other common causes are interpersonal violence, falls and suicide (usually postpartum). Fifty per cent of foetal loss occurs after what is usually considered 'minor' trauma.

Special considerations of trauma in obstetric patients include the potential for miscarriage, preterm rupture of membrane, placenta abruptio, inadequate uteroplacental blood flow, preterm labour, and foetal distress and demise. The gravid uterus displaces the bowel cephalad so visceral injuries are less common after lower abdominal injuries. The dilated pelvic vasculature increases the risk of retroperitoneal haemorrhage following pelvic injuries. Head injuries and haemorrhagic shock account for most maternal deaths, whereas placental abruption and maternal death are the most frequent causes of foetal death.

PRIMARY AND SECONDARY SURVEY

Initial resuscitation should follow the normal plan of attention to airway, breathing and circulation. Unless a spinal injury is suspected, the pregnant patient should be transported and examined in the left-lateral tilt position or with manual left uterine displacement. Blood volume is increased during pregnancy and

hypotension may not be evident until 35% or more of total blood volume is lost. Uterine blood flow is not autoregulated and may be decreased despite normal maternal haemodynamics, so that slight overhydration may be preferred to underhydration. Excessive resuscitation with crystalloids or non-blood colloids may increase the mortality from severe haemorrhage. Continuous foetal heart rate monitoring should be used.

In trauma assessment the increased significance of pelvic fractures in terms of uterine injury and retroperitoneal haemorrhage should be considered.

- Ultrasound is the investigation of choice.
- Diagnostic peritoneal lavage, if performed, should be through an open surgical incision above the fundus.
- Chest drains are placed slightly higher than normal, in the third or fourth intercostal space.
- It is important to exclude herniation of abdominal contents through a ruptured diaphragm.
- Vaginal examination to look for either leak of amniotic fluid and/or vaginal bleeding is vital.

Necessary radiological investigations should be performed as indicated as the radiation hazard to the foetus is very small, except in the early first trimester when exposure to more than 50–100 mGy is a cause for concern. A chest X-ray delivers less than 5 mGy to the lungs and very little to the shielded abdomen. The foetal radiation dose from abdominal examinations can range from 1 mGy for a plain film up to 20–50 mGy for an abdominal pelvic computed tomography (CT) with fluoroscopy.[17]

DEFINITIVE CARE

Cardiotocographic monitoring is essential, but there is wide variation in practice and recommended duration of monitoring. Premature labour and placental abruption may not be diagnosed unless regular monitoring is continued for at least 6 hours and even 24 hours if indicated. Rh immune globulin 300 µg should be considered for all Rh D-negative within 72 hours of injury to prevent future Rh alloimmunisation of the newborn. The Kleihauer–Betke test can be used to detect foetal blood in the maternal circulation and give an estimate of the volume of foeto-maternal haemorrhage.

BURNS[18,19]

Approximately 7% of women of reproductive age are seen for treatment for major burns. Although the women are usually young and healthy, pregnancy is already a hypermetabolic state and the foetus is at great risk from many complications. Factors influencing morbidity and mortality include the depth and size of burn wound, the underlying health and age of the pregnant women, the estimated gestational age of the foetus, associated inhalational injury, and significant secondary complications. Preterm labour and stillbirth are more likely in the first few days after the burn injury. The presumed pathogenesis is due to the high levels of prostaglandins and maternal acidosis.

SPECIAL CONSIDERATIONS IN PREGNANT BURN PATIENTS

FLUID RESUSCITATION

Replacement of fluid loss from burns must keep in mind the normally increased circulating volume of pregnancy. Pregnant burn patients usually require significantly more fluid to maintain haemodynamic stability. Pregnancy affects the total body surface area as the abdomen increases in size. The Lund–Browder chart is still the commonly used method for burn area estimation.

DEFINITIVE BURN CARE

Topical povidone-iodine solution should be avoided because the iodine may be absorbed and affect foetal thyroid function. Inhalational injuries with hypoxia and carbon monoxide are especially detrimental to the foetus because carbon monoxide has a greater affinity and longer half-life when it is bound to foetal haemoglobin.

SEVERE OBSTETRIC HAEMORRHAGE

Obstetric haemorrhage accounts for 27% of all maternal deaths.[20] The aim of management is rapid restoration of circulating volume, correct coagulopathy and remedy of the underlying cause of haemorrhage. There should be a Massive Transfusion Protocol activated at the appropriate time to aid timely and optimal transfusion of blood products.

Antepartum haemorrhage is defined as bleeding from the genital tract after 24 weeks of gestation. Its incidence is 2%–5% of all pregnancies. The common causes are placenta praevia and placental abruption; both are ultimately managed by delivery. In placenta praevia, the placenta implants in advance of the presenting part and classically presents as painless bleeding during the second or third trimester. Placenta praevia is relatively common (1 in 200 pregnancies) but severe haemorrhage is relatively rare. In placental abruption, a normally implanted placenta separates from the uterine wall. The incidence of placental abruption is low (0.5%–2%) but perinatal mortality may be as high as 50%. In concealed abruption, vaginal bleeding can be absent and several litres of blood may be concealed in the uterus.

Postpartum haemorrhage is most commonly due to uterine atony and abnormal placentation, with retained tissues, trauma to the genital tract and coagulopathy as other causes. In an emergency, the aorta can

be compressed against the vertebral column by a fist pressed on the abdomen above the umbilicus.

Uterine atony is managed initially with bimanual compression, uterine massage and drugs that include[21]:

- *oxytocin:* 5 units slow intravenous injection, or infusion (40 units in 500 mL Ringer lactate solution at 125 mL/h)
- *ergonovine (ergometrine):* 0.5 mg slow intravenous or intramuscular injection (contraindicated in patients with hypertension)
- *carboprost:* 250 µg intramuscular injection, repeated at intervals of not less than 15 minutes to a maximum of 8 doses (contraindicated in patients with asthma) or 500 µg direct intramyometrial injection
- *misoprostol:* 1000 µg rectally.

If bleeding persists, tamponade techniques using gauze packs or balloons can be useful.

In severe postpartum haemorrhage, as well as activating the Massive Transfusion Protocol, tranexamic acid should be given as early as possible. The large WOMAN trial of over 20,000 women found that tranexamic acid 1 g reduced death due to bleeding with no adverse effects, and it should be given as soon as possible after the onset of bleeding.[22]

Specific invasive management – such as angiographic arterial embolisation, laparotomy for uterine haemostatic suturing techniques such as B-lynch and multiple square sutures, surgical bilateral uterine artery ligation, or definitive hysterectomy – may be required. Recombinant factor VIIa has been used but should be given as part of a research protocol. The initial dose is 90 µg/kg, and a second dose can be given 20–60 minutes later if there is no response.

For patients with known and suspected risk factors for postpartum haemorrhage, prophylactic interventional radiology can be employed. Balloons are placed in the internal iliac or uterine arteries before delivery, and are inflated to occlude the vessels in the event of postpartum haemorrhage.[23]

Disseminated intravascular coagulation still develops in 10%–30% of cases, partly because tissue thromboplastin is released during abruption.

SEPSIS AND SEPTIC SHOCK[24,25]

Maternal sepsis and septic shock are relatively uncommon but increasing, with rates of approximately 10 cases per 10,000 deliveries. Sepsis should always be considered because the underlying physiological changes in pregnancy and the response to labour can confound the presentation of sepsis and make its diagnosis difficult. Delays in recognition and management have been noted in 70% of cases. The total Sequential Organ Failure Assessment (SOFA) score performs well in obstetric patients.[26]

The most common sources of infection are chorioamnionitis, postpartum endometritis, urinary tract infections, pyelonephritis and septic abortion. Animal studies suggest that pregnancy increases the susceptibility to endotoxin, and that metabolic acidosis and cardiovascular collapse occur earlier.

Management of septic shock follows the same guidelines as for the non-pregnant population, with initial resuscitation, source control and prompt antibiotics. Vasopressors may reduce placental perfusion so the foetal heart rate should be monitored. Norepinephrine is still the first-line drug of choice. It has been used to maintain blood pressure during caesarean delivery without foetal effects.[27] Gram-negative organisms are the frequent causative organisms, but streptococci and *Bacteroides* may also be present. Antimicrobial therapy is dependent on hospital prevalence and susceptibility patterns; empirical broad-spectrum therapy should be started early. Typical combinations are ampicillin, gentamicin and clindamycin, or carbapenem and vancomycin. Tetracyclines and quinolones should not be used in pregnancy.

VENOUS THROMBOEMBOLISM[28,29]

The incidence of venous thromboembolism (VTE) ranges from 0.5 to 2 episodes per 1000 deliveries, which is a 5- to 10-fold increase in risk compared with those reported in non-pregnant women of comparable age. Pulmonary thromboembolism is a common cause of maternal death, accounting for 15%–25% of maternal mortality. Major international guidelines for the management of VTE in pregnancy have slight differences.[29]

Pregnancy is associated with increased risk of VTE because of:

- venous stasis
- hypercoagulable state
- vascular injury associated with delivery.

Accurate diagnosis of VTE is crucial because of the long-term implications for therapy. Symptoms of dyspnoea or pain in the leg or chest require accurate diagnosis, especially in the immediate postpartum period. Although contrast venography is the gold-standard test for diagnosing deep-vein thrombosis, the radiation exposure and invasive nature of the test mean that compression ultrasonography is the usual first choice. D-dimer testing is not recommended in some guidelines because D-dimer values normally increase throughout pregnancy. Venography, perfusion lung scanning, pulmonary angiography and helical CT scan should not be avoided if indicated.

TREATMENT OF VTE DURING PREGNANCY[29]

Treatment is either subcutaneous LMWH or intravenous unfractionated heparin. LMWH has gradually

replaced unfractionated heparin, based on the results of large trials in non-pregnant patients showing that LMWHs are at least as safe and effective as unfractionated heparin. In addition, the risk of heparin-induced thrombocytopenia and osteoporosis appears lower with LMWH than unfractionated heparin. The need for dose adjustments in proportion to change in weight over the course of pregnancy remains controversial. Full-dose anticoagulation should be continued during pregnancy. Subcutaneous LMWH can be discontinued 24–36 hours before, and intravenous unfractionated heparin 4–6 hours before elective induction of labour or caesarean section. A temporary retrievable venous filter can be inserted and removed postpartum. LMWH or unfractionated heparin should be restarted in the postpartum patient for at least 6–12 weeks. Neuraxial anaesthesia should not be used on patients with full anticoagulation.

With life-threatening massive pulmonary embolus, surgical treatment or thrombolysis must be considered. Thrombolysis obviously carries the risk of maternal and foetal haemorrhagic complications. No controlled trials are feasible and outcome data must be extracted from case reports. A review found that thrombolytic therapy was associated with a low maternal mortality rate of 1%, with a 6% rate of foetal loss and a 6% rate of premature delivery.[30] The foetal risks appear to be lower than that obtained with surgical intervention in pregnant patients, and maternal risks lower than reported risks for surgery, thrombolysis or transvenous filters in non-pregnant patients. Although heparin remains the treatment of choice, guidelines suggest that thrombolysis may be considered when there is limb- or life-threatening thromboembolism.

AMNIOTIC FLUID EMBOLISM[31]

Amniotic fluid embolism (AFE) has signs and symptoms in common with other obstetric emergencies and it is a diagnosis of exclusion, so the true incidence and mortality rates are uncertain. The incidence of AFE has been reported as 1 in 13,000 deliveries in the United States, and 1 in 50,000 deliveries in the United Kingdom. The maternal mortality rate in developed countries ranges from 20% to 60%.

PATHOPHYSIOLOGY

The pathophysiology of AFE remains uncertain. Traditionally, it was thought that amniotic fluid and foetal debris entered the maternal circulation by forceful uterine contraction and caused embolic effects. However, recent studies show that foetal cells are commonly found in the maternal circulation, and that AFE has more in common with anaphylaxis and septic shock than other embolic diseases. The term 'anaphylactoid syndrome of pregnancy' has been proposed but the condition is still commonly referred to as AFE. The exact trigger is unknown. There is an abnormal maternal immune response to foetal antigen exposure, and inflammatory mediators cause pulmonary vasoconstriction, complement activation and coagulopathy.

CLINICAL PRESENTATION

AFE is a clinical diagnosis. Classically, patients present with severe hypoxia, hypotension or sudden cardiovascular collapse, and coagulopathy during labour, but AFE may occur earlier during pregnancy, during delivery or in the early puerperium. There is no gold standard test for diagnosis, although biomarkers, such as the insulin-like growth factor-binding protein-1, have been proposed.

Animal studies indicate that AFE causes a biphasic haemodynamic response. The early phase probably lasts less than half an hour and is characterised by severe hypoxia and right heart failure as a result of pulmonary hypertension from vasoconstriction or vessel damage. Patients who survive this first phase develop left ventricular failure with the return of normal right ventricular function. Left ventricular failure may be a result of the initial hypoxia or the depressant effects of mediators. Disseminated intravascular coagulation is present in most patients. It could be caused by a specific activator of factor X, tissue factor or other substances, such as trophoblasts, in the amniotic fluid.

TREATMENT

Treatment is supportive. Invasive monitoring and echocardiography are useful to evaluate the effects of haemodynamic support. Survivors of AFE regain normal cardiorespiratory function but may have neurological sequelae.

ACUTE RESPIRATORY FAILURE[32]

Pregnant women should receive medication for optimal asthma control. There is no evidence that appropriate use of inhaled glucocorticosteroids, beta agonists and leukotriene modifiers is associated with increased incidence of foetal abnormalities. In contrast, there is a substantial risk of preterm delivery posed by poorly controlled maternal asthma.[33] Acute exacerbation should also be treated aggressively with systemic glucocorticosteroids when necessary.

Pulmonary oedema is more likely in the pregnant patient (1:1000 pregnancies) because of the increased cardiac output and blood volume, and the decreased plasma oncotic pressure. The principles of treatment are relatively straightforward in terms of determining the cause of the oedema and improving oxygenation, although it can be difficult to distinguish between hydrostatic and permeability oedema.

The prevalence of acute respiratory distress syndrome (ARDS) during pregnancy has been estimated at 16–70 cases per 100,000 pregnancies, with mortality rates from 23% to 50%.[34] Important causes of ARDS in pregnancy are sepsis, aspiration and pre-eclampsia. Non-invasive positive-pressure ventilation has not been evaluated for treatment of hypoxaemic respiratory failure in pregnancy. Clinical criteria for intubation are similar to those in non-pregnant patients, but arterial blood gases must be interpreted carefully because of the underlying respiratory alkalosis in pregnancy. The ARDS Network lung protective strategy can be adopted in pregnant patients by using the non-pregnant predicted body weight and gestational age-appropriate blood gas targets. Permissive hypercapnia may cause foetal respiratory acidosis that will reduce the ability of foetal haemoglobin to bind oxygen. Furthermore, the transfer of CO_2 across the placenta requires a gradient of 10 mm Hg (1.33 kPa). Therefore, $PaCO_2$ should probably be kept below 45 mm Hg (6.0 kPa) and Pa_{O_2} above 70 mm Hg (9.3 kPa). If conventional ventilation fails, the effectiveness of alternative strategies, such as prone ventilation and extracorporeal membrane oxygenation (ECMO), have only been reported in case studies. Although ECMO has been effective in pregnant patients with severe ARDS from influenza H1N1, a review of the topic was more cautious in its overall recommendation.[35]

ACID ASPIRATION (MENDELSON SYNDROME)

Obstetric patients are at increased risk of acid aspiration because of decreased gastric emptying, increased gastric acidity and volume, and increased intra-abdominal pressure. Aspiration of acidic material will cause acute lung injury, the severity being related to the amount, content and acidity of the aspirate.

The initial presentation is hypoxaemia and bronchospasm. Chemical pneumonitis and increased permeability pulmonary oedema develop over several hours.

Treatment includes standard respiratory support. Rigid bronchoscopy may be required to remove large food particles. Bronchoalveolar lavage and steroids are not useful and antibiotics should only be given for proven infection.

TOCOLYTIC THERAPY AND PULMONARY OEDEMA[36]

Pulmonary oedema is an uncommon (1 in 400 pregnancies) but serious complication of tocolytic therapy, especially with beta-adrenergic agonists. The underlying mechanism for pulmonary oedema is unclear, but it is probably related to fluid overload and the cardiovascular effects of beta-adrenergic agonists leading to increased pulmonary capillary hydrostatic pressure. The initial management of pulmonary oedema is discontinuation of the tocolytic and oxygen therapy, with further monitoring, diuretics and respiratory support as necessary. Pulmonary oedema is less common but can occur with other tocolytics such as nifedipine and nicardipine.

PERIPARTUM CARDIOMYOPATHY[37]

Peripartum cardiomyopathy (PPCM) is characterised by a new onset of heart failure between the late third trimester of pregnancy and 6 months postpartum in previously healthy women. Diagnosis requires echocardiographic evidence of left ventricular dysfunction (ejection fraction <45%). The incidence varies from 1:1000 to 1:10,000 pregnancies and is significantly higher in Afro-Caribbean women. PPCM often presents as acute heart failure. The echocardiogram usually shows features of dilated cardiomyopathy.

The exact aetiology of PPCM remains controversial with possible causes including angiogenic imbalance, genetic factors, volume overload, inflammatory, autoimmune and hormonal imbalance. Treatment is largely supportive with diuretics, inotropes and non-invasive positive-pressure ventilation. Intra-aortic balloon pump and left ventricular assist device may be used in severe cases. Bromocriptine therapy is used but is controversial and based on animal studies where the prolactin blockade prevented PPCM.

OVARIAN HYPERSTIMULATION SYNDROME[38,39]

Ovarian hyperstimulation syndrome (OHSS) is a rare iatrogenic complication of ovarian stimulation, which usually occurs during the luteal phase or early part of pregnancy. The prevalence of severe OHSS is low, at 0.5%–5% of stimulated ovarian cycles, but it has become more recognised owing to the increasing number of women undergoing assisted reproductive techniques.

The exact aetiology and pathogenesis of OHSS remain uncertain. It appears that exogenous or endogenous human chorionic gonadotropin (hCG) is the central triggering factor. The stimulated ovaries become markedly enlarged with the overproduction of ovarian hormones and vasoactive substances, including cytokines, angiotensin and vascular endothelial growth factor (VEGF). As a result, the capillary permeability increases leading to hypovolaemia with haemoconcentration, oedema and accumulation of fluid in the abdomen and pleural spaces.

OHSS can be classified as mild, moderate, severe or critical. Critical OHSS patients may have oliguria, renal failure, tense ascites, hydrothorax, thromboembolism, pericardial effusion, liver derangement, ovarian torsion, cerebral oedema and ARDS.

The treatment of OHSS is supportive until the condition resolves. In most cases, the syndrome follows a self-limiting course that parallels the decline in serum

hCG level. Abdominal and pleural tapping is needed to release the accumulated fluid. Albumin can be used as a plasma expander. Prophylaxis for thromboembolism with an anticoagulant should be given, and surgical intervention may be necessary for ovarian torsion.

REFERENCES

1. Zwart JJ, Dupuis JR, Richters A, et al. Obstetric intensive care unit admission: a 2-year nationwide population-based cohort study. *Intensive Care Med*. 2010;36(2):256–263.
2. Wanderer JP, Leffert LR, Mhyre JM, et al. Epidemiology of obstetric-related intensive care unit admissions in Maryland: 1999-2008. *Crit Care Med*. 2013;41(8):1844–1852.
3. Knight M, Nair M, Tuffnell D, et al., eds. *Saving Lives, Improving Mothers' Care – Surveillance of Maternal Deaths in the UK 2012-14 and Lessons Learned to Inform Maternity Care From the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009-14*. Oxford, UK: National Perinatal Epidemiology Unit, University of Oxford; 2016.
4. Lapinsky SE. Severe illness in pregnancy. *Crit Care Med*. 2014;42(5):1284–1285.
5. Carle C, Alexander P, Column M, et al. Design and internal validation of an obstetric early warning score: secondary analysis of the Intensive Care National Audit and Research Centre Case Mix Programme database. *Anaesthesia*. 2013;68:354–367.
6. Chamberlain G, Broughton-Pipkin F. *Clinical Physiology in Obstetrics*. 3rd ed. Oxford, UK: Blackwell Science; 1998.
7. Mushambi MC, Kinsella SM, Popat M, et al. Obstetric Anaesthetists' Association and Difficult Airway Society guidelines for the management of difficult and failed tracheal intubation in obstetrics. *Anaesthesia*. 2015;70:1286–1306.
8. Ende H, Varelmann D. Respiratory considerations including airway and ventilation issues in critical care obstetric patients. *Obstet Gynecol Clin North Am*. 2016;43:699–708.
9. Dennis AT. Transthoracic echocardiography in obstetric anaesthesia and obstetric critical illness. *Int J Obstet Anesth*. 2011;20(2):160–168.
10. Ngan Kee WD. Prevention of maternal hypotension after regional anaesthesia for caesarean section. *Curr Opin Anaesthesiol*. 2010;23(3):304–309.
11. Truhlar A, Deakin CD, Soar J, et al. European Resuscitation Council Guidelines for Resuscitation 2015. Section 4. Cardiac arrest in special circumstances. *Resuscitation*. 2015;95:148–201.
12. Jeejeebhoy FM, Zelop CM, Lipman S, et al. Cardiac arrest in pregnancy: a scientific statement from the American Heart Association. *Circulation*. 2015;132(18):1747–1773.
13. Pearce C, Martin SR. Trauma and considerations unique to pregnancy. *Obstet Gynecol Clin North Am*. 2016;43:791–808.
14. Oxford CM, Ludmir J. Trauma in pregnancy. *Clin Obstet Gynecol*. 2009;52(4):611–629.
15. Battaloglu E, McDonnell D, Chu J, et al. Epidemiology and outcomes of pregnancy and obstetric complications in trauma in the United Kingdom. *Injury*. 2016;47(1):184–187.
16. Deshpande NA, Kucirka LM, Smith RN, et al. Pregnant trauma victims experience nearly 2-fold higher mortality compared to their nonpregnant counterparts. *Am J Obstet Gynecol*. 2017;217(5):590.e1–590.e9.
17. Goldman SM, Wagner LK. Radiological management of abdominal trauma in pregnancy. *AJR Am J Roentgenol*. 1996;166:763–767.
18. Parikh P, Sunesara I, Lutz E, et al. Burns during pregnancy: implications for maternal-perinatal providers and guidelines for practice. *Obstet Gynecol Surv*. 2015;70(10):633–643.
19. Kennedy BB, Baird SM, Troiano NH. Burn injuries and pregnancy. *J Perinat Neonatal Nurs*. 2008;22(1):21–30.
20. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health*. 2014;2(6):e323–e333.
21. Mavrides E, Allard S, Chandraharan E, et al. Prevention and management of postpartum haemorrhage. *BJOG*. 2016;124:e106–e149.
22. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality hysterectomy and other morbidities in women with post-partum haemorrhage (WOMAN): an international randomized, double-blind, placebo-controlled trial. *Lancet*. 2017;389:2105–2116.
23. Royal College of Obstetricians and Gynaecologists. The Role of Emergency and Elective Interventional Radiology in *Postpartum Haemorrhage (Good Practice No. 6)*. 2007. Available from: http://www.rcog.org.uk.
24. Barton JR, Sibai BM. Severe sepsis and septic shock in pregnancy. *Obstet Gynecol*. 2012;120:689–706.
25. Plante LA. Management of sepsis and septic shock for the obstetrician–gynecologist. *Obstet Gynecol Clin North Am*. 2016;43:659–678.
26. Jain S, Guleria K, Suneja A, et al. Use of the Sequential Organ Failure Assessment score for evaluating outcome among obstetric patients admitted to the intensive care unit. *Int J Gynaecol Obstet*. 2016;132(3):332–336.
27. Ngan Kee WD, Lee SW, Ng FF, et al. Randomized double-blinded comparison of norepinephrine and phenylephrine for maintenance of blood pressure during spinal anesthesia for cesarean delivery. *Anesthesiology*. 2015;122(4):736–745.
28. Stone SE, Morris TA. Pulmonary embolism during and after pregnancy: maternal and fetal issues. *Crit Care Med*. 2005;33(suppl 10):S294–S300.
29. Bates SM, Middeldorp S, Rodgrs M, et al. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. *J Thromb Thrombolysis*. 2016;41:92–128.
30. Ahearn GS, Hadjiliadas D, Govert JA, et al. Massive pulmonary embolism during pregnancy successfully treated with recombinant tissue

plasminogen activator: a case report and review of treatment options. *Arch Intern Med*. 2002;162(11): 1221–1227.
31. Shamshirsaz AA, Clark SL. Amniotic fluid embolism. *Obstet Gynecol Clin North Am*. 2016;43: 779–790.
32. Lapinsky SE. Acute respiratory failure in pregnancy. *Obstet Med*. 2015;8(3):126–132.
33. Bakhireva LN, Schatz M, Jones KL, et al. Asthma control during pregnancy and the risk of preterm delivery or impaired fetal growth. *Ann Allergy Asthma Immunol*. 2008;101:137–143.
34. Cole DE, Taylor TL, McCullough DM, et al. Acute respiratory distress syndrome in pregnancy. *Crit Care Med*. 2005;33(suppl 10):S269–S278.
35. Saad AF, Rahman M, Maybauer DM, et al. Extracorporeal membrane oxygenation in pregnant and postpartum women with H1N1-related acute respiratory distress syndrome. A systematic review and meta-analysis. *Obstet Gynecol*. 2016;127(2): 241–247.
36. Lamont RF. The pathophysiology of pulmonary oedema with the use of beta-agonists. *BJOG*. 2000;107(4):439–444.
37. Patel PA, Roy A, Javid R, et al. A contemporary review of peripartum cardiomyopathy. *Clin Med*. 2017;17(4):316–321.
38. Practice Committee of the American Society for Reproductive Medicine. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. *Fertil Steril*. 2016;106:1634–1667.
39. Royal College of Obstetricians and Gynaecologists. *Green-top guideline no. 5. The management of ovarian hyperstimulation syndrome*; February 2016. https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg_5_ohss.pdf.

66

Severe cardiac disease in pregnancy

Alice Green, Steve M Yentis, Jeremy P Campbell

INTRODUCTION

Cardiac disease is now the leading cause of maternal mortality in the developed world. It is estimated to be present in 0.2%–4% of pregnancies,[1–4] and this figure is increasing as more women with congenital heart disease (CHD) reach childbearing age.[5] In addition, advancing maternal age and co-morbidities such as diabetes, obesity and hypertension all increase the risk of acquired cardiovascular disease in pregnancy.[1,6]

With early diagnosis and management, many women with cardiac conditions can deliver safely; however, some conditions are associated with significant morbidity and mortality. Cardiac disease remains the largest single cause of maternal death in the United Kingdom.[7] Of the women who died from a cardiac condition in the period 2009–2014, 47 (31%) were classified as sudden adult death syndrome (SADS), 34 (22%) were classed as ischaemic deaths, 27 (18%) had myocardial disease/cardiomyopathy, 21 (14%) had an aortic dissection, 11 (7%) had valvular heart disease, 6 (4%) had essential hypertension, and 7 (5%) had other cardiac conditions.[7]

Most cardiac mortality occurs in women with structurally normal hearts who were not known to have heart disease before pregnancy; only 17% of women who died between 2009–2014 were known to have pre-existing cardiac problems.[2,7] It is therefore important to identify women at risk of heart disease and to be aware of the presentation and management of cardiac disease in pregnancy.[2,6]

PHYSIOLOGY AND PATHOPHYSIOLOGY

Pregnancy places a high physiological demand on the cardiovascular system. Blood volume increases by 50%, starting as early as the sixth week, rising rapidly to mid-pregnancy, then rising at a slower rate.[1] Red cell mass increases at a slower rate, resulting in a physiological anaemia. Cardiac output increases by 50%, as a combination of early increased stroke volume and increased heart rate in the third trimester. Pregnancy may therefore be poorly tolerated if this increase is limited by disease.[2] There is a reduction in systemic vascular resistance (SVR) and blood pressure falls during the first trimester, returning to pre-gestational levels before term.

Anxiety, pain and contractions during labour and delivery increase cardiac output, oxygen consumption (threefold) and blood pressure.[1] After delivery, there is a temporary increase in intracardiac pressures due to relief of caval compression and autotransfusion from the contracting uterus. This may cause a deterioration in susceptible patients and the risk can remain for several weeks after delivery.[2]

PRECONCEPTION

Preconception counselling should be offered to all women known to have heart disease and efforts should be made to prevent unwanted pregnancies.

The most common complications in those with pre-existing disease are arrhythmias, heart failure and thromboembolic events.[1] Patients with stenotic valvular lesions, pulmonary hypertension, mechanical heart valves, Eisenmenger syndrome and severe cardiomyopathies have the poorest outcomes and tolerate the haemodynamic changes of pregnancy, delivery, anaesthesia and surgery less than women with other cardiac disorders.[3,8] These are the women most likely to need critical care support pre- or postnatally. Women with impaired ventricular function should be made aware that this may deteriorate with pregnancy and may not fully recover.[2]

The World Health Organization (WHO) risk classification categorises cardiac lesions as low-risk (WHO I), medium-risk (WHO II), high-risk (WHO III) and lesions where pregnancy is contraindicated (WHO IV). The European Society of Cardiology (ESC) guidelines include minor modifications to this classification (Table 66.1).[2,4]

ANTEPARTUM MANAGEMENT

Pregnant women with cardiac disease should be seen early in a joint cardiac, obstetric and anaesthetic clinic to perform a risk assessment, including any further investigations, and formulate a management plan.[8,9]

ABSTRACT

Cardiac disease in pregnancy is a leading cause of maternal morbidity and as more women with congenital heart disease are reaching childbearing age, and with risk factors for acquired heart disease increasing, it is important that critical care physicians are aware of the presentation and management of these women. It is also necessary to understand the physiological changes that occur during pregnancy, how they can alter the presentation of cardiac disease and how they influence peri-partum management.

KEYWORDS

Pregnancy
cardiac disease
peripartum
cardiomyopathy
valve disease

Table 66.1 ESC-modified World Health Organization risk classification of cardiac lesions

CONDITIONS IN WHICH PREGNANCY IS WHO I	
No detectable increase in maternal mortality and no or mild increase in morbidity	Uncomplicated small or mild • Pulmonary stenosis • Patent ductus arteriosus • Mitral valve prolapse Successfully repaired simple lesions (atrial or ventricular septal defects, patent ductus arteriosus, anomalous pulmonary venous drainage) Atrial or ventricular ectopic beats, isolated
CONDITIONS IN WHICH PREGNANCY RISK IS WHO II OR III	
WHO II (if otherwise well and uncomplicated)	
Small increase in maternal mortality and moderate increase in morbidity	Operated atrial or ventricular septal defect Repaired tetralogy of Fallot Most arrhythmias
WHO II–III (depending on individual)	
	Mild left ventricular impairment Hypertrophic cardiomyopathy Native or tissue valvular heart disease not considered WHO I or IV Marfan syndrome without aortic dilatation Aorta <45 mm in aortic disease associated with bicuspid aortic valve Repaired coarctation
WHO III	
Significantly increased risk of maternal mortality or severe morbidity. Expert counselling required if pregnancy is decided upon. Intensive specialist cardiac and obstetric monitoring needed throughout pregnancy, childbirth and puerperium.	Mechanical valve Systemic right ventricle Fontan circulation Cyanotic heart disease (unrepaired) Other complex congenital heart disease Aortic dilatation 40–45 mm in Marfan syndrome Aortic dilatation 45–50 mm in aortic disease associated with bicuspid aortic valve
CONDITIONS IN WHICH PREGNANCY IS WHO IV (PREGNANCY CONTRAINDICATED)	
Extremely high risk of maternal mortality or severe morbidity, pregnancy is contraindicated. If pregnancy occurs, termination should be discussed. If pregnancy continues, care as for class III.	Pulmonary arterial hypertension of any cause Severe systemic ventricular dysfunction (LVEF <30%, NYHA III–IV) Previous peripartum cardiomyopathy with any residual impairment of left ventricular function Severe mitral stenosis, severe symptomatic aortic stenosis Marfan syndrome with aorta dilated >45 mm Aortic dilatation >50 mm in aortic disease associated with bicuspid aortic valve Native severe coarctation

ESC, European Society of Cardiology; *LVEF,* left ventricular ejection fraction; *NYHA,* New York Heart Association; *WHO,* World Health Organization. Adapted from Emmanuel Y, Thorne SA. Heart disease in pregnancy. *Best Pract Res Clin Obstet Gynaecol.* 2015;29:579–597; Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. ESC guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J.* 2011;32:3147–3197.

High-risk women should be seen regularly in the clinic during pregnancy and a plan for delivery should be made at approximately 32–34 weeks, including the mode of delivery, length of the second stage, appropriate prophylaxis against postpartum haemorrhage, length of hospital stay and the possible need for critical care support (both planned and unplanned). Such support may not necessarily require admission to a critical care unit, depending on what resources/facilities can be provided within the maternity unit, but it is important that intensivists are involved at this planning stage. Appropriate antithrombotic prophylaxis must also be discussed and planned, with the risks from maternal thrombosis weighed against the maternal and foetal risks from anticoagulation.[2]

INTRAPARTUM MANAGEMENT

Women with high-risk conditions should deliver at centres that are able both to accommodate pregnant/postpartum women requiring high-dependency or intensive care, and to provide appropriate specialist cardiac support.[6,9] Vaginal delivery is usually the delivery of choice, as it is associated with less blood loss, smaller fluid shifts, and lower rates of thrombosis and infection.[4,8,9] Caesarean section is generally done for obstetric indications, although planned operative delivery may be appropriate in women with worsening and/or severe conditions. Women with severe or life-threatening structural abnormalities may benefit from delivery in a cardiothoracic centre.

The general principle of management during labour is to reduce cardiovascular stress, in most cases with early epidural analgesia, a limited second stage and assisted delivery. Monitoring of electrocardiography (ECG), invasive arterial blood pressure and central venous pressure is done according to the risk factors and complexity of each case.

Regional anaesthesia is usually preferred for caesarean section, as for women without cardiac disease, unless there are concerns over coagulation. In women with severe cardiac disease, both regional and general anaesthesia have advantages and disadvantages that must be weighed up for each case, the general rule being that extreme care and attention to detail are probably more important than the choice of technique itself.

POSTPARTUM MANAGEMENT

It is important to appreciate that maternal deaths from cardiac disease may commonly occur after delivery. Arrhythmias, heart failure and thrombotic events are particular hazards, and introduction (or re-introduction) of appropriate medication, including thromboprophylaxis, must be considered.[2]

SPECIFIC CONDITIONS

STRUCTURAL HEART DISEASE

VALVULAR DISEASE

Valvular disease may present for the first time during pregnancy.[2] Careful cardiovascular assessment is required early in pregnancy in all women born in a country without effective medical screening for rheumatic heart disease (25% of women giving birth in the United Kingdom were born elsewhere).[6] Pregnant women can usually tolerate valvular incompetence better than stenosis, as a reduced SVR improves forward flow and reduces the regurgitation.[9] The use of antibiotic prophylaxis to reduce the risk of endocarditis in these patients remains controversial.[4,9]

Because of the physiological changes of pregnancy, measurements of flow across valves may be misleading, and valve areas are often preferred.[10]

Mitral disease

Mitral stenosis is poorly tolerated and women are at an increased risk of pulmonary oedema and atrial fibrillation due to left atrial enlargement. Drug treatment includes anticoagulation because of the increased risk of an intracardiac thrombus, diuretics to relieve congestion, and beta-blockers to preserve sinus rhythm.[2] Management around delivery should include invasive arterial monitoring and any sudden drops in SVR treated with vasoconstrictors or cautious volume expansion.[9]

Aortic disease

Those with severe stenosis will not tolerate blood loss, tachycardia or caval compression; therefore, fluid depletion and hypotension should be avoided.[9] Women with severe disease have traditionally undergone operative delivery in a tertiary centre under general anaesthesia, with invasive cardiovascular monitoring, although regional anaesthesia has also been described and there are increasing reports of successful vaginal delivery in women with severe aortic stenosis.[2] These women will require postpartum monitoring in a high-dependency area.

Aortic dissection is associated with unrepaired coarctation of the aorta, Marfan syndrome and other connective tissue disorders.[2] Hormonal, haemodynamic and thromboembolic changes during pregnancy contribute to the elevated risk, which is highest in the third trimester and early postpartum period.[9,11] Systolic hypertension is a risk factor and strict blood pressure control is advised (e.g. with methyldopa and beta-blockers), with invasive arterial pressure monitoring in severe cases.[4,11] Serial echocardiograms during pregnancy are useful for monitoring ventricular function and aortic root diameter.

Vaginal delivery with epidural analgesia, as above, is usually aimed for, although for patients on oral anticoagulants and in vascular Ehlers-Danlos syndrome, ascending aortic aneurysms greater than 45 mm, or acute or chronic aortic dissection, caesarean section is sometimes preferred.[11]

Mechanical heart valves

Pregnant women with a mechanical heart valve are at increased risk of infection, thrombotic events and – through the need for anticoagulation – bleeding and possible foetal toxicity.[2,9,12] Valve thrombosis has been reported in 4.7% of women with mechanical valves during pregnancy, with a 20% mortality and haemorrhagic complications in 23%.[12]

PULMONARY HYPERTENSION

Pulmonary hypertension (defined as mean pulmonary artery pressure >25 mm Hg) has a reported

maternal mortality of 25%–56% and is classified by the modified WHO criteria as Class IV; therefore, women should be advised to avoid pregnancy.[13] Targeted pulmonary vasodilator therapies (e.g. inhaled iloprost or intravenous prostacyclin) have gained some improvement, but mortality remains up to 33%.[2] Pregnancy outcome is also poor, with high rates of preterm delivery, foetal growth restriction and foetal/neonatal loss.[13]

Women who proceed with pregnancy should be seen at regular intervals and a plan is often made for elective caesarean section at ~34 weeks of gestation.[2,14] In severe cases, this should be in a tertiary centre with close monitoring in the ICU pre- and post-delivery, as sudden death a few days postpartum, due to intractable right heart failure, is well reported.[2,9,13–14]

FONTAN CIRCULATION

The Fontan procedure is used to palliate any single ventricle circulation that is not suitable for surgical repair into a two-ventricle circulation. Decompensation may cause arrhythmias, heart failure, chest pain and hypoxia, and therefore may present antenatally to ICU.[5] Maintenance of preload and forward flow through the pulmonary vessels is essential in these patients and dehydration and caval compression should be avoided. Reduced venous return caused by positive-pressure ventilation is particularly hazardous.

ISCHAEMIC HEART DISEASE

Pregnancy increases the risk of acute myocardial infarction (MI) three- to fourfold and if MI occurs within 2 weeks of delivery, mortality is up to 45%.[2,9] The incidence of ischaemic heart disease in pregnancy is increasing along with maternal age, obesity, diabetes, smoking, hyperlipidaemia and hypertension; many of these women will be asymptomatic.[6]

A high index of suspicion is required for any pregnant woman presenting with chest pain.[6] Aortic dissection and pulmonary embolism should also be ruled out. Treatment of MI is as for the non-pregnant population, with urgent angiography +/– primary percutaneous coronary intervention. Aspirin, clopidogrel and beta-blockers appear relatively safe during pregnancy, except for an increased risk of bleeding at delivery with antiplatelet drugs.[2]

The most common cause of MI immediately postpartum is spontaneous coronary artery dissection, 78% of whose sufferers will have no risk factors for coronary artery disease.[9] The use of ergometrine to induce uterine contraction after delivery is associated with MI secondary to coronary artery spasm in patients at risk. Patients should be treated with sublingual or intravenous glyceryl trinitrate and may require immediate coronary angiography.[9]

FUNCTIONAL HEART DISEASE

VENTRICULAR DYSFUNCTION

Ventricular impairment may present during pregnancy due to unmasking of an undiagnosed condition or precipitating peripartum cardiomyopathy.[2] In overt failure, admission, bed rest, diuretics and anticoagulation should be considered and early delivery planned. Inotropic support may be required and may be a bridge to transplantation in some patients.[2,15]

Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is a rare idiopathic form of heart failure that presents in the last month of pregnancy or within 5 months of delivery.[16,17] It is a diagnosis of exclusion and left ventricular ejection fraction is nearly always less than 45%.[15,16] Risk factors include multiparity, twin pregnancy and extremes of age, and mortality is ~15%–30%.[2,9,16] The presentation can be challenging, as symptoms can mimic those experienced during normal pregnancy and it may be confused with pre-eclampsia.[6,17] Symptoms include increasing shortness of breath, peripheral oedema and fatigue.[16]

Treatment, timing and mode of delivery depend on disease severity, with vaginal delivery acceptable for most stable patients and caesarean preferred for those who are unstable.[16,17] Treatment is similar to that of patients with systolic heart failure and includes salt restriction, diuretics, beta-blockers and peripheral vasodilators.[9] The choice of agents is limited during pregnancy and breastfeeding but can be changed to standard therapy postpartum. Patients with PPCM are at high risk of thrombotic complications during and for several months after pregnancy. In those presenting with cardiogenic shock, an intra-aortic balloon pump or extracorporeal membrane oxygenation may be required. Studies have found that bromocriptine may be useful in those with acute onset PPCM.[15,16]

The clinical course varies between complete recovery within 6 months in most patients, and rapid progression to heart failure and death. Those with a history of PPCM have a 20%–30% risk of relapse and worsening heart failure in subsequent pregnancies, with those whose cardiac function has not returned to normal having a 45%–50% risk of recurrence.[2,17]

Hypertrophic cardiomyopathy

If ventricular function is preserved, then pregnancy is generally well tolerated; however, those with significant outflow obstruction, ventricular arrhythmias and severe hypertrophy are at increased risk of decompensation.[2] The highest risk period is around delivery and the first 48 hours postpartum, due to rapid fluid shifts that can precipitate heart failure and arrhythmias.[2]

ARRHYTHMIAS AND IMPLANTABLE CARDIOVERTER DEFIBRILLATORS

Palpitations are relatively common in pregnancy; however, if they are sustained or women become symptomatic, they should be investigated further.[2] A high number of ventricular ectopics on ambulatory ECG monitoring may be an early sign of ventricular dysfunction. Beta-blockers are the first line of drug treatment for supraventricular and ventricular tachycardias in pregnancy.[2]

Patients with implantable cardioverter defibrillators (ICDs) may undergo pregnancy with no increase in ICD discharge.[2] Delivery should be planned in a centre with the resources to manage ICDs, as it may be appropriate to turn off the device and have continuous ECG monitoring with a manual defibrillator available if proceeding to surgery, as diathermy may cause interference.[2]

REFERENCES

1. Elkayam U, Goland S, Pieper PG, et al. High-risk cardiac disease in pregnancy: part I. *J Am Coll Cardiol*. 2016;68:396–410.
2. Emmanuel Y, Thorne SA. Heart disease in pregnancy. *Best Pract Res Clin Obstet Gynaecol*. 2015;29:579–597.
3. Stergiopoulos K, Shiang E, Bench T. Pregnancy in patients with pre-existing cardiomyopathies. *J Am Coll Cardiol*. 2011;58:337–350.
4. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32:3147–3197.
5. Monteiro RS, Dob DP, Cauldwell MR, et al. Anaesthetic management of parturients with univentricular congenital heart disease and the Fontan operation. *Int J Obstet Anesth*. 2016;28:83–91. doi:10.1016/j.ijoa.2016.08.004.
6. Royal College of Obstetricians and Gynaecologists. *Good Practice No. 13. Cardiac Disease and Pregnancy*. London: RCOG; 2011. https://www.rcog.org.uk/globalassets/documents/guidelines/goodpractice13cardiacdiseaseandpregnancy.pdf.
7. Knight M, Tuffnell D, Kenyon S, et al., eds; on behalf of MBRRACE-UK. *Saving Lives, Improving Mothers' Care: Surveillance of Maternal Deaths in the UK 2012-14 and Lessons Learned to inform Maternity Care from UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–14*. Oxford, UK: National Perinatal Epidemiology Unit; 2016.
8. Sachs A, Aaronson J, Smiley R. The role of the anesthesiologist in the care of the parturient with cardiac disease. *Semin Perinatol*. 2014;38:252–259.
9. Ray P, Murphy GJ, Shutt LE. Recognition and management of maternal cardiac disease in pregnancy. *Br J Anaesth*. 2004;93:428–439.
10. Liu S, Elkayam U, Naqvi TZ. Echocardiography in pregnancy: part 1. *Curr Cardiol Rep*. 2016;18:92.
11. Bons LR, Roos-Hesselink JW. Aortic disease and pregnancy. *Curr Opin Cardiol*. 2016;31:611–617.
12. van Hagen IM, Roos-Hesselink JW, Ruys TP, et al. Pregnancy in women with a mechanical heart valve: data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). *Circulation*. 2015;132:132–142.
13. Sliwa K, van Hagen IM, Budts W, et al. Pulmonary hypertension and pregnancy outcomes: data from the Registry of Pregnancy and Cardiac Disease (ROPAC) of the European Society of Cardiology. *Eur J Heart Fail*. 2016;18:1119–1128.
14. Konstantinides SV. Trends in pregnancy outcomes in patients with pulmonary hypertension: still a long way to go. *Eur J Heart Fail*. 2016;18:1129–1131.
15. Bauersachs J, Arrigo M, Hilfiker-Kleiner D, et al. Current management of patients with severe acute peripartum cardiomyopathy: practical guidance from the Heart Failure Association of the European Society of Cardiology Study Group on peripartum cardiomyopathy. *Eur J Heart Fail*. 2016;18:1096–1105.
16. Blauwet LA, Cooper LT. Diagnosis and management of peripartum cardiomyopathy. *Heart*. 2011;97:1970–1981.
17. Ersbøll AS, Damm P, Gustafsson F, et al. Peripartum cardiomyopathy: a systematic literature review. *Acta Obstet Gynecol Scand*. 2016;95:1205–1219.

This page intentionally left blank

Part Ten

Infections and Immune Disorders

This page intentionally left blank

67

Anaphylaxis

Peter R Platt, Paul HM Sadleir

First I feel I must explain and indeed justify the use of the word itself, for it may seem somewhat barbarous at first glance. This neologism I invented twelve years ago on the assumption, which I think is still valid, that a new idea calls for a new word in the name of scientific precision of language. Phylaxis, a word seldom used, stands in the Greek for protection. Anaphylaxis will thus stand for the opposite. Anaphylaxis, from its Greek etymological source, therefore means that state of an organism in which it is rendered hypersensitive, instead of being protected.

Charles Richet, Nobel Lecture, 11 December 1913.[1]

DEFINITION AND CRITERIA FOR DIAGNOSIS

Anaphylaxis is an acute multisystem disorder with a variable presentation secondary to the release of multiple mediators from mast cells and/or basophils. Since its original description and later the recognition of a new immunoglobulin, IgE in 1968, the term anaphylaxis has been generally used specifically for an acute hypersensitivity reaction to a foreign substance mediated by IgE. With the recognition that the mast cell could be triggered to release mediators via other mechanisms producing an identical pathophysiological syndrome, the collective term '*anaphylactoid*' was coined to distinguish these reactions from those mediated by IgE. To some extent this term and the ICD9/10 coding limited to 'anaphylactic shock' resulted in failure to capture accurate epidemiological data resulting in calls for a change of diagnostic criteria. Using anaphylaxis guidelines published from 2010 by major allergy/immunology organisations,[2–4] the World Allergy Organization (WAO) aligned these guidelines.[5] Importantly, it was agreed that a diagnosis of anaphylaxis should be based upon symptoms and signs as defined by Sampson et al.[6] in 2006 (Table 67.1). These clinical criteria may be limited to signs in the sedated or anaesthetised patient in the critical care environment; hypotension that is relatively unresponsive to vasopressors may be the only warning sign of anaphylaxis in these settings. The WAO recommended abandonment of the terms *anaphylactoid* and *pseudo-allergy* to describe non-IgE mediated reactions. They redefined *anaphylaxis* as 'a serious, life-threatening generalized or systemic hypersensitivity reaction' that may be *immune mediated* (IgE or non IgE) or *non-immune mediated*, although this has not met with universal agreement. The pathophysiological mechanisms of anaphylaxis are discussed in detail below, with particular emphasis on the most prevalent immunological, IgE-dependent mechanism. Immunological non-IgE mechanisms including complement activation and activation of the kallikrein-kinin contact system are discussed in the section detailing representative agents. Non-immunological mechanisms include direct activation of the only recently identified MrgprX2 mast cell receptor[7] responsible for histamine release caused by drugs such as opioids. Physical factors such as exercise, cold and heat can co-contribute as causes of anaphylaxis and those that are unexplained are classified as idiopathic.

EPIDEMIOLOGY

For decades the prevalence of allergic diseases worldwide has been dramatically increasing with as many as 20% of the population of developed countries being affected. Estimates of incidence rates of anaphylaxis are widely variable around 10–20 per 100,000 population. Less than one-third of these patients will require hospital admission. In the United Kingdom between 1992 and 2012, hospital admissions[8] increased by 615% and critical care admissions between 2005 and 2009 almost doubled[9] but annual fatality rates remained stable at 0.047 cases per 100,000 population. In contrast, Australian total hospital admissions for anaphylaxis increased almost fourfold and fatal anaphylaxis almost doubled in the period 1997–2013.[10] Although anaphylaxis is a potentially lethal condition, it only accounts for a small proportion of the workload of critical care units being responsible for as few as 0.1% of childhood and 0.3% of adult admissions; greater than 90% of these cases can be expected to survive.

RISK FACTORS

Anaphylaxis may be associated with a number of risk factors that can increase the severity, risk of fatality and decreased response to treatment. The largest number of incident cases of anaphylaxis is in children but it is teenagers with food allergy and poorly controlled asthma that are at risk of critical bronchospasm

ABSTRACT

Anaphylaxis is an acute, life-threatening disorder that requires rapid recognition and immediate treatment. Its prevalence is increasing in line with the overall allergic disease problem affecting the developed world. Most cases are treated successfully in the community or hospital emergency department. Severe cases with critical airway obstruction, from angioedema or bronchospasm, or cardiovascular collapse require expert management in a critical care environment. All age groups are susceptible but the causes differ, with food allergy being the main cause in the young and medications in the older. Although recognition is straightforward in most cases, cryptogenic anaphylaxis is not uncommon in the perioperative or intensive care setting. Treatment continues to evolve; epinephrine and volume replacement remain critically important but the use of transoesophageal echocardiography and extracorporeal membrane oxygenation are increasingly utilised in those unresponsive to first-line therapy. Deaths continue to occur both in the community and hospital; anaphylaxis is one of the few unpredictable and non-discriminatory causes of death during surgery and anaesthesia.

KEYWORDS

Anaphylaxis-definition
anaphylaxis-pathophysiology
anaphylaxis-clinical and laboratory diagnosis
anaphylaxis-causes
anaphylaxis-treatment

Table 67.1 Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalised hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING:
   a. Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxaemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g. generalised hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxaemia)
   c. Reduced BP or associated symptoms (e.g. hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
3. Reduced BP after exposure *to known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + (2 × age)) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.
BP, Blood pressure; *PEF*, peak expiratory flow.
Modified from Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report – second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117:391–397.

that can be rapidly fatal. Increasing age and co-morbidities such as coronary artery disease or hypertension, particularly if treated with beta-blockers and/or angiotensin-converting enzyme (ACE) inhibitors, are associated with unresponsiveness to treatment, hospitalisation and increased fatality. Systemic mastocytosis (SM) and other variants of mast cell activation disorders are often only recognised after unexpectedly severe reactions to insect stings or drugs.

PATHOPHYSIOLOGY OF ANAPHYLAXIS

Mast cells and basophils release mediators such as histamine that are responsible for the physiological changes seen during anaphylaxis. Although there are a number of mechanisms of release, the focus of this section is IgE-mediated anaphylaxis. Mast cells are found in the tissues and basophils in the circulation. Both have high affinity receptors (FcεRI) on their surfaces. The number of FcεRI varies between 29,000 and 680,000 per cell in different individuals.[11] A correspondingly variable amount of IgE is bound with a very high affinity to the FcεRI. Binding of an allergen to adjacent FcεRI/antibody complexes, 'cross-linking', will lead to a sequence of signalling events resulting in mediator release from the mast cell or basophil; however, this is not all or none – maximal stimulation will only release 10%–20% of stored mediators. A minimum number of cross-linking events, between 100 and 1000, are required for any degree of release.[12]

MEDIATOR RELEASE

After full activation of the FcεRI and maintenance of the receptor complex for as little as 100 seconds, there is transduction of intracellular signals that lead to the release of pre-synthesised mediators such as histamine, serotonin, various proteases such as tryptase, carboxypeptidases and other enzymes contained in granular stores.[13] These, particularly histamine, are responsible for the immediate cardiovascular, respiratory and skin changes that are seen at the onset of anaphylaxis. Phospholipid metabolites are the second group of mediators, generated as a consequence of the release of phospholipaseA_2, such as platelet activating factor (PAF) and the eicosanoids PGD_2, LTC_4, and LTB_4 that individually can have physiological consequences such as bronchospasm and local or generalised angioedema. Enhanced gene expression leads to the generation of the third group of mediators, the cytokines and chemokines that are responsible for cell signalling and chemotaxis.[14] The physiological response results from the complex interaction of these multiple mediators with their individual receptors and thus may be variable in duration, intensity and clinical features.

FcεRI engagement also generates negative intracellular signals that limit the duration and intensity of the release process and also triggers endocytosis of the activated complexes, thus removing them from the cell surface and terminating the response. This results in acute desensitisation of the mast cell to the triggering allergen.

THE PHYSIOLOGICAL RESPONSE TO MEDIATOR RELEASE

In a setting of patient heterogeneity, complex mediator release mechanisms and different triggers, the physiological response is unpredictable in both the individual organ and in overall severity.

SKIN CHANGES DURING ANAPHYLAXIS

Skin eruptions are the most consistent feature of anaphylaxis, although their absence does not exclude the

condition and generalised erythema may frequently not manifest until after resolution of haemodynamic instability. Urticarial lesions (hives) develop rapidly and are pruritic, raised, patchy erythema. Angioedema describes swelling of the deeper dermis and subcutaneous tissues (non-pitting, non-pruritic, oedematous swelling), and may also involve mucosal surfaces. In anaphylaxis, both urticaria and angioedema are frequent, and usually the consequence of IgE-dependent activation of cutaneous mast cells resulting in increased vascular permeability which is predominantly a consequence of activation of H1 histamine receptors. Nervous system stimulation, axonal reflexes and other mediators, such as tryptase, cytokines and chemokines may play a role in amplifying the reaction.

RESPIRATORY CHANGES DURING ANAPHYLAXIS

Respiratory manifestations of anaphylaxis may involve the lower airway (dyspnoea, bronchospasm, hypoxaemia) or upper airway (stridor or upper airway obstruction, tongue swelling, dysphonia or dysphagia, rhinitis). Mast cell-derived mediators cause vasodilatation, smooth muscle contraction and mucus secretion in the nasal and bronchial mucosa. Autopsy findings in cases of fatal anaphylaxis include pulmonary oedema, laryngeal and/or pharyngeal oedema, lung hyperinflation and mucous plugging (suggesting bronchospasm and air-trapping), and evidence of asphyxiation (petechial haemorrhages). Upper airway oedema or obstruction is more common in food allergies compared to medication-triggered anaphylaxis.

Anaphylaxis during surgery and anaesthesia is most commonly associated with mild increases in airway pressure and severe bronchospasm is rare except in patients with a history of increased airway responsiveness such as in asthma, smoking and other conditions associated with chronic airflow limitation. There are rare reports of bronchospasm being the only presenting feature.

CARDIOVASCULAR CHANGES DURING ANAPHYLAXIS

Fisher[15] from clinical observations of anaphylaxis under anaesthesia found the most common manifestation was cardiovascular depression characterised by profound hypotension, sinus tachycardia, loss into the interstitial space of up to 35% of blood volume and low cardiac filling pressures. Although simplistic, it is not unreasonable to regard histamine as the principal mediator that is responsible for the initial cardiovascular effects.[16,17]

PERIPHERAL VASCULATURE

Hypotension occurs not only as a result of a fall in systemic vascular resistance but also because of failure of venous return due to both interstitial loss and sequestration of blood in the peripheral venous systems. Vasopressors, essential to increase systemic vascular resistance, will be ineffectual on their own unless cardiac output is maintained by volume repletion. Having studied details of 214 deaths associated with anaphylaxis, Pumphrey in 2003 reported a striking pattern of sudden death after a change to an upright posture in 10 of 38 anaphylactic shock deaths that occurred outside hospital.[18] He described a mechanism based on lack of venous return to explain this phenomenon. He went on to express the importance of the recumbent position with legs raised in first aid of shocked patients and explained why epinephrine can be ineffective in these patients. The benefit of posture has also been echoed by Brown[19] in the emergency medicine setting, as has the benefit of the pneumatic antishock garment or MAST suit.[20] The importance of venous capacitance has largely been forgotten or ignored in discussions of the circulatory changes during anaphylactic shock, although the relationship between venous capacitance and cardiac output are well described.[21,22]

THE HEART

The use of echocardiography during anaphylaxis characteristically shows a hyperdynamic but empty heart.[23,24] Rarely, Takotsubo cardiomyopathy[25] may occur that is characterised by apical ballooning and systolic dysfunction of apical and mid segments of the left ventricle with compensatory hyperkinesis of the basal segments. The electrocardiogram may show changes consistent with ischaemia and cardiac enzymes may be elevated but angiography reveals normal coronary arteries. Endogenous and exogenous epinephrine in large doses may lead to catecholamine cardiotoxicity or coronary microvascular dysfunction.

Allergic events may be associated with angina and angiographic evidence of coronary spasm in both adults and rarely children and also with atheromatous plaque erosion or rupture, causing myocardial infarction. This association between acute allergic reactions and coronary events is known as Kounis syndrome.[26]

CAUSES OF ANAPHYLAXIS

FOOD

Almost 10% of the population of developed countries have a food allergy with one-third being severe.[27] Almost any food may be responsible for allergy, but only eight food groups account for 90% of food-related allergy; peanuts, tree nuts, fish and crustacea often persist into adulthood, whereas milk, egg, wheat and soy often resolve before the teens. Food allergy is responsible for almost all allergic hospital admissions

in under 4-year-old age group and most fatalities in teenagers, particularly when associated with asthma. By middle age food-related allergy is relatively uncommon as a cause of hospital admissions and fatalities compared to those due to drug and insect stings. Latex allergy can be associated with cross-reactivity to fruits including avocado, banana, chestnut, kiwifruit and papaya. Food-associated, exercise-induced anaphylaxis can occur when an otherwise harmless food is consumed 2–4 hours before exercise.

DRUGS

Cephalosporins. Historically, penicillin has been the most common antibiotic causing anaphylaxis and fatalities but with changing patterns of antibiotic prescribing, cephalosporins[28] have become a greater issue. In the hospital setting antibiotics are often administered intravenously, which increases the risk compared to the oral route and cephalosporins are widely used as prophylaxis during surgery. Although cephalosporins share a common beta-lactam ring with penicillins, it is becoming clearer that the classic, beta-lactam derived determinants of penicillin allergy are less important than the side chains in cephalosporin allergy. The amino-penicillins may cross-react with early generation cephalosporins that share identical side chains. Although cross reactivity occurs between cephalosporins, it is not determined by the 'generation' of the drug but the side chains.

Vancomycin will cause the 'red man syndrome' if administered rapidly. Very rarely anaphylaxis to vancomycin may be IgE mediated but most commonly histamine release results from direct activation of the mast cell, possibly via the MrgprX2 G-protein coupled receptor in the surface membrane of the mast cell. Temporary discontinuation of the infusion and administration of low-dose epinephrine will lead to rapid resolution of the symptoms except in the rare instances that the reaction is IgE mediated.

Sulphonamides. Patients often express an allergy to sulpha or sulphur[29] drugs because of an adverse reaction to sulphonamide antibiotics. It is still common practice to avoid other drugs containing a sulphur-containing moiety such as frusemide, acetazolamide and parecoxib even though there is no convincing evidence of cross-reactivity. There is no contraindication, as has been suggested, to use epinephrine that contains metabisulphite as a preservative for the treatment of individuals having an anaphylactic reaction who claim to have a sulphite or 'sulfa' allergy.

Neuromuscular blocking drugs (NMBDs)[30] are the commonest cause of anaphylaxis in the perioperative period with as many as 4% of cases being fatal. Although NMBD reactions are universally IgE mediated, they depart in several ways from those seen with most other causes. Prior exposure is seen in less than half the cases caused by NMBD, suggesting exposure to other sensitisers in the environment. There is convincing evidence that pholcodine in cough suppressants is the responsible agent.[31] Although a relatively small molecule, there is no evidence that haptenisation is required to generate an allergic response to NMBD. The ability of these drugs to cross-link adjacent receptor bound antibody is the result of the bivalency of the NMBD that has two substituted ammonia groups in its structure. Suxamethonium and rocuronium have the greatest potential for inducing anaphylaxis, whereas atracurium[32] and particularly cis-atracurium less so.

Non-steroidal anti-inflammatory drugs (NSAIDs) and *aspirin*[33] are both associated with hypersensitivity reactions such as aspirin-exacerbated respiratory disease (AERD) and urticaria-angioedema without respiratory involvement that are mediated via cyclooxygenase 1 (COX-1) inhibition and the leucotriene shunt. Bronchospasm is precipitated in around 10% of asthmatics via this pathway. Specific IgE has been identified in over 50% of patients with a history of anaphylaxis to propyphenazone but only rarely to diclofenac that in some causes an immediate hypersensitivity reaction indistinguishable from an IgE-mediated reaction. It is possible that the testing methods are not sensitive enough to identify the NSAID-specific IgE.

Iodinated contrast media (ICM). There is a widely held belief that hypersensitivity to ICM is related to iodine and thus the misconception that there is cross-sensitivity with other iodine-rich foods such as fish or shellfish and iodine-containing surgical antiseptics.[34] Fish allergy is caused by sensitivity to specific proteins and antiseptic allergy to povidone. Mild immediate reactions to ICM[35] are common and are related to the physical properties of the media such as high osmolality and ionic preparations. Modern non-ionic, low-osmolality formulations have reduced this problem and radiology departments have pre-treatment protocols[36] for susceptible individuals. Less commonly, severe anaphylaxis may occur with an individual contrast agent associated with a positive skin test suggesting an IgE-mediated mechanism.[37] Referral to an Immunologist for cross sensitivity testing with other agents can identify a suitable alternative; pre-treatment will clearly be of no benefit in this group.

Protamine[38] is used for the neutralisation of heparin in cardiac and vascular surgery, dialysis and cardiac catheterisation. It has also been incorporated in intermediate and long-acting insulin preparations, resulting in a cohort of exposed patients with a significant risk of sensitisation.

Its use is associated with IgE-mediated anaphylaxis in this group of patients but also has a direct histamine-releasing effect on mast cells, the magnitude of which is dose and rate related and may be of critical significance in the unstable patient. Rarely, heparin/protamine complexes are responsible for complement activation and release of thromboxane in the pulmonary arterial circulation, causing severe

right-sided heart failure that should be distinguished from anaphylaxis.

Chlorhexidine[39] exposure is common in both hospital and the community, leading to widespread sensitisation. In the hospital setting skin application may rarely cause anaphylaxis but is unlikely unless the epidermis is breached by vascular cannulation or surgical incision, particularly if the antiseptic is not allowed to dry. Anaphylaxis after application in the mouth during dental surgery or urethra during catheterisation using chlorhexidine-containing gel lubricants is more likely due to rapid absorption into the circulation from mucous membranes. Of particular importance in the critical care environment is the risk of chlorhexidine-coated central venous lines that can present as cryptogenic or recurrent anaphylaxis.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). Although not responsible for inducing anaphylaxis, this group of drugs may exacerbate hypotension by blocking the compensatory response and reduce the effectiveness of treatment, particularly when prescribed with a beta-blocker.

ACEIs are associated with the spontaneous onset of laryngopharyngeal angioedema that can cause critical airway obstruction.[40] It may occur shortly after onset of treatment of the drug but also after months or years of uneventful use. The initial episode can occur at the time of anaesthesia and surgery and may be triggered by the minor trauma of laryngeal mask or endotracheal tube insertion; if associated with hypotension, anaphylaxis may be erroneously suspected. Bradykinin is thought to be the mediator responsible and thus ARBs are suitable alternatives when ACEIs are ceased after an episode of oedema. Occasionally, angioedema can occur weeks or months after cessation of ACEIs. If an ARB has been prescribed in the place of the ACEI, the oedema may be incorrectly ascribed to the ARB.

GELATIN-BASED COLLOIDS, MEAT AND CETUXIMAB

Although seemingly unrelated, these three causes of anaphylaxis have the oligosaccharide galactose-alpha-1,3-galactose (alpha-gal) in common. This sugar is common to all mammals except the higher primates, including human. With both gelatin-based colloid and Cetuximab (Erbitux, Bristol-Myers Squibb and ImClone Systems), acute hypersensitivity reactions occurred on first exposure, raising speculation as to the sensitisation process. In the late 2000s reports from the United States, Sweden and Australia clarified the association between ticks, delayed anaphylaxis after the ingestion of red meat[41] and anaphylaxis after initial exposure to Cetuximab,[42] a chimeric mouse-human IgG1 monoclonal antibody used in the treatment of colorectal cancer and squamous-cell cancers of the head and neck. In these patients, pre-existing antibodies to alpha-gal were identified in the serum, the generation of which was sensitisation by exposure to tick bites. The alpha-gal is transferred from host mammal to human with resultant production of antibodies that are specific for the alpha-gal present in gelatin, cetuximab and meat.

With the recognition of complications associated with the use of starch-based colloids in critically ill patients, gelatin-[43]based colloids have had a resurgence but also an increased risk of anaphylaxis. This should be considered as a greater risk in patients allergic to red meat and in tick-prone areas, although the pathogenic relationship, as yet, is not fully elucidated.

Intraoperative anaphylaxis may be caused by Floseal Haemostatic Matrix (Baxter Healthcare Co., Hayward, California), a topical haemostatic agent containing bovine-derived gelatin. Other gelatin-containing haemostatic agents such as Gelfoam (Pfizer, New York) and SurgiFlo (Ethicon, Somerville, New Jersey) have also been implicated.

BLOOD PRODUCTS

Anaphylaxis occurs in 1:20,000–1:50,000 whole blood transfusions. The mechanisms implicated include (1) IgA-deficient recipients who have anti-IgA antibodies, (2) transfusing an allergen in the donor blood such as penicillin or nuts to a sensitised recipient, (3) recipient with antibodies to plasma proteins such as transferrin or IgG and less commonly (4) transfusion of IgE antibody from the donor that reacts with an allergen in the recipient. A haemolytic transfusion reaction should be considered in the differential diagnosis.

LATEX

In the 1980s, coincident with, and in part due to, the human immunodeficiency virus epidemic, latex allergy became a major health issue. Massive demand for latex gloves resulted in the production of a low quality, highly allergenic product leading to widespread sensitisation, particularly of workers in the health care setting. The use of cornstarch in powdered gloves resulted in an effective means of dispersion of airborne latex particles into the hospital environment, particularly the operating room. Of the greater than 200 polypeptides occurring in natural rubber latex (NRL), 13 are the primary allergens (Hevea braziliensis [Hev b] 1–13), which induce antibody formation detectable by specific IgE testing. In the late 90s Mertes[44] reported latex as the second most common cause of perioperative anaphylaxis in France (16.7%); this incidence has not fallen but has not been reported as being so common elsewhere. Surgery in infancy, particularly spina bifida that often requires multiple surgeries and catheterisations, was responsible for greater than 75% of anaphylaxis cases in children. With the introduction of better quality control in the manufacture of low allergenic gloves, the discontinuation of powder and the adoption of latex-free

policies in the health care environment, both sensitisation and anaphylaxis rates have fallen significantly.

ANAPHYLATOXINS

The anaphylatoxins C3a, C4a and C5a are produced on activation of the complement system and act on a group of G-protein coupled anaphylatoxin receptors. This pathway is an alternative to the IgE pathway of mast cell activation with resultant mediator release and clinical syndrome of anaphylaxis.

In early 2008 many severe adverse events were reported worldwide associated with heparin therapy, including over 100 deaths in North America. Subsequent investigation identified a highly sulphated heparin-like contaminant – oversulphated chondroitin sulphate (OSCS) as the cause.[45] The associated activation of the kinin-kallikrein system with formation of bradykinin enhanced the hypotensive response.

Polyethoxylated castor oil has been used widely in the formulation of poorly water-soluble drugs such as the anticancer agent paclitaxel, intravenous multivitamin preparations, early formulations of propofol and diazepam and the obsolete anaesthetic induction agents Althesin and Propanidid. There have been several mechanisms of activation of anaphylaxis linked to this agent, including direct histamine release, IgE, IgG and complement.

MAST CELL DISORDERS

The descriptions above relate to normal populations of mast cells. There are a number of disorders of mast cells associated with abnormal proliferation or increased susceptibility to activation.[46]

SM is a condition associated with a mutation of the tyrosine kinase receptor c-KIT that results in both increased numbers and aberrant activation of mast cells. Such patients may have variable symptoms attributable to mast cell activation or may present with particularly severe anaphylaxis to hymenoptera stings. Skin lesions, typically urticaria pigmentosa, are present in most cases. A baseline mast cell tryptase (MCT) over 20 ng/mL is consistent with a diagnosis of SM. The primary diagnostic feature is the finding of multifocal mast cell clusters of atypical morphology in bone marrow.

Monoclonal mast cell activation syndrome (MMAS) presents with the same symptoms as SM and is associated with a KIT mutation and abnormal mast cell clones but the baseline tryptase is normal. There are no skin changes and atypical cell clusters in the bone marrow are sparse or absent.

Non-clonal mast cell activation syndrome (nc-MCAS) has a similar clinical presentation to MMAS but no atypical clonal mast cells or evidence of KIT mutation. It is possible, but not proven, that the increased susceptibility to activation is due to an intrinsic defect in the mast cell causing increased sensitivity to activation.

Surgery, anaesthesia and the critical care environment are associated with anxiety, stress, pain and exposure to innumerable drugs that may trigger the susceptible mast cells in these conditions. Perioperative management[47] of patients can be achieved successfully with mast cell stabilising drugs and the avoidance of opioids and muscle relaxants that have histamine-releasing properties.

LABORATORY TESTS

MAST CELL TRYPTASE

The principal effector cell of anaphylaxis from whatever cause is the mast cell with, as yet, incompletely defined contributions from the basophil. There are assays of many of the mediators released from the mast cell on degranulation but most of these are only available in research laboratories. The only useful widely available laboratory test to aid in the clinical diagnosis of anaphylaxis is MCT.[48] Immature forms of tryptase, alpha- and beta-protryptase, that are secreted in small amounts from the unstimulated mast cell account for a baseline level in plasma with a range of 1–11.4 ng/mL. This level is determined genetically and in any one individual varies little over time. Mature tryptase in significant amounts is only detected in the plasma after degranulation. In disorders in which there is an increase in the mast cell population such as the various forms of mastocytosis, baseline levels of protryptase may be elevated. ImmunoCAP tryptase (Thermo Fisher Scientific, Uppsala, Sweden) is widely available in commercial laboratories and measures both immature and mature forms. Any elevation over the upper limit of the reference range in the clinical setting of suspected anaphylaxis is considered diagnostic if the baseline level (measured either prior or 24 hours post event) is in the normal range. Peak levels of tryptase are seen 15–120 minutes after the onset of the reaction with a decline determined by the biological half-life of about 2 hours. If tryptase is still elevated after 24 hours, it should be repeated weeks later; if still elevated, mastocytosis or a haematological neoplasm should be suspected. In severe anaphylactic events, MCT levels greater than 300 ng/mL are not uncommon. In as many as one-third of perioperative, food or insect sting anaphylaxis, MCT may not be elevated above 11.4 ng/mL. Baseline tryptase varies little and if the peak level after a suspected episode of mast cell degranulation is greater than 20% above baseline plus 2 ng/mL, it would be suspicious. Thus, a relatively small rise of MCT from 5–8 ng/mL may be of significance. Optimal timing of the recommended three blood samples for MCT is 1, 4 and 24 hours after the initiation of the event. Activation limited to basophils may be rarely responsible for anaphylaxis, in which case

Table 67.2 Grading of anaphylaxis

Grade I Skin symptoms and/or mild fever reaction
Grade II Measurable but not life-threatening CVS, GI or respiratory disturbance
Grade III Life-threatening hypotension (shock) and/or bronchospasm
Grade IV Cardiac and/or respiratory arrest

CVS, Cardiovascular system; *GI*, gastrointestinal.
Modified from Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet*. 1977;1:466–469.

the tryptase level would not rise. When anaphylaxis is suspected as a cause of death, a postmortem blood sample may aid in the diagnosis, although significant elevations have been reported with other causes such as cardiac or trauma.

GRADING OF ANAPHYLAXIS

Ring and Messmer[49] classified hypersensitivity reactions to colloid volume substitutes into four grades based on the severity of symptoms and signs in 1977 (see Table 67.2). This classification system has been used with only minor modifications to describe the severity of immediate hypersensitivity reactions to all food-, environmental- and drug-induced allergens since. Its great success has been the ability to classify both IgE- and non-IgE-mediated reactions and reactions that do not meet the 'life-threatening' criterion required for anaphylaxis. In 2004, Brown[50] proposed a classification system (see Table 67.3) in which the discriminating features of the two grades representing anaphylaxis were identified by retrospective analysis of cases to determine which were highly correlated with hypotension and hypoxia (grade 3) or only less closely associated (grade 2). The majority of cases that will require review by intensive care staff are likely to fall into Brown's grade 3. Additional classification systems have been developed for the signs of intraoperative anaphylaxis; however, none have been demonstrated to be more effective in guiding management or predicting outcome than Ring and Messmer, and some omit cases of immediate hypersensitivity in which early intervention has prevented progression to anaphylaxis (see Table 67.3).

TREATMENT OF ANAPHYLAXIS

Anaphylaxis is a hyperacute syndrome that may rapidly progress to respiratory or cardiac arrest and death. Early signs and symptoms may have a wide differential diagnosis, and indeed anaphylaxis may be a retrospective diagnosis (indicated by the MCT). Simultaneous assessment and resuscitation should begin immediately. The natural history of anaphylaxis

Table 67.3 Grading system after Brown SG

GRADE	DEFINED BY
1. Mild (skin and subcutaneous tissues only)*	Generalised erythema, urticaria, periorbital oedema or angioedema
2—Moderate (features suggesting respiratory, cardiovascular, or gastrointestinal involvement)	Dyspnoea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain
3—Severe (hypoxia, hypotension, or neurological compromise)	Cyanosis or Sp_{O_2} ≤92% at any stage, hypotension (SBP <90 mm Hg in adults), confusion, collapse, LOC or incontinence

*Mild reactions can be further subclassified into those with and without angioedema (see text).
LOC, Loss of consciousness; *SBP*, systolic blood pressure.
Modified from Brown SG. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol*. 2004;114(2):371–376.

is that it is a temporary condition that will resolve if the patient can be sustained for the period required to allow it do to so. Overall, life-threatening respiratory symptoms are more common than lethal cardiovascular derangement, although cardiovascular collapse is more common in iatrogenic medication reactions.[51] Priorities in the initial management are the early administration of epinephrine, rapid administration of intravenous fluids to correct hypovolaemic/maldistributive shock, and aggressive management of threatened or established respiratory failure from reduced airway compliance (bronchospasm) or upper airway obstruction (Table 67.4).

GENERAL MEASURES

Management of a patient with a syndrome that may be anaphylaxis should include the mobilisation of a resuscitation team, application of supplemental oxygen, and establishment of intravenous access (14–16 g). The patient should be placed supine or in the Trendelenburg position with the legs above the level of the heart. Sudden death has been described on adoption of an erect posture in anaphylaxis, of importance when considering elevation of the torso if respiratory distress is present. Pregnant patients should be placed in the left lateral position or with partial left uterine tilt. Electrocardiography monitoring, pulse oximetry and non-invasive blood pressure monitoring should be applied to all patients. In the presence of cardiovascular shock, intra-arterial blood pressure monitoring allows rapid detection of deterioration and titration of therapy as well as the ability to take blood samples for gas and

Table 67.4 Drug doses for life-threatening anaphylaxis

DRUG	ADULT	CHILD (20 KG)
Epinephrine (IM;1 : 1000)	500 µg	0.01 mg/kg (200 µg)
Epinephrine (IV)	50–100 µg initial dose; 0.1–1 µg/kg per minute infusion	Bolus not recommended 0.1–1 µg/kg per minute infusion
Norepinephrine	0.1–1 µg/kg per minute infusion	0.1–1 µg/kg per minute infusion
Vasopressin	2-unit bolus, infusion 0.03–0.06 U/min	0.0001–0.0003 UI/kg per minute[55]
Methylene Blue	2 mg/kg over 20 min	2 mg/kg over 20 min
Glucagon	1–5 mg IV; 5–15 µg/min infusion	20–30 µg/kg up to 1 mg; 5–15 µg/min
Aminophylline	5.6 mg/kg over 20 min	5.6 mg/kg over 20 min
Methylprednisolone	1–2 mg/kg	1–2 mg/kg
Diphenhydramine	25–50 mg IV	1 mg/kg IV
Ranitidine	50 mg IV	1 mg/kg IV
Icatibant	30 µg sc injection (max 90 µg/d)	N/A

IM, Intramuscular; *IV*, intravenous.

acid-base analysis. Central venous access is also useful for administering vasopressor and inotropic agents and grossly assessing response to volume expansion. Neither should delay the immediate management of presumed anaphylaxis.

AIRWAY AND BREATHING

A rapid assessment of the patency of the airway should include an examination of the upper airway for evidence of oedema. Early intubation should be considered in patients who develop stridor, hoarseness, difficulty swallowing or significant facial or tongue oedema. Interim measures may include the use of inhaled epinephrine (adult dose 5 mg of 1:1000 epinephrine) and inhaled heliox to reduce the work of breathing; however, the first-line treatment for both upper airway obstruction and bronchospasm in anaphylaxis is systemic epinephrine. Therapeutic effects include bronchodilatation, reduced upper airway mucosal oedema and reduced mast cell and basophil mediator release. Upper airway or external neck landmarks may be distorted due to oedema. Endotracheal intubation and induction of anaesthesia in this situation is likely to be difficult and requires the availability of – and familiarity with – difficult intubation adjuncts including flexible fibreoptic bronchoscope, videolaryngoscopy or surgical cricothyroidotomy.

Severe bronchospasm not responsive to intravenous epinephrine should be treated according to guidelines for the management of acute asthma.

CIRCULATION

Epinephrine is the first-line treatment. Sinus tachycardia is a common feature of anaphylaxis, and should not discourage its use. In the absence of significant cardiovascular derangement, intramuscular epinephrine is commonly administered. The adult dose is 500 µg repeated at 5 minute intervals based on response. An epinephrine autoinjector for intramuscular use contains 0.15 mg (for children over 10 kg) or 0.3 mg (for children over 30 kg) to administer the paediatric dose of approximately 0.01 mg/kg. Intravenous epinephrine is preferred in the presence of severe hypotension as the intramuscular route has unpredictable absorption.[52] An initial dose of 50–100 µg IV, followed by incremental increases in the bolus dose or infusion titrated to response, is recommended. Human epidemiological and therapeutic animal studies suggest that delayed or inadequate administration of epinephrine increases the likelihood of fatal anaphylaxis. Therapeutic effects include vasoconstriction and increased peripheral vascular resistance, decreased venous capacitance, and increased myocardial contractility (as well as increased coronary blood flow due to an increased diastolic:systolic time ratio and coronary vasodilatation).

Intravenous fluids should be administered with an initial rapid bolus of 20 mL/kg of crystalloid. Effective resuscitation of anaphylactic shock may require up to 50 mL/kg in the first 15 minutes in order to maintain cardiac preload.[53] Positive-pressure ventilation with a high mean intrathoracic pressure or inadequate expiration resulting in the development of significant auto-positive-end-expiratory-pressure may also impede venous return.

If cardiovascular shock has not responded to intravenous fluids (50 mL/kg in the first 15 minutes) and epinephrine boluses (total 2 mg) and subsequent infusion (e.g. up to 40 µg/min), further management is best guided by immediate transthoracic or

transoesophageal echocardiography. This will distinguish insufficient fluid resuscitation (low left ventricular [LV] end-diastolic diameter) from vasoplegia (low LV end-systolic diameter with reasonable LV end-diastolic diameter), pump failure (poor cardiac contractility) or acute pulmonary hypertension (with right ventricular failure). It is also useful in the assessment of Kounis syndrome (acute ST-elevation during anaphylaxis). Regional wall motion abnormalities with ST segment changes may require angiography with coronary intervention to exclude or treat plaque rupture or coronary vasospasm.

Typical echocardiography findings in anaphylactic shock are the finding of a left ventricle that is hyperdynamic with a low end-systolic diameter, with or without reduced end-diastolic diameter depending on the adequacy of volume resuscitation. If nonresponsive to epinephrine, consideration should be given to a norepinephrine infusion, followed by nonadrenergic vasopressors such as vasopressin (initial adult dose 2–4 units IV, followed by infusion).[54] Other agents used in nonresponsive shock include methylene blue (2 mg/kg over 20 minutes followed by infusion) or glucagon (1–5 mg IV).

Pulseless electrical activity or asystole occurs in up to 20% of cases of intraoperative anaphylaxis. Contrary to expectations, external chest compressions have been observed to produce an effective arterial waveform during anaphylaxis, and the neurological-deficit-free survival from grade 4 intraoperative anaphylaxis is over 95%. Good outcomes have been observed in patients after prolonged resuscitations (over 60 minutes) and resuscitative attempts should proceed for longer than is usual for cardiac arrest as a result of other pathophysiological conditions.

EXTRACORPOREAL MEMBRANE OXYGENATION

The presence of significant pump failure (poor cardiac contractility) in resuscitated anaphylactic shock is an indication for veno-arterial extracorporeal membrane oxygenation (VA ECMO) support. This has been described as an effective therapy in multiple case reports. Effective circuit flows may be difficult to achieve in the presence of maldistributive-hypovolaemic shock due to poor venous drainage, although echocardiography-guided resuscitation should allow this to be rapidly corrected. Successful use of VA ECMO will allow time for the resolution of anaphylaxis or reversal of the conditions that caused secondary cardiac decompensation.

ECMO does have a significant iatrogenic complication rate, and side effects of ECMO therapy may be synergistic with the features of anaphylaxis (low venous pressures, oedema, bleeding diathesis), increasing the complication rate from cannulation or circuit operation. VA ECMO in refractory anaphylactic shock in the absence of intrinsic cardiac pump failure is also likely to be problematic. If the cause of refractory shock is low afterload, then it may be that peripheral VA ECMO circuit flows are still insufficient to produce an adequate systemic arterial pressure. Significant cardiac ejection may also occur in this situation and result in upper-body hypoxaemia in the presence of pulmonary dysfunction or underventilation and the use of peripheral arterial (return) cannulation ECMO configurations.

The use of veno-venous ECMO support in bronchospasm secondary to anaphylaxis has the same indications and considerations as that which apply to the use of ECMO in severe acute asthma.

SUPPLEMENTAL MANAGEMENT

ANTIHISTAMINES

Patients with immediate hypersensitivity who do not have life-threatening signs may be administered antihistamines, which are an effective treatment for skin (urticarial and pruritic), gastrointestinal and mild respiratory symptoms (rhinorrhea). A combination of H1 (diphenhydramine) and H2 (ranitidine) antagonists are most effective; however, neither are recommended in severe reactions due to the exacerbation of hypotension, sedation or QT-interval prolongation associated with intravenous administration. Antihistamines should not delay or replace the use of epinephrine in anaphylaxis, and are generally omitted in guidelines for the management of life-threatening anaphylaxis.

CORTICOSTEROIDS

Corticosteroids will not alter the course of the acute reaction in anaphylaxis. Their administration is thought to possibly prevent prolonged anaphylaxis or biphasic reactions. It is also a reasonable intervention in patients with bronchospasm or a history of asthma. Methylprednisolone 1–2 mg/kg should be administered after agents effective for acute anaphylaxis have been administered.

GLUCAGON

As patients who are currently taking beta-adrenergic blocking agents have been observed to have a poorer outcome in anaphylaxis, the traditional treatment for beta-blocker overdose is suggested. However, it is unclear if excess mortality is a consequence of beta-blocker therapy or the comorbidities associated with its prescription.

NON-URTICARIAL ANGIOEDEMA

Angioedema without urticaria can occur in patients taking ACEIs or in patients with inherited or acquired C1-esterase inhibitor deficiency. Although the first-line therapy for acute angioedema involving the airways is antihistamines, corticosteroids and epinephrine, this is likely to be ineffective in these patients in which the

angioedema may be at least partly mediated by excess bradykinin. Specific treatments for non-histaminergic angioedema include a bradykinin receptor antagonist (icatibant), a plasma kallikrein inhibitor (ecallantide) or an antifibrinolytic agent (tranexamic acid). For suspected hereditary or acquired C1-esterase deficiency, a purified C1-esterase inhibitor may be indicated.

REMOVING THE TRIGGER

Anaphylaxis results from interaction between the patient and the environment; however, the dose-response curve of IgE-mediated phenomena is such that more allergen exposures causing anaphylaxis are supramaximal doses. Anaphylaxis also represents the consequences of activation of an amplification-cascade sequence of neurological and hormonal events. As such, once the response to a supramaximal dose of allergen is detected (anaphylaxis), the process is now possibly independent of the initial mast-cell degranulation trigger. It is therefore rare that removal of the triggering allergen is an important part of managing anaphylaxis. An exception to this may be food allergens, which may be absorbed slowly and result in a dose-response-sensitive syndrome. Of particular concern is the presence of chlorhexidine and antibiotic-impregnated inserted devices (central venous catheters) and potential for ongoing or prolonged anaphylaxis.

OBSERVATION AFTER ANAPHYLAXIS

Mild cases of anaphylaxis should be observed for 4 hours, while cases that have been administered epinephrine should be observed for 6 hours after the last dose. Severe cases including those that have suffered cardiovascular collapse should be observed at least overnight. Patients with food anaphylaxis or a history of recurrent anaphylaxis are at increased risk of late complications.

Of cases admitted to intensive care for positive pressure ventilation after intraoperative anaphylaxis, 30% are extubated within 6 hours of admissions and 70% within 24 hours.[56] Extubation over an airway exchange catheter after confirmation of sufficient airway patency to allow a leak around a deflated endotracheal tube cuff appears to have a low complication rate.

FOLLOW-UP MANAGEMENT

After recovery from the acute event, it is essential that the patient, family and all health care personnel involved in the patient's care are aware of the trigger and risk of future exposure. Discharge must be with a letter with copies to all concerned detailing the event and advice should be given regarding procurement of an alert bracelet. Follow-up should be arranged with an allergy specialist for further investigations such as allergen skin tests and specific IgE tests if the trigger is unknown. Also a risk reduction strategy should be planned including avoidance of specific triggers and training in the use of self-injectable epinephrine or desensitisation. Anaphylaxis caused by a drug or therapeutic agent should be reported to the appropriate State or National agency.

REFERENCES

1. Richet Charles. *Nobel Lecture, 11 December 1913. The Nobel Prize in Physiology or Medicine 1913.* Nobelprize.org.
2. Simons FER, Ardusso LRF, Bilo MB, et al.; for the World Allergy Organization. World Allergy Organization guidelines for the assessment and management of anaphylaxis. *J Allergy Clin Immunol*. 2011;127:587–593.
3. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol*. 2010;126:477–480.
4. Muraro A, Roberts G, Worm M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy*. 2014;69:1026–1045.
5. Simons FE, Ardusso LR, Bilo MB, et al. International consensus on (ICON) anaphylaxis. *World Allergy Organ J*. 2014;7:9. http://www.waojournal.org/content/7/1/9.
6. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006; 117(2):391–397.
7. McNeil BD, Pundir P, Meekar S, et al. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. *Nature*. 2015;519:237–241.
8. Turner PJ, Gowland MH, Sharma V, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. *J Allergy Clin Immunol*. 2015;135(4):956–963.
9. Gibbison B, Sheikh A, McShane P, et al. Anaphylaxis admissions to UK critical care units between 2005 and 2009. *Anaesthesia*. 2012;67:833–838.
10. Mullins RJ, Wainstein BK, Barnes EH, et al. Increases in anaphylaxis fatalities in Australia from 1997 to 2013. *Clin Exp Allergy*. 2016;46(8): 1099–1110.
11. Knol EF. Requirements for effective IgE cross-linking on mast cells and basophils. *Mol Nutr Food Res*. 2006;50:620–624.
12. Schweitzer-Stenner R, Pecht I. Parameters determining the stimulatory capacity of the type I Fc epsilon-receptor. *Immunol Lett*. 1999;68(1):59–69.
13. Peavy RD, Metcalf DD. Understanding the mechanisms of anaphylaxis. *Curr Opin Allergy Clin Immunol*. 2008;8(4):310–315.
14. Stone SF, Cotterell C, Isbister GK, et al. Elevated serum cytokines during human anaphylaxis: identification of potential mediators of acute allergic

reactions. *J Allergy Clin Immunol*. 2009;124(4): 786–792.
15. Fisher M. Clinical observations on the pathophysiology and treatment of anaphylactic cardiovascular collapse. *Anaesth Intens Care*. 1986;14: 17–21.
16. Moss J, Fahmy NR, Sunder N, et al. Hormonal and haemodynamic profile of an anaphylactic reaction in man. *Circulation*. 1981;63:210–213.
17. Lorenz W, Doenicke A, Meyer R, et al. Histamine release in man by propanidid and thiopentone: pharmacological effects and clinical consequences. *Br J Anaesth*. 1972;44:355–369.
18. Pumphrey RS. Fatal posture in anaphylactic shock. *J Allergy Clin Immunol*. 2003;112(2):451–452.
19. Brown SGA. Cardiovascular aspects of anaphylaxis: implications for treatment and diagnosis. *Curr Opin Allergy Clin Immunol*. 2005;5:359–364.
20. O'Connor RE, Domeier RM. An evaluation of the pneumatic anti-shock garment (PASG) in various clinical settings. *Prehosp Emerg Care*. 1997;1(1): 36–44.
21. Tyberg JV. How changes in venous capacitance modulate cardiac output. *Eur J Physiol*. 2002;445: 10–17.
22. Gow BS. Circulatory correlates: vascular impedance, resistance, and capacity. In: Bohr AP, Somlyo AP, Sparks HV Jr, eds. *Handbook of Physiology, Section 2: The Cardiovascular System*. Vol. II. Vascular Smooth Muscle. Bethesda, MD. American Physiological Society; 1983:35.
23. Clarke R, Sadleir P, Van Niekerk AW, et al. Quantification of volume loss and haemodynamic changes of Gelofusine-induced anaphylaxis during cardiopulmonary bypass. *Anaesth Intens Care*. 2011; 39:492–495.
24. Tan CO, Brace G, Weinberg L, et al. Successful resuscitation of class 4 anaphylaxis guided by transthoracic echocardiography. *Anaesth Intensive Care*. 2014;42:134–148.
25. Chlus N, Cavayero C, Kar P, et al. Takotsubo cardiomyopathy: case series and literature review. *Cureus*. 2016;8(6):e649.
26. Kounis NG. Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management. *Clin Chem Lab Med*. 2016; 54(10):1545–1559.
27. Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. *J Allergy Clin Immunol*. 2014;133: 291–307.
28. Kim MH, Lee JM. Diagnosis and management of immediate hypersensitivity reactions to cephalosporins. *Allergy Asthma Immunol Res*. 2014; 6(6):485–495.
29. Smith WB, Kateralis CH. 'Sulfur allergy' label is misleading. *Aust Prescr*. 2008;31:8–10.
30. Sadleir PH, Clarke RC, Bunning DL, et al. Anaphylaxis to neuromuscular blocking drugs: incidence and cross-reactivity in Western Australia from 2002 to 2011. *Br J Anaesth*. 2013;110:981–987.
31. Harboe T, Johansson SG, Florvaag E, et al. Pholcodine exposure raises serum IgE in patients with previous anaphylaxis to neuromuscular blocking agents. *Allergy*. 2007;62(7):1445–1450.
32. Reddy JI, Cooke PJ, van Schalkwyk JM, et al. Anaphylaxis is more common with rocuronium and succinylcholine than with atracurium. *Anesthesiology*. 2015;122:39–45.
33. Stevenson DD, Sanchez-Borges M, Szczeklik A. Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes. *Ann Allergy Asthma Immunol*. 2001;87:177.
34. Kateralis CH, Smith WB. 'Iodine allergy' label is misleading. *Aust Prescr*. 2009;32:125–128.
35. Bottinor W, Polkampaly P, Jovin I. Adverse Reactions to iodinated contrast media. *Int J Angiol*. 2013;22:149–154.
36. Greenberger PA, Patterson R. The prevention of immediate generalized reactions to radiocontrast media in high-risk patients. *J Allergy Clin Immunol*. 1991;87(4):867–872.
37. Dewachter P, Laroche D, Mouton-Faivre C, et al. Immediate reactions following iodinated contrast media injection: a study of 38 cases. *Eur J Radiol*. 2011;77(3):495–501.
38. Park KW. Protamine and protamine reactions. *Int Anesth Clin*. 2004;42(3):135–145.
39. Calogiuri GF, Di Leo E, Trautmann A, et al. Chlorhexidine hypersensitivity: a critical and updated review. *J Allergy Ther*. 2013;4:141–148.
40. Guyer AC, Banerji A. *ACE inhibitor-induced angioedema*. In: Saini S, ed. *UpToDate*; 2017. Retrieved from: https://www.uptodate.com/contents/ace-inhibitor-induced-angioedema.
41. Van Nunen SA, O'Connor KS, Clarke LR, et al. An association between tickbite reactions and red meat allergy in humans. *Med J Aust*. 2009;190:510–511.
42. Chung CH, Mirakhur B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. *N Engl J Med*. 2008;358: 1109–1117. [PubMed:18337601].
43. Mullins RJ, James H, Platts-Mills TAE, et al. The relationship between red meat allergy and sensitization to gelatin and galactose-alpha-1,3-galactose. *J Allergy Clin Immunol*. 2012;129(5):1334–1342.
44. Mertes PM, Laxenaire MC, Alla F, et al. Anaphylactic and anaphylactoid reactions during anesthesia in France in 1999-2000. *Anesthesiology*. 2003;99(3):536–545.
45. Guerrini M, Beccati D, Shriver Z, et al. Oversulfated chondroitin sulfate is a contaminant in heparin associated with adverse clinical events. *Nat Biotechnol*. 2008;26:669–675.
46. Valent P, Akin C, Arock M, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol*. 2012;157(3):215–225.
47. Dewachter P, Castells MC, Hepner DL, et al. Perioperative management of patients with mastocytosis. *Anesthesiology*. 2014;120:753–759.

48. Schwartz LB. *Laboratory tests to support the clinical diagnosis of anaphylaxis*. In: Kelso JM, ed. *UpToDate*; 2016. Retrieved from: https://www.uptodate.com/contents/laboratory-tests-to-support-the-clinical-diagnosis-of-anaphylaxis.
49. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet*. 1977;1:466–469.
50. Brown SG. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol*. 2004;114(2):371–376.
51. Pumphrey RSH, Roberts ISD. Postmortem findings after fatal anaphylaxis reactions. *J Clin Pathol*. 2000;53:273–276.
52. Bautista E, Simons FER, Simons KJ, et al. Epinephrine fails to hasten hemodynamic recovery in fully developed canine anaphylactic shock. *Int Arch Allergy Immunol*. 2002;128:151–164.
53. Clark R, Sadleir P, Van Niekerk AW, et al. Quantification of volume loss and haemodynamic changes of Gelofusine-induced anaphylaxis during cardiopulmonary bypass. *Anaes Intensive Care*. 2011;39:492–495.
54. Mertes PM, Malinovsky JM, Jouffroy L, et al. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol*. 2011;21(6):442–453.
55. Di Chiara L, Stazi GV, Ricci Z, et al. Role of vasopressin in the treatment of anaphylactic shock in a child undergoing surgery for congenital heart disease: a case report. *J Med Case Reports*. 2008;2:36.
56. Sadleir PHM, Clarke RC, Bozic B, et al. Consequences of proceeding with surgery after resuscitation from intra-operative anaphylaxis. *Br J Anaesth*. 2017;73(1):32–39.

68

Host defence and immunodeficiency

Alexander A Padiglione, Steve McGloughlin

Diverse host defence mechanisms protect the body from a great variety of microorganisms, and also play a role in protecting us from cancer. There is a coordinated immunological response to infection, involving both cellular and humoral components. The immune system can be defective in many ways, leading to an increased propensity to infections, and sometimes cancer. However, the response also needs to be controlled to avoid inappropriate and excessive activation, such as when excessive systemic activation results in disseminated intravascular coagulation (DIC).

INNATE IMMUNITY

The innate immune system is the first line of defence against many microorganisms, providing immediate but non-specific responses that do not require prior exposure to antigens from those microorganisms. This system consists of plasma proteins (including components of the complement system, via the alternative pathway or mannose-binding lectin [MBL] pathway), some lymphocytes with cytotoxic activity (natural killer or NK cells) and some macrophage functions. It also has an important role in antigen presentation to stimulate the longer-lasting adaptive immune response.

ACUTE-PHASE REACTION

The acute-phase reaction is a response of the haematopoietic and hepatic systems, involving many plasma proteins and cellular components of the blood. It occurs within hours of acute physical stress or infection. Most of the proteins are inflammatory mediators or inhibitors of transport proteins. Fibrinogen, the bulk protein of the coagulation system, is one of the plasma proteins to show the greatest rise in the acute-phase reaction, and is responsible for the elevation in the erythrocyte sedimentation rate. Decreases in haemoglobin, serum iron and albumin can all occur. The fall in albumin is due to redistribution and decreased synthesis and generally does not require supplementation. The function of many acute-phase proteins remains unclear, but may be beneficial to the patient.

THE ADAPTIVE IMMUNE SYSTEM

Adaptive immune responses exhibit specificity, memory, amplification and diversity. This specificity (immune response against a particular antigen) and memory (prompt response on subsequent exposures) is mediated by antigen receptors on the surface of lymphocytes. Amplification and diversity of immune responses are regulated by cytokines, which are secreted by lymphocytes and other cells, and through the effects of various lymphocyte surface molecules, including adhesion molecules and co-stimulatory molecules. Cytokines have various activities, the most important of which are cell activation (e.g. interferon gamma [IFN-γ]), regulation of immune responses (e.g. interleukin [IL]-10) and pro-inflammatory effects (e.g. tumour necrosis factor [TNF] and lymphotoxins).

ANTIGEN PRESENTATION AND THE ROLE OF T AND B LYMPHOCYTES

The adaptive immune response is initiated by the processing and presentation of fragments of a microorganism in a form that makes them antigenic to lymphocytes. Major histocompatibility complex (MHC) class I (human leucocyte antigen [HLA]-A, B, C) and class II (HLA-DR, DP, DQ) molecules are the major cell-surface antigen presentation molecules, and determine the nature of the subsequent response against the antigen.

Class I MHC molecules are present on most nucleated cells, and present processed *endogenous* peptides (such as fragments of viruses) to the T-cell receptor (TcR) of CD8+ (cytotoxic) T lymphocytes. Activated CD8+ T cells have a cytotoxic effect on the presenting cell, resulting in the death of the cell and inhibition of viral replication.

Class II MHC molecules are found on macrophages and monocytes (where they present fragments of phagocytosed microorganisms to TcRs on CD4+ [helper] T cells) and B cells (where antigen is bound to specific surface immunoglobulins, the B-cell antigen receptor).

Activation of CD4+ T cells by these *exogenous* antigens results in the expression of cell-surface molecules

ABSTRACT

The innate immune system provides immediate but non-specific responses to infection. The adaptive immune response is delayed and relies on antigen presentation to lymphocytes, but exhibits specificity, memory, amplification and diversity. Immunodeficiency disorders can be classified functionally into five groups: antibody deficiency, complement deficiency, cellular immunodeficiency, phagocyte dysfunction and combined immunodeficiency (T cells, B cells and NK cells). Aetiologically, they may be primary (which are rarer, usually more severe and manifest at a younger age) or acquired.

Critical illness itself can be immunosuppressive. Asplenic/hyposplenic patients are at lifelong risk of overwhelming sepsis, and require education, vaccination and appropriate use of antibiotics.

KEYWORDS

Immunodeficiency
CVID
immunoglobulins
immunity
asplenia
spleen

Table 68.1 Immunoglobulin isotypes

IMMUNOGLOBULIN	TYPES	CHARACTERISTICS
IgM	1	Large pentamer Major effect within circulation early in the immune response – presence may indicate recent infection Important opsonin Activates complement and works as a bacterial agglutinator
IgA	2	IgA_1 & IgA_2 Produced at secretory surfaces, such as the mucosa of the gut and respiratory tract, and also in the breast, where it is a major constituent of colostrum and provides secretory antibody to the gut of the neonate
IgE	1	Produced at mucosal surfaces Important part of the immune response against parasitic infections
IgD	1	Mainly acts as a B-cell receptor
IgG	4	Only antibody able to cross the placenta IgG_1 & IgG_3: Important opsonin, particularly effective at activating complement and binding to Fc receptors on phagocytic cells IgG_2: mainly active against polysaccharide antigens, such as those present in bacterial cell walls IgG_4: functions remain uncertain

and secretion of cytokines with immunoregulatory effects. These immunoregulatory molecules augment the functions of many other cells, including B cells, T cells and macrophages (T-cell help). CD4+ T-cell activation may also elicit macrophage activation (critically dependent on the production of IFN-γ) to assist in killing of the microorganism.

Proliferating B cells differentiate into plasma cells, which secrete immunoglobulins with antibody activity against the initiating antigen, or into memory B cells, which live for a long time and rapidly respond on re-exposure to an antigen.

IMMUNOGLOBULINS

Nine isotypes of immunoglobulin (also known as antibodies) can be produced, each of which has a different function (see Table 68.1).

SECONDARY ANTIBODY FUNCTION

Antibodies act through one of several secondary effector mechanisms. Antibodies complexed with antigens can activate the complement system through the classical pathway, resulting in the generation of biologically active molecules, such as C3b, which is an important opsonin, and the activation of the membrane attack complex (MAC), which directly lyses bacterial cell walls.

Antibodies of the IgM, IgG_1 and IgG_3 isotypes are also important opsonins. These molecules, when bound to the surface of a microorganism, enhance binding to immune cells and facilitate their phagocytosis. These effects of complement and antibody are mediated through complement receptors (CRs) and receptors for the Fc portion of the immunoglobulin molecules (Fc receptors) on the surface of phagocytic cells such as neutrophils and macrophages.

DIVERSITY OF IMMUNE RESPONSES

Different microorganisms elicit different types of immune response. Virus-infected cells elicit a cytotoxic CD8+ T-cell response; intracellular pathogens such as mycobacteria and protozoa elicit a CD4+ T-cell response, which results in macrophage activation; encapsulated bacteria elicit an opsonising antibody response; other bacteria such as *Neisseria* spp. elicit a complement-activating antibody response, which lyses the cell wall of the bacterium. The nature of the immune response is regulated by cytokines, which provide T-cell help (Th) in the course of an immune response. Thus IL-2, IL-12 and IFN-γ production induces a predominantly cellular immune response (Th1), whereas the production of IL-4 and IL-13 induces a predominantly antibody-mediated immune response (Th2).

IMMUNODEFICIENCY DISORDERS

Immunodeficiency can be classified functionally into five groups: antibody deficiency, complement deficiency, cellular immunodeficiency, phagocyte dysfunction and combined immunodeficiency (T cells, B cells and NK cells).

Immunodeficiency can also be classified aetiologically as either primary or acquired.

Primary immunodeficiency disorders are the result of a developmental anomaly or a genetically determined defect of the immune system. Primary immunodeficiency due to an absent or non-functional gene product critical for normal function is more severe, so it tends to present early in life. Primary immunodeficiency due to aberrant regulation of lymphocyte differentiation, which is probably determined by the products of several genes and may be influenced by environmental factors, tends to be less severe so it presents later. Our understanding of the genetic basis of many of these conditions is improving, including a number of specific gene defects that lead to selective susceptibility to single pathogens.

Acquired immunodeficiency disorders are more common than primary immunodeficiency disorders and may present at any time after early childhood. Most result from an immune defect that is a consequence of a disease process, infection (e.g. human immunodeficiency virus [HIV]) or complication of a therapeutic procedure such as splenectomy, immunosuppressant therapy or haemopoietic stem cell transplantation (HSCT).

An immunodeficiency disorder may be considered in an adult patient with an unexplained abnormal propensity to infections, such as recurrent or multiple serious infections (e.g. deep abscess, meningitis, osteomyelitis, sepsis, pneumonia), persistent thrush, opportunistic infections or poor response to antimicrobial therapy, and requires the demonstration of a specific immune defect (Table 68.2).

ANTIBODY DEFICIENCY

A poor systemic antibody response most commonly results in a lack of opsonising antibody, and a propensity to infections with encapsulated bacteria such as *Streptococcus pneumoniae* or *Haemophilus influenzae*, often manifesting as recurrent respiratory tract infections including sinusitis. Chronic enterovirus infections of the nervous system and infection with some mycoplasmas may also occur in children with severe primary immunoglobulin deficiency (agammaglobulinaemia).

PRIMARY ANTIBODY DEFICIENCY DISORDERS

Failure of B-cell production or differentiation is the cause of most primary antibody deficiency disorders.[1]

X-linked agammaglobulinaemia (XLA) is a rare disorder due to mutations of the *Btk* gene on the X-chromosome that results in the absence of a B-cell tyrosine kinase necessary for the maturation of B cells, and hence absent mature B cells in blood and secondary lymphoid tissues and consequent immunoglobulin deficiency. In the hyper-IgM immunodeficiency syndrome, B cells are able to differentiate into plasma cells secreting IgM at elevated levels, but not IgG, IgA or IgE.

Common variable immunodeficiency (CVID) is a group of disorders that appear to be the consequence of immunoregulatory defects that result in impaired B-cell differentiation, leading to hypogammaglobulinaemia. It may manifest as recurrent respiratory tract infections, enteropathy and malignancies.

IgA deficiency also results from impaired B-cell differentiation. Deficient secretory antibody responses are common in patients with IgA deficiency, but most affected individuals are able to produce compensatory secretory IgM or IgG antibody responses and are asymptomatic. Some may also have a defect of systemic antibody responses, such as an IgG subclass deficiency and/or impairment of antibody responses to polysaccharide antigens, and hence suffer from recurrent respiratory tract infections.[2]

The immunoregulatory defect underlying CVID and IgA deficiency sometimes results in an increased propensity to autoimmunity. This can include the production of anti-IgA antibodies, which may result in anaphylactoid reactions to blood products containing IgA.

ACQUIRED ANTIBODY DEFICIENCY DISORDERS

B-cell chronic lymphocytic leukaemia or lymphoma and myeloma are commonly associated with reduced synthesis of normal immunoglobulins, which may result in bacterial infections.[3] A thymoma is a rare cause of immunoglobulin deficiency, and should be considered in a patient presenting with primary immunoglobulin deficiency after the age of 40.[4]

Asplenic patients have impaired production of antibodies against polysaccharide antigens, leading to infection with encapsulated bacteria, such as pneumococcus, *H. influenzae* type B and meningococcus.[5]

Drugs occasionally affect B-cell differentiation and cause immunoglobulin deficiency, particularly IgA deficiency. The most common offender is phenytoin. Most patients do not have antibody deficiency severe enough to cause infections. Intensive plasmapheresis may also cause severe immunoglobulin deficiency if immunoglobulin replacement is not used.

TREATMENT OF ANTIBODY DEFICIENCY DISORDERS

Infections can be prevented by regular monthly infusions of intravenous immunoglobulin (IVIg) in patients with primary or acquired antibody deficiency. Acute infections should be treated with appropriate antibiotics. The routine use of IVIg as an adjunct in the management of sepsis in adults cannot be recommended, as higher-quality studies have failed to confirm earlier suggestions of benefit.

CELLULAR IMMUNODEFICIENCY

Impairment of cell-mediated immune responses leads to an increased propensity to infections normally controlled by cellular immune responses (see Table 68.2). These pathogens typically replicate intracellularly

Table 68.2 Tests of immunocompetence

IMMUNE DEFICIENCY SYNDROME	CLINICAL MANIFESTATION	TESTS
Antibody-mediated	Recurrent bacterial infection, especially with encapsulated bacteria, e.g.: *Streptococcus pneumoniae* *Neisseria meningitidis* *Haemophilus influenzae*	Immunoglobulin G, A and M levels IgG subclasses Peripheral blood B-cell count (CD 19) *Consider:* Immunisation response to: Polysaccharide antigens (e.g. pneumococcal, pre and post vaccination) Protein antigens (e.g. tetanus and diphtheria antibodies)
Cell-mediated immunity	Predominantly intracellular pathogens: Viruses Herpes simplex viruses Cytomegalovirus Varicella-zoster virus Epstein–Barr virus Molluscum contagiosum virus JC virus (cause of progressive multifocal leucoencephalopathy) Mycobacteria *Mycobacterium tuberculosis* *Non-tuberculous mycobacteria* Bacterial *Salmonella* spp. *Shigella* spp. *Listeria monocytogenes* Fungi and yeasts *Candida* spp. (mucosal infections) Cryptococci *Aspergillus* spp. Protozoa *Toxoplasma gondii* Cryptosporidia *Pneumocystis jiroveci*	Peripheral blood T-cell subsets (CD3+, CD4+ and CD8+) Serology for HIV (+/– HTLV) *Consider:* T-cell response to antigens Cytokine assays Delayed-type hypersensitivity (DTH) skin test responses to antigens (rarely done now)
Phagocyte function	Recurrent severe bacterial infection, esp. *N. meningitidis*	Neutrophil count *Consider:* Tests of oxidative killing mechanisms, e.g. nitroblue tetrazolium reduction test (NBT) *or* dihydrorhodamine oxidation Neutrophil migration assays Bacteria *or Candida* killing assays
Complement system	*S. pneumoniae* *N. meningitidis* *Moraxella* spp. *Acinetobacter* spp.	Immunochemical quantitation of C3 and C4 Functional assay of the classical pathway (CH50) *Consider:* Functional assay of the alternative pathway (AH50) Immunochemical quantification of other individual components

and cause persistent (latent) infections that reactivate when the cellular immune response against them becomes ineffective.

PRIMARY CELLULAR IMMUNODEFICIENCY

Children with the DiGeorge syndrome have a complete or partial absence of the thymus, resulting in depletion of T cells from blood and lymphoid tissue.[6]

Chronic mucocutaneous candidiasis describes a heterogeneous, and often a less severe, group of cellular immune deficiencies. In some populations it has been associated with specific mutations in the autoimmune regulator (AIRE) gene and be an early manifestation of the autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) syndrome, together with adrenal insufficiency and autoimmune hypoparathyroidism.[7]

ACQUIRED CELLULAR IMMUNODEFICIENCY

HIV infection is the most common cause of acquired cellular immunodeficiency (see Chapter 69). Less common causes include Hodgkin disease, T-cell lymphomas and sarcoidosis, which may also be complicated by opportunistic infections. A thymoma is a rare cause of chronic mucocutaneous candidiasis that occurs later in life.[4]

Suppression of cellular immune responses is an intended effect of many immunosuppressant drugs used to treat allograft rejection, graft-versus-host disease (GvHD), autoimmune diseases and vasculitis. Opportunistic infections may complicate this type of immunodeficiency.

TREATMENT OF CELLULAR IMMUNODEFICIENCY DISORDERS

Most infections complicating cellular immunodeficiency are reactivated latent infections. The degree and duration of cellular immunodeficiency determines the risk and type of infection. Use of prophylactic antimicrobials is important, and best defined in HIV-induced immunodeficiency.[8]

Acquired cellular immunodeficiency may be corrected by removing its cause (e.g. treating HIV, or ceasing immunosuppressives). Thymus transplantation may be effective in children with thymus aplasia.

COMPLEMENT COMPONENT DEFICIENCY

Deficiency of complement components is an uncommon but often overlooked cause of recurrent bacterial infections. Complement-mediated lysis of bacterial cell walls is a critical defence against certain bacteria, especially *Neisseria* spp. and related bacteria such as *Moraxella* spp. and *Acinetobacter* spp. Deficiency of classical pathway components may also result in impaired antibody responses.

PRIMARY COMPLEMENT DEFICIENCY

Congenital deficiency of C3 is extremely rare. C3b is an important opsonin and C3 deficiency will often impair phagocytosis of bacteria, causing a propensity to severe pyogenic infections. Deficiency of MAC components is more common, and should be considered in patients with recurrent meningococcal infections.[9] Deficiency of classical pathway components (C1, C2, C4) may also result in an increased propensity to infection with meningococci and other bacteria, but most affected individuals do not experience recurrent infections.

ACQUIRED COMPLEMENT DEFICIENCY

Disease processes that cause persistent activation of the complement system may cause depletion of complement components, particularly classical pathway components. This can result in infections with *Neisseria* spp. or related bacteria, and sometimes overwhelming septicaemia when the complement deficiency is severe. Systemic lupus erythematosus, myeloma and chronic atrioventricular shunt infections are rare causes of complement component deficiency.

MANAGEMENT OF PATIENTS WITH COMPLEMENT DEFICIENCY

An awareness of the possibility of complement deficiency is the most important aspect of management. Replacement therapy is not available. If a complement component deficiency is identified, screening of family members should be considered.

PHAGOCYTE DISORDERS

Phagocytosis of a bacterium or fungus by a neutrophil, leucocyte or macrophage is dependent on chemotaxis (attraction of phagocytes to the site of infection), adhesion (to endothelial cells via molecules such as integrins), binding (to opsonins on the microorganism), ingestion and intracellular killing (which involves both oxidative and non-oxidative mechanisms).

Depletion or functional impairment of phagocytes results in an increased propensity to bacterial and fungal infections, particularly infection with *Staphylococcus aureus*, Gram-negative enteric bacteria, *Candida* spp. and *Aspergillus* spp. Primary or acquired defects of phagocytes may result in localised pyogenic infections or pneumonia. Patients with severe neutropenia, however, may have little inflammatory reaction and overwhelming systemic infections, including systemic fungal and yeast infections, are common.

PRIMARY DISORDERS OF PHAGOCYTOSIS

Congenital neutropenias are rare. Defects of phagocyte function usually affect chemotaxis, adhesion or intracellular killing, either alone or in combination. The best-characterised defect of phagocyte adherence results from a congenital absence of the β-subunit of CD18 integrins in patients with leucocyte adhesion deficiency syndrome type 1.[10]

Defects of intracellular killing are usually caused by a deficiency of microbicidal enzymes. Chronic granulomatous disease (CGD) results from a deficiency of a phagosome enzyme (NADPH oxidase) leading to ineffective oxidative killing.[11] CGD usually presents in childhood but may present in adults. It should be considered in patients with recurrent abscesses or suppurative lymphadenitis, and in patients with pneumonia caused by *S. aureus* or *Aspergillus* spp. infection.

ACQUIRED DISORDERS OF PHAGOCYTOSIS

Severe neutropenia may be complicated by bacterial or fungal infections. There are many causes of neutropenia, including autoimmune neutropenia, drug therapy and haematological diseases such as cyclic neutropenia, myelodysplastic syndromes and aplastic anaemia. Cytotoxic chemotherapy commonly causes

neutropenia, and is often complicated by severe bacterial and fungal infections.

MANAGEMENT OF PHAGOCYTE DISORDERS

Acquired neutropenia may be corrected by removing the underlying cause and/or use of granulocyte colony-stimulating factor (G-CSF). Febrile neutropenia requires investigation for the source of sepsis and empirical antibiotics. If fever persists, then antifungals should be added. IFN-γ therapy may be effective in patients with CGD.

COMBINED IMMUNODEFICIENCY DISORDERS

Several immunodeficiency disorders result from a combination of immune defects, some of which are so severe that death is common unless the defect can be corrected. Such conditions are classified as severe combined immune deficiency (SCID) syndromes.

PRIMARY COMBINED IMMUNODEFICIENCY

There are many primary combined immunodeficiency syndromes, which present in early childhood.[12] Specific molecular defects have now been demonstrated for many of them. For example, defective expression of MHC class II molecules, adenosine deaminase (ADA) deficiency, and deficiency of the common γ-chain of the receptor for several interleukins (IL-2, 4, 7, 9, 15, 21) all result in a deficiency and/or functional impairment of B cells, T cells and sometimes NK cells. Deficiency of the IL receptor common γ-chain results from mutations of its gene on the X-chromosome and is the underlying defect of X-linked SCID.

Treatment of primary combined immunodeficiency

HSCT is the main treatment for many types of primary SCID, though enzyme replacement therapy can be effective in ADA deficiency and gene replacement therapy has been used to treat X-linked SCID. Antibody replacement with IVIg therapy and prophylaxis for opportunistic infections are also important in primary SCID.

ACQUIRED COMBINED IMMUNODEFICIENCY

Combined immune defects may also be acquired from disease or its treatment.

Haemopoietic stem cell transplantation

Combined immune defects may result in severe infections in patients who have received HSCT.[13] Following transplantation, an immunodeficient state exists until the recipient's immune system is reconstituted with donor cells. Consequently, both antibody-mediated and cell-mediated immunity are deficient in the first 3–4 months after transplantation and may remain deficient for a longer period of time in patients with GvHD. This immune defect is often compounded by neutropenia and/or the effects of corticosteroid or immunosuppressant therapy for GvHD. Defective antibody responses may persist for several years after transplantation, particularly antibody responses against polysaccharide antigens.

Critical illness

Many patients who are critically ill as a result of surgery, trauma, burns or overwhelming sepsis also have acquired immune defects. These defects include abnormalities of cellular immunity, immunoglobulin deficiency and impaired neutrophil function and appear to be associated with an increased risk of infection. Impairment of cell-mediated immune responses usually manifests as decreased T-cell proliferation and impaired delayed-type hypersensitivity responses, and probably results from a combination of factors, including the effects of anaesthetic drugs, blood transfusion, negative nitrogen balance and serum suppressor factors, including cytokines such as TNF. Phagocyte defects are mostly due to impairment of neutrophil chemotaxis by serum factors, and impaired intracellular killing. Deficiency of serum immunoglobulins also occurs, especially IgG deficiency, and may be associated with antibody deficiency. Serum leakage is a factor in patients with burns, and reduced synthesis and increased catabolism of immunoglobulins occur in many critically ill patients.

There is no specific treatment for immune defects in critically ill patients. General measures such as adequate nutrition, achieving a positive nitrogen balance and excision of burns appear helpful. Biological response modifiers, cytokine and mediator inhibitors, and IVIg therapy have all been evaluated. IVIg therapy reduces the number of acute infections, particularly pneumonia, but patient survival is not increased. Administration of G-CSF is safe in intensive care patients, but does not improve outcomes and cannot be routinely recommended.

Asplenia and hyposplenism

The spleen is an important part of the immune system's response to infections, particularly bloodstream infections. Splenic macrophages remove opsonised microorganisms from the blood, and IgM memory B cells produce an early antibody response to the polysaccharide antigens of encapsulated bacteria. The risk of overwhelming post-splenectomy infection (OPSI) is around 1 in 500 per annum, with 50% mortality. OPSI is most commonly caused by encapsulated bacteria, such as *Pneumococcus, Meningococcus* and *H. influenzae*, for which vaccines are available. Other important infections may include group A *Streptococcus, Capnocytophaga canimorsus* (following dog bites), *Salmonella, Enterococcus* and *Bacteroides*.

Asplenic/hyposplenic patients require education, vaccination and appropriate use of antibiotics. Pneumococcal, meningococcal and *H. influenzae* vaccines, including regular boosters, and annual influenza vaccine are

recommended, preferably 14 days before removal of the spleen if performed electively, or at least 14 days after if not.[14] Antibiotic prophylaxis (penicillin, or if allergic, macrolides) should be given in accordance with national guidelines. Enrolment of patients in spleen registries, where available, can offer ongoing patient education, vaccination reminders and access to updated recommendations (e.g. https://spleen.org.au/VSR/index.html).

Biological immune response modulators

Anti-TNF agents such as infliximab have been associated with increased rates of bacterial infection,[15] tuberculosis and some opportunistic infections.

Antibodies targeting various B- and T-cell antigens are increasingly used for rheumatological and haematological diseases. Not unexpectedly, these agents are associated with infections. For example, the anti-CD20 antibody rituximab specifically targets B cells for its therapeutic action, but is associated with infectious complications such as recurrent bacterial infection, reactivation of hepatitis B, cytomegalovirus (CMV) infection and progressive multifocal leukoencephalopathy (PML).

KEY REFERENCES

1. Buckley RH. Primary immunodeficiency diseases due to defects in lymphocytes. *N Engl J Med*. 2000;343:1313–1324.
8. Kovacs JA, Masur H. Prophylaxis against opportunistic infections in patients with human immunodeficiency virus infection. *N Engl J Med*. 2000;342:1416–1429.
9. Fijen CA, Kuijper EJ, te Bulte MT, et al. Assessment of complement deficiency in patients with meningococcal disease in The Netherlands. *Clin Infect Dis*. 1999;28:98–105.
12. Buckley RH. Advances in the understanding and treatment of human severe combined immunodeficiency. *Immunol Res*. 2001;22:237–251.
13. Ninin E, Milpied N, Moreau P, et al. Longitudinal study of bacterial, viral, and fungal infections in adult recipients of bone marrow transplants. *Clin Infect Dis*. 2001;33:41–47.
14. Shatz DV, Schinsky MF, Pais LB, et al. Immune responses of splenectomized trauma patients to the 23-valent pneumococcal polysaccharide vaccine at 1 versus 7 versus 14 days after splenectomy. *J Trauma*. 1998;44:760.
15. Curtis JR, Patkar N, Xie A, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor α antagonists. *Arthritis Rheum*. 2007;56:1125–1133.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Buckley RH. Primary immunodeficiency diseases due to defects in lymphocytes. *N Engl J Med*. 2000;343: 1313–1324.
2. French MA, Denis K, Dawkins RL, et al. Infection susceptibility in IgA deficiency: correlation with low polysaccharide antibodies and deficiency of IgG_2 and/or IgG_4. *Clin Exp Immunol*. 1995;100: 47–53.
3. Tsiodras S, Samonis G, Keating MJ, et al. Infection and immunity in chronic lymphocytic leukemia. *Mayo Clin Proc*. 2000;75:1039–1054.
4. Tarr PE, Sneller MC, Mechanic LJ, et al. Infections in patients with immunodeficiency with thymoma (Good syndrome). Report of 5 cases and review of the literature. *Medicine (Baltimore)*. 2001;80:123–133.
5. Cherif H, Landgren O, Konradsen HB, et al. Poor antibody response to pneumococcal polysaccharide vaccination suggests increased susceptibility to pneumococcal infection in splenectomized patients with hematological diseases. *Vaccine*. 2006;24: 75–81.
6. Hong R. The DiGeorge anomaly. *Clin Rev Allergy Immunol*. 2001;20:43–60.
7. Collins SM, Dominguez M, Ilmarinen T, et al. Dermatological manifestations of autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy syndrome. *Br J Dermatol*. 2006;154: 1088–1093.
8. Kovacs JA, Masur H. Prophylaxis against opportunistic infections in patients with human immunodeficiency virus infection. *N Engl J Med*. 2000; 342:1416–1429.
9. Fijen CA, Kuijper EJ, te Bulte MT, et al. Assessment of complement deficiency in patients with meningococcal disease in The Netherlands. *Clin Infect Dis*. 1999;28:98–105.
10. Bunting M, Harris ES, McIntyre TM, et al. Leukocyte adhesion deficiency syndromes: adhesion and tethering defects involving beta 2 integrins and selectin ligands. *Curr Opin Hematol*. 2002;9: 30–35.
11. Winkelstein JA, Marino MC, Johnston RB Jr, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. *Medicine (Baltimore)*. 2000;79:155–169.
12. Buckley RH. Advances in the understanding and treatment of human severe combined immunodeficiency. *Immunol Res*. 2001;22:237–251.
13. Ninin E, Milpied N, Moreau P, et al. Longitudinal study of bacterial, viral, and fungal infections in adult recipients of bone marrow transplants. *Clin Infect Dis*. 2001;33:41–47.
14. Shatz DV, Schinsky MF, Pais LB, et al. Immune responses of splenectomized trauma patients to the 23-valent pneumococcal polysaccharide vaccine at 1 versus 7 versus 14 days after splenectomy. *J Trauma*. 1998;44:760.
15. Curtis JR, Patkar N, Xie A, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor α antagonists. *Arthritis Rheum*. 2007;56:1125–1133.

69

Human immunodeficiency virus and acquired immunodeficiency syndrome

Alexander A Padiglione, Steve McGloughlin

HUMAN IMMUNODEFICIENCY VIRUS/ ACQUIRED IMMUNODEFICIENCY SYNDROME AND THE INTENSIVE CARE UNIT

Modern antiretroviral therapy (ART) is so effective that the mortality of patients with treated human immunodeficiency virus (HIV) approaches that for the general population. Correspondingly, in developed countries the mortality risk for patients with treated HIV in intensive care unit (ICU) is now more closely related to their acute illness severity than to their degree of immunosuppression.[1]

Patients with HIV may be admitted to intensive care because of:

- *direct complications of immune deficiency:* classically, infections such as *Pneumocystis jiroveci* pneumonia (PJP) or cryptococcal meningitis, or tumours, especially lymphoma
- *indirect complications of HIV or its treatment not due to immune deficiency:* examples include sepsis or myocardial infarction, or treatment side effects
- *problems unrelated to HIV infection:* e.g. major surgery, self-poisoning or trauma; these represent an increasing proportion of the HIV infected patients in intensive care.[2]

Respiratory failure remains the commonest cause for admission; an HIV test is indicated in any critically ill patient with unexplained respiratory failure. PJP was the predominant cause, but bacterial pneumonia and non–HIV-related respiratory illnesses (e.g. chronic obstructive pulmonary disease, asthma) are increasing in prevalence. Immune reconstitution disease can also cause respiratory failure in patients with opportunistic infections recently commenced on ART.

Sepsis is an important cause of admission to ICUs amongst HIV patients; bloodstream and lower respiratory tract infections are most common. Whilst some studies suggest that HIV is an independent risk factor for sepsis and sepsis mortality, others suggest mortality is the same as in the HIV-negative population; local epidemiology (e.g. access to combination ART [cART], socioeconomic status, drug use) and co-morbidities, especially hepatitis C co-infection, may explain these differences. Early recognition of bacterial sepsis as a cause for an acute illness in HIV patients is vital. HIV patients in the ICU may also be at an increased risk of severe nosocomial infections.[1]

HUMAN IMMUNODEFICIENCY VIRUS REPLICATION

Human immunodeficiency viruses 1 and 2 are retroviruses that infect cells of the immune system with subsequent immune disturbance, especially immunodeficiency. The major cell surface receptor for HIV is the CD4 molecule, but chemokine receptors (CCR5 or CXCR4) act as a co-receptor. Inside the cell, the viral RNA is reverse-transcribed into DNA by a viral reverse transcriptase enzyme. This proviral DNA is integrated into the host DNA by a viral integrase enzyme. The proviral DNA remains in the nucleus until the cell is activated, when it is transcribed into RNA, which provides the template for assembly of new HIVs under the control of viral enzymes such as proteases. Budding of new virus from the cell leads to infection of new cells and a repeat of the replication cycle.

PRIMARY HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Primary HIV infection ('seroconversion illness') occurs in 50%–75% of infected patients, typically 1–4 weeks after exposure to HIV. This infectious mononucleosis-like syndrome is characterised by fever, lymphadenopathy, headache, photophobia, fatigue and myalgia. However, mucocutaneous lesions, neurological disease and even transient immunodeficiency with secondary infections may occur.[3]

CHRONIC HUMAN IMMUNODEFICIENCY VIRUS INFECTION

The viraemia in primary HIV infection is partially controlled by cellular and antibody-mediated immune responses, which corresponds with resolution of symptoms. However, HIV replication continues to take place even though most patients are

ABSTRACT

The widespread uptake of effective antiretroviral therapy has seen a shift from intensive care unit (ICU) admissions directly related to human immunodeficiency virus or its treatment, to admissions for unrelated problems. Similarly, prognosis is now more closely related to severity of the acute illness than degree of immunosuppression. Antiretrovirals rarely need to be started urgently, but patients already on treatment should continue it during their ICU admission if possible; this can be challenging, as most antiretrovirals are oral. Serious interactions between antiretrovirals and common ICU drugs are frequent. Patients on effective antiretrovirals pose little risk to staff; needlestick injuries on undiagnosed and untreated patients pose a more significant risk but can be minimised by good infection control and protocols that enable access to post-exposure prophylaxis with antiretrovirals.

KEYWORDS

Human immunodeficiency virus
HIV
acquired immunodeficiency syndrome
AIDS
antiretroviral
ART
pneumocystis
Kaposi sarcoma
CMV
cryptococcal meningitis
needlestick

asymptomatic. This results in activation of the immune system, immune dysregulation, and eventually cellular immunodeficiency, in particular depletion of CD4+ T cells. These abnormalities develop at different rates in different individuals, depending on both host and viral factors. The median from acquiring HIV infection to developing the acquired immunodeficiency syndrome (AIDS) in the pre-ART era was around 9 years. However, about 5% of HIV-infected individuals have no evidence of CD4 loss even after 15 years and are referred to as long-term non-progressors.

There is a persistent immune response against the virus, but this usually slowly fails owing to CD4 cell depletion, immune dysregulation and viral mutation; viral replication increases and other cells become infected, including macrophages and microglial cells of the nervous system.

Chronic HIV infection may cause weight loss, fevers, lymphadenopathy and diarrhoea, though such symptoms are more likely to be caused by an opportunistic infection. Worsening HIV infection leads to a T-cell immunodeficiency syndrome, manifesting as opportunistic infections (e.g. PJP) and tumours (classically, Kaposi sarcoma [KS] and T-cell lymphoma). Neurological disease may also develop. Very severe T-cell deficiency (<100 cells/mL) presents with diseases such as cryptococcal meningitis, CMV retinitis, disseminated *Mycobacterium avium* complex (MAC) and cerebral toxoplasmosis. Globally, tuberculosis (TB) is the most common opportunistic infection; at higher CD4 counts, pulmonary disease predominates, whilst unusual extrapulmonary manifestations (including meningitis and miliary disease) are increasingly likely at lower CD4 counts.

DIAGNOSIS

HIV infection is diagnosed by demonstrating anti-HIV antibodies in the patient's serum. It may take a number of weeks for HIV antibody to become positive during seroconversion. Current testing is with combination antigen/antibody tests, which dramatically reduce any window period.[4] Most patients with HIV have positive antibodies by 3 months; after this time, absence of antibodies excludes HIV infection in almost all cases.

HUMAN IMMUNODEFICIENCY VIRUS VIRAL LOAD MONITORING/GENOTYPE TESTING

Polymerase chain reaction (PCR) testing allows the quantification of viral nucleic acid. The serum HIV viral load is usually tested every 3–4 months, and is useful in monitoring response to treatment.[5] Specific mutations in the viral RNA confer resistance to specific antiretroviral drugs. These mutations can be detected by PCR and sequencing; this genotyping is done at first diagnosis, or when a treatment regimen is failing, to guide subsequent therapy.[6]

IMMUNOLOGICAL MONITORING

Immunodeficiency and neurological disease caused by HIV infection usually develop gradually over years. The blood CD4+ T-cell count/percentage is the best indicator of the severity of HIV-induced immunodeficiency, and therefore of the patient's susceptibility to opportunistic infections. Whilst significant AIDS-related illnesses tend to occur at a CD4+ count of less than 200, there is clear benefit of starting therapy in any patient with HIV irrespective of CD4+ count, both to decrease AIDS-related morbidity/mortality, and to minimise risk of HIV transmission to others ('treatment as prevention').[7]

MANAGEMENT OF THE HUMAN IMMUNODEFICIENCY VIRUS-INFECTED PATIENT

cART has had a dramatic impact on the morbidity and mortality associated with HIV infection. Patients on effective treatment can expect a near-normal lifespan. Six classes of antiretroviral drugs are available, and function at various points in the HIV replication cycle (Table 69.1).

Antiretroviral drugs should not be used individually. Triple combination therapy against a sensitive virus usually leads to sustained virological control without the development of resistance. Adherence to ART is critical. The choice of drug therapy should be based on national guidelines and individualised for patient characteristics and genotyping results.[8]

The potency of some newer integrase inhibitors has led to renewed interest in using fewer than 3 agents to maintain virological control while minimising long-term toxicity.

DRUG TOXICITY

Improvements in ART have seen reductions in serious side effects. Older agents previously associated with lipodystrophy, lactic acidosis, peripheral neuropathy and pancreatitis are now rarely used in the developed world.[9] Severe allergic reactions to abacavir are prevented by HLA-B*5701 screening to exclude those with a predisposition.

Long-term toxicities including liver, kidney and bone disease remain significant concerns. Other factors may play a role in toxicity; for example, co-infection with hepatitis C virus is a significant risk factor for hepatotoxicity and at least some cases are probably a type of immune restoration syndrome.[10]

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

Immune reconstitution inflammatory syndrome (IRIS) is a complication related to the commencement of

Table 69.1 Antiretroviral drugs used to treat human immunodeficiency virus infection

ANTIRETROVIRAL CLASS AND EXAMPLES	MECHANISM
NUCLEOSIDE/NUCLEOTIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS	Substitute natural nucleoside or nucleotide analogues during HIV replication, thereby inhibiting DNA chain elongation and the effects of the reverse transcriptase enzyme
NUCLEOSIDE ANALOGUES	
Abacavir (ABV) Didanosine (ddI) Emtricitabine (FTC) Lamivudine (3TC) Stavudine (d4T) Zidovudine (AZT)	
NUCLEOTIDE ANALOGUES	
Tenofovir (TDF), Tenofovir Alafenamide (TAF)	
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS	Inhibit the reverse transcriptase enzyme preventing the formation of HIV DNA
Efavirenz Etravirine (ETR) Nevirapine Rilpivirine	
INTEGRASE INHIBITORS	Block integration of viral DNA into host DNA
Dolutegravir Elvitegravir Raltegravir	
PROTEASE INHIBITORS	Inhibit the viral protease
Atazanavir Darunavir Fosamprenavir Indinavir Lopinavir Nelfinavir Saquinavir Tipranavir	
FUSION/ENTRY INHIBITORS	Block binding/fusion of the virus with the cell membrane
Enfuvirtide (T20) Maraviroc	
BOOSTER MEDICATIONS Ritonavir Cobicistat	Used in conjunction with other drugs to increase serum levels/permit less frequent dosing

DNA, Deoxyribonucleic acid; *HIV*, human immunodeficiency virus.

ART and the subsequent reconstitution of the immune system. The syndrome can lead to a worsening of treated opportunistic infections or unmask untreated infections. IRIS is more common in those patients with a history of cytomegalovirus (CMV) retinitis, cryptococcal meningitis and TB, and in those with low CD4 counts. However, it can occur with virtually any opportunistic infection. ART is usually continued if mild IRIS develops. Corticosteroids, other immunosuppressive agents and even cessation of ART may be considered for the management of severe IRIS.[11-13]

HUMAN IMMUNODEFICIENCY VIRUS TREATMENT IN THE INTENSIVE CARE UNIT

ART is a lifelong therapy that should be started in consultation with an HIV specialist. Patients already on ART should continue their therapy during an acute ICU admission, if possible, though a single short interruption (1–2 days) of therapy in patients who have been compliant and have long-term virologic control is unlikely to be harmful. Maintenance of adequate drug delivery and absorption of ART is a particular challenge in the ICU, and should be managed in consultation with a pharmacist with specialist HIV knowledge. Options include syrup formulations, crushing tablets and the use of intravenous preparations; drug levels of some medications can also be monitored.

ART also has the potential for serious drug interactions, particularly when ART includes 'booster' medications (ritonavir or cobicistat), protease inhibitors or efavirenz (metabolised via the P450 hepatic enzyme system). Certain antimicrobials, antiemetics, anticonvulsants, anticoagulants, cardiac drugs, and statins are all commonly used drugs that may be contraindicated with ART. For example, protease inhibitors can significantly potentiate the effect of midazolam. Acid-reducing drugs decrease absorption of some antiretrovirals. Web-based tools are available to check potential interactions (e.g. http://www.HIV-druginteractions.org). Renal or hepatic failure may also affect the dosing of ART.

A patient not on ART admitted to the ICU for a problem unrelated to immunosuppression can delay commencement of ART until after they recover. In patients admitted for an AIDS-related illness, the timing of therapy is more controversial. The earlier improvements in immune function need to be balanced against potential side effects from the introduction of new drugs and increased risk of complications from immune reconstitution. In most opportunistic infections, early ART therapy is associated with improved survival.[14] Our practice is to initiate ART within 2–4 weeks after diagnosis of most AIDS-related infections, as by this time the patient's clinical status has stabilised, and tolerability of treatment for the infection has been established. Specific exceptions to early treatment are cryptococcal meningitis and probably TB meningitis, where early therapy may be associated with life-threatening IRIS reactions, and drug interactions and side effects are problematic. In these conditions, we delay ART for at least 4–6 weeks.

HUMAN IMMUNODEFICIENCY VIRUS-INDUCED IMMUNODEFICIENCY

The degree of immunodeficiency, as indicated by CD4+ count/percentage, is strongly related to susceptibility to opportunistic infections, and guides the need for prophylaxis (Fig. 69.1). Some patients also have impaired antibody responses and phagocyte dysfunction, predisposing them to bacterial sepsis.

MAJOR OPPORTUNISTIC INFECTIONS

PNEUMOCYSTIS JIROVECI *PNEUMONITIS*

Interstitial pneumonitis due to *P. jiroveci* presents as subacute progressive dyspnoea, non-productive cough and fever. Respiratory examination reveals fever and tachypnoea, but focal signs are uncommon. The critical finding is hypoxia. The chest X-ray or computed tomography (CT) scan classically demonstrates interstitial 'ground glass' infiltrates but can be normal. Diagnosis is made by demonstrating *Pneumocystis* cysts in an induced sputum specimen, bronchoalveolar lavage fluid or a transbronchial biopsy.

Severe PJP is best treated with high-dose intravenous co-trimoxazole (trimethoprim-sulfamethoxazole). Many patients develop a hypersensitivity reaction to co-trimoxazole; only severe reactions necessitate changing to intravenous pentamidine. Steroid therapy must be used if the Pa_{O_2} is less than 70 mm Hg (9.3 kPa)[15] with an Fi_{O_2} of 0.21 or if the A-a gradient is greater than 35 mm Hg. These patients are at high risk of a pneumothorax; this needs to be considered if there is a sudden deterioration in respiratory status. Non-invasive ventilation can be effective for severe hypoxaemia; however, if mechanical ventilation is required, then lung protective strategies such as low tidal volumes and plateau pressures must be implemented.

Patients with a CD4 T-cell count of less than 200/mL should receive PJP prophylaxis; co-trimoxazole is most effective, which also protects against cerebral toxoplasmosis.[16]

OESOPHAGEAL CANDIDIASIS

Oesophageal candidiasis is a common presentation of HIV infection, and typically presents with odynophagia and dysphagia. These symptoms in association with oral candidiasis are usually sufficient to start treatment with fluconazole. Definitive diagnosis is by endoscopy. Patients with prior azole exposure may have azole resistance and require an intravenous echinocandin or amphotericin.

CRYPTOCOCCAL MENINGITIS

Meningitis is the most common manifestation of *Cryptococcus neoformans* infection. Subacute headache and fever are typical, but confusion or behavioural abnormalities may predominate. Neck stiffness is often minimal or absent, as the immune response needed to produce this sign is minimal. Cerebrospinal fluid examination (performed after CT imaging has excluded a space-occupying lesion) may also reveal little evidence of inflammation, particularly in the most severe cases. Cryptococcal antigen is virtually always present in both serum and cerebrospinal fluid, and cultures for

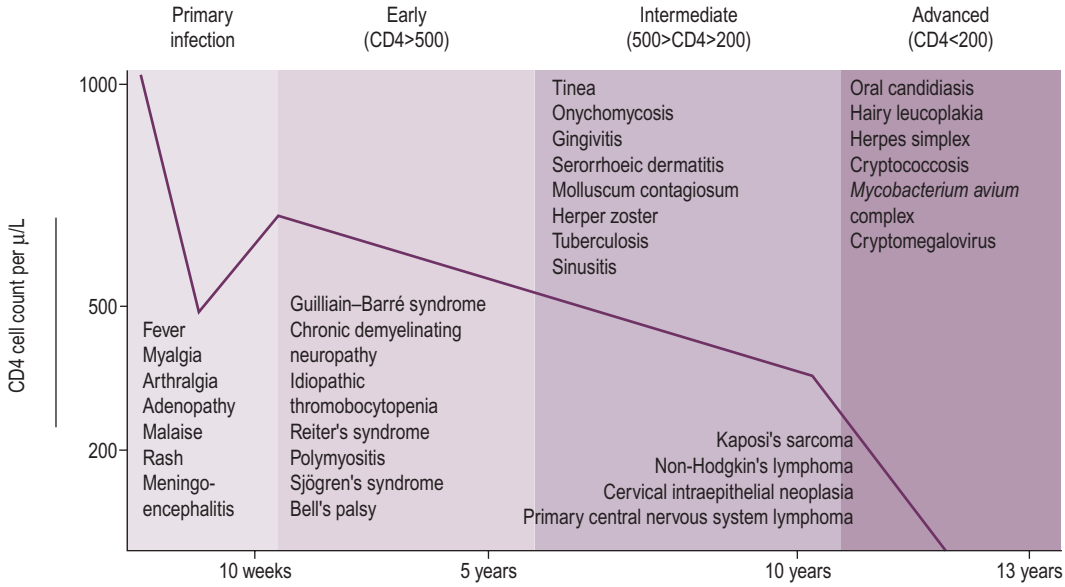


Figure 69.1 Chronological framework for understanding human immunodeficiency virus disease and its management.

cryptococci are positive.[17] Intravenous amphotericin is the treatment of choice, usually given in combination with flucytosine; it is followed by suppressive therapy with oral fluconazole until immune reconstitution is achieved with ART.[18]

TOXOPLASMA *ENCEPHALITIS*

Reactivation of *Toxoplasma gondii* infection most commonly presents as focal encephalitis, causing headaches, fever, focal neurological deficits, convulsions and coma. Contrast CT brain scan typically shows multiple ring-enhancing lesions with surrounding oedema, classically with a predilection for the basal ganglia. Serum *Toxoplasma* antibody is present in most patients; its absence strongly favours an alternative diagnosis. Treatment is oral pyrimethamine, together with either intravenous sulfadiazine or clindamycin. Hypersensitivity reactions to sulfadiazine and clindamycin are common. A brain CT scan after 2–3 weeks of therapy should show improvement; if not, consider an alternative diagnosis. Cerebral lymphoma can produce similar lesions to *Toxoplasma* encephalitis. A brain biopsy is often necessary to make the diagnosis.[19]

CYTOMEGALOVIRUS DISEASE

CMV reactivation usually occurs in patients with severe immunodeficiency (CD4 T-cell count <50/mL). The most common site is the retina. CMV retinitis usually presents with unilateral blurred vision, visual field loss or 'floaters'. Diagnosis is by fundoscopy and should be confirmed by an ophthalmologist. Treatment is usually with oral valganciclovir; intravenous ganciclovir or foscarnet are alternatives, and rarely intravitreal treatment is given. Induction is followed by suppressive therapy to prevent relapses until there is immune reconstitution following the use of ART.

CMV can reactivate in other organs, particularly the oesophagus, bile ducts or colon. It is diagnosed on biopsy of affected tissue. High or increasing CMV viral load in blood should prompt a search for end-organ CMV disease. CMV PCR can be used to monitor the response to therapy and detect antiviral resistance.

CRYPTOSPORIDIOSIS

Infection of the gastrointestinal tract by *Cryptosporidium parvum* causes a severe, intractable diarrhoea, often associated with a malabsorption syndrome. It can also cause cholangitis. Diagnosis is by demonstrating *Cryptosporidium* oocysts in faeces and/or a rectal or duodenal biopsy. The best treatment is ART to raise the CD4 count.

MYCOBACTERIUM AVIUM *COMPLEX INFECTION*

Infection with MAC is usually disseminated and affects blood leucocytes, liver, spleen and lymph nodes, and the gastrointestinal tract. It presents as nonspecific symptoms such as weight loss, fatigue, fevers, anaemia and diarrhoea. The diagnosis is usually made by culturing MAC from blood, but sometimes stool microscopy and culture or biopsy of affected tissues are necessary. Multidrug therapy (e.g. clarithromycin, rifabutin and ethambutol) is required. Suppressive therapy is continued until there is immune reconstitution following the use of ART.[20]

ACQUIRED IMMUNODEFICIENCY SYNDROME-RELATED NEOPLASMS

Certain neoplasms with a viral pathogenesis characteristically occur in HIV-induced immunodeficiency. KS is an angioproliferative tumour originating from vascular endothelium, and is a complication of human herpesvirus-8 (HHV-8) infection. It usually presents as skin lesions that have a reddish-purple colour. They vary in extent from one or two small papules to numerous bulbous lesions. The gastrointestinal tract, lymph nodes and internal organs can be involved in the severely immunosuppressed. KS is confirmed on biopsy of a lesion. KS may present at any time, but occurs most often, and is more severe, in patients with moderate to severe immunodeficiency. New antimitotic agents plus ART have resulted in KS essentially disappearing as a clinical problem in treated individuals.

Lymphomas can also complicate HIV-induced immunodeficiency. Most are B-cell lymphomas (non-Hodgkin), and reactivation of Epstein–Barr virus infection is implicated in the pathogenesis. Primary cerebral lymphoma or extracerebral lymphoma, which often has extranodal involvement, is common and usually high grade in patients with severe immunodeficiency. Treatment consists of whole brain radiation, steroids and ART.[21]

Cervical intraepithelial neoplasia and cancer are more common and aggressive in women with HIV infection, as are anal neoplasia and cancer in males.

HUMAN IMMUNODEFICIENCY VIRUS-RELATED NEUROLOGICAL DISEASE

HIV infection of macrophages and microglial cells in the nervous system often results in neurological disease. In a small number of patients, neurological disease is more problematic than immunodeficiency. Encephalopathy, myelopathy and peripheral neuropathy are all possible; an HIV test is indicated in any unexplained neurological disease. The encephalopathy usually develops insidiously in individuals with advanced immunodeficiency and eventually results in cognitive, motor and behavioural abnormalities. Myelopathy, now rare, results in an ataxic spastic paraparesis.[22]

Investigation of HIV patients with space-occupying cerebral lesions requires analysis of serology, cerebrospinal fluid and neuroimaging investigations. Analysis of cerebrospinal fluid includes PCR for Epstein–Barr virus (indicative of lymphoma), herpes simplex virus,

CMV, varicella–zoster virus (viral encephalitis), JC virus (indicative of progressive multifocal leucoencephalopathy), toxoplasmosis and *Mycobacterium tuberculosis*.

NEEDLESTICK INJURIES AND POST-EXPOSURE PROPHYLAXIS

Patients on effective ART with undetectable viral load pose minimal risk to staff. However, known patients with HIV in an ICU may be outnumbered by undiagnosed patients with HIV. ICU staff must therefore practice stringent infection control procedures on all patients at all times; this will also protect against other bloodborne viruses.

Risk of HIV transmission from needlestick injury from a patient not on ART is approximately 0.3%, and from mucosal exposure approximately 0.009%. There are no reported seroconversions after skin exposure. The major risk factors for infection after a needlestick injury are: (1) deep injury; (2) visible blood on device; (3) needle placement in a vein or artery; and (4) high viral load.

Post-exposure antiretroviral prophylaxis dramatically reduces transmission rates.[23] A protocol for dealing with blood and body fluid exposure should be in place for every health care institution.

KEY REFERENCES

1. Greenberg JA, Lennox JL, Martin GS. Outcomes for critically ill patients with HIV and severe sepsis in the era of highly active antiretroviral therapy. *J Crit Care*. 2012;27(1):51–57.
2. Masur H. Caring for AIDS patients in the ICU: expanding horizons. *Chest*. 2009;135(1):1–2.
11. Müller M, Wandel S, Colebunders R, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10(4):251–261.
12. French MA, Lenzo N, John M, et al. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. *HIV Med*. 2000;1:107–115.
14. Zolopa AR, Andersen J, Komarow L, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS ONE*. 2009;4(5):e5575.
23. Young TN, Arens FJ, Kennedy GE, et al. Antiretroviral post-exposure prophylaxis (PEP) for occupational HIV exposure. *Cochrane Database Syst Rev*. 2007;(1):CD002835.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Greenberg JA, Lennox JL, Martin GS. Outcomes for critically ill patients with HIV and severe sepsis in the era of highly active antiretroviral therapy. *J Crit Care*. 2012;27(1):51–57.
2. Masur H. Caring for AIDS patients in the ICU: expanding horizons. *Chest*. 2009;135(1):1–2.
3. Cohen MS, Shaw GM, McMichael AJ, et al. Acute HIV-1 infection. *N Engl J Med*. 2011;364(20):1943–1954.
4. Brust S, Duttmann H, Feldner J, et al. Shortening of the diagnostic window with a new combined HIV p24 antigen and anti-HIV-1/2/O screening test. *J Virol Methods*. 2000;90(2):153–165.
5. Mellors JW, Rinaldo CR, Gupta P, et al. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science*. 1996;272:1167–1170.
6. Durant J, Clevenbergh P, Halfon P, et al. Drug resistance genotyping in HIV-1 therapy: the VIRADAPT randomised controlled trial. *Lancet*. 1999;353:2195–2199.
7. INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*. 2015;373(9):795–807. doi:10.1056/NEJMoa1506816. [Epub 2015 Jul 20].
8. *US DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. (Last updated: July 14, 2016; last reviewed: July 14, 2016) Accessed at https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/.
9. Carr A, Miller J, Law M, et al. A syndrome of lipoatrophy, lactic acidaemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome. *AIDS*. 2000;14(3):F25–F32.
10. John M, Flexman J, French MA. Hepatitis C virus-associated hepatitis following treatment of HIV-infected patients with HIV protease inhibitors: an immune restoration disease? *AIDS*. 1998;12:2289–2293.
11. Müller M, Wandel S, Colebunders R, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10(4):251–261.
12. French MA, Lenzo N, John M, et al. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. *HIV Med*. 2000;1:107–115.
13. French MA. Disorders of immune reconstitution in patients with HIV infection responding to antiretroviral therapy. *Curr HIV/AIDS Rep*. 2007;4:16–21.
14. Zolopa AR, Andersen J, Komarow L, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS ONE*. 2009;4(5):e5575.
15. Consensus statement on the use of corticosteroids as adjunctive therapy for *Pneumocystis* pneumonia in the acquired immunodeficiency syndrome. The National Institutes of Health University of California expert panel for corticosteroids as adjunctive therapy for *Pneumocystis* pneumonia. *N Engl J Med*. 1990;323:500–504.
16. Kovacs JA, Masur H. Prophylaxis against opportunistic infections in patients with human immunodeficiency virus infection. *N Engl J Med*. 2000;342:1416–1429.
17. Dismukes WE. Cryptococcal meningitis in patients with AIDS. *J Infect Dis*. 1998;157:624–628.
18. Powderly WG, Sagg MS, Cloud GA, et al. A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. *N Engl J Med*. 1992;326:793–798.
19. Porter SB, Sande M. Toxoplasmosis of the central nervous system in the acquired immunodeficiency syndrome. *N Engl J Med*. 1992;327:1643–1648.
20. Aberg AJ, Yajko DM, Jacobson MA. Eradication of AIDS-related disseminated *Mycobacterium avium* complex infection after twelve months of antimycobacterial therapy combined with highly active antiretroviral therapy. *J Infect Dis*. 1998;178:1446–1449.
21. Straus DJ, Huang J, Testa MA, et al. Prognostic factors in the treatment of human immunodeficiency virus-associated non-Hodgkin's lymphoma: analysis of AIDS Clinical Trials Group Protocol 142-low-dose versus standard-dose m-BACOD plus granulocyte-macrophage colony-stimulating factor. *J Clin Oncol*. 1998;16:3601–3606.
22. McArthur JC, Brew B, Nath A. Neurological complications of HIV infection. *Lancet Neurol*. 2005;4:543–555.
23. Young TN, Arens FJ, Kennedy GE, et al. Antiretroviral post-exposure prophylaxis (PEP) for occupational HIV exposure. *Cochrane Database Syst Rev*. 2007;(1):CD002835.

70

Sepsis and septic shock

A Raffaele De Gaudio, Stefano Romagnoli

INTRODUCTION

Sepsis remains a major challenge for intensive care clinicians, researchers and health care systems worldwide due to its high mortality rate, and ongoing challenges in early identification. A recent epidemiological study involving high-income country data estimated that there are 31.5 million sepsis cases, 19.4 million severe sepsis cases, and potentially 5.3 million sepsis-related deaths annually.[1] Increased awareness of the problem of sepsis and compliance with Surviving Sepsis Campaign (SSC) bundles (see later) have led to improvements in diagnostic procedures, the early administration of broad-spectrum antibiotics and more aggressive supportive therapy, with a resultant decrease in sepsis-related mortality in recent years.[2–4] According to a recent study by Levy et al. on compliance with bundles, crude mortality rates differed between Europe and the United States (41.1% vs. 28.3%).[3] However, when adjusted for disease severity, there was little difference between the two (32.3% vs. 31.3%) – a statistic that is probably due to the effect of intensive care unit (ICU) bed availability. Sepsis-related mortality varies depending on organ dysfunction: in patients without organ dysfunction, mortality is less than 20%[5]; for severe sepsis, according to an old definition, mortality ranges between 20% and 50%[2,6]; and in case of septic shock (see below) mortality is frequently over 50%.[7] Despite this reduction in mortality, the absolute number of patients dying from sepsis is increasing due to greater prevalence.[5] The present chapter addresses current insights regarding the definitions, aetiopathogenesis, clinical presentation and treatment of sepsis and septic shock.

OLD AND NEW DEFINITIONS

The first consensus definition of sepsis by the Society of Critical Care Medicine (SCCM) and the American College of Chest Physicians (ACCP)[8] dates back to 1992 (Table 70.1). The clinical criteria for systemic inflammatory response syndrome (SIRS), sepsis (SIRS in the presence of known or suspected infection) and severe sepsis and septic shock, as well as the progression to organ dysfunction, were similarly defined. In order to clarify and simplify the identification of septic patients, an international task force recently modified the old definitions – the 'Third International Consensus Definitions for Sepsis and Septic Shock' (Table 70.2).[9] As SIRS criteria (temperature, heart rate, respiratory rate, white cell count) obtained from a large electronic database totalling approximately 1 million patients,[10] may reflect a normal/appropriate host response to infection, sepsis is now defined as a 'life-threatening organ dysfunction caused by a dysregulated host response to infection'. In this new version, the terms 'dysfunction' and 'dysregulated' are key aspects of the definition. The alteration of metabolic pathways (e.g. pro- and anti-inflammatory host reaction, neural, hormonal, metabolic, coagulation activation, and macro- and microvascular dysfunction) eventually lead to organ dysfunction, which is now described by a rise in the Sepsis-related Organ Failure Assessment (SOFA) score ≥2 (Tables 70.2 and 70.3)[11] with an associated mortality risk exceeding 10%.[9] As such, what was formerly termed 'severe sepsis' has become the new 'sepsis'. The task force has recommended a change in baseline of the total SOFA score of two points or more, as patients with chronic comorbidities may already have known elevated levels of indices, particularly renal (creatinine) and hepatic (bilirubin). 'Septic shock' is denoted by hypotension and hyperlactatemia that persist after adequate volume resuscitation (see Table 70.2). Definitively, the terms SIRS and severe sepsis have been eliminated.

THE PREDISPOSITION, INFECTION, RESPONSE AND ORGAN DYSFUNCTION SYSTEM

In the past, a staging system was used to identify and stage septic patients. Known as predisposition, infection, response and organ dysfunction (PIRO), designed to deal with the inherent heterogeneity of septic patients (Table 70.4),[12] this stratification tool included domains for predisposition (pre-morbid illness), insult/infection (site, microbiology of infection and severity of other insults, such as trauma), response (hypotension)

ABSTRACT

Increased awareness of sepsis and higher compliance with Surviving Sepsis Campaign bundles have led to decreased sepsis-related mortality. Nevertheless, sepsis remains a major challenge for intensive care clinicians, and mortality is still high. In order to clarify and simplify the identification of these patients, a new definition has recently replaced the old ones. Organ dysfunction and dysregulated host response are leading aspects of this new definition. Recent research has focused on the pro- and anti-inflammatory phases now considered intercurrent and overlapped in time rather than a continuum of events. Unbalanced progression and resolution of the septic process may lead to a state of immune paralysis that exposes many survived patients to secondary infections and late mortality. Most of the research is now focused on immune status and immune therapies. Until more personalised therapies become available, infection source control, broad-spectrum antibiotics, and organ support remain core therapies for sepsis.

KEY WORDS

Sepsis
septic shock
immune paralysis
qSOFA
PIRO
Surviving Sepsis Campaign
adjuvant therapies

Table 70.1 Sepsis: previous definitions

SIRS	Two of the following: • Temperature >38°C or <36°C • Heart rate >90 beats/min • Respiratory rate >20 breaths/min or $PaCO_2$ < 32 mm Hg • WBC count >12 × 10^9/L or <4 × 10^9/L
Sepsis	SIRS with proven or suspected infection
Severe sepsis	Sepsis with acute organ dysfunction
Septic shock	Sepsis with hypotension despite adequate fluid resuscitation

SIRS, Systemic inflammatory response syndrome; *WBC*, white blood cells.
Bone R, Balk R, Cerra F, et al. The ACCP-SCCM consensus conference for sepsis and organ failure. *Chest*. 1992;101:1644–1655.

Table 70.2 Third international consensus definitions for sepsis and septic shock – terms and definitions

Sepsis	A life-threatening organ dysfunction caused by a dysregulated host response to infection
Organ dysfunction	Acute change in total SOFA score ≥2 points consequent to the infection • The baseline SOFA score can be assumed to be zero in patients not known to have pre-existing organ dysfunction
Septic shock	Is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality (hospital mortality >40%) Sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation
qSOFA	• Systolic blood pressure ≤100 mm Hg • Altered mentation • Respiratory rate ≥22 breaths/min

MAP, Mean arterial pressure; *qSOFA*, quick SOFA; *SOFA*, sequential (sepsis-related) organ failure assessment.
Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA*. 2016; 315:801–810.

and organ dysfunction (SOFA). The PIRO system has recently re-emerged as a potential means to predict multiple organ dysfunction, ICU admission, and 28-day mortality in emergency department septic patients.[13,14]

THE QUICK SEPSIS-RELATED ORGAN FAILURE ASSESSMENT FOR SEPSIS OUTSIDE THE INTENSIVE CARE UNIT

Evaluating all six components of the SOFA score can be time consuming, and some of them require laboratory measurements. A new rapid bedside score – the quick SOFA (qSOFA) – identifies patients at risk of sepsis outside the ICU (emergency departments and wards). Patients showing two or more of systolic blood pressure ≤100 mm Hg, altered mentation and/or respiratory rate ≥22 breaths/min must be screened for sepsis (see Table 70.2). The predictive validity and role of qSOFA in such patients has yet to be defined. Indeed, sepsis can be present without a qSOFA score ≥2 when different forms of organ dysfunction occur (e.g. hypoxemia, renal failure, coagulopathy) – a factor that has led to much discussion and controversy in recent times. Equally, patients may have a qSOFA ≥2 without infection (e.g. hypovolemia, cardiogenic shock or pulmonary embolism).[15]

AETIOPATHOGENESIS

In terms of organs and tissues, sepsis is a progression from a localised infection to systemic involvement of all the systems. Significant variations may be observed, depending on the initial site of infection, the causative pathogen, the pattern and degree of organ injury and dysfunction, the chronic clinical state of the patient, their genetic characteristics, and the timing and type of intervention.

Data for more than 14,000 adult patients across 1265 ICUs were reported in the 2007 Extended Prevalence of Infection in Intensive Care (EPIC II) study.[16] The sites of infection were lung (64% of cases), abdomen (20%), bloodstream (15%) and renal or genitourinary tract (14%).[16] Among the infected patients with positive cultures (70%), the isolated causes were Gram-negative (62%; 20% *Pseudomonas* spp. and 16% *Escherichia coli*), Gram positive (47%; 20% *Staphylococcus aureus*) and fungi (19%).[16]

Sepsis Prevalence, Outcomes, and Therapies (SPROUT) Study Investigators and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network[17] is a point prevalence study of paediatric sepsis published in 2015. Of 569 children with severe sepsis (8.2% prevalence), the sites of infection were lung (40% of cases), bloodstream (29%), abdomen (8%), central nervous system (4%) and genitourinary system (4%). The isolated causes were Gram-negative bacteria (28%), Gram-positive bacteria (27%), viruses (21%) and fungi (13%).[17]

INFLAMMATION AND IMMUNE SUPPRESSION

Pathogens activate immune cells through an interaction with pattern recognition receptors (PRRs). Four main

Table 70.3 Sequential (sepsis-related) organ failure assessment score

	SCORES				
SYSTEM	0	1	2	3	4
RESPIRATION					
Pa_{O_2}/Fi_{O_2}, mm Hg (KPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
COAGULATION					
Platelets × 10^3/μL	≥150	<150	<100	<50	<20
LIVER					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm	Dopamine <5 or dobutamine (any dose)*	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1*	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1*
CENTRAL NERVOUS SYSTEM					
GCS	15	13–14	10–12	6–9	<6
RENAL					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (440)
Urine output, mL/d				<500	<200

*Catecholamine doses are given as μg/kg/min for at least 1 hour.

Fi_{O_2}, Fraction of inspired oxygen; *GCS*, Glasgow Coma Score; *MAP*, mean arterial pressure; Pa_{O_2}, partial pressure of oxygen.

Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA*. 2016; 315:801–810.

classes (toll-like receptors [TLRs], C-type lectin receptors, retinoic acid inducible gene-1-like receptors and nucleotide-binding oligomerisation domain-like receptors) have been identified to date.[18,19] These receptors recognise structures called pathogen-associated molecular patterns (PAMPS), which are molecules associated with groups of pathogens resulting in the activation of inflammatory gene transcription.[19,20] Interestingly, the same receptors are recognised and linked by a different group of molecules (high-mobility group protein B1, S100 proteins and extracellular RNA, DNA). Known as alarmins or damaged-associated molecular patterns (DAMPs), these are released by sterile injured cells (e.g. trauma) and share most of the pathophysiological features of sepsis in the absence of infection.[21,22]

The activation of PRRs results in several effects aimed at stimulating the host immune response to the newly identified pathogen. For instance, TLRs activate cytosolic nuclear factor-κB (NF-κB), which induces the release of several cytokines (CKs) with predominantly pro-inflammatory activities, for example tumour necrosis factor-α (TNF-α), interleukins (IL-1β, IL-2, IL-6, IL-8) and interferon-γ (IFN-γ).[23] CKs, in turn, have local and systemic effects including fever, capillary leak and the activation of both the coagulation system and neutrophils. Increased gluconeogenesis and lipolysis, and the generation of acute phase proteins, have also been observed.[23] Chemokines are locally released (e.g. intercellular adhesion molecule-1, vascular cell adhesion molecule-1, nitric oxide), promoting chemotaxis of polymorphonuclear leucocytes, which aggregate and marginate at the vascular endothelium.[23]

Traditionally, two different phases were considered sequential and biphasic: the pro-inflammatory phase, driven by CK and inflammatory mediators released by the innate immune system; and the anti-inflammatory phase, characterised by a period of immune suppression. Nowadays, the pro- and anti-inflammatory phases are considered intercurrent and overlapped in time.[24] In view of this, the resolution of inflammation is not simply a passive process; rather, it involves a complex interaction between cells and molecular signals.[25] The pro-inflammatory reaction triggered by the host-pathogen interaction is counterbalanced by an anti-inflammatory response aimed at attenuating the potentially harmful effects of inflammation.[20] Cellular

Table 70.4 The predisposition, infection, response and organ dysfunction system for staging sepsis

DOMAIN	PRESENT	FUTURE	RATIONALE
Predisposition	Pre-morbid illness with reduced probability of short-term survival. Cultural or religious beliefs, age, sex	Genetic polymorphisms in components of inflammatory response (e.g. TLR, TNF, IL-1, CD14); enhanced understanding of specific interactions between pathogens and host diseases	In the present, pre-morbid factors impact on the potential attributable morbidity and mortality of an acute insult; deleterious consequences of insult heavily dependent on genetic predisposition (future)
Insult infection	Culture and sensitivity of infecting pathogens; detection of disease amenable to source control	Assay of microbial products (LPS, mannan, bacterial DNA); gene transcript profiles	Specific therapies directed against inciting insult require demonstration and characterisation of that insult
Response	SIRS, other signs of sepsis, shock, CRP	Non-specific markers of activated inflammation (e.g. PCT or IL-6) or impaired host responsiveness (e.g. HLA-DR); specific detection of target of therapy (e.g. protein C, TNF, PAF)	Both mortality risk and potential to respond to therapy vary with non-specific measures of disease severity (e.g. shock); specific mediator-targeted therapy is predicated on presence and activity of mediator
Organ dysfunction	Organ dysfunction as number of failing organs or composite score (e.g. MODS, SOFA, LODS, PEMOD, PELOD)	Dynamic measures of cellular response to insult – apoptosis, cytopathic hypoxia, cell stress	Response to pre-emptive therapy (e.g. targeting microorganism or early mediator) not possible if damage already present; therapies targeting the injurious cellular process require that it be present

CRP, C-reactive protein; *HLA-DR*, human leucocyte antigen-DR; *IL*, interleukin; *LODS*, logistic organ dysfunction system; *LPS*, lipopolysaccharide; *MODS*, multiple organ dysfunction syndrome; *PAF*, platelet-activating factor; *PCT*, procalcitonin; *PELOD*, paediatric logistic organ dysfunction; *PEMOD*, paediatric multiple organ dysfunction; *SIRS*, systemic inflammatory response syndrome; *SOFA*, sepsis-related organ failure assessment; *TLR*, toll-like receptor; *TNF*, tumour necrosis factor.

Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003;31:1250–1256.

phenotype may change into an anti-inflammatory type; phagocytes may promote tissue repair; while regulatory T cells and myeloid-derived suppressor cells further reduce inflammation.[19] IL-10, released by many types of leucocytes, inhibits the production of IL-6 and IFN-γ, and activates the production of a soluble TNF receptor and IL-1 receptor antagonist, helping to neutralise the potent TNF-α and IL-1.[26] Autophagy is a mechanism that helps to clear DAMPs and PAMPs by wrapping pathogens and damaged organelles and proteins in vesicles that undergo lysosomal degradation.[27]

FROM IMMUNE SUPPRESSION TO IMMUNE PARALYSIS

There is evidence that many patients who survive sepsis develop viral reactivation and/or secondary nosocomial infections, frequently by organisms that would not typically cause disease in immunocompetent hosts (e.g. *Candida* sp., *Acinetobacter* sp., or *Stenotrophomonas*). This has led to the conclusion that some patients enter a phase of 'immune paralysis'.[28,29] During the last 10–15 years, mortality in sepsis has substantially decreased.[2] This improvement in outcomes is due to the wider and more timely application of the SSC bundles (Table 70.5), entailing greater expertise in managing organ failure, earlier and more aggressive fluid management, timely administration of broad-spectrum antimicrobial therapy and increased attention to infectious source control (e.g. abdominal abscesses, cholangitis).[3] Most of these interventions limit the organ damage that occurs during the pro-inflammatory phase of sepsis (CK storm and shock state). As more patients survive this phase, questions of impaired immunity and secondary infections become pertinent to longer-term outcomes (Fig. 70.1).[21] Studies of patients who have died following sepsis have shown biochemical, flow cytometric and immunohistochemical findings consistent with immunosuppression.[30] Apoptosis of T- and B-lymphocytes phenomena resulting in lymphopenia and tissue lymphocyte depletion have been demonstrated.[31] In an interesting study performed for patients who have died of sepsis (40 patients and 49 controls), a sort of

Table 70.5 Surviving sepsis campaign bundles

BUNDLES	DOCUMENT REASSESSMENT OF VOLUME STATUS AND TISSUE PERFUSION
To be completed within 3 h: • Measure lactate level • Obtain blood cultures prior to administration of antibiotics • Administer broad-spectrum antibiotics • Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L	Either: • Repeat focused exam (after initial fluid resuscitation) including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings. Or two of the following: • Measure CVP • Measure Scv_{O_2} • Perform bedside cardiovascular ultrasound • Perform dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge
To be completed within 6 h: • Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mm Hg • In the event of persistent hypotension after initial fluid administration (MAP <65 mm Hg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion and document findings according to 'Document reassessment of volume status and tissue perfusion' (column 2) • Re-measure lactate if initial lactate elevated	

CVP, Central venous pressure; Scv_{O_2}, central venous oxygen saturation.
www.survivingsepsisguidelines.org.

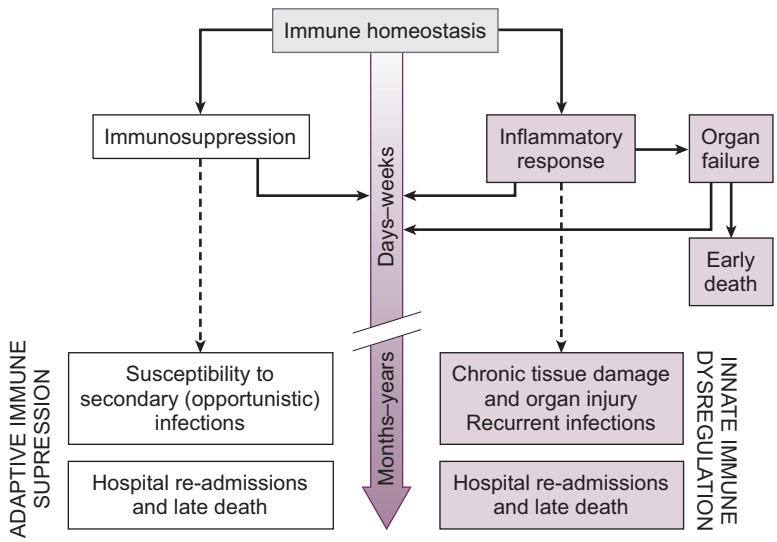


Figure 70.1 Immune system in sepsis. *Modified from Delano MJ, Ward PA. Sepsis-induced immune dysfunction: can immune therapies reduce mortality?* J Clin Invest. *2016;126:23–31.*

'immune exhaustion' was observed within 3 hours of death.[30] CKs secretion assays and the immunophenotyping of cell surface receptor-ligand expression profiles were performed and tested in harvested tissues (lung and spleen) to identify potential immune dysfunction mechanisms. Immunohistochemical staining was performed to evaluate the loss of immune effector cells. Following the administration of lipopolysaccharides (LPS; also known as 'endotoxin') – a component of the outer membrane of Gram-negative bacteria – patients with sepsis had significantly reduced levels (less than 10% compared with non-septic controls)

of splenic pro-inflammatory CKs (e.g. TNF-α, IFN-γ, IL-6 and IL-10). By inference, patients with 'immune exhaustion' or immunoparalysis may thus be prone to secondary infections and/or viral reactivation.

ENDOTHELIUM AND COAGULATION SYSTEM

The endothelium has various important roles, including regulating vascular tone, immunological function, haemostasis, vascular permeability, solute transport and osmotic balance. The transfer of fluids and nutrients into and out of tissues, the coagulation system and the inflammatory/anti-inflammatory equilibrium can be profoundly altered in sepsis.[32] Failure of the endothelium structure and function is central to the progression towards organ failure during sepsis. The integrity of the endothelium in the regulation of solutes transport and fluid leakage is largely determined by the endothelial glycocalyx (EG) – a 0.2–0.5 μm thick gel-like layer of proteoglycans, glycoproteins and glycosaminoglycans. The EG regulates the vascular barrier function, haemostasis, leucocyte and platelet adhesion, transmission of shear stress to the endothelium, and anti-inflammatory and antioxidant defences.[33]

Vascular tone and endothelium/EG alteration eventually lead to global microcirculation dysfunction. Impaired response to local stimulation (release in nitric oxide and/or endothelin is common in sepsis),[32] and obstruction of capillary lumen by thrombi and plugs of white and red blood cells frequently worsen tissue perfusion.[32] In addition, loss-of-barrier function mediated by EG is associated with tissue oedema – another key contributor to sepsis-induced organ failure.

Sepsis is also almost invariably associated with altered coagulation.[34] Haemostasis – a complex interaction between endothelium, soluble plasma molecules, platelets and leucocytes – is commonly deregulated during sepsis. Indeed, sepsis-mediated inflammation drives haemostasis towards a prothrombotic and antifibrinolytic state, which can lead to microvascular thrombosis, tissue hypoxia and organ dysfunction.[32] Tissue factor exposure and impaired anticoagulant mechanisms (including activated protein C and antithrombin) can lead to disseminated intravascular coagulation syndrome, with associated organ injury, bleeding (consumption of platelets and clotting factors) and high mortality rate.[35] In sepsis, glycocalyx shedding exposes adhesion molecules that promote leucocyte link and transmigration to the tissues, where they can release inflammatory mediators and molecules that are reactive against pathogens but which can potentially cause tissue damage.

CLINICAL PRESENTATION

Profound derangements in cellular and humoral homeostasis eventually lead to organ injury and dysfunction.

The cardiovascular system is primarily involved; intravascular volume must be promptly restored to maintain an adequate cardiac output (CO) and perfusion pressure in the presence of low systemic vascular resistance due to altered vascular tone and impedance.[36] Acute biventricular dysfunction frequently occurs in sepsis[37] with hyperlactatemia, commonly used as an indicator of oxygen delivery (DO_2)/oxygen consumption (VO_2) imbalance, a central factor in diagnosis, prognosis and therapeutic response in septic patients. Increased lactate and lactate trend/clearance is a mortality indicator.[38] Although hyperlactatemia has traditionally been related to tissue hypoxia and anaerobic metabolism subsequent to DO_2/VO_2 imbalance, the adjunctive parallel mechanisms of sepsis-induced hyperlactatemia (e.g. enhanced adrenergic tone) are recognised as relatively common phenomena.[39]

The lungs are frequently the first organ to be compromised, either as the primary infection site or, in case of extrapulmonary infection, in a subsequent phase of the disease, resulting in mild, moderate or severe acute respiratory distress syndrome (ARDS).[40]

Sepsis-associated acute kidney injury (AKI) is an independent predictor of increased mortality and morbidity.[41] Traditionally considered the result of macro haemodynamic alterations (hypotension, hypoperfusion), AKI can also occur in the absence of these conditions. Sepsis-induced AKI, however, can occur in conditions of normal or even increased renal blood flow. Functionally, sepsis-induced AKI is characterised by a dramatic decline in glomerular filtration rate and variable tubular dysfunction. Recent evidence suggests that AKI originates from a combination of co-acting factors, including inflammation, microvascular flow alteration and cell cycle arrest. The interaction between DAMPs and PAMPs is a primary function, with PRRs at the epithelial and parenchymal cell levels.[42]

The liver – a mechanical and immunological filter for portal blood – may be a major source of CKs. It is involved in the host response, and participates in the clearance of the infectious agents/products. Liver damage can occur in sepsis via haemodynamic alterations (hypotension/hypoperfusion) and through a direct assault on the hepatocytes. It has been suggested that microcirculatory changes in the liver sinusoids, neutrophil sequestration, and platelet activation and adhesion are the main contributors to known hepatic dysfunction parameters. Cholestasis, steatosis, hepatocellular injury, impaired cellular regeneration and impaired hepatic mitochondrial respiration are factors implicated in clinical septic hepatic dysfunction. An increase in aminotransferase and bilirubin levels is therefore common. However, severe hepatic failure is uncommon.[43] Subclinical liver injury has been recently identified in critically ill patients.

Cerebral dysfunction is often present in sepsis, and may precede the signs of other organ failure. It is better defined as 'sepsis-associated encephalopathy'

(SAE), to stress the absence of direct infection of the central nervous system. The main sign of SAE is altered mental status. Electroencephalography, the most sensitive diagnostic test, allows the severity of cerebral dysfunction to be graded. SAE is potentially reversible, but always worsens the prognosis. The pathophysiology of SAE is still not completely understood, and it is most likely multifactorial. Indeed, brain dysfunction in sepsis may be related to microorganism toxin activity, the effects of inflammatory mediators, metabolic alterations and abnormalities in cerebral circulation. Experimental studies have shown that microcirculatory dysfunction – a consequence of endothelial activation – is an early pathogenic step.[44]

PRINCIPLES OF TREATMENT

ANTIBIOTICS AND SEPSIS SOURCE CONTROL

Prompt identification of bacteria is fundamental to the management of septic patients. Unfortunately, the gold standard for aetiologic identification is based on outdated techniques that require a delay of 48 hours or more between samples (e.g. haemoculture) and isolation. New systems (i.e. matrix assisted laser desorption ionisation time-of-flight [MALDI-TOF] and polymerase chain reaction–electrospray ionisation mass spectrometry [PCR-ESI/MS]) significantly shorten this timeframe.[45,46] The recommended approach is based on the administration of empiric broad-spectrum antibiotic therapy as soon as sepsis is diagnosed, to be switched or de-escalated once identification and sensitivities have been obtained.[47] The timely administration of antibiotics, together with the appropriate control of the source of infection, is crucial to limit sepsis and prevent organ injury progression.[48] The current SSC guidelines recommend administering broad-spectrum intravenous (IV) antibiotics within an hour of severe sepsis (old definition) or septic shock being diagnosed.[47] However, a retrospective review of 2700 patients with septic shock showed that only 50% received antibiotics within 6 hours of the onset of hypotension.[49] A 12% reduction in survival was associated with each hour of delay in the administration of antibiotics following the onset of septic shock.[49] A recent retrospective analysis of 18,000 ICU patients with septic shock or severe sepsis (old definition) found that adjusted hospital mortality steadily increased as the delay in antibiotic administration increased (1 hour: 25.9%; >6 hours: 33.1%).[50]

The balance between the advantages and potential damages of broad-spectrum antibiotics should be regularly evaluated, as these may entail the overgrowth of potentially pathogenic bowel flora and the selection of resistant bugs.[51] The use of appropriate infectious biomarkers may help physicians avoid inappropriate or excessive antibiotic therapy. While not perfect, procalcitonin (PCT) may be helpful for this purpose; however, new specific and sensitive biomarkers are warranted to optimise an antibiotic sparing strategy that preserves the efficacy of new classes of antibiotics (ceftalozane–tazobactam, ceftazidime–avibactam, ceftaroline–avibactam, plazomicin).[52] Imaging studies aimed at identifying potential sources of infection are a key component of SSC. In the first 12 hours following diagnosis, a specific anatomical diagnosis of the infection should be carried out as rapidly as possible, and intervention undertaken to establish source control (e.g. infected peripancreatic necrosis, infected intravascular devices).[47]

RESUSCITATION TARGETS WITH FLUID AND VASOACTIVE DRUGS

Although many aspects of the mechanisms involved in the development of tissue damage are yet to be elucidated, impaired tissue oxygenation is a central issue in septic patients. A major part of early resuscitation is directed towards the correction of DO_2/VO_2 imbalance.[47,53] Hypotension, microvascular thrombosis, tissue oedema and reduced red-cell deformability contribute to microvascular derangement and obstruct DO_2 to cells. In addition, oxygen utilisation is impaired by mitochondrial damage caused by oxidative stress and other mechanisms.[54] To help clinicians apply the package of diagnostic–therapeutic interventions in a timely manner, the SSC guidelines set out a series of intervention bundles. Aimed at simplifying the care process, these bundles lie at the core of efforts to improve the treatment of sepsis (see Table 70.5).[3,47]

The swift re-establishment of an optimal DO_2/VO_2 ratio is a crucial goal for the resuscitation of septic patients. The focus here is on mean arterial pressure (MAP), central venous O_2 saturation ($Scv_{O_2} > 70\%$) and lactate level (see Table 70.5). The maintenance of adequate arterial pressure is a key factor for organ perfusion, and the MAP target is hence used as an indicator of tissue perfusion pressure. While the optimal pressure target is yet to be defined,[55] and an individualised therapy based on pre-existing hypertension and response to therapy seems the more appropriate approach, a MAP ≥65 mm Hg is currently recommended.[47] Increased lactate levels are associated with poor outcomes, and rapid lactate decreases are associated with higher survival. The value of lactate kinetics seems valid regardless of the initial value.[56] Microcirculation is frequently impaired during sepsis. However, while it is attractive, using microcirculation as a resuscitation target is premature as indicators of microvessels perfusion and reactivity are still some way from being employed in clinical practice.[57] Fluids are the principal drugs for haemodynamic resuscitation in septic patients.[3] However, there is increased awareness that these must be used with the same caution as any other IV drug in terms of both amount and type. Following the publication of randomised controlled trials (RCTs) on fluid therapy in septic patients, there is

convincing evidence that colloids containing hydroxyethyl starch (HES) are associated with a higher incidences of AKI and mortality.[58–60] Recent international studies have shown significant reductions in HES administration in critically ill patients; medical regulatory authorities and clinical practice guidelines recommend against the use of HES.[61] To date, there is no clear evidence to support the use of colloids over crystalloids in sepsis.[62] On the contrary, there is evidence that 0.9 % sodium chloride (so-called 'normal saline') causes hyperchloremic acidosis (or strong ion difference [SID]-acidosis), particularly when administered in higher doses.[63,64] This may result in AKI and increased mortality in critically ill patients, compared to balanced crystalloid solutions.[65] Apart from quality, it is an established fact that a net positive fluid balance due to the over-administration of fluid is associated with adverse outcomes in patients with sepsis.[66] Strategies based on early fluid resuscitation followed by the removal of excess fluid are therefore strongly recommended.[35,66,67] Most critical care physicians give at least 2–3 L crystalloids before starting a vasopressor to maintain the MAP target, as is commonly required in patients with sepsis. Norepinephrine is the recommended first-line vasopressor, with epinephrine (adrenaline) or low-dose vasopressin as second-line agents.[3] New vasopressors that could limit the occurrence of capillary leak are currently being investigated (e.g. selepressin, angiotensin-II, methylene blue).[68–70] As the use of vasopressors is associated with untoward side effects including organ dysfunction and atrial fibrillation, it is also important that the administration of such drugs be limited.[71] To re-establish haemodynamic stability, IV hydrocortisone is recommended (grade of recommendation 2C) in conditions where fluid resuscitation and vasopressor therapy are insufficient.[3] Myocardial dysfunction is very common in sepsis. While recent multicentre studies have questioned the merits of the protocolised early goal-directed therapy,[72] maintaining optimal CO is an important aim of septic shock resuscitation. A complete and accurate understanding of haemodynamic instability in patients with septic shock can be provided by a detailed echocardiography.[73,74] Cardiac dysfunction is clearly deleterious. High-dose dobutamine to increase CO is equally dangerous, however, as excessive catecholamine stimulation may cause tachycardia, arrhythmias, myocardial injury and direct toxic effects.[75] An interesting alternative to catecholamines currently under evaluation is the calcium sensitiser, levosimendan, which increases the affinity of the myocardium to calcium by binding to troponin C. The net effect is an increase in myocardial contractility with no accompanying increase in VO_2. In addition, this opens vascular smooth muscle potassium channels, leading to vasodilation and ameliorating ventricular–arterial coupling.[76] Finally, the use of short-term beta blockers has been investigated in a single-centre trial, the encouraging results of which are yet to be confirmed by larger RCTs.[77] Other frequently discussed topics include transfusion practices and haemoglobin thresholds. Three RCTs have concluded that a strategy of increasing DO_2 with red blood cell transfusions as part of haemodynamic goal-directed therapy did not influence survival. Equally, a recent Transfusion Requirements in Septic Shock (TRISS) study that randomised nearly 1000 patients with septic shock to a transfusion threshold of 70 or 90 g/L haemoglobin found no difference in 90-day mortality or the rate of ischemic events.[78]

ADJUVANT SUPPORTIVE CARE

Sepsis is a highly complex, heterogeneous condition. Different pathogens affect various sites in patients of all ages with multiple and varied comorbidities and immune statuses. As such, it is unlikely that any single therapy will be adequate to treat all patients with sepsis. Heterogeneity is probably one of the main reasons behind the failure of many RCTs to demonstrate the efficacy of one specific treatment (e.g. activated protein C, endotoxin adsorption, corticosteroids, antithrombin III, etc.).[79] Nevertheless, adjuvant or adjunctive therapeutic approaches (mainly adjuvant directed towards immunomodulation) have been advocated for over 10 years[80]; currently, approaches under clinical evaluation include immunoglobulins and corticosteroids.

The role of *immunoglobulins* as adjuvant therapy for sepsis still unclarified, and these are not recommended in adults or paediatric populations (grade 2B in the SSC).[47,81] Pathogen recognition and clearance, scavenging of toxins, and non-apoptotic and antiapoptotic immune cell effects are the main advocated potential beneficial effects of immunoglobulin in sepsis.[82,83] A Cochrane review found that polyclonal IgG reduced short-term mortality in adults with sepsis; however, a sensitivity analysis including only trials with a low risk of bias did not show any impact of IVIg (either polyclonal or IgM enriched) on mortality, concluding that 'adjunctive therapy with monoclonal IVIgs remains experimental'.[84] Nonetheless, some positive and encouraging data on the beneficial effects of IVIg in septic shock can be found in the literature, and there remains a need for further trials. A recent retrospective evaluation involving a large prospective multicentre cohort of patients with septic shock and multidrug-resistant Gram-negative bacteria infection showed reduced 28-day mortality in patients treated with IgM-enriched immunoglobulin preparation, compared with a matched control group.[85] Similarly, a previous retrospective cohort study of 168 patients with septic shock found that IV IgM administered for 3 consecutive days, and initiated during the first 24 hours of septic shock management, was independently associated with a decrease in 30-day mortality.[86] Finally, many questions remain unanswered regarding the potential

role of adjuvant therapy, including its optimal composition. IgM-enriched solutions perhaps offer the most promising effects on outcomes – more so than IgG solutions alone.[81]

According the SSC, IV *corticosteroids* in septic shock patients are only recommended if adequate fluid resuscitation and vasopressor therapy are not able to restore haemodynamic stability; IV hydrocortisone at a dose of 200 mg per day is suggested (grade 2C).[47] Steroids have a long history in sepsis treatment, from high doses as anti-inflammatory agents to more moderate doses to correct impaired cortisol metabolism. However, RCTs have reported no clear benefits, and the topic remains under discussion.[81] It seems probable that certain patients require steroid supplements, while others do not. Identifying the former remains a challenge, however, without a reliable biomarker of glucocorticoid-receptor activation.[87]

EXTRACORPOREAL THERAPIES

The complex interplay and imbalance of host pro-inflammatory and anti-inflammatory processes are among the principal obstacles to further reductions in sepsis-related morbidity and mortality. In recent years, most research has focused on re-establishing an equilibrium in the CK-mediated inflammation by clearing CKs from the blood using continuous renal replacement (CRRT) techniques.[88] Various forms of extracorporeal blood purification techniques, from apheresis to hemofiltration, are commonly used for the worldwide management of sepsis and sepsis-associated AKI. Nevertheless, their efficacy remains unknown, and there is currently no consensus on how extracorporeal blood purification therapies (BPTs) should be applied or studied in patients with sepsis.[89] Again, the huge heterogeneity in sepsis phenotypes may represent the principal obstacle to identifying those patients able to benefit from BPT. Most of the immune mediators in sepsis are water-soluble middle molecular-weight molecules (e.g. eicosanoids, leukotrienes, complement, CKs, chemokines), which can theoretically be removed by extracorporeal treatments including convection, diffusion, and adsorption. However, existing renal replacement technology is rather limited in its ability to achieve biologically relevant reductions in inflammation mediations, and dedicated techniques and/or materials have been developed.[89] Beyond correcting specific uremic toxins, CRRT seems to restore other physiological homeostatic mechanisms. At higher doses – or 'overdoses' – it may play a role in ridding the blood of water-soluble CKs produced during systemic inflammatory and septic states. This concept has led to speculation that high-volume hemofiltration (HVHF) may have benefits in septic patients beyond the removal of classic markers. HVHF – identified as continuous treatment with a convective (prescribed) target dose greater than 35 mL/kg per hour[90] – has been applied in septic patients to enhance the purge of middle-molecular-weight molecules, such as CKs. While encouraging results from experimental studies have been reported in the literature, large clinical trials have failed to demonstrate the benefits of HVHF as an extracorporeal treatment of sepsis.[91]

Haemoperfusion/plasmaperfusion is a technique based on blood or plasma circulation through a column containing specific sorbents, with adsorption as the only removal mechanism.[92] These techniques have been shown to increase the removal of inflammatory mediators and increase survival via hydrophobic interactions, electrostatic attraction, hydrogen bonding and van der Waals forces.[93] Hybrid techniques combining the advantages of different purification methods have been designed to increase the clearance of inflammatory mediators. Coupled plasma filtration and adsorption (CPFA), for instance, is a technique that has shown positive, if inconsistent results. Here, plasma is first extracted from the blood using a plasma filter, then slowly directed across an adsorbent material. Following this, the purified plasma is mixed with the blood from which it was previously separated, and is directed towards a second hemofilter.[94] In a larger study, the COMbining Plasma-filtration and Adsorption Clinical Trial (COMPACT)-1 trial, CPFA was combined with standard septic shock care for 5 days. Unfortunately, circuit coagulation and related issues limited the volume of plasma treated, leading to numerous protocol violations. Nevertheless, the subgroup of patients who received the higher 'dose' of CPFA had a lower mortality rate compared with controls.[95] The ongoing COMPACT-2 trial (NCT 01639664) was designed to address this question by preventing problems with regional citrate coagulation. Another haemoperfusion technique is polymyxin B haemoperfusion (PMX-HP) – a blood purification technique based on the application of polymyxin B, an old antibiotic with high affinity for endotoxin (a component of the outer membrane of Gram-negative bacteria), to polystyrene fibres used for haemoperfusion. Circulating endotoxin is bound and retained by the filter. Following the encouraging results of the randomised Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis (EUPHAS) trial, which showed a survival benefit for patients receiving PMX-HP in intra-abdominal infection-related severe sepsis,[96] a large multicentre randomised control study including 232 patients with septic shock were treated with PMX-HP (119 vs. 113 controls) within 12 hours of the surgical control of the sepsis source (perforation). The latter recently published study did not reveal any beneficial effects in patients treated versus controls.[97] The Evaluating the Use of Polymyxin B Hemoperfusion in a Randomised controlled trial of Adults Treated for Endotoxemia and Septic Shock (EUPHRATES) trial, which is currently ongoing (NCT 01046669), will provide additional information regarding the potential usefulness of polymyxin B haemoperfusion in sepsis.

High cut-off haemofiltration (HCO-HF) uses membranes with a cut-off value that approximates the molecular weight of albumin,[92] facilitating the removal of middle-molecular weight, including pro- and anti-inflammatory CKs. Clinical and experimental studies have shown that HCO-HF techniques remove CKs effectively, with a safety profile for albumin clearance.[98,99] In addition, studies have shown the clearance of CKs from the bloodstream to be associated with significant improvements in haemodynamics, oxygenation, and organ dysfunction.[99] Nonetheless, mortality reduction in septic patients undergoing HCO-HF remains undemonstrated. Finally, a number of confounding factors prevent the published studies on blood purification from being fully comparable. Over the last decade, significant new insights have been made regarding sepsis pathophysiology, and it is probably time for us to re-evaluate blood purification techniques in light of these new findings. Careful stratification based on the microbiological source of sepsis, ways of finding a more precise biological rationale and identifying the optimal timing for specific interventions are possible starting points for future trials in this complex category of patients. Coupling the right patient (at the right moment) with the appropriate technology is a new challenge in the management of sepsis and septic AKI.

IMMUNOSTIMULATION

The immune status of a patient with sepsis varies during the course of the disease according to a number of co-acting factors. This may entail the transition from a predominantly pro-inflammatory response to a largely immunosuppressed phase.[21] Depending on the patient's specific immune status, immunostimulatory therapy may be preferable to an immunosuppressive approach.[100] IL-7, which is essential for lymphocyte survival and is involved in many leucocyte functions, is a potential adjuvant therapy in sepsis. In experimental models, recombinant human IL-7 has been shown to limit the apoptosis phenomena of CD4+ and CD8+ T cells, restore IFN-γ production, and improve leucocyte recruitment to the infected nidus.[101] In a small clinical trial for patients with sepsis-induced immunosuppression (defined by a decreased expression of monocyte human leucocyte antigen-DR [HLA-DR]), granulocyte macrophage-colony stimulating factor (GM-CSF) was shown to restore HLA-DR expression. Moreover, TLR-induced pro-inflammatory monocytic CK production was restored ex vivo. Clinical outcomes (duration of mechanical ventilation, organ dysfunctions and length of ICU and hospital stay) were also improved in the GM-CSF group.[102] Similar to GM-CSF, ex vivo IFN-γ can restore the immune functions of stimulated leucocytes in septic patients. In healthy volunteers receiving IV LPS, IFN-γ limited the reduction of the LPS-induced TNF response, compared with the placebo. IFN-γ also increased monocyte HLA-DR expression.[103] In addition, IFN-γ seems to accelerate recovery from invasive fungal infections by restoring immune function, when added to standard care.[104]

CONCLUSIONS

The past two decades have seen a remarkable growth in our understanding of the complex interconnection of the multiple biological pathways involved in the sepsis pathogenesis. Significant progress on sepsis-related mortality and morbidity has been achieved in the past decade thanks to clinicians' increased awareness regarding sepsis, and the timely application of SSC-recommended diagnostic and therapeutic bundles.[3] Enhanced understanding of sepsis-induced immunosuppression has led to the development and application of potential adjunctive therapies aimed at modulating the pathologic inflammatory response and limiting its deleterious consequences. Since heterogeneity is one of the major determinant aspects in sepsis, most of the adjuvant treatments still lack a well-defined application, and research is needed to further reduce mortality. Until such time as more tailored therapies become available, infection source control, the timely application of broad-spectrum antibiotics and organ support will remain core topics in the treatment of septic patients.

REFERENCES

1. Fleischmann C, Scherag A, Adhikari NKJ, et al. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. *Am J Respir Crit Care Med*. 2016;193: 259–272.
2. Kaukonen K-M, Bailey M, Suzuki S, et al. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. *JAMA*. 2014;311:1308–1316.
3. Levy MM, Rhodes A, Phillips GS, et al. Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study. *Crit Care Med*. 2015;43:3–12.
4. Miller RR, Dong L, Nelson NC, et al. Multicenter implementation of a severe sepsis and septic shock treatment bundle. *Am J Respir Crit Care Med*. 2013;188:77–82.
5. Martin GS, Mannino DM, Eaton S, et al. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*. 2003;348: 1546–1554.
6. Esteban A, Frutos-Vivar F, Ferguson ND, et al. Sepsis incidence and outcome: contrasting the intensive care unit with the hospital ward. *Crit Care Med*. 2007;35:1284–1289.
7. Vincent J-L, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med*. 2006;34:344–353.
8. Bone R, Balk R, Cerra F, et al. The ACCP-SCCM consensus conference for sepsis and organ failure. *Chest*. 1992;101:1644–1655.

9. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA*. 2016;315: 801–810.
10. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA*. 2016;315: 762–774.
11. Kaukonen K-M, Bailey M, Pilcher D, et al. Systemic inflammatory response syndrome criteria in defining severe sepsis. *NEJM*. 2015;372:1629–1638.
12. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003;31:1250–1256.
13. Chen Y-X, Li C-S. Risk stratification and prognostic performance of the predisposition, infection, response, and organ dysfunction (PIRO) scoring system in septic patients in the emergency department: a cohort study. *Crit Care*. 2014;18:R74.
14. Chen YX, Li CS. Evaluation of community-acquired sepsis by PIRO system in the emergency department. *Intern Emerg Med*. 2013;8:521–527.
15. Vincent J-L, Martin GS, Levy MM. qSOFA does not replace SIRS in the definition of sepsis. *Crit Care*. 2016;20:210.
16. Vincent J, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA*. 2009;302:2323–2329.
17. Weiss SL, Fitzgerald JC, Pappachan J, et al. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. *Am J Respir Crit Care Med*. 2015;191:1147–1157.
18. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell*. 2010;140:805–820.
19. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med*. 2013;369:840–851.
20. van der Poll T, Opal SM. Host-pathogen interactions in sepsis. *Lancet Infect Dis*. 2008;8:32–43.
21. Delano MJ, Ward PA. Sepsis-induced immune dysfunction: can immune therapies reduce mortality? *J Clin Invest*. 2016;126:23–31.
22. Bertheloot D, Latz E. HMGB1, IL-1α, IL-33 and S100 proteins: dual-function alarmins. *Cell Mol Immunol*. 2016;14:1–22.
23. Yadav H, Cartin-Ceba R. Balance between hyperinflammation and immunosuppression in sepsis. *Semin Respir Crit Care Med*. 2016;37:42–50.
24. Hotchkiss R, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. *Nat Rev Immunol*. 2013;13:862–874.
25. Gotts JE, Matthay MA. Sepsis: pathophysiology and clinical management. *BMJ*. 2016;353:i1585.
26. Schulte W, Bernhagen J, Bucala R. Cytokines in sepsis: potent immunoregulators and potential therapeutic targets – an updated view. *Mediators Inflamm*. 2013;2013:165974.
27. Deretic V, Saitoh T, Akira S. Autophagy in infection, inflammation and immunity. *Nat Publ Gr*. 2013;13:722–737.
28. Otto GP, Sossdorf M, Claus RA, et al. The late phase of sepsis is characterized by an increased microbiological burden and death rate. *Crit Care*. 2011;15:R183.
29. Hotchkiss RS, Monneret G, Payen D. Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. *Lancet Infect Dis*. 2013;13:260–268.
30. Boomer JS, To K, Chang KC, et al. Immunosuppression in patients who die of sepsis and multiple organ failure. *JAMA*. 2011;306:2594–2605.
31. Hotchkiss RS, Nicholson DW. Apoptosis and caspases regulate death and inflammation in sepsis. *Nat Rev Immunol*. 2006;6:813–822.
32. Ince C, Mayeux PR, Nguyen T, et al. The endothelium in sepsis. *Shock*. 2016;45:259–270.
33. Martin L, Koczera P, Zechendorf E, et al. The endothelial glycocalyx: new diagnostic and therapeutic approaches in sepsis. *Biomed Res Int*. 2016;2016:1–8.
34. Levy M, Van der Pol T. Coagulation and sepsis. *Thromb Res*. 2016;19:38–44.
35. Fiusa MML, Carvalho-Filho MA, Annichino-Bizzacchi JM, et al. Causes and consequences of coagulation activation in sepsis: an evolutionary medicine perspective. *BMC Med*. 2015;13:105.
36. Vincent J, Backer De D. Circulatory shock. *N Engl J Med*. 2013;369:1726–1734.
37. Romero-Bermejo FJ, Ruiz-Bailen M, Gil-Cebrian J. Huertos-Ranchal MJ: Sepsis-induced cardiomyopathy. *Curr Cardiol Rev*. 2011;7:163–183.
38. Lokhandwala S, Andersen LW, Nair S, et al. Absolute lactate value vs relative reduction as a predictor of mortality in severe sepsis and septic shock. *J Crit Care*. 2017;37:179–184.
39. Garcia-Alvarez M, Marik P, Bellomo R. Sepsis-associated hyperlactatemia. *Crit Care*. 2014;18:503.
40. Curley G, Hayes M, Laffey JG. Can 'permissive' hypercapnia modulate the severity of sepsis-induced ALI/ARDS? *Crit Care*. 2011;15:212.
41. Doyle JF, Forni LG. Update on sepsis-associated acute kidney injury: emerging targeted therapies. *Biologics*. 2016;10:149–156.
42. Gomez H, Ince C, De Backer D, et al. A unified theory of sepsis-induced acute kidney injury: inflammation, microcirculatory dysfunction, bioenergetics, and the tubular cell adaptation to injury. *Shock*. 2014;41:3–11.
43. Nesseler N, Launey Y, Aninat C, et al. Clinical review: the liver in sepsis. *Crit Care*. 2012;16:235.
44. Chaudhry N, Duggal AK. Review article sepsis associated encephalopathy. *Adv Med*. 2014;2014: 1–16.
45. Azzari C, Moriondo M, Indolfi G, et al. Realtime PCR is more sensitive than multiplex PCR for diagnosis and serotyping in children with culture negative pneumococcal invasive disease. *PLoS ONE*. 2010;5:e9282.

46. Farina C, Arena F, Casprini P, et al. Direct identification of microorganisms from positive blood cultures using the lysis-filtration technique and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS): a multicentre study. *New Microbiol*. 2015;38: 245–250.
47. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41:580–637.
48. Puskarich MA, Trzeciak S, Shapiro NI, et al. Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol*. *Crit Care Med*. 2011;39:2066–2071.
49. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34:1589–1596.
50. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med*. 2014;42: 1749–1755.
51. Armand-Lefèvre L, Angebault C, Barbier F, et al. Emergence of imipenem-resistant gram-negative bacilli in intestinal flora of intensive care patients. *Antimicrob Agents Chemother*. 2013;57:1488–1495.
52. Bassetti M, Righi E. New antibiotics and antimicrobial combination therapy for the treatment of gram-negative bacterial infections. *Curr Opin Crit Care*. 2015;21:402–411.
53. Rivers EP, Yataco AC, Jaehne AK, et al. Oxygen extraction and perfusion markers in severe sepsis and septic shock: diagnostic, therapeutic and outcome implications. *Curr Opin Crit Care*. 2015;21:381–387.
54. Galley HF. Oxidative stress and mitochondrial dysfunction in sepsis. *Br J Anaesth*. 2011;107:57–64.
55. Asfar P, Meziani F, Hamel J-F, et al. High versus low blood-pressure target in patients with septic shock. *NEJM*. 2014;370:1583–1593.
56. Vincent J-L, Quintairos Silva A, Couto L Jr, et al. The value of blood lactate kinetics in critically ill patients: a systematic review. *Crit Care*. 2016;20:257.
57. De Backer D, Donadello K, Sakr Y, et al. Microcirculatory alterations in patients with severe sepsis. *Crit Care Med*. 2013;41:791–799.
58. Haase N, Perner A, Hennings LI, et al. Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. *BMJ*. 2013;346:f839.
59. Perner A, Haase N, Winkel P, et al. Long-term outcomes in patients with severe sepsis randomised to resuscitation with hydroxyethyl starch 130/0.42 or Ringer's acetate. *Intensive Care Med*. 2014;40:927–934.
60. Myburgh J, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367:1901–1911.
61. Cecconi M, Hofer C, Teboul JL, et al. Fluid challenges in intensive care: the FENICE study: a global inception cohort study. *Intensive Care Med*. 2015;41:1529–1537.
62. Patel A, Laffan MA, Waheed U, et al. Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality. *BMJ*. 2014;349:g4561.
63. Reddy S, Weinberg L, Young P. Crystalloid fluid therapy. *Crit Care*. 2016;20:59.
64. Sen A, Keener CM, Sileanu FE, et al. Chloride content of fluids used for large-volume resuscitation is associated with reduced survival. *Crit Care Med*. 2016;45:e146–e153.
65. Yunos NM, Bellomo R, Glassford N, et al. Chloride-liberal vs. chloride-restrictive intravenous fluid administration and acute kidney injury: an extended analysis. *Intensive Care Med*. 2014;41:257–264.
66. de Oliveira FSV, Freitas FGR, Ferreira EM, et al. Positive fluid balance as a prognostic factor for mortality and acute kidney injury in severe sepsis and septic shock. *J Crit Care*. 2015;30:97–101.
67. McDermid RC. Controversies in fluid therapy: type, dose and toxicity. *World J Crit Care Med*. 2014;3:24.
68. Maybauer MO, Maybauer DM, Enkhbaatar P, et al. The selective vasopressin type 1a receptor agonist selepressin (FE 202158) blocks vascular leak in ovine severe sepsis*. *Crit Care Med*. 2014;42:e525–e533.
69. Chawla LS, Busse LW, Brasha-Mitchell E, et al. The use of angiotensin II in distributive shock. *Crit Care*. 2016;20:137.
70. Kirov MY, Evgenov O V, Evgenov N V, et al. Infusion of methylene blue in human septic shock: a pilot, randomized, controlled study. *Crit Care Med*. 2001;29:1860–1867.
71. Walkey AJ, Wiener RS, Ghobrial JM, et al. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA*. 2011;306:2248–2254.
72. Angus DC, Barnato AE, Bell D, et al. A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. *Intensive Care Med*. 2015;41:1549–1560.
73. Ng P, Sin W, Ng A, et al. Speckle tracking echocardiography in patients with septic shock: a case control study (SPECKSS). *Crit Care*. 2016;20: 1–8.
74. Aneman A, Vieillard-Baron A. Cardiac dysfunction in sepsis. *Intensive Care Med*. 2016;42: 1–4.
75. Andreis DT, Singer M. Catecholamines for inflammatory shock: a Jekyll-and-Hyde conundrum. *Intensive Care Med*. 2016;42:1387–1397.

76. Koster G, Wetterslev J, Gluud C, et al. Effects of levosimendan for low cardiac output syndrome in critically ill patients: systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med*. 2014;41:203–221.
77. Morelli A, Singer M, Ranieri VM, et al. Heart rate reduction with esmolol is associated with improved arterial elastance in patients with septic shock: a prospective observational study. *Intensive Care Med*. 2016;1–7.
78. Holst LB, Hasse N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med*. 2014;371:1381–1391.
79. Vincent J-L. We should abandon randomized controlled trials in the intensive care unit. *Crit Care Med*. 2010;38:S534–S538.
80. Vincet J. New therapies in sepsis. *Chest*. 1997;112: 330S–338S.
81. Vincent J. Emerging therapies for the treatment of sepsis. *Curr Opin Anesthesiol*. 2015;28:411–416.
82. Bermejo-Martin JF, Giamarellos-Bourboulis EJ. Endogenous immunoglobulins and sepsis: new perspectives for guiding replacement therapies. *Int J Antimicrob Agents*. 2015;46:S25–S28.
83. Shankar-Hari M, Spencer J, Sewell WA, et al. Bench-to-bedside review: immunoglobulin therapy for sepsis - biological plausibility from a critical care perspective. *Crit Care*. 2012;16:206.
84. Alejandria MM, Lansang MAD, Dans LF, et al. Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock. *Cochrane Database Syst Rev*. 2013;(9):CD001090.
85. Giamarellos-Bourboulis EJ, Tziolos N, Routsi C, et al. Improving outcomes of severe infections by multidrug-resistant pathogens with polyclonal IgM-enriched immunoglobulins. *Clin Microbiol Infect*. 2015;22:499–506.
86. Cavazzuti I, Serafini G, Busani S, et al. Early therapy with IgM-enriched polyclonal immunoglobulin in patients with septic shock. *Intensive Care Med*. 2014;40:1888–1896.
87. Jardine D, Emond M, Meert KL, et al. A single nucleotide polymorphism in the corticotropin receptor gene is associated with a blunted cortisol response during pediatric critical illness. *Pediatr Crit Care Med*. 2014;15:1–8.
88. Rimmelé T, Kellum JA. Clinical review: blood purification for sepsis. *Crit Care*. 2011;15:205.
89. Kellum JA, Gómez H, Gómez A, et al. Acute Dialysis Quality Initiative (ADQI) XIV sepsis phenotypes and targets for blood purification in sepsis: The Bogotà Consensus. *Shock*. 2016;45:242–248.
90. Villa G, Neri M, Bellomo R, et al. Nomenclature for renal replacement therapy and blood purification techniques in critically ill patients: practical applications. *Crit Care*. 2016;20:283.
91. Clark E, Molnar AO, Joannes-Boyau O, et al. High-volume hemofiltration for septic acute kidney injury: a systematic review and meta-analysis. *Crit Care*. 2014;18:R7.
92. Neri M, Cerdà J, Garzotto F, et al. Nomenclature for renal replacement therapy in acute kidney injury. In: Kellum JA, Bellomo R, Ronco C, eds. *Continuous versus Intermittent Renal Replacement Therapy: A Meta-analysis*. New York, NY: Oxford University Press; 2016:21–34.
93. Peng Z-Y, Carter MJ, Kellum JA. Effects of hemoadsorption on cytokine removal and short-term survival in septic rats. *Crit Care Med*. 2008;36:1573–1577.
94. Ronco C, Brendolan A, Lonnemann G, et al. A pilot study of coupled plasma filtration with adsorption in septic shock. *Crit Care Med*. 2002;30:1250–1255.
95. Livigni S, Bertolini G, Rossi C, et al. Efficacy of coupled plasma filtration adsorption (CPFA) in patients with septic shock: a multicenter randomised controlled clinical trial. *BMJ Open*. 2014;4:e003536.
96. Cruz D, Antonelli M, Fumagalli R, et al. Early use of polymyxin B hemoperfusion in abdominal sepsis. *JAMA*. 2009;301:2445–2452.
97. Payen DM, Guilhot J, Launey Y, et al. Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial. *Intensive Care Med*. 2015;41:975–984.
98. Morgera S, Haase M, Kuss T, et al. Pilot study on the effects of high cutoff hemofiltration on the need for norepinephrine in septic patients with acute renal failure. *Crit Care Med*. 2006;34:2099–2104.
99. Villa G, Zaragoza JJ, Sharma A, et al. Cytokine removal with high cut-off membrane: review of literature. *Blood Purif*. 2014;38:167–173.
100. Leentjens J, Kox M, Van Der Hoeven JG, et al. Immunotherapy for the adjunctive treatment of sepsis: from immunosuppression to immunostimulation time for a paradigm change? *Am J Respir Crit Care Med*. 2013;187:1287–1293.
101. Unsinger J, McGlynn M, Kasten KR, et al. IL-7 promotes T cell viability, trafficking, and functionality and improves survival in sepsis. *J Immunol*. 2010;184:3768–3779.
102. Meisel C, Schefold JC, Pschowski R, et al. Granulocyte-macrophage colony-stimulating factor to reverse sepsis-associated immunosuppression: a double-blind, randomized, placebo-controlled multicenter trial. *Am J Respir Crit Care Med*. 2009;180:640–648.
103. Leentjens J, Kox M, Koch RM, et al. Reversal of immunoparalysis in humans in vivo: a double-blind, placebo-controlled, randomized pilot study. *Am J Respir Crit Care Med*. 2012;186:838–845.
104. Delsing CE, Gresnigt MS, Leentjens J, et al. Interferon-gamma as adjunctive immunotherapy for invasive fungal infections: a case series. *BMC Infect Dis*. 2014;14:166.

71

Nosocomial infections

James Hatcher, Rishi H-P Dhillon

Nosocomial or health care-associated infections (HCAIs) are a major problem in hospitals, affecting up to 9% of inpatients at any one time. Intensive care units (ICUs) represent 2%–10% of hospital beds, but are responsible for 25% of all nosocomial bloodstream and pulmonary infections. In the European Prevalence of Infection in Intensive Care (EPIC) and EPIC II studies' snapshot of prevalence, the infection rate in ICU was 44.8% and 51%, respectively, with ICU-associated infection 20.6% in the EPIC study.[1,2] Nosocomial infection is, at least in theory, a preventable cause of morbidity and mortality (Box 71.1).

EPIDEMIOLOGY

The prevalence of nosocomial infection is reported as being between 3% and 12% in most institutions, but varies considerably between different sites within each institution.[3] The vulnerability of the patient population, the nature of interventions and cross-infection are but three of many factors. This is seen clearly if one compares the range between ophthalmology and critical care: 0%–23%.[4]

Ventilator-associated pneumonia (VAP) is common, has significant morbidity with increased length of stay, associated costs and a twofold increase in mortality.[5] It has been suggested that bloodstream infections, surgical wound infections and nosocomial pneumonia result in 14, 12 and 13 attributable extra hospital days, respectively.[6] Catheter-related bloodstream infection (CR-BSI) was also associated with major morbidity, although, curiously, not necessarily mortality.[7] The mortality rates directly due to these infections are hard to separate from the mortality attributed to the presenting severity of illness, which, in its own right, may have predisposed to infection. It is clear that nosocomial infection is associated with increased mortality, and huge financial and resource costs.[2]

INTERACTION BETWEEN PATIENT, ORGANISM AND ENVIRONMENT

A number of factors come together to enable nosocomial infection to occur. Some may be risk factors in their own right, whereas others may simply represent an identifier of a sicker and therefore more vulnerable population (Box 71.2).

The host usually lives in symbiotic tranquillity with a huge range of organisms (Table 71.1). Antibiotics suppress commensal organisms and allow the overgrowth of a usually insignificant organism or a resistant organism of the same type. An organism such as *Candida* will flourish in the presence of broad-spectrum antibiotics, and this overgrowth may result in symptomatic or even invasive candidiasis; cephalosporin use may encourage the intrinsically resistant but quiescent enterococci to emerge as a problematic organism.

Extrinsic organisms may be introduced from the environment, patients, staff or from surfaces. These may be organisms that are thriving in that environment because of local pressures (e.g. antibiotics), or from poor hygiene. Examples include *Acinetobacter baumanii* and methicillin-resistant *Staphylococcus aureus* (MRSA). On admission, patients will be carrying a range of organisms that have the potential to cause problems, but during their stay they are likely to acquire a new ecology from their surroundings.

The great debate remains as to the interpretation of microbiology results in the context of a non-septic patient; is this infection or colonisation? This challenge needs a multidisciplinary approach, taking into account clinical evidence together with diagnostic results.

A vast range of organisms can cause nosocomial infection but a smaller number of particular organisms cause the majority of infections (Box 71.3). It must be emphasised that each hospital and each ICU will have its own local ecology. Regional, national and international surveys give indications of general trends, but this does not supplant local knowledge.

The individual characteristics of the organism are important. These include their resilience in the local environment, the ease of transmission and the individual pathogenicity. This clearly interacts with the vulnerability of the host, as some usually innocuous organisms, such as *Candida* spp. or *Serratia marcescens*, will cause problems only in vulnerable hosts, whereas some strains of *S. aureus, Pseudomonas aeruginosa* or *Clostridium difficile* may be intrinsically more virulent.

ABSTRACT

Intensive care units are particularly vulnerable to nosocomial infections, which are associated with increased morbidity, mortality and economic cost. Endogenous microbes have a symbiotic relationship with their human host, but critical illness in the vulnerable patient leads to the breakdown of the normal human defence mechanisms resulting in health care-associated infection. Increasing population age with complex co-morbidities (coupled with the bewildering array of iatrogenic immunosuppressive treatment regimens) makes nosocomial infection a dynamic challenge. The regional, national and international spread of multidrug-resistant bacteria alongside declining therapeutic options is of particular concern for the future management of these infections. This chapter will focus on the relationship between pathogen and host, organisms causing disease including the role of multidrug resistance, routes of infection and methods to prevent and treat these challenging infections.

KEYWORDS

Nosocomial
health care-associated infection
bacteria
resistance
carbapenemase
antibiotic
colonisation
infection control

Box 71.1 Principles of diagnosis of nosocomial infections

- Diagnosis of infection usually requires the combination of clinical findings and the results of diagnostic tests
- Diagnosis of infection from direct observation at surgery, endoscopy or other diagnostic procedure is an acceptable criterion
- It must be hospital-acquired with no evidence that the infection was present or incubating at the time of hospital admission. Infection acquired in hospital, but only evident after hospital discharge, also fulfils the criteria
- Usually no specific time during or after hospitalisation is given to determine whether an infection is nosocomial or community-acquired. Each infection is examined for evidence that links it to hospitalisation (this is a matter of controversy)

Box 71.2 Risk factors for nosocomial infection

Patient
- Severity of illness
- Significant co-morbidities
- Nutritional state
- Immunosuppression
- Open wounds
- Invasive devices
- Multiple procedures
- Prolonged stay
- Ventilation
- Multiple or prolonged antibiotics
- Blood transfusion

Environment
- Changes in procedures or protocols
- Multiple changes in staff; new and locum staff
- Poor aseptic practice – poor hand washing
- Patient-to-patient – busy, crowded unit, staff shortages

The organism
- Resistance
- Resilience in terms of survival
- Formation of slime or ability to adhere – biofilm formation
- Pathogenicity
- Prevalence

Box 71.3 Organisms responsible for the majority of nosocomial infections

Methicillin-resistant *Staphylococcus aureus* (MRSA)
Coagulase-negative *Staphylococcus* (CNS)
Enterococcus spp. (*E. faecalis, E. faecium*)
Pseudomonas aeruginosa
Acinetobacter baumanii
Stenotrophomonas maltophilia
Enterobacter spp.
Klebsiella spp.
Escherichia coli
Serratia marcescens
Proteus spp.
Candida spp. (*C. albicans, C. glabrata, C. krusei*)

Other organisms may be a problem in the severely immunocompromised, such as those with acquired immunodeficiency syndrome (AIDS; see Chapter 69).

Table 71.1 Common commensals that may cause infection in a vulnerable host

SITE	COMMON COMMENSAL ORGANISMS
Skin	*Staphylococcus epidermidis*, streptococci, *Corynebacterium* (diphtheroids), *Candida* spp.
Throat	*Viridans group streptococci*, diphtheroids
Mouth	*Viridans group streptococci, Moraxella catarrhalis, Actinomyces*, spirochaetes
Respiratory tract	*Viridans group streptococci, Moraxella*, diphtheroids
Vagina	Lactobacilli, diphtheroids, streptococci, yeast
Intestines	*Bacteroides* spp., anaerobic streptococci, *Clostridium perfringens, Escherichia coli, Klebsiella* spp., *Proteus* spp., enterococci

The combination of sick patients and widespread use of potent antibiotics selects out problematic organisms and, as this epitomises intensive care practice, it is in the ICU where multiresistance is common.

RESISTANT ORGANISMS

There are several mechanisms involved in resistance and in its spread. Generally speaking, there are four main mechanisms of antibiotic resistance[8]:

1. Enzymatic inactivation of drug
2. Altered drug-binding site
3. Decreased uptake of drug, either by decreased penetration or by up-regulated efflux pumps
4. Bypass pathways.

Resistance is acquired in a variety of ways. Mutation of any gene occurs at a rate of one cell in 10^7 and, if this cell is then presented with antibiotics that it can survive, it will become a dominant cell, reproducing at a rate of 10^9 overnight.

Enzymes, such as the β-lactamases, inactivate a large array of antibiotics. Class 1 β-lactamase is effective against some β-lactam-containing antibiotics but extended-spectrum β-lactamases (ESBLs), which incorporate enzymes such as TEM-24, will produce

cross-resistance to multiple classes of antibiotics, including fluoroquinolones and aminoglycosides.[9–12]

The Ambler classification categorised all β-lactamases into four classes A–D, based upon molecular structure, and ESBLs are Class A enzymes. The major ESBL types are TEM, SHV and CTX-M – the latter being the predominant genotype globally.

AMPc enzymes are Class C, and differ chiefly in the fact they are not inhibited by clavulanate in vitro. *Enterobacter*, *Serratia* and *Citrobacter* can all produce AMPc β-lactamases. This fact is mainly of use in the diagnostic laboratory, where different markers aid in helping define potential therapeutic options. For example, β-lactam/β-lactamase inhibitor drug combinations, such as co-amoxiclav (amoxicillin and clavulanic acid) and piperacillin-tazobactam, may be considered in ESBL producers with mild infection, but not in AMPc producers. However, this is rarely appropriate in the ICU setting.

Resistance may be produced by a combination of mechanisms, such as in *P. aeruginosa* where the resistance is due to a combination of protein efflux systems, cephalosporinases and derepression of AmpC enzyme.

Carbapenemases were first described in the 1980s but have become prominent over the last 10 years, especially with the rise of Class B metallo β-lactamases (MBLs). In particular the New Delhi MBL (NDM-1), which was characterised in 2008, is of growing concern as the plasmid carrying the enzyme also carries other resistance mechanisms, rendering such infections extremely drug resistant.[13] Other carbapenemase enzymes exist (such as KPC and OXA enzymes), and the degree to which they inhibit the action of the drug varies. This has implications for both the detection and management of these infections

The big problem particularly with carbapenemases and ESBLs is that they can spread by plasmid transmission, which is very rapid. The enzyme production is encoded chromosomally within an organism, and can then be transferred between bacteria by plasmids. Transposons transfer genes between plasmids.

The phenomenon of induction is the process whereby the presence of an antibiotic appears to 'induce' or switch on the production of the relevant enzyme so that the organism becomes resistant. For example, staphylococcal resistance to methicillin occurs due to an altered penicillin-binding protein that has low affinity for all β-lactam agents. It is linked to a *MecA* gene, which is usually expressed only when stressed by antibiotic pressure. This gene does not develop readily and the spread of methicillin resistance is by vector transmission, not de novo production of resistance (Table 71.2).[9]

PROBLEM ORGANISMS

See Box 71.3 for organisms responsible for the majority of nosocomial infections.

Table 71.2 The influence of extended-spectrum β-lactamases (ESBL) on resistance in *Klebsiella*

ANTIBIOTICS	ESBL-NEGATIVE (% RESISTANT)	ESBL-POSITIVE (% RESISTANT)
Gentamicin	8	76
Amikacin	3	52
Ciprofloxacin	3	31
All the above	0	5

Reproduced from Livermore DM, Yuan M. Antibiotic resistance and production of extended-spectrum beta-lactamases amongst *Klebsiella* spp. from intensive care units in Europe. *J Antimicrob Chemother*. 1996;38:409–424.

These infections are likely to be associated with an increase in morbidity and mortality, primarily due to delayed recognition, an association with other resistant mechanisms (ESBLs are often aminoglycoside and quinolone resistant too) and a lack of therapeutic options.[11]

An indication of their perceived importance is that in 2016 the United Nations General Assembly passed a resolution on antimicrobial resistance (AMR), aimed at improving country action plans. In the United Kingdom the government published a 5-year AMR strategy and as a result AMR was placed on the UK government risk register in 2015.[14] The World Health Organization released their Global Action Plan in 2015 stating 'antimicrobial resistance threatens the very core of modern medicine'.[15] The epidemiological evidence shows that the prevalence of such infections is increasing worldwide.[12]

EXTENDED-SPECTRUM β-LACTAMASE-PRODUCING ENTEROBACTERIACEAE

Enterobactericeae encompass a large family of enteric, oxidase-negative, Gram-negative bacilli. In terms of nosocomial infection, *Escherichia coli* and *Klebsiella* spp. are the most frequently seen but *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp. and *Proteus* spp. (amongst others) are also implicated.

Of these, *E. coli* and *Klebsiella* are particularly able to produce ESBLs, which may be defined as transferable plasmid-mediated enzymes that hydrolyse third-generation cephalosporins (ceftriaxone) but are inhibited in vitro by clavulanate.[10]

CARBAPENEMASE-PRODUCING ENTEROBACTERIACEAE (CPE)

Of major public health concern over the last decade has been the rise of CPEs. Enterobacteriaceae implicated tend to be *E. coli* and *Klebsiella pneumoniae*, but the range of organisms capable of producing these enzymes is expanding. The organisms are resistant

to carbapenems, and frequently the majority of other antibiotic classes, rendering treating patients extremely difficult, with colistin as the only reliable therapeutic option. As such these organisms are associated with increased morbidity and mortality and have the capacity to cause outbreaks. International guidance recommends combination antibiotic therapy in treating these infections, with strict adherence to infection control practice.[13,16,17]

PSEUDOMONAS AERUGINOSA

P. aeruginosa is one of the commonest pathogens associated with hospital-acquired pneumonia (HAP). Due to a large genome, it is inherently resistant to a significant number of commonly used antibiotics, rendering therapy challenging. It is of particular importance in patients suffering from chronic lung disease (such as cystic fibrosis, chronic obstructive pulmonary disease [COPD] or bronchiectasis), where colonisation within the respiratory tract leads to recurrent infections, and subsequently worse morbidity and mortality. Resistance is able to develop in a range of ways and produces a very broad spectrum of resistance, making combination antibiotic therapy a popular option.[18] It is associated with an adverse outcome in the critically ill[19] and, like the ESBL producers, multidrug-resistant pseudomonal strains are growing in number.[20]

STENOTROPHOMONAS MALTOPHILIA

This is an increasingly common and troublesome environmental organism. It is often resistant to β-lactam antibiotics, quinolones and aminoglycosides. Co-trimoxazole is the only reliably effective antibiotic agent. It also produces a carbapenemase, which makes it intrinsically resistant to carbapenems, and prolonged treatment with carbapenems predisposes to *S. maltophilia* colonisation and subsequent infection.

ACINETOBACTER BAUMANII

A. baumanii is an increasing and major problem. It survives even in dry environments and, despite its name, spreads and cross-infects readily (*a cineto*: without movement). It is multiresistant and, although generally sensitive to carbapenems, it is increasingly resistant even to these agents. It becomes rapidly resistant and the profile of resistance is unpredictable but can be extremely broad, with some organisms sensitive only to colistin.[21]

COAGULASE-NEGATIVE STAPHYLOCOCCI (CoNS)

CoNS are low-virulence organisms and common skin commensals, but are increasingly causing nosocomial infection. Their resilience may be in part due to the production of biofilm, when associated with catheter-related or bone and joint infections. They are resistant to multiple classes of antibiotics, but are usually sensitive to glycopeptides. As glycopeptide resistance patterns alter, agents such as linezolid and tigecycline have a therapeutic role.

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS

S. aureus is a virulent pathogen causing a wide range of infections. It has a plethora of virulence factors but endogenous toxins produce most of the clinical syndromes such as invasive skin and soft tissue infections, food poisoning and necrotising pneumonia.

Methicillin resistance was first noted in the early 1960s and, although rates between countries and ICUs vary considerably, there has been an inexorable rise in its prevalence in most countries. Glycopeptides are currently commonly used to treat invasive MRSA infections but, as ever, source control is of paramount importance. Newer anti-MRSA agents include linezolid, tigecycline and daptomycin. Anti-MRSA cephalosporins have also been developed (ceftaroline, ceftobiprole). MRSA has been a model of the failure of some infection control methods and is a well-publicised marker of quality in a health care setting.

CLOSTRIDIUM DIFFICILE

This originally emerged as an organism considered a problem after administration of certain antibiotics, including clindamycin. It is now clear that in the critically ill it often emerges after using almost any broad-spectrum antibiotics. The organism produces toxins that can cause pseudomembranous colitis, a potentially catastrophic disease leading to toxic megacolon. Although it usually settles on metronidazole or vancomycin orally, recurrence is common and it can ultimately lead to radical surgery, such as a colectomy.[22] Fidaxomicin shows promise against recurrent disease.[23] Faecal microbiota transplant has developed a good evidence base and use for recurrent disease is increasing.[24] Surgery carries a high mortality rate, quoted at 11% for total colectomy, and very high mortality for less aggressive surgery, such as hemicolectomy in the presence of toxic megacolon.[25]

CANDIDA *SEPSIS*

Candida sepsis is the fourth commonest bloodstream infection in the United States and the sixth commonest in Europe.[26]

The prevalence of species is defined by each unit, but *Candida albicans* is most common. There is some evidence to suggest that the widespread use of azoles may have influenced the relative increase in *C. glabrata* and *C. krusei* species. *C. auris* has recently emerged as a difficult pathogen in the ICU with multidrug resistance and persistence in the environment.[27] Definitive diagnosis is by blood culture, but presumptive diagnosis is suggested by the triad of clinical infection, a high-risk patient and *Candida* at more than two sites (Fig. 71.1). Antifungal treatment should depend on the sensitivity of the species involved.

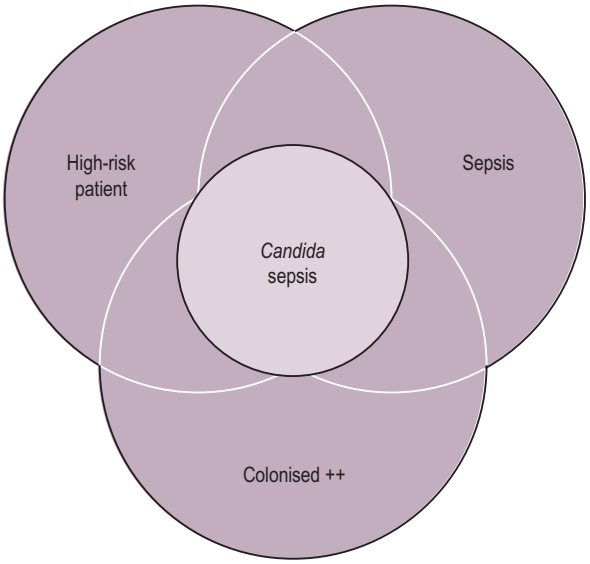


Figure 71.1 Diagnostic triad of *Candida* sepsis.

Box 71.4 Principles for the diagnosis of nosocomial pneumonia

Crackles on auscultation or dullness to percussion on physical examination of the chest and any of the following:

- New onset of purulent sputum
- Organism isolated from blood cultures
- Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing or biopsy
- Chest radiography examination shows new or progressive infiltration, consolidation, cavitation or pleural effusion
- Isolation of virus or detection of virus antigen in respiratory secretions
- Diagnostic single antibody titre immunoglobulin (Ig)M or fourfold increase in paired serum samples (IgG) for pathogen
- Histopathological evidence of pneumonia

SITES OF INFECTION

The main sites of nosocomial infection are the respiratory system, surgical site wounds and intravenous lines. Urinary tract infection appears to be relatively uncommon compared with non-critical care environments, with only 14% point prevalence in the EPIC II study compared with 64% of respiratory-related infections.

NOSOCOMIAL PNEUMONIA

Nosocomial pneumonia is a common problem in the critically ill, particularly in ventilated patients with an attributable mortality of 13%.[28]

AETIOLOGY

There are several possible mechanisms, including aspiration from the nasopharynx, local spread and haematogenous spread of infection. Some 45% of healthy adults aspirate in their sleep. In the sick the nasopharynx colonises rapidly with a wide range of organisms, usually Gram negatives, and aspiration is encouraged by the unconscious state, the presence of a nasogastric tube or endotracheal intubation. Pneumonia will develop in up to 25% of colonised patients, compared with a 3% incidence in non-colonised patients.

Patient factors predisposing to nosocomial pneumonia include acute severity of illness, chronic illness, especially chronic lung disease, diabetes, immunosuppression, advanced age, recent surgery to thorax or abdomen, intubation and bronchoscopy. Environmental factors include broad-spectrum and prolonged use of antibiotics, potential pathogens in the vicinity, bacterial properties such as the ability to adhere to surfaces, cross-infection, 24-hour ventilator tubing changes and foreign bodies such as nasogastric tubes. Intubated and ventilated patients have a higher rate of nosocomial infection than patients receiving non-invasive ventilation. However, this may be due to different patient populations with different underlying problems and background morbidity.[29] The role of neutralisation by H_2 antagonists and proton pump inhibitors is still debated.[30–32]

DIAGNOSIS

The general criteria for diagnosis are clinical signs of a chest infection, purulent sputum, rising inflammatory markers, radiological evidence and positive cultures from sputum or blood.[28] These criteria are non-specific, and obtaining deep respiratory samples with quantitative analysis remains the stated gold standard method of diagnosis. This can be achieved with protected brush specimens bronchoalveolar lavage (BAL) and protected BAL. These are difficult and time consuming, and it appears that non-bronchoscopic techniques, such as blind tracheal aspirates through the endotracheal tube, are both practical and reasonably effective from a clinical – if not a research – viewpoint.[28] A Cochrane review showed there was no evidence that quantitative cultures (compared with qualitative analysis) reduced mortality, length of stay, time on mechanical ventilation or antibiotic change (Box 71.4).[33]

THE ORGANISMS

The majority of VAP is due to aerobic Gram-negative organisms such as *Klebsiella* spp., *E. coli* and *Pseudomonas* spp., but early-onset VAP, between 48 hours and 5 days, may be due to community pathogens, such as methicillin-sensitive *S. aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. This has been described as early endogenous infection.

In late-onset VAP (after 5–7 days), multidrug-resistant organisms, such as MRSA, *P. aeruginosa*, *Acinetobacter baumannii* and *S. maltophilia*, occur more commonly than in non-ICU patients.[28,34]

PREVENTION

Prevention is by methods that reduce aspiration, cross-infection and contamination of respiratory devices.[30] Recommended methods include:

- hand washing
- limiting antibiotic use
- changing ventilator circuits at longer intervals – 1 week
- orotracheal, rather than nasotracheal intubation
- removing nasogastric tubes
- semi-recumbent position – this reduces aspiration
- avoiding muscle relaxants
- avoiding re-intubation
- using non-invasive ventilation, where possible.

TREATMENT

The use of inappropriate antibiotics leads to an increased mortality, so current trends are towards initial broad-spectrum antibiotics followed by reassessment and de-escalation.[35,36] As the spectrum of resistance grows, it is highly likely that it will be increasingly difficult to apply this broad-spectrum empirical treatment, especially with late-onset VAP. Surveillance of current colonisation, awareness of an individual ICU's ecology and targeted treatment will replace empiric regimens. Most international guidance advocate the empirical use of combination therapy to cover *S. aureus*, *P. aeruginosa* and other Gram-negative bacilli, in patients with suspected VAP.[28,35,37–39] The evidence is not conclusive, however, and many studies have shown good results with monotherapy.[40,41]

Duration of treatment has always been widely debated. Shorter courses are increasingly being advocated, with a 7-day course shown to be effective.[28,42] Pseudomonal or MRSA pneumonia may require longer courses, of 14 and 21 days, respectively, depending on severity.[43] Linezolid and vancomycin have similar efficacy for HAP.[44]

SURGICAL SITE INFECTIONS

Surgical site infections remain the second most common HCAI in Europe and the United States affecting up to one-third of surgical procedures. The organisms involved may be those introduced at the time of surgery or from later contamination.[45]

RISK FACTORS

- The procedure itself and the level of contamination prior to or during surgery. Highest cumulative incidence (9.5%) was for colon surgery compared to 1.0% and less in orthopaedic prosthetic surgery in Europe.[46]
- Poor surgical technique and low volume of surgery[47]
- Host factors: see Box 71.2
- Inappropriate use of antibiotic prophylaxis
- Prolongation of stay in the ICU.

PREVENTION

Clean theatres, good operating technique and thorough asepsis, both in the theatre and postoperatively, are important.

ANTIBIOTIC PROPHYLAXIS

Efficacy of antibiotic prophylaxis has clearly been demonstrated. If there is no risk of infection with a clean procedure, there is no place for antibiotics. If contamination is either seen or likely to occur, the use of antibiotics is to provide cover for the spillage. Effective prophylaxis requires an antibiotic:

- that covers the most likely organisms
- to be given prior to contamination (0–2 hours pre-operatively)[48]
- at peak dosage at the time of contamination.

A single dose should suffice, although a second dose is recommended if the procedure extends beyond 4 hours or a significant amount of blood loss occurs. Prolonged administration:

- increases the chance of antibiotic resistance
- unnecessarily exposes the patient to adverse effects from the drugs
- encourages colonisation and late infections with resistant organisms.

In many circumstances the evidence supporting prophylaxis is minimal, and frequently the antibiotics used are inappropriate to the perceived risk. Most hospitals will have specific guidance on appropriate antibiotic prophylaxis tailored to the procedure, taking into account local microbial resistance data. With grafts, mesh or prostheses the morbidity from infection is so great as to justify using prophylaxis even if the evidence is marginal (Table 71.3).

LINE SEPSIS

The use of intravascular devices in hospital practice is ubiquitous. There is a significant morbidity associated with line sepsis with 64% of bloodstream infections occurring in patients with a vascular access device.[49] The catheter type influences the rate of infection. A systematic review[50] showed the following rates per 1000 catheter days:

- peripheral intravenous catheters – 0.5 (95% confidence interval [CI] 0.2–0.7)
- non-cuffed central venous catheters (CVCs)
  - non-medicated and non-tunnelled – 2.7 (95% CI 2.6–2.9)
  - non-medicated and tunnelled – 1.7 (95% CI 1.2–2.3)

Table 71.3 Surgical prophylaxis

TYPE OF SURGERY	
Abdominal wall	Insertion of mesh. Staphylococcal or streptococcal cover. In the groin, Gram-negative cover may be needed
Cardiac	Protection of valves and grafts. Staphylococci may be resistant
Vascular	Protection of grafts. Staphylococci are a major consideration. If the groin is involved, it may require Gram-negative cover
Orthopaedic	Prostheses. Staphylococci are an increasing problem
Biliary upper GI	Usually Gram-negative and anaerobic cover, with an awareness of resistant enterococci
Colorectal	Protection against faecal flora. Cephalosporins and metronidazole have been popular but predispose to developing enterococci, such as *Enterococcus faecalis* or *E. faecium*, which may be multiresistant
Gynaecological	Conventionally broad-spectrum involving cephalosporins or, currently, co-amoxiclav. Metronidazole is also favoured
Urological	Protection from instrumentation of the urinary tract, Gram-negative cover. Awareness of any existing infection

GI, Gastrointestinal.

- cuffed and tunnelled CVCs – 1.6 (95% CI 1.5–1.7)
- arterial catheters for haemodynamic monitoring – 1.7 (95% CI 1.2–2.3)
- pulmonary artery catheters – 3.7 (95% CI 2.4–5.0)
- peripherally inserted central catheters
  - inpatient – 2.1 (95% CI 1.0–3.2)
  - outpatient – 1.0 (95% CI 0.8–1.2)
- peripherally inserted midline catheters – 0.2 (0.0–0.5).

Many other factors influence the development of infection, such as conditions of insertion, catheter care and duration of catheter. Peripheral catheters should be inspected daily and removed when complications occur or when they are no longer required. CVCs should not be routinely replaced to prevent infection (Box 71.5).[49]

CENTRAL VENOUS CATHETERS

Colonisation of catheters is common and it is likely that this is a precursor of infection. Colonisation rates are in the order of 5%–40%, determined in part by the risk factors involved (see below). Infection rates are approximately 10% of the colonised catheters.[51]

Box 71.5 Risk factors for catheter infection

Host risk factors
Site: subclavian is a lower risk than internal jugular and femoral
Catheter material: antibacterial catheters recommended for central catheters >5 days
Number of lumens: multilumen catheters increase the infection risk[30]
Number of administrations through the lines
Dressing type: frequency of changes
Skin preparation
Experience of technique of personnel
Occurrence of bacteraemia
Tunnelling: often used for long-term access but the data are contentious[31]

DEFINITIONS

1. *Colonised catheter:* growth of greater than 15 colony-forming units (semi-quantitative) or 10^3 (quantitative) from a proximal or distal catheter segment in the absence of accompanying clinical symptoms and signs.
2. *CR-BSI:* isolation of the same organism from the catheter segment (see above) as from a peripheral blood culture in a patient with signs of infection and in the absence of another source.

THE ORGANISMS

The organisms involved in catheter sepsis are influenced predominantly by the patient's endogenous flora. There is a 25% incidence of CoNS, which are increasingly recognised as pathogens due to their ability to form biofilms on prosthetic material. A biofilm is a three-dimensional matrix of extracellular polymeric material (slime) that allows bacteria to live in communities. These are important owing to the increased resistance to antimicrobials and strong adherence to prosthetic material.[52] *S. aureus* and *Candida* spp. can cause significant bacteraemia, and seeding to other organs, such as the eyes and heart valves, must be ruled out. Gram-negative pathogens predominate in patients with haematological malignancies, and *Pseudomonas* is frequent in burns patients.

TREATMENT OF CATHETER INFECTION

The most important aspect of treatment is a high index of suspicion that leads to removal of the device if infection is present either locally or systemically.[49] Antimicrobials after line removal are recommended and duration is dependent upon the organism. CoNS need up to 5 days, but *Candida* spp. and S. *aureus* require a minimum of 14 days. Guidewire-assisted

catheter exchange is not recommended if bacteraemia are present, and a period of central line free days prior to re-insertion is optimum. Salvage therapy for infected lines is not routinely recommended, especially if the organism is highly virulent, but 14 days of antibiotics via the line would be the minimum.

PREVENTION

Important issues include insertion under aseptic conditions, an intravenous team to insert and manage lines, the anchoring of lines to prevent excessive movement, closed systems with limited interruptions to the lines, the application of sterile dressings to the insertion site, and daily inspection of the catheter site. Administration sets in continuous use do not need to be replaced more than every 96 hours unless they are used for blood or total parenteral nutrition (TPN). Daily chlorhexidine cleansing at the line site and use of transparent semipermeable dressings should be considered.[49,53,54]

Techniques of unproven benefit include antiseptic cream at the insertion site, antibiotic lock therapy, occlusive antimicrobial dressings, in-line filters, tunnelling of CVCs and routine flushing of long-term CVCs.

METHODS OF INFECTION CONTROL

Each hospital has an infection control team that can employ techniques to reduce infection (Box 71.6). Prevention of nosocomial infection, thus reducing length of stay, will decrease antibiotic utilisation and therefore the generation of multidrug resistance.

The most important aspects of preventing nosocomial infection and facilitating infection control are simple hygiene, such as hand washing, and being aware that the problem exists. There are several ways in which the issue of nosocomial infection can be addressed. These include surveillance, screening, isolation and strategic planning.[55]

SURVEILLANCE AND SCREENING

Routine culture surveillance of both patients and environment provides information on the organisms currently prevalent, and is a useful tool in guiding management when infection occurs. Molecular typing of specific pathogens allows the identification of cross-infection, and gives the clinician the ability to track the organism during an outbreak.

Screening of patients allows the identification of multidrug-resistant organisms and therefore barrier precautions to be implemented. MRSA, carbapenem-resistant Enterobacteriaceae (CRE), vancomycin-resistant Enterococci (VRE) and *Acinetobacter baumanii* are organisms often targeted during screening.

Box 71.6 Roles of infection control teams

- Surveillance and investigation of infection outbreaks
- Education of staff
- Review of antibiotic utilisation
- Review of antibiotic resistance patterns
- Review of infection control procedures and policies

ISOLATION

Although physical barriers undoubtedly reduce cross-contamination, isolation may be hazardous as it often indicates lower-intensity care. The relative risks need to be addressed.

STRATEGIC PLANNING

There are two elements. One is enforcing hygienic practice, which is simple, cheap and very effective. The other is looking towards means of reducing both nosocomial infection and the emergence of resistance by good antimicrobial stewardship.

On an individual basis the approach to management must change. In the past, empirical treatment on the basis of likely organisms led to the use of very-broad-spectrum antibiotics. Narrow-spectrum targeted treatment will cease to be an option and will become a necessity. Prolonged broad-spectrum antibiotic management aimed at dealing with any eventuality will be replaced by short-duration specific and effective regimens.

SELECTIVE DIGESTIVE DECONTAMINATION OR OROPHARYNGEAL DECONTAMINATION

Selective digestive decontamination (SDD) and selective oropharyngeal decontamination (SOD) are based on the idea that elimination of colonising organisms in the gastrointestinal tract will reduce nosocomial infection as the majority of infections arise from endogenous flora. SDD administers oral non-absorbable antibiotics, such as polymyxin and nystatin, in conjunction with a parenteral cephalosporin. SOD limits therapy to oral antiseptics such as chlorhexidine. The uptake of this technique has been limited owing to concerns over antibiotic resistance generation, but it is associated with a higher survival at day 28, a lower incidence of bacteraemia and reduced VAP.[34,56–58] It is likely that SDD would be most effective in ICUs with low levels of antibiotic resistance, and SOD should be considered in ICUs with concerns of higher levels of resistant organisms.[59]

KEY REFERENCES

1. Vincent JL, Bihari DJ, Suter PM, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of

Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. *JAMA*. 1995;274:639–644.
8. Hawkey P. The origins and molecular basis of antibiotic resistance. *BMJ*. 1998;317:657.
9. Holmes AH, Moore LS, Sundsfjord A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet*. 2016;387(10014):176–187.
13. Centers for Disease Control and Prevention. *2012 CRE toolkit – guidance for control of carbapenem-resistant Enterobacteriaceae. (CRE)*. http://www.cdc.gov/hai/organisms/cre/cre-toolkit/index.html.
23. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med*. 2011;364:422–431.
28. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator–associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and American Thoracic Society. *Clin Infect Dis*. 2016;63:e61–e111.
49. Loveday HP, Wilson JA, Pratt RJ, et al. Epic 3: national evidence-based guidelines for preventing healthcare-associated infections in the NHS hospitals in England. *J Hosp Infect*. 2014;86 Suppl 1:S1–S70.

Access the complete references list online at http://www.expertconsult.com

WEBSITES

http://www.cdc.gov/ncidod/dhqp/pdf/nnis/NosInfDefinitions.pdf.

http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/index.aspx.

REFERENCES

1. Vincent JL, Bihari DJ, Suter PM, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. *JAMA*. 1995;274:639–644.
2. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA*. 2009;302:2323–2329.
3. Rosenthal VD, Guzman S, Orellano PW. Nosocomial infections in medical–surgical intensive care units in Argentina: attributable mortality and length of stay. *Am J Infect Control*. 2003;31:291–295.
4. Sax H, Ghugonnet S, Harbarth P, et al. Variation in nosocomial infection prevalence according to patient setting: a hospital wide survey. *J Hosp Infect*. 2001;48:27–32.
5. Safdar N, Dezfulian C, Collard HR, et al. Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. *Crit Care Med*. 2005;33:2184–2193.
6. Pittet D. Pneumonie nosocomiale: incidence, morbidité et mortalité chez le patient intubé-ventilé. *Schweiz Med Wochenschr*. 1994;124:227–235.
7. Blot SI, Depuydt P, Annemans L, et al. Clinical and economic outcomes in critically ill patients with nosocomial catheter-related bloodstream infections. *Clin Infect Dis*. 2005;41:1591–1598.
8. Hawkey P. The origins and molecular basis of antibiotic resistance. *BMJ*. 1998;317:657.
9. Holmes AH, Moore LS, Sundsfjord A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet*. 2016;387(10014):176–187.
10. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. *Clin Microbiol Rev*. 2005;18:657–686.
11. *Report by the Joint Working Group of DARC and ARHAI. ESBLs – A threat to human and animal health?* Public Health England; Feb 2012.
12. Dhillon RH, Clark J. ESBLs: a clear and present danger? *Crit Care Res Pract*. 2012;2012:625170. doi:10.1155/2012/625170.
13. Centers for Disease Control and Prevention. *2012 CRE toolkit – guidance for control of carbapenem-resistant Enterobacteriaceae (CRE)*. Available at: http://www.cdc.gov/hai/organisms/cre/cre-toolkit/index.html.
14. Walsh TR. Emerging carbapenemases: a global perspective. *Int J Antimicrob Agents*. 2010;36(suppl 3):S8–S14.
15. *Department of Health UK Five Year Antimicrobial Resistance Strategy 2013 to 2018*. Available online: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf.
16. The World Health Organization. *Global Action Plan on Antimicrobial Resistance*. Available online: http://apps.who.int/iris/bitstream/10665/193736/1/9789241509763_eng.pdf?ua=1.
17. Deleted in review.
18. *Public Health England. Acute trust toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae*. Available online: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/329227/Acute_trust_toolkit_for_the_early_detection.pdf.
19. Aloush V, Navon-Venezia S, Seigman-Igra Y, et al. Multidrug-resistant *Pseudomonas aeruginosa*: risk factors and clinical impact. *Antimicrob Agents Chemother*. 2006;50:43–48.
20. Driscoll JA, Brody SL, Kollef MH. The epidemiology, pathogenesis and treatment of *Pseudomonas aeruginosa* infections. *Drugs*. 2007;67:351–368.
21. Cisneros JM, Rodriguez-Bano J. Nosocomial bacteremia due to Acinetobacter baumannii: epidemiology, clinical features and treatment. *Clin Microbiol Infect*. 2002;8:687–693.
22. Gerding DN. Treatment of *Clostridium difficile*-associated diarrhea and colitis. *Curr Top Microbiol Immunol*. 2000;250:127–139.
23. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med*. 2011;364:422–431.
24. Cammarota G, Ianiro G, Tilg H, et al. European consensus on faecal microbiota transplantation in clinical practice. *Gut*. 2017;66(4):569–580.
25. Koss K, Clark MA, Sanders DS, et al. The outcome of surgery in fulminant *Clostridium difficile* colitis. *Colorectal Dis*. 2006;8:149–154.
26. Pfaller MA, Diekema DJ, Jones RN, et al. International surveillance of bloodstream infections due to Candida species: frequency of occurrence and in vitro susceptibilities to fluconazole, ravuconazole, and voriconazole of isolates collected from 1997 through 1999 in the SENTRY antimicrobial surveillance program. *J Clin Microbiol*. 2001;39:3254–3259.
27. Clancy CJ, Nguyen MH. Emergence of Candida auris: an international call to arms. *Clin Infect Dis*. 2017;64:141–143.
28. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator–associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and American Thoracic Society. *Clin Infect Dis*. 2016;63:e61–e111.
29. Girou E, Brun-Buisson C, Taille S, et al. Secular trends in nosocomial infections and mortality associated with noninvasive ventilation in patients with exacerbation of COPD and pulmonary edema. *JAMA*. 2003;290:2985–2991.
30. Keenan SP, Heyland DK, Jacka MJ, et al. Ventilator-associated pneumonia. Prevention, diagnosis, and therapy. *Crit Care Clin*. 2002;18:107–125.
31. Dodek P, Keenan S, Cook D, et al. Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. *Ann Intern Med*. 2004;141:305–313.

32. Cook D, Heyland D, Griffith L, et al. Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation. *Crit Care Med*. 1999;27:2812–2817.
33. Berton DC, Kalil AC, Cavalcanti M, et al. Quantitative versus qualitative cultures of respiratory secretions for clinical outcomes in patients with ventilator-associated pneumonia. *Cochrane Database Syst Rev*. 2008;(4):CD006482.
34. Silvestri L, Mannucci F, van Saene HK. Selective decontamination of the digestive tract: a life saver. *J Hosp Infect*. 2000;45:185–190.
35. Bodmann KF. Current guidelines for the treatment of severe pneumonia and sepsis. *Chemotherapy*. 2005; 51:227–233.
36. Porzecanski I, Bowton DL. Diagnosis and treatment of ventilator-associated pneumonia. *Chest*. 2006;130: 597–604.
37. Costa SF, Newbaer M, Santos CR, et al. Nosocomial pneumonia: importance of recognition of aetiological agents to define an appropriate initial empirical therapy. *Int J Antimicrob Agents*. 2001; 17:147–150.
38. Rello J, Lorente C, Diaz E, et al. Incidence, etiology, and outcome of nosocomial pneumonia in ICU patients requiring percutaneous tracheotomy for mechanical ventilation. *Chest*. 2003;124:2239–2243.
39. Alvarez-Lerma F, Alvarez B, Luque P, et al. Empiric broad-spectrum antibiotic therapy of nosocomial pneumonia in the intensive care unit: a prospective observational study. *Crit Care*. 2006;10:R78.
40. Aarts MA, Hancock JN, Heyland D, et al. Empiric antibiotic therapy for suspected ventilator-associated pneumonia: a systematic review and meta-analysis of randomized trials. *Crit Care Med*. 2008;36:108–117.
41. Heyland DK, Dodek P, Muscedere J, et al. Canadian Critical Care Trials Group. Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. *Crit Care Med*. 2008;36:737–744.
42. Chastra J, Wolff M, Fagon JY, et al. PneumA Trial Group. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA*. 2003;290: 2588–2598.
43. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis*. 2011;52:285–292.
44. Kalil AC, Klompas M, Haynatzki G, et al. Treatment of hospital-acquired pneumonia with linezolid or vancomycin: a systematic review and meta-analysis. *BMJ Open*. 2013;3:e003912.
45. The World Health Organization. *Global Guidelines on the prevention of surgical site infection*. Available at: http://apps.who.int/iris/bitstream/10665/250680/1/9789241549882-eng.pdf?ua=1.
46. *Surveillance of surgical site infections in Europe 2010–2011*. Stockholm: European Centre for Disease Prevention and Control; 2013 (https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/SSI-in-europe-2010-2011.pdf).
47. Holzheimer RG, Haupt W, Thiede A, et al. The challenge of postoperative infections: Does the surgeon make a difference? *Infect Control Hosp Epidemiol*. 1997;18:449–456.
48. Classen DC, Evans RS, Pestotnik SL, et al. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *N Engl J Med*. 1992;326:281–286.
49. Loveday HP, Wilson JA, Pratt RJ, et al. Epic 3: national evidence-based guidelines for preventing healthcare-associated infections in the NHS hospitals in England. *J Hosp Infect*. 2014;86 Suppl 1: S1–S70.
50. Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. *Mayo Clin Proc*. 2006; 81:1159–1171.
51. Hannan M, Juste RN, Umasanker S, et al. Antiseptic-bonded central venous catheters and bacterial colonisation. *Anaesthesia*. 1999;54:868–872.
52. Yousif A, Jamal MA, Raad I. Biofilm-based central line-associated bloodstream infections. *Adv Exp Med Biol*. 2015;830:157–179.
53. Chatzinikolaou I, Raad II. Intravascular catheter-related infections: a preventable challenge in the critically ill. *Semin Respir Infect*. 2000;15:264–271.
54. Rizzo M. Striving to eliminate catheter-related blood stream infection; a literature review of evidence-based strategies. *Semin Anesth Periop Med Pain*. 2005;24:4.
55. Bearman GM, Munro C, Sessler CN, et al. Infection control and the prevention of nosocomial infections in the intensive care unit. *Semin Respir Crit Care Med*. 2006;27:310–324.
56. de Smet AM, Kluytmans JA, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med*. 2009;360: 20–31.
57. Zwaveling JH, Maring JK, Klompmaker IJ, et al. Selective decontamination of the digestive tract to prevent postoperative infection: a randomized placebo-controlled trial in liver transplant patients. *Crit Care Med*. 2002;30:1204–1209.
58. de Smet AM, Bonten MJ, Kluytmans JA. For whom should we use selective decontamination of the digestive tract? *Curr Opin Infect Dis*. 2012;25: 211–217.
59. de Smet AM, Kluytmans JA, Blok HE, et al. Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study. *Lancet Infect Dis*. 2011;11: 372–380.

Severe soft-tissue infections

Mohamed Abbas, Ilker Uçkay, Tristan Ferry, Elif Hakko, Didier Pittet

PATHOGENESIS

The skin is the largest organ and acts as an excellent barrier against infection. Microorganisms cause skin and soft-tissue infections (SSTIs) (1) if there is a break in the skin because of a traumatic lesion or maceration; (2) if the soft tissues are ischaemic; (3) if virulent bacteria is present, such as community-acquired methicillin-resistant *S. aureus* (CA-MRSA)[1]; (4) if there are surgical site infections[2]; or (5) if the patient is severely immunocompromised.[2,3] Skin lesions can on occasion be manifestations of systemic infection; examples are bacteraemia with meningococci or endocarditis.

In this chapter, we do not address secondary infections; fungal, parasitic or mycobacterial infections; dressings; surgical techniques; wound care; or the epidemiology and prevention of healthcare-associated SSTIs.

EPIDEMIOLOGY

SSTIs are a diverse group of clinical syndromes that have varying severity and are associated with a wide range of pathogens. There has been a steady increase in the incidence of SSTIs,[4,5] and rates of emergency department visits increased between 2000 and 2010, from 6.4 to 13.5 per 1000 persons.[6] Also, SSTIs frequently cause severe sepsis and can be responsible for 6.5% of cases of septic shock.[7] The burden of SSTIs was shown in a European study where adult patients had a median length of hospital stay of 12 days; 6.5% required admission to the ICU, and 37% required surgical intervention.[8] Necrotising fasciitis (NF) and myositis are the most feared SSTIs that can affect even the healthiest young individual with very rapid onset and rapid progression to death.[9–11] Mortality rates historically range between 20% and 30%.[12–16] More recently, a study of death certificates showed a crude mortality rate of 4.8 deaths/1,000,000 person-years, with no significant time trend in the number of fatal NF during the study period.[17] Another study showed that, despite increasing co-morbidities, there has been a decrease in mortality from 9.0% to 4.9%.[18]

MICROBIOLOGY

The microbiota of the human skin is highly diverse; different body sites represent different ecological niches and have different compositions.[19,20] In healthy adults it remains stable for up to 2 years,[21] and is probably independently of gender, race, or age. Its alterations are associated with disease or colonisation status (e.g. up to 30% of healthy adults are colonised with *S. aureus*); specifically, it has been suggested that microbe–microbe interactions may help prevent colonisation by pathogenic bacteria.[22] Transient colonisation by Gram-negative bacteria occurs in hospitalised patients, particularly in the ICU.[23] A high proportion of Gram-negative pathogens may be encountered in the clinic. For example, in Southern China, 41% of SSTIs in an inpatient population were reported to be due to Gram-negative bacteria, of which one-third were due to *Escherichia coli*.[24] Severe cellulitis with haemorrhagic bullous lesions can be caused by marine trauma, such as with *Vibrio* spp.[25]

Significant SSTIs due to human skin flora in absence of implants, lymphatic disease or trauma are exceptions. The classical pathogens of deep layer SSTIs are beta-haemolytic streptococci, notably *S. pyogenes*, and *S. aureus*.[26]

This microbiological pattern has not changed significantly over the last decades[27] with three main exceptions: CA-MRSA, often producing a necrotic cytotoxin (Panton-Valentine Leukocidin), is an emerging burden of severe SSTIs worldwide[1,28]; severe *Acinetobacter* infections following war trauma and natural disasters in arid regions[25,29]; and earthquakes (with associated tsunamis) highlight the potential for atypical microorganisms (*Aeromonas* spp., *Vibrio* spp., *Pseudomonas* spp.) causing soft tissue infections.[25,30,31]

DIAGNOSIS

Diagnosis of SSTIs can be difficult, and is essentially based on clinical presentation (e.g. rapid-onset redness, pain, and discomfort that spreads over time, which may be accompanied by fever, shivering or hypotension;

ABSTRACT

Skin and soft-tissue infections are a heterogeneous group of infections, which are mostly caused by bacteria, and may be severe, such as cellulitis/erysipelas, necrotising fasciitis and myositis. The most frequent causative bacteria are *Staphylococcus aureus* and beta-haemolytic streptococci (especially *Streptococcus pyogenes*), although Gram-negative bacteria may also play an important role in specific circumstances (e.g. *Acinetobacter* infections after trauma in arid regions, *Vibrio* spp. infections after marine trauma). Antibiotic therapy is the mainstay of treatment, and should be adapted according to local epidemiology (e.g. coverage of community-acquired methicillin-resistant *S. aureus*), the immune status of the host, and whether the infection is nosocomial or community-acquired. In severe and/or necrotising infections, surgery for source control is paramount. The jury is still out regarding the role of adjunctive therapy (toxin production inhibition, intravenous immunoglobulins, hyperbaric oxygen therapy) as well as that of newly marketed and approved antibiotics.

KEYWORDS

Skin and soft-tissue infections
cellulitis
erysipelas
necrotising fasciitis
fasciitis
myositis

or the presence of an abscess with pus). Misdiagnosis is common,[32] and has important consequences for patients.[33] Although microbiological confirmation is necessary for targeted antibiotic therapy, it is only rarely obtained.[34,35] Growth of microorganisms *per se* in swabs is not proof of infection, since some differential diagnoses of SSTIs (ischaemia, necrosis, allergy, pyoderma gangrenosum, venous thrombosis or stasis dermatitis) may equally be associated with a breach of the cutaneous barrier with consequent bacterial colonisation.[36] The classification of SSTIs can be confusing because almost every pathogen can be associated with a wide range of clinical presentations; for example, *S. pyogenes* can be responsible for erysipelas, but can spread into deeper tissues and cause fasciitis with or without associated myositis. It is not known why some infections remain superficial, while others become bacteraemic, and others still penetrate deeper structures.

Of note, colonisation with healthcare-associated MRSA poorly correlates with the pathogen of the SSTIs,[37] and patients receiving antibiotics before hospital admission may present negative culture results. The only useful serology is the antistreptolysin-O-antibody that may help diagnose infection by beta-haemolytic streptococci groups A, C and G.[38] Histology may confirm clinical suspicion, especially for NF,[39] whereas radiology detects abscesses or confirms fasciitis,[40] eventually guiding the surgeon for appropriate debridement.[35]

CLINICAL PRESENTATIONS

Cellulitis and erysipelas are skin infections that differ from each other based on the depth of involvement in the skin layers: erysipelas involves the dermis and lymphatics, whereas cellulitis is defined as a deep dermal and subcutaneous infection.[35] Both can lead to bacteraemia in roughly 2% of cases.[3,41,42] In erysipelas, prominent lymphatic blockade results in a painful bright red patch with a raised sharp border, delineating infection from the surrounding skin. In cellulitis, less lymphatic involvement causes less-well-defined borders. Differentiation between cellulitis and erysipelas is sometimes difficult; because of this, and the lack of standardised definitions, many authors prefer classifying cellulitis and erysipelas together to form one clinical entity.[9,41,43] In cases of unsatisfactory evolution, abscesses requiring drainage should be excluded. Patients with lymphedema, chronic venous insufficiency, ipsilateral deep vein thrombosis and peripheral vascular disease are at risk of recurrence.[44] In selected patients with recurrent erysipelas, secondary prophylaxis with (benzathyl)-penicillin may be useful.[9,45]

TOXIN DISEASE

Some bacteria may cause sepsis not only through local inflammatory damage but also by the production of superantigens and toxins, aptly named staphylococcal or streptococcal 'toxic shock syndromes' (TSSs). Streptococcal TSSs is often associated with NF, whereas staphylococcal TSSs is not imperatively associated with locally spreading infection. A fine macular rash on the patient's skin, with palmar and plantar distribution, and ultimately desquamation, may be subtle clues to the presence of toxin.[46]

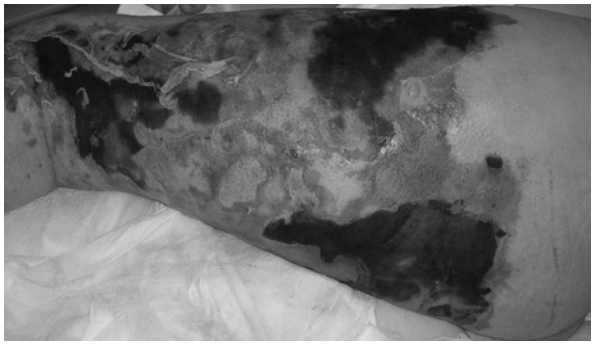


Figure 72.1 Necrosis on the calf due to progressive underlying necrotising fasciitis.

NECROTISING FASCIITIS AND MYOSITIS

Initially, NF presents as cellulitis/erysipelas that eventually fails to improve on antibiotics and quickly spreads along fascial planes; it is associated with the production of destructive bacterial enzymes and toxins that cause necrosis and liquefaction of the surrounding tissue[47] (Fig. 72.1). The intensity of the pain is often disproportionate with the extent of visible erythema or injury. Fever and crepitus may be rare and are not required for diagnosis.[48] Microthrombi[39] and impaired local blood supply lead to deep gangrene. Spontaneous drainage of debris and pus does not occur, and bullae may form. Late lesions may resemble deep burns, which may become pain-free because of nerve fibre necrosis.

Involvement of genitalia is called Fournier's gangrene.[14] Immunosuppression (e.g. diabetes mellitus) is a risk factor for NF.[47] Formally, there are two types: type I infections are mixed (in immunosuppressed patients), while type II infections are *per definition* caused by *S. pyogenes* and are very rapidly progressive (in otherwise healthy patients).[11] However, this distinction is academic because, apart from the choice of a targeted antimicrobial agent, the morbidity, mortality or management approach between the two types of infection are similar.

Often, the fasciitis also involves muscle, therefore, anatomically speaking, most NF cases are musculofascitiis, or fasciomyositis. The bacterial infection of muscles by *Clostridium perfringens* or *C. septicum*, named 'gas gangrene' (due to the presence of crepitus), is rare nowadays (Fig. 72.2). Largely contaminated

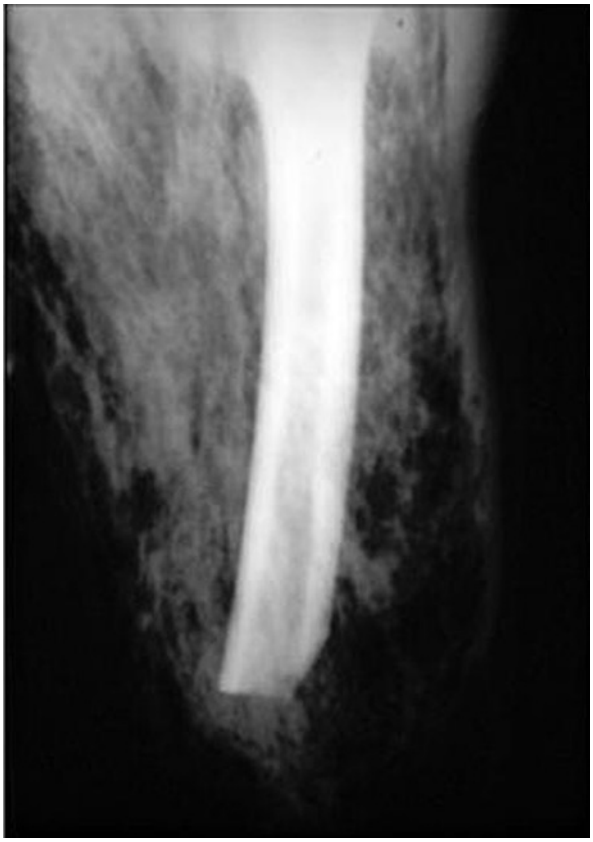


Figure 72.2 Gaseous cellulitis in a standard X-ray.

anaerobic wounds (e.g. in war or septic abortions) are predisposing conditions for gas gangrene *sensu strictu*. Of note, many bacteria, such as *E. coli*, may produce gas in soft-tissue infection.

TREATMENT

Superficial SSTIs, erysipelas and cellulitis, can be treated by antibiotics alone,[12,49] whereas abscesses, fasciitis or myositis require combined surgical and medical treatment (Table 72.1).[50] Many authors groups advocate that a successfully drained superficial abscess, up to 5 cm in diameter and without accompanying erysipelas, does not need systemic or local antibiotics (unless antibiotics are used for systemic decolonisation of CA-MRSA body carriage).

SURGICAL TREATMENT

Timely surgery for source control in the management of severe SSTIs is paramount, as highlighted in guidelines,[51,52] and demonstrated in a cohort study of ICU patients with sepsis, where 45.7% of SSTI patients required source control.[53] Early consultation by a surgeon experienced in treating fasciitis, even if no immediate surgery is performed, is important. Often, experienced surgeons may delay or avoid surgery if the patient remains stable at close follow-up intervals, and if clinical diagnosis is unclear; yet this is not without risk. In a cohort study of patients with *V. vulnificus* necrotising SSTI, mortality was improved when

Table 72.1 Pathogens and presumptive antibiotic therapy in severe soft-tissue infections

DISEASE	MAIN PATHOGENS	ANTIBIOTIC CHOICE*	REMARKS†
Cellulitis/erysipelas	*Streptococcus pyogenes, Staphylococcus aureus*; rarely, various other organisms	First-generation cephalosporin, amoxicillin/clavulanate clindamycin (for severe penicillin allergy)	Clindamycin resistance in *S. pyogenes* and *S. aureus* exists. Vancomycin when high suspicion of MRSA
Necrotising fasciitis	Type I: mixed. Anaerobic species together streptococci and *Enterobacteriaceae* Type II: *S. pyogenes* or *S. aureus*	Empirically, high-dose amoxicillin/clavulanate IV, plus clindamycin IV	Surgical debridement essential. Add vancomycin if MRSA very likely Immunoglobulins in case of severe life-threatening sepsis
Gas gangrene	*Clostridium spp., C. perfringens, C. septicum*	Empirically, high-dose amoxicillin/clavulanate IV, plus clindamycin IV	Surgical debridement essential
Myositis	*S. aureus*, beta-haemolytic streptococci, rarely *C. perfringens*	Empirically, high-dose amoxicillin/clavulanate IV, plus clindamycin IV	Surgical debridement essential Add vancomycin if MRSA likely. Immunoglobulins in case of severe life-threatening sepsis

*Once causative pathogens have been identified, antibiotic choice can be modified and its spectrum narrowed.

†Be aware of local endemicity of community- or hospital-acquired MRSA. Co-trimoxazole or clindamycin are the choice in most community-acquired low-grade infections; for all other cases vancomycin is used.

IV, Intravenous; *MRSA*, methicillin-resistant *Staphylococcus aureus.*

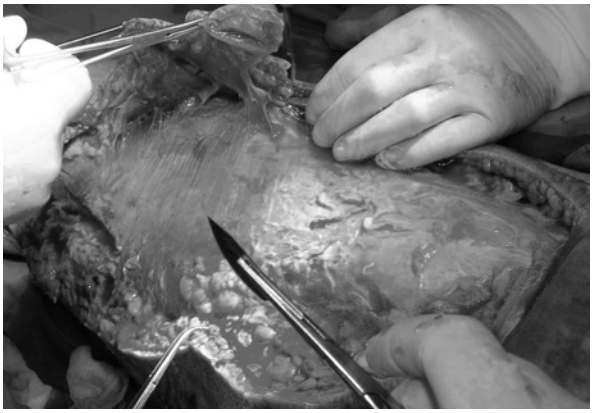


Figure 72.3 Debridement of fascia. All infected tissue is elevated off.

surgical debridement was performed within 12 hours of admission, even after controlling for the severity of infection.[54] When surgery is decided, the removal of damaged tissues is essential[55,56] without compromising viable tissue, which is ultimately needed for wound coverage. During surgery, greyish necrotic fascia, a lack of resistance of normally adherent muscular fascia to blunt finger dissection, a lack of bleeding from the fascia or dishwater pus may be observed. All involved tissue that can be easily elevated off the fascia with gentle pressure or finger spreading, is debrided (Fig. 72.3).[47] The extent of the debridement area is determined clinically and intraoperatively, and it is unnecessary to perform intraoperative histological assessment of multiple sites for this purpose. A planned second look at a 24- to 48-hour interval is recommended.[51,52] In extreme cases, amputation may be life saving. When infection is treated and necrotic tissues debrided, wound closure may become a major problem. Besides healing by secondary intention or mesh, musculocutaneous flaps or vacuum-assisted closure therapy[57] are modern approaches of reconstructive surgery.

MEDICAL TREATMENT

Besides supportive care, discussed elsewhere, the armamentarium against NF, myositis, cellulitis/erysipelas, is antimicrobial therapy. The role of intravenous immunoglobulins (IVIG) or hyperbaric oxygen therapy (HBOT) is considered as supportive at best.

Despite the variety of possible microorganisms involved, with different resistance patterns, the choice of empirical antibiotic treatment lies in the severity of the infection, the host's immune status, and whether it is nosocomial.[51] It is important to regard local epidemiology of multidrug-resistant bacteria, such as CA-MRSA, extended spectrum beta-lactamase- or carbapenemase-producing *Enterobacteriaceae*, and resistant *Pseudomonas aeruginosa*.[58]

Patients with community-acquired septic shock,[51,59] or who are immune-suppressed, often receive empirical antibiotic therapy that includes broad-spectrum antibiotics (plus vancomycin), while awaiting culture results. However, this is more due to fear of a potentially lethal evolution than to microbiological data. Indeed, most causal pathogens are susceptible to narrow-spectrum antibiotics. Apart from contraindication (e.g. allergy) or nosocomial infection, there is no need to increase coverage, and in the majority of instances, initial broad-spectrum coverage retrospectively reveals itself to be too broad, and could have been restricted to penicillins.[11,35,43] Major exceptions are CA-MRSA (which depends on local epidemiology) or fasciitis after trauma.

Evidence is lacking regarding the optimal duration of antibiotic therapy for non-bacteraemic severe SSTI. Often, the clinical course, the presence of undrained abscesses and the experience of the physician determine the duration.[60] It is unclear whether antibiotics should be administered until skin lesions disappear, or can be stopped when systemic infection improves despite the persistence of redness. A randomised study with 121 cellulitis patients suggested that 5 days of levofloxacin therapy were equivalent to 10 days.[61] A large multicentre randomised controlled trial (RCT) is ongoing (ClinicalTrials.gov NCT02032654) comparing 6–12 days of antibiotic therapy.[62]

For TSS, there is a case for using antibiotics that target protein synthesis, such as clindamycin, combined with systemic beta-lactam antibiotic therapy during the first 3–5 days.[63] The rationale lies in the inhibition of toxin production, which is mostly supported by in vitro data.[63] In vivo, to the best of our knowledge, only one observational study investigated this strategy and found a positive result – albeit with a large confidence interval (univariate analysis, non-adjusted odds ratio 4.7; 95% confidence interval [CI] 1.0–25).[64] Likewise, the duration of clindamycin administration for 3–5 days lies on expert opinion or that of the treating physician.[65]

NEWER ANTIBIOTICS

New antibiotics targeting Gram-positive bacteria with MRSA coverage have been developed and approved by regulatory agencies in recent years.[66,67] Some are long-acting, and allow out-patient treatment.[68] Three new US Food and Drug Administration-approved lipoglycopeptides completed phase III trials showing non-inferiority to vancomycin for the treatment of SSTI: oritavancin, dalbavancin and telavancin.[67,69] The European Medicines Agency also approved oritavancin and dalbavancin. In the family of oxazolidinones, there is linezolid and tedizolid. These lipoglycopeptides and oxazolidinone molecules include MRSA coverage, but are strictly limited to Gram-positive pathogens.

Ceftaroline and ceftobiprole conserve anti-Gram-negative activity, but are also active against MRSA.[67] A new fluoroquinolone, delafloxacine, which also has anti-Gram-negative and anti-MRSA activity, has completed phase III trials showing that it is non-inferior to vancomycin and aztreonam for the treatment of SSTI.[70]

Lastly, a phase IIa trial of an innovative drug targeting a T-lymphocyte receptor, CD28, whose aim is the reduction of the inflammatory response to superantigen toxins, suggested that it could be a useful agent, while demonstrating that it was safe for ICU patients.[71]

IVIG are regularly debated as supportive therapy, and the rationale behind their use is the activation of complement, the promotion of antibody-dependent cytotoxicity, the reduction of interleukin-6 and TNF-alpha production[64] and the inhibition of superantigens.[72] Several in vitro and in vivo articles published in one scientific journal[49,63,64,72–74] by the same group of researchers. They published the best available evidence in a multicentre, European, randomised, double-blind, placebo-controlled trial among patients with TSS, which was prematurely terminated. For the primary endpoint, there was a non-significant trend to decreased 28-day mortality in the IVIG group compared to placebo (2/10 vs. 4/11).[73] Adjustment for case-mix could not be performed due to the small study population of only 21 patients. The authors concluded that IVIG are very probably beneficial. Two more recent observational studies, with small sample sizes, showed that adjunctive IVIG, in addition to clindamycin, are associated with decreased mortality, although the association was statistically significant in only one of these studies.[75,76] This uncertainty leads to differing positions by professional societies: the Infectious Diseases Society of America (IDSA) states that the paucity of studies precludes the formulation of a recommendation,[51] whereas the World Society of Emergency Surgery (WSES) states that IVIG may be considered in all patients with necrotising soft tissue infection (weak recommendation, low to very-low quality of evidence).[52]

HBOT is costly, labour-intensive and not risk-free, but it can nonetheless be safely delivered to critically ill patients.[77] There is conflicting evidence on the effect of HBOT on mortality in necrotising SSTI, with some studies suggesting no effect, and others describing decreased mortality.[18,78] HBOT is not recommended by the IDSA guidelines, as 'it has not been proven as a benefit to the patient and may delay resuscitation and surgical debridement' (strong recommendation, low level of evidence).[51] However, the WSES guidelines suggest that it may be considered when available.[52] Importantly, HBOT should never delay surgery.[47] Another role of HBOT may lie in enhanced cicatrisation of ischaemic and/or infected scars, which is another question that requires confirmation in prospective trials.

FUTURE ASPECTS

The future will hopefully show robust prospective RCTs on the optimal management of severe SSTIs. Due to the heterogeneous case-mix of these infections, multidisciplinary and multicentre trials are needed regarding all aspects of care, from the post-debridement surgical approach to the role and dosing of clindamycin and immunoglobulins in the early management of these infections. Future developments also should include additive strategies to inhibit toxins and determine the minimal duration of antibiotic administration. Finally, the benefit of vaccines against *S. pyogenes* or invasive *S. aureus* must be further elucidated.[13,79,80]

REFERENCES

1. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Methicillin-resistant S. aureus infections among patients in the emergency department. *N Engl J Med*. 2006;355(7):666–674.
2. Uckay I, Harbarth S, Peter R, et al. Preventing surgical site infections. *Expert Rev Anti Infect Ther*. 2010;8(6):657–670.
3. Vinh DC, Embil JM. Rapidly progressive soft tissue infections. *Lancet Infect Dis*. 2005;5(8):501–513.
4. Esposito S, Noviello S, Leone S. Epidemiology and microbiology of skin and soft tissue infections. *Curr Opin Infect Dis*. 2016;29(2):109–115.
5. Miller LG, Eisenberg DF, Liu H, et al. Incidence of skin and soft tissue infections in ambulatory and inpatient settings, 2005–2010. *BMC Infect Dis*. 2015;15:362.
6. Mohareb AM, Dugas AF, Hsieh YH. Changing epidemiology and management of infectious diseases in US EDs. *Am J Emerg Med*. 2016;34(6):1059–1065.
7. SepNet Critical Care Trials Group. Incidence of severe sepsis and septic shock in German intensive care units: the prospective, multicentre INSEP study. *Intensive Care Med*. 2016;42(12):1980–1989.
8. Ostermann H, Blasi F, Medina J, et al. Resource use in patients hospitalized with complicated skin and soft tissue infections in Europe and analysis of vulnerable groups: the REACH study. *J Med Econ*. 2014;17(10):719–729.
9. Bisno AL, Stevens DL. Streptococcal infections of skin and soft tissues. *N Engl J Med*. 1996;334(4):240–245.
10. Chelsom J, Halstensen A, Haga T, et al. Necrotising fasciitis due to group A streptococci in western Norway: incidence and clinical features. *Lancet*. 1994;344(8930):1111–1115.
11. Giuliano A, Lewis F Jr, Hadley K, et al. Bacteriology of necrotizing fasciitis. *Am J Surg*. 1977;134(1):52–57.
12. Hsiao GH, Chang CH, Hsiao CW, et al. Necrotizing soft tissue infections. Surgical or conservative treatment? *Dermatol Surg*. 1998;24(2):243–247, discussion 7–8.
13. O'Loughlin RE, Roberson A, Cieslak PR, et al. The epidemiology of invasive group A streptococcal

infection and potential vaccine implications: United States, 2000–2004. *Clin Infect Dis*. 2007;45(7): 853–862.
14. Yeniyol CO, Suelozgen T, Arslan M, et al. Fournier's gangrene: experience with 25 patients and use of Fournier's gangrene severity index score. *Urology*. 2004;64(2):218–222.
15. Anaya DA, McMahon K, Nathens AB, et al. Predictors of mortality and limb loss in necrotizing soft tissue infections. *Arch Surg*. 2005;140(2):151–157, discussion 8.
16. Bair MJ, Chi H, Wang WS, et al. Necrotizing fasciitis in southeast Taiwan: clinical features, microbiology, and prognosis. *Int J Infect Dis*. 2009; 13(2):255–260.
17. Arif N, Yousfi S, Vinnard C. Deaths from necrotizing fasciitis in the United States, 2003–2013. *Epidemiol Infect*. 2016;144(6):1338–1344.
18. Psoinos CM, Flahive JM, Shaw JJ, et al. Contemporary trends in necrotizing soft-tissue infections in the United States. *Surgery*. 2013;153(6): 819–827.
19. Gao Z, Tseng CH, Pei Z, et al. Molecular analysis of human forearm superficial skin bacterial biota. *Proc Natl Acad Sci USA*. 2007;104(8):2927–2932.
20. Grice EA, Kong HH, Conlan S, et al. Topographical and temporal diversity of the human skin microbiome. *Science*. 2009;324(5931):1190–1192.
21. Oh J, Byrd AL, Park M, et al. Temporal stability of the human skin microbiome. *Cell*. 2016;165(4): 854–866.
22. Singh J, Johnson RC, Schlett CD, et al. Multi-body-site microbiome and culture profiling of military trainees suffering from skin and soft tissue infections at fort Benning, Georgia. *mSphere*. 2016;1(5).
23. Cassir N, Papazian L, Fournier PE, et al. Insights into bacterial colonization of intensive care patients' skin: the effect of chlorhexidine daily bathing. *Eur J Clin Microbiol Infect Dis*. 2015;34(5):999–1004.
24. Li X, Chen Y, Gao W, et al. Epidemiology and outcomes of complicated skin and soft tissue infections among inpatients in Southern China from 2008 to 2013. *PLoS ONE*. 2016;11(2):e0149960.
25. Uckay I, Sax H, Harbarth S, et al. Multi-resistant infections in repatriated patients after natural disasters: lessons learned from the 2004 tsunami for hospital infection control. *J Hosp Infect*. 2008;68(1): 1–8.
26. Chira S, Miller LG. Staphylococcus aureus is the most common identified cause of cellulitis: a systematic review. *Epidemiol Infect*. 2010;138(3): 313–317.
27. Tognetti L, Martinelli C, Berti S, et al. Bacterial skin and soft tissue infections: review of the epidemiology, microbiology, aetiopathogenesis and treatment: a collaboration between dermatologists and infectivologists. *J Eur Acad Dermatol Venereol*. 2012;26(8):931–941.
28. Miller LG, Perdreau-Remington F, Rieg G, et al. Necrotizing fasciitis caused by community-associated methicillin-resistant Staphylococcus aureus in Los Angeles. *N Engl J Med*. 2005;352(14): 1445–1453.
29. Sebeny PJ, Riddle MS, Petersen K. Acinetobacter baumannii skin and soft-tissue infection associated with war trauma. *Clin Infect Dis*. 2008;47(4):444–449.
30. Kang M, Xie Y, Mintao C, et al. Antimicrobial susceptibility of clinical isolates from earthquake victims in Wenchuan. *Clin Microbiol Infect*. 2009; 15(1):87–92.
31. Huang KC, Weng HH, Yang TY, et al. Distribution of fatal vibrio vulnificus necrotizing skin and soft-tissue infections: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2016;95(5): e2627.
32. Arakaki RY, Strazzula L, Woo E, et al. The impact of dermatology consultation on diagnostic accuracy and antibiotic use among patients with suspected cellulitis seen at outpatient internal medicine offices: a randomized clinical trial. *JAMA Dermatol*. 2014;150(10):1056–1061.
33. Weng QY, Raff AB, Cohen JM, et al. Costs and consequences associated with misdiagnosed lower extremity cellulitis. *JAMA Dermatol*. 2016;doi: 10.1001/jamadermatol.2016.3816.
34. Crisp JG, Takhar SS, Moran GJ, et al. Inability of polymerase chain reaction, pyrosequencing, and culture of infected and uninfected site skin biopsy specimens to identify the cause of cellulitis. *Clin Infect Dis*. 2015;61(11):1679–1687.
35. Toleman MS, Vipond IB, Brindle R. Specific PCR, bacterial culture, serology and pharyngeal sampling to enhance the aetiological diagnosis of cellulitis. *J Med Microbiol*. 2016;65(1):44–47.
36. Raff AB, Kroshinsky D. Cellulitis: a review. *JAMA*. 2016;316(3):325–337.
37. Reber A, Moldovan A, Dunkel N, et al. Should the methicillin-resistant Staphylococcus aureus carriage status be used as a guide to treatment for skin and soft tissue infections? *J Infect*. 2012;64(5): 513–519.
38. Uckay I, Ferry T, Stern R, et al. Use of serum antistreptolysin O titers in the microbial diagnosis of orthopedic infections. *Int J Infect Dis*. 2009;13(4): 421–424.
39. Stamenkovic I, Lew PD. Early recognition of potentially fatal necrotizing fasciitis. The use of frozen-section biopsy. *N Engl J Med*. 1984;310(26): 1689–1693.
40. Kim KT, Kim YJ, Won Lee J, et al. Can necrotizing infectious fasciitis be differentiated from nonnecrotizing infectious fasciitis with MR imaging? *Radiology*. 2011;259(3):816–824.
41. Swartz MN. Clinical practice. Cellulitis. *N Engl J Med*. 2004;350(9):904–912.
42. Perl B, Gottehrer NP, Raveh D, et al. Cost-effectiveness of blood cultures for adult patients with cellulitis. *Clin Infect Dis*. 1999;29(6):1483–1488.
43. Ward RG, Walsh MS. Necrotizing fasciitis: 10 years' experience in a district general hospital. *Br J Surg*. 1991;78(4):488–489.

44. Tay EY, Fook-Chong S, Oh CC, et al. Cellulitis Recurrence Score: a tool for predicting recurrence of lower limb cellulitis. *J Am Acad Dermatol*. 2015;72(1): 140–145.
45. Thomas KS, Crook AM, Nunn AJ, et al. Penicillin to prevent recurrent leg cellulitis. *N Engl J Med*. 2013;368(18):1695–1703.
46. Lappin E, Ferguson AJ. Gram-positive toxic shock syndromes. *Lancet Infect Dis*. 2009;9(5):281–290.
47. Roje Z, Roje Z, Matic D, et al. Necrotizing fasciitis: literature review of contemporary strategies for diagnosing and management with three case reports: torso, abdominal wall, upper and lower limbs. *World J Emerg Surg*. 2011;6(1):46.
48. Sarani B, Strong M, Pascual J, et al. Necrotizing fasciitis: current concepts and review of the literature. *J Am Coll Surg*. 2009;208(2):279–288.
49. Norrby-Teglund A, Muller MP, McGeer A, et al. Successful management of severe group A streptococcal soft tissue infections using an aggressive medical regimen including intravenous polyspecific immunoglobulin together with a conservative surgical approach. *Scand J Infect Dis*. 2005;37(3):166–172.
50. Eckmann C. The importance of source control in the management of severe skin and soft tissue infections. *Curr Opin Infect Dis*. 2016;29(2):139–144.
51. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(2):e10–e52.
52. Sartelli M, Malangoni MA, May AK, et al. World society of emergency surgery (WSES) guidelines for management of skin and soft tissue infections. *World J Emerg Surg*. 2014;9(1):57.
53. Martinez ML, Ferrer R, Torrents E, et al. Impact of source control in patients with severe sepsis and septic shock. *Crit Care Med*. 2016.
54. Chao WN, Tsai CF, Chang HR, et al. Impact of timing of surgery on outcome of Vibrio vulnificus-related necrotizing fasciitis. *Am J Surg*. 2013;206(1):32–39.
55. Baxter CR. Surgical management of soft tissue infections. *Surg Clin North Am*. 1972;52(6):1483–1499.
56. Mokoena T, Luvuno FM, Marivate M. Surgical management of retroperitoneal necrotising fasciitis by planned repeat laparotomy and debridement. *S Afr J Surg*. 1993;31(2):65–70.
57. Ozturk E, Ozguc H, Yilmazlar T. The use of vacuum assisted closure therapy in the management of Fournier's gangrene. *Am J Surg*. 2009;197(5): 660–665, discussion 5.
58. Guillamet CV, Kollef MH. How to stratify patients at risk for resistant bugs in skin and soft tissue infections? *Curr Opin Infect Dis*. 2016;29(2):116–123.
59. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA*. 2016;315(8): 801–810.
60. Nobre V, Harbarth S, Graf JD, et al. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. *Am J Respir Crit Care Med*. 2008;177(5):498–505.
61. Hepburn MJ, Dooley DP, Skidmore PJ, et al. Comparison of short-course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. *Arch Intern Med*. 2004;164(15):1669–1674.
62. Cranendonk DR, Opmeer BC, Prins JM, et al. Comparing short to standard duration of antibiotic therapy for patients hospitalized with cellulitis (DANCE): study protocol for a randomized controlled trial. *BMC Infect Dis*. 2014;14:235.
63. Russell NE, Pachorek RE. Clindamycin in the treatment of streptococcal and staphylococcal toxic shock syndromes. *Ann Pharmacother*. 2000;34(7–8): 936–939.
64. Kaul R, McGeer A, Norrby-Teglund A, et al. Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome – a comparative observational study. The Canadian Streptococcal Study Group. *Clin Infect Dis*. 1999;28(4):800–807.
65. Eagle H. Experimental approach to the problem of treatment failure with penicillin. I. Group A streptococcal infection in mice. *Am J Med*. 1952;13(4): 389–399.
66. Bettiol E, Harbarth S. Development of new antibiotics: taking off finally? *Swiss Med Wkly*. 2015; 145:w14167.
67. Bassetti M, Righi E, Carnelutti A. New therapeutic options for skin and soft tissue infections. *Curr Opin Infect Dis*. 2016;29(2):99–108.
68. Russo A, Concia E, Cristini F, et al. Current and future trends in antibiotic therapy of acute bacterial skin and skin-structure infections. *Clin Microbiol Infect*. 2016;22(suppl 2):S27–S36.
69. Zhanel GG, Calic D, Schweizer F, et al. New lipoglycopeptides: a comparative review of dalbavancin, oritavancin and telavancin. *Drugs*. 2010;70(7):859–886.
70. O'Riordan W, McManus A, Teras J, et al. *A Global Phase 3 Study of Delafloxacin (Dlx) Compared to Vancomycin/Aztreonam (Van/Az) in Patients With Acute Bacterial Skin and Skin Structure Infections (ABSSSI)*. Poster #1347. IDweek; New Orleans 2016.
71. Bulger EM, Maier RV, Sperry J, et al. A novel drug for treatment of necrotizing soft-tissue infections: a randomized clinical trial. *JAMA Surg*. 2014; 149(6):528–536.
72. Norrby-Teglund A, Kaul R, Low DE, et al. Plasma from patients with severe invasive group A streptococcal infections treated with normal polyspecific IgG inhibits streptococcal superantigen-induced T cell proliferation and cytokine production. *J Immunol*. 1996;156(8):3057–3064.
73. Darenberg J, Ihendyane N, Sjolin J, et al. Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. *Clin Infect Dis*. 2003;37(3):333–340.
74. Darenberg J, Soderquist B, Normark BH, et al. Differences in potency of intravenous polyspecific

immunoglobulin G against streptococcal and staphylococcal superantigens: implications for therapy of toxic shock syndrome. *Clin Infect Dis*. 2004; 38(6):836–842.
75. Linner A, Darenberg J, Sjolin J, et al. Clinical efficacy of polyspecific intravenous immunoglobulin therapy in patients with streptococcal toxic shock syndrome: a comparative observational study. *Clin Infect Dis*. 2014;59(6):851–857.
76. Carapetis JR, Jacoby P, Carville K, et al. Effectiveness of clindamycin and intravenous immunoglobulin, and risk of disease in contacts, in invasive group a streptococcal infections. *Clin Infect Dis*. 2014;59(3):358–365.
77. Weaver LK. Hyperbaric oxygen in the critically ill. *Crit Care Med*. 2011;39(7):1784–1791.
78. Shaw JJ, Psoinos C, Emhoff TA, et al. Not just full of hot air: hyperbaric oxygen therapy increases survival in cases of necrotizing soft tissue infections. *Surg Infect (Larchmt)*. 2014;15(3):328–335.
79. Steer AC, Carapetis JR, Dale JB, et al. Status of research and development of vaccines for Streptococcus pyogenes. *Vaccine*. 2016;34(26): 2953–2958.
80. Nelson GE, Pondo T, Toews KA, et al. Epidemiology of invasive group a streptococcal infections in the United States, 2005–2012. *Clin Infect Dis*. 2016;63(4):478–486.

73

Fungal infection

Alaistair Craig Carr

The incidence of fungal sepsis has increased steadily over the last 30 years. The use of broad-spectrum antibiotics and the treatment of increasingly debilitated patients are likely contributors to this trend. *Candida* species were the fourth commonest isolates from blood cultures in a recent US study[1] and the sixth commonest in a European one.[2] Global incidences of candidaemia in blood culture samples have been recorded between 0.2 and 34/1000 intensive care unit (ICU) patients in different locations. Primary and opportunistic fungal infections are associated with high mortality when systemic infection occurs.

Late diagnosis and treatment worsens outcomes. Unfortunately, the diagnosis of invasive fungal infections (IFI) may be extremely challenging; cultures may take weeks to isolate certain fungi, serological testing often proves insensitive or nonspecific and radiological changes become evident late in the disease process. While newer rapid, sensitive, specific diagnostic analyses, such as polymerase chain reaction (PCR) and matrix-assisted laser desorption/ionisation - time of flight (MALDI-TOF) spectrometry exist to amplify and identify specific fungal DNA, they are not widely available. An understanding of fungal infections, their clinical characteristics and predisposing factors remains critical to early diagnosis, appropriate management and improvement in outcomes.

Classical markers for infection are less reliable in fungal than bacterial infections. Meta-analysis suggests an elevated but low procalcitonin (PCT) (>0.5 but <2 ng/mL) in the presence of clinical sepsis may have diagnostic merit in indicating IFI.[3,4] The value of C-reactive protein (CRP) is less clear with a spectrum of values (including normal) being reported in instances of proven IFI.

Almost all IFI (Fig. 73.1) can cause cutaneous lesions and these readily lend themselves to biopsy if recognised.

BACKGROUND MYCOLOGY

Fungi are complex eukaryotic organisms. Whilst a few exist in unicellular states (yeasts), most exist in multicellular states (mould) and expand through multicellular hyphal growth. Rarer, dimorphic species exist in either unicellular yeast or multicellular mould states. Controversy exists around precise classifications with certain fungi considered yeasts by some and moulds by others; *Candida albicans* exists in yeast, pseudo-hyphal and true hyphal forms.

A network of interdigitating hyphae is termed a mycelium. The multicellular mould with its mycelium is described as a 'colony' but is a single microorganism rather than a collection of discrete microorganisms.

Moulds reproduce through the production of mononuclear or multinuclear, unicellular or multicellular spores along their hyphae. The spores break off and form new colonies distinct from their point of origin. Hyphae secrete lytic enzymes that digest complex organic structures into simpler nutrients, and mycotoxins that inhibit the growth of competitor microorganisms.

Certain mycotoxins may benefit humans; penicillin antibiotic production. Others are harmful: carcinogenic, neurotoxic and hepatotoxic aflatoxins produced by aspergillus in improperly stored foodstuffs; neurotoxic ergot alkaloids from *Claviceps purpurea* in ergotism. Even devoid of toxins or angioinvasion, moulds may lead to harmful inflammatory, allergic and progressive respiratory diseases.

The Centers for Disease Prevention and Control estimates 1.5 million fungal species exist, with around 600 recognised as human pathogens. This chapter will largely restrict itself to the diagnosis and management of respiratory and systemic IFIs.

INVASIVE FUNGAL INFECTIONS

There are two main categories of IFI:

(i) **Primary Mycoses** occur in immunocompetent patients. These are endemic in geographical locations where the spores are abundant. The infecting agent has innate virulence that overcomes normal host defences.

(ii) **Secondary or Opportunistic Mycoses** have less innate virulence than primary mycoses but occur in patients with increased susceptibility or impaired immunity. General debility, cancer, malnutrition, immunosuppressive drugs, burns, HIV, broad-spectrum antibiotics and diabetes all increase susceptibility.

ABSTRACT

Invasive fungal infections (IFI) present an increasing challenge in intensive care medicine as we care for increasingly debilitated and immunocompromised patients. The use of broad-spectrum antibiotics in sepsis and prophylactic antifungal agents in certain 'at-risk' patient populations is associated with both a rising incidence of IFI generally and previously rare multiresistant fungal infections specifically. Mortality from IFI remains very high and a significant obstacle to early initiation of appropriate management and subsequent improved outcomes is the lack of widely available sensitive, specific and rapid diagnostic testing. Without a high index of suspicion and understanding of the limitations of the standard diagnostic testing and antifungal therapies available, this is unlikely to improve.

This chapter outlines the five main primary mycoses and six secondary mycoses associated with IFI, together with current diagnostic techniques and treatment recommendations for each group.

KEYWORDS

Invasive fungal infection
primary mycoses
secondary mycoses
β-D-glucan
galactomannan
mannan

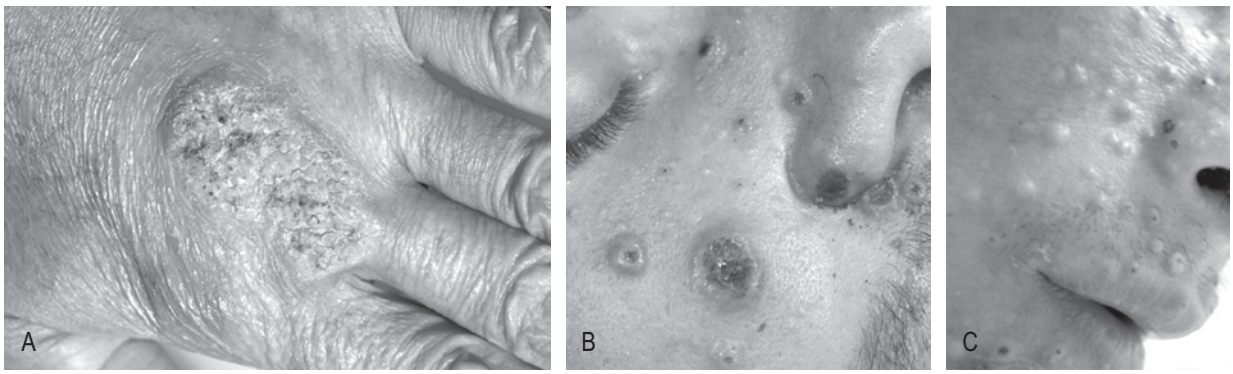


Figure 73.1 (A) Blastomycosis (Gilchrist disease) showing progression of initial subcutaneous nodules into a larger ulcerated crusting lesion. *Reproduced under licence from Getty Images.* (B) Cryptococcosis showing characteristic raised skin lesions with rolled edges and central necrosis and scabbing. *Reproduced under licence from Getty Images.* (C) Penicillinosis: raised papules with a central necrotic area similar to molluscum contagiosum. *Reproduced from Wong SYN, Wong KF. Penicillium marneffei infection in AIDS.* Patholog Res Int. *2011 Feb 10;764293. doi 10.4061/2011/764293 with permission under open access.*

TREATMENT OPTIONS

Treatment of most IFI is largely limited to four classes of agent:

(i) Polyenes, effectively amphotericin B presentations, bind to ergosterol in the fungal wall causing damage and cell death.

(ii) Azoles (imidazoles and triazoles) inhibit ergosterol synthesis in the fungal wall. They are usually fungistatic but can exhibit organism-dependent fungicidal activity too (e.g. voriconazole in aspergillus).

(iii) Echinocandins inhibit β-glucan synthesis leading to cell wall instability. These are fungicidal for many yeasts and fungistatic for aspergillus.

(iv) Flucytosine is converted to 5-fluorouracil within yeasts and incorporated into RNA there. Efficacy is much better in yeasts than moulds.

Certain IFIs have alternative or additional therapeutic options. Folic acid inhibition is employed in managing pneumocystosis. Adjuvant interferon-γ is being investigated for invasive candidiasis and aspergillosis management.[5] Adoptive T-cell therapy is being assessed for prevention of invasive aspergillosis in stem-cell transplant recipients.[6,7]

The site of infection is important when selecting appropriate antifungal therapy. For example, caspofungin has minimal renal excretion and poor efficacy in treating renal tract infection, whereas amphotericin and fluconazole enjoy good efficacy.

Surgical excision of primary and secondary lesions is often required for disease control or eradication.

PRIMARY MYCOSES

There are five main primary mycoses. Four (not cryptococcus) are dimorphic pathogens.

(i) Blastomycosis (Gilchrist disease) is caused by blastomycoses dermatitidis found largely in soil in North America.[8] While not transmitted directly from dogs to humans, dogs are susceptible and often exhibit symptoms ahead of their owners during outbreaks.

Primary infection is usually pulmonary. However, wound inoculation is also described. Initial infection may be asymptomatic or cause myalgia, malaise, fever and arthralgia. Later, cough, pleurisy, haemoptysis and acute respiratory distress syndrome (ARDS) may develop. Granulomas form at the initial site then spread haematogenously in 50% of patients. Skin, bone, prostatic, epididymal and testicular infections are common. Central nervous system (CNS) infection occurs in around 10% of disseminated cases.

Untreated, disseminated blastomycosis mortality exceeds 80%. Early recognition is difficult as symptoms are non-specific. Even in established disease, symptoms of night sweats, weight loss, cough and respiratory failure may be mistaken for malignancy or tuberculosis. Similarly, skin and oropharyngeal lesions (see Fig. 73.1) can be mistaken for carcinomas. The detection of fungi in skin lesions or sputum requires specific staining; the thick capsule evades routine stains. Culture is more reliable than microscopy but commonly takes 4–6 weeks to yield positive results.

Treatment with amphotericin is preferred in severe disease and immunocompromised patients. Courses of 12 months may be required for cure. Itraconzaole has proven efficacy in moderate disease and as step-down therapy from amphotericin. Case reports suggest reasonable efficacy for voriconazole and posaconazole but not fluconazole. Echinocandins have poor efficacy in-vitro and are not recommended.

(ii) Coccidiodomycosis is caused by *Coccidioides immitis* and *Coccidioides posadasii*, endemic in regions of North America. Infection results from inhalation of spores or, less frequently, wound inoculation. Sixty-five per cent of primary infections are asymptomatic; the rest develop fever, headache and symptoms of respiratory tract infection. Immunological sequelae distant from the primary site may present as erythema multiforme or nodosum and arthralgia (originally called Jaoquin Valley Fever). Chest X-ray (CXR) may show patchy infiltration, lobar pneumonia or effusions. ARDS can occur. Around 5% of patients develop chronic pulmonary infection with cavitation.

One per cent of patients develop disseminated coccidiodomycosis with granulomatous lesions of skin, bone, joints and meninges being commonest. Disseminated disease has high associated mortality and is often diagnosed late in non-endemic areas where suspicion is low. Travel to North America and occupational, agricultural exposure should be sought in the history.

Amphotericin B is recommended to treat disseminated disease. Localised disease can be managed with triazoles or imidazoles but not echinocandins.

(iii) Cryptococcosis as a primary infection is usually associated with the encapsulated yeast *Cryptococcus gattii* rather than *Cryptococcus neoformans*. Both are covered later under opportunistic infections.

(iv) Histoplasmosis is caused by *Histoplasma capsulatum* found throughout Africa, Indonesia, Australasia, the North American mid-west and Central and South America.[9] Some adult populations evidence almost ubiquitous prior exposure on serological testing. Spores from soil and bird droppings are inhaled and invade pulmonary macrophages, divide and result in granuloma formation.

Pulmonary disease may remain contained running a self-limiting course or disseminate, particularly in the immunocompromised, via the bloodstream and reticuloendothelial systems causing lymphadenopathies often with hepatic, splenic, gastrointestinal and even CNS involvement; 90% of cases are asymptomatic not requiring treatment. Symptomatic patients experience non-specific malaise, headaches, fever, myalgia and occasionally arthralgia. Immune-related erythema nodosum or multiforme may be seen during initial pulmonary infections whilst infected papules and mucosal ulceration (see Fig. 73.1) develop only in disseminated disease. Dyspnoea, chest pain and haemoptysis may occur. Chronic pulmonary infection is not uncommon in those with pre-existing respiratory disease.

Amphotericin B is the agent of first-choice, azoles can be used in less severe disease. Untreated, mortality is around 50%.

(v) Paracoccidiodomycosis (South American Blastomycosis) is caused by *Paracoccidioides brasiliensis* and *lutzii*. It is largely confined to South and Central America and southern Mexico.[10] Invasion occurs via the lungs where it may cause (usually lobar) pneumonia, pleurisy or remain asymptomatic before spreading to involve skin, mucous membranes, lymphatics, bone and meninges.

Acute and subacute forms are both associated with lymphadenopathy, fever, malaise and anorexia. These are normally self-limiting and resolve over time. Respiratory symptoms, skin and mucous membrane lesions are rare in acute cases but are common in chronic disease.

Mortality is high without treatment; 50% of chronic disease progresses to pulmonary fibrosis and 5% develop pulmonary hypertension and cor pulmonale.

Where affordable, itraconazole is the treatment of choice for moderate disease and amphotericin B for severe and refractory cases.[11] Sulphonamides were once the mainstay of therapy being inexpensive compared to azoles and amphotericin B in endemic areas. Maintenance azole therapy lasting several years is required to achieve eradication, and relapse is common. Echinocandins are not recommended.

OPPORTUNISTIC MYCOSES

There are six main classes of opportunistic mycoses. Generic predispositions include: central venous cannulation, recent cavity surgery, neutropenia greater than 10 days, steroids greater than 7 days, immunosuppressive therapies or diseases (e.g. HIV, disseminated malignancy), ICU stay greater than 7 days, total parenteral nutrition (TPN), malnutrition, organ transplantation and burns.

Antifungal prophylactic therapy has become a norm in certain high-risk patient groups (e.g. haematopoietic stem-cell transplant patients). This has shifted the characteristic fungal infections seen with increases in previously rare, highly resistant IFI by *Candida parapsilosis*, zygomycoses[12] and fusarium.[13]

Rarely, opportunistic mycoses develop in immunocompetent patients; IFI should not be excluded solely because of lack of obvious predisposition. Diagnosing IFI with certainty is difficult, requiring isolation of fungal material from a normally sterile site. While positive identification on culture or microscopy may be diagnostic, negative microscopy and cultures cannot exclude fungal infection. Up to 50% of blood cultures are negative in patients with proven, disseminated IFI and/or deep-seated infection. More usually, diagnostic probability is achieved through the amalgamation of recognised risk factors, clinical picture, serological, microbiological, radiological and DNA-amplification

techniques. Sequential rather than isolated data points are more informative in both diagnostic and treatment response assessments.

ASPERGILLOSIS

Aspergillosis is caused by the ubiquitous Aspergillus genus of moulds. In humans, *A. fumigatus*, *flavus* and *niger* are frequent invasive species. In addition, *A. clavatus* is a significant cause of allergic respiratory disease.

While aspergillus infection is usually evidenced in immunosuppressed patients (chemotherapy, HIV, steroids, transplant recipients), it also occurs in apparently immunocompetent patients with intercurrent illnesses, such as pancreatitis, liver disease and diabetes. Additionally, patients with chronic lung disease, especially when on regular low-dose steroids and otherwise well patients exposed to high spore loads are at increased risk of aspergillosis.

The usual route of entry is inhalation of spores into the lungs or sinuses. The signs of disease are non-specific: dyspnoea, cough, fever, haemoptysis, malaise and discomfort in the chest. Pneumothorax is a well-recognised but rare complication. Resting hypoxaemia is common at presentation.

Pulmonary aspergillosis describes a spectrum of disorders from localised simple aspergilloma (this may still result in haemorrhage or bronchopleural fistula by tissue erosion) through allergic bronchopulmonary aspergillosis in asthmatic and cystic fibrosis patients, to progressive multisite pulmonary disease with extensive, cavitating, tissue destruction. Invasive disease can lead to systemic infection with lesions in the brain and solid organs.

Even when identified and treated with amphotericin, overall mortality of 50%–66% is cited from invasive aspergillosis with maxima around 88% in disseminated disease to minima of 24% in localised sinus or pulmonary disease managed by surgical resection and amphotericin.[14] Haemopoietic stem-cell transplant recipients (especially from matched unrelated donors) have poorer outcomes regardless of the infective magnitude, although mortality has fallen from greater than 95% in the 1990s to between 80% and 90% since 2002.[15]

DIAGNOSIS

(a) Greatest certainty requires positive cultures or microscopic identification from pathology samples.

(b) Focal lesions may be found on chest, liver or brain computed tomography (CT) or magnetic resonance imaging (MRI) scans with or without the characteristic halo sign (Fig. 73.2). Changes may be subtle and easily overlooked even in established disease.

(c) Positive PCR of body or bronchoalveolar lavage (BAL) fluids is a useful diagnostic test facilitating faster diagnosis than culture and microscopy with sensitivities and specificities up to 90% being reported.

(d) Galactomannan identification in BAL-fluid, urine, serum or cerebrospinal fluid (CSF) is relatively specific for aspergillus although cross-reactivity can occur with Penicillium species. Beta-lactam antibiotics and dietary ingestion of galactomannan (dairy and cereal products) can also cause false positives. Sensitivities of 80% have been achieved in patients not receiving prophylactic therapy. Prophylactic therapy may reduce fungal load, and sensitivity is reported to fall to around 20%

(e) β-D-Glucan detection in BAL-fluid or serum is useful but shows cross-reactivity with other fungal pathogens (e.g. candida) and false positives with beta-lactam antibiotics, albumin and immunoglobulin administration and during renal replacement therapies using cellulose membranes.

(f) The combination of positive galactomannan and β-D-glucan tests may improve specificity reducing the likelihood of a false-positive result.[16]

TREATMENT

First-line therapy of invasive aspergillosis is usually with systemic voriconazole.[17] Liposomal amphotericin B and isavuconazole are alternatives.[18] Echinocandins should not be used as first-line agents. Combination therapies with echinocandins and azoles or amphotericin have been described; some small studies suggest superiority to single-agent regimens.[19] The outcomes of larger studies are awaited and routine combination therapy remains unusual.

Treatment duration is determined by clinical and radiological response rather than serological marker determination. Conversion to oral therapy with voriconazole or itraconazole may be considered once significant improvement is secured.

Resection of pulmonary lesions, pulmonary-vascular therapeutic embolisation for pulmonary haemorrhage, granulocyte transfusions,[20] and the use of interferon-gamma[21]/antifungal agent combination therapy (in refractory disease) are described in the medical literature.

CANDIDIASIS

Candidiasis remains the commonest IFI diagnosed globally, accounting for greater than 60% of ICU IFIs. Mortality exceeding 50% is commonly reported. Late diagnosis and suboptimal treatment lead to poorer outcomes.

Candida albicans' predominance has gradually been overtaken by *tropicalis*, *glabrata*, *parapsilosis* and *krusei* in some locations, particularly following prophylactic therapy with fluconazole. Where broader spectrum prophylactic agents (voriconazole and posaconazole) are used, the overall incidence of opportunistic candidiasis is falling but infections with resistant fungi (e.g. zygomycoses and fusarium) are rising.

Early symptoms of invasive candidiasis are non-specific; fever, chills, malaise and dyspnoea. Sites of

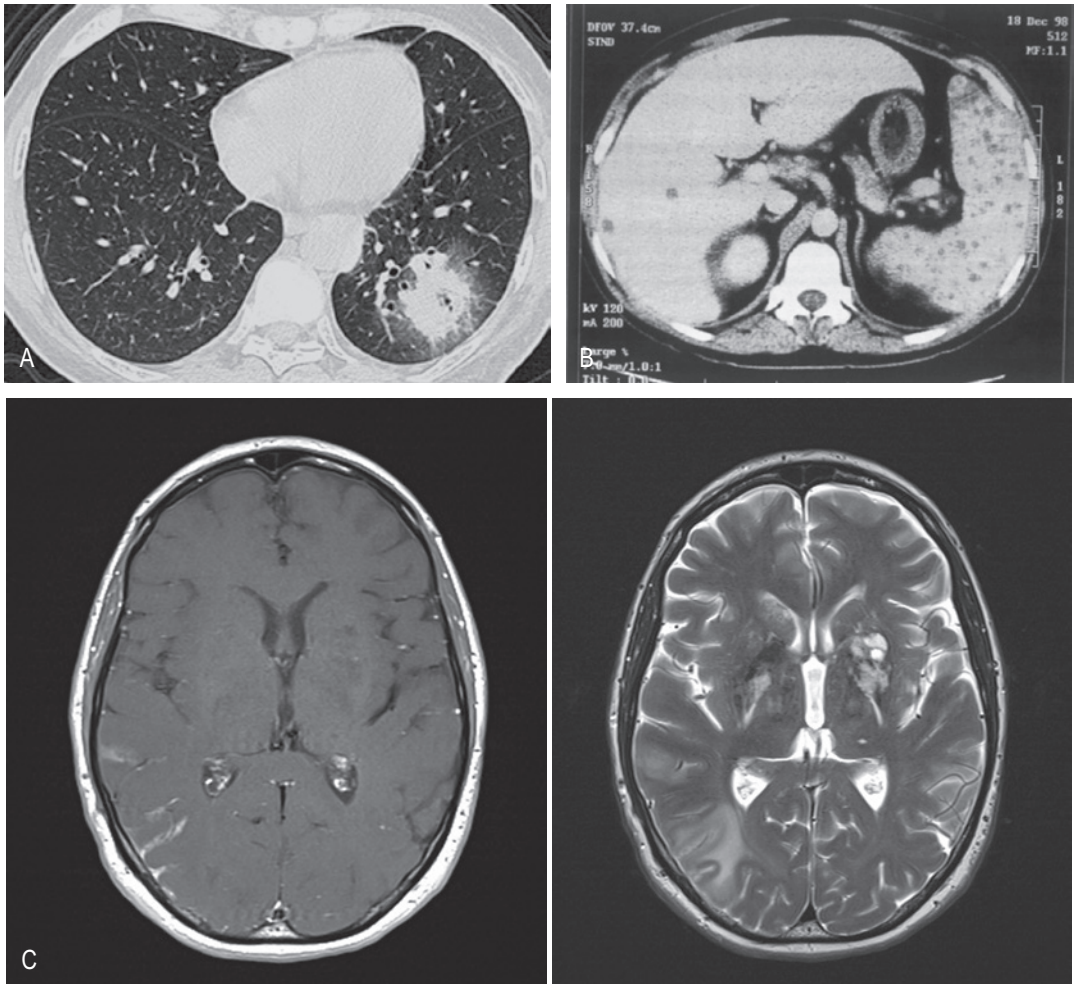


Figure 73.2 (A) Computed tomography (CT) of chest scan showing typical angioinvasive pulmonary aspergilloma with a characteristic halo around the periphery of the lesion in the posterior aspect of the left lung. *Reproduced with permission from Caillot D, Mannone L, Cuisenier B, Couaillier J-F. Role of early diagnosis and aggressive surgery in the management of invasive pulmonary aspergillosis in neutropenic patients.* Clin Microbiol Infect. *2001;7:54–61. doi:10.1111/j.1469-0691.2001.tb00010.x.* (B) CT of liver and spleen showing two hypodense lesions in the liver and numerous lesions in the spleen consistent with candida abscesses. *Reproduced with permission from Ratip S, Odabaşi Z, Karti S, et al. Clinical microbiological case: chronic disseminated candidiasis unresponsive to treatment.* Clin Microbiol Infect. *2002;8(7):442–444. doi:10.1046/j.1469-0691.2002.00464.x.* (C) Magnetic resonance imaging (MRI) of patient with cryptococcal leptomeningeal disease showing low signal in T1-weighted and high signal in T2-weighted scans. *Case reproduced courtesy of Dr Mauricio Macagnan,* Radiopaedia.org, *rID: 53172.*

secondary infection may offer more localised signs and symptoms (e.g. joint pain, visual impairment with loss of red reflex on ophthalmoscopy and neurological disturbances).

DIAGNOSIS

(a) Greatest certainty requires positive cultures or microscopic identification in samples from normally sterile sites.

(b) Focal lesions may be found on chest, liver or brain CT or MRI scans (see Fig. 73.2) but frequently lag behind serological testing for fungal DNA or cell wall components. During neutropenia, radiological appearances of abscess can almost entirely disappear from CT with reappearance when counts recover, misleading the unwary.[22]

(c) Positive PCR in is increasingly showing promise with test sensitivities and specificities of greater than 90% being achieved.

(d) Mannan Ag/Antimannan antibodies, when measured concurrently, may offer sensitivity and specificity of testing of above 80%.[23]

Table 73.1 Typical sensitivity chart of *Candida species* to different antifungal agents

	C. albicans	*C. glabrata*	*C. tropicalis*	*C. parapsilosis*	*C. krusei*
Amphotericin	++	++	++	++	+/–
Anidulafungin	++	++/–	++/–	+/–	++/–
Caspofungin	++	++/–	++/–	+/–	++/–
Micafungin	++	++/–	++/–	+/–	++/–
Fluconazole	++/–	–	+/–	+/––	–
Isavuconazole	++	+/–	++/–	+/–	+/–
Itraconazole	++/–	++/–	+++/–	++/–	++/–
Posaconazole	++	++/–	++/–	++/–	++/–
Voriconazole	+++	++/–	+++/–	+++/–	++/–
Flucytosine	+/–	+/–	–	+/–	–

Data extracted from multiple sources. Recommended reading as overview: Matthaiou DK, Christodoulopoulou T, Dimopoulos G. How to treat fungal infections in ICU patients. *BMC Infect Dis.* 2015;15:205.

(e) β-D-Glucan detection in BAL fluid or serum with the same caveats as outlined for use in aspergillus diagnosis.

(f) Scoring systems (Table 73.1), such as Paphitou's, Ostrosky-Zeichner's and Nebraska Clinic's, all offer high (>95%) negative predictive values but low positive predictive values (<50%). They better advise who should probably not receive antifungal therapy than who should.

(g) Limited-availability PCR, nanoparticle hybridisation techniques are being developed and reportedly show excellent sensitivity and specificity.

(h) ELISA for serum enolase, an enzyme secreted by many candida species, and immunoglobulin G (IgG) to enolase are being investigated but are not yet widely available.

(i) Early clinical investigations suggest detection of D-arabinitol, a metabolite of most candida species, in serum or BAL fluid, appears to predict invasive candida infection significantly ahead of culture positivity, and normalisation appears to correlate with successful therapy. The utility of this assay remains under investigation.

TREATMENT

Pharmacological treatment of candidiasis is dependent upon the species and local sensitivity pattern. A typical sensitivity chart is offered (Table 73.2) but local knowledge and antibiograms should guide therapy. When CNS involvement or endophthalmitis is present, combination therapy with flucytosine, which enjoys excellent CNS penetration, has evidence of improved efficacy. Some experts also recommend combining the primary agent with flucytosine when candida endocarditis is being managed.[24] Regular therapeutic drug monitoring is required and peak flucytosine levels should be maintained below 100 mg/L to avoid toxicity (target 2-h post-dose peak = 70-80 mg/L).

CRYPTOCOCCOSIS

Cryptococcosis – *C. neoformans*, an encapsulated yeast found in soil and bird excrement, enters the body via inhalation. Initial infection may cause non-specific inflammatory symptoms of fever, cough and dyspnea or may be asymptomatic. In immunocompromised hosts – especially those with HIV, solid organ transplants or concomitant cytomegalovirus (CMV) infection – it then spreads haematogenously, causing disseminated disease with particular affinity for the CNS. CNS infection classically results in meningoencephalitis with hydrocephalus, seizures, a reduced Glasgow Coma Scale and neurological deficits. Permanent cranial nerve palsies, visual and hearing impairment are common.

Cryptococcus can exert immunomodulatory effects including inhibition of phagocytosis and stimulation of peripheral blood monocyte interleukin-10 secretion with consequent pro-inflammatory cytokine production suppression.[25] Following the eradication of Cryptococcus from the CNS, paradoxical inflammation may occur[26] as the immunosuppressive, anti-inflammatory effects of the pathogen diminish; Cryptococcus-immune reconstitution syndrome (c-IRS). A similar syndrome occurs when highly active anti-retroviral therapy (HAART) is commenced too soon after antifungal therapy in Cryptococcus presenting as AIDS, and immunity is restored before fungal load in the CNS reduces sufficiently.[27] In addition, autoimmune damage may occur during active infection.[28]

C. gattii is also an encapsulated yeast found in soil, trees and animal faeces. Previously largely confined to northern Australia and Papua New Guinea, more

Table 73.2 Rules for ascertaining high risk of invasive candidiasis in ICU patients

Paphitou et al. *Med Mycol.* 2005 May;43(3): 235–243	**Candida Score Leon C et al. *Crit Care Med.* 2006 Mar;34(3):730–737 & Leon C et al. *Crit Care Med.* 2009;37(5):1624–1633**	**Ostrosky-Zeichner et al. *Eur J Clin Microbiol Infect Dis.* 2007 Apr;26(4):271–276**	**Nebraska Clinic Hermsen et al. *Crit Care.* 2011;15:R198**
ICU stay greater than or equal to four days	Major surgery Multifocal colonisation TPN Severe sepsis	Any systemic antibiotic (days 1 to 3) OR Presence of a central venous catheter (days 1 to 3)	Any systemic antibiotic (days 1 to 3) Presence of a central venous catheter (days 1 to 3) TPN (days 1 to 3) Steroids (days –7 to 3) Abdominal surgery (days –7 to 3) Presence of any of above scored 1 and absence scored 0
AND at least two of	Prediction rule = (0.908 × TPN) + (0.997 × surgery) + (1.112 × multifocal colonisation) + (2.038 × severe sepsis)	AND at least two of	Prediction rule = (1.54 × BSAbx) + (0.87 × CVC) + (0.92 × TPN) + (0.40 × steroid) + (0.88 × abdominal surgery) + (0.04 × Pre-ICU LOS in days) =
Diabetes mellitus, Haemodialysis (days 1 to 3) TPN (days –7 to 0), Broad-spectrum antibiotics (days –7 to 3)	Total <2.5: No need for antifungals as probability of invasive candida low. Total >2.5 – consider antifungals	TPN (days 1 to 3) Dialysis (days 1 to 3) Major surgery (days –7 to 0) Pancreatitis (days –7 to 0) Steroids (days –7 to –3) Immunosuppressives (days –7 to 0)	Total <2.45: No need for antifungals as probability of not developing candidemia 99.4% Total ≥2.45: Consider antifungals on individual basis as probability of developing candidemia 4.7%
Sensitivity 41%	Sensitivity 81%	Sensitivity 34%	Sensitivity 84.1%
Specificity 81%	Specificity 74%	Specificity 90%	Specificity 60.2%
PPV 4.8%	PPV(score >3) 23.8%	PPV 1%	PPV 4.7%
NPV 98.3%	NPV(score <3) 97.7%	NPV 97%	NPV 99.4%

BSAbx, Broad spectrum antibiotics; *CVC*, central venous catheter; *ICU*, intensive care unit; *LOS*, length of stay; *NPV*, negative predictive value; *PPV*, positive predictive value; *TPN*, total parenteral nutrition.

recently it emerged in America and India. Unlike *C. neoformans*, *C. gattii*, readily causes infections in immunocompetent hosts and can multiply within white blood cells. CNS infection remains common but is more rapidly progressive with high fatality rates in previously healthy individuals.

DIAGNOSIS

A high index of suspicion is required to facilitate early diagnosis and treatment. Diagnosis typically occurs around 2 weeks sooner from the onset of symptoms in HIV or post-transplantation patients than in other groups owing to the well-recognised association. This has been suggested as the cause of the better outcomes for cryptococcosis in HIV patients compared with other groups.

Diagnostic steps include:

(a) Positive serum cryptococcal antigen.
(b) MRI scanning may demonstrate dilated perivascular spaces and basal ganglia pseudocysts. Cryptococcomas demonstrate high signal in T2/flair (see Fig. 73.2) and low signal in T1 (without Gd). CT brain scans are not recommended to exclude diagnosis: 40% are normal, 40% reveal non-specific abnormalities and 10%–20% offer suggestive features such as abnormal masses and hydrocephalus.
(c) Tissue biopsy and microscopy with India Ink, Alcian Blue or Fontana-Masson staining.
(d) CSF sampling, microscopy, biochemistry, cytology and testing for cryptococcal antigen.
(e) CSF cultures for at least 5 days on Saboraud Agar if CSF analysis reveals increased leucocytes or low glucose.

TREATMENT

In severe cryptococcal or CSF antigen-positive infection, prolonged, high-dose, intravenous (IV), antifungal therapy is indicated.

(a) Efficacy is best proven for liposomal amphotericin B in combination with IV flucytosine therapy.
(b) Fluconazole 400 mg/day may be required for 1–2 years in those with residual irresectible

cryptococcomas. Posaconazole crosses the blood–brain barrier well and has been shown to be efficacious against cryptococcal CNS infection in small case series – doses of 800 mg/day in divided doses are recommended. Randomised controlled trials comparing posaconazole, voriconazole and fluconazole are required. Itraconazole does not cross the blood–brain barrier and should be avoided.

(c) Management of raised intracranial pressure (ICP) using shunts or drains is required if obstructive hydrocephalus develops.

(d) Dexamethasone may offer benefits to some patients with persistent neurological abnormalities despite normal ICP and culture-negative CSF following successful antifungal therapy for *C. gattii*[29] and in treatment of confirmed immune reconstitution syndrome (IRS) following anti-retroviral therapy (ART) in AIDS; however, routine co-prescription with anti-cryptococcal therapy worsens outcomes.[30]

(e) c-IRS may benefit from corticosteroids, thalidomide or other immunomodulators.[31]

In disseminated disease without CNS involvement, fluconazole, itraconazole or posaconazole may be used. Treatment should continue from 6 to 24 months depending upon the immunocompetence of the patient.

PENICILLINOSIS

Most commonly found in patients with HIV and CD4 counts less than 100/μL, who have lived or travelled in China and Southeast Asia, penicillinosis is caused by inhalation of spores of the dimorphic fungus *Penicillium marneffei*. Presentation usually occurs at the stage of disseminated rather than pulmonary infection with fever, weight loss, dyspnea, cough, anaemia, lymphadenopathy and hepatomegaly. Papular and follicular skin lesions (see Fig. 73.1), sometimes with central necrosis, and oropharyngeal lesions are common.

Diagnosis is by microscopy and culture of biopsied lesions. A PCR assay is under development. With prompt treatment, mortality falls to around 20%. Amphotericin B enjoys the greatest success in case series to date. Two weeks of IV amphotericin followed by 6 weeks of IV itraconazole and then on-going maintenance prophylactic oral itraconazole is recommended.

PNEUMOCYSTOSIS

Pneumocystis jirovecii pneumonia (PJP) was once considered a protozoan rather than fungal infection. Modern gene sequencing techniques resulted in its reclassification. Nonetheless, it differs from most fungi by the substitution of cholesterol for ergosterol in the cell wall; the rarity of extrapulmonary invasion or infection is often attributed to this. This substitution renders the standard antifungal polyenes (amphotericin B), and azoles impotent. In animal models, echinocandins reduce the number of cystic forms[32] (the third of three stages in *Pneumocystis jirovecii* [PJ] life cycle) seen, but not the number of trophic forms (the first stage) that constitute >90% of all PJ fungal forms in infected lungs. Only the cyst walls express B-glucans, the target of echinocandin activity. Whilst disease progression slowed or even halted, cessation of echinocandins was associated with immediate relapse.

Evidence derived from measurement of IgE and IgG informs that asymptomatic childhood infections with PJP are common. For PJP to cause symptomatic pathology normally requires impaired host immunity, especially that associated with CD4 cell counts less than 200/mm3 in HIV. Non–HIV-related PJP infections are usually associated with immunosuppression secondary to haematological malignancy or immunosuppressive therapies used in transplant, cancer or rheumatological disease management. Previous or current CMV infection also predisposes to PJP infection through its effect on reducing helper T-cell function. PJP infections are often more severe and are diagnosed later in the non-HIV patient population – this is likely related to the widespread use of prophylactic therapy and a higher awareness of PJP amongst HIV+ patients.

Symptoms of PJP are often non-specific early in the disease course. They include malaise, dyspnoea and a non-productive cough. As the disease progresses, pyrexia, weight-loss, worsening cough, dyspnoea and exertion induced hypoxia are also characteristic. Pneumothorax arises in a minority of patients. Although CXR appearances are classically of widespread infiltration arising from the hila, occasionally more localised, infiltrative patterns and cavitating lesions are seen. CXR may appear normal in early disease, whereas high resolution computed tomography (HRCT) normally demonstrates ground-glass opacification.

DIAGNOSIS

Clinically suspected PJP on the basis of history, characteristic radiological findings and a known predisposition should be taken as sufficient grounds to initiate treatment. Up to 40% of patients have a normal CXR at presentation. Delays in treatment initiation, even by one day, are associated with significant increases in mortality. As soon as practicable thereafter, confirmation or exclusion of the diagnosis should be undertaken by:

(a) demonstration of PJP using immunofluorescence or silver staining of induced sputum or BAL samples

(b) demonstration of PJP DNA on PCR of BAL and/or peripheral serum samples.

TREATMENT

Co-trimoxazole, inhibits folic acid synthesis in *P. jirovecii* via two separate pathways. It is the agent of first choice. Administered intravenously in high dose (120 mg/kg per day in divided doses) for 21 days, drug intolerance results in around 50% of patients

requiring a change of agent. Co-administration of IV steroids has been shown to reduce mortality in HIV patients. Their use is recommended in severe disease where the A-a gradient is less than 35 mm Hg (4.6 kPa) and may reduce the inflammatory response and worsening respiratory failure associated with treatment-induced fungal lysis. Different studies have used different dose regimens with most in the range 1–2 mg/kg methylprednisolone for the first 10 days of antifungal therapy.[33] Some regimens recommend reduced dosing for subsequent days whilst receiving IV cotrimoxazole.

Alternative therapeutic regimens for those intolerant of cotrimoxazole include:

(a) pentamidine IV 4 mg/kg o.d. (1× daily), or
(b) clindamycin 450 mg q.i.d. (4× daily) and primaquine 30 mg o.d., or
(c) dapsone 100 mg o.d. and trimethoprim 5 mg/kg q.i.d., and
(d) atavaquone 750 mg b.d. (2× daily)

In addition, combination therapy with clindamycin and caspofungin has been described as providing successful treatment of severe PJP in isolated case reports.[34]

ZYGOMYCOSES

Zygomycoses[35] consists of two orders of fungi; Mucorales and Entomophthorales. Sometimes the term is used interchangeably with muromycosis as the majority of infection seen is secondary to Mucorales, a ubiquitous, angioinvasive mould that causes tissue necrosis and characteristic cutaneous, sinus, cerebral, pulmonary, gastrointestinal and disseminated infections. The main species causing human infection are *M. Rhizopus*, *M. Lichtheimia* and *M. Mucor*. Fungal spores may be inhaled, ingested or cause direct infection via damaged membranes.

Disseminated disease is usually fatal in immunocompromised hosts. Muromycosis is the third commonest invasive fungal disease (IFD) in patients receiving haematopoietic stem-cell transplants, causing 1%–2% of IFI in this group. The incidence is rising secondary to the widespread use of broad-spectrum, prophylactic anti-fungal agents such as voriconazole in a bid to reduce aspergillus and candida infections.[36] In addition, infections are associated with poorly controlled diabetes, haematological malignancy (especially acute myeloid leukaemia [AML]), trauma, iron overload, acidosis (especially ketoacidosis), malnutrition and steroids.

Symptoms are often non-specific initially and reflect inflammation at the site of initial inoculation (e.g. sinusitis). After a period of malaise, fever (only in 50% of patients) and symptoms of site-specific local inflammation, evidence of invasion may become more apparent with progression of a cough and dyspnea to haemoptysis or a sinusitis to cellulitis of the skin over the paranasal sinuses. Unmanaged, further invasion will lead to massive pulmonary haemorrhage, bronchial occlusion and mediastinitis in the pulmonary cases and orbital, ocular and cerebral invasion, cranial nerve palsies, and skin necrosis in sinus ones. Where skin invasion occurs, a black eschar is often seen.

DIAGNOSIS

Early diagnosis and treatment of muromycosis before angioinvasion and dissemination is essential to improve survival. Diagnostic steps include:

(a) a high degree of suspicion based on clinical risk profile
(b) early recognition of characteristic skin lesions
(c) CT findings (e.g. nodules, halo signs, reverse halo signs and wedge infiltrates on lung CT), and MRI findings with low intensity on T1 and high intensity on T2 with leptomeningeal disease
(e) microscopy of samples from sinus drainage, abscess drainage, BAL or tissue biopsy using wet mount slides with calcofluor staining and periodic acid-Schiff (PAS) or Grocott's methenamine silver (GMS) dry-mount staining
(f) culture – usually positive in 3–5 days unless receiving appropriate antifungal therapy at the time of sample collection
(g) PCR and molecular diagnostic techniques are currently in evolution but are not yet widely commercially available.

TREATMENT

Amphotericin B (preferably as a lipid formulation) is the mainstay of treatment with proven efficacy in vitro and in vivo. A dose of 5 mg/kg lipid formulation per day has been suggested. Retrospective human studies and prospective animal studies suggest improved survival utilising combination therapy of a lipid formulated polyene and an echinocandin.[37] Azoles are not recommended in the treatment of human mucormycosis, although very high-dose posaconazole has seen some success in animals.

Entomophthorales infection is usually restricted to skin and subcutaneous infections in tropical areas and largely occurs as a primary rather than opportunistic infection. It is not normally angioinvasive and disseminated disease is largely confined to immunocompromised individuals.

OTHERS

A large and growing variety of opportunistic fungal infections is increasingly recognised and it is beyond the scope of this chapter to cover all of those that may be encountered. In addition to the commonest infections outlined above, the possibilities of rarer infections with fusarosis, hyalophomycoses, phaeohyphomycoses and scedosporium merit consideration in immune-compromised patients with infection of unknown aetiology, especially haematopoietic transplant recipients.[38]

CONCLUSION AND GENERAL CONSIDERATIONS

The definitive diagnosis of IFI is one of the great challenges of modern medicine. Identification of fungi in samples from normally sterile sites allows definitive diagnosis, but certain species take up to 6 weeks to grow even in ideal media; tissue samples are rarely obtained early during a patient's ICU stay and even then, certain fungi require specific, non-routine staining to identify them. Antibody/antigen testing of fungal components and PCRs of fungal DNA are improving rapidly and certainty of diagnosis for certain species but are far from perfect across the range of pathogenic fungi.

In 2008, a revised consensus definition of IFD was published by the European Organisation for Research and Treatment of Cancer/IFI Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group.[39] This classified secondary IFI as definite, probable or possible. The consensus definitions' utility lies in categorising patient groups during research and epidemiological studies facilitating comparisons between different studies using a common definition. They should not be used to determine a tipping point as to whether to treat a patient for 'probable' IFI or not, and are deliberately omitted here. A retrospective re-analysis of neutropenic patients treated for IFI based on the 2002 criteria demonstrated a significant shift of treated patients from 'probable' (2002) to 'possible' (2008), and an increased survival in the group now re-classified as 'possible'. As all had received treatment, the authors suggested this may indicate that treatment earlier in the course of infection, before diagnostic certainty increased, resulted in better outcomes.[40]

Until the advent and widespread availability of high sensitivity and specificity test(s) covering the spectrum of recognised fungal infections seen in the ICU, a high awareness of the possibility of primary and secondary mycoses, an understanding of the available diagnostic tests and algorithms together with knowledge of their limitations, offers the best chances of early diagnosis and the instigation of appropriate treatment. Even with appropriate treatment, the mortality of IFD in the ICU remains over 50% for many fungi. Poorer outcomes are seen when diagnosis and treatment are delayed.

REFERENCES

1. Pfaller MA, Diekema DJ, Jones RN, et al. International surveillance of bloodstream infections due to Candida species: frequency of occurrence and in vitro susceptibilities to fluconazole, ravuconazole, and voriconazole of isolates collected from 1997 through 1999 in the SENTRY antimicrobial surveillance program. *J Clin Microbiol*. 2001;39: 3254–3259.
2. Marchetti O, Bille J, Fluckiger U, et al. Fungal Infection Network of Switzerland. Epidemiology of candidaemia in Swiss tertiary care hospitals: secular trends 1991–2000. *Clin Infect Dis*. 2004;38: 311–320.
3. Doua YH, Dua JK, Liua HL, et al. The role of procalcitonin in the identification of invasive fungal infection – a systemic review and meta-analysis. *Diag Microbiol and Inf Dis*. 2013;76:464–469.
4. Cortegian A, Russotto V, Montalto F, et al. Procalcitonin as a marker of Candida species detection by blood culture and polymerase chain reaction in septic patients. *BMC Anesthesiol*. 2014;14:9.
5. Delsing CE, Gresnigt MS, Leentjens J, et al. Interferon-gamma as adjunctive immunotherapy for invasive fungal infections: a case series. *BMC Infect Dis*. 2014;14:166.
6. Perruccio K, Tosti A, Burchielli E, et al. Transferring functional immune responses to pathogens after haploidentical hematopoietic transplantation. *Blood*. 2005;106:4397–4406.
7. Deo SS, Gottlieb DJ. Adoptive T-cell therapy for fungal infections in haematology patients. *Clin Transl Immunology*. 2015;4:e40.
8. Saccente M, Woods GL. Clinical and laboratory update on blastomycosis. *Clin Microbiol Rev*. 2010; 23(2):367–381.
9. Kauffman CA. Histoplasmosis: a clinical and laboratory update. *Clin Micro Rev*. 2007;20(1):115–132.
10. Bocca AL, Amaral AC, Teixeira MM, et al. Paracoccidioidomycosis: eco-epidemiology, taxonomy and clinical and therapeutic issues. *Future Microbiol*. 2013;8(9):1177–1191.
11. Manns BJ, Baylis BW, Urbanski SJ, et al. Paracoccidioidomycosis: case report and review. *Clin Infect Dis*. 1996;23:1026–1032.
12. Kontoyiannis DP, Lionakis MS, Lewis RE, et al. Zygomycoses in a tertiary-care cancer center in the era of Aspergillus-active antifungal therapy: a case-control observational study of 27 recent cases. *J Infect Dis*. 2005;191:1350–1360.
13. Pongas GN, Lewis RE, Samonis G, et al. Voriconazole-associated zygomycosis: a significant consequence of evolving antifungal prophylaxis and immunosuppression practices? *Clin Microbiol Infect*. 2009;15(suppl 5):93–97.
14. Lin SW, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis*. 2001;32(3):358–366.
15. Jantunen E, Anttila V-J, Ruutu T. Immune reconstitution. Aspergillus infections in allogeneic stem cell transplant recipients: have we made any progress? *Bone Marrow Transplant*. 2002;30:925–929.
16. Jin X, Chen Y, Yu N, et al. Detection of galactomannan and (1-3)-B-D glucan for early diagnosis of invasive aspergillosis in hematological cancer patients. *Int J Pharmacol*. 2013;9(1):86–91.
17. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *NEJM*. 2002;347(6): 408–415.

18. Patterson KC, Strek ME. Diagnosis and treatment of pulmonary aspergillosis syndromes. *Chest*. 2014; 146(5):1358–1368.
19. Marr KA, Schlamm HT, Herbrecht R, et al. Combination antifungal therapy for invasive aspergillosis: a randomized trial. *Ann Intern Med*. 2015;162(2):81–89.
20. Bhatia S, McCullough J, Perry EH, et al. Granulocyte transfusions: efficacy in treating fungal infections in neutropenic patients following bone marrow transplantation. *Transfusion*. 1994;34(3): 226–232.
21. Corine ED, Mark SG, Jenneke L, et al. Interferon-gamma as adjunctive immunotherapy for invasive fungal infections: a case series. *BMC Infect Dis*. 2014;14:166.
22. Pestalozzi BC, Krestin GP, Schanz U, et al. Hepatic lesions of chronic disseminated candidiasis may become invisible during neutropenia. *Blood*. 1997;90(10):3858–3864.
23. Mikulska M, Calandra T, Sanguinetti M, et al. The use of mannan antigen and anti-mannan antibodies in the diagnosis of invasive candidiasis: recommendations from the Third European Conference on Infections in Leukemia. *Crit Care*. 2010;14(6):R222.
24. Pappas PG, Rex JH, Sobel JD, et al. Guidelines for treatment of candidiasis. *Clin Infect Dis*. 2004; 38:161–189.
25. Buchanan KL, Murphy JW. What makes cryptococcus neoformans a pathogen? *Emerging Infec Dis*. 1998;4(1):71–83.
26. Einsiedel L, Gordon DL, Dyera JR. Paradoxical inflammatory reaction during treatment of cryptococcus neoformans var. gattii meningitis in an HIV-seronegative woman. *Clin Infect Dis*. 2004; 39:e78.
27. Perfecta JR, Bicanicb T. Cryptococcosis diagnosis and treatment: what do we know now. *Fung Gen Biol*. 2015;78:49–54.
28. Panackal AA, Wuest SC, Lin YC, et al. Paradoxical immune responses in non-HIV cryptococcal meningitis. *PLoS Pathog*. 2015;11(5):e1004884.
29. Phillips P, Chapman K, Sharp M, et al. Dexamethasone in Cryptococcus gattii central nervous system infection. *Clin Infect Dis*. 2009;49(4):591–595.
30. Beardsley J, Wolbers M, Kibengo FM, et al. Adjunctive dexamethasone in HIV-associated cryptococcal meningitis. *N Engl J Med*. 2016;374: 542–554.
31. Somerville LK, Henderson AP, Chen SCA, et al. Successful treatment of Cryptococcus neoformans immune reconstitution inflammatory syndrome in an immunocompetent host using thalidomide. *Med Mycol Case Rep*. 2015;7:12–14.
32. Cushion MT, Linke MJ, Ashbaugh A, et al. Echinocandin treatment of pneumocystis pneumonia in rodent models depletes cysts leaving trophic burdens that cannot transmit the infection. *PLoS ONE*. 2010;5(1):1–12, e8524.
33. Briel M, Boscacci R, Furrer H, et al. Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV infection: a meta-analysis of randomised controlled trials. *BMC Infect Dis*. 2005;5:101.
34. Li H, Huang H, He H. Successful treatment of severe Pneumocystis pneumonia in an immunosuppressed patient using caspofungin combined with clindamycin: a case report and literature review. *BMC Pulm Med*. 2016;16:144.
35. Advances against mucormycosis: a tribute to the memory and courage of Hank Schueler. *Clin Infect Dis*. 2012;54(suppl 1). Available at: https://doi.org/10.1093/cid/cir877.
36. Marty FM, Cosimi LA, Baden LR. Breakthrough mucormycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. *N Engl J Med*. 2004;350:950–952.
37. Spellberg B, Ibrahim A, Roilides E, et al. Combination therapy for mucormycosis: why, what, and how? *Clin Infect Dis*. 2012;54(suppl 1):S73–S78.
38. Marr KA, Carter RA, Crippa F, et al. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2002;34:909–917.
39. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organisation for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. 2008;46:1813–1821.
40. Cornely OA, Maertens J, Bresnik M, et al. Efficacy outcomes in a randomised trial of liposomal amphotericin B based on revised EORTC/MSG 2008 definitions of invasive mould disease. *Mycoses*. 2011;54(5):e449–e455.

74

Principles of antibiotic use in the ICU

Jeffrey Lipman

The intensive care unit (ICU) is always the area of any hospital associated with the greatest use of antibiotics. Much of this high usage is unavoidable, but the clinician working in the ICU must realise that there is an essential consequence of this use. Antibiotic use, which should eliminate susceptible bacteria, promotes (over) growth of other non-susceptible organisms, especially fungi. As far as bacteria are concerned, antibiotics confer enormous selective advantage to resistant strains, and therefore these strains will congregate where their advantage is greatest – in the ICU. Resistance (and fungal overgrowth) is a direct consequence of usage, and every course of inappropriate antibiotics should be avoided to help reduce the burden of resistance.

Antibiotic stewardship[1,2] has been suggested as a new strategy to help limit resistance. This involves selecting an appropriate drug and optimising its dose and duration to cure an infection while minimising toxicity and conditions for the selection of resistant bacterial strains. Inadequate doses of even the 'correct' antibiotic may lead to the survival of initially susceptible organisms.[3,4] For the optimal use of antibiotics not only should antibiotic pharmacokinetics be understood but also there should be clear and rational principles on which each specific antibiotic prescription in the ICU is based. In addition, it is probably better to have portions of the ICU population receive different classes of antibiotics at the same time.[5]

Although this chapter will provide basic principles for most of the antibiotic classes commonly used in ICUs, some important antimicrobial agents will not be specifically addressed here, namely macrolides, clindamycin and the antifungal agents.

GENERAL PRINCIPLES[6,7]

1. All appropriate microbiological specimens, including blood cultures, should be obtained before commencing antibiotic therapy. An immediate Gram-stained report may indicate the appropriate antibiotic to use, otherwise a 'best guess' choice is made depending on the clinical situation. This important and common clinical phenomenon involves trying to predict the infecting organism(s).
2. Blood cultures should be taken from a venepuncture site, after adequate skin antisepsis, and not from an intravenous or arterial catheter. Two *separate* sets of 20 mL (for adults) should be taken, the timing of which is less important.[8] Depending on what system is used, probably 10 mL should be placed into two different blood culture bottles.
3. Once a decision is made to administer antibiotics, they should be administered *without delay*, as delay to antibiotic therapy **in shock** increases morbidity and mortality.[9]
4. The decision for empirical therapy (i.e. cover for the most 'likely' organisms causing any specific infection) must include various factors such as: the site of the infecting organism (respiratory tract pathogens differ from those of abdominal infections), community- versus hospital-associated infection, recent previous antibiotic prescription, ward- versus ICU-acquired infection, travel history and knowledge of the organisms commonly grown in patients in any specific area. This latter point is where ward/unit surveillance becomes important.[10,11]
5. Although there should be an attempt to use a narrow-spectrum antibiotic whenever practicable, appropriate therapy, particularly for empirical choice for nosocomial sepsis, often requires starting off with broad-spectrum antibiotics, even a combination, until culture results are back[12,13] – at which time de-escalation should be embarked upon (see below).[7] Inappropriate[14] and/or delayed correct[9] antibiotic use in the ICU has been shown to impact on morbidity and mortality (Table 74.1).[7]
6. Monotherapy with a single agent effective against the expected organisms aims to decrease the risk of drug antagonism, reaction or toxicity.[15] Monotherapy often costs less than multiple antibiotic usage and limits co-lateral damage.
7. The clinical response to treatment already given should always be considered when bacteriological results suggest reduced susceptibility.
8. A standard 2-week course of antibiotics is unnecessary[16–18] and probably harmful (see Table 74.1). After a single day of imipenem a French study demonstrated some patients will grow imipenem-resistant bacteria in their faeces.[19] The overgrowth

ABSTRACT

Antibacterial agents kill bacteria, but allow growth of other organisms, including resistant bacteria. Critically ill patients need different doses to those in the wards. Often critically ill patients have augmented renal clearance predisposing them to underdosing and the development of resistance. It is therefore prudent to use high-dose, short courses and as narrow a spectrum as possible. Therapeutic drug monitoring not only for toxicity but also for efficacy (including for beta-lactams) can help with dosing requirements. Delay in the initiation of antibiotics in septic shock is harmful, but cultures need to be taken prior to initiation of the antibiotic. Evidence suggests double Gram-negative cover is unnecessary. Prophylactic antibiotics should be administered just prior to surgery and continued for any length of time. Infection control is just as important, if not more so, in treating infected patients.

KEYWORDS

Critical care
antibiotics
duration
pharmacokinetics
augmented renal clearance
antibiotic resistance
therapeutic drug monitoring

Table 74.1 New paradigm of treatment for nosocomial sepsis

OLD	NEW
Start with penicillin	Get it right 1st time (broad spectrum)
Cost-efficient low dose	Hit hard up front
Low doses = fewer side effects	Low dose → resistance
Long courses ≥2 weeks	Seldom longer than 7 days

From Lipman J, Boots R. A new paradigm for treating infections: 'go hard and go home'. *Crit Care Resusc.* 2009;11:276–281.

of resistant organisms, a 'natural' consequence of broad-spectrum antibiotic use, is termed 'co-lateral damage'.

9. In consultation with infectious disease specialists, additional tests, such as antibiotic minimum inhibitory concentration (MIC), antibiotic assay, serum bactericidal activity and synergy tests of antibiotic combinations, may be useful in serious infections (e.g. endocarditis and infections in immunocompromised patients). Susceptibility tests should be interpreted carefully. In vitro sensitivity does not equate with clinical effectiveness; in vitro resistance is a better negative predictor.
10. Consultations with the laboratory staff, infectious diseases/clinical microbiology specialists and clinical pharmacists are always useful and should be mandatory in serious infections (e.g. meningococcal sepsis, methicillin-resistant staphylococci and multiresistant Enterobacteriaceae).
11. The pharmacokinetics and pharmacodynamics (e.g. penetration into relevant tissues) as well as the spectrum of activity of the antibiotic must be considered. Antibiotic pharmacokinetic principles should determine the dosage and frequency of antibiotic regimens (see below).[20,21]
12. Adequate drug doses should be given. Underdosing leads to overgrowth of resistant organisms.[3,4] The intravenous route is preferable in critically ill patients, but other routes should be considered when appropriate.
13. Serum levels of potentially toxic antibiotics should be monitored not only for toxicity but also for efficacy (prevention of underdosing).[22,23] Recent data suggest that many patients are underdosed in ICUs.[24]
14. Prophylactic use of antibiotics should be limited to certain situations, should cover organisms that potentially can cause infections in that specific group of patients (e.g. organisms causing skin and soft-tissue infections differ from those implicated in intra-abdominal infections) and should be given at the appropriate timing (see below).
15. General signs of infection are signs of systemic inflammation. Although bacterial infection is likely, non-bacterial infection and non-infective causes should also be considered. High procalcitonin and C-reactive protein levels may be discriminatory for infection but are often too non-specific and have significant limitations.[25,26]
16. Antibiotic guidelines are only one aspect of infection control.[27–29] Hand washing and hand hygiene in general are vital and the fundamental aspect of infection control.[27] Identification and elimination of reservoirs of infection,[28,29] blocking transmission of infection,[29] barrier nursing as well as terminal cleaning of high-touch areas are imperative controls that need to be in place in every ICU.[28,29]

COMMON ERRORS WHEN USING ANTIBIOTICS

1. Administration of antibiotics before microbiological specimens are obtained.
2. Quantity and quality of blood cultures.
3. Extended use of antibiotics after eradication of infection (e.g. a 2-week course for ventilation-associated pneumonia).[16–18] With adequate source control, even intra-abdominal sepsis can be treated with a short course of antibiotics.[18]
4. Antibiotic 'surfing' (i.e. switching from one combination to another) when the patient is not improving without delving into the cause of persistent inflammatory response.
5. Inadequate and delayed therapy and/or incorrect dosing of antibiotics, the latter is increasingly more commonly recognised.
6. Failure to recognise patients with high creatinine clearances (augmented renal clearance). These patients have high clearance of renally excreted drugs (beta-lactams, glycopeptides, aminoglycosides) and therefore are predisposed to underdosing of these drugs.[20–24,30]
7. Failure to adequately predict 'resident' microbial flora and therefore the inability to correctly choose empiric antibiotics for nosocomial infections (i.e. no adequate surveillance data).
8. Failure to recognise toxic effects of antibiotics, particularly when polypharmacy is used.
9. Use of combination therapy, irrespective of infection.

SPECIFIC ISSUES

PHARMACOKINETIC PRINCIPLES

The goal of antimicrobial prescription is to achieve effective active drug concentrations (a combination of dose and duration) at the site of infection whilst avoiding, or at least minimising, toxicity.

The various antibiotic classes have different 'kill characteristics' and therefore should be dosed differently (Table 74.2).[20,31]

Table 74.2 Pharmacodynamic properties of selected antibiotics

Antibiotics	Aminoglycosides	Fluoroquinolones Glycopeptides	β-lactams Carbapenems Glycopeptides
PD kill characteristics	Concentration dependent	Concentration dependent with time dependence	Time dependent
Optimal PK parameter	C_{max}:MIC	AUC:MIC	$T > MIC$

AUC, Area under concentration time curve; C_{max}, peak serum concentration; *MIC*, minimum inhibitory concentration; *PD*, pharmacodynamics; *PK*, pharmacokinetic; $T > MIC$, time above MIC.

From Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. *Crit Care Med*. 2009;37:840–851.

β-LACTAMS (ALL PENICILLINS AND CEPHALOSPORINS, MONOBACTAMS)[20,31]

1. Studies of β-lactam antibiotics on Gram-negative bacilli show a bactericidal activity that is relatively slow, time-dependent and maximal at relatively low concentrations. Bacterial killing is almost entirely related to the time that levels in tissue and plasma exceed a certain threshold. The maximum time that plasma β-lactam levels should be allowed to fall below MIC is 40% of the dosing interval.
2. β-lactam antibiotics lack a significant post-antibiotic effect (PAE) particularly against Gram-negative organisms, and it is not necessary to achieve very high peak plasma concentrations. PAE is the continued suppression of bacterial growth despite zero serum concentration of the antibiotic. It is suggested that concentrations of any β-lactam should be maintained at about four to five times MIC for long periods, as maximum killing of bacteria in vitro occurs at this level. If antibiotic concentrations fall below this threshold in the in vitro models, bacterial growth is immediately resumed.[3,4,20,31]
3. Thus, it is important for the efficacy of β-lactams that the dosing regimen maintains adequate plasma levels for as long as possible during the dosing interval. Although a recent double blind, randomised, controlled trial of 420 patients could not demonstrate benefit of continuous infusions,[32] it may be that in the sicker patients continuous infusions may be beneficial.[33] A 7000-patient, randomised, controlled trial is currently planned, which formally addresses the place of continuous infusions of β-lactams.[34]

CARBAPENEMS

1. Similar to β-lactams, the carbapenems also have time-dependent kill characteristics but have some PAE.
2. Prolonged infusions (over 3 hours) have been utilised to improve time above MIC.[35]
3. In vitro data suggest that low concentrations may predispose to development of resistant organisms.[4]

AMINOGLYCOSIDES[20,31]

1. The agents above contrast with the kill characteristic of the aminoglycosides, which is concentration-dependent. Experimentally, a high peak concentration of an aminoglycoside antibiotic provides a better, faster killing effect on standard bacterial inocula.
2. All aminoglycosides exhibit a significant PAE. The duration of this effect is variable, but the higher the previous peak the longer the PAE. This phenomenon allows drug concentration to fall significantly below MIC of the pathogen without allowing regrowth of bacteria.
3. These principles allow for single daily doses of aminoglycosides (also termed extended interval dosing). Combining various meta-analyses involving thousands of patients, once-daily administration was found to be more efficacious with reduced toxicity, higher peak/MIC ratios, further prolonged PAE and reduced administration costs.
4. With renal dysfunction there should be the same loading dose but then the dose should be altered according to creatinine clearance.[21] If ≥60 mL/min give 5–7 mg/kg per day; if 59–40 mL/min, give the same dose at an interval of 36 hours; 39–20 mL/min increases the dosing interval to 48 hours.[36]

QUINOLONES[20,31]

1. Ciprofloxacin, in contrast, has a combination of both of the above characteristics (i.e. concentration-dependent and time-dependent effects), as well as some PAE.
2. Although one suggested 'target' parameter for a good clinical bactericidal effect is a high peak, the most validated parameter is the area under the inhibitor curve (AUIC) – that is, AUC/MIC > 125.
3. There is general concern about the emergence of resistance related to inappropriately low doses of ciprofloxacin (see Table 74.1).

GLYCOPEPTIDES[20,37]

1. Vancomycin induces a PAE and a post-antibiotic sub-MIC effect. These combined effects suggest that bacterial regrowth will not occur for prolonged periods following a fall in drug concentrations to levels below the MIC.
2. Continuous infusions of vancomycin may have some advantages.

Aminoglycosides and glycopeptides distribute well into fluids of the extravascular, extracellular space, and less well into tissues. This has two important implications. First, these agents should not be first-line agents, or monotherapy, for solid organ infections (lung, kidney, liver, etc.). Second, in situations where extravascular fluid shifts are significant (e.g. in situations of 'third-space losses' of abdominal sepsis, in severe burns, etc.), the volume of distribution of these drugs is significantly affected. Hence for any serum level required a larger than usual dose may have to be administered.[37] The volume of distribution of the quinolones (very large) suggests penetration is excellent into most tissues and hence these drugs are good for solid organ infections. Similarly, β-lactams as a group (including carbapenems) all have reasonable tissue penetration.

ANTIBIOTIC PROPHYLAXIS[6,38]

The main indications for prophylaxis are:

- when surgery involves incision through an area of colonisation or normal commensal flora and a resultant potential infection has morbidity or mortality
- when a procedure (e.g. catheterisation, instrumentation, intubation, dental work) potentially produces a bacteraemia in the presence of an immunocompromised patient, or when the potential bacteraemia occurs in the presence of an abnormal heart valve or a prosthesis.

Basic principles of choice of prophylactic regimen should include the following:

1. The organisms colonising the area through which the incision is made should be covered (Gram positives if skin is breached, Gram negatives and anaerobes if bowel is opened).
2. A similar case should be made for colonising organisms through the area breached by catheterisation or instrumentation, etc. (Gram negatives for bladder catheterisation, Gram positives and anaerobes for dental procedures).
3. If prevalence of a resistant organism in a specific area is high (e.g. *Pseudomonas* in burns units) then those organisms should be covered by the prophylactic regimen.

TIMING AND DURATION OF PROPHYLAXIS

1. Optimal blood levels of antibiotic(s) are needed when the occurrence of the potential bacteraemia occurs (i.e. for surgery the optimal timing of the antibiotic should be at, or just prior to, induction of anaesthesia and skin incision).[38]
2. For prolonged procedures where bacteraemias are still a potential occurrence, a second dose of antibiotic(s) may be considered.
3. There is no extra benefit to postoperative antibiotic prophylaxis.

DOSES[20–25,31,37]

Comments on dosing regimens are provided below. Doses suggested below are intravenous, for a 70-kg adult with *normal* renal function. All these drugs accumulate with renal dysfunction and modified doses should be used accordingly. It should be noted that some patients with 'normal' renal function may have increased renal clearance of antibiotics and hence need a higher than usual dose.[20,21,31]

1. Doses for β-lactams vary with each different drug, *but* recent emphasis supports lower boluses with more frequent administration (i.e. 4-hourly versus 8-hourly, or b.d. versus daily).[31] Continuous infusions (or possibly prolonged infusions) may become standard practice.[33,34,35]
2. *Aminoglycosides:* give tobramycin and gentamicin at 7 mg/kg as a loading dose on the first day, followed by 5 mg/kg per day. Amikacin 25 mg/kg as the loading dose followed by 15 mg/kg per day. These doses are the same for adults and children, neonates excluded.
3. *Quinolones:* the ciprofloxacin dose is *at least* 400 mg b.d. (up to t.d.s.).
4. *Glycopeptides:* the vancomycin[37] dose is at least 30 mg/kg loading and similar/day either as continuous infusion or in divided doses (40 mg/kg per day for children).
5. *Carbapenems:* give meropenem or imipenem at 3 g/day in at least three divided doses.

SURVEILLANCE

Some type of simple laboratory-oriented surveillance, which primarily collects data and resistance patterns of microbiological isolates, is important. Each unit should have access to its own such data as there is an increasing prevalence of resistant organisms in intensive care units. This is complicated even further by different units having differing resistance patterns.[10] Empirical antibiotic therapy must take these factors into account. Some form of surveillance that provides units with their own microbiological data, updateable quarterly or biannually, is therefore beneficial in helping to choose empirical and prophylactic regimens that are applicable to any specific unit.[10]

MULTIRESISTANT ORGANISMS

Although this chapter is on antibiotics, the point must be made that without good, efficient and effective infection control policies in all areas treating critically ill patients the spread of multiresistant organisms would be rampant and their control useless.[27–29] Part of these policies should involve attention to good hand hygiene and the use of antiseptic soaps and alcohol-based hand rubs.[27] Hands are still the most documented and incriminated mode of transmission of infection. In

this regard a decrement in nursing numbers has also been incriminated in outbreaks of infections possibly due to the time it takes to adequately wash between procedures.[27] High-touch areas are important areas to address with terminal cleaning procedures.[28,29]

1. Multiresistant streptococci and vancomycin-resistant enterococci, although not common in all countries, are an increasing worldwide problem, as is community-acquired MRSA.
2. New agents are available for the treatment of resistant Gram-positive infections.[39]
3. Antibiotic resistance is agent-specific. Often resistance is claimed to be against third-generation cephalosporins, but this is largely to ceftazidime (particularly the extended-spectrum β-lactamases of *Klebsiella pneumoniae, E. coli* and some Enterobacteriaceae).
4. Worrying Gram-negative organisms are *K. pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumanii* spp. and *Stenotrophomonas maltophilia* (the latter specifically, for which trimethoprim may need to be used). A common feature of these organisms is intrinsic resistance to multiple antibiotics. *P. aeruginosa* and *Acinetobacter* complex (also named *A. baumanii*) have become particular problems. Sulbactam and polymyxin B or colistin have been used for these problem organisms.
5. Although the antibiotic pipeline is drying up, there are some new agents on the horizon.[40]
6. Finally, the most worrying of all organisms from an infection control point of view is *Acinetobacter baumanii* spp. It has intrinsic abilities to rapidly, and often, swap genetic material and hence it develops resistance very quickly.[41] It is also able to survive on inanimate object for months. These features allow it not only to become highly resistant, but also to become endemic in ICUs.[42] Isolation of patients infected, or even colonised with, multiresitant *Acinetobacter* spp. is therefore important, as is terminal cleaning of the environment.

MONO VERSUS COMBINATION THERAPY[12,13,15]

1. Much of the work in this area was performed before the clinical introduction of the carbapenems, penicillin/β-lactamase combinations and fourth-generation cephalosporins. It seems that newer single agents are adequate, apart possibly from resistant pseudomonal infections.[15]
2. There is no clear evidence supporting the claim that combination antimicrobial therapy prevents the emergence of resistance.[15]
3. However, combination therapy is often suggested for endocarditis and some pseudomonal infections.[13] When combination therapy is used, preference should be given to the combination therapy of two different classes of antibiotics that act synergistically. The combination of two β-lactam antibiotics should not be used.

BROAD-SPECTRUM INITIAL COVER WITH DE-ESCALATION[7,13,14]

In view of the morbidity and mortality of delayed appropriate therapy for nosocomial sepsis,[9,14] patients with risk factors for infection with resistant pathogens should initially receive broad-spectrum antibiotics, possibly even combination therapy,[7,13,14] then, as soon as the pathogen and the susceptibilities are available, treatment should be simplified to a more targeted one – so-called 'de-escalation' therapy (see Table 74.1).[7] In the limited studies to date, de-escalation has led to less antibiotic usage, shorter durations of therapy, fewer episodes of secondary pneumonia and reduced mortality, without increasing the frequency of antibiotic resistance.

REFERENCES

1. Fishman N. Antimicrobial stewardship. *Am J Med*. 2006;119:S53–S61, discussion S62–S70.
2. Dryden M, Saeed K, Townsend R, et al. Antibiotic stewardship and early discharge from hospital: impact of a structured approach to antimicrobial management. *J Antimicrob Chemother*. 2012;67(9):2289–2296. doi:10.1093/jac/dks193.
3. Bergen P, Bulitta J, Kirkpatrick C, et al. Effect of different renal function on anti-bacterial effects of piperacillin against Pseudomonas aeruginosa evaluated via the hollow fibre infection model and mechanism-based modelling. *J Antimicrob Chemother*. 2016;71:2509–2520.
4. Roberts JA, Kruger P, Paterson D, et al. Antibiotic resistance – what's dosing got to do with it? *Crit Care Med*. 2008;36:2433–2440.
5. Bergstrom CT, Lo M, Lipsitch M. Ecological theory suggests that antimicrobial cycling will not reduce antimicrobial resistance in hospitals. *Proc Natl Acad Sci*. 2004;101:13285–13290.
6. Mandell GL, Douglas RG, Bennett JE. *Principles and practice of infectious diseases*. 4th ed. New York, NY: Churchill Livingstone; 1994.
7. Lipman J, Boots R. A new paradigm for treating infections: 'go hard and go home'. *Crit Care Resusc*. 2009;11:276–281.
8. Weinstein MP. Current blood culture methods and systems: clinical concepts, technology, and interpretation of results. *Clin Infect Dis*. 1996;23:40–46.
9. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34:1589–1596.
10. Namias N, Samiian L, Nino D, et al. Incidence and susceptibility of pathogenic bacteria vary between intensive care units within a single hospital: implications for empiric antibiotic strategies. *J Trauma*. 2000;49:638–645.
11. Marchese A, Schito GC. Role of global surveillance in combating bacterial resistance. *Drugs*. 2001;61:167–173.

12. Mutlu GM, Wunderink RG. Severe pseudomonal infections. *Curr Opin Crit Care*. 2006;12:458–463.
13. Traugott KA, Echevarria K, Maxwell P, et al. Monotherapy or combination therapy? The *Pseudomonas aeruginosa* conundrum. *Pharmacotherapy*. 2011;31:598–608.
14. Kollef MH. Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. *Clin Infect Dis*. 2000;31(suppl 4):S131–S138.
15. Safar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis. *Lancet Infect Dis*. 2004;4:519–527.
16. Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA*. 2003;290:2588–2598.
17. Havey TC, Fowler RA, Daneman N. Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis. *Crit Care*. 2011;15:R267. (Review).
18. Sawyer RG, Claridge JA, Nathens AB, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. *N Engl J Med*. 2015;372: 1996–2005.
19. Armand-Lefèvre L, Angebault C, Barbier F, et al. Emergence of imipenem-resistant gram-negative bacilli in intestinal flora of intensive care patients. *Antimicrob Agents Chemother*. 2013;57:1488–1495.
20. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. *Crit Care Med*. 2009;37:840–851.
21. Roberts JA, Taccone FS, Lipman J. Understanding PK/PD. *Intensive Care Med*. 2016;42:1797–1800.
22. Jager NG, van Hest RM, Lipman J, et al. Therapeutic drug monitoring of anti-infective agents in critically ill patients. *Expert Rev Clin Pharmacol*. 2016;9: 961–979.
23. Huttner A, Harbarth S, Hope WW, et al. Therapeutic drug monitoring of the β-lactam antibiotics: what is the evidence. *J Antimicrob Chemother*. 2015;70:3178–3183.
24. Roberts JA, Paul SK, Akova M, et al. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? *Clin Infect Dis*. 2014;58: 1072–1083.
25. Andriolo BN, Andriolo RB, Salomão R, et al. Effectiveness and safety of procalcitonin evaluation for reducing mortality in adults with sepsis, severe sepsis or septic shock. *Cochrane Database Syst Rev*. 2017;(1):CD010959.
26. Ho KM, Lipman J. An update on C-reactive protein for intensivists. *Anaesth Intens Care*. 2009;37:234–241.
27. Pittet D, Allegranzi B, Sax H, et al. Evidence-based model for hand transmission during patient care and the role of improved practices. *Lancet Infect Dis*. 2006;6:641–652.
28. Morgan DJ, Rogawski E, Thom KA, et al. Transfer of multidrug-resistant bacteria to healthcare workers' gloves and gowns after patient contact increases with environmental contamination. *Crit Care Med*. 2012;40:1045–1051.
29. Thom KA, Johnson JK, Lee MS, et al. Environmental contamination because of multidrug-resistant *Acinetobacter baumannii* surrounding colonized or infected patients. *Am J Infect Control*. 2011;39: 711–715.
30. Udy AA, Roberts JA, Boots RJ, et al. ARC – Augmented renal clearance: implications for antibiotic dosing in the critically ill. *Clin Pharmacokinet*. 2010;49:1–16.
31. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis*. 1998;26:1–10.
32. Dulhunty JM, Roberts JA, Davis JS, et al. A multicenter randomized trial of continuous versus intermittent β-lactam infusion in severe sepsis. *Am J Respir Crit Care Med*. 2015;192:1298–1305.
33. Abdul-Aziz MH, Sulaiman H, Mat-Nor MB, et al. Beta-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis. *Intensive Care Med*. 2016;42:1535–1545.
34. *NHMRC Project Grant 2017-2021 – BLING III: A phase III randomised controlled trial of continuous beta-lactam infusion compared with intermittent beta-lactam dosing in critically ill patients*.
35. Lomaestro BM, Drusano GL. Pharmacodynamic evaluation of extending the administration time of meropenem using a Monte Carlo simulation. *Antimicrob Agents Chemother*. 2005;49:461–463.
36. Nicolau DP, Freeman CD, Belliveau PP, et al. Experience with a once daily aminoglycoside program administered to 2,184 adult patients. *Antimicrob Agents Chemother*. 1995;39:650–655.
37. Roberts JA, Taccone FS, Udy AA, et al. Vancomycin dosing in critically ill patients – robust methods for improved continuous infusion regimens. *Antimicrob Agents Chemother*. 2011;55:2704–2709.
38. Classen DC, Evans RS, Pestotnik SL, et al. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *N Engl J Med*. 1992;326:281–286.
39. Stryjewski ME, Corey GR. New treatments for methicillin-resistant *Staphylococcus aureus*. *Curr Opin Crit Care*. 2009;15:403–412.
40. Bassetti M, Righi E. New antibiotics and antimicrobial combination therapy for the treatment of gram-negative bacterial infections. *Curr Opin Crit Care*. 2015;21:402–411.
41. Fournier PE, Vallenet D, Barbe V, et al. Comparative genomics of multidrug resistance in Acinetobacter baumannii. *PLoS Genet*. 2006;2:e7.
42. Weber DJ, Rutala WA, Miller MB, et al. Role of hospital surfaces in the transmission of emerging health care-associated pathogens: Norovirus, Clostridium difficile, and Acinetobacter species. *Am J Infect Control*. 2010;38:S25–S33.

75

Tropical diseases

Vivekanandan M Pillai, Ramachandran Sivakumar

Once an exotic and esoteric topic, modern travel and the quest for unusual holidays has the potential to bring tropical diseases to every intensive care unit (ICU). This chapter covers some important diseases, which are common in the tropical belt.

MALARIA

EPIDEMIOLOGY AND PATHOGENESIS

It is estimated that four species of *Plasmodium* (*vivax, malariae, ovale* and *falciparum*) cause 200 million infections per year with about 300,000–600,000 deaths. Most of the deaths are caused by *Plasmodium falciparum* and the majority of deaths are in children under 5 years in Sub-Saharan Africa. Malaria is also widely prevalent in the Indian subcontinent and Southeast Asia. It is transmitted from human to human by the bite of infected female Anopheles mosquitoes. After development in the liver, there is invasion of red cells by parasites, which is followed by their multiplication and the rupture of the red cells. The cycle is then repeated in red cells. In *vivax* and *ovale* infections, development to dormant forms can occur in the liver, which may lead to relapse. A fifth species, *Plasmodium knowlesi*, is a parasite of the macaque monkeys. It has been identified across almost all Southeast Asian countries and in travellers returning from these areas.[1]

CLINICAL FEATURES

UNCOMPLICATED MALARIA

Uncomplicated malaria typically presents as an undifferentiated febrile illness and resembles a viral illness. Classic symptoms of fever, body ache, and headache are usually, but not always, present. Other features such as diarrhoea, vomiting, cough and abdominal pain, may confuse the unwary. Unusual presentations are more common in children and may be missed. Initially the fever is irregular. Later on a pattern of cyclic paroxysms of chills and rigors, fever and drenching sweats may develop. Classically, these paroxysms last for a few hours only, and repeat every 24, 48 or 72 hours depending upon the species. The spleen becomes palpable in non-immune individuals only after several days. Mild hepatomegaly may occur. Rash is not a feature. Very rarely, petechiae may occur in severe *falciparum* malaria. Lymphadenopathy is very rare. Neck stiffness and photophobia do not occur.

SEVERE MALARIA

Severe malaria is usually seen with *falciparum* infection but also occurs with *vivax* and *knowlesi* infections.

Risk factors for severe malaria

- Children under 5 years in high transmission areas
- People of any age in areas of low transmission
- Non-immune travellers to endemic areas
- Pregnancy, human immunodeficiency virus (HIV) infection, people who have undergone splenectomy[2]

Definition

Clinical features:

- impaired consciousness: Glasgow Coma Score less than 11 or Blantyre Coma Score less than 3 in children
- prostration (i.e. generalised weakness) so that the patient is unable to sit stand or walk without assistance
- failure to feed
- multiple convulsions – more than two episodes in 24 hours
- deep breathing, respiratory distress (acidotic breathing)
- shock: compensated shock is defined as capillary refill 3 or more seconds but no hypotension; decompensated shock is defined as systolic blood pressure less than 80 mm Hg in adults and less than 70 mm Hg in children, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill)
- clinical jaundice plus evidence of other vital organ dysfunction
- haemoglobinuria
- abnormal spontaneous bleeding
- pulmonary oedema (radiological)

Laboratory findings:

- hypoglycaemia (blood glucose <2.2 mmol/L or <40 mg/dL)

ABSTRACT

Tropical diseases are no longer unique or limited to tropical and subtropical regions alone. Increasing globalisation and ease of travel mean that tropical diseases can present as emergencies to intensive care units (ICUs) anywhere in the world. Malaria, typhoid, leptospirosis, rickettsial infections and dengue fever and other viral haemorrhagic fevers are some of the important infections that may be seen in the ICU. Emergencies related to tuberculosis, though not strictly a tropical disease, may also pose a diagnostic challenge to the ICU physician. These diseases may present with severe sepsis, multiorgan dysfunction, renal failure, acute respiratory distress syndrome, jaundice, liver failure, meningoencephalitis or bleeding manifestations, singly or in combination. There is considerable overlap in the clinical presentation of various tropical infections. In addition, these exotic illnesses must also be differentiated from locally prevalent illnesses. Detailed travel history, including details such as exposure to animals and vectors, terrains visited, recreational activities indulged in, food habits, details of vaccinations and drug prophylaxis, are some of the important factors in narrowing down the diagnosis. Incubation period of various illnesses should be kept in mind. Findings such as rash, eschar, hepatomegaly, splenomegaly and lymphadenopathy can help in the differential diagnosis. Adequate knowledge of the available laboratory tests and their limitations is very important. Empirical therapy may be justified in the critically ill while awaiting laboratory results.

KEYWORDS

Malaria
typhoid
leptospirosis
rickettsial infections
dengue fever
viral haemorrhagic fever tuberculosis

- metabolic acidosis (plasma bicarbonate <15 mmol/L)
- severe normocytic anaemia (Hb <5 g/dL, packed cell volume [PCV] <15%)
- haemoglobinuria
- hyperparasitaemia (>10%)
- hyperlactataemia (lactate >5 mmol/L)
- renal impairment serum creatinine greater than 265 µmol/L or urea more than 20 mmol/L.

The incubation period is 7 days (usual range 9–14 days) but this may be prolonged. Several of the above co-exist or may develop in rapid succession. Cough, convulsions and hypoglycaemia are more common in children. Jaundice is common, but hepatic failure is uncommon. The acidosis of malaria is multifactorial and probably very similar to other forms of sepsis involving tissue hypoxia, liver dysfunction and impaired renal handling of bicarbonate.

The differential diagnosis of malaria includes

- Meningitis, typhoid fever, septicaemia
- Severe influenza, dengue and other arboviral infections
- Haemorrhagic fevers
- Hepatitis, leptospirosis
- Rickettsial diseases (e.g. scrub typhus)
- Relapsing fever (*Borrelia recurrentis*)
- Febrile convulsions in children.

Pregnancy increases the risk of developing severe malaria. During pregnancy both maternal and foetal morbidity and mortality are increased.

Poor prognostic indicators include age under 3 years, cerebral malaria, circulatory collapse and organ dysfunction. Laboratory evidence of poor prognosis includes hyperparasitaemia (>250,000/µL or >5%), peripheral schizontaemia, severe anaemia (PCV <15% or Hb <50 g/L), raised blood urea greater than 60 mg/dL and serum creatinine greater than 265 µmol/L (>3.0 mg/dL), raised venous lactate (>5 mmol/L), raised cerebrospinal fluid (CSF) lactate (>6 mmol/L), low CSF glucose and a very high concentration of tumor necrosis factor α.

Cerebral malaria

Cerebral malaria[3] may be the most common non-traumatic encephalopathy worldwide. The term is restricted to the syndrome in which altered consciousness due to malaria could not be attributed to convulsions, sedatives, hypoglycaemia or a non-malarial cause.

Clinical, histopathological and laboratory studies have suggested two potential mechanisms:

- mechanical hypothesis – cytoadherence of parasitised erythrocytes
- cytotoxic hypothesis – neuronal injury by malarial toxin and excessive cytokine production.

Cerebral malaria has few specific features, but there are differences in clinical presentation between African children and non-immune adults.[3]

Clinical findings include:

- coma
- convulsions
- raised intracranial pressure
- hypoglycaemia
- acidosis
- abnormalities of tone and posture (the commonest being symmetrical pyramidal signs)
- retinopathy – patchy macular whitening sparing foveola, white-centred retinal haemorrhages orange or whitish discoloration of retinal vessels, capillary whitening.

DIAGNOSIS

- Microscopy of thick and thin films remains the gold standard for both the diagnosis and to follow the efficacy of treatment. In the non-immune patient there is a close association between parasite levels and complications; however, severe complications can occur in patients with low counts.
- Rapid diagnostic tests (RDT), which detect specific antigens (proteins) produced by malaria parasites, are useful in diagnosis. Current tests are based on the detection of histidine-rich protein 2 (HRP2), (which is specific for *P. falciparum*) pan-specific or species-specific parasite lactate dehydrogenase (pLDH) or other pan-specific antigens such as aldolase. Many commercial assays are available. Some tests detect only one species (*P. falciparum*), while others detect one or more of the other three species. RDTs do not give information about the parasite load, and their sensitivity drops at low parasite densities, making them less useful for the diagnosis of malaria in non-immune travellers who may experience symptoms of malaria even at low parasite densities. It is important to seek microbiological advice regarding the RDT tests used locally.
- In one study of returned travellers in France, a US Food and Drug Administration (FDA)-approved rapid test, based on HRP2 for *P. falciparum*, had a sensitivity of 96% and specificity of 99%.[4] In another study of returned travellers in the United States, the sensitivity of rapid test was 100% for facliparum compared to only 88% for blood smear, using polymerase chain reaction (PCR) as the reference standard.[5] HRP2-based tests may be persistently positive up to 28 days after treatment. RDTs for *Plasmodium vivax* are less sensitive. *P. knowlesi* cannot be specifically identified by microscopy. It will be reported as *Plasmodium malariae* or less commonly as *P. falciparum*. There are no specific rapid tests for *P. knowlesi*. Pan-specific tests have low sensitivity. Species-specific rapid tests for *P. vivax* or *P. falciparum* may be positive in *P. knowlesi* infection. *P. knowlesi* infection can only be confirmed through PCR.

- PCR tests based on detecting malarial DNA are more sensitive than microscopy but are expensive and do not give estimates of parasite load.

TREATMENT OF MALARIA

The World Health Organization (WHO) has recently issued new guidelines for the treatment of malaria.[6]

FALCIPARUM MALARIA

To counter the threat of resistance of *P. falciparum* to monotherapies, and to improve treatment outcome, combinations of antimalarials are now recommended by the WHO for the treatment of *falciparum* malaria. Antimalarial combination therapy is the simultaneous use of two or more blood schizontocidal drugs with independent modes of action. Artemisin-based combination therapy (ACT) is the recommended treatment for uncomplicated *falciparum* malaria (Box 75.1). The choice of ACT in a country or region will be based on the level of resistance of the partner medicine in the combination.

Box 75.1 World health organization recommendations for treatment of uncomplicated *falciparum* malaria

Artesunate + amodiaquine

4 mg/kg of artesunate and 10 mg base/kg of amodiaquine given once a day for 3 days.

Artesunate + sulfadoxine–pyrimethamine

4 mg/kg of artesunate given once a day for 3 days and a single administration of sulfadoxine–pyrimethamine (25/1.25 mg base/kg BW) on day 1.

Artesunate + mefloquine

4 mg/kg of artesunate given once a day for 3 days and 25 mg base/kg of mefloquine usually split over 2 or 3 days.

Artemether–lumefantrine

Available as co-formulated tablets containing 20 mg of artemether and 120 mg of lumefantrine. The recommended treatment for persons weighing more than 34 kg is four tablets twice a day for 3 days.

Dihydroartemisinin + piperaquine

4 mg/kg per day of dihydroartemisinin and 18 mg/kg per day of piperaquine once a day for 3 days. The piperaquine dose in children weighing <25 kg should be at least 20 mg/kg per day

During the first trimester of pregnancy, quinine with clindamycin should be used. During the second and third trimesters ACT should be used. Tetracycline should be avoided in breast-feeding women. In HIV-infected patients, avoid artesunate + sulfadoxine–pyrimethamine if they are receiving co-trimoxazole, and avoid artesunate + amodiaquine if they are receiving efavirenz or zidovudine

Second-line antimalarial treatment (as per older WHO recommendation made in 2010)

Artesunate (2 mg/kg once a day) plus doxycycline (3.5 mg/kg once a day) or clindamycin (10 mg/kg twice a day) for 7 days.

Quinine plus tetracycline or doxycycline or clindamycin for 7 days.

ACT, Artemisin-based combination therapy; *BW*, body weight; *HIV*, human immunodeficiency virus.

Severe falciparum malaria

Two classes of drugs are currently available for the parenteral treatment of severe malaria: the cinchona alkaloids (quinine and quinidine) and the artemisinin derivatives (artesunate, artemether and artemotil). A recent Cochrane review showed that treatment with artesunate significantly reduced the risk of death both in adults (relative risk 0.61) and children (relative risk 0.76) as compared to quinine.[7] The dosage of artemisinin derivatives does not need adjustment in vital organ dysfunction. The WHO recommended regimens for severe *falciparum* malaria are listed below (Box 75.2).

In patients with features of severe malaria, a mixed infection with *falciparum* should be assumed even if only a benign species is identified in the film. If the clinical suspicion is high, a therapeutic trial of antimalarial treatment is justified even if the film is negative.

Severe malaria may lead to septic shock, and the principles of management are the same including resuscitation and provision of supportive treatment. These patients are at risk of acute lung injury but do need adequate fluid resuscitation. A major trial in children showed convincingly that bolus fluids lead to increased mortality. The relevance of this study for adults is not clear.[8] Patients with malaria and shock should also receive empirical antibiotic therapy after the collection of samples for cultures, as bacterial sepsis may co-exist, particularly so in

Box 75.2 World health organization recommendations for treatment of severe *falciparum* malaria

Artesunate

2.4 mg/kg IV or IM given on admission (time = 0), then at 12 h and 24 h, then once a day. Children weighing less than 20 kg should receive 3 mg/kg per dose. Artesunate is recommended in pregnant women in any of the trimesters, and in lactating women and infants.

Artemether or, less preferably, quinine, should be used if parenteral artesunate is not available: artemether 3.2 mg/kg BW IM given on admission then 1.6 mg/kg BW per day; or quinine 20 mg salt/kg BW on admission (IV infusion or divided IM injection), then 10 mg/kg BW every 8 h; infusion rate should not exceed 5 mg salt/kg BW per hour.

Give parenteral antimalarials in the treatment of severe malaria for a minimum of 24 h, once started (irrespective of the patient's ability to tolerate oral medication earlier), and, thereafter, once oral therapy is tolerated, complete treatment by giving a complete course of one of the regimens listed in Box 75.1.

BW, body weight; *IM*, intramuscularly; *IV*, intravenously.

children. Shock may also be due to complications such as severe metabolic acidosis, gastrointestinal (GI) bleed or splenic rupture. Convulsions must be actively treated. Complications should be managed as they present. The threshold for dialysis should be low.

Exchange transfusion has been used in severe malaria. It has been advocated for use in patients with high parasitaemia (>10%) in the presence of severe disease. It helps by removing infected red cells which may lead to organ dysfunction by sequestration in organs. Red cells with mature parasite forms are more likely to lead to sequestration. Quinine kills primarily mature parasites so immature parasites may still mature despite ongoing treatment leading to further sequestration; artesunate kills young parasite forms as well and it more rapidly lowers parasitaemia. Hence exchange transfusion is less likely to add to artesunate therapy. In fact, a recent meta-analysis did not find an association between exchange transfusion and survival outcome (odds ratio 0.84; 95% confidence interval [CI], 0.44–1.60).[9] Nevertheless, exchange transfusion may be considered as an adjunctive therapy in patients with persistent acidosis and/or multiorgan impairment unresponsive to first-line treatment. It may also be considered in children with sickle cell anaemia and severe malaria. Such use should be considered experimental.[10]

OTHER FORMS OF MALARIA (Box 75.3)

Box 75.3 World health organization recommendations for treatment of *vivax*, *ovale*, *malariae* and *knowlesi* malaria

Uncomplicated *vivax*, *ovale*, *malariae* and *knowlesi* malaria:

For chloroquine sensitive malaria, use ACT or chloroquine.

For chloroquine resistant malaria use ACT.

ACTs containing piperaquine, mefloquine or lumefantrine are recommended as sulfadoxine–pyrimethamine and amodiaquine are not effective against *Plasmodium vivax* in many places.

Chloroquine is safe during pregnancy. For chloroquine-resistant malaria during the first trimester of pregnancy, quinine should be used in place of ACT.

To prevent relapse in case of *vivax* or *ovale* malaria, primaquine should also be given in addition to ACT or chloroquine except in pregnant women, infants younger than 6 months, women breast-feeding children younger than 6 months and those with G6PD deficiency. The dose of primaquine is 0.25 mg base/kg, taken with food once daily for 14 days. In Oceania and Southeast Asia, the dose of primaquine should be 0.5 mg/kg.

The dose of chloroquine is 25 mg base/kg divided over 3 days.

Severe *vivax* or *knowlesi* malaria

Treat as for severe *falciparum* malaria.

ACT, Artemisin-based combination therapy.

PROGNOSIS

Data are largely derived from endemic areas where presentation with convulsions, acidosis or hypoglycaemia is associated with a poorer outcome. The mortality of severe malaria even with artesunate therapy is still high (24% in adults and 11% in children).[7] In cerebral malaria, mortality is around 20%. The prognosis of cerebral malaria frequently is determined by the management of other complications, such as renal failure and acidosis, but neurological sequelae are increasingly recognised.

TUBERCULOSIS

EPIDEMIOLOGY

Tuberculosis (TB) continues to be a devastating disease worldwide. *Mycobacterium tuberculosis* infects one-third of the world's population; each year about 10 million individuals develop active disease and 1.4 million die from the disease. Medical conditions that predispose to TB include HIV infection, silicosis, diabetes, chronic renal failure/haemodialysis, malnutrition, solid organ transplant, gastrectomy, jejunoileal bypass, injection and inhalational drug abuse, alcoholism, chronic pulmonary disease and prolonged steroid use. Social factors such as institutional living conditions (nursing homes, homeless shelters, prisons), urban dwelling and poverty are associated with an increased risk of TB.

PATHOGENESIS

TB is usually caused by *M. tuberculosis* and four others (*M. bovis, M. africanum, M. microti* and *M. canetti*) grouped in the *Mycobacterium* complex. The genus *Mycobacterium* consists of many different species all of which appear similar on acid-fast staining.

Inhalation of tubercle bacilli leads to one of four possible outcomes: immediate clearance of the organism, primary or progressive primary disease, chronic or latent infection, and reactivation disease. Latent infection refers to the presence of tuberculous infection (positive tuberculin reaction) without the disease.

The primary focus of infection is in the lungs which usually heal spontaneously. The primary infection is symptomatic in only 5%–10% of adults with a higher incidence in children and those with HIV infection. It may present with hilar lymphadenopathy or with progressive pneumonic consolidation. Limited lymphohaematogenous dissemination commonly occurs during primary infection and leads to silent seeding of multiple organs. These sites remain dormant (latent infection) but may become reactivated after a period of months to years. This is called secondary or reactivation TB. This is responsible for 90% of TB in patients not infected with HIV. Occasionally,

lymphohaematogenous seeding may lead directly to disseminated miliary and meningeal disease.

CLINICAL SPECTRUM

The manifestations of TB are protean, and TB should be considered in the differential diagnosis of all patients with fever of unknown origin, night sweats or unexplained weight loss. Besides the lungs, it can also involve central nervous system (CNS), peritoneum, pericardium, GI and genitourinary tract, bone and joints, lymph nodes and skin. Occasionally it can be disseminated in the form of miliary TB.

PULMONARY TUBERCULOSIS

Secondary pulmonary TB is usually seen in adults; it is usually due to reactivation but may be due to re-infection. It typically starts in the apex of one or both lungs as a small infiltrate that spreads progressively. Later caseation necrosis leads to cavitation surrounded by fibrosis. The caseous material liquefies and drains into the bronchus. Coughing generates infectious aerosol leading to spread within the lung via bronchial tree as well as to close contacts. Progressive spread can lead to severe disease with extensive bilateral lung involvement characterised by infiltration, cavitation and fibrosis. Rupture of a lesion into the pleura may lead to spontaneous pneumothorax. Clinically, the patient presents with insidious onset of non-specific symptoms such as fever, night sweats, anorexia, weight loss and malaise. A cough develops and haemoptysis may occur. Dyspnoea is seen with more extensive disease.

Sputum, induced sputum, bronchial washings and transbronchial biopsy of infiltrates should be performed to isolate the organism. Computed tomography (CT) is more sensitive than chest radiography for detection of infiltrates, cavities, lymphadenopathy, miliary disease, bronchiectasis, bronchial stenosis, bronchopleural fistula and pleural effusion.

Tuberculous pleural effusion

Pleural TB may result in pleural effusion, or pleural empyema with or without bronchopleural fistula. Thoracentesis should be performed. The pleural fluid should be examined for total protein and glucose content, white blood cell count and differential count, and fluid pH. Positive fluid cultures are found in less than 25% of cases. Pleural fluid adenosine deaminase (ADA) levels more than 70/L strongly favour tuberculous aetiology, and levels less than 40 U/L make it less likely. In populations with a high prevalence of TB and clinical suspicion, an elevated ADA level might be considered as a confirmatory test justifying treatment initiation.[11] If the ADA level is more than 70 U/L and the lymphocyte percentage in the fluid is more than 75%, the diagnosis is virtually certain and pleural biopsy may not be needed.[12] In low prevalence countries, pleural biopsy may be required if diagnosis is doubtful. Pleural biopsy shows granulomatous inflammation in approximately 60% of patients, and culture may be positive even in those without granulomas. When culture of three biopsy specimens is combined with histologic examination, the diagnosis can be made in up to 90% of cases. Pleuroscopy-guided biopsies increase the yield in pleural sampling. Nucleic acid amplification tests have high specificity but low and variable sensitivity.

TUBERCULOUS MENINGITIS

Tuberculous meningitis[13] remains the most serious manifestation of TB for the intensive care physician. It results from haematogenous spread. Pathologically there is a thick gelatinous exudate around the sylvian fissures, basal cisterns, brainstem and cerebellum. Classically it presents as a subacute meningitic illness. The majority of patients with TB meningitis have had recent contact with infectious TB particularly during the preceding 12 months. A prodrome of vague ill-health lasting 2–8 weeks is commonly seen followed by signs and symptoms of meningeal irritation. Occasionally TB meningitis may present acutely without a prodromal period. Neck stiffness is usually absent during early disease.

Cranial nerve palsies occur in 20%–25% of patients, and papilledema may be present. Choroidal tubercles are rare but almost pathognomonic. Visual loss due to optic nerve involvement may occasionally be the presenting feature. There may be focal neurological deficit such as hemiplegia; extrapyramidal movements and seizures are other manifestations. As the disease progresses, cerebral dysfunction sets in and the mortality approaches 50%.

Both a diagnostic algorithm[14] and consensus case definition[15] have been published. The key is a high degree of clinical suspicion especially in the critically ill.

Definitive diagnosis of TB meningitis depends upon the detection of the organism in the CSF, either by smear examination or by bacterial culture. The yield from smear is variable, but generally low. The sensitivity of CSF culture is 60%–70% in adults and is considerably lower in children.[16] The sensitivity of smear and culture may be increased by using the centrifuged deposit from relatively large volume of CSF. Given the need for urgent diagnosis, Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test for CSF specimens. This test is discussed in a later section.

CT or magnetic resonance imaging of the brain, which are sensitive but not specific, may reveal thickening and intense enhancement of meninges, especially in basilar regions. Hydrocephalus and tuberculomas may also be present. Infarcts due to either vasculitis or mechanical strangulation of the vessels by the surrounding exudates are detected in up to 40%. The radiological differential diagnosis includes cryptococcal

meningitis, cytomegalovirus encephalitis, sarcoidosis, meningeal metastases and lymphoma.

TUBERCULOUS EMERGENCIES

- Massive haemoptysis
- Respiratory failure
- Pericardial tamponade
- Small intestinal obstruction
- Tuberculous meningitis
- Status epilepsy due to tuberculomas

DIAGNOSIS OF TUBERCULOSIS

Once considered, isolate the patient and sample all potential sites for acid-fast staining and culture. Pleural, peritoneal, pericardial and other fluids must be cultured and analysed for differential cell count, protein, glucose and ADA.

Histological examination for granulomatous infection is useful in bronchial tissue, pleural, peritoneal and skeletal tissues. Peritoneal biopsies are best obtained via laparoscopy. Newer culture media have reduced the time for culture to 2 weeks.

Nucleic acid amplification (NAA) tests amplify target nucleic acid regions that uniquely identify the *M. tuberculosis* complex, and are available as commercial kits or in-house assays. A sensitive and specific fully automated and commercially available NAA Xpert MTB/RIF assay (Cepheid, Sunnyvale, California) can produce results in less than 2 hours permitting a specific TB diagnosis and rapidly detect rifampicin resistance. However, NAA tests cannot entirely replace conventional diagnostic approaches using microscopy and culture.

For Xpert MTB/RIF as an initial test replacing smear microscopy, a Cochrane review reported a pooled sensitivity of 89% and pooled specificity of 99%. In sputum smear negative specimens, the pooled sensitivity was lower at 67%; for people with HIV infection, the pooled sensitivity was 79%.[17]

Its performance in extrapulmonary TB is inferior and varies with sample type.[18] In CSF, Xpert's pooled sensitivity was 80.5% (95% CI, 59.0%–92.2%) against culture and 62.8% (95% CI, 47.7%–75.8%) against a composite reference standard (CRS). The pooled sensitivities were somewhat better with lymph node tissue or aspirate and significantly lower with pleural fluid. The pooled specificity was consistently over 98.7% against CRS across different sample types.

The current status of NAA tests is summarised below:

- NAA tests, in general, have high specificity and positive predictive value; they are useful in ruling in rather than ruling out TB. Resources permitting, the WHO recommends usage of Xpert MTB/RIF as the initial diagnostic test in sputum, CSF, lymph nodes and other tissues but not for blood, urine or stool.[19]
- A positive NAA test in smear-positive patients can differentiate *M. tuberculosis* from non-tuberculous mycobacteria (NTM); treatment can then be started.
- The interpretation of smear-positive but negative NAA test is controversial.
- In smear-negative and NAA-positive patients with a high clinical suspicion treatment can be started, particularly when prompt treatment is imperative.
- If clinical suspicion is high, TB is not excluded by both a negative smear and NAA.
- NAA results may remain positive for months. This method should be used only for initial diagnosis and not follow-up.

Serological tests are not recommended for the diagnosis of TB but highly specific tests are currently under development. The tuberculin skin test (TST) and interferon gamma release assays (IGRAs) assess cell-mediated immune response to tubercle bacillus. IGRAs are at least as sensitive as and more specific than TST as the latter test is also positive in those infected with NTM and those who have been vaccinated with BCG (Bacillus Calmette-Guerin). They indicate infection with tubercle bacillus but cannot differentiate between active disease and latent infection. They are primarily used in the diagnosis of latent infection as sensitivities and specificities are not high enough to confirm or rule out active disease.

Drug susceptibility tests should be performed on initial isolates from all patients in order to identify an effective antituberculous regimen, and may have to be repeated if the patient remains culture positive after 3 months.

TREATMENT OF TUBERCULOSIS

Local guidelines are of paramount importance and advice should be sought.[20] The commonest regimen used is isoniazid (5 mg/kg), rifampicin (10 mg/kg) pyrazinamide (1000–2000 mg daily depending upon body weight) and ethambutol (800–1600 mg depending upon the body weight) for the first 2 months and isoniazid and rifampicin for the next 4 months. Steroids are generally recommended in tuberculous meningitis and pericardial TB.

DRUG RESISTANT TUBERCULOSIS

This is an increasing problem. Multidrug-resistant TB (defined as resistance to two or more of the first-line antituberculous drugs, usually isoniazid and rifampicin) can be primary (no prior antituberculous therapy) or secondary (development of resistance during or after chemotherapy). Extensively drug-resistant (XDR) TB, defined by additional resistance to one of the fluoroquinolones and one of the injectable drugs, is more difficult to treat and may be incurable.

Diagnosis depends upon the collection of adequate specimens for culture prior to the initiation of antituberculous therapy. In critically ill patients, rapid

diagnosis of drug resistance is of paramount importance. With the improvements in the culture methods and the availability of newer techniques, rapid identification of resistance is possible. When resistance is present to two or more first-line agents, multiple drugs including parenteral aminoglycoside (streptomycin, amikacin, etc.) and fluoroquinolones are generally added.[21] Specialist microbiological advice should be sought.

TYPHOID FEVER

Typhoid fever is caused by *Salmonella typhi* and less commonly by paratyphi A, B and C. Even non-typhoidal salmonellae have occasionally been isolated.[22] Typhoid fever, common in South and Southeast Asia, is almost exclusively caused by faecal-oral spread. In the developed world, cases either are seen in international travellers or are occasionally caused by infected food.

CLINICAL FEATURES

The incubation period is 5–21 days. Typhoid presents non-specifically with fever, chills, abdominal pain and constitutional symptoms. Constipation may be more frequent than diarrhoea. Hepatosplenomegaly, erythematous macular rash (30%) and relative bradycardia, which is a non-specific but useful clue,[23] may be present.

COMPLICATIONS

- Shock
- Intestinal perforation
- GI haemorrhage
- Jaundice and encephalopathy[24]
- Neuropsychiatric manifestations
- Septic arthritis, pericarditis
- Obstetric complications in pregnant women.

DIAGNOSIS

Anaemia, leukopenia and deranged liver function are common.[25] Leukocytosis may occur and is more common in children. Blood cultures are positive in up to 60% of cases,[26] and are the investigation of choice; 10–15 mL yields higher success than smaller volumes.[27] Though culturing urine, stool, rose spots and duodenal contents are useful, bone marrow culture is the most sensitive, and its yield remains unchanged up to 5 days after commencement of treatment.

Serodiagnosis using Widal tests has limited clinical value. Commercial serological tests, such as Typhidot-M, and Tubex, which detect immunoglobulin (Ig)M antibodies against different *S. typhi* antigens, have a higher sensitivity and specificity.[28] Nested PCR is very promising in the diagnosis of typhoid fever.

TREATMENT

For uncomplicated typhoid fever, fluoroquinolones are the drug of choice.[29] There is some concern in using fluoroquinolones in children as they have been shown to cause cartilage toxicity in immature animals, but this appears largely unfounded in clinical trials.[30] Azithromycin, cefixime or ceftriaxone should be used for infections acquired in South Asia or other areas with a high risk of reduced susceptibility to fluoroquinolones. For severe typhoid fever, ceftriaxone is the drug of choice. A parenteral fluoroquinolone is also an appropriate alternative if infection has been acquired in regions where reduced susceptibility to quinolones is not a concern. The duration of therapy is 7 days for azithromycin, 7–14 days for fluoroquinolones and 10–14 days for cephalosporins.

Dexamethasone reduces mortality in severe typhoid fever: delirium, obtundation, stupor, coma or shock.[31] Intestinal, especially ileal, perforation – which may occur classically in the third week of febrile illness – requires prompt surgical intervention.[32]

CHOLERA

Cholera is caused by enterotoxin producing *Vibrio cholera*.[33] The incubation period varies from 12 hours to several days. The clinical case: infection ratio is about 1:10. It starts abruptly with painless watery diarrhoea associated with vomiting and painful muscle cramps. Vomiting may be the first symptom before diarrhoea. Stool output can reach as high as 1 L/h in the most severe cases. Typically, fever is absent.

Stool examination shows neither leukocytes nor erythrocytes. Dark field microscopy examination may reveal rapidly motile comma-shaped bacilli in fresh stool. Commercial assays detecting O antigen in stool samples, which take less than 5 minutes, are now available and are as sensitive and specific as stool culture. Aggressive rehydration is the mainstay of treatment; very large quantities of fluid may be needed. Adjunctive antimicrobial therapy is effective in shortening the duration of diarrhoea. A recent Cochrane review concluded azithromycin and tetracycline may have some advantages over other antibiotics.[34]

LEPTOSPIROSIS

This is caused by *Leptospira interrogans*. It occurs due to exposure to contaminated water. The disease has an incubation period of 7–10 days with a range of 2–20 days. It has two phases: a septicaemic phase and an immune phase. Clinical features include conjunctival suffusion or haemorrhages (useful diagnostic clue), uveitis, severe muscle tenderness, non-oliguric renal failure, hypokalaemia, hepatic dysfunction, pulmonary haemorrhage, acute respiratory distress syndrome

(ARDS), myocarditis, rhabdomyolysis, thrombocytopenia, disseminated intravascular coagulation (DIC), haemorrhage into the skin and internal organs, and digital gangrene. Weil syndrome is characterised by hepatorenal dysfunction, bleeding diathesis and pulmonary involvement.

Diagnosis is made with isolation of the organism by culture (blood, urine, CSF) or serology using the gold standard microscopic agglutination test (MAT). Alternative serology tests including enzyme-linked immunosorbent assay (ELISA) tests are available. Both culture and serology should be attempted if available, and local microbiological advice should be sought. Treatment is with penicillin G or ceftriaxone. In penicillin-allergic patients, doxycycline can be used.

DENGUE FEVER

EPIDEMIOLOGY AND PATHOGENESIS

It is estimated that 50 million cases of dengue fever (DF) occur worldwide annually and half a million people suffering from dengue haemorrhagic fever (DHF) require hospitalisation each year, a very large proportion of whom (approximately 90%) are children younger than 5 years old.[35] The causative agent is a flavivirus with four distinct serogroups, which is transmitted by the bite of Aedes mosquitoes. Two patterns of transmission have been recognised: (1) epidemic due to isolated introduction of dengue to a region, usually due to a single serotype; and (2) hyperendemic referring to the continuous circulation of multiple dengue virus serotypes.

Following a mosquito bite, viremia begins and usually lasts up to 7 days. Infection with one of the four serotypes (primary infection) provides life-long immunity against that serotype but not against the other serotypes (secondary infection). Epidemiological studies have suggested that the risk of severe disease (DHF/dengue shock syndrome [DSS]) is significantly higher in secondary infection than primary infection.

CLINICAL FEATURES

Dengue virus infection may be asymptomatic or may cause undifferentiated febrile illness (viral syndrome), DF or DHF, including DSS.[36]

DF has an incubation period of 3–14 days and is characterised by the sudden onset of fever, severe headache, retro-orbital pain on moving the eyes, and fatigue. The fever usually lasts for 2–7 days. It is often associated with severe myalgia and arthralgia (breakbone fever). Maculopapular rash, flushed facies and injected conjunctiva are common. Haemorrhagic manifestations can occur in DF and do not necessarily mean DHF.

DHF occurs primarily in children younger than 10 years old and is characterised by plasma leakage syndrome as evidenced by haemoconcentration (20% or greater rise in haematocrit), pleural effusion or ascites. The diagnosis is made if all of the following symptoms and signs are present: bleeding or positive tourniquet test, a platelet count of less than 100,000 per cubic millimetre, and plasma leakage. Haemorrhagic manifestations without evidence of plasma leakage do not constitute DHF. The mechanism underlying the profound capillary leak in DHF but not in DF is poorly understood. It is important to watch for the onset of DHF, which typically occurs 4–7 days after the onset of the disease, approximately at the time of defervescence. A decrease in the platelet count and a rise in haematocrit are useful clues.[36]

DSS is characterised by profound hypotension and shock.

Due to the limitations of the 1997 WHO classification, a new classification was adopted by them in 2009[37]:

- Dengue without warning signs
- Dengue with warning signs
- Severe dengue

Warning signs include any one of abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy; restlessness, liver enlargement greater than 2 cm, laboratory: an increase in haematocrit, concurrent with a rapid decrease in platelet count.

Criteria for severe dengue include any one of:

1. Severe plasma leakage leading to shock (DSS) or fluid accumulation with respiratory distress
2. Severe bleeding as evaluated by the clinician
3. Severe organ involvement (any) such as liver (aspartate aminotransferase [AST] or alanine aminotransferase ≥ 1000), CNS (impaired consciousness), heart and other organs referred to as expanded dengue syndrome.

DIAGNOSIS

Dengue should be suspected in all febrile patients who live in, or have returned from, endemic areas in the preceding 2 weeks. Leukopenia, thrombocytopenia with a positive tourniquet test, and raised AST are frequently seen; the former two tests have the highest sensitivity (about 90%) for the diagnosis of early dengue.[36] A positive tourniquet test alone cannot differentiate DHF from DF.

IgM immunoassay allows rapid confirmation of the diagnosis. If it is negative, particularly in the first 6 days of the illness, the diagnosis should not be ruled out. Acute and convalescent sera should be analysed by immunoassay or haemagglutination assay to demonstrate seroconversion or a fourfold rise in titre.

Virus isolation, viral nucleic acid detection by techniques such as reverse transcriptase PCR and viral antigen detection are the other diagnostic tests available. The dengue NS1 antigen test has a high specificity (93%–100%). It is very useful for early diagnosis before

the antibodies become positive. Sensitivity is highest on day 1 of the illness and declines gradually over time, and is 45%–57% at the time of hospital admission.[38]

TREATMENT

Supportive therapy for shock, especially appropriate and prompt fluid replacement, can reduce mortality. Fluid management is complex and WHO guidelines are available.[39] In DSS, steroids have not been shown to be useful. Once capillary leakage abates, fluid overload and pulmonary oedema can become problematic.

HANTAVIRUS

Hantaviruses[40] are rodent viruses distributed worldwide, with over 150,000 cases being registered annually. There are two major clinical syndromes: haemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS). Both are typically acquired by exposure to aerosols of rodent excreta.

HANTAVIRUS CARDIOPULMONARY SYNDROME

The incubation period is about 3 weeks. There are two phases: (1) the prodromal phase is characterised by a relatively mild febrile illness, typically lasting 3–5 days; and (2) the cardiopulmonary phase, which is characterised by severe, rapidly progressive respiratory failure. In the latter phase, acute pulmonary oedema due to increased capillary permeability occurs. The progress from the prodromal phase to the cardiopulmonary phase is dramatic. In severe cases, significant myocardial depression also occurs, resulting in low cardiac output and hypotension. Acute renal failure can occur. The combination of thrombocytopenia, myelocytosis, haemoconcentration, lack of significant toxic granulation in neutrophils and immunoblastic morphology of more than 10% of the lymphocytes is highly sensitive and specific. ELISA for IgM and IgG antibodies is useful in the diagnosis. The hantavirus infection can also be confirmed by detection of hantavirus genome in blood or serum samples by reverse transcription (RT)-PCR. Treatment is mainly supportive with mechanical ventilation, early use of vasopressors, and careful administration of intravenous fluids and blood products. Because shock in HCPS is cardiogenic rather than distributive in nature, the lack of improvement in response to a fluid challenge is characteristic of HCPS. Mortality rates are estimated to be as high as 60% in HCPS and 12% in HFRS and extracorporeal membrane oxygenation may be effective.[41]

HAEMORRHAGIC FEVER WITH RENAL SYNDROME

This is characterised by fever, renal failure and haemorrhagic manifestations. The disease has five progressive stages: febrile, hypotensive, oliguric, diuretic and convalescent. Non-specific constitutional symptoms are followed by shock, oliguria, DIC and haemorrhagic manifestations. Diagnosis is made using ELISA for IgG and IgM antibodies. Treatment is supportive including renal support. Ribavirin has been found to be useful.

ARBOVIRAL ENCEPHALITIS

Viruses transmitted to human beings by the bites of arthropods (especially mosquitoes and ticks) are major causes of encephalitis worldwide. Although different viruses can cause encephalitis, an antigenically related group of flaviviruses[42] accounts for a major proportion of cases worldwide. These include mosquito-borne diseases such as Japanese encephalitis, West Nile virus encephalitis, St. Louis encephalitis, Murray Valley encephalitis[43] and tick-borne encephalitis.[44] Viral encephalitis is characterised by a triad of fever, headache and an altered level of consciousness. Other common clinical findings include disorientation, behavioural and speech disturbances, and focal or diffuse neurological signs such as hemiparesis or seizures. The incubation period is usually 5–15 days. Other manifestations include recurrent seizures, including status epilepticus, a flaccid paralysis resembling that of poliomyelitis, and Parkinsonian-type movement disorders. Flavivirus encephalitis is diagnosed usually by the IgM capture ELISA. Treatment is supportive. Interferon-α, ribavirin and intravenous Ig have all been tried with mixed success.

VIRAL HAEMORRHAGIC FEVERS (VHFs)

VHF is a general term for a severe illness, sometimes associated with bleeding, caused by a number of viruses.

EPIDEMIOLOGY

Lassa virus, Rift Valley fever, Crimean-Congo haemorrhagic fever (CCHF), HFRS, Marburg and Ebola virus disease, yellow fever and DHF are some of the most important VHFs. An Ebola epidemic started in 2014 in West Africa. Haemorrhagic fever viruses have an affinity for the vascular system and increased vascular permeability is the primary defect. Petechial haemorrhages are usually associated with fever and myalgias. Later, frank mucous membrane haemorrhage may occur, with accompanying hypotension, shock and circulatory collapse. Multisystem organ failure can occur. There is a wide variation in the relative severity of the clinical presentation.

The source of infection is rodent for the Lassa virus and the hantavirus, mosquito for Rift Valley fever,

yellow fever and DHF, and tick for the CCHF virus. At least four of the haemorrhagic fevers, Lassa fever (LF), Ebola virus, Marburg virus and CCHF are capable of person-to-person transmission through close contact with infected blood and other body secretions. Epidemiological studies of VHF in humans indicate that although possible, the airborne route does not readily transmit infection from person to person.

CLINICAL FEATURES

The patient will have either been in an endemic area or been in contact with someone from an endemic area.

VHFs generally have an abrupt onset with an incubation period less than 10 days. The incubation period can be up to 21 days. They present as acute febrile illnesses with a prodrome that often includes severe headache, dizziness, flushing, conjunctival injection, myalgia, lumbar pain and prostration. GI symptoms with nausea, vomiting, abdominal pain and diarrhoea may occur.

Leukopenia or leukocytosis, thrombocytopenia and elevated serum aminotransferases may be evident early in the disease; a petechial rash may appear on days 3–10. Coagulation profiles become progressively more abnormal, and overt haemorrhagic features of the disease (ecchymoses, epistaxis, gingival bleeding, malaena, and haematuria) may supervene from day 5 onward, or sometimes even earlier. Multiple organ failure supervenes and death may ensue. Clinical improvement becomes apparent toward the end of the second week of illness in patients who survive.

DIAGNOSIS

A high index of suspicion is needed and VHF should be suspected in the following circumstances:

- Unexplained fever in patients who have visited areas where VHF is endemic within 3 weeks of becoming ill. The likelihood is greater if they have camped in the bush, slept on the ground or in rural farms, or had any bites or contact with sick animals.
- Febrile medical and nursing staff in the endemic areas and laboratory workers who handle VHF viruses.
- Febrile contacts.

Tests on samples present an extreme biohazard risk. Diagnosis is mainly based on direct detection of viral antigens or viral RNA in blood or other body fluids through immunoassays or RT-PCR.[45] Serological tests have several limitations and are not very useful for diagnosing VHF in the acute phase

TREATMENT

Therapy is essentially supportive for a severe shock state. Haemorrhage is managed by replacement of blood, platelets and clotting factors as indicated. Ribavirin is useful in treating LF, and in CCHF. Ribavirin may reduce mortality by 10-fold if treatment is begun within 6 days of onset. Other treatment options are post-exposure vaccination.

PRECAUTIONS

These diseases must be notified immediately. In addition to universal blood and body fluid precautions, airborne isolation – including the use of goggles, high-efficiency masks, a negative-pressure room with no air circulation and positive-pressure filtered air respirators – has been recommended, as is surveillance of contacts. If applicable, to prevent further mosquito transmission, patients should be isolated in well-screened rooms sprayed with residual insecticides. Guidelines on infection control in the management of highly pathogenic infectious diseases have been published.[46]

RICKETTSIAL INFECTIONS

Rickettsial infections require early diagnosis and treatment to prevent severe outcomes. Scrub typhus, murine typhus, and to an uncertain extent spotted fever rickettsiosis (*Rickettsia conorii, Rickettsia africae*, etc.) are important treatable causes of undifferentiated febrile illness in the tropics and among travellers.[47] Scrub typhus is widespread in the Indian subcontinent and Southeast Asia. Murine typhus has a worldwide distribution: Africa, Southeast Asia and South Asia are the common sites of disease acquisition in the returning traveller. *R. conorii* causes Mediterranean spotted fever or boutonneuse fever. It also occurs in the Indian subcontinent. *R. africae* causes African tick typhus or African tick bite fever seen in Sub-Saharan Africa. Rickettsial infections present with fever, headache and myalgia. Rash is common and is usually maculopapular. An inoculation site eschar is characteristic. Eschar is absent in murine typhus but may be multiple in African tick typhus. GI and respiratory symptoms, meningoencephalitis, hepatomegaly and splenomegaly, and localised or generalised lymphadenopathy may occur. Multiorgan dysfunction, including ARDS, may develop in severe cases especially if treatment is delayed. Leukopenia or leucocytosis may occur, while thrombocytopenia and elevated transaminase levels are common. CSF may show lymphocytic pleocytosis and elevated protein. Diagnosis is suspected on clinical grounds and a dramatic response to doxycycline or azithromycin is a strong pointer. Beta-lactams and quinolones are ineffective in rickettsial infections. Diagnosis may be confirmed by antibody detection or PCR in specialised laboratories.

REFERENCES

1. Cramer JP. *Plasmodium knowlesi* malaria: overview focussing on travel-associated infections. *Curr Infect Dis Rep*. 2015;17:469.

2. WHO. *Management of Severe Malaria. A Practical Handbook*. 3rd ed. Geneva: WHO; 2012.
3. Idro R, Jenkins NE, Newton CJRC. Pathogenesis, clinical features, and neurological outcome of cerebral malaria. *Lancet Neurol*. 2005;4:827–840.
4. De Monbrison F, Gerome P, Chaulet JF, et al. Comparative diagnostic performance of two commercial rapid tests for malaria in a non-endemic area. *Eur J Clin Microbiol Infect Dis*. 2004;23: 784–786.
5. Stauffer WM, Cartwright CP, Olson DA, et al. Diagnostic performance of rapid diagnostic tests versus blood smears for malaria in US clinical practice. *Clin Infect Dis*. 2009;49:908–913.
6. WHO. *Guidelines for the Treatment of Malaria*. 3rd ed. Geneva: WHO; 2012. Online. Available: http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf.
7. Sinclair D, Donegan S, Isba R, et al. Artesunate versus quinine for treating severe malaria. *Cochrane Database Syst Rev*. 2012;(6):CD005967.
8. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med*. 2011;364:2483–2495.
9. Tan KR, Wiegand RE, Arguin PM. Exchange transfusion for severe malaria: evidence base and literature review. *Clin Infect Dis*. 2013;57:923–928.
10. The World Health Organization, The Medicines for Malaria Venture, Roll Back Malaria and The Wellcome Trust. Severe malaria. *Trop Med Int Health*. 2014;19(suppl 1):7–131.
11. Vorster MV, Allwood B, Diacon A, et al. Tuberculous pleural effusions: advances and controversies. *J Thorac Dis*. 2015;7(6):981–991.
12. Light RW. Update on tuberculous pleural effusion. *Respirology*. 2010;15:451–458.
13. Török ME. Tuberculous meningitis: advances in diagnosis and treatment. *Br Med Bull*. 2015;113: 117–131.
14. Thwaites GE, Chau TT, Stepniewska K, et al. Diagnosis of adult tuberculous meningitis by use of clinical and laboratory features. *Lancet*. 2002;360: 1287–1292.
15. Marais S, Thwaites G, Schoeman JF, et al. Tuberculous meningitis: a uniform case definition for use in clinical research. *Lancet Infect Dis*. 2010;10: 803–812.
16. Ho J, Marais BJ, Gilbert GL, et al. Diagnosing tuberculous meningitis – have we made any progress? *Trop Med Int Health*. 2013;18:783–793.
17. Steingart KR, Schiller I, Horne DJ, et al. Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev*. 2014;(1):CD009593.
18. Denkinger CM, Schumacher SG, Boehme CC, et al. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *Eur Respir J*. 2014;44:435–446.
19. WHO. *Xpert MTB/RIF Implementation Manual: Technical and Operational 'How-to'; Practical Considerations*. Geneva: WHO; 2014. Online. Available: http://www.who.int/tb/publications/xpert_implem_manual/en/.
20. Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis*. 2016;63:e147–e195.
21. WHO. *WHO Treatment Guidelines for Drug Resistant Tuberculosis*. Update. Geneva: WHO; 2016. Online. Available: http://apps.who.int/iris/bitstream/10665/250125/1/9789241549639-eng.pdf?ua=1.
22. Obeogbulam SI, Oguike JU, Gugnani HC. Microbiological studies on cases diagnosed as typhoid/enteric fever in Nigeria. *J Commun Dis*. 1997;27:97–100.
23. Ostergaard L, Huniche B, Anderson PL. Relative bradycardia in infectious diseases. *J Infect*. 1996; 33:185–191.
24. Anand AC, Garg HK. Approach to clinical syndrome of jaundice and encephalopathy in tropics. *J Clin Exp Hepatol*. 2015;5(suppl 1):S116–S130.
25. Bhutta ZA. Current concepts in the diagnosis and treatment of typhoid fever. *BMJ*. 2006;333(7558):78–82.
26. Mogasale V, Ramani E, Mogasale VV. What proportion of *Salmonella typhi* cases are detected by blood culture? A systematic literature review. *Ann Clin Microbiol Antimicrob*. 2016;15:32.
27. Bhan MK, Bahl R, Bhatnagar S. Typhoid and paratyphoid fever. *Lancet*. 2005;366:749–762.
28. Olsen SJ, Pruckler J, Bibb W, et al. Evaluation of rapid diagnostic tests for typhoid fever. *J Clin Microbiol*. 2004;42:1885–1889.
29. WHO. *The Diagnosis, Treatment, and Prevention of Typhoid Fever. Background Document*. Geneva: WHO; 2003. Online. Available: http://www.who.int/rpc/TFGuideWHO.pdf.
30. Forsythe CT, Ernst ME. Do fluoroquinolones commonly cause arthropathy in children? *CJEM*. 2007;9:459–462.
31. Hoffman SL, Punjabi NH, Kumala S, et al. Reduction of mortality in chloramphenicol-treated severe typhoid fever by high-dose dexamethasone. *N Engl J Med*. 1984;310:82–88.
32. Ukwenya AY, Ahmed A, Garba ES. Progress in management of typhoid perforation. *Ann Afr Med*. 2011;10:259–265.
33. Harris JB, LaRocque RC, Qadri F, et al. Cholera. *Lancet*. 2012;379(9835):2466–2476.
34. Leibovici-Weissman Y, Neuberger A, Bitterman R, et al. Antimicrobial drugs for treating cholera. *Cochrane Database Syst Rev*. 2014;(6):CD008625, doi:10.1002/14651858.CD008625.
35. WHO. *Comprehensive Guidelines for Prevention and Control of Dengue and Dengue Haemorrhagic Fever*. Geneva: WHO; 2011. Online. Available: http://www.searo.who.int/entity/vector_borne_tropical_diseases/documents/SEAROTPS60/en/.
36. Wilder-Smith A, Schwartz E. Dengue in travelers. *N Engl J Med*. 2005;353:924–932.

37. WHO. *Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control*. Geneva: WHO; 2009. Online. Available: http://www.who.int/tdr/publications/documents/dengue-diagnosis.pdf?ua=1.
38. Blacksell SD, Jarman RG, Gibbons RV, et al. Comparison of seven commercial antigen and antibody enzyme-linked immunosorbent assays for detection of acute dengue infection. *Clin Vaccine Immunol*. 2012;19:804–810.
39. WHO. *Handbook for Clinical Management of Dengue*. Geneva: WHO; 2012:2012. Online. Available: http://www.who.int/denguecontrol/9789241504713/en/.
40. Avšič-Županc T, Saksida A, Korva M. Hantavirus infections. *Clin Microbiol Infect*. 2015;S1198-743X(15):00536–4.
41. Hartline J, Mierek C, Knutson T, et al. Hantavirus infection in North America: a clinical review. *Am J Emerg Med*. 2013;31:978–982.
42. Gould EA, Solomon T. Pathogenic flaviviruses. *Lancet*. 2008;371(9611):500–509.
43. Solomon T. Flavivirus encephalitis. *N Engl J Med*. 2004;351:370–378.
44. Lindquist L, Vapalahti O. Tick-borne encephalitis. *Lancet*. 2008;371(9627):1861–1871.
45. Racsa LD, Kraft CS, Olinger GG, et al. Viral hemorrhagic fever diagnostics. *Clin Infect Dis*. 2016;62:214–219.
46. WHO. *Infection Prevention and Control Guidance for Care of Patients in Health-Care Settings, with Focus on Ebola. Interim Guidance*. Geneva: WHO; 2014. Online. Available: http://www.who.int/csr/resources/publications/ebola/filovirus_infection_control/en/.
47. Paris DH, Dumler JS. State of the art of diagnosis of rickettsial diseases: the use of blood specimens for diagnosis of scrub typhus, spotted fever group rickettsiosis, and murine typhus. *Curr Opin Infect Dis*. 2016;29:433–439.

Part Eleven

Severe and Multiple Trauma

This page intentionally left blank

76

Severe and multiple injuries

Li C Hsee

Trauma can be defined as physical injury from mechanical energy. It is usually categorised as blunt or penetrating. In Western countries, severe blunt trauma is common, caused by road crashes, falls and, less frequently, blows and assaults. Severe penetrating trauma, usually from stabbings and gunshots, is less common except in larger cities of the United States,[1,2] South Africa and war zones. Blunt injuries are frequently internal, multiple and not obvious initially. The severity of penetrating injury depends on its trajectory and the force of energy involved. The risk of missing serious injuries can only be lessened by a systematic approach and repeated assessments.[3–5]

ASSESSMENT AND PRIORITIES

TRIAGE

An important first step is triage – sorting patients with acute life-threatening injuries and complications from those whose lives are not in danger. Depending on the complexity of injury, it is important to ensure resources are available for treatment. If institutional capacity is lacking, consider transferring the patient to an advanced trauma unit. The severity of total body injury is related to the number of separate injuries present, and to the severity of individual injuries. Assessment can be made either at the scene of injury or on arrival at hospital. As in any emergency, assessment, diagnosis and treatment need to be concurrent. There is limited time for detailed histories, examinations, investigations or well-considered diagnoses before starting emergency care.

RECOGNITION OF SEVERITY

Most patients with severe injury can be distinguished early by the following:

- *Signs of shock:* shock is almost always hypovolaemic from blood loss, but other types of shock occasionally occur in trauma.
- *Depressed consciousness:* in the trauma patient, depressed consciousness can be related to brain injury, hypoxaemia, shock, alcohol or other ingested drugs, or precipitating neurological or cardiac events. Frequently, a combination of factors is present, and the precise extent of physical brain injury is not initially known. Initial treatment is, in any case, determined by the level of consciousness rather than its exact cause.
- *Breathing difficulty:* this is common in patients with trauma to the head, face, neck and chest. If rapid or distressed breathing is present then airway obstruction, laryngeal injury, pulmonary aspiration and lung or chest wall injury (especially pneumothorax and lung contusion) must be considered.

PRIORITIES

A trauma patient often has multiple problems requiring attention. Determining priorities is not always easy. In general, the priorities are to:

- *support life:* the patient is kept alive with resuscitative techniques, while the various injuries and complications are attended to
- *locate and control bleeding*, which may be varied
- *prevent brainstem compression* and spinal cord damage
- *diagnose and treat* all other injuries and complications.

BASIC TREATMENT PRINCIPLES

A systematic approach to managing severe and multiple trauma is important. Effective programmes developed by the American College of Surgeons are now well established.[6] A number of basic treatment principles apply to all severe trauma patients.

EMERGENCY ASSESSMENT (PRIMARY SURVEY)

While airway, breathing, circulation (ABC) management is traditionally followed, battlefield trauma is managed using a <C>ABC approach, where <C> refers to the management of catastrophic external bleeding. The treatment priorities are as follows:

- <C> – *Catastrophic bleeding:* life-threatening external haemorrhage should be dealt with rapidly using the

ABSTRACT

The management of severe and multiple trauma requires a team approach. These patients are often critical with life-threatening injuries. In order to optimise outcomes, the patient must be evaluated in a systematic manner. This chapter highlights the key systems required for evaluation. They include assessment and priorities, primary and secondary surveys and resuscitation principles. The use of radiological evaluation in trauma is described. In this chapter, topics such as damage control resuscitation and massive transfusion protocols have been updated and emphasised. The severity and morbidity of trauma measurement tools such as Injury Severity Scores (ISS) and Abbreviated Injury Scales (AIS) are presented. Finally, emphasis is given to the organisation of trauma care to reduce the morbidity and mortality.

KEYWORDS

Initial assessment
triage
priorities
damage control resuscitation
massive transfusion protocol

field-dressing, tourniquet and topical haemostatic agents. Following management, or in the absence of catastrophic external bleeding, the ABC approach should be followed.

- *A – Airway obstruction:* is suggested by noisy (or silent) breathing, with paradoxical chest movements and breathing distress, and inadequate airway protection from impaired gag reflexes in patients with depressed consciousness. Airway obstruction should be managed with cervical spine protection.
- *B – Breathing difficulty:* is suggested by tachypnoea, abnormal pattern of breathing, cyanosis or mental confusion.
- *C – Circulatory shock:* is manifested by cold peripheries with delayed capillary refill, rapid weak pulse or low blood pressure (see below).
- *D – Disability:* neurological status needs to be evaluated by checking the pupils and Glasgow Coma Scale (GCS). A decreased level of consciousness can be caused by poor cerebral perfusion, direct cerebral injuries, alcohol, recreational drugs and opiates.[6]
- *E – Exposure:* the patient needs to be exposed for examination, but at the same time hypothermia must be prevented and dignity preserved.[6]

OXYGEN AND VENTILATORY THERAPY

High-flow oxygen by mask is given to all trauma patients. Patients with severe trauma frequently require ventilatory support. A restless uncooperative patient should be anaesthetised and intubated under a rapid sequence induction to facilitate resuscitation.

BLOOD CROSS-MATCH AND TESTS

Blood is concurrently sent for baseline haematological and biochemical tests, including blood ethanol level. Blood ethanol level is clinically useful in assessing individual patients with depressed consciousness, quite apart from epidemiological and preventive medicine,[7] and for legal considerations. Six units of red cells should be cross-matched urgently, but it is impossible to predict the amount of blood that will be required. Most institutions have policies on transfusion in the unstable patient.

FLUID RESUSCITATION

Resuscitation fluids are given (see below). If necessary, two or three large 14- or 16-gauge intravenous (IV) cannulae are inserted in upper limb, external jugular or femoral veins. Intraosseous cannulation can be useful initially if intravenous access is not obtainable.

ANALGESIA

Analgesia is easily overlooked. Opioid agents should be titrated IV, and not given intramuscularly or subcutaneously as the latter routes give unpredictable absorption in shock states. Large doses may be needed.

URINE OUTPUT

A urinary catheter is inserted unless a ruptured urethra is suspected (because of blood at the urinary meatus, severe fractured pelvis or abnormal prostate position on rectal examination), in which case a urethrogram is indicated before catheterisation. Urine output monitoring is an important guide to resuscitation.

CLINICAL EVALUATION OF INJURIES (SECONDARY SURVEY)

Injuries are easily missed in an emergency, especially when one injury is obvious. A secondary, and even a tertiary, survey should be performed.[5] The back and the front of the patient should be examined. Special attention is paid to regions with external lacerations, contusions and abrasions. All body regions are examined systematically.

HEAD

Neurological observations are made. The ears and nose are inspected for cerebrospinal fluid and blood, and the scalp is examined thoroughly.

FACE

Bleeding into the airway should be excluded, and the face and jaws tested for abnormal mobility.

SPINE

A cervical spine fracture or dislocation is assumed in all patients with depressed consciousness until proved otherwise. Signs of spinal cord injury should be sought (e.g. warm dilated peripheries from loss of vasomotor tone, diaphragmatic breathing, paralysis, priapism and loss of anal tone). The thoracic and lumbar spine should be inspected and palpated.

THORAX

Fractured ribs in themselves are not usually life threatening, but haemothorax, pneumothorax, lung contusion and chest wall instability (flail chest) will require attention if present. Tension pneumothorax is a life-threatening emergency that needs to be detected and treated early. Less common but very serious injuries can occur to the heart and great vessels (see Chapter 79).

ABDOMEN

The spleen, liver and mesenteries are often damaged. Retroperitoneal haemorrhage is common. Injuries to

the pancreas, duodenum and other hollow viscera are less frequent, and may be missed until signs of peritonitis occur. Renal injury with retroperitoneal haemorrhage is suggested by haematuria and loin pain (see Chapter 81).

PELVIS

Pelvic fractures may be difficult to detect clinically, especially in the unconscious patient. Blood loss may be massive, particularly with posterior fractures involving sacroiliac dislocation. Consideration of a pelvic binder may be useful in the initial stages of resuscitation. Ruptured bladder and ruptured urethra may occur with anterior fractures.

EXTREMITIES

A litre or more of blood may be lost into a fractured femur. Long-bone fractures are more serious when they are open, comminuted or displaced, or if associated with nerve or arterial damage.

EXTERNAL

Contusions may be extensive and serious, especially in falls from heights, and may be overlooked if the victim's back is not examined. Road crash victims may sustain serious burns or abrasions.

SHOCK IN THE TRAUMA PATIENT

The earliest, most constant and reliable signs of shock are seen in the peripheral circulation. A patient with cold, pale peripheries has shock until proved otherwise. Tachycardia is not always present and hypotension is a late sign of shock. The commonest form of shock in trauma is hypovolaemic shock.

HYPOVOLAEMIC SHOCK

If the neck veins are empty, hypovolaemic shock should be inferred. Possible sites of blood loss causing shock are:

- *external loss*, which is obvious clinically from blood-soaked clothing and pooled blood
- *major fractures*, which are obvious clinically by deformity, swelling, crepitus, pain and tenderness (e.g. femurs) or seen on a plain X-ray (e.g. pelvis)
- *pleural cavity*, detected on urgent chest X-ray. Intrapleural drains will reveal the amount and rate of blood loss
- *peritoneal cavity*, detected by laparotomy, diagnostic peritoneal lavage (DPL), computed tomography (CT) scan or ultrasound. Clinical examination of the abdomen can be misleading when the patient is intoxicated, has depressed consciousness or has multiple injuries. A single clinical examination is of limited value; changes over time are more important
- *retroperitoneum*, detected at laparotomy or by CT scan, or inferred when all the above are negative, especially in the presence of pelvic or lumbar spine fracture.

CARDIOGENIC SHOCK

If the trauma patient with shock has distended neck veins, possible causes are tension pneumothorax, concurrent myocardial infarction, cardiac tamponade or myocardial contusion.

NEUROLOGICAL SHOCK

Patients with paraplegia or tetraplegia from spinal cord injury may have low blood pressure with warm dilated peripheries accompanied by lax anal tone and by priapism in the male (see Chapter 80). This is a diagnosis of exclusion and all causes of hypovolaemic shock (see above) must be sought.

SEPTIC SHOCK

Occasionally, patients with pulmonary aspiration may develop septic shock. This is unlikely to confuse the initial trauma assessment soon after injury, but may require consideration some hours or a day or two later.

ABDOMINAL ULTRASOUND

The non-invasive nature and increasing availability of FAST (focused assessment with sonography for trauma) scanning in emergency departments has made this modality attractive in trauma to detect haemoperitoneum and haemopericardium.

However[8]:

- it is operator dependent and needs to be performed by trained personnel
- it may have an unacceptably high false-negative rate
- there is a small but important false-positive rate for intra-abdominal bleeding
- it is unable to diagnose ruptured bowel
- it is not good for bleeding in the pelvis.

Its main usefulness is in the shocked patient, where a positive FAST indicates the need for immediate laparotomy without further investigation.[6,9,10]

DIAGNOSTIC PERITONEAL LAVAGE

DPL is now less commonly performed and is largely replaced by FAST. However, it may still be used to diagnose intra-abdominal bleeding and bowel injury in some circumstances.

This is an invasive procedure that may make subsequent clinical abdominal examination difficult.[6,11]

Caution is needed with pregnancy, previous abdominal surgery or massive pelvic injury. Isotonic saline

1 L (or 10 mL/kg) is instilled into the peritoneal cavity, after drainage of the stomach and bladder. The presence of more than 10 mL frank blood on catheter aspiration necessitates immediate laparotomy; otherwise a lavage fluid specimen should be examined for red and white cell counts and amylase concentration. A red cell count over 100,000 per mm^3, white cell count over 500 per mm^3 or an increased amylase concentration suggests bleeding or viscus injury, and laparotomy should be undertaken immediately. These absolute figures are debatable, however, and lower values are accepted in penetrating trauma.[6,12,13]

COMPUTED TOMOGRAPHY ABDOMEN

Improved availability, reduced scanning times and better definition increasingly favour CT abdomen over DPL in patients who are sufficiently stable to tolerate the procedure safely. It needs to be performed quickly and safely, with gastric and IV contrast, and interpreted by radiologists experienced in trauma. Visualisation of abdominal and pelvic organs and haemorrhage is excellent.[14,15] Diaphragm, pancreas and hollow viscus injuries may be difficult to visualise on CT, but the presence of free fluid in the absence of solid organ injury raises suspicion of hollow viscus injury.[16]

FLUID RESUSCITATION

TYPES OF FLUIDS

Almost all patients who are hypotensive or noticeably vasoconstricted will need a blood transfusion but, in general, early control of bleeding is the key. Isotonic saline or a balanced salt solution should be the first fluid infused. Shocked patients will need to be resuscitated early with blood and blood products. One-litre bags or bottles and giving sets with in-line pumps should be used on all IV lines. If fluid resuscitation is likely to be extensive, warmed fluids and rapid infusion devices should be used. Albumin solutions (and probably other colloid resuscitation fluids) are contraindicated in trauma patients as the SAFE study, comparing albumin and saline for fluid resuscitation, conducted in intensive care unit (ICU) patients showed higher mortality in patients given albumin, in the predetermined trauma subgroup, particularly in those with traumatic brain injury.[17] Initiation of massive transfusion protocol (MTP) can be life saving in the exsanguinating patient.

All resuscitation fluids have a high sodium concentration, similar to that of extracellular fluid. Glucose 5% and glucose–saline solutions are not effective resuscitation fluids. Few trauma patients actually require them in the first day.

THE EXSANGUINATING PATIENT

With exsanguination secondary to penetrating thoracic injury, there is a place for emergency room thoracotomy, but this approach has little place in blunt trauma.[18] The exsanguinating blunt trauma patient needs rapid intubation, volume resuscitation, bilateral intrapleural drains, chest and pelvic X-rays, and a rapid trip to the operating room if it seems likely that the bleeding is in the thorax or abdomen.

MASSIVE TRANSFUSION PROTOCOL

Coagulopathy is common in patients with haemorrhagic shock and can be made worse by fluid resuscitation. Many institutions will have a MTP for exsanguinating patients. The principle of MTP is to increase plasma to platelet to red blood cell (RBC) ratios during the resuscitation phase.[19] MTP is shown to improve outcome. Haemostatic agents such as tranexamic acid[20,21] and other novel adjunct therapies are now available. Prothrombin complex concentrate and fibrinogen concentrate do not have any known infectious complications and are increasingly used in trauma management.[22]

PERMISSIVE HYPOTENSION

In penetrating trauma, there is some evidence that extensive fluid resuscitation prior to haemostasis may be detrimental, presumably because of higher blood pressure, the displacement of a blood clot and dilution of the coagulation factors.[23,24]

Permissive hypotension is the limited use of crystalloid during the initial phase of resuscitation. The aim is to prevent bleeding and haemodilution secondary to fluid resuscitation causing a loss of coagulation factors and platelets. With such fluid restriction, the goal is to allow enough end-organ perfusion and maintenance of systolic blood pressure (SBP) to 90 mm Hg before surgical correction. The use of hypotensive resuscitation has demonstrated early intraoperative survival benefit in penetrating torso trauma.[25]

Traumatic brain injury is often present in blunt trauma, which frequently involves several body regions. Hypotension is disastrous to an already injured brain, and must not be prolonged by underresuscitation (see Chapter 77, section on traumatic brain injury – emergency treatment).[26–28]

DAMAGE CONTROL RESUSCITATION

Damage control surgery was described some years ago as abbreviated surgery to stop bleeding and contamination, followed by a period of ICU care before further surgery, to try to arrest the lethal triad of acidosis, hypothermia and coagulopathy.[29] US military experience with combat patients is extending this concept to fluid resuscitation as well, with a tendency to give no (or only small amounts of) resuscitation fluids before haemostatic surgery.

Following the evolution of the damage control surgery concept, trauma resuscitation is often widely referred to as ‘damage control resuscitation’ (DCR), which is defined as a systematic approach to major

exsanguinating trauma incorporating strategies of haemostatic resuscitation, permissive hypotension and damage control surgery.[30,31]

Haemostatic resuscitation is the early use of combined blood components and, in some situations whole blood, as primary resuscitation fluids. The aim is to provide the same ratio of each blood component (RBC, fresh frozen plasma and platelets) to treat intrinsic coagulopathy. Recent studies have shown that higher ratios of component therapy have increased patient survival. Other factors that need to be considered in the haemostatic resuscitation are fibrinogen and calcium levels.

Regular assessments of the efficacy of replacement therapy are required to guide and monitor coagulation parameters. Thrombelastography (TEG) and thromboelastometry (ROTEM) are frequently used to guide the real-time coagulation therapy.[32]

Some enthusiasts are now injudiciously extending DCR to other types of trauma.[33] As mentioned above under permissive hypotension, great caution should be exercised before extending this concept to non-exsanguinating blunt trauma, particularly if a traumatic brain injury is present,[28] or if the patient is remote from a trauma centre.

URINE OUTPUT

Hourly urine output is a useful guide to resuscitation from shock. Minimal acceptable urine output is 0.5 mL/kg per hour, but 1–2 mL/kg per hour is more adequate. Furosemide has no place in initial resuscitation. Apart from adequate resuscitation, diuresis can be due to ethanol, mannitol, dopamine, nephrogenic or neurogenic diabetes insipidus, or non-oliguric renal failure. Polyuria may mask early recognition of acute renal failure.

INADEQUATE RESUSCITATION

Patients in shock have depleted interstitial fluid as well as circulating blood volume, and need trauma resuscitation fluid volumes greater than the actual volume of blood lost. With blunt injury, volume losses often continue for 24–48 hours. Prolonged shock from delayed and inadequate resuscitation leads to renal failure, acute respiratory distress syndrome (ARDS), sepsis, disseminated intravascular coagulation (DIC) and multiple organ dysfunction.[34,35]

PULMONARY OEDEMA

Pulmonary oedema during resuscitation may be related to fluid overload, direct lung trauma, aspiration of gastric contents, pulmonary responses to non-thoracic trauma and reactions to resuscitation fluids. They can all cause leaky capillaries and produce non-cardiogenic pulmonary oedema.

RADIOLOGY FOR TRAUMA PATIENTS

Patients with depressed consciousness, breathing difficulties or unstable circulation should be X-rayed in the emergency department, and not sent to a radiology department remote from skilled resuscitation facilities. Conversely, extensive imaging examinations of shocked patients in the emergency department are unacceptable. Only a maximum of three examinations should ever be requested in the emergency department.

CHEST

A supine film is usually sufficient in the major trauma setting. An erect film is better for showing intrapleural air or fluid, ruptured diaphragm, free abdominal gas and for defining an abnormal mediastinum, but it is often impractical in shock or suspected spinal injury. Tension pneumothorax is a clinical diagnosis and does not require a chest X-ray before insertion of an intercostal drain.

LATERAL CERVICAL SPINE

Lateral cervical spine X-ray in the severely injured patient is now largely replaced by CT. It is no longer routinely done in the resuscitation room in major trauma. With head or facial injuries, a cervical fracture should be initially assumed and a cervical collar applied.

PELVIS

Unexplained blood loss can be due to a missed pelvic fracture. A dislocated hip can be missed in multiple injuries. Pelvic X-ray is an important adjunct of primary survey in an unstable trauma patient.

OTHER RADIOLOGICAL INVESTIGATIONS

Other X-rays should be performed after adequate resuscitation in the radiology department, operating room or ICU:

- *Skull*: plain skull X-rays are not useful and do not guide immediate treatment. An urgent CT scan of the brain is a more useful investigation.
- *Extremities*: X-rays of the extremities to assess bony injuries are not urgent unless there is vascular injury. Therefore these films should not be taken in the emergency department, unless the patient is going directly to the operating room for fracture fixation.
- *Spine*: X-rays of thoracic or lumbosacral spine are seldom indicated in the emergency department.
- *Abdomen*: a plain abdominal X-ray is of limited value in the initial evaluation of trauma. It may be helpful in high-velocity penetrating injuries, such as gunshot wounds, to help determine trajectory.
- *CT abdomen*: this can be valuable to evaluate a patient who is haemodynamically sufficiently stable to tolerate the procedure safely (see above).

- *CT head*: this is vital in the treatment of traumatic brain injuries.
- *CT neck*: the most reliable way to exclude or delineate cervical spine injuries is by a CT neck scan,[4,36] which can conveniently be done when the patient is going to the CT scanner for other examinations.
- *CT thorax*: apart from diagnosis of aortic injury, CT thorax is of limited value in the trauma patient. Visualisation of thoracic structures is excellent, but it seldom discovers important undiagnosed injuries that affect patient treatment.[37] If aortic injury is suspected, multislice CT is the current definitive diagnostic test. The use of aortic stent grafts for this injury, in locations where this technology is available, means that CT not only is the best diagnostic test but also is necessary for preoperative planning.[38] Aortography is no longer the definitive diagnostic test for traumatic aortic rupture.
- *Urethrography*: this is used when urethral injury is suspected. Properly done CT abdomen may well demonstrate bladder injury; otherwise *cystography* is used.
- *Interventional radiology*: percutaneous transcatheter embolisation is therapeutic rather than diagnostic. It can provide life-saving haemostasis in massive retroperitoneal haemorrhage associated with pelvic fracture.[39] The logistics of managing such haemodynamically unstable patients in the radiology department are formidable.

TRAUMATIC BRAIN INJURY (SEE CHAPTER 77)

Injuries to the head region are common, but those requiring urgent cranial operations are less so. Traumatic brain injury may initially be obvious amongst multiple injuries, but may not be the most important injury. Conversely, traumatic brain injury may seem initially unimportant. Traumatic brain injury is a major determinant of outcome in critically injured patients.

EMERGENCY TREATMENT

Resuscitation measures, as in the emergency assessment (primary survey) section above, are undertaken. Victims with one or both dilated unreactive pupils, or a rapidly deteriorating level of consciousness not due to hypoxia or shock, should be given mannitol 1 g/kg IV to relieve brainstem compression until definitive diagnosis and treatment can be arranged. However, mannitol should be given only if the patient has been adequately volume-resuscitated as it may add to hypovolaemia. In the ICU, concentrated salt is often preferred to mannitol because it is readily available and does not produce hypovolaemia.[40,41]

Shocked trauma patients with or without traumatic brain injuries require the same crystalloid resuscitation fluids. Treatment of shock and maintenance of cerebral perfusion are vital, as hypotension is disastrous to an already damaged brain.[26–28] Contrary to common belief, sodium-containing fluids are not inherently dangerous in traumatic brain injury. However, after adequate resuscitation, further sodium administration is usually not indicated. Excessive (free) water is potentially dangerous, however, as it can lead to hypo-osmolar brain swelling.[42]

NEUROLOGICAL EVALUATION

Factors such as hypoxaemia, shock, alcohol, analgesics, anaesthetic agents, muscle relaxants and other drugs confound neurological signs. Clinical neurological evaluation includes the GCS[43,44] and a search for lateralising signs.

CT scanning is indicated in all patients who will not obey verbal commands, especially if they are rendered neurologically inaccessible by sedative and relaxant agents. Lateralising motor or pupillary signs with a deteriorating level of consciousness are indications for immediate CT scanning (or, if unavailable, emergency burr holes). In an unstable patient, a laparotomy for intra-abdominal haemorrhage should take priority over a head CT scan.[45]

SEVERITY AND MORBIDITY OF TRAUMA

Severity of injury is measured by the Abbreviated Injury Scale (AIS), updated over the years, most recently in 2008.[46–48] AIS divides the body into six regions: head and neck, face, thorax, abdomen, pelvis and extremities, and external. Specific injuries in each body region are coded on a scale of 1 (minor), 2 (moderate), 3 (serious, not life threatening), 4 (severe, life threatening, survival probable), 5 (critical, survival uncertain) and 6 (unsurvivable). The AIS was designed for motor vehicle injuries, but has been validated for blunt and penetrating trauma. It can provide a basis for research, education, audit and allocation of resources.

Severity of trauma is related not just to the severity of individual injuries, but also to the combined effects of multiple injuries. Multiple injuries are graded by the Injury Severity Score (ISS), which is an empirical system based on the AIS grades for the three worst body regions.[49,50] ISS gives a score between 0 and 75 for total body injury; 16 or more indicates major trauma. Death with an ISS below 24 should be rare. Above an ISS of 25, there is a stepwise increase in mortality, with very high rates over 50.[51,52]

The AIS and ISS study mostly the anatomy of injury. Other factors influence trauma mortality and morbidity, including age, pre-existing health, degree of physiological derangement, standard of prehospital and early hospital care, and complications. Degree of physiological derangement can be measured by the Revised Trauma Score (RTS),[53] which is computed from the coded values of the GCS, systolic blood pressure and respiratory rate, usually at admission to the

emergency department. The Trauma Score – Injury Severity Score (TRISS) is based on the RTS, ISS and patient age.[54] It correlates well with outcome, and has been used to compile survival norms for blunt and penetrating trauma.[51,52] Physiological scoring systems such as APACHE (Acute Physiology and Chronic Health Evaluation) do not work well for trauma patients (see Chapter 3).[55,56] Preinjury illness (co-morbidity) has a profound effect on trauma outcome.[57]

Shock influences trauma mortality and morbidity. Complications of shock include renal failure, ARDS, sepsis, liver failure and multiorgan dysfunction.[34,35,58] Acute oliguric renal failure on the first day after trauma is now rare, but non-oliguric renal failure is often seen 2–4 days later, caused by the shock and delayed or inadequate resuscitation. It is often heralded by polyuria, which is misinterpreted as a sign of adequate resuscitation.

EPIDEMIOLOGY OF INJURIES

Only a minority of victims of severe trauma reach hospital alive.[59,60] The majority of deaths are immediate (within minutes) at the scene of injury. Some deaths are early (within hours) in the emergency department or the operating room, and a few are late (after days or weeks) and occur in the ICU or ward.[61] Those in the ICU are mostly from severe head injury within a few days and, less commonly, multiorgan dysfunction later.

Of trauma admissions to hospital, only a minority have severe or multiple trauma.[62] In order of frequency, life-threatening injuries involve the head, abdomen and chest (Table 76.1), and are often multiple. The hospital services that this small number of severely injured patients use out of proportion to their numbers are major surgery, intensive care, radiography and CT scanning.[62] Major trauma outcome studies in the United States,[51] the United Kingdom[52] and Australasia[63,64] offer valuable epidemiological data. The US study found that the mortality of direct admissions is strongly related to serious head injury.

Table 76.1 Percentage of intensive care unit trauma patients with grades of injury in different body regions

	AIS ≥4	AIS 3	AIS 1 or 2	AIS 0
Head and neck	63	9	9	19
Face	2	11	8	79
Thorax	10	17	7	66
Abdomen	17	6	2	75
Extremities	1	31	11	57
External	0	<1	63	37

Data on 5031 trauma patients (excluding burns) in the Department of Critical Care Medicine, Auckland City Hospital, 1988–2011. AIS-80 codes: 0 = no injury; 1 = minor; 2 = moderate; 3 = serious, not life threatening; 4 = severe, life threatening, survival probable; 5 = critical, survival uncertain; 6 = unsurvivable. In tertiary referral centres (like Auckland City Hospital) these figures will vary with the mix of local and referred patients.[63]

AIS, Abbreviated Injury Scale.

ORGANISATION OF TRAUMA CARE

Many of the problems of trauma care are organisational. Problems faced by health authorities are the provision of advanced care at the scene of injury, rapid transportation to hospital, policies on which hospitals should receive trauma patients, systems for rapid evaluation and decision making in hospitals, and rapid, safe patient transfer between hospitals. If survival from major trauma is to be maximised then prehospital and hospital care must be coordinated.

Regionalisation of trauma care has become an accepted concept.[2,65] Trauma centres are designated hospitals that meet certain requirements. The main prerequisites are rapidly available experienced surgeons, anaesthetists and neurosurgeons, and a minimum number of patients seen annually for staff expertise. Regionalisation involves the concept of ambulances bypassing non-designated hospitals.[2] Helicopters are used increasingly to speed patient transportation.[66] Trauma teams are teams of surgeons and intensivists or anaesthetists who immediately attend the trauma victim on arrival at hospital.[2–4,58]

Trauma registries and databases are important tools in organising and improving trauma care. The UK major trauma outcome study[52] showed that the doctors in charge of resuscitation were often junior, delays in performing urgent operations were common and the number of preventable deaths was significant. A hospital may not see enough trauma patients to justify a trauma team or supply adequate experience for its staff, and may not have all the facilities required by trauma patients. Transfer to a trauma hospital may be desirable, but geography and limited transport facilities may make such transfers hazardous.

In Western countries, trauma is a leading cause of death and disability under the age of 38 years.[51] Reduction of mortality and morbidity depends on public education, new legislations, on-site advanced care, rapid evacuation (see Chapter 4), hospital trauma expertise and coordination of services.[67,68]

KEY REFERENCES

6. Committee on Trauma, American College of Surgeons. *Advanced Trauma Life Support (ATLS) Program for Doctors: Student Course Manual*. 8th ed. Chicago: American College of Surgeons; 2008.
19. Holcomb JB, Wade CE, Michalek JE, et al. Increased plasma and platelet to red blood cell

ratios improves outcome in 466 massively transfused civilian trauma patients. *Ann Surg*. 2008;248:447–458.
21. CRASH 2 Trial Collaborators. Effect of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant hemorrhage (CRASH-2): a randomised placebo-controlled trial. *Lancet*. 2011;376:23–32.
23. Morrison CA, Carrick MM, Norman MA, et al. Hypotensive resuscitation strategy reduces transfusion requirements and severe post operative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial. *J Trauma*. 2011;70:652–663.
28. Brain Trauma Foundation. *Guidelines for the Management of Severe Traumatic Brain Injury*. 3rd ed. New York: Brain Trauma Foundation; 2007. Online. Available: http://www.braintrauma.org/.
47. Committee on Injury Scaling. *The Abbreviated Injury Scale – 1980 revision*. Morton Grove, IL: American Association for Automotive Medicine. 1980.
63. Gardiner JP, Judson JA, Smith GS, et al. A decade of ICU trauma admissions in Auckland, New Zealand. *N Z Med J*. 2000;113:326–327.


Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Trunkey DD. Trauma. *Sci Am*. 1983;249:20–27.
2. Trunkey DD. Overview of trauma. *Surg Clin North Am*. 1982;62:3–7.
3. Trunkey DD. Initial treatment of patients with extensive trauma. *N Engl J Med*. 1991;324:1259–1263.
4. Enderson BL, Maull KI. Missed injuries: the trauma surgeon's nemesis. *Surg Clin North Am*. 1991;71:399–418.
5. Janjua KJ, Sugrue M, Deane SA. Prospective evaluation of early missed injuries and the role of tertiary trauma survey. *J Trauma*. 1998;44:1000–1006.
6. Committee on Trauma, American College of Surgeons. *Advanced Trauma Life Support (ATLS) Program for Doctors: Student Course Manual*. 8th ed. Chicago: American College of Surgeons; 2008.
7. Soderstrom CA, Cowley RA. A national alcohol and trauma center survey: missed opportunities, failures of responsibility. *Arch Surg*. 1987;122:1067–1071.
8. Shackford SR, Rogers FB, Osler TM, et al. Focused abdominal sonogram for trauma: the learning curve of nonradiologist clinicians in detecting hemoperitoneum. *J Trauma*. 1999;46:553–564.
9. Branney SW, Moore EE, Cantrill SV, et al. Ultrasound based key clinical pathway reduces the use of hospital resources for the evaluation of blunt abdominal trauma. *J Trauma*. 1997;42:1086–1090.
10. Nordenholz KE, Rubin MA, Gularte GG, et al. Ultrasound in the evaluation and management of blunt abdominal trauma. *Ann Emerg Med*. 1997;29:357–366.
11. Root HD. Abdominal trauma and diagnostic peritoneal lavage revisited. *Am J Surg*. 1990;159:363–364.
12. Day AC, Rankin N, Charlesworth P. Diagnostic peritoneal lavage: integration with clinical information to improve diagnostic performance. *J Trauma*. 1992;32:52–57.
13. Weigelt JA, Kingman RG. Complications of negative laparotomy for trauma. *Am J Surg*. 1988;156:544–547.
14. Trunkey DD, Federle MP. Computed tomography in perspective [editorial]. *J Trauma*. 1986;26:660–661.
15. Padbani HR, Watson CJE, Clements L, et al. Computed tomography in abdominal trauma: an audit of usage and image quality. *Br J Radiol*. 1992;65:397–402.
16. Ng AK, Simons RK, Torreggiani WC, et al. Intra-abdominal free fluid without solid organ injury in blunt abdominal trauma: an indication for laparotomy. *J Trauma*. 2002;52:1134–1140.
17. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350:2247–2256.
18. Boyd M, Vanek VW, Bourguet CC. Emergency room resuscitative thoracotomy: when is it indicated? *J Trauma*. 1992;33:714–721.
19. Holcomb JB, Wade CE, Michalek JE, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. *Ann Surg*. 2008;248:447–458.
20. Hauser CJ, Boffard K, Dutton R, et al. Results of CONTROL trial: efficacy and safety of recombinant activated factor VII in the management of refractory traumatic hemorrhage. *J Trauma*. 2010;69:489–500.
21. CRASH 2 Trial Collaborators. Effect of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant hemorrhage (CRASH-2): a randomised placebo-controlled trial. *Lancet*. 2011;376:23–32.
22. Sheiber M. Redefining Resuscitation. Trauma Critical and Acute Care Surgery Manual. In: *Trauma, Critical Care and Acute Care Surgery Conference*; 2012.
23. Morrison CA, Carrick MM, Norman MA, et al. Hypotensive resuscitation strategy reduces transfusion requirements and severe post operative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial. *J Trauma*. 2011;70:652–663.
24. Bickell WH, Wall MJ, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med*. 1994;331:1105–1109.
25. Duke M, Guidry C, Guice J, et al. Restrictive fluid resuscitation in combination with damage control surgery: time for adaptation. *J Trauma Acute Care Surg*. 2012;73(3):674–678.
26. Chestnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma*. 1993;34:216–222.
27. Wilden JN. Rapid resuscitation in severe head injury. *Lancet*. 1993;342:1378.
28. Brain Trauma Foundation. *Guidelines for the Management of Severe Traumatic Brain Injury*. 3rd ed. New York: Brain Trauma Foundation; 2007. Online. Available: http://www.braintrauma.org/.
29. Rotondo MF, Schwab CW, McGonigal MD, et al. Damage control': an approach for improved survival in exsanguinating penetrating abdominal injury. *J Trauma*. 1993;35:375–378.
30. Holcomb JB. Damage control resuscitation. *J Trauma*. 2007;62:S36–S37.
31. Frauenfelder C, Raith E, Griggs M, et al. Damage control resuscitation of the exsanguinating trauma patient. *J Military Veteran's Health*. 2011;19:19–24.
32. Bougle A, Harrois A, Duranteau J. Resuscitative strategies in traumatic haemorrhagic shock. *Ann Intensive Care*. 2013;3:1.
33. Harris T, Thomas GOR, Brohi K. Early fluid resuscitation in severe trauma. *BMJ*. 2012;345:e5752.
34. Cowley RA, Trump BF. Editors' summary: Organ dysfunction in shock. In: Cowley RA, Trump BF, eds. *Pathophysiology of Shock, Anoxia, and Ischaemia*. Baltimore, MD: Williams & Wilkins; 1982:281–284.
35. Faist E, Baue AE, Dittmer H, et al. Multiple organ failure in polytrauma patients. *J Trauma*. 1983;23:775–787.
36. Daffner RH, Sciulli RL, Rodriguez A, et al. Imaging for evaluation of suspected cervical spine trauma: a 2-year analysis. *Injury*. 2006;37:652–658.

37. Paul A, Blostein PA, Hodgman CG. Computed tomography of the chest in blunt thoracic trauma: results of a prospective study. *J Trauma*. 1997;43: 13–18.
38. Nzewi O, Slight RD, Zamvar V. Management of blunt thoracic aortic injury. *Eur J Vasc Endovasc Surg*. 2006;31:18–27.
39. Panetta T, Sclafani SJA, Goldstein AS, et al. Percutaneous transcatheter embolisation for massive bleeding from pelvic fractures. *J Trauma*. 1985;26:1021–1029.
40. Suarez JI, Qureshi AI, Bhardwaj A, et al. Treatment of refractory intracranial hypertension with 23.4% saline. *Crit Care Med*. 1998;26:1118–1122.
41. Prough DS, Zornow MH. Mannitol: an old friend on the skids? *Crit Care Med*. 1998;26:997–998.
42. Fishman RA. Effects of isotonic intravenous solutions on normal and increased intracranial pressure. *AMA Arch Neurol Psychiatry*. 1953;70:350–360.
43. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet*. 1974;2:81–84.
44. Jennett B, Teasdale G. Aspects of coma after severe head injury. *Lancet*. 1977;1:878–881.
45. Thomason M, Messick J, Rutledge R, et al. Head CT scanning versus urgent exploration in the hypotensive blunt trauma patient. *J Trauma*. 1993;34:40–45.
46. American Medical Association Committee on Medical Aspects of Automotive Safety. Rating the severity of tissue damage: I – the abbreviated scale. *JAMA*. 1971;215:277–280.
47. Committee on Injury Scaling. *The Abbreviated Injury Scale – 1980 revision*. Morton Grove, IL: American Association for Automotive Medicine. 1980.
48. Committee on Injury Scaling. *The Abbreviated Injury Scale – 2005, update 2008*. Barrington, IL: Association for the Advancement of Automotive Medicine. 2008.
49. Baker SP, O'Neill B, Haddon W, et al. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma*. 1974;14:187–196.
50. Baker SP, O'Neill B. The injury severity score: an update. *J Trauma*. 1976;16:882–885.
51. Champion HR, Copes WS, Sacco WJ, et al. The major trauma outcome study: establishing national norms for trauma care. *J Trauma*. 1990;30:1356–1365.
52. Yates DW, Woodford M, Hollis S. Preliminary analysis of the care of injured patients in 33 British hospitals: first report of the United Kingdom major trauma outcome study. *BMJ*. 1992;305:737–740.
53. Champion HR, Sacco WJ, Copes WS, et al. A revision of the trauma score. *J Trauma*. 1989;29:623–629.
54. Boyd CR, Tolson MA, Copes WS. Evaluating trauma care: the TRISS method. *J Trauma*. 1987;27: 370–378.
55. McAnena OJ, Moore FA, Moore EE, et al. Invalidation of the APACHE II scoring system for patients with acute trauma. *J Trauma*. 1992;33: 504–507.
56. Roumen RMH, Redl H, Schlag G, et al. Scoring systems and blood lactate concentrations in relation to the development of adult respiratory distress syndrome and multiple organ failure in severely traumatized patients. *J Trauma*. 1993;35:349–355.
57. Sacco WJ, Copes WS, Bain LW, et al. Effect of pre-injury illness on trauma patient survival outcome. *J Trauma*. 1993;35:538–543.
58. Cowley RA, Dunham CM, eds. *Shock Trauma/ Critical Care Manual*. Baltimore, MD: University Park Press; 1982.
59. Baker CC, Oppenheimer L, Stephens B, et al. Epidemiology of trauma deaths. *Am J Surg*. 1980;140: 144–150.
60. Smeeton WMI, Judson JA, Synek BJ, et al. Deaths from trauma in Auckland: a one year study. *N Z Med J*. 1987;100:337–340.
61. Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: a reassessment. *J Trauma*. 1995;38: 185–193.
62. Streat SJ, Donaldson ML, Judson JA. Trauma in Auckland: an overview. *N Z Med J*. 1987;100: 441–444.
63. Gardiner JP, Judson JA, Smith GS, et al. A decade of ICU trauma admissions in Auckland, New Zealand. *N Z Med J*. 2000;113:326–327.
64. Cameron P, Dziukas L, Hadj A, et al. Major trauma in Australia: a regional analysis. *J Trauma*. 1995;39: 545–552.
65. Eggold R. Trauma care regionalisation: a necessity. *J Trauma*. 1983;23:260–262.
66. Freeark RJ. The trauma center: its hospitals, head injuries, helicopters, and heroes (1982 AAST presidential address). *J Trauma*. 1983;23:173–178.
67. Judson JA. Trauma management: modern concepts [editorial]. *N Z Med J*. 1985;9:88–99.
68. Trunkey DD. On the nature of things that go bang in the night. *Surgery*. 1982;92:123.

77

Severe head injuries

Manoj K Saxena, John A Myburgh

EPIDEMIOLOGY

Head injury is a heterogeneous disease entity that can be defined as either an alteration in brain function, or evidence of structural brain pathology, which is caused by an external force.[1] Traumatic head injury is the leading cause of death in those under 45 years of age, affecting males disproportionately.[2] Data from the Global Burden of Disease suggest that traumatic head injury contributes to between 8% and 15% of years lost due to disability as a proportion of the total global injury burden.[3] Overall, the incidence of the disease is probably increasing, driven primarily by an increase in low- and middle-income countries.[4]

In addition to high mortality, the cost to survivors in emotional, social and financial terms is substantial as the effects of the original injury may persist for many years.

AETIOLOGY

Traumatic head injury may be due to transport accidents, unintentional falls, assaults due to interpersonal violence or exposure to external forces and other causes. Increasingly, traumatic head injury related to military conflict and sports or recreational activity is being recognised. In high-income countries the incidence of head injury due to vehicular trauma has significantly decreased due to technical improvements in vehicle design and safety, and in public health initiatives.[1] However, the ageing demography of the population are now influencing the presentation of the disease in this setting.[4]

DEMOGRAPHICS

The numbers of patients with traumatic head injury presenting to hospitals vary widely in accordance with hospital admission policies and capabilities. The incidence of hospitalisation for traumatic brain injury has been reported to be between 69.7 cases per 100,000 population in America[5] and 101 cases per 100,000 in Europe.[6] A recent population-based study of moderate and severe traumatic head injury reported a rate of 40 (95% confidence interval 32–51) cases per 100,000 in New Zealand.[7] Age- and gender-specific data typically show two peaks: one in the second and third decades, with a male:female ratio of 2:1, and the latter in the seventh to ninth decades with a more equal gender ratio.

PATTERNS OF INJURY

Traumatic head injury represents a range of injury from mild head injury that may fully recover to severe injury associated with high mortality or high levels of disability. Injury may be either blunt or penetrating, with the latter associated with a higher mortality.

Although most head injuries (70%–80%) are minor, a significant proportion of these patients have poor functional outcomes due to secondary brain insults and co-morbidities. Of the 20%–30% who constitute moderate to severe head injury, approximately 10% of these are dead on admission, whereas the remainder will usually require admission to the intensive care unit (ICU) for management in the first 7–10 days.

PATHOPHYSIOLOGY

Head injury is a heterogeneous pathophysiological process.[8] It encompasses a spectrum of injury that includes the degree of brain damage at the time of injury (primary injury) in addition to insults that occur during the post-injury phase (secondary injury). These processes are depicted in Fig. 77.1.

PRIMARY BRAIN INJURY

The severity of primary injury is determined by the degree of neuronal damage or death at the time of impact. This is the major determinant of outcome from traumatic brain injury.

Primary brain injuries include all types of injury to the brain parenchyma and vasculature. Primary injuries that are associated with adverse outcome include traumatic subarachnoid haemorrhage and non-evacuable mass lesions, particularly in critical parts of the brain, such as the posterior fossa.

ABSTRACT

Traumatic head injury is a global public health problem, with a high mortality and survivors affected by appreciable disability. The epidemiology, aetiology and demography of the disease is changing in high-income as well as low- and middle-income settings. Despite improvements in resuscitation and vital organ support, the management of patients with traumatic head injury in the intensive care unit remains a challenge to all members of the critical care team. Following initial resuscitation, good intensive care management forms the basis of management. This takes priority over brain-specific therapies, which to date remain inconclusive in their efficacy. There is no standard or uniform method of managing traumatic head injury, and practices are determined by local factors (preferences, experience, caseload and resources) and local interpretation of evidence. A debate is emerging about disability in survivors from the varied perspectives of clinicians, families and society; the generation of high-quality evidence remains challenging.

KEYWORDS

Severe traumatic head injury
critical care
neuromonitoring
clinical management

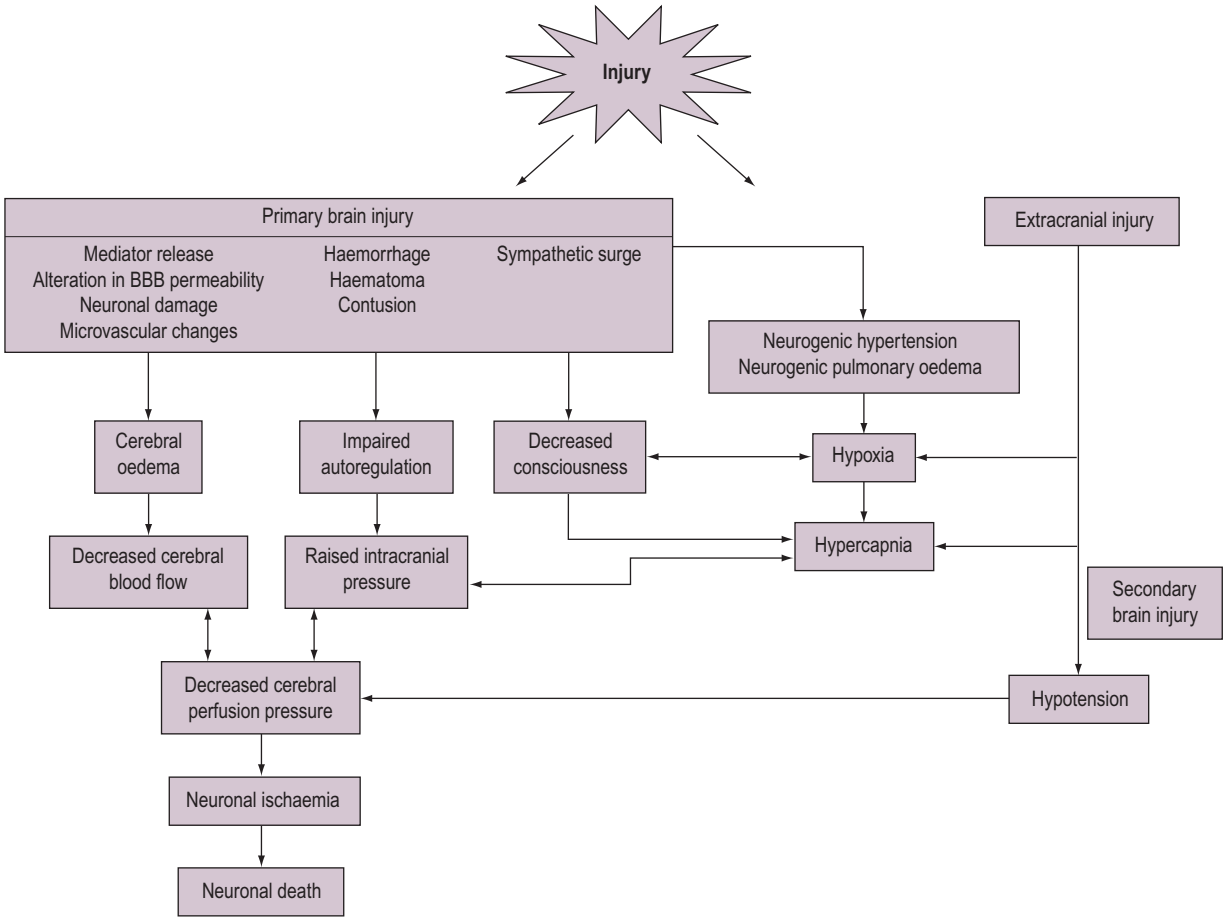


Figure 77.1 Pathophysiology of traumatic brain injury. *BBB*, Blood–brain barrier.

Box 77.1 Secondary brain insults following traumatic brain injury that are associated with increased morbidity and mortality

SYSTEMIC	INTRACRANIAL
Hypoxia	Seizure
Hypotension	Delayed haematoma
Hypocapnia	Subarachnoid haemorrhage
Hypercapnia	Vasospasm
Hypothermia	Hydrocephalus
Hyperthermia	Neuroinfection
Hypoglycaemia	
Hyperglycaemia	
Hyponatraemia	
Hypernatraemia	
Hyperosmolality	
Infection	

SECONDARY BRAIN INJURY

Secondary brain insults are characterised by a reduction in cerebral substrate availability and use (Box 77.1). Of these, hypotension (defined as a systolic blood pressure of <90 mm Hg [11.97 kPa]), hypoxia (oxygen saturation <90% or PaO_2 <50 mm Hg [6.65 kPa]), hypoglycaemia, hypothermia (temperature <35°C), hyperpyrexia (temperature >39°C) and prolonged hypocapnia ($PaCO_2$ <30 mm Hg [3.99 kPa]) have been associated with worse survival following traumatic brain injury.

Secondary insults may occur during initial resuscitation, transport both between and within hospitals, during anaesthesia and surgery, and in the ICU. These insults may initiate or propagate pathophysiological processes that may damage neurons already rendered susceptible by the primary injury.

INTRACRANIAL INFLAMMATION

As the brain is enclosed within the rigid skull and dura, small increases in intracranial volume result in sharp increases in intracranial pressure (ICP; Monroe–Kelly doctrine). Consequently, the brain is a poorly elastant organ with a limited capacity to accommodate pathological increases in ICP.

Traumatic head injury invokes an inflammatory response characterised by the release of pro- and anti-inflammatory mediators. The consequence of this response is disruption and alteration in the permeability of the blood–brain barrier, glial swelling and alterations in regional and global cerebral blood flow. The extent of this inflammatory process is an important determinant of ICP that may persist for some time following injury. Furthermore, alteration in blood–brain permeability may change the normal physiology of the cerebral circulation and alter the response to intravenous fluids, osmotic diuretics and vasoactive drugs.

CEREBRAL BLOOD FLOW AND AUTOREGULATION

Normally, cerebral blood flow is maintained at a constant rate in the presence of changing perfusion pressures by regional myogenic and metabolic autoregulation. These homeostatic mechanisms are impaired following head injury due to neuronal damage and intracranial inflammation. Research techniques that measure cerebral blood flow have described phases of cerebral blood flow following head injury that include an early hypoperfusive phase, and in a proportion of patients, subsequent hyperaemic followed by vasospastic phases.[9] The clinical significance of these described changes in blood flow and cerebral autoregulation is uncertain but these described changes may be used to provide a rationale for justifying haemodynamic targets during the evolution of the brain injury.

RESUSCITATION

INITIAL ASSESSMENT

The resuscitation of head-injured patients should follow the principles outlined in the Advanced Trauma Life Support (ATLS) guidelines for the early management of severe trauma.[10]

The initial emphasis is directed at assessing and controlling the airway, ensuring adequate oxygenation and ventilation, establishing adequate intravenous access and correcting hypotension. Neurological assessment and brain-specific treatment should follow only after cardiorespiratory stability has been established.

AIRWAY

All patients with severe head injury (traumatic coma), marked agitation or significant extracranial trauma require early oral endotracheal intubation.

Depending on the skill of the operator and available facilities, this should be performed using a rapid sequence induction of anaesthesia with cricoid pressure and in-line immobilisation of the cervical spine.

All head-injured patients should be assumed to have a potential cervical spine injury, and should be immobilised in a rigid collar until that possibility has been appropriately evaluated.

BREATHING (= VENTILATION)

Patients should be ventilated with 100% oxygen using 6–10 mL/kg tidal volumes until blood gas analysis is available.

Oxygenation should be maintained at 80–100 mm Hg (13 kPa) and the ventilator adjusted to achieve a normal arterial carbon dioxide tension (35–40 mm Hg; 4.5–5.0 kPa).

Non-depolarising muscle relaxants and narcotics, such as fentanyl, may facilitate ventilation in the immediate post-intubation period in combative patients.

Empirical hyperventilation during initial resuscitation is not indicated.

CIRCULATION (= CONTROL OF SHOCK)

Prompt restoration of circulating blood volume and restoration of euvolaemia is critical.

Early arterial monitoring for accurate measurement of mean arterial pressure and central venous catheter placement and the administration of blood and drugs is essential. The placement of these lines must not delay volume resuscitation.

Blood transfusion should be commenced as soon as possible in actively bleeding patients with early administration of coagulation factors where appropriate.

Crystalloid, specifically 0.9% saline, is recommended for fluid resuscitation of patients with traumatic brain injury.[11] Hypertonic saline may have a role as a small-volume resuscitation fluid in patients with traumatic brain injury, although there is no evidence of reduced mortality when used in the pre-hospital period.[12]

Vasoactive drugs, such as epinephrine (adrenaline) or norepinephrine (noradrenaline), may be used to defend blood pressure once correction of hypovolaemia is under way. This may be necessary if sedatives or narcotics are co-administered.

DISABILITY (= NEUROLOGICAL ASSESSMENT)

Assessment of neurological function following injury is important to quantify the severity of traumatic brain injury and to provide prognostic information. This may be influenced by associated injuries, hypoxia, hypotension and/or drug or alcohol intoxication.

Recording the mechanism of injury is important, as high-velocity injuries are associated with more neuronal damage. It is important to review ambulance and emergency personnel and records to obtain the most accurate information.

Level of consciousness

A rapid and practical initial assessment of consciousness during initial resuscitation is based on the

Table 77.1 The Glasgow Coma Score – the best response following non-surgical resuscitation is scored

BEST EYES OPEN SCORE		BEST VERBAL RESPONSE		BEST MOTOR RESPONSE	
Spontaneously	4	Orientated, adequate	5	Obeys spoken command	6
On spoken command	3	Disorientated, confused	4	Localised pain	5
To pain	2	Inappropriate words	3	Flexion withdrawal	4
No response	1	Incomprehensible	2	Abnormal flexion	3
		No response	1	Extension	2
		INTUBATED PATIENTS:	5	No response	1
		Appears able to converse	3		
		Questionable ability to converse	1		
		Unresponsive			

Adapted from Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet*. 1974;2:81–84.

response to incremental stimulation, and the response may be graded as Awake, responsive to Verbal stimulation, responsive to Painful stimulation only or Unresponsive (AVPU).

The Glasgow Coma Scale (GCS) has an established place in the management of traumatic head injury and is the most widely accepted and understood scale.[8] Although originally described as a prognostic index, it provides an overall assessment of neurological function, derived from three parameters: eye opening, verbal response and motor response (Table 77.1).

The best responses in the GCS components should be recorded following cardiorespiratory resuscitation and prior to sedation or anaesthesia. A GCS of 14–15 indicates a mild injury, 9–13 a moderate injury and 3–8 is classified as severe injury (traumatic coma). In severely injured patients or those who are intubated or with ocular or facial trauma, the motor response is the most reliable and reproducible of the three GCS components.

Pupillary responses

Pupil size and reactivity are important when consciousness is impaired. Whilst not part of the GCS, pupillary function should always be assessed and recorded at the same time as the GCS, particularly prior to the administration of narcotics, sedatives or muscle relaxants.

In the absence of traumatic mydriasis, abnormalities of pupil size and reactivity may indicate compression of the third cranial nerve, suggesting raised ICP or impending herniation, particularly when associated with lateralising motor signs and depressed consciousness.

Papilloedema is uncommon in the acute phase of head injuries.

Global peripheral motor function

In addition to the motor response of the GCS, decerebrate or decorticate posturing, hemiparesis or lateralising signs, paraparesis and quadriparesis (given the high association with spinal injuries with traumatic brain injury) should be documented concurrently with the GCS and pupillary responses.

SECONDARY SURVEY

Once the initial assessment is complete and resuscitation under way, a thorough secondary survey, as outlined in the ATLS, is mandatory.

The principles outlined in the initial assessment form the basis for prioritising interventions in the secondary survey. Extracranial causes of hypoxia, such as haemo/pneumothorax, must be excluded and promptly treated. Haemorrhage – both externally from fractures or lacerations and internally from major vascular disruption or visceral injuries – must be aggressively treated until circulatory stability is achieved. There is no place for 'permissive hypotension' in head-injured patients as has been advocated in selected cases of penetrating trauma.

Target mean arterial pressure should be estimated in the context of the patient's premorbid blood pressure. Higher pressures may be necessary in hypertensive or elderly patients. The early use of vasoactive drugs, such as epinephrine or norepinephrine, may be necessary to achieve this.

An approach of 'damage-control surgery' is recommended in patients with traumatic brain injury to minimise secondary insults.[13] In the initial 24–48 hours following injury, only life- or limb-threatening injuries should be addressed, following which patients should be transferred to the ICU for stabilisation and monitoring. Thereafter, semi-urgent surgery, such as fixation of closed fractures or delayed plastic repairs, may be done.[14] Patients with severe traumatic head injury undergoing prolonged emergency surgery should have ICP monitoring placed as soon as possible.

BRAIN-SPECIFIC RESUSCITATION

The place of interventions and therapies specifically directed at reducing ICP has been extensively reviewed

in evidence-based guidelines for the management of severe head injury.[15,16]

HYPERVENTILATION

Ventilation-induced reductions in $PaCO_2$ result in marked reductions in cerebral blood flow and consequently in ICP. However, as cerebral blood flow may be reduced during the initial period following injury, further reductions in cerebral perfusion will result if hyperventilation is used during this phase. Consequently, empirical hyperventilation is not indicated during initial resuscitation.[17]

In the resuscitated head-injured patient with unequivocal clinical signs of raised ICP or impending tentorial herniation (new pupillary dilatation or lateralising signs or a witnessed neurological deterioration), temporary hyperventilation is an option. Reductions of $PaCO_2$ to levels ≤30 mm Hg (4 kPa) may be considered prior to urgent imaging or surgery for evacuation of a mass lesion.

OSMOTHERAPY

Osmotically active agents, such as mannitol, are administered to increase plasma osmolality to cause net efflux of fluid from areas of oedematous brain, with resultant reduction in ICP. An intact blood–brain barrier is necessary for this to occur. Following intravenous administration of mannitol, an immediate plasma-expanding effect that reduces haematocrit and viscosity ensues, which temporarily increases cerebral blood flow. Subsequent reductions in ICP may result from restoration in cerebral perfusion pressure (CPP) and rheological changes in cerebral blood flow rather than specific cerebral dehydration.

Osmotherapy is associated with several potential adverse effects. Mannitol exerts an osmotic effect over a narrow range of plasma osmolality (290–330 mOsm/L), above which theoretically beneficial effects may be negated, and induces an osmolal gap between measured and calculated osmolality. This gap may be increased by alcohol, which is frequently present in the acute period. Mannitol will enter the brain where the blood–brain barrier is damaged, thereby potentially increasing cerebral oedema by increasing brain osmolality. It is a potent osmotic diuretic that may compromise haemodynamic stability by inducing an inappropriate diuresis in a hypovolaemic patient.

Given the high risk with minimal benefit during resuscitation, the routine use of mannitol is not recommended in the absence of raised ICP.[15]

Similarly to hyperventilation, mannitol can be considered in resuscitated patients with unequivocal signs of raised ICP prior to imaging or evacuation of a mass lesion. Although doses are frequently quoted as 0.25–1.0 g/kg, lower doses are equally as effective as higher doses in terms of improving cerebral perfusion and are associated with a lower incidence of side effects.

Hypertonic saline (3% solution) exerts similar osmotic plasma-expanding effects to mannitol. These solutions do not exert an osmolal gap so serum sodium reflects serum osmolality allowing easier titration.[14]

EMERGENCY SURGICAL DECOMPRESSION ('BURR HOLES')

The advent of advanced in-field resuscitation, medical retrieval, imaging, teleradiology and telemedicine in high-income countries has largely superseded the need to perform urgent, undirected craniotomy in patients with traumatic head injury. In most instances, patients are resuscitated, stabilised and imaged with computed tomography (CT) scans prior to any surgical intervention. This usually involves transfer to a specialised trauma centre.

In remote communities or in low- and middle-income countries without immediate access to CT scanning, surgical evacuation may be life saving in selected patients with a strong clinical probability of an expanding mass lesion, such as an extradural or subdural haematoma. These include patients with low-velocity injuries to the temporal region with an associated skull fracture and evolving lateralising neurological signs.

IMAGING

X-RAYS

Routine 'trauma series' of X-rays, namely chest, pelvis, skull and cervical spine, have been superseded by high-resolution, multislice CT. In areas without immediate access to CT, X-rays should focus on identifying injuries or confirmation of placement of lines and tubes post resuscitation.

COMPUTED TOMOGRAPHY SCAN

CT scanning is now standard in all patients following traumatic head injury. As CT scanning requires moving the patient to a radiological suite, this must be done only when initial assessment and resuscitation are complete and the patient is stable enough to be transported by appropriately trained and equipped personnel.

The following patients should undergo CT head scan following traumatic head injury:

- all patients with a history of loss of consciousness or traumatic coma (GCS <8)
- combative patients where clinical assessment is masked by associated alcohol, drugs or extracranial injuries; these patients may require endotracheal intubation, sedation and ventilation to facilitate completion of CT scanning
- to exclude a cervical spine injury.[18]

The most important role of CT scanning is prompt detection of intracranial mass lesions such as extradural

Table 77.2 Classification of computed tomography scan appearance following traumatic brain injury*

CATEGORY	DEFINITION
DI I (diffuse injury)	No visible intracranial pathology seen on CT scan
DI II (diffuse injury)	Cisterns are present with midline shift 0–5 mm and/or: Lesion densities present No high- or mixed-density lesion >25 mm May include bony fragments and foreign bodies
DI III (swelling)	Cisterns are compressed or absent with midline shift 0–5 mm No high- or mixed-density lesion >25 mm
DI IV (shift)	Midline shift >5 mm No high- or mixed-density lesion >25 mm
Evacuated mass lesion	Any lesion surgically evacuated
Non-evacuated mass lesion	High- or mixed-density lesion >25 mm, not surgically evacuated

*An example is shown in Fig. 77.2A.

CT, Computed tomography.

Adapted from Marshall L, Marshall SB, Klauber M, et al. The diagnosis of head injury requires a classification based on computed axial tomography. *J Neurotrauma*. 1992;9:S287–S292.

or subdural haematomas. Thereafter, the degree of brain injury may be quantified by radiological criteria (Table 77.2 and Fig. 77.2A).[19]

These criteria are important for providing an index of injury severity, providing criteria for ICP monitoring, comparing the progression of injuries with subsequent scans and providing an index for prognosis. Examples of typical injuries appear in Fig. 77.2A and B.

The presence of traumatic subarachnoid haemorrhage should be recorded. This is an important index of severity of injury and is relevant for prognostication.[20]

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) provides accurate details of parenchymal damage, specifically small collections and non-haemorrhagic contusions. The information provided is not significantly better than that obtained from CT scanning to warrant routine use of MRI in the acute phase of injury.

In patients when a major intracranial vascular injury is suspected, such as carotid artery dissection where the patient's clinical condition is not consistent with the CT findings (e.g. a dense hemiparesis in the absence of a mass lesion), magnetic resonance angiography or direct cerebral angiography is indicated.

MRI has an emerging role in prognostication at a later stage in management.[21]

INTERHOSPITAL TRANSFER

All severely head-injured patients should be managed at a specialised neurotrauma centre in close collaboration with intensive care physicians and neurosurgeons. This may involve intra- or interhospital transportation. Appropriately skilled and equipped personnel should do this only once resuscitation, stabilisation and initial imaging are completed.

A full primary and secondary survey and review of all documentation and investigation is required following transfer to a secondary or tertiary centre.

INTENSIVE CARE MANAGEMENT

The Brain Trauma Foundation of the American Association of Neurological Surgeons has published iterative evidence-based recommendations for the management of severe brain injury for treatment and monitoring for areas where sufficient evidence is available for synthesis.[15] The stated intention is that the recommendations are used by clinicians to develop protocols, incorporating local consensus and clinical judgment, for the many areas where currently high-quality evidence is lacking or insufficient. There is therefore no standard or uniform method of managing traumatic head injury in the ICU. Most practices are determined by local preferences and experience, caseload and resources.

Following initial resuscitation, good intensive care management forms the basis of head injury management and is regarded as a continuum of care. This takes priority over brain-specific therapies, which to date remain inconclusive in their efficacy.

HAEMODYNAMIC MANAGEMENT

Monitoring

Accurate measurement of systemic blood pressure is essential and should be measured via an arterial catheter referenced to the aortic root. A large artery, such as the femoral artery, should be considered in haemodynamically unstable patients as radial or dorsalis pedis arterial catheters may underestimate systemic pressure in shocked patients. Given the importance of maintaining adequate systemic blood pressure, non-invasive measurement of blood pressure is not recommended during the acute phase of monitoring.

Maintaining systolic blood pressure (SBP) at ≥100 mm Hg for patients 50–69 years old or at ≥110 mm Hg or above for patients 15–49 or over 70 years old is recommended.[15]

Volume status should be assessed using clinical criteria including an estimate of fluid and blood losses from the available history, pulse rate, mean arterial

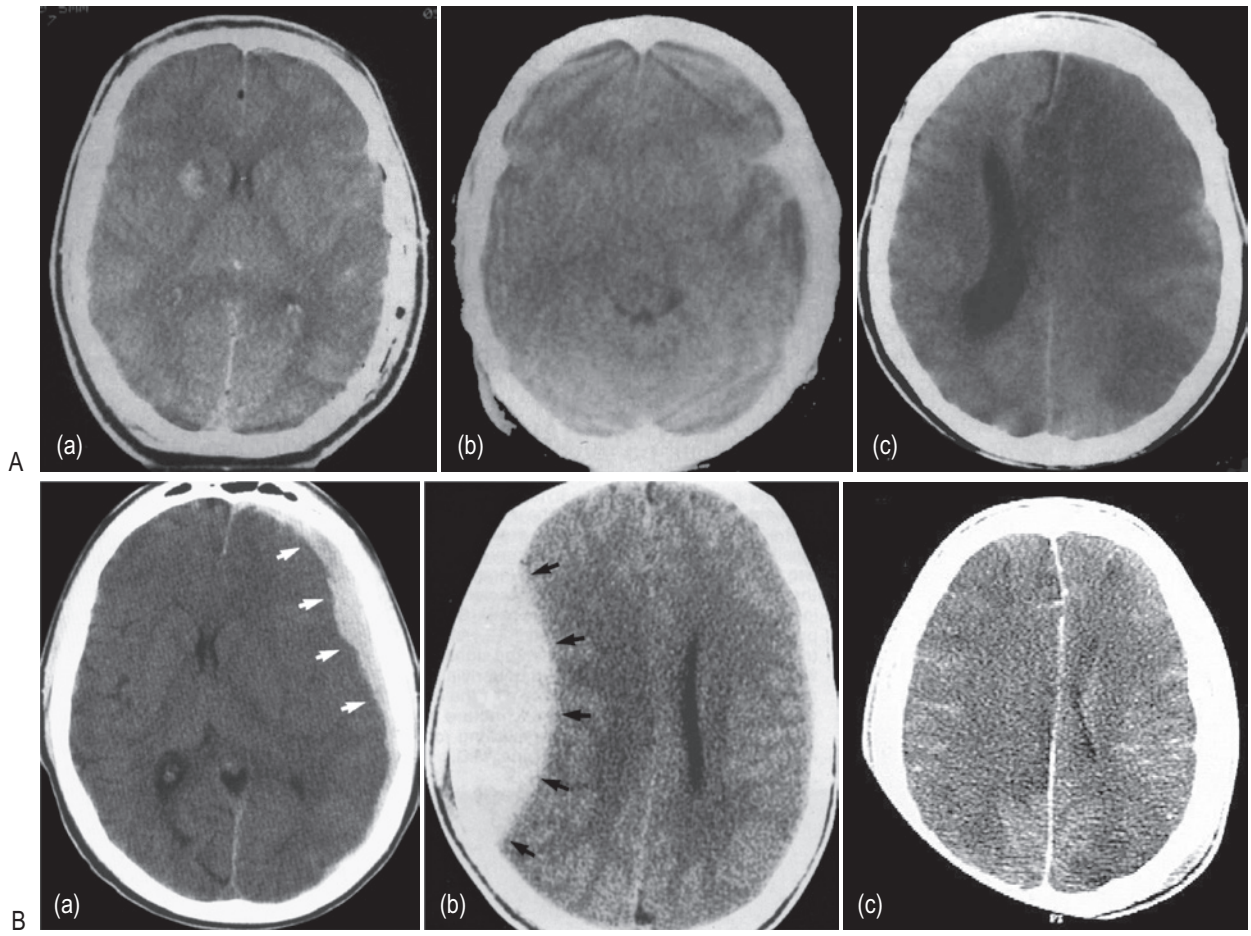


Figure 77.2 (A) Computerised tomographic classification of diffuse axonal injury (see Table 77.2): panel *(a)* diffuse injury II; panel *(b)* diffuse injury III; panel *(c)* diffuse injury IV. (B) Intracranial haemorrhages: panel *(a)* acute subdural haematoma; panel *(b)* acute extradural haematoma; panel *(c)* acute traumatic subarachnoid haemorrhage. *Stocchetti N, Maas AI. Traumatic intracranial hypertension.* N Engl J Med. *2014;370(22):2121–2130.*

pressure, urine output, serum sodium and osmolality, urea and creatinine.

Pulmonary artery catheterisation and other advanced haemodynamic monitoring techniques for the measurement of cardiac output and pulmonary artery pressures are rarely indicated in head-injured patients and are not recommended.

Fluid management

The attainment of euvolaemia is essential throughout intensive care management; both dehydration and fluid overload should be avoided.

0.9% saline is the resuscitation fluid of choice for patients with traumatic brain injury. The use of albumin is associated with increased ICP and mortality; whether this applies to other colloids is unknown but, on current evidence, resuscitation with colloids should probably be avoided.[11] Equally, hypotonic crystalloids, such as compounded sodium lactate (Ringer's lactate or Hartmann's solution), should be avoided.

Maintenance fluids should be restricted to a minimum and directed at maintaining normal serum sodium (140–145 mmol/L) and osmolality (290–310 mOsmol/L). As a general principle, glucose-containing solutions are not recommended; however, these may be required if patients become hyperosmolal (>320 mOsm/L).

Vasoactive therapy

Catecholamines such as epinephrine, norepinephrine or dopamine are frequently used to augment mean arterial pressure to attain an adequate CPP. These should be commenced once volume resuscitation is actively under way. The early use of vasoactive drugs is increasingly being advocated during resuscitation as an important strategy during the hypoperfusion phase.[22]

There are no conclusive trials to recommend one vasoactive drug over another or a combination of drugs. Epinephrine, norepinephrine and dopamine are equally effective in augmenting CPP.[23] The degree by

which these agents directly affect the cerebral circulation following head injury is unknown, although there is some evidence suggesting that dopamine has both direct cerebrovascular and adverse neuroendocrine effects.

Norepinephrine is currently regarded as the initial agent of choice for patients with traumatic brain injury in doses titrated to achieve a target mean arterial or CPP. Epinephrine is widely used, particularly in low-income countries, but may be associated with transient metabolic side effects such as hyperlactataemia and hyperglycaemia, which may confound assessment of the adequacy of circulatory and metabolic resuscitation.[24]

Doses may range widely between and within patients to attain a target CPP. However, excessive doses of catecholamines (i.e. >40 µg/min) should be avoided, particularly after 72 hours after injury when lower CPP targets (i.e. 40–60 mm Hg) may be appropriate.[9] At all times, other causes of hypotension, such as dehydration, sedatives, bleeding and sepsis, must be excluded.

Vasopressin is commonly used as a catecholamine-sparing agent or as a primary vasopressor in septic and distributive shock, but its role in traumatic brain injury has not been established and is not recommended.

Neurogenic hypertension

Neurogenic hypertension is common in the latter phases following injury (>5 days) and is usually centrally mediated. It may be associated with electrocardiography changes and/or supraventricular arrhythmias. It is usually self-limiting and correlates with the severity of injury, although a small proportion may require long-term therapy. Treatment depends on the severity of the problem: beta blockers or centrally acting agents, such as clonidine, are usually effective in the short- to medium-term; vasodilators are contraindicated.

RESPIRATORY THERAPY

Monitoring

Continuous measurement of arterial oxygen saturation is essential.

Continuous measurement of end-tidal carbon dioxide is frequently performed in ventilated patients, although the reliability is questionable and should be intermittently checked with arterial blood gases to maintain normocapnia.

The monitoring of ventilatory parameters should be consistent with standard approaches and includes measurement of tidal volumes, respiratory rates, and inspiratory and expiratory airway pressures.

Ventilation

Most patients with severe head injury will require mechanical ventilation to ensure adequate oxygenation and to maintain normocapnia (36–40 mm Hg; 4.8–5.3 kPa).

The principles of optimal ventilation, humidification and weaning are addressed elsewhere. Strategies such as 'permissive hypercapnia' that are advocated for selected patients with acute lung injury or acute respiratory distress syndrome do not have a role in head-injured patients owing to the requirement to maintain normocapnia.

Positive end-expiratory pressure (PEEP) is recommended at low levels (5–10 cm H_2O) to maintain functional residual capacity and oxygenation. Higher levels may compromise systemic blood pressure, particularly in hypovolaemic patients, and should be used with caution. High levels of PEEP (>15 cm H_2O) may compromise cerebral venous return but adverse effects on ICP are uncommon.

Weaning from ventilation should commence once intracranial pathology has stabilised – that is, the resolution of cerebral oedema on CT scan and the control of intracranial hypertension.

Extubation should be carefully considered so that subsequent hypoxic episodes do not occur, as these are potent secondary insults.

Patients with slow recovery of adequate consciousness should be considered for early tracheostomy, either percutaneously or surgically.

Neurogenic pulmonary oedema

This is a dramatic clinical syndrome that occurs in some patients with severe head injury and correlates with the severity of injury. The underlying pathophysiological process is complex, but is primarily related to centrally mediated sympathetic overactivity. It is characterised by the sudden onset of clinical pulmonary oedema, hypoxia, low filling pressures, poor lung compliance and bilateral lung infiltrates, usually within 2–8 hours following injury.

The process is usually self-limiting and treatment is primarily supportive, aimed at ensuring adequate oxygenation and ventilation. This usually requires endotracheal intubation and mechanical ventilation with the administration of PEEP. Ablation of sympathetic overactivity is effectively done with adequate sedation; beta blockade is usually unnecessary. Diuretics are effective, particularly if patients have received substantive fluid resuscitation, and must be titrated against the volume status of the patient.

The development of pulmonary oedema in patients with cardiac disease should be regarded as cardiogenic until proven otherwise.

Nosocomial pneumonia

Head-injured patients who require prolonged ventilation are at increased risk of nosocomial pneumonia. Risk factors include the severity of the head injury, barbiturate use and hypothermia therapy. Diagnosis and treatment are discussed elsewhere.

SEDATION, ANALGESIA AND MUSCLE RELAXANTS

There are no standards for sedation and analgesia in head-injured patients – protocols will depend on

local preferences and resources. The level of sedation and analgesia required for head-injured patients depends on the degree of traumatic coma, haemodynamic stability, ICP and systemic effects of the head injury itself.[15]

During the initial resuscitation phase, sedation should be titrated to cause the least effect on systemic blood pressure. During this period, short-acting narcotics, such as fentanyl, are useful, particularly if patients have associated extracranial injuries. These agents have relatively little adverse effect on haemodynamics and have the additional benefit of tempering the systemic sympathetic surges that frequently occur after injury. As narcotics affect pupillary responses, these must be documented before administration. Short-term muscle relaxants, such as vecuronium, are useful to control combative patients following intubation, ventilation and sedation.

During the intensive care phase, the requirements for sedation are different. Sedation should be titrated to have the patient sedated as lightly as possible to allow clinical assessment of neurological function and to facilitate mechanical ventilation. The level of sedation will depend on haemodynamic stability and ICP. Infusions of narcotics and benzodiazepines (e.g. morphine and midazolam) are useful in providing moderate to deep levels of sedation and are effective in controlling surges of ICP. However, these agents may accumulate, resulting in a delay in the return of consciousness or may be associated with an emergent delirium state or other nosocomial complications related to increased length of stay.

The use of propofol as a sole sedating agent has become popular. It provides deep levels of sedation, which is effective in controlling systemic sympathetic swings and rises in ICP. It is rapidly reversible on cessation allowing prompt assessment of neurological status and does not accumulate. In addition, pupillary responses are not directly affected. Propofol should be used with caution in haemodynamically unstable patients, however, as it is a potent vasodilator and negative inotrope. The prolonged use of propofol is associated with tachyphylaxis and significant caloric loading from the lipid vector. Concerns have been raised about myocardial depression and sudden cardiac death, particularly if large doses are administered.[25]

The routine use of muscle relaxants is not recommended either to facilitate sedation or to control raised ICP.

BODY POSITION AND PHYSIOTHERAPY

Patients should be nursed at 30–45 degrees head elevation to facilitate ventilation, improve oxygenation and reduce the risk of aspiration. The head should be kept in a neutral position.

Physiotherapy has an important role in the removal of lung secretions and the prevention of contractures and venous thrombosis. Patients with raised ICP may require boluses of sedation before chest physiotherapy to prevent acute rises in ICP.

METABOLIC MANAGEMENT

Routine measurement of biochemistry is essential.

Hyperglycaemia is common following severe head injury and is usually centrally mediated and transient. Blood sugar levels should be maintained with insulin infusions if necessary, between 6.0 and 10.0 mmol/L; hypoglycaemia should be avoided and is less likely with this strategy, compared to strategies that target normoglycaemia (4.4–6.1 mmol/L).[26]

Core temperature should be routinely monitored, as both hypothermia (<35°C) and hyperthermia (>39°C) have been associated with adverse outcomes and may contribute to secondary injury.[27,28]

NUTRITION

The caloric needs of head-injured patients must be addressed following resuscitation. Early enteral feeding is recommended.[15]

Placement of a nasogastric and/or enteral feeding tube in head-injured patients is usually via the oral route until an anterior cranial fossa (fractured cribriform plate) is excluded.

STRESS ULCER PROPHYLAXIS

The incidence of gastric erosions and 'stress ulceration' has markedly decreased with better resuscitation and early enteral feeding. Head-injured patients are at no more risk than other critically ill patients for developing stress ulceration.

H_2 antagonists or proton pump inhibitors should be used in ventilated patients until enteral feeding is established, following which they may be ceased.

Patients with a history of recent peptic ulceration should remain on proton pump inhibitors for the duration of the intensive care stay.

THROMBOPROPHYLAXIS

Head-injured patients, particularly those requiring prolonged ventilation and sedation or with extracranial injuries, are at increased risk for developing thromboembolism.

The use of anticoagulants, such as fractionated or low-molecular-weight heparins, is contraindicated in patients with clinically significant intracranial haemorrhage. Consequently, the role of pharmacological thromboprophylactic agents in head injury is difficult and there are no standards for their use.[15]

Generally, anticoagulants should not be used in head-injured patients with any evidence of destructive intracranial pathology or haemorrhage unless there is resolution or stabilisation of these processes on CT scan.

Non-pharmacological methods of thromboprophylaxis, such as elastic stockings or pneumatic calf compressors, are of unproven effectiveness but are a

reasonable first approach. Surveillance using Doppler ultrasound of the iliofemoral veins in high-risk patients, such as those with pelvic fractures, should be considered.

Pharmacological prophylaxis may be considered after the period of ICP guided management has been completed, and stabilisation or resolution of intracranial pathology, as indicated on serial cranial CT scans, has occurred.

Patients who develop deep-vein thromboses and who cannot be anticoagulated should be considered for inferior vena caval filters. The use of anticoagulants in head-injured patients with proven pulmonary embolism will depend on the relative risk to the patient's life.

ANTIBIOTICS

These should be used sparingly and in accordance with accepted microbiological principles. Prophylactic antibiotics should be prescribed only to cover insertion of ICP monitors and are not recommended for basal skull fractures. Frequent cultures of leaking or draining cerebrospinal fluid should be taken and infection specifically treated.[15]

BRAIN-SPECIFIC MONITORING

The most accurate assessment of brain function following traumatic brain injury is a full clinical neurological examination in the absence of drugs or sedatives. However, this is often not possible for most head-injured patients managed in the ICU.

Ideally, neuromonitoring should provide accurate and integrated information about ICP, patterns and adequacy of cerebral perfusion, and an assessment of cerebral function. No such monitor exists, although each of these parameters may be monitored in various ways with variable levels of accuracy and clinical utility.

CLINICAL ASSESSMENT

Regular assessments of GCS, pupillary signs and motor responses should be made and recorded in the ICU flow chart. Concomitant sedation may influence the level of consciousness and this should be recorded. Initially, these assessments are recorded hourly, but this may change as patients become more stable.

A witnessed deterioration in GCS, especially the motor response, or the development of new lateralising signs should be regarded as life-threatening intracranial hypertension or tentorial herniation until proven otherwise.

INTRACRANIAL PRESSURE MONITORING[15]

The recognition that raised ICP is associated with adverse outcome led to the measurement of this parameter to quantify the degree of injury and to assess the response to treatments directed at reducing ICP.

Indications

The Brain Trauma Foundation guidelines recommend the ICP monitoring of all salvageable patients with:

- Traumatic coma (GCS 3–8 after resuscitation) and an abnormal CT scan defined by the presence of hematomas, contusions, swelling, herniation or compressed basal cisterns.
- Traumatic coma (GCS 3–8 after resuscitation) with a normal CT scan if ≥2 of the following features are noted at admission: age greater than 40 years, unilateral or bilateral motor posturing or SBP less than 90 mm Hg.

Coagulopathy is a relative contraindication to ICP monitoring.

Methods

The measurement of ICP with an intraventricular catheter is the most accurate and clinically useful method. It has the advantages of zero calibration and drainage of cerebrospinal fluid drainage. Disadvantages include technical difficulty with insertion, particularly in patients with cerebral oedema and compression of the lateral ventricles, and an increased incidence of infection.

Solid-state systems, such as fibre optic (e.g. Camino) or strain gauge tipped catheters (e.g. Codman), may be placed intraparenchymally or intraventricularly. These systems transduce ICP to provide high-fidelity waveforms. They are small calibre and, although requiring a small craniotomy (burr hole) for insertion, may be inserted at the bedside. Disadvantages include the inability to perform zero calibration after insertion and baseline drift, which may be significant after 5 days.

Fluid-filled subdural catheters have been used for many years. However, these are no longer recommended owing to the development of more accurate solid-state systems. Subdural pressures do not accurately reflect global ICP, particularly in the presence of a craniectomy. Pressure readings may also be affected by local clot formation within the catheter.

Thresholds

Measurements are used to calculate CPP: mean arterial pressure minus ICP. For this calculation, both measurements should be referenced to the external auditory meatus (equivalent to the circle of Willis).

ICP monitoring should be continued until the patient can be assessed clinically and ICP has stabilised (<20 to 25 cm H_2O). This occurs in the majority of patients within 7 days. Patients with refractory intracranial hypertension may require monitoring for longer periods, although this may be complicated by drift (with solid-state systems), infection (with intraventricular catheters) or occlusion (subdural catheters). In this situation, ICP monitors may need to be replaced or removed and patients assessed by serial CT scan or clinically.

CEREBRAL BLOOD FLOW MONITORING

Currently, there is no method of routinely measuring cerebral blood flow at the bedside. Technological advances, such as mapping with labelled xenon under CT and laser Doppler flowmetry, provide useful imaging of regional and cerebral blood flow. However, these techniques are intermittent, labour-intensive and limited to research-based units.

Several qualitative measurement techniques are available that provide an indirect assessment of cerebral blood flow and have a limited and undefined role in routine management.

Jugular bulb oximetry

The measurement of oxygen saturation in the jugular bulb by the retrograde placement of a fibre optic catheter provides an indirect assessment of cerebral perfusion. Low jugular venous saturations (<55%) may be indicative of cerebral hypoperfusion, whereas high levels of jugular venous saturation (>85%) may be indicative of cerebral hyperaemia or inadequate neuronal metabolism, such as occurs during the hyperaemic phase or during the evolution of brain death. Both low and high jugular venous saturations are associated with adverse outcomes.[29]

There are insufficient data to provide evidence-based indications for the routine use of jugular bulb oximetry. Its use is limited to experienced units when an index of cerebral blood flow may be required during adjunctive therapies in patients with intracranial hypertension, for example augmentation with catecholamines, barbiturate coma, hyperventilation or induced cooling.

Transcranial Doppler

Transcranial Doppler ultrasonography with a 2-MHz pulsed Doppler probe allows non-invasive, intermittent or continuous assessment of the velocity of blood flow through large cerebral vessels. Directing the probe through a naturally occurring acoustic window, such as the transtemporal approach, allows insonation of the anterior, middle and posterior cerebral arteries, the terminal internal carotid artery and the anterior and posterior communicating arteries. However, the technique is operator-dependent and there may be significant variations in velocity patterns during the course of the injury. Measured indices of flow include systolic, mean and diastolic flow velocities.

Distinct patterns associated with normal, hyperaemic, vasospastic and absent flow are recognised. Derived indices, such as the Gosling pulsatility index (systolic/diastolic difference divided by the mean velocity) and the Lindegaard ratio (between middle cerebral artery to extracranial internal carotid artery), may assist in differentiating these flow patterns.

Despite the increasing use of transcranial Doppler to diagnose post-traumatic hyperaemia and vasospasm, there are insufficient data to provide evidence-based indications for its routine use.

CEREBRAL FUNCTION AND METABOLISM

Electroencephalography

Electroencephalography has been used for many years to assess seizure activity that may be masked by sedatives or muscle relaxants and to provide an objective estimate of the degree of electrical neuronal depression with barbiturate therapy. Although seizures may not be clinically apparent in a proportion of patients, and may constitute an important secondary insult, the accuracy and reliability of electroencephalography in ICU is questionable owing to outside electrical interference from monitors and ventilators.[30]

The development of bispectral index (BIS monitoring) as a measurement of depth of anaesthesia has led to the suggestion that this may be an alternative to the use of electroencephalography with barbiturate or sedative therapy in traumatic head injury. Nevertheless, BIS has not been validated in this context and cannot be recommended as a titration end-point.[31]

Evoked potentials

Measurement of evoked potentials, assessing the integrity of sensory and motor pathways, may provide diagnostic and prognostic information; however, because of the complexity of the technique it is not recommended for general use. The reliance on one variable, such as evoked potentials, to predict the outcome from a traumatic head injury is not recommended.[32]

Neuronal function

Research developments in microprobe technology have resulted in specific electrodes that may be placed into the brain parenchyma to measure tissue brain oxygen tension, brain temperature, pH, lactate and carbon dioxide tensions. These may be individual electrodes or combined with other sensors, such as pressure monitors, to form multimodal tissue monitors.[15]

Cerebral microdialysis is a technique that measures brain extracellular fluid metabolites. Dialysate is obtained through a microdialysis catheter inserted through the same burr hole as an ICP monitor to measure time-dependent changes in markers of neuronal health (e.g. glucose, lactate, pyruvate and other indices of inflammation and metabolism).

Although these systems provide highly specific information about the biochemical milieu of focal areas of brain tissue, their clinical utility is limited to research centres.

BRAIN INJURY SURVEILLANCE

Serial assessment of the anatomical injury is an important part of monitoring head injury. This is done by serial CT scanning at frequent intervals depending on the neurological status of the patient.

Any patient who develops an unexplained neurological deterioration or significant validated deviation of monitored parameters should have a CT scan so that new or delayed intracranial mass lesions are identified.

CT scans should be assessed and scored according to the classification outlined in Table 77.2. The progression or resolution of axonal injury, cerebral oedema, contusion and haemorrhages should be recorded. However, as CT scanning requires transport of the patient to a radiology suite, this should be done only by experienced personnel, when the patient is stable.

BRAIN-SPECIFIC THERAPY

Treatment options directed at ameliorating brain injury are limited. Despite intensive research into defining the pathobiological processes in primary injury, studies analysing therapies designed to modulate intracranial inflammation have not been successful. These include aminosteroids, calcium channel blockade, *N*-methyl-D-aspartic acid antagonists and erythropoietin.

Brain-specific or 'targeted' therapy is directed at maintaining CPP and minimising ICP. Although there is an inherent relationship between these two principles, priorities are different depending on the time course of the underlying injury. This is important as strategies directed at one may have adverse effects on the other.

DEFENCE OF CEREBRAL PERFUSION PRESSURE

The Brain Trauma Foundation guidelines recommend a range of CPP of between 60 and 70 mm Hg.[15] The guidelines also state that the minimum optimal CPP threshold is unclear and may depend upon the autoregulatory status of the patient and varies with time after injury. CPP targets maybe prescribed based on an early hypoperfusive phase and a subsequent hyperaemic phase that have been described in literature.

Early hypoperfusion phase

Soon after injury, cerebral hypoperfusion is present in many patients with severe head injury (GCS ≤8). During this phase, there is an imperative to maintain CPP by supporting systemic haemodynamic function. CPP of at least 60 mm Hg is recommended.

In addition to reduced cerebral blood flow, ICP may be increased by mass lesions or 'cytotoxic' cerebral oedema. During this phase, medical therapies directed at raised ICP, such as osmotherapy or hyperventilation, should be used only if CPP is maintained at an appropriate level and the patient is adequately monitored.

Assessment of adequacy of the response to augmentation of CPP is made by ICP trends, CT scan appearance and, where possible, neurological assessment. If patients appear to have stabilised, sedation may be reduced with the aim of extubation.

Hyperaemic phase

Approximately 25%–30% of patients will develop clinical signs of cerebral hyperaemia, characterised by increased ICP and persistent cerebral oedema on CT scan from 3 to 7 days after brain injury. This may occur due to vasogenic cerebral oedema caused by intracranial inflammation or be associated with increased catecholamines requirements (e.g. >40 μg/min of epinephrine or norepinephrine) to maintain a CPP of 60–70 mm Hg.

In this context, lowering the target CPP target can be considered.

If patients continue to have raised ICP, strategies directed at reducing ICP should be considered.

REDUCTION OF INTRACRANIAL PRESSURE[15]

In the absence of intracranial mass lesions, raised ICP is usually an indicator of severity of the underlying injury and represents exhausted intracranial elastance.

The most effective methods of reducing raised ICP are mechanical interventions such as the removal of mass lesions, the drainage of cerebrospinal fluid or a decompressive craniectomy.

Several medical strategies directed at reducing ICP have been used for many years. Despite widespread use and firmly held beliefs, there is little evidence to support the routine use of these therapies.

ICP should be maintained at less than 20–25 cm H_2O. Trends of ICP are equally as important and should be assessed within the context of CPP and the methods used to defend it.

Surgical evacuation of mass lesions

The prompt detection and evacuation of mass lesions causing raised ICP is the most effective method of relieving intracranial hypertension. Although many of these lesions will be present immediately after injury and will be treated during the resuscitative phase, approximately 10% of patients will develop delayed intracranial haematomas. These are detected by acute unexplained rises in ICP or by CT scan surveillance.

Cerebrospinal fluid drainage

Drainage of cerebrospinal fluid through an intraventricular catheter is an effective method of reducing ICP. If present, these catheters should be placed 5–10 cm above the head and opened for drainage every 1–4 hours.

Decompressive craniectomy

Unilateral or bilateral, frontoparietal craniectomies are highly effective in reducing elevated ICP after traumatic coma.

However, two large, randomised, controlled trials of early and late decompressive craniectomy in patients with traumatic intracranial hypertension have provided important information for understanding the role of surgery. Early decompressive craniectomy did not improve mortality or clinical outcomes of survivors[33] and later decompressive craniectomy, performed because of a raised ICP that was refractory to medical management, not only reduced mortality, but also was associated with an overall increase in disability in

survivors.[34] The role of decompressive craniectomy is now questioned in these patients.

Osmotherapy

The rationale and role of osmotherapy using mannitol or hypertonic solution are addressed above (in the section 'Brain-specific resuscitation'). These same principles also apply during intensive care management.

Mannitol or hypertonic saline should be used only in patients with validated intracranial hypertension who are euvolaemic, haemodynamically stable, with a serum osmolality less than 320 mOsm/L.

There is no evidence that osmotherapy or induced dehydration improves outcome or is more effective in cytotoxic than vasogenic cerebral oedema.[15]

Hyperventilation

The role of hyperventilation during intensive care management is limited to the indications outlined in the section 'Brain-specific resuscitation'.

The routine prolonged use of hyperventilation in head-injured patients is associated with a worse outcome than patients ventilated to normocapnia. This is probably due to the reduction of cerebral blood flow and secondary brain ischaemia.

Current evidence-based guidelines do not recommend the use of routine hyperventilation.[15,17]

Hypothermia

Induced physical cooling reduces cerebral metabolism and tissue oedema, modifies inflammation and reduces ICP.

Induced hypothermia has been used early after injury for prophylactic cerebral protection and later after brain injury to control intracranial hypertension.

However, experimentally demonstrated benefits have not been translated in clinical trials.[35,36]

Active cooling often requires the use of sedatives, neuromuscular blockade and additional antishivering strategies, and the intervention may be associated with hypotension and reduced cerebral blood flow, altered vital organ function, delayed drug metabolism, prolonged length of stay and associated nosocomial complications.

Induced hypothermia for prophylactic early cerebral protection or for raised ICP cannot be recommended.

Avoiding pyrexia ('normothermia')

Pyrexia is common after traumatic brain injury as core temperature gradually increases with time after brain injury.

Experimental models and clinical cohort studies report an association between pyrexia and adverse outcome,[27,28] but the effect of avoiding pyrexia on patient-centred outcomes has not been evaluated. Avoiding pyrexia is challenging as pharmacological agents have modest effects (reducing the temperature by <0.5°C),[37] and the use of induced cooling may be associated with adverse effects as outlined earlier.

The Brain Trauma Foundation does not make a recommendation on avoiding pyrexia, reflecting an absence of appropriate evidence. Avoiding pyrexia cannot be recommended, but remains a common goal in clinical practice (<39°C).

Barbiturate coma

The role of barbiturates in traumatic head injury is similar to hypothermia. Despite experimental evidence that barbiturates reduce cerebral metabolism and reduce ICP, no definitive studies have shown a benefit in clinical trials. Barbiturates have invariably been used in patients with refractory intracranial hypertension where a positive outcome was unlikely, making interpretation of these trials difficult.

Barbiturates may cause hypotension and reduce cerebral blood flow, potentially exacerbating secondary insults in patients with cerebral oligaemia. Prolonged use of barbiturates will delay awakening and predispose the patient to nosocomial complications.

Barbiturates are not recommended on current evidence.[15]

Steroids

Steroids have been advocated for many years to ameliorate intracranial inflammation, thereby reducing ICP. A large international study has provided conclusive evidence that high doses of steroids are associated with adverse outcomes in traumatic head injury, and therefore have no place in management.[15,38]

SEIZURE PROPHYLAXIS

Seizures are infrequent following traumatic head injury and usually present at the time of injury. These should be treated with anticonvulsants (e.g. diazepam, midazolam) when they occur. Subsequent prophylaxis with phenytoin or valproate may be considered for patients with destructive parenchymal lesions on CT scan to prevent early post-traumatic seizures (within 7 days). Short-term seizure prophylaxis does not prevent late-onset post-traumatic epilepsy.[15]

OUTCOME AND PROGNOSIS

Patient factors that determine outcome from traumatic head injury include severity of primary and secondary injuries, traumatic coma (GCS <8), age greater than 60 years, cranial CT scan findings and co-morbidities. Prediction of outcome is difficult as significant functional improvements, particularly in young patients, may occur over time.

There are patients in whom the prognosis is clearly very poor or hopeless. A proportion of these patients will become brain dead and may be considered for organ donation. In other patients, it may be

appropriate to withdraw active treatment. This increasingly complex process requires time, careful consideration and consensus with all members of the health care team and the patient's relatives.

Outcomes from traumatic head injury are difficult to quantify. Although mortality is an easy end-point to measure, functional outcome is an equally important measurement as the effects of traumatic brain injury on psychosocial recovery and duration of rehabilitation often take extended periods of time. In an inception cohort study of patients hospitalised with traumatic head injury in Australia and New Zealand, at 12 months after injury 26.9% of the population had died, and a further 42.7% had moderate or severe disability, or were in a vegetative state.[39] Importantly, even in the group classified as having good recovery (30.4%), over half had impairment of relationships with families or friends, or restriction of social and leisure activities. There is an important debate emerging about the interpretation of disability after brain injury from the varied perspectives of clinicians, families and health care service providers.[40]

CONCLUSION

Severe traumatic head injury is an important and heterogeneous global health problem, with evolving demography and disease patterns. The intensive care management of the condition is challenging and the cornerstone of management remains general intensive care, with brain-specific therapies of unproven efficacy beyond improvements in short-term physiology. There is no standard or uniform method of managing traumatic head injury, and practices are determined by local factors (preferences, experience, caseload and resources) and local interpretation of evidence. Generating high-quality evidence in this context remains a challenging endeavour.[41]

KEY REFERENCES

15. Carney N. *The 4th edition of Guidelines for Management of Severe Traumatic Brain Injury*. 2016. https://braintrauma.org/coma/guidelines.
33. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med*. 2011;364(16):1493–1502.
34. Hutchinson PJ, Kolias AG, Timofeev IS, et al. Trial of decompressive craniectomy for traumatic intracranial hypertension. *N Engl J Med*. 2016;375(12):1119–1130.
35. Clifton GL, Valadka A, Zygun D, et al. Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial. *Lancet Neurol*. 2011;10(2):131–139.
36. Andrews PJ, Sinclair HL, Rodriguez A, et al. Hypothermia for intracranial hypertension after traumatic brain injury. *N Engl J Med*. 2015;373(25):2403–2412.
37. Saxena MK, Taylor C, Billot L, et al. The effect of paracetamol on core body temperature in acute traumatic brain injury: a randomised, controlled clinical trial. *PLoS ONE*. 2015;10(12):e0144740.
38. Collaborators CT. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury—outcomes at 6 months. *Lancet*. 2005;365(9475):1957–1959.
39. Myburgh JA, Cooper DJ, Finfer SR, et al. Epidemiology and 12-month outcomes from traumatic brain injury in Australia and New Zealand. *J Trauma Acute Care Surg*. 2008;64(4):854–862.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Menon DK, Schwab K, Wright DW, et al. Position statement: definition of traumatic brain injury. *Arch Phys Med Rehabil*. 2010;91(11):1637–1640.
2. Shakur H, Roberts I, Piot P, et al. A promise to save 100 000 trauma patients. *Lancet*. 2013; 380(9859):2062–2063.
3. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2013;380(9859):2163–2196.
4. Roozenbeek B, Maas AI, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol*. 2013;9(4):231–236.
5. Langlois JA, Kegler SR, Butler JA, et al. Traumatic brain injury-related hospital discharges. *MMWR Surveill Summ*. 2003;52(4):1–18.
6. Koskinen S, Alaranta H. Traumatic brain injury in Finland 1991-2005: a nationwide register study of hospitalized and fatal TBI. *Brain Inj*. 2008;22(3): 205–214.
7. Feigin VL, Theadom A, Barker-Collo S, et al. Incidence of traumatic brain injury in New Zealand: a population-based study. *Lancet Neurol*. 2013;12(1): 53–64.
8. McAllister TW. Neurobiological consequences of traumatic brain injury. *Dialogues Clin Neurosci*. 2011;13(3):287–300.
9. Martin NA, Patwardhan RV, Alexander MJ, et al. Characterization of cerebral hemodynamic phases following severe head trauma: hypoperfusion, hyperemia, and vasospasm. *J Neurosurg*. 1997;87(1): 9–19.
10. *Advanced Trauma and Life Support* (American College of Surgeons). 2017. https://www.facs.org/quality-programs/trauma/atls.
11. Myburgh J, Cooper DJ, Finfer S, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med*. 2007;357(9):874–884.
12. Cooper DJ, Myles PS, McDermott FT, et al. Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. *JAMA*. 2004;291(11):1350–1357.
13. Curry N, Davis P. What's new in resuscitation strategies for the patient with multiple trauma? *Injury*. 2012;43(7):1021–1028.
14. Flierl MA, Stoneback JW, Beauchamp KM, et al. Femur shaft fracture fixation in head-injured patients: When is the right time? *J Orthop Trauma*. 2010; 24(2):107–114.
15. Carney N. *The 4th Edition of Guidelines for Management of Severe Traumatic Brain Injury*. 2016. https://braintrauma.org/coma/guidelines.
16. Stocchetti N, Maas AI. Traumatic intracranial hypertension. *N Engl J Med*. 2014;370(22):2121–2130.
17. Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. *J Neurosurg*. 1991;75(5):731–739.
18. Cooper D, Ackland H. Clearing the cervical spine in unconscious head injured patients – the evidence. *Crit Care Resusc*. 2005;7(3):181.
19. Marshall L, Marshall SB, Klauber M, et al. The diagnosis of head injury requires a classification based on computed axial tomography. *J Neurotrauma*. 1992;9:S287–S292.
20. Servadei F, Murray GD, Teasdale GM, et al. Traumatic subarachnoid hemorrhage: demographic and clinical study of 750 patients from the European brain injury consortium survey of head injuries. *Neurosurgery*. 2002;50(2):261–269.
21. Hilario A, Ramos A, Millan J, et al. Severe traumatic head injury: prognostic value of brain stem injuries detected at MRI. *AJNR Am J Neuroradiol*. 2012;33(10):1925–1931.
22. Myburgh J. Driving cerebral perfusion pressure with pressors: how, which, when? *Crit Care Resusc*. 2005;7(3):200.
23. Myburgh JA, Upton R, Grant C, et al. A comparison of the effects of norepinephrine, epinephrine, and dopamine on cerebral blood flow and oxygen utilisation. *Acta Neurochir Suppl*. 1998;71:19–21.
24. Myburgh JA, Higgins A, Jovanovska A, et al. A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med*. 2008; 34(12):2226.
25. Cremer OL, Moons KG, Bouman EA, et al. Long-term propofol infusion and cardiac failure in adult head-injured patients. *Lancet*. 2001;357(9250): 117–118.
26. Australian N-SSIft, Group NZICSCT, Group tCCCT. Intensive versus conventional glucose control in critically ill patients with traumatic brain injury: long-term follow-up of a subgroup of patients from the NICE-SUGAR study. *Intensive Care Med*. 2015;41:1037–1047.
27. Bao L, Chen D, Ding L, et al. Fever burden is an independent predictor for prognosis of traumatic brain injury. *PLoS ONE*. 2014;9(3):e90956.
28. Saxena M, Young P, Pilcher D, et al. Early temperature and mortality in critically ill patients with acute neurological diseases: trauma and stroke differ from infection. *Intensive Care Med*. 2015;41(5):823–832.
29. Macmillan C, Andrews P, Easton V. Increased jugular bulb saturation is associated with poor outcome in traumatic brain injury. *J Neurol Neurosurg Psychiatry*. 2001;70(1):101–104.
30. Procaccio F, Polo A, Lanteri P, et al. Electrophysiologic monitoring in neurointensive care. *Curr Opin Crit Care*. 2001;7(2):74–80.
31. Myles PS, Cairo S. Artifact in the bispectral index in a patient with severe ischemic brain injury. *Anesth Analg*. 2004;98(3):706–707.
32. Carter BG, Butt W. Review of the use of somatosensory evoked potentials in the prediction of outcome after severe brain injury. *Crit Care Med*. 2001;29(1):178–186.
33. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med*. 2011;364(16):1493–1502.

34. Hutchinson PJ, Kolias AG, Timofeev IS, et al. Trial of decompressive craniectomy for traumatic intracranial hypertension. *N Engl J Med*. 2016; 375(12):1119–1130.
35. Clifton GL, Valadka A, Zygun D, et al. Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial. *Lancet Neurol*. 2011;10(2):131–139.
36. Andrews PJ, Sinclair HL, Rodriguez A, et al. Hypothermia for intracranial hypertension after traumatic brain injury. *N Engl J Med*. 2015;373(25): 2403–2412.
37. Saxena MK, Taylor C, Billot L, et al. The effect of paracetamol on core body temperature in acute traumatic brain injury: a randomised, controlled clinical trial. *PLoS ONE*. 2015;10(12):e0144740.
38. Collaborators CT. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury—outcomes at 6 months. *Lancet*. 2005;365(9475): 1957–1959.
39. Myburgh JA, Cooper DJ, Finfer SR, et al. Epidemiology and 12-month outcomes from traumatic brain injury in Australia and New Zealand. *J Trauma Acute Care Surg*. 2008;64(4):854–862.
40. Hutchinson PJ, Kolias AG, Menon D. *"Beholders" or patients and families? Life in the fastlane*. 2017. https://lifeinthefastlane.com/beholders-or-patients-and-families/.
41. Kochanek PM, Bell MJ. Tackling the challenges of clinical trials for severe traumatic brain injury in children: screening, phenotyping, and adapting. *Crit Care Med*. 2015;43(7):1544–1546.

78

Maxillofacial and upper-airway injuries

Cyrus Edibam, Hayley Robinson

MAXILLOFACIAL INJURIES

Blunt or penetrating maxillofacial injuries may be isolated or part of multisystem trauma. Life-threatening associated injuries occur in 6.2% of patients with facial injuries and commonly include head, cervical spine and chest injury.[1] Life-threatening airway haemorrhage and airway obstruction are challenging issues and require skilled airway management to prevent adverse outcomes. This chapter outlines the basic anatomy, pathology, complications and common pitfalls in the emergency management of maxillofacial and upper-airway trauma.

EPIDEMIOLOGY

Maxillofacial trauma occurs most frequently in the 15- to 25-year age group and occurs three to five times more often in males than in females.[1–3] Blunt injury mechanisms account for nearly 98% of all maxillofacial injuries.[4] Motor vehicle trauma and physical assault account for the majority of injuries, with the remainder being due to falls, contact sports and industrial accidents.[2,3] The distribution of mechanisms is dependent on demographics and socioeconomic status. Preceding use of alcohol is widely variable and particularly dependent on age group.[3] In multiple trauma patients with an Injury Severity Score >15, maxillofacial injury occurs in up to 16%, with a corresponding mortality rate of 10.5%.[4]

ANATOMICAL ASPECTS

Fractures, haemorrhage, soft-tissue damage and oedema are the commonest manifestations of blunt facial trauma. The severity of facial injury is directly related to the velocity of force applied. Common maxillofacial fractures involve the midface (including orbital) (71.5%), mandible (24.3%) and frontal bone (4.2%).[5]

MANDIBULAR FRACTURES

The mandible is a unique horseshoe-shaped bone that is tubular and weakest where the cortices are thinnest. Most fractures occur at vulnerable points, regardless of the point of impact.[6] Common sites of weakness include the condylar area, followed by the symphyseal and parasymphyseal area and then the angle. Multiple fractures are common (64%),[6] with the body of mandible fractures often being accompanied by fractures of the opposite angle or neck due to transmitted forces. Mandibular fragments are often distracted owing to the action of the lower jaw muscles. Respiratory obstruction may occur after bilateral mandibular angle or body fractures due to the posterior displacement of the tongue – the 'Andy Gump' fracture.[7]

MIDFACIAL FRACTURES

The bones of the middle third of the face are relatively thin and poorly reinforced. Fracture dislocations occur through the bones and suture lines and the facial skeleton acts as a compressible energy-absorbing mass that gives on impact. The series of compartments (nasal cavity, paranasal sinuses and orbits) within the bony framework collapse progressively, absorbing energy and protecting the brain, spinal cord and other vital structures.[8] Multiple complex facial fractures usually result and isolated facial bone fractures are rare. Le Fort described three great lines of weakness in the facial skeleton and subsequently derived the Le Fort fracture classification (Fig. 78.1).[9] Le Fort fractures are perpendicular to the three main vertical buttresses of the facial skeleton – the nasomaxillary, zygomaticomaxillary and pterygomaxillary 'pillars'. Such fractures usually occur with mixed patterns as impact to the face is rarely centred (e.g. right hemifacial Le Fort I and left hemifacial Le Fort II). Airway obstruction may occur from posterior movement of the soft palate against the tongue and the posterior pharyngeal wall.

LE FORT I (ALSO KNOWN AS GUERIN'S FRACTURE)

This fracture involves only the maxilla at the level of the nasal fossa. It follows a horizontal plane at the level of the nose. The fracture separates the palate from the remainder of the facial skeleton (i.e. palate–facial disjunction) and is usually caused by direct low-maxillary blows or by a lateral blow to the maxilla.

ABSTRACT

Maxillofacial injuries may be isolated or part of multisystem trauma. The priorities of management are airway and control of haemorrhage. Elective intubation is the ideal but facilities to preform a surgical airway must be available. Haemorrhage is extremely common but life-threatening bleeding is rare. Urgent surgical opinion should be sought to determine if angiographic or surgical intervention is appropriate. Definitive surgical management is usually delayed 4–10 days to allow swelling to subside. Laryngeal trauma is rare due to protection provided by the sternum and mandible or death at the scene. The degree of injury is not easily assessable based on clinical symptoms, and airway obstruction can be insidious. Up to three-quarters of patients require intubation, and the safest mode is tracheostomy under local anaesthetic.

KEYWORDS

Maxillofacial trauma
facial fracture
laryngeal trauma
airway trauma

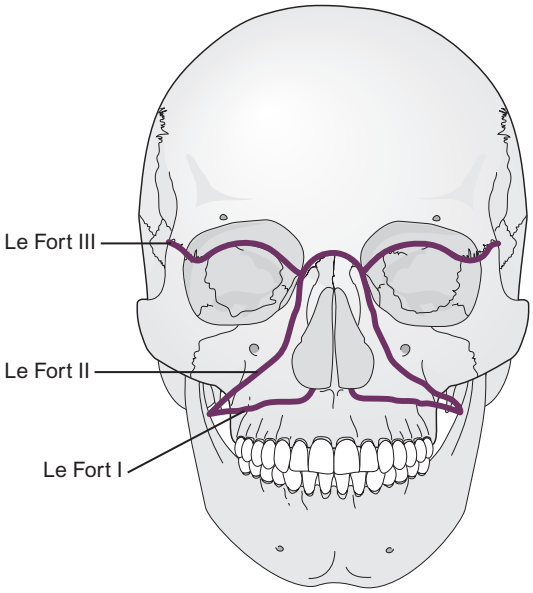


Figure 78.1 Le Fort classification of facial fractures.

LE FORT II

This is the most common midface fracture. The maxilla, nasal bones and medial aspect of the orbit are involved, which results in a freely mobile, pyramidal-shaped portion of the maxilla (i.e. pyramidal disjunction). The fracture line extends from the lower nasal bridge through the medial wall of the orbit, and crosses the zygomaticomaxillary process. It is caused by direct blows to the mid-alveolar area, or by lateral impacts and inferior blows to the mandible when the mouth is closed.

LE FORT III

This is known as craniofacial disjunction because the fracture line runs parallel to the base of the skull, separating the midfacial skeleton from the cranium. The fracture extends through the upper nasal bridge and most of the orbit and across the zygomatic arch. It involves the ethmoid bone, and thus may transect the cribriform plate at the base of the skull.[10] These fractures result from superiorly directed blows to the nasal bones.[10]

TEMPOROMANDIBULAR JOINT

Mechanical temporomandibular joint impairment may result from condylar or zygomatic arch fractures and can prevent jaw opening even after muscle relaxants have been administered.

ZYGOMATIC, ORBITAL AND NASAL FRACTURES

Zygomatic fractures account for approximately 30% of all facial bone fractures.[2,3] Its attachments to the maxilla, frontal and temporal bones are vulnerable and may be disrupted. Orbital injury is commonly associated with midface trauma. The severity of injury in the orbital region varies from oedema and ecchymosis of the periosteal soft tissue to subconjunctival haemorrhage,[11] and loss of visual acuity or ocular rupture. Facial fractures are associated with visual loss and blinding in 0.8% of patients.[12] The blinding mechanism is usually associated with globe perforation rather than optic nerve injury. Orbital blowout fractures occur when pressure that is directly applied to the eye is hydraulically transmitted via the globe to the interior bony structures. The weaker inferior orbital wall usually fractures, causing enophthalmos, diplopia, impaired eye movement and infraorbital hypoaesthesia. Ocular injuries are frequently missed and warrant further examination after primary survey and resuscitation have been completed. Nasal fractures are common, with epistaxis and septal haematoma being the prime concerns.

SOFT-TISSUE INJURIES

Abrasions, contusions and lacerations to the tongue, palate, pharynx, cheek, eyelids, nasolacrimal duct, ear, parotid gland and facial nerve can occur. Oedema evolving over 24–48 hours can be massive and cause gross distortion of soft-tissue structures. Patency of an initially unobstructed airway may become compromised during this period.

ASSOCIATED INJURIES

More than half of all patients with maxillofacial injuries will have other injuries and these are listed below.

BASILAR SKULL FRACTURE

The anterior cranial fossa is often involved in craniofacial injuries. Fractures involving the frontal bone, frontal sinus, nasoethmoid complex or fronto-orbital complex result in bone defects in the skull base and can cause dural tears with resultant leakage of cerebrospinal fluid (CSF). CSF fistulae occur in 10%–30% of basilar skull fractures.[13] The clinical finding of CSF rhinorrhoea represents only the site of exiting CSF and is not diagnostic for anterior cranial fossa lesions. The origin may be from a temporal bone fracture because CSF from the middle ear discharges into the nose via the Eustachian tube. A middle cranial fossa defect can produce rhinorrhoea through the sphenoid sinus. The vast majority of fistulae present within 1 week of injury. Meningitis in patients with midface fractures is uncommon, despite the fact that approximately 25% develop CSF leaks.[14]

Pulsating exophthalmos and the presence of an orbital bruit may lead to the diagnosis of a carotido-cavernous fistula, which may develop following fractures involving the skull base and orbit.

HEAD AND CERVICAL SPINE INJURY

The incidence of head injury in those with maxillofacial trauma has been variably reported to be from 15% for severe head injury, increasing to 80% if all grades of head injuries are included,[15,16] with around 8% requiring neurosurgical intervention.[17] Cervical spine injury has been reported in up to 11% of patients. The prevalence of cervical spine fracture with mandibular injury is 6.5%[18] and is attributed to forces exerted directly or indirectly from the facial skeleton to the neck. C1/C2 and C5-C7 are at particular risk.

The association between maxillofacial and cervical spine injury depends on the mechanism of injury. Falls and motor vehicle accident victims are more likely to have cervical injury than are sporting or personal assault victims.

OTHER INJURIES

In patients with severe maxillofacial trauma; thoracic trauma (~40%), abdominal trauma (~30%) and limb fractures (~40%) are other common co-existent injuries.[15] Dental injuries are present in 15%–20% of patients with maxillofacial fractures.[19,20]

ASSESSMENT OF INJURY

The obvious priorities are airway management and control of haemorrhage and identification of other life-threatening injuries. These are discussed later in detail. Once the patient is stable, formal assessment of the facial injuries can proceed.

HISTORY

Evaluation of facial fractures begins with a history of the injury. The mechanism of injury is important in order to assess the likelihood of other injuries.

EXAMINATION

Physical examination includes inspection for deformity, the presence of enophthalmos, asymmetry, dental malocclusion, nasal septal deviation or haematoma, CSF rhinorrhoea and the extent of jaw opening. Other signs associated with basal skull fracture also should be noted (haemotympanum, Battle's sign, raccoon eyes). Tenderness and mobility on bimanual palpation of the alveolar process and the infraorbital rim or frontozygomatic suture indicates the presence of a complex midfacial fracture. Naso-orbito-ethmoid instability also can be established by bimanual palpation. Visual acuity (in the conscious patient), corneal integrity and pupillary reflexes as well as eye movements (failure of upward movements in orbital blowout fracture) should be assessed early and thoroughly. Facial nerve function also should be assessed if possible. The presence of a bruit over the orbit may indicate a carotido-cavernous fistula.

INVESTIGATION

Computed tomography (CT) scanning, especially with three-dimensional reconstruction, is the preferred and most accurate method of imaging.[21] In addition to bony distortion, fluid in the paranasal sinuses, optic nerve integrity and soft-tissue distortion, the brain, upper cervical spine and other body areas can be visualised concurrently. Other investigations, such as colour Doppler ultrasound studies, CT angiography or standard angiography of the great vessels in the neck, may be required in cases of possible carotid dissection or carotid-cavernous fistulae. Nasal discharge should be tested for β_2-transferrin to confirm the presence of a CSF fistula.[22]

AIRWAY MANAGEMENT

Airway management in maxillofacial injury is potentially complex owing to multiple concurrent compromising factors (Table 78.1).

IMMEDIATE PRIORITIES

- Assess and monitor for signs of airway obstruction whilst maintaining cervical spine precautions
- Clear airway, assist respiration
- Provide high flow oxygen
- Definitive airway intervention.

An initially unobstructed airway may become compromised as swelling and oedema can progress in the initial hours after injury. Careful close monitoring in an intensive care unit or high-dependency unit is essential. Maintaining the head-up position and the use of humidified oxygen may lessen the likelihood of later airway compromise. Sudden obstruction may occur with clot dislodgement and inhalation. Signs of partial obstruction include noisy breathing, stridor, intercostal or supraclavicular recession and restlessness.

Occasionally, patients may assume positions that lessen airway obstruction (e.g. sitting forward or even prone). Simple measures, such as suction and clearing the airway and insertion of an oropharyngeal airway, may suffice.

In midfacial injuries, anterior digital traction on the mobile midsegment may relieve obstruction. In bilateral mandibular fractures of the angle or body, a towel clip or suture through the tongue may allow anterior traction on the unsupported tongue and relieve obstruction.

Bag and mask ventilation may be difficult owing to distorted anatomy, and this should be borne in mind when a decision to intubate is made. Failure of these simple manoeuvres necessitates definitive airway management.

TECHNIQUES (Fig. 78.2)

Facilities to perform a surgical airway must be available prior to elective intubation. The chosen technique

Table 78.1 Airway problems in maxillofacial trauma

GENERAL PROBLEMS	MANAGEMENT
Haemorrhage/debris Impaired laryngoscopy Aspiration risk from blood swallowing Clot inhalation/obstruction Teeth, bone fragments	Suction, volume replacement Head down Definitive control of haemorrhage (see text)
Oedema soft-tissue haematomas Increases over 48 h Mask fit can be poor	Monitor airway closely Head up 30° Maintain spontaneous ventilation during airway Manipulation; laryngeal mask ventilation
SPECIFIC PROBLEMS	
Bilateral mandibular body/angle fractures Posterior displacement of tongue	Anterior traction on tongue or jaw, towel clip or suture through tongue and elevate
TMJ impairment from mandibular condyle and or zygomatic arch fracture Mouth opening limited	Nasotracheal intubation (blind/fibre optic) or surgical airway may be required
Midfacial fracture Mask seal poor Soft palate collapses against pharynx	Anterior traction on mobile segment
Basilar skull Nasotracheal intubation contraindicated Pneumocephalus from mask ventilation	Avoid nasal intubation
Cervical spine injury	Orotracheal intubation with in-line stabilisation; fibre optic intubation; surgical airway

TMJ, Temporomandibular joint.

for securing the airway depends on the presence of airway obstruction and the likelihood of difficult direct laryngoscopy (extent of jaw opening, gross anatomical distortion and swelling, bleeding, operator experience). In a combative patient, or if urgent intubation is necessary, a rapid sequence induction can be used if difficulty in direct laryngoscopy is not anticipated. If direct laryngoscopy is likely to be difficult or impossible, spontaneous respiration must be maintained and intubation carried out under local anaesthesia.

Analgesia can be achieved with a combination of sprayed or nebulised local anaesthetic to the posterior pharynx as well as a transcricoid injection. The orotracheal route for intubation is the route of choice in the presence of a basal skull fracture.

If cervical spine injury is present or suspected, in-line stabilisation is mandatory. A variety of intubation techniques can be used, for example direct laryngoscopy, awake fibre-optic-guided laryngoscopy, video laryngoscopy and retrograde intubation techniques.[23] The operator should use the technique with which he/she is most comfortable. Excessive bleeding or debris may render fibre optic techniques difficult.

Failure to intubate and ventilate in the presence of airway obstruction necessitates the passage of an appropriate-sized laryngeal mask. If ventilation is not possible with a laryngeal mask in situ then emergency cricothyroidotomy should be performed. Formal tracheostomy may be required in those likely to need prolonged ventilatory support (e.g. multiple facial fractures combined with a head injury) and is best performed as a semi-elective procedure in the operating room.[24]

HAEMORRHAGE

Haemorrhage following blunt maxillofacial injury is extremely common. Life-threatening bleeding is rare with an approximate incidence of 1%.[25] Most severe haemorrhage is associated with midfacial fractures, although soft-tissue lacerations alone can cause significant blood loss. Swallowing of large quantities of blood may conceal haemorrhage and predispose to vomiting and aspiration.[26]

The origin of bleeding in facial trauma is complicated as the vascular supply is derived from both the internal and external carotid arteries, with anastomoses occurring between them as well as between both halves of the face. The internal maxillary artery, especially the intraosseous branches, is the main source of bleeding in facial injury because the artery passes within the common Le Fort fracture borders.[24,25] The

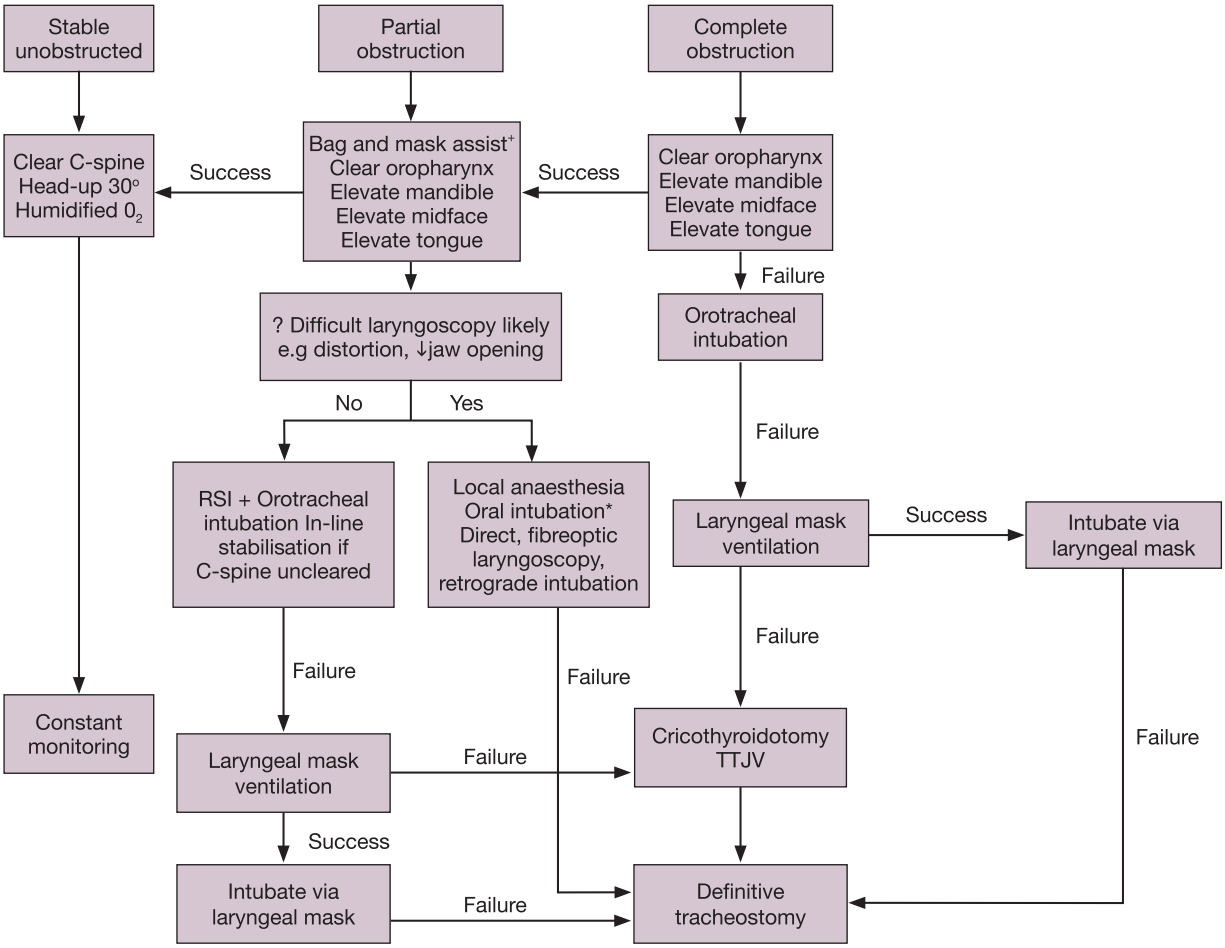


Figure 78.2 An airway management algorithm for maxillofacial trauma. *C-spine*, Cervical spine; *RSI*, rapid sequence induction; *TTJV*, transtracheal jet ventilation. +Mask seal may be poor. *Nasotracheal route contraindicated in basilar skull fracture.

comminuted nature of maxillary fractures makes the detection of an exact site of vessel damage nearly impossible.[24] Branches of the internal carotid artery, such as the lacrimal and zygomatic branches as well as the anterior and posterior ethmoidal arteries, may contribute to bleeding.

The priority is to secure the airway as required. Direct pressure and aggressive packing to open bleeding wounds, nasal cavities and oropharyngeal cavities is then required.[27] Topical vasoconstrictors may not be effective with ongoing nasal haemorrhage. Anterior or posterior nasopharyngeal packs are often an effective at reducing blood loss. Foley catheters passed into the posterior nasopharynx with the balloons filled with air may stem blood loss. These can be used as a second-line option but may displace fractures further. Permissive hypotension in these patients is controversial due to the high rate of concomitant head injuries.[27] Plastic or maxillofacial surgical opinion should always be sought early on regarding the appropriateness of angiographic versus operative intervention for persistent haemorrhage. Angiographic embolisation has an increasing role as a first-line approach for life-threatening intractable bleeding for blunt and penetrating trauma, with a success rate of greater than 85%.[25,28] Operative intervention includes reduction and stabilisation of fractures and direct ligation of bleeding vessels.

DEFINITIVE MANAGEMENT

Definitive surgery is generally delayed 4–10 days to allow swelling to subside. The timing of surgery may be further delayed if a severe head injury co-exists. Early surgery may be warranted if orbital injury with optic nerve compromise is present. The use of high-dose steroids in optic nerve compression is controversial, and no good data exist regarding its efficacy.[24]

Irrigation and debridement of open wounds, closure of facial lacerations and removal of foreign bodies must be undertaken as soon as is practicable, preferably within 24 hours.

The use of prophylactic antibiotics for a CSF leak is debateable, and local protocols should be followed. The timing of operative intervention is still under discussion but the recent trend is for conservative management due to the high rate of spontaneous closure, with lumbar drain insertion for leakage lasting longer than 5–7 days and endoscopic or surgical closure for those that persist.[29] Appropriate tetanus prophylaxis must be given.

The use of modern internal fixation techniques has reduced the need for intermaxillary fixation following elective facial fracture repair, with only unstable comminuted fractures requiring this form of fixation. Submental intubation during fracture repair is being used as an alternative to tracheostomy in some centres.[30]

INJURIES TO THE LARYNX AND TRACHEA

Direct trauma to the airway is rare, accounting for less than 1% of traumatic injury seen in most major centres.[31,32] The bony protection afforded to the airway by the sternum and mandible and death from asphyxia at the accident scene account for the rarity of the injury. Common associations with laryngotracheal injury include thoracic spine injury (15.5%), cervical spine injury (9%), closed head injury (8.5%), facial fractures (20.2%) and vascular injuries (11.3%); exact values vary depending on case series.[31,33]

Laryngotracheal injury can be classified as blunt or penetrating. Failure to recognise these injuries, their complications and specific pitfalls in airway management can lead to death.[34]

MECHANISM OF INJURY

BLUNT INJURY

Common causes include motor vehicle accidents where the extended neck impacts with the steering wheel or dashboard. The 'clothes-line injury' occurs when a cyclist or horse rider collides with a cable or wire causing direct injury to the upper airway. Assaults and strangulation account for the remainder of blunt injuries. Direct blows are more likely to injure the cartilages of the larynx, whereas flexion/extension injuries are most commonly associated with tracheal tears and laryngotracheal transection.[35] The larynx above the cricoid cartilage is injured in 35%, manifesting as oedema, contusions, haematomas, lacerations, avulsion and fracture dislocation, most commonly of the thyroid and arytenoid cartilages.

When the cricoid cartilage itself is injured this may cause recurrent laryngeal nerve dysfunction. The cervical trachea is injured in 45%.[36] Tracheal transection most often occurs at the junction between the cricoid cartilage and trachea. Oedema fluid and air dissecting within submucosal layers of the larynx and trachea may cause airway obstruction. Air in the soft tissues can cause epiglottic emphysema and narrowing of the supraglottic airway. Straining, talking and coughing may worsen the oedema.

PENETRATING INJURY

Penetrating injuries usually result from stab or gunshot wounds. The anterior triangle of the neck is the most common site of entry. The cervical trachea is most commonly involved in stab wounds. Of patients with penetrating laryngotracheal trauma, 19% also had cervicothoracic vascular injury, 15% had oesophageal injury and 34% had chest trauma.[31]

ASSESSMENT OF INJURY

Definitive investigation and management depend on the airway status and presence of associated injury. The degree of injury is not readily assessable on the basis of any one clinical symptom or sign (Box 78.1) and delayed diagnosis is common. Up to 14% of patients may have no presenting sign or symptom suggesting

Box 78.1 Clinical features in laryngotracheal injury

Symptoms
Respiratory distress, stridor, noisy breathing
Neck tenderness or oedema
Hoarseness
Dysphonia
Cough
Dysphagia
Signs
Abnormal laryngeal contour
Subcutaneous emphysema
Cervical ecchymosis
Haemoptysis
Investigations
Plain radiography
- Air in soft tissues
- Pneumomediastinum
- Pneumothorax
- Cervical spine fracture

CT scan
- Cartilage and soft-tissue injury
- Altered airway patency

Laryngoscopy
- Vocal paralysis
- Mucosal or cartilage disruption
- Haematoma
- Laceration

CT, Computed tomography.

Table 78.2 Summary of Schaefer's classification of laryngeal trauma and management

GROUP	SIGNS	SYMPTOMS	MANAGEMENT
1	Minor endolaryngeal haematomas or laceration without detectable fractures	No airway compromise	Humidified oxygen. Consider ICU/HDA admission for observation. Consider steroids
2	More severe oedema, haematoma, minor mucosal disruption without exposed cartilage or non-displaced fractures	Varying degrees of airway compromise	Direct laryngoscopy with oesophagoscopy, possible tracheostomy. Fractures treated expectantly. Likely ICU admission. Consider steroids
3	Massive oedema, large mucosal lacerations, exposed cartilage, displaced fractures or vocal cord immobility	Airway compromise	Tracheostomy, direct laryngoscopy with oesophagoscopy. Admit to ICU as required. Early exploration, reduce fractures and repair. No stent necessary
4	Same as group 3, but more severe with disruption of anterior larynx, unstable fractures, two or more fracture lines, or severe mucosal injuries	Airway compromise	Tracheostomy, direct laryngoscopy. Admit to ICU as required. Early exploration, reduce fractures and repair. May require the use of a stent

HDA, High dependency area; *ICU*, intensive care unit.

Adapted from: Schaefer SD. Management of acute blunt and penetrating external laryngeal trauma. *Laryngoscope*. 2014;124(1):233–244; Schaefer SD. The acute management of external laryngeal trauma. A 27-year experience. *Arch Otolaryngol Head Neck Surg*. 1992;118(6):598–604; Fuhrman GM, Stieg 3rd FH, Buerk CA. Blunt laryngeal trauma: classification and management protocol. *J Trauma*. 1990;30(1):87–92.

laryngotracheal injury.[33] Airway obstruction can be delayed and insidious, therefore frequent reassessment is required. The emphasis has moved towards CT scanning in the first instance in stable patients with laryngeal tenderness, endolaryngeal oedema and small haematomas. CT demonstrates fractures of cartilages, haematomas and other injuries. Further investigation with fibreoptic laryngotracheoscopy under local anaesthesia can be used to demonstrate vocal cord dysfunction, integrity of the cartilaginous framework and laryngeal mucosa. Rigid laryngoscopy can be used when adequate visualisation is not achieved with the former. Pharyngo-oesophagoscopy, contrast studies, open exploration and angiography may be required to exclude aerodigestive tract and major vascular injuries (Table 78.2).

AIRWAY MANAGEMENT

Up to three-quarters of patients with laryngotracheal injury require intubation.[32] The safest mode of intubation is via tracheostomy under local anaesthesia (Fig. 78.3).[37] Blind intubation can lead to complete airway obstruction owing to mucosal disruption and the creation of false passages.[34] Cricoid pressure can lead to laryngotracheal separation and is contraindicated. Positive-pressure ventilation can rapidly worsen air leaks and wherever possible the patient should maintain spontaneous respiration until a tube has been placed distal to the site of injury. Cricothyroidotomy is not recommended as it may compound laryngeal injury. In an emergency, gaping airway wounds (e.g. with tracheal transection) can be intubated under direct vision pending subsequent surgery.

SURGICAL MANAGEMENT

In many case series early fixation leads to fewer complications.[38,39] It is indicated in laryngeal injuries when there is unstable fractures, significant mucosal injuries, haematomas, uncontrolled bleeding or damaged vocal cords. Delays in repair may lead to granulation and scar tissue formation, which can lead to laryngeal stenosis.[34] Laryngeal stenting is still controversial and the risks versus benefits of skeletal stability versus mucosal lining harm must be weighed up.

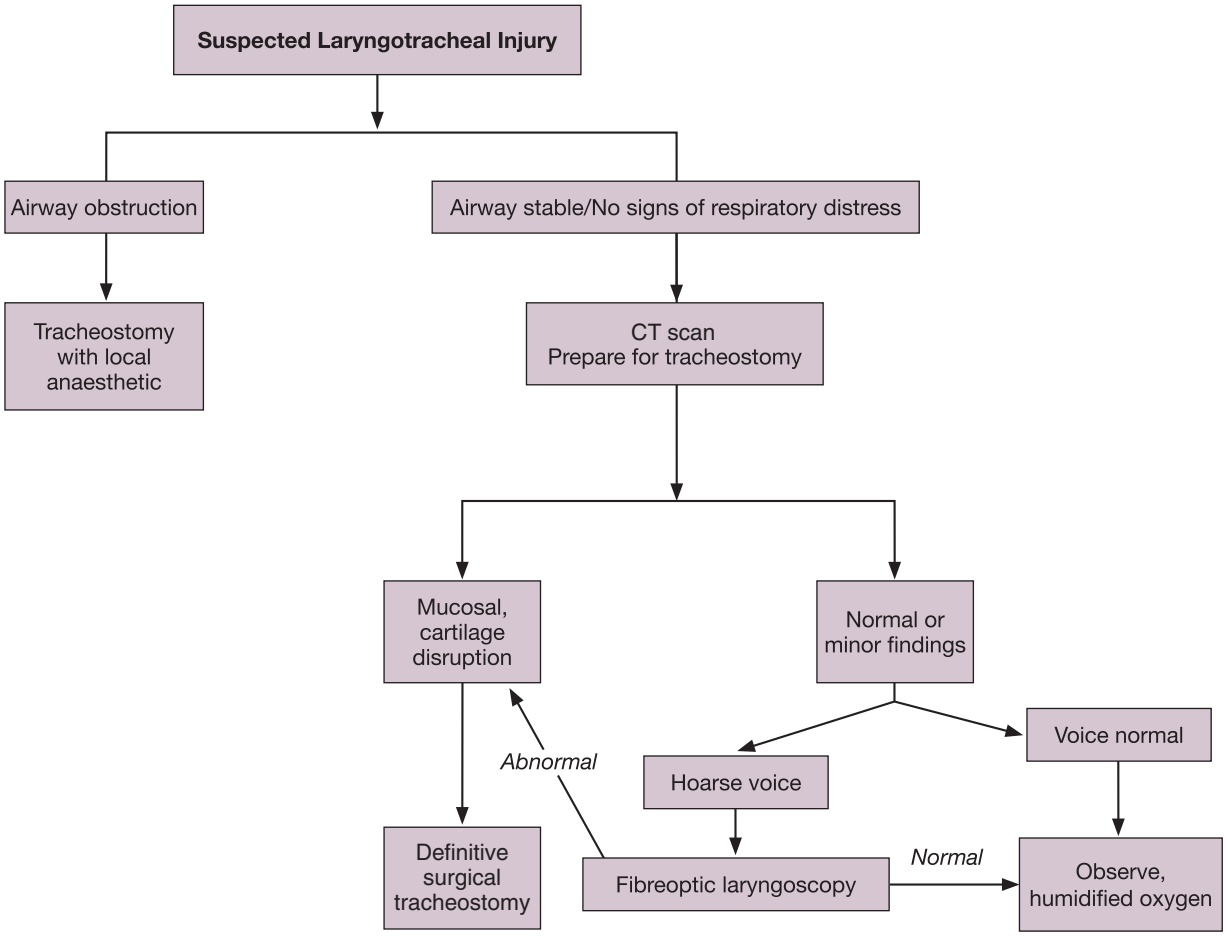


Figure 78.3 Airway assessment and management algorithm for suspected laryngotracheal trauma. *CT*, Computed tomography.

KEY REFERENCES

1. Tung TC, Tseng WS, Chen CT, et al. Acute life-threatening injuries in facial fracture patients: a review of 1,025 patients. *J Trauma*. 2000;49(3):420–424.
3. Cabalag MS, Wasiak J, Andrew NE, et al. Epidemiology and management of maxillofacial fractures in an Australian trauma centre. *J Plast Reconstr Aesthet Surg*. 2014;67(2):183–189.
23. Kellman RM, Losquadro WD. Comprehensive airway management of patients with maxillofacial trauma. *Craniomaxillofac Trauma Reconstr*. 2008;1(1):39–47.
28. Cogbill TH, Cothren CC, Ahearn MK, et al. Management of maxillofacial injuries with severe oronasal hemorrhage: a multicenter perspective. *J Trauma*. 2008;65(5):994–999.
37. Schaefer SD. Management of acute blunt and penetrating external laryngeal trauma. *Laryngoscope*. 2014;124(1):233–244.

Access the complete references list online at http://www.expertconsult.com.

REFERENCES

1. Tung TC, Tseng WS, Chen CT, et al. Acute life-threatening injuries in facial fracture patients: a review of 1,025 patients. *J Trauma*. 2000;49(3): 420–424.
2. Mijiti A, Ling W, Tuerdi M, et al. Epidemiological analysis of maxillofacial fractures treated at a university hospital, Xinjiang, China: a 5-year retrospective study. *J Craniomaxillofac Surg*. 2014; 42(3):227–233.
3. Cabalag MS, Wasiak J, Andrew NE, et al. Epidemiology and management of maxillofacial fractures in an Australian trauma centre. *J Plast Reconstr Aesthet Surg*. 2014;67(2):183–189.
4. Shahim FN, Cameron P, McNeil JJ. Maxillofacial trauma in major trauma patients. *Aust Dent J*. 2006; 51(3):225–230.
5. Gassner R, Tuli T, Hachl O, et al. Cranio-maxillofacial trauma: a 10 year review of 9,543 cases with 21,067 injuries. *J Craniomaxillofac Surg*. 2003;31(1):51–61.
6. Halazonetis JA. The 'weak' regions of the mandible. *Br J Oral Surg*. 1968;6(1):37–48.
7. Seshul MB, Sinn DP, Gerlock AJ Jr. The Andy Gump fracture of the mandible: a cause of respiratory obstruction or distress. *J Trauma*. 1978;18(8): 611–612.
8. Wenig BL. Management of panfacial fractures. *Otolaryngol Clin North Am*. 1991;24(1):93–101.
9. Tessier P. The classic reprint. Experimental study of fractures of the upper jaw. I and II. Rene Le Fort, M.D. *Plast Reconstr Surg*. 1972;50(5):497–506.
10. Manson PN, Hoopes JE, Su CT. Structural pillars of the facial skeleton: an approach to the management of Le Fort fractures. *Plast Reconstr Surg*. 1980;66(1):54–62.
11. Ardekian L, Samet N, Shoshani Y, et al. Life-threatening bleeding following maxillofacial trauma. *J Craniomaxillofac Surg*. 1993;21(8):336–338.
12. MacKinnon CA, David DJ, Cooter RD. Blindness and severe visual impairment in facial fractures: an 11 year review. *Br J Plast Surg*. 2002;55(1):1–7.
13. Phang SY, Whitehouse K, Lee L, et al. Management of CSF leak in base of skull fractures in adults. *Br J Neurosurg*. 2016;30(6):596–604.
14. Eljamel MS. Fractures of the middle third of the face and cerebrospinal fluid rhinorrhoea. *Br J Neurosurg*. 1994;8(3):289–293.
15. Adams CD, Januszkiewcz JS, Judson J. Changing patterns of severe craniomaxillofacial trauma in Auckland over eight years. *Aust N Z J Surg*. 2000; 70(6):401–404.
16. Hogg NJ, Stewart TC, Armstrong JE, et al. Epidemiology of maxillofacial injuries at trauma hospitals in Ontario, Canada, between 1992 and 1997. *J Trauma*. 2000;49(3):425–432.
17. Salentijn EG, Peerdeman SM, Boffano P, et al. A ten-year analysis of the traumatic maxillofacial and brain injury patient in Amsterdam: incidence and aetiology. *J Craniomaxillofac Surg*. 2014;42(6): 705–710.
18. Mulligan RP, Mahabir RC. The prevalence of cervical spine injury, head injury, or both with isolated and multiple craniomaxillofacial fractures. *Plast Reconstr Surg*. 2010;126(5):1647–1651.
19. Rahimi-Nedjat RK, Sagheb K, Walter C. Concomitant dental injuries in maxillofacial fractures - a retrospective analysis of 1219 patients. *Dent Traumatol*. 2014;30(6):435–441.
20. Ruslin M, Wolff J, Boffano P, et al. Dental trauma in association with maxillofacial fractures: an epidemiological study. *Dent Traumatol*. 2015;31(4): 318–323.
21. Schuknecht B, Graetz K. Radiologic assessment of maxillofacial, mandibular, and skull base trauma. *Eur Radiol*. 2005;15(3):560–568.
22. Bernal-Sprekelsen M, Bleda-Vazquez C, Carrau RL. Ascending meningitis secondary to traumatic cerebrospinal fluid leaks. *Am J Rhinol*. 2000;14(4): 257–259.
23. Kellman RM, Losquadro WD. Comprehensive airway management of patients with maxillofacial trauma. *Craniomaxillofac Trauma Reconstr*. 2008;1(1): 39–47.
24. Ardekian L, Rosen D, Klein Y, et al. Life-threatening complications and irreversible damage following maxillofacial trauma. *Injury*. 1998;29(4):253–256.
25. Khanna S, Dagum AB. A critical review of the literature and an evidence-based approach for life-threatening hemorrhage in maxillofacial surgery. *Ann Plast Surg*. 2012;69(4):474–478.
26. Perry M, Morris C. Advanced trauma life support (ATLS) and facial trauma: can one size fit all? Part 2: ATLS, maxillofacial injuries and airway management dilemmas. *Int J Oral Maxillofac Surg*. 2008;37(4):309–320.
27. Krausz AA, Krausz MM, Picetti E. Maxillofacial and neck trauma: a damage control approach. *World J Emerg Surg*. 2015;10:31.
28. Cogbill TH, Cothren CC, Ahearn MK, et al. Management of maxillofacial injuries with severe oronasal hemorrhage: a multicenter perspective. *J Trauma*. 2008;65(5):994–999.
29. Sherif C, Di Ieva A, Gibson D, et al. A management algorithm for cerebrospinal fluid leak associated with anterior skull base fractures: detailed clinical and radiological follow-up. *Neurosurg Rev*. 2012; 35(2):227–237, discussion 237–238.
30. Gadre KS, Waknis PP. Transmylohyoid/submental intubation: review, analysis, and refinements. *J Craniofac Surg*. 2010;21(2):516–519.
31. Bhojani RA, Rosenbaum DH, Dikmen E, et al. Contemporary assessment of laryngotracheal trauma. *J Thorac Cardiovasc Surg*. 2005;130(2): 426–432.
32. Verschueren DS, Bell RB, Bagheri SC, et al. Management of laryngo-tracheal injuries associated with craniomaxillofacial trauma. *J Oral Maxillofac Surg*. 2006;64(2):203–214.
33. Randall DR, Rudmik LR, Ball CG, et al. External laryngotracheal trauma: incidence, airway

control, and outcomes in a large Canadian center. *Laryngoscope*. 2014;124(4):E123–E133.
34. Hwang SY, Yeak SC. Management dilemmas in laryngeal trauma. *J Laryngol Otol*. 2004;118(5): 325–328.
35. Mathisen DJ, Grillo H. Laryngotracheal trauma. *Ann Thorac Surg*. 1987;43(3):254–262.
36. Cicala RS, Kudsk KA, Butts A, et al. Initial evaluation and management of upper airway injuries in trauma patients. *J Clin Anesth*. 1991;3(2):91–98.
37. Schaefer SD. Management of acute blunt and penetrating external laryngeal trauma. *Laryngoscope*. 2014;124(1):233–244.
38. Becker M, Leuchter I, Platon A, et al. Imaging of laryngeal trauma. *Eur J Radiol*. 2014;83(1):142–154.
39. Butler AP, Wood BP, O'Rourke AK, et al. Acute external laryngeal trauma: experience with 112 patients. *Ann Otol Rhinol Laryngol*. 2005;114(5): 361–368.

79

Chest injuries

Ubbo F Wiersema

Chest injuries account for a quarter of all trauma deaths. Blunt trauma accounts for more than 90% of chest injuries in most civilian environments. Immediate death from severe blunt trauma is usually due to blunt rupture of the thoracic aorta, heart or major vessel. Patients who survive to hospital presentation may still have life-threatening chest injuries that require immediate intervention. The majority of chest injuries can be managed with simple measures such as intercostal tube thoracostomy, oxygen therapy, analgesia and mechanical ventilation.[1-3] Tension pneumothorax, open pneumothorax or massive haemothorax require immediate intercostal tube drainage. Urgent thoracotomy is indicated for pericardial tamponade, diaphragmatic rupture and massive haemothorax with ongoing bleeding.[2] Following the resuscitation phase, extensive pulmonary contusions with respiratory failure may require prolonged ventilatory support. Chest injuries that are initially missed may also significantly prolong intensive care stay.

IMMEDIATE MANAGEMENT

Identification of chest injuries forms a core component of the initial assessment of a patient with major trauma – both because immediate intervention can be lifesaving, and because restoration of respiratory and circulatory stability minimises secondary injury to extrathoracic organs, particularly traumatic brain injury.[1] A history of the mechanism and force of injury should be sought as this will guide the likelihood of different injuries and determine the need for more extensive investigation.

During the primary survey the airway patency is ensured, oxygen is administered by face mask and ventilation is assessed. The degree of circulatory compromise is determined and obvious external bleeding is controlled. Two large-bore intravenous cannulae are sited, blood samples taken and intravenous fluids commenced. Intravenous opioid analgesia is given as repeated small boluses, titrated to effect. Complete exposure of the patient is important to facilitate examination of the chest and facilitate intercostal tube insertion, if required. With penetrating trauma all surface wounds must be located so that the pathway of potential injuries can be determined.[2] There are four life-threatening chest injuries that require immediate intervention:

- tension pneumothorax
- open (sucking) pneumothorax
- massive haemothorax
- pericardial tamponade.

In addition, the clinical features of flail chest should be sought, as these will no longer be apparent if positive-pressure ventilation is instituted. Interventions required during initial management are outlined in Box 79.1. A chest radiograph is integral to the initial assessment and should be performed promptly. However, the severity of physiological derangement will dictate the time available for confirmatory imaging, and a patient with clinical signs of tension pneumothorax should undergo immediate intercostal tube thoracostomy before the chest radiograph. If there is no physiological improvement after unilateral tube thoracostomy, a second intercostal tube should be inserted in the contralateral chest.

Lung ultrasound can be completed faster than a chest radiograph, and has significantly higher diagnostic accuracy for pneumothorax and haemothorax when performed by experienced operators.[4] However, clinicians not experienced with lung ultrasound should avoid decision making based on this technique. Subcostal ultrasonography of the heart to look for pericardial fluid forms part of the focused assessment with sonography for trauma (FAST) and should be performed with penetrating chest trauma, or if there is haemodynamic instability with blunt trauma.[2,4,5] An electrocardiogram (ECG) is important in the assessment for blunt cardiac injury.[2,6]

Endotracheal intubation and mechanical ventilation are indicated for the patient with a compromised airway, severe head injury, or gross hypoventilation and/or hypoxaemia not attributable to pneumothorax. Haemodynamic instability should be anticipated (Box 79.2). Rarely, emergency cricothyroidotomy or tracheostomy is required when an airway obstruction cannot be bypassed by translaryngeal intubation. A nasogastric or orogastric tube (if facial injuries are suspected)

ABSTRACT

Chest injuries account for a quarter of all trauma deaths, usually from rupture of the thoracic aorta. On presentation to hospital, life-threatening chest injuries that require immediate identification and management include tension pneumothorax, open pneumothorax, massive haemothorax and pericardial tamponade. Most chest injuries can be managed with simple measures including intercostal tube insertion, oxygen therapy, analgesia and mechanical ventilation. Urgent thoracotomy is indicated for pericardial tamponade, diaphragmatic rupture and massive haemothorax with ongoing bleeding. Emergency thoracotomy is indicated after penetrating chest trauma with witnessed loss of vital signs. Significant blunt aortic injury requires good blood pressure control and endovascular or operative repair. Tracheobronchial and oesophageal injuries are uncommon, but require prompt treatment to avoid significant morbidity. Delayed identification of injuries and severe chest wall injuries may require prolonged intensive care stay.

KEYWORDS

Pneumothorax
haemothorax
pericardial tamponade
thoracotomy
thoracostomy
flail chest
blunt aortic injury
blunt cardiac injury
rib fracture
TEVAR

Box 79.1 Immediate management of chest trauma

Indications for intercostal drain insertion
- Pneumothorax
- Haemothorax

Indications for urgent thoracotomy
- Pericardial tamponade
- Diaphragmatic rupture
- Massive haemothorax with ongoing bleeding

Indications for emergency thoracotomy
- Witnessed loss of vital signs after penetrating trauma

Indications for intubation and positive-pressure ventilation
- Airway compromise
- Gross hypoventilation and/or hypoxaemia (not attributable to pneumothorax)
- Severe head injury

Box 79.2 Causes of cardiovascular collapse on induction of anaesthesia and positive-pressure ventilation in chest-injured patients

- Excessive anaesthetic agent
- Hypovolaemia
- Oesophageal intubation with hypoxaemia
- Tension pneumothorax
- Pericardial tamponade
- Anaphylaxis
- Systemic air embolism
- Severe blunt cardiac injury

should be inserted to decompress the stomach after endotracheal intubation.

PNEUMOTHORAX

Pneumothorax visible on the initial chest radiograph should be treated with insertion of an intercostal tube connected to an underwater seal drainage system (Fig. 79.1). A single bottle drainage system without suction is usually adequate. Low-pressure suction (20 cm H_2O) is applied if the pneumothorax fails to fully resolve, or if there is associated haemothorax (Fig. 79.2). A three-bottle system (or a commercially available three-in-one system) allows more accurate control of suction (Fig. 79.3). Use of antibiotics (to prevent empyema or pneumonia) is controversial, but contamination during intercostal tube insertion is common and a 24-hour course of a first-generation cephalosporin may be appropriate.[7,8]

Tension pneumothorax results from progressive accumulation of air in the pleural space, positive intrapleural pressure and cardiorespiratory decompensation.[9] In awake patients, slow development of positive intrapleural pressure leads to progressive hypoxaemia and respiratory distress. Tachycardia is common, but preserved venous return maintains cardiac function

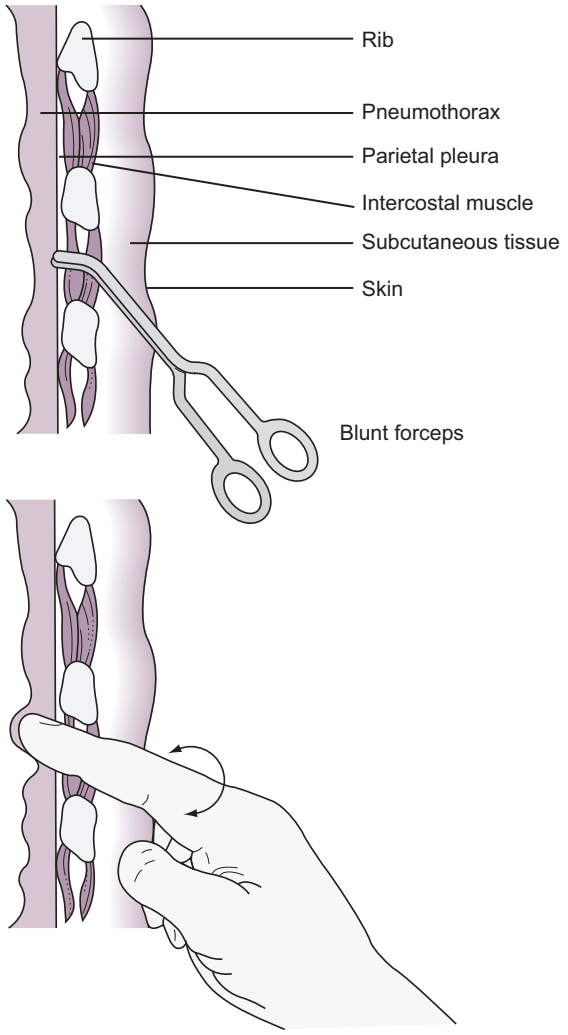


Figure 79.1 Intercostal tube insertion. After sterile preparation and drape, 1% lidocaine is infiltrated in the midaxillary line at the level of the nipple. A 2–3 cm transverse skin incision is made. Dissection is performed by blunt forceps down to the pleura passing just superior to the rib surface to avoid injury to neurovascular structures. A gloved finger is used to confirm separation of lung from chest wall. A large-bore (28–32 Fr) intercostal tube is inserted without a trocar and advanced in a postero-superior direction. Curved forceps clamped to the distal side hole of the tube can be used to guide the tube through the chest wall. The tube is immediately connected to an underwater seal drainage system (see Figs 79.2 and 79.3) and checked for satisfactory drainage and tidal rise and fall in the fluid level with respiration. Non-absorbable sutures are used to seal the skin incision around the tube and secure the tube. The intrathoracic position of the tube is checked with a chest radiograph.

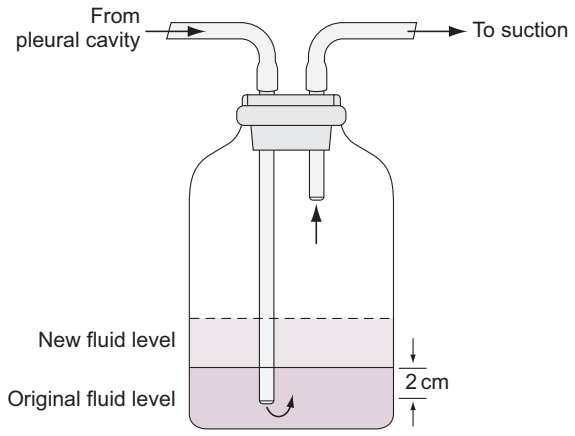


Figure 79.2 Single-bottle drainage system for haemopneumothorax. Air drainage will become more difficult if there is also fluid drainage, raising the fluid level in the bottle *(dashed line)* and increasing the depth of immersion of the hollow rod. This can be overcome by applying low-pressure suction (20 cm H_2O). *Arrows* indicate direction of air flow.

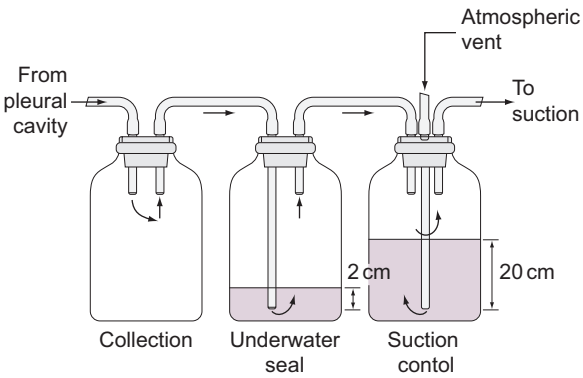


Figure 79.3 Three-bottle chest drainage system. The first bottle (connected to the intercostal tube) is a fluid collection chamber, the second functions as a one-way valve (underwater seal), and the third (connected to wall suction) limits the amount of suction applied. The level of suction is set by adjusting the depth of the atmospheric vent whilst ensuring that it bubbles continuously. Commercially available drainage systems function on the same principles as the three-bottle system. *Arrows* indicate direction of air flow.

and blood pressure. In sedated patients on positive-pressure ventilation, the positive intrapleural pressure throughout the respiratory cycle can lead to the rapid development of hypoxaemia. Cardiac output is compromised by obstructed venous return; hypotension is prominent and may progress to cardiac arrest. In both awake and ventilated patients, chest signs (hyperexpansion, decreased breath sounds and tracheal deviation) are not reliably present.[9]

If tension pneumothorax is suspected clinically, an intercostal tube should be inserted immediately, prior to the chest radiograph. Blunt dissection and insertion of a gloved finger into the pleural space allow rapid decompression of tension, prior to intercostal tube insertion.[7] Needle thoracostomy with a large-bore cannula inserted into the second intercostal space in the midclavicular line may be used to drain air more rapidly for patients in extremis. However, this is rarely necessary and may puncture the lung or a blood vessel, fail to reach the pleural space or kink when the needle is removed from within the cannula.[7] Furthermore, the landmarks for needle thoracostomy are often identified incorrectly, increasing the risk of adverse outcome. Whether successful or not, needle thoracostomy must be followed by intercostal tube drainage.

Open pneumothorax occurs when a chest wall defect allows direct communication of a pneumothorax with the exterior, usually after penetrating trauma. Tension can develop if air can enter but not exit through the defect. Treatment involves the application of an occlusive, non-adherent, square dressing sealed along three edges over the wound after sterile skin preparation. This allows air to escape but not enter through the wound, but should be followed by intercostal tube insertion at a site not immediately adjacent to the wound.

Simple pneumothorax may develop tension at any stage, especially with positive-pressure ventilation (see Box 79.2). A small pneumothorax may be missed on the initial chest radiograph. In the supine position pleural air collects anteroinferiorly and is demonstrated radiologically by a deep sulcus sign or increased radiolucency of one side of the chest compared with the other (Fig. 79.4).[10]

Occult pneumothorax is defined as visible on chest computed tomography (CT), or upper slices of an abdominal CT, but not plain radiograph. Drainage is not usually required, but should be considered if prolonged surgery is anticipated, there is significant cardiorespiratory compromise or interhospital transport is necessary. With a conservative approach the patient should be carefully monitored for deterioration from expansion of the pneumothorax.[11,12]

Subcutaneous emphysema over the chest wall in a patient with blunt chest trauma is almost always associated with pneumothorax, but should raise suspicion of other injuries (Box 79.3). The pneumothorax may not be visible on chest radiograph, either because it is obscured by the emphysema, or because it has largely decompressed into subcutaneous tissues. An intercostal tube should be inserted.

If there is no associated fluid collection, the intercostal tube can be removed once the pneumothorax is no longer visible on chest radiograph and there has been no air drained for at least 24 hours. Persistent air leak and incomplete drainage of a pneumothorax after

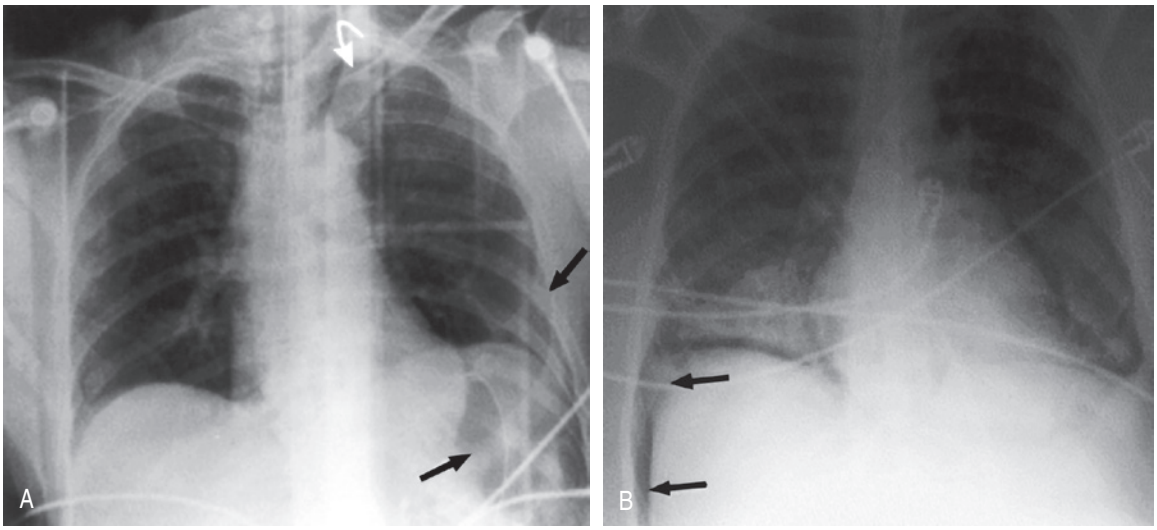


Figure 79.4 (A) Moderate-sized left pneumothorax on supine chest radiograph. The visceral pleura is visible at the lung apex *(curved arrow)*. Hyperlucency is visible in the left lower chest *(straight arrows)*. (B) Supine chest radiograph of right-sided deep sulcus sign *(arrows)*. *From Miller LA. Chest wall, lung, and pleural space trauma.* Radiol Clin North Am. *2006;44(2):213–224, viii.*

Box 79.3 Causes of pneumothorax, subcutaneous emphysema and/or pneumomediastinum

Lung puncture
Tracheobronchial injury
Oesophageal injury
Facial or pharyngeal injury
Abdominal or retroperitoneal injury (air tracking up)

intercostal tube insertion should prompt investigation for tracheobronchial or oesophageal injury. However, the depth of the tube within the pleural space and tubing connections should be checked to ensure that air is not being inadvertently entrained from outside the chest. Incomplete drainage with no air leak is usually due to tube malplacement.

HAEMOTHORAX

Haemothorax visible on chest radiograph should be drained as completely as possible (see Fig. 79.1). The tube can be removed once radiographic clearance is achieved, with <100 mL per 24 hours drainage. A small haemothorax (<300 mL) (visible on ultrasound or CT) may initially be managed conservatively, but should be drained if it enlarges. Persistent opacity on chest radiograph after tube placement should be investigated with CT or ultrasound to determine whether there is significant undrained fluid (see section "RETAINED HAEMOTHORAX AND EMPYEMA" later).

Massive haemothorax, defined as >1500 mL, causes life-threatening circulatory compromise from hypovolaemia and vena caval compression, as well as hypoxaemia. This requires immediate tube drainage and consideration of surgical exploration.[12] If the amount of ongoing bleeding following initial drainage is low, and if the patient remains haemodynamically stable after initial resuscitation and the blood is venous in appearance, the patient can be managed with close observation. Ongoing bleeding of >200 mL per hour, or >600 mL over 6 hours (massive haemothorax equivalent), is an indication for thoracotomy.

PERICARDIAL TAMPONADE

Pericardial tamponade should be suspected in any patient with a gunshot wound to the chest, or stab wound to the precordium. It occurs rarely with blunt trauma, but should be suspected if there is hypotension out of proportion to blood loss, and distended neck veins. Pulsus paradoxus may be detected in the spontaneously breathing patient. The differential diagnosis includes tension pneumothorax (most likely), cardiogenic shock from severe blunt cardiac injury, or inadequate resuscitation. Pericardial fluid can be detected with ultrasound via a subcostal view (as part of the FAST scan).[4] Echocardiography, or an operative subxiphoid window, can be used if diagnostic uncertainty remains.

Haemodynamically unstable patients should undergo thoracotomy.[13,14] Subxiphoid pericardiotomy can be performed in selected stable patients, but may

require conversion to open thoracotomy. Needle pericardiocentesis is rarely effective in the acute setting, but may have a role in the drainage of delayed pericardial effusions following stab wounds.[13]

CARDIAC ARREST AND EMERGENCY THORACOTOMY

External cardiac massage is invariably unsuccessful in the trauma setting; it may cause further injury to intrathoracic structures and obstruct access to the patient for more potentially useful interventions such as bilateral pleural decompression. For patients with witnessed loss of vital signs after penetrating chest trauma, emergency thoracotomy should be considered if suitably experienced medical personnel are available.[13–16] This is rarely successful for blunt trauma. The standard approach is a left-sided anterolateral thoracotomy. Access to the thoracic cavity facilitates specific interventions[13–15]:

- release of pericardial tamponade and control of cardiac bleeding
- control of intrathoracic bleeding
- control of massive bronchovenous air embolism
- control of bronchopleural fistula with pulmonary hilar cross-clamping
- temporary cross-clamping of the descending aorta, to redistribute blood volume to the brain, improve coronary perfusion and control intra-abdominal blood loss
- internal cardiac massage.

These temporising (damage control) measures are followed by transfer to the operating room for completion of surgery[14,15,17]:

- definitive repair of cardiac injury
- pulmonary tractotomy, wedge resection, or lobectomy/pneumonectomy for lung injury
- repair or grafting of vascular injury.

Postoperatively, the patient is admitted to the intensive care unit (ICU) for rewarming, correction of coagulopathy and resuscitation.

SPECIFIC INJURIES

After addressing initial management issues, a secondary survey and further imaging are performed to identify all injuries. Extrathoracic injuries causing haemodynamic instability should be addressed (e.g. laparotomy) before completion of thoracic imaging; unstable patients should not be transferred to an imaging department away from resuscitation facilities. With the widespread availability of multislice helical CT, chest CT angiography has become the primary imaging modality for the diagnosis of specific chest injuries. This is usually performed as part of a whole body 'pan scan' (CT head, neck, chest, abdomen and pelvis) with injection of intravenous contrast timed to provide aortic angiography. Endotracheal intubation and mechanical ventilation may be required to facilitate CT (e.g. the combative trauma patient with ethanol intoxication). Exposure to high doses of radiation has raised concern about the liberal use of the pan scan.[18] Chest CT is unlikely to identify additional significant injuries if the chest radiograph is normal and the mechanism of injury was low risk.[19]

BLUNT AORTIC INJURY

Blunt aortic injury usually occurs as a result of severe deceleration injury causing a tear at the junction between the fixed descending aorta and the mobile aortic arch, just distal to the origin of the left subclavian artery.[5] Less frequently the ascending aorta (or arch vessels) is injured by direct trauma. Most patients with blunt aortic injury die at the scene from complete aortic wall transection, or associated injuries. Of those that reach hospital, 90% will have a significant aortic injury and 50% of these will die with 24 hours.[5,20] Blunt aortic injuries may be divided into[21–23]:

- *significant aortic injury*, with disruption of the intima and full thickness of the media; there is a high risk of rupture
- *minimal aortic injury*, with laceration limited to the intima and inner media – radiologically this manifests as an intimal flap or pseudoaneurysm <1 cm in length, with minimal or no periaortic haematoma; there is a low risk of rupture.

Aortic injury should be suspected if the mechanism of injury is suggestive of rapid deceleration, such as high-speed (greater than 50 km/h) motor vehicle or motorcycle crash, pedestrian hit by a vehicle, or fall from a height greater than 3 m.[5,24] Clinical signs of significant aortic injury include unequal upper limb pulses, pseudocoarctation or interscapular murmur, but these are often absent.

Historically, chest radiography has been the screening test (to detect mediastinal haematoma), and aortic angiography the diagnostic test for blunt aortic injury.[22] Helical CT chest angiography is now the diagnostic test of choice, although transoesophageal echocardiography may be more appropriate in certain circumstances[23,25]:

- *Chest radiograph* features of blunt aortic injury are caused by distortion of normal mediastinal contour by periaortic haemorrhage. A widened mediastinum (greater than 8 cm at the level of the aortic knuckle) is the principal finding (Box 79.4).[26] A supine chest radiograph accentuates mediastinal width and in the acute trauma setting is often of suboptimal quality. Measurement of left mediastinal width (>6 cm), or left mediastinal width to mediastinal width ratio (>0.6), may improve specificity.[26]

Box 79.4 Chest radiograph signs of blunt aortic injury

SIGNS OF PERIAORTIC HAEMATOMA	INDIRECT SIGNS
Widened mediastinum (>8 cm)	Left haemothorax
Obscured aortic knuckle	Left pleural cap
Opacification of aortopulmonary window	Fractured first or second ribs
Deviation of trachea, left main bronchus or nasogastric tube	
Thickened paratracheal stripe	

Box 79.5 Signs of aortic branch vessel injury

- Supraclavicular haematoma
- Pulse discrepancy in arms
- Brachial plexus palsy or stroke
- Widened upper mediastinum on chest radiograph

- *Multislice helical (multiple row detector) chest CT angiography* (with more than 16 detectors) provides sufficient resolution in multiple planes for CT to be used as the sole diagnostic test, and has largely superseded other imaging modalities for diagnosis of aortic injury.[20,23]
- *Single-slice helical chest CT* may demonstrate direct signs of aortic injury. However, more commonly, aortic injury manifests indirectly with periaortic haematoma, and a further diagnostic test is required.[23] Nevertheless, by differentiating periaortic haematoma from other types of mediastinal haematoma, and excluding other causes of an abnormal mediastinal contour, single-slice helical CT provides a useful screening test[23] where multislice CT is not available.
- *Transoesophageal echocardiography* is rapid and portable, making it suitable for examination of the unstable patient (e.g. in the operating room). It provides high diagnostic accuracy for aortic injury and also allows examination for blunt cardiac injury.[25] However, imaging of the distal ascending aorta, proximal arch and major branches is limited. Thus if signs of mediastinal haematoma are detected, but an aortic injury is not identified, further diagnostic imaging is warranted.[23] It is contraindicated if an upper airway or oesophageal injury is suspected.
- *Aortic angiography* is relatively time consuming and requires transfer of the patient to the angiography room, making it potentially hazardous for the unstable patient. However, it is the preferred diagnostic test if branch vessel injury is suspected (Box 79.5), or if uncertainty remains after other diagnostic imaging.[23] It is also necessary for endovascular aortic repair, and may be required for operative planning.

Significant aortic injury requires prompt surgical or thoracic endovascular aortic repair (TEVAR).[5,20,22,27] However, this should not take priority over other life-saving interventions (e.g. control of external or pelvic bleeding, laparotomy, or craniotomy for intracranial haemorrhage). Open surgical repair requires a left posterolateral thoracotomy and selective right-lung ventilation. Operative techniques include direct repair (clamp and sew), or techniques that maintain distal aortic perfusion (bypass).[5,22,27] The latter reduce the risk of postoperative paraplegia from spinal cord ischaemia, but often require systemic heparinisation, which may exacerbate bleeding from other injuries. Sometimes a lumbar drain for cerebrospinal fluid (CSF) drainage is placed perioperatively to improve spinal cord perfusion and potentially reduce the incidence of paraplegia. Postoperatively, CSF is drained freely to maintain a CSF pressure less than 10 mm Hg. The drain is removed after 3 days if there are no neurological complications. Surgery should be deferred, sometimes indefinitely, if severe associated injuries or co-morbidities make the operative risk unacceptably high. In such cases TEVAR may still be feasible and in many institutions has become the primary method of aortic repair.[5,20,22,27] The procedure involves isolation of the injured section of aorta by deployment of endoluminal stents, usually via cannulation of the iliac or femoral artery. Although less invasive and less time consuming than open repair, long-term outcome data are lacking and complications may occur.[5,20,22,27] Endoleaks can arise from incomplete exclusion of the site of injury, or inadequate apposition along the lesser curve of the aorta. Lesions immediately adjacent to the left subclavian artery may require stent coverage of the artery to fully exclude the site of injury. This may result in endoleak due to retrograde blood flow from the left subclavian artery, or ischaemia of the left upper limb or vertebral artery territory requiring left subclavian to left carotid artery grafting. Device collapse causing catastrophic aortic occlusion can occur if the endograft is oversized. With improvements in technology and operator experience, TEVAR now has a lower risk of mortality, paraplegia and blood loss than open surgery.[20] Serial follow-up imaging is recommended after TEVAR.[5,22]

In patients unfit for immediate intervention, beta blocker +/− vasodilator therapy is given as tolerated to decrease aortic wall shear forces, aiming for a systolic blood pressure <100 to 120 mm Hg and heart rate <100 beats per minute. Delayed repair, after effective blood pressure control, has not been shown to worsen outcome and may reduce the peri-procedural risk of paraplegia.[20]

Minimal aortic injury, with no associated periaortic haematoma or pseudoaneurysm on initial CT can be managed expectantly, with serial imaging.[21] Development of pseudoaneurysm, or periaortic haematoma should prompt consideration for TEVAR.[22]

BLUNT CARDIAC INJURY

Blunt cardiac injury results from compression of the heart between the sternum and the spine, abrupt

pressure changes within cardiac chambers, or deceleration shear injury. A wide spectrum of injuries has been described, but may be classified according to the clinical sequelae and the need for intervention[6]:

- *Minor ECG and cardiac enzyme abnormalities:* sinus tachycardia and premature beats are common, but usually resolve within 24 hours without intervention.
- *Complex arrhythmias:* these may cause heart failure, or persistent hypotension, and may warrant antiarrhythmic therapy.
- *Free wall rupture:* this is usually fatal, but atrial rupture may present with haemopericardium +/− tamponade. Immediate drainage and repair is required.
- *Heart failure:* this may develop from gross myocardial injury, septal rupture (causing left to right shunt), or valvular injury (causing regurgitation). The latter may not manifest until weeks later. Septal rupture and severe valvular injury require surgery. Myocardial dysfunction may require inotrope therapy.
- *Coronary artery injury:* this is very rare and ST elevation on ECG is more likely to be due to a primary myocardial infarction.

All patients should have an ECG on admission. If this is normal and the patient is young, haemodynamically stable and has no history of cardiac disease, the risk of significant injury is very low and no further cardiac evaluation is required. Other patients should be monitored for late sequelae of significant cardiac injury (arrhythmia or heart failure).[6,28] Patients who remain haemodynamically stable with only minor ECG changes, and who have a normal troponin level at 6–8 hours post injury, have a low risk of cardiac complications.[28]

Echocardiography is indicated for patients with hypotension unexplained by other injuries, heart failure or persistent arrhythmias.[2,28] Undisplaced sternal fracture does not of itself warrant cardiac evaluation.[28,29]

TRACHEOBRONCHIAL INJURY

Blunt rupture of the trachea or bronchi results from crush injury or rapid deceleration with shearing of the airway between a fixed trachea and mobile lungs. The proximal right main bronchus is the most common site of injury.[2,30] Large injuries present with respiratory distress, subcutaneous emphysema and haemoptysis (see Box 79.3).[31] The chest radiograph demonstrates pneumothorax and mediastinal emphysema. Dramatic deterioration may follow the institution of positive-pressure ventilation (see Box 79.2). With smaller injuries, initial findings are often overshadowed by associated injuries with delay in diagnosis. Persistent pneumothorax with a large air leak, or recurrent pneumothoraces and pulmonary collapse, should prompt further investigation. Flexible bronchoscopy confirms the diagnosis and identifies the level of injury. Treatment is usually primary repair, although non-operative management has been described.[32] Late complications of either approach include post-obstructive pneumonia, empyema or bronchiectasis.[30]

With penetrating trauma the cervical trachea is most commonly injured. Immediate management involves tracheal intubation (preferably with flexible bronchoscopy) with the cuff positioned distal to the tear to ablate the air leak. With a large neck wound the endotracheal tube can be passed directly through the wound in emergency situations.

DIAPHRAGMATIC RUPTURE AND DIAPHRAGMATIC PARESIS

The usual mechanism of diaphragmatic rupture is gross abdominal compression from direct vehicular intrusion. The risk of rupture is higher with lateral impact collisions, but not seat belt use.[33] Associated injuries are very common.[33] Rupture of the left hemidiaphragm is more common because the right hemidiaphragm is congenitally stronger and protected by the liver.

Symptoms (dyspnoea and chest pain) are non-specific. Rarely bowel sounds are audible on chest auscultation. Diagnostic chest radiograph findings are herniation of bowel into the thoracic cavity and nasogastric tube above the left hemidiaphragm. Indirect signs include an elevated or distorted diaphragmatic outline, or pleural effusion, but these may be obscured by adjacent pulmonary pathology, phrenic nerve injury or by positive-pressure ventilation.[34] The low diagnostic accuracy of chest radiography often results in delayed diagnosis unless further imaging is performed. Multislice helical CT has high diagnostic accuracy, but magnetic resonance imaging, or video-assisted thoracoscopic surgery (VATS) may be required if uncertainty persists.[34,35] Prompt operative repair is important to prevent bowel incarceration or perforation. The choice of surgical approach (laparotomy or thoracotomy) is dictated by associated injuries.

Traumatic phrenic nerve palsy, or postoperative diaphragmatic dysfunction, may go unrecognised whilst the patient is on mandatory positive-pressure ventilation. With the transition to spontaneous ventilation, paradoxical abdominal and chest wall movement, reduced vital capacity and difficulty weaning from ventilatory support become evident.

OESOPHAGEAL INJURY

Rupture of the oesophagus from blunt trauma is rare. Penetrating trauma is more likely to injure the cervical portion of the oesophagus than the thoracic portion. Oesophageal perforation may also result from attempted endotracheal intubation or gastric tube insertion during resuscitation of the trauma patient.[36] Clinical features of thoracic oesophageal injury include

chest pain, dysphagia, pain on swallowing, haematemesis and subcutaneous emphysema (see Box 79.3). Chest radiograph findings include pneumothorax and/or hydrothorax, mediastinal emphysema, or widened mediastinum.[31] Suspected oesophageal injury from blunt trauma to the chest, or penetrating trauma to the chest or lower neck (zone 1), should be investigated with CT angiography.[14,36] Perioesophageal air and/or fluid on CT should be investigated further with oesophagoscopy or oesophagography (gastrografin swallow).[36] Treatment is immediate surgical repair.[36] Postoperatively, nutrition is provided by an enteral feeding tube, with nil per oral for 5 days, until confirmation of healing with a normal oesophagography.[36] Occasionally, stable patients with a small, isolated thoracic oesophageal injury can be managed with oesophageal stenting, clips and thoracoscopic debridement and drainage.[36] Delayed recognition or repair (more than 12 hours post injury) leads to septic shock from mediastinal contamination. Extensive irrigation and drainage is then required, but postoperative complications are common.[36]

PULMONARY INJURY

Pulmonary contusion is characterised by interstitial haemorrhage and oedema, with a secondary inflammatory reaction. Clinically there are signs of increased work of breathing, associated with impaired gas exchange and sometimes haemoptysis. The chest radiograph demonstrates patchy interstitial infiltrates, or consolidation not confined to anatomical segments. Gas exchange and radiographic findings may initially be unremarkable, with deterioration over the first 24–48 hours.[3,10] CT and lung ultrasound are more sensitive at detecting contusion, and quantification of lung volume affected predicts risk of acute respiratory distress syndrome (ARDS).[37,38] In the absence of complications (ARDS, pneumonia or aspiration) clinical and radiological recovery can be expected within 3–5 days.[10]

Treatment is supportive with humidified oxygen therapy, and encouragement of deep breathing and coughing in the spontaneously breathing patient. Non-invasive ventilation can be used in selected patients if gas exchange is poor. Intubation and mechanical ventilation is indicated for refractory hypoxaemia, or if intubation is required for non-pulmonary reasons. Routine corticosteroids are not indicated. Antibiotics should be reserved for superimposed pneumonia.[3] After adequate initial fluid resuscitation, unnecessary further fluid resuscitation should be avoided.

Pulmonary laceration occurs when disruption of lung architecture, with formation of an air or blood-filled cavity, occurs after blunt or penetrating trauma. On chest radiography, lacerations are often initially obscured by adjacent contusion, but typically take many weeks to resolve and may be complicated by abscess formation or bronchopleural fistula.[10]

BONY INJURIES

Half of all rib fractures are missed on plain chest radiography, but should be suspected if there is localised tenderness over the chest wall. Good analgesia to prevent pulmonary complications from sputum retention is essential.[39] This risk may not be clinically apparent initially, but deterioration in respiratory status over the next few days should be anticipated, especially in the elderly, smokers or patients with pre-existing pulmonary disease. First- and second-rib fractures, scapula fracture and sternoclavicular dislocation are markers of high-energy trauma.[3]

Most sternal fractures occur in restrained occupants involved in frontal impact vehicular crashes. Associated thoracolumbar spine fractures are common.[29] Blunt cardiac injury should be suspected with displaced sternal fractures.[29]

FLAIL CHEST

The fracture of at least four consecutive ribs in two or more places results in a flail segment with paradoxical movement of the chest wall during tidal breathing (Fig. 79.5).[3] Associated pulmonary contusion is often present. Younger patients with no other major injuries, no pulmonary co-morbidities and good analgesia can often be managed with non-invasive ventilation or oxygen therapy alone.[40] Deteriorating gas exchange and sputum retention are indications for intubation and mechanical ventilation. Prolonged ventilatory support is often not necessary in patients whose associated injuries and co-morbidities are not severe. Surgical stabilisation has been advocated for severe flail (without severe pulmonary contusion) to reduce duration of ventilation, although the optimal technique for surgical fixation remains uncertain.[41,42]

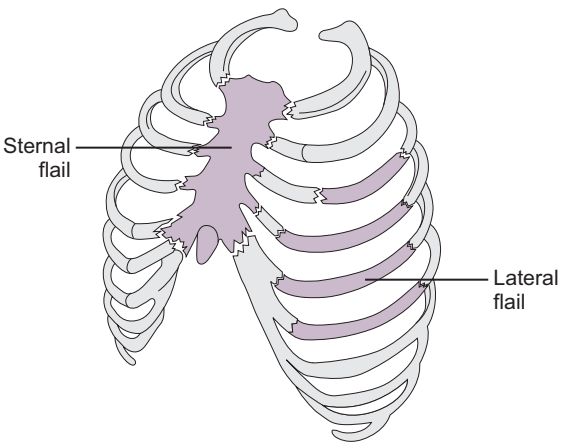


Figure 79.5 Types of flail chest. *Modified from Wanek S, Mayberry JC. Blunt thoracic trauma: flail chest, pulmonary contusion, and blast injury.* Crit Care Clin. *2004;20:71–81.*

EXTRAPLEURAL HAEMATOMA

Traumatic extrapleural haemorrhage arises when chest wall bleeding does not enter the pleural space.[43] Chest radiography shows a parietal shadow that does not cause blunting of the costophrenic angle or shift with gravity. A large haematoma should be evacuated with an intercostal tube or by thoracotomy.

SYSTEMIC AIR EMBOLISM

This is more frequent with penetrating injuries and is immediately life threatening. The typical presentation is circulatory collapse after the institution of positive-pressure ventilation, when the pulmonary air-space pressure exceeds pulmonary venous pressure (see Box 79.2). Focal neurological changes in the absence of head injury also suggest the diagnosis. Characteristic head CT findings have been described.[44]

When suspected, maintenance of spontaneous ventilation is preferred. If positive-pressure ventilation is necessary, an inspired oxygen concentration of 1.0 should be used, with ventilatory pressures and volumes reduced to a minimum. Selective lung ventilation, using a double-lumen endotracheal tube or bronchial blocker, and/or high-frequency ventilation, should be considered.[44] However, urgent thoracotomy, with hilar clamping or lung isolation, is usually indicated.[13] Hyperbaric oxygen therapy has been used to treat cerebral air embolism, but is often impractical.[44]

COMPLICATIONS AND INTENSIVE CARE UNIT MANAGEMENT

On admission to the ICU, rewarming, correction of coagulopathy and ongoing fluid resuscitation are often required. Pericardial tamponade and persistent air leak should be anticipated in post-thoracotomy patients.[17] A restrictive approach to fluid therapy is indicated for patients who have undergone lung surgery. However, care should be taken to ensure adequate fluid resuscitation. A judicious transfusion policy should be employed with all patients.[45]

As with other critically ill or injured patients, prophylactic measures against thromboembolism[46] and upper gastrointestinal stress ulceration should be used. Adequate nutrition is important to ameliorate the hypermetabolic and catabolic metabolic changes, reduce the incidence of sepsis and improve outcome. Nutrition should be instituted early, preferably via the enteral route.

ACUTE RESPIRATORY FAILURE AND MECHANICAL VENTILATION

Respiratory complications are common. When acute lung injury occurs early after trauma, common causes are pulmonary contusion, aspiration, massive transfusion and prolonged shock or delayed resuscitation with severe systemic inflammatory response. Aspiration with persistent lobar collapse is an indication for bronchoscopy to exclude bronchial obstruction from particulate obstruction. When lung injury develops several days later, sepsis of either pulmonary or non-pulmonary origin is a more likely cause.

The approach to mechanical ventilation for intubated patients follows the same principles as with other critically ill patients.

- Patients with acute lung injury/ARDS should be ventilated with a lung-protective strategy. However, high positive end-expiratory pressure (PEEP) and permissive hypercapnia are contraindicated if there is associated head injury.
- Patients with pneumothorax or tracheobronchial injury should be managed with low PEEP, low peak airway pressures, and early transition to spontaneous ventilation if possible.
- Patients with flail chest may benefit from the splinting effect of moderate levels of PEEP.
- Failure to wean from mechanical ventilation should raise suspicion of fluid overload, diaphragmatic injury, cardiac dysfunction or flail.

Select patients with hypoxaemia refractory to optimal mechanical ventilation may be supported with venovenous extracorporeal membrane oxygenation.

SPUTUM RETENTION

Sputum retention leads to progressive pulmonary collapse, with impaired gas exchange, increased work of breathing and increased risk of infection. Smokers, or patients with pre-existing respiratory disease, are particularly at risk. In the spontaneously breathing patient, good analgesia and incentive spirometry facilitate coughing and deep breathing. In the intubated/ventilated patient, humidification, tracheal suctioning and regular position changes are important.

ANALGESIA

Adequate analgesia is essential for deep breathing and effective coughing, which, if achieved, will reduce the likelihood that endotracheal intubation will be needed for less severely injured patients. Analgesia also facilitates chest physiotherapy and early mobilisation, reducing pulmonary morbidity. The choice of analgesia depends on the severity of illness and may vary over time. Options include the following[39]:

- *Intravenous morphine or fentanyl by frequent small boluses or continuous infusion:* this is the mainstay of analgesia for severely injured patients who are intubated and ventilated. Patient-controlled analgesia can be used for cooperative unintubated patients.
- *Thoracic epidural infusion of combined opioid and local anaesthetic agent (e.g. fentanyl 2 μg/mL + bupivicaine*

0.125% at 5–15 mL/h): this may be the preferred option for unintubated patients, particularly the elderly, if four or more ribs are fractured, or if there are cardiopulmonary co-morbidities. It may also be used to facilitate successful extubation of ventilated patients who still have significant analgesia requirements.

- *Intercostal nerve block:* this can be used if only a few lower ribs are fractured. Either a single bolus (20 mL of 0.5% bupivicaine) can be injected into one intercostal space, or smaller amounts can be injected at multiple levels. Repeated injections may be required.
- *Paravertebral block:* this is rarely used unless thoracic surgery is performed.
- *Non-steroidal anti-inflammatory agents:* these should be used only in fully resuscitated patients with normal renal function and no other contraindications.
- *Paracetamol:* this is given regularly except in the presence of hepatic dysfunction.

PNEUMONIA

Sepsis is the principal cause of late death after major trauma. Breach of the skin surface barrier, devitalised tissues and the presence of invasive drains and catheters make the trauma patient especially prone to bacterial invasion. In the chest-injured patient, pulmonary contusion, emergency intubation, shock, blood transfusion and the presence of extrathoracic injuries increase the risk of nosocomial pneumonia.

Early-onset pneumonia (within the first few days of hospitalisation) may result from aspiration at the time of injury, particularly after head injury. Common pathogens are *Haemophilus influenzae*, *Pneumococcus* and anaerobes. Later-onset nosocomial pneumonia is more likely to be due to aerobic Gram-negative bacilli and *Staphylococcus aureus*.

The diagnosis of pneumonia is suspected if there are new or progressive infiltrates on the chest radiograph and deterioration in respiratory status. However, new infiltrates may also be caused by pulmonary contusion, pleural fluid collections, atelectasis, aspiration and pulmonary oedema. Infection is supported by the presence of purulent sputum, new fever and leucocytosis. Confirmation depends on culture of tracheal aspirate or bronchoscopic samples.[47]

Antibiotic therapy should be targeted at causative organisms. Prompt empirical antibiotics should be started in unstable patients, with re-evaluation at 48–72 hours.

Preventative measures include careful hand cleansing, reduced duration of intubation and ventilation, semirecumbent position, enteral nutrition, avoidance of excessive sedation or hyperglycaemia, and avoidance of prolonged prophylactic antibiotics.[47]

RETAINED HAEMOTHORAX AND EMPYEMA

Haemothorax that is not adequately drained within a few days becomes clotted and unable to drain via intercostal tube. The clot becomes organised and fibrosed with progressive pleural thickening (fibrothorax). This results in loss of lung volume, impaired pulmonary compliance and increased risk of empyema formation. Patients with persistent opacity on chest radiograph after intercostal tube placement should undergo ultrasound or CT imaging to determine whether a significant retained haemothorax is present.[12,14] Small haemothoraces (<300 mL) in clinically stable patients where the pleural cavity has not been breached may be observed. However, in the presence of respiratory compromise, suspected empyema, or retained haemothorax over 300 mL, further intervention is required. Several management options are available, but complete drainage should be achieved within 3–7 days, before the development of fibrothorax or empyema.

If the initial intercostal tube is poorly positioned, or blocked, a second tube may be placed through a different skin incision, preferably under ultrasound or CT guidance. In other circumstances a second intercostal tube should be avoided because of the increased risk of empyema formation and a high failure rate.[12,14,48] If the initial intercostal tube remains patent, evacuation of the retained haemothorax can be attempted with intrapleural administration of a fibrinolytic agent, after the exclusion of a bleeding diathesis or intrathoracic organ injury.[12,49] Fibrinolysis is most likely to be successful if attempted within 3 days of initial haemothorax. Tissue plasminogen activator 50 mg in 100 mL saline is instilled into the intercostal tube for 1 hour each day, for up to 3 days, until resolution of haemothorax with minimal further drain losses.[12,49] Intrapleural administration of a combination of tissue plasminogen activator and DNase has been advocated to assist drainage of early retained empyema, but has not been evaluated for retained haemothorax and may increase the risk of bleeding.[50]

VATS is the recommended approach in haemodynamically stable patients who can tolerate single-lung ventilation.[12,14,35,48,51] Failure of these techniques, or empyema formation, requires formal thoracotomy +/− decortication.[51] VATS and thoracotomy allow direct inspection for a missed pulmonary, diaphragmatic or oesophageal injury.[35]

Patients who did not require initial intercostal tube drainage, but who subsequently develop respiratory compromise or opacification on chest radiograph, should be imaged with ultrasound or CT to look for delayed haemothorax. This should also prompt reconsideration of an occult injury to the diaphragm or an intrathoracic organ.

FAT EMBOLISM SYNDROME

Fat embolism is very common in patients with long-bone fractures[52] and frequently causes oxygen desaturation, which may be severe and prolonged in patients with parenchymal lung injury.[53] However, fat embolism *syndrome*, with pulmonary, neurological and cutaneous

sequelae, is rare. The treatment of fat embolism is supportive, but early resuscitation and fracture stabilisation are important preventative measures.[52] Early (<24 hours) intramedullary nailing is the fixation method of choice, resulting in fewer orthopaedic complications than other fixation methods, and fewer pulmonary complications than delayed surgery.[54,55] However, internal fixation may provoke further fat embolism, require a longer operative time and result in more blood loss than external fixation.[54] Thus in severely chest-injured patients, temporary stabilisation using external fixation with intramedullary nailing several days later is preferred.[54]

PROGNOSIS

Risk of death and length of intensive care stay depend on severity of chest injury, extent of extrathoracic injuries and pre-existing co-morbidities.[1,55] Initial physiological markers that predict adverse outcome are a low Glasgow Coma Scale score, hypotension and a high respiratory rate. In patients with severe blunt trauma the mortality is significantly higher with bilateral than with unilateral chest injuries, and depends more on the extent of parenchymal lung injury than the extent of chest wall injury.[56] Older age correlates strongly with worse outcome, even though the elderly are more likely to suffer rib fractures than parenchymal lung injury.[55,56] In the elderly the risk of death or pneumonia increases with each additional rib fractured.

REFERENCES

1. Kulshrestha P, Munshi I, Wait R. Profile of chest trauma in a level I trauma center. *J Trauma*. 2004;57(3): 576–581.
2. Bernardin B, Triquet JM. Initial management and resuscitation of severe chest trauma. *Emerg Med Clin North Am*. 2012;30:377–400.
3. Wanek S, Mayberry JC. Blunt thoracic trauma: flail chest, pulmonary contusion, and blast injury. *Crit Care Clin*. 2004;20(1):71–81.
4. Kirkpatrick AW. Clinician-performed focused sonography for the resuscitation of trauma. *Crit Care Med*. 2007;35:S162–S172.
5. Cook CC, Gleason TG. Great vessel and cardiac trauma. *Surg Clin North Am*. 2009;89:797–820.
6. Schultz JM, Trunkey DD. Blunt cardiac injury. *Crit Care Clin*. 2004;20(1):57–70.
7. Fitzgerald M, Mackenzie CF, Marasco S, et al. Pleural decompression and drainage during trauma reception and resuscitation. *Injury*. 2008;39:9–20.
8. Moore FO, Duane TM, Hu CKC, et al. Presumptive antibiotic use in tube thoracostomy for traumatic hemopneumothorax: an Eastern Association for the Surgery of Trauma practice management guideline. *J Trauma Acute Care Surg*. 2012;73:S341–S344.
9. Leigh-Smith S, Harris T. Tension pneumothorax-time for a re-think? *Emerg Med J*. 2005;22:8–16.
10. Miller LA. Chest wall, lung, and pleural space trauma. *Radiol Clin North Am*. 2006;44(2):213–224, viii.
11. Moore FO, Goslar PW, Coimbra R, et al. Blunt traumatic occult pneumothorax: is observation safe? – results of a prospective, AAST multicenter study. *J Trauma*. 2011;70:1019–1025, discussion 1023–1025.
12. Mowery NT, Gunter OL, Collier BR, et al. Practice management guidelines for management of hemothorax and occult pneumothorax. *J Trauma*. 2011;70:510–518.
13. Hunt PA, Greaves I, Owens WA. Emergency thoracotomy in thoracic trauma – a review. *Injury*. 2006;37(1):1–19.
14. Karmy-Jones R, Namias N, Coimbra R, et al. Western Trauma Association critical decisions in trauma: penetrating chest trauma. *J Trauma Acute Care Surg*. 2014;77:994–1002.
15. Burlew CC, Moore EE, Moore FA, et al. Western Trauma Association critical decisions in trauma: resuscitative thoracotomy. *J Trauma Acute Care Surg*. 2012;73:1359–1364.
16. Seamon MJ, Haut ER, Arendonk KV, et al. An evidence-based approach to patient selection for emergency department thoracotomy: a practice management guideline from the Eastern Association for Surgery of Trauma. *J Trauma Acute Care Surg*. 2015;79:159–173.
17. Rotondo MF, Bard MR. Damage control surgery for thoracic injuries. *Injury*. 2004;35(7):649–654.
18. Stengel D, Frank M, Matthes G, et al. Primary pan-computed tomography for blunt multiple trauma: can the whole be better than its parts? *Injury*. 2009;40:S36–S46.
19. Plurad D, Green D, Demetriades D, et al. The increasing use of chest computed tomography for trauma: is it being overutilized? *J Trauma*. 2007;62: 631–635.
20. Fox N, Schwartz D, Salazar JH, et al. Evaluation and management of blunt aortic injury: a practice management guideline from the Eastern Association for Surgery of Trauma. *J Trauma Acute Care Surg*. 2015;78:136–146.
21. Paul JS, Neideen T, Tutton S, et al. Minimal aortic injury after blunt trauma: selective nonoperative management is safe. *J Trauma*. 2011;71:1519–1523.
22. Neschis DG, Scalea TM, Flinn WR, et al. Blunt aortic injury. *N Engl J Med*. 2008;359:1708–1716.
23. Gunn ML. Imaging of aortic and branch vessel trauma. *Radiol Clin North Am*. 2012;50:85–103.
24. Conroy C, Hoyt DB, Eastman B, et al. Motor vehicle-related cardiac and aortic injuries differ from other thoracic injuries. *J Trauma*. 2007;62:1462–1467.
25. Khalil A, Tarik T, Porembla DT. Aortic pathology: aortic trauma, debris, dissection and aneurysm. *Crit Care Med*. 2007;35:S392–S400.
26. Wong YC, Ng CJ, Wang LJ, et al. Left mediastinal width and mediastinal width ratio are better radiographic criteria than general mediastinal width for predicting blunt aortic injury. *J Trauma*. 2004; 57(1):88–94.

27. Karmy-Jones R, Ferrigno L, Teso D, et al. Endovascular repair compared with operative repair of traumatic rupture of the thoracic aorta: a nonsystemic review and a plea for trauma-specific reporting guidelines. *J Trauma*. 2011;71:1059–1072.
28. Clancy K, Velopulos C, Bilaniuk JW, et al. Screening for blunt cardiac injury: an Eastern Association for the Surgery of Trauma practice management guideline. *J Trauma Acute Care Surg*. 2012;73: S301–S306.
29. Von Garrel T, Ince A, Junge A, et al. The sternal fracture: radiographic analysis of 200 fractures with special reference to concomitant injuries. *J Trauma*. 2004;57(4):837–844.
30. Kiser AC, O'Brien SM, Detterbeck FC. Blunt tracheobronchial injuries: treatment and outcomes. *Ann Thorac Surg*. 2001;71(6):2059–2065.
31. Euathrongchit J, Thoongsuwan N, Stern EJ. Nonvascular mediastinal trauma. *Radiol Clin North Am*. 2006;44(2):251–258, viii.
32. Self ML, Mangram A, Berne JD, et al. Nonoperative-management of severe tracheobronchial injuries with positive end-expiratory pressure and low tidal volume ventilation. *J Trauma*. 2005;59(5):1072–1075.
33. Reiff DA, McGwin G Jr, Metzger J, et al. Identifying injuries and motor vehicle collision characteristics that together are suggestive of diaphragmatic rupture. *J Trauma*. 2002;53(6):1139–1145.
34. Eren S, Kantarci M, Okur KA. Imaging of diaphragmatic rupture after trauma. *Clin Radiol*. 2006;61:467–477.
35. Carrillo EH, Richardson JD. Thoracoscopy for the acutely injured patient. *Am J Surg*. 2005;190(2): 234–238.
36. Biffl WL, Moore EE, Feliciano DV, et al. Western Trauma Association critical decisions in trauma: diagnosis and management of esophageal injuries. *J Trauma Acute Care Surg*. 2015;79:1089–1095.
37. Miller PR, Croce MA, Bee TK, et al. ARDS after pulmonary contusion: accurate measurement of contusion volume identifies high-risk patients. *J Trauma*. 2001;51(2):223–228, discussion 229–230.
38. Soldati G, Testa A, Silva FR, et al. Chest ultrasonography in lung contusion. *Chest*. 2006;130:533–538.
39. Simon BJ, Cushman J, Barraco R, et al. Pain management guidelines for blunt thoracic trauma. *J Trauma*. 2005;59(5):1256–1267.
40. Gunduz M, Unlugenc H, Ozalevli M, et al. A comparative study of continuous positive airway pressure (CPAP) and intermittent positive pressure ventilation (IPPV) in patients with flail chest. *Emerg Med J*. 2005;22(5):325–329.
41. Lafferty PM, Anavian J, Will RE, et al. Operative treatment of chest wall injuries: indications, technique, and outcomes. *J Bone Joint Surg Am*. 2011; 93:97–110.
42. Simon B, Ebert J, Bokhari F, et al. Management of pulmonary contusion and flail chest: an Eastern Association for the Surgery of Trauma practice management guideline. *J Trauma Acute Care Surg*. 2012;73:S351–S361.
43. Rashid MA, Wikstrom T, Ortenwall P. Nomenclature, classification, and significance of traumatic extrapleural hematoma. *J Trauma*. 2000;49(2):286–290.
44. Ho AM, Ling E. Systemic air embolism after lung trauma. *Anesthesiology*. 1999;90(2):564–575.
45. Croce MA, Tolley EA, Claridge JA, et al. Transfusions result in pulmonary morbidity and death after a moderate degree of injury. *J Trauma*. 2005;59(1):19–23, discussion 24.
46. Guyatt GH, Akl EA, Crowther M, et al. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:7S–47S.
47. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63:e61–e111.
48. duBose J, Inaba K, Demetriades D, et al. Management of post-traumatic retained hemothorax: a prospective observational, multicenter AAST study. *J Trauma Acute Care Surg*. 2012;72:1–22, discussion 22–24.
49. Kimbrell BJ, Yamzon J, Petrone P, et al. Intrapleural thrombolysis for the management of undrained traumatic hemothorax: a prospective observational study. *J Trauma*. 2007;62:1175–1179, discussion 1178–1179.
50. Rahman NM, Maskell NA, West A, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. *N Engl J Med*. 2011;365:518–526.
51. Moore HR, Moore EE, Burlew CC, et al. Western Trauma Association critical decisions in trauma: management of parapneumonic effusion. *J Trauma Acute Care Surg*. 2012;73:1372–1379.
52. White T, Petrisor BA, Bhandari M. Prevention of fat embolism syndrome. *Injury*. 2006;37(suppl 4): S59–S67.
53. Wong MW, Tsui HF, Yung SH, et al. Continuous pulse oximeter monitoring for inapparent hypoxemia after long bone fractures. *J Trauma*. 2004;56(2): 356–362.
54. Pape HC, Giannoudis P, Krettek C. The timing of fracture treatment in polytrauma patients: relevance of damage control orthopedic surgery. *Am J Surg*. 2002;183(6):622–629.
55. Gandhi RR, Overton TL, Haut ER, et al. Optimal timing of femur fracture stabilization in polytrauma patients: a practice management guideline from the Eastern Association for Surgery of Trauma. *J Trauma Acute Care Surg*. 2014;77:787–795.
56. Battle CE, Hutchings H, Evans PA. Risk factors that predict mortality in patients with blunt chest wall trauma: a systematic review and meta-analysis. *Injury*. 2012;43:8–17.
57. Pape HC, Remmers D, Rice J, et al. Appraisal of early evaluation of blunt chest trauma: development of a standardized scoring system for initial clinical decision making. *J Trauma*. 2000;49(3):496–504.

80

Spinal injuries

Sumesh Arora, Oliver Flower

INTRODUCTION

Spinal cord injury (SCI) has immense consequences for patients, their families, health care resources and society. Initial management of SCI and prevention of secondary injury may make substantial differences to long-term functional outcome. SCI is best managed in specialised spinal injury units, with specialist medical, nursing, and allied health expertise.[1,2] The prognosis for SCI has improved tremendously in the last 50 years, and despite their disability, survivors often report high levels of life satisfaction years after their injury.[3] Non-traumatic SCI, from a broad range of aetiologies, shares many clinical and pathological features with traumatic SCI. However, as the specific differences in managing non-traumatic SCI are beyond the scope of this chapter, we will focus on traumatic SCI.

EPIDEMIOLOGY

Approximately 5% of trauma victims have spinal fractures, and 20% of these have SCI.[4] The incidence of traumatic SCI ranges from 2.3 to 83 cases per million population per year, with a prevalence ranging from 236–1800 cases per million population in developed countries.[5] Approximately 80% of victims are male, usually in the 15–35 age group. Motor vehicle accidents are the commonest cause, followed by falls and sports-related injuries. The proportion of injuries related to falls, especially in people over the age of 60 years, is increasing.[4,6] Pre-existing spinal pathology such as spinal canal stenosis, osteoporosis or ankylosing spondylitis increases the risk of SCI from relatively minor trauma. Improved availability and quality of pre-hospital treatment has increased prevalence of SCI survivors. The epidemiology of neurological level of injury (NLI) varies, depending on location. In developed countries, more than 50% are cervical SCI, but developing countries report lower rates. This may be because of early mortality, as well as aetiological, geographical and economic global variation.[5] Approximately one-third of patients are tetraplegic and half of patients with SCI have complete injuries.[7]

PATHOGENESIS

APPLIED ANATOMY AND PHYSIOLOGY

The spinal cord extends from the foramen magnum to approximately the L1-L2 level. The conical lower end of spinal cord is called the conus medullaris, from which a filament of fibrous tissue, known as filum terminale, continues inferiorly. The cauda equina refers to the bundle of spinal nerves, for the lumbo-sacral segments, that continue below the spinal cord. Compared to the spinal cord in the cervical and thoracic regions, the cauda equina is less susceptible to injury due to a relatively larger canal size in the lumbar region.[8] Corresponding to each intervertebral level, dorsal and ventral roots exit the spinal cord and join within the dural sac to form the spinal nerve. The spinal nerves run caudally within the spinal column until they reach the corresponding vertebral levels, then exit through the spinal foramen. During development, the vertebral column elongates more than the spinal cord, so there is an increasing discrepancy between the anatomical level of spinal cord segments and their corresponding vertebrae as we go caudally.

The sympathetic nerve supply originates from the intermediolateral column of segments T1-L2. The parasympathetic outflow originates from S2-S4 level and supplies the pelvic viscera. A cross section of the spinal cord is shown in Fig. 80.1.

SPINAL CORD INJURY

The pathophysiology of SCI is described as biphasic, consisting of primary and secondary phases.

PRIMARY INJURY

Direct mechanical injury may produce focal compression, haematoma, laceration or traction injury to the cord. Actual transection is unusual. Ischaemic injury may result from injury to the segmental spinal

ABSTRACT

Spinal cord injury (SCI) commonly affects young people, and results in permanent disability. Judicious management in the intensive care unit may reduce secondary SCI and prevent complications. Cervical SCI results in severe respiratory dysfunction, and weaning from the ventilator may take several weeks to months. Patients with cervical SCI may have unique cardiovascular problems like autonomic dysreflexia, which may be life threatening. In this chapter, we discuss the epidemiology, classification, imaging, intensive care management and outcome of SCI.

KEYWORDS

Spinal cord injury
tetraplegia
neurological level of injury
autonomic dysreflexia

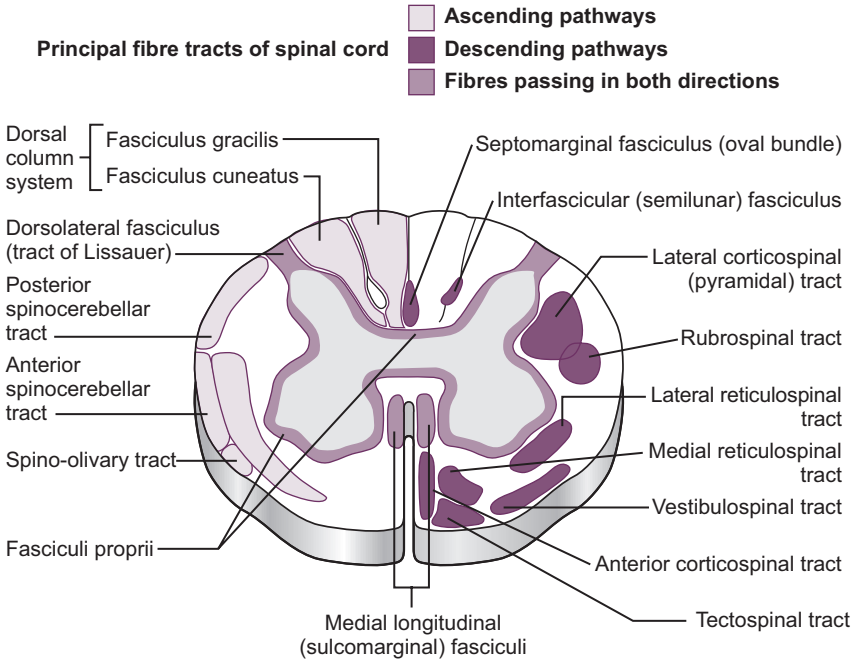


Figure 80.1 Cross-section of the spinal cord. *(From Principal Tracts of Spinal Cord, Image ID: 60477, published in Rubin M, Safdieh JE, Gross anatomy of the brain and spinal cord. In:* Netter's Concise Neuroanatomy*; 2007:49.)*

arterial supply. Initial pathological changes include the traumatic severing of axons, blood vessels and cell membranes.[9,10]

SECONDARY INJURY

Local ischaemia begins at the site of injury, extending progressively, over several hours, from the site of injury in both directions. There is loss of autoregulation of blood flow to the spinal cord, often complicated by arterial hypotension in high SCI. Other mechanisms that may contribute to the secondary injury include release of free radicals, reactive oxygen species, eicosanoids, calcium, proteases, phospholipases and excitotoxic neurotransmitters (e.g. glutamate).[9,10]

Petechial haemorrhages begin in the grey matter, progress over hours, and may result in significant haemorrhage into the cord. There is oedema, cellular chromatolysis and vacuolation, and ultimately neuronal necrosis. Apoptosis, especially of oligodendrocytes, also occurs.[9] In the white matter, vasogenic oedema, axonal degeneration and demyelination follow. Polymorphs infiltrate the haemorrhagic areas. Late coagulative necrosis and cavitation subsequently take place.[11]

INITIAL ASSESSMENT AND MANAGEMENT

Early management of SCI should focus on prevention of secondary injury and provide optimum conditions for neurological recovery. This is achieved by immobilisation until the spine is stable, prevention of hypoxia, defending blood pressure and avoiding metabolic abnormalities.

In general, the principles of managing severe trauma are outlined in Chapter 77. Resuscitation must occur simultaneously with evaluation, initial investigations and management. The specific considerations in the acute setting are outlined in Table 80.1.

NEUROLOGICAL ASSESSMENT

A thorough neurological examination should be performed as early as feasible after presentation, prior to administration of any sedative or paralytic agents. The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) outlines a comprehensive clinical exam for patients with SCI (Fig. 80.2). The American Spinal Injury Association (ASIA) impairment scale[12] is the most validated instrument for diagnosing and classifying SCI. It is currently the only standardised neurological examination available that allows prognostication, and has sufficient inter-rater reliability for local and international data collection and comparison. A bilateral sensory and motor exam, including digital rectal examination, determines a single NLI, completeness of injury and the ASIA grade (see Fig. 80.2). Table 80.2 describes the grades of the ASIA impairment scale.[12]

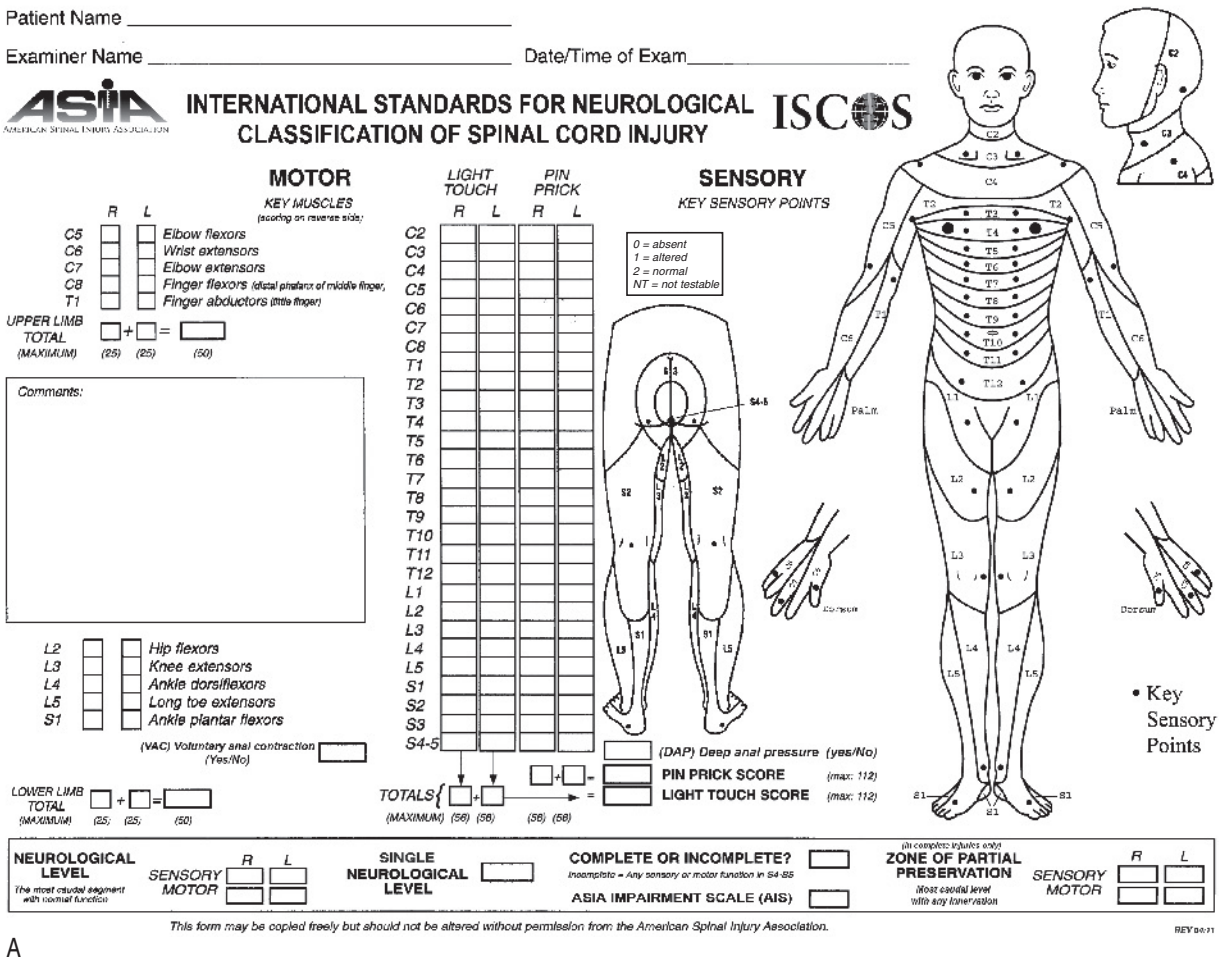
Table 80.1 Acute issues following spinal cord injury

ISSUE	PATHOPHYSIOLOGY RELEVANT TO SCI	MANAGEMENT
Need for intubation	Paralysis of muscles of respiration below NLI Increased secretions and bronchospasm from loss of sympathetic innervation	Consider intubation for Respiratory failure Decreased level of consciousness Transport to another hospital or for imaging Surgical intervention
Intubation	Excessive movement of neck in unstable cervical injury may cause further spinal cord damage	If intubation is urgent, rapid sequence induction & intubation with manual in-line stabilisation Minimise neck movement Video laryngoscopy improves view and minimises movement Consider awake fibre-optic intubation if time and expertise available
Hypotension	Loss of vasomotor tone below NLI Bradycardia for NLI above T1 Traumatic abdominal or long-bone haemorrhage presents differently in patients insensate below the NLI	Must exclude hypovolaemia/haemorrhagic shock Vasoplegia and bradycardia from SCI causes neurogenic distributive shock Give fluids initially Have low threshold for inserting central line and using vasopressors Consider targeting a MAP of 85 mm Hg to maintain spinal cord perfusion
Bradycardia	Loss of cardiac sympathetic innervation (T1-T4)	May require anticholinergics (e.g. atropine), chronotropics (e.g. isoprenaline) or pacing
Neurological examination	NLI and ASIA grade may be difficult to assess once patient is intubated	Obtain NLI and ASIA grade if patient alert, before sedation or intubation
Medications	Sedation may prevent accurate assessment of neurological status	Use short-acting sedatives and analgesics to permit repeat neurological assessment Avoid paralytic agents if possible
Pressure area care	Loss of sensation and paralysis predisposes to early decubitus ulcers	Transfer off hard board as early as possible Change collar to Miami J as soon as possible Roll every 2 h Skin inspection twice a day
Hypothermia	Vasoplegia Loss of thermoregulatory control Exposure during resuscitation Pre-hospital environmental factors	External passive and active warming may be required
Urinary retention	Paralysis of detrusor Loss of bladder sensation	Indwelling bladder catheter
Gastroparesis	Loss of gastrointestinal sympathetic innervation Ileus Gastroparesis	Nasogastric insertion
Refer & transfer	Better outcome in specialist spinal care centres	Early liaison and transfer to SCI specialist unit

ASIA, American Spinal Injury Association; *MAP*, mean arterial pressure; *NLI*, neurological level of injury; *SCI*, spinal cord injury.

In conscious, alert patients, SCI may be obvious, with weakness, reduced sensations and absence of reflexes below the NLI, vasodilatation, priapism, urinary retention and paralytic ileus. When assessing sensation, it should be remembered that the C4 dermatome can extend as low as the nipple line, misleading the examiner to believe that T4 dermatome has sensation. An initial ASIA classification may reliably predict long-term motor outcome.[13] However, other injuries, pain, alcohol or the administration of analgesic or other drugs may make initial assessment impossible. Signs of SCI in unconscious or uncooperative patients include:

- Response to pain above, but not below, a suspected level of injury



A

Figure 80.2 American Spinal Injury Association. International Standards for Neurological Classification of Spinal Cord Injury, revised 2011. *(From Kirshblum SC, Burns SP, Biering-Sorensen F, et al. International standards for neurological classification of spinal cord injury (Revised 2011).* J Spinal Cord Med. *2011;34(6):535–546.)*

- Flaccid areflexia in the legs and/or arms
- Paradoxical pattern of breathing with in-drawing of upper chest during inspiration (in the absence of upper airway obstruction or chest injury)
- Inappropriate vasodilatation (in association with hypothermia, or in the legs but not the arms with thoracolumbar SCI)
- Unexplained bradycardia, hypotension
- Priapism
- Loss of anal tone and reflexes

TERMINOLOGY OF SPINAL CORD INJURY

The terminology for SCI has now been standardised by the ISNCSCI.[12]

Tetraplegia

Tetraplegia (preferred to quadriplegia) is defined as impairment of motor and/or sensory function in the cervical segments of spinal cord due to damage of the neural elements of the spinal canal. Tetraplegia typically affects both upper and lower limbs.

Paraplegia

Motor and/or sensory deficits affecting only lower limbs due to SCI in the thoracic, lumbar or sacral (but not cervical) segments of the spinal cord. The term is also used in referring to the cauda equina or conus medullaris injuries.

Neurological level of injury

The most caudal cord segment with normal sensory and antigravity motor function bilaterally, provided there is intact sensory and motor function rostrally (above the level). As differences often exist, it is preferred to describe the individual motor (better than antigravity power) and sensory levels on each side.

Muscle Function Grading

0 = total paralysis

1 = palpable or visible contraction

2 = active movement, full range of motion (ROM) with gravity eliminated

3 = active movement, full ROM against gravity

4 = active movement, full ROM against gravity and moderate resistance in a muscle specific position.

5 = (normal) active movement, full ROM against gravity and full resistance in a muscle specific position expected from an otherwise unimpaired peson.

5* = (normal) active movement, full ROM against gravity and sufficient resistance to be considered normal if identified inhibiting factors (i.e. pain, disuse) were not present.

NT = not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of >50% of the range of motion).

ASIA Impairment (AIS) Scale

☐ **A = Complete.** No sensory or motor function is preserved in the sacral segments S4-S5.

☐ **B = Sensory Incomplete.** Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5 (light touch, pin prick at S4-S5: or deep anal pressure (DAP)), AND no motor function is preserved more than three levels below the motor level on either side of the body.

☐ **C = Motor Incomplete.** Motor function is preserved below the neurological level**, and more than half of key muscle functions below the single neurological level of injury (NLI) have a muscle grade less than 3 (Grades 0-2).

☐ **D = Motor Incomplete.** Motor function is preserved below the neurological level**, and at least half (half or more) of key muscle functions below the NLI have a muscle grade ≥ 3.

☐ **E = Normal.** If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

**For an individual to receive a grade of C or D, i.e. motor incomplete status, they must have either (1) voluntary anal sphincter contraction or (2) sacral sensory sparing with sparing of motor function more than three levels below the motor level for that side of the body. The Standards at this time allows even non-key muscle function more than 3 levels below the motor level to be used in determining motor incomplete status (AIS B versus C).

NOTE: When assessing the extent of motor sparing below the level for distinguishing between AIS B and C, the ***motor level*** on each side is used; whereas to differentiate between AIS C and D (based on proportion of key muscle functions with strength grade 3 or greater) the ***single neurological level*** is used.

Steps in Classification

The following order is recommended in determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
2. Determine motor levels for right and left sides.
   Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal.
3. Determine the single neurological level.
   This is the lowest segment where motor and sensory function is normal on both sides, and is the most cephalad of the sensory and motor levels determined in steps 1 and 2.
4. Determine whether the injury is Complete or Incomplete. (i.e. absence or presence of sacral sparing)
   If voluntary anal contraction = **No** *AND all S4-5 sensory scores =* **0** *AND deep anal pressure =* **No,** *then injury is COMPLETE. Otherwise, injury is incomplete.*
5. Determine ASIA Impairment Scale (AIS) Grade:

Is injury Complete? If **YES,** AIS=A and can record ZPP (lowest dermatome or myotome on each side with some preservation)

NO ↓

Is injury motor Incomplete? If **NO**, AIS=B (Yes=voluntary anal contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)

YES ↓

Are at least half of the key muscles below the single neurological level graded 3 or better?

NO ↓ AIS=C YES ↓ AIS=D

If sensation and motor function is normal in all segments, AIS=E
Note: AIS E is used in follow-up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact; the ASIA Impairment Scale does not apply.

B

Figure 80.2, cont'd

Table 80.2 American spinal injury association impairment scale

A	Complete: No sensory or motor function is preserved in the sacral segments S4-S5
B	Sensory Incomplete: Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5
C	Motor Incomplete: Motor function is preserved below the neurological level, and less than half of key muscles below the neurological level have a muscle grade ≥3
D	Motor Incomplete: Motor function is preserved below the neurological level, and half or more of key muscles below the neurological level have a muscle grade ≥3
E	Normal: Sensory and motor function is normal and the patient with previous SCI. If initial testing after injury does not show any impairment, this classification does not apply.

SCI, Spinal cord injury.

The single NLI is then the most rostral of these levels. Note that as the spinal cord is shorter than the vertebral column, with more caudal SCI, the NLI may differ from the radiological level of injury (see Fig. 80.2).

Complete spinal cord injury

SCI is complete when there is absence of both motor and sensory function in the lowest sacral segments, S4 and S5 (i.e. no voluntary anal contraction and no perianal sensation).

Zone of partial preservation

This term is used to describe complete (ASIA A) SCI. This refers to the spinal segments that have any motor or sensory function below the NLI.

Spinal shock

The period of flaccid paralysis, anaesthesia, loss of bowel and bladder function, and areflexia following a spinal injury is called spinal shock. It may last from 48 hours to several weeks. Emergence from spinal shock occurs gradually. During emergence, deep

plantar reflex and the cutaneous reflexes (e.g. bulbocavernosus, cremasteric reflex) recover first, within 1–3 days. This is followed by reappearance of deep tendon reflexes, usually after a few weeks.[14] Only once spinal shock has resolved may autonomic dysreflexia (AD) manifest.

Neurogenic shock

A form of distributive (cardiovascular) shock following SCI due to loss of sympathetic tone in peripheral vasculature.

SYNDROMES OF INCOMPLETE SPINAL CORD INJURY

Incomplete SCI may occur in the form of characteristic syndromes.[12]

Central cord syndrome

Weakness and sensory loss, greater in the arms than the legs. Typically follows a hyperextension injury in patients with pre-existing canal stenosis, such as an elderly person falling onto chin. Ischaemia or haematoma in the centre of the cord predominantly affects the cervical segment due to the pattern of lamination of the corticospinal and spinothalamic tracts.

Anterior cord syndrome

Loss of motor function, pain and temperature sensation below the level of injury, with preservation of fine touch and proprioception. Anterior cord syndrome typically follows interruption of the blood supply to the anterior spinal cord, and may be seen in patients with aortic pathology or surgery.

Brown-Séquard syndrome

Ipsilateral loss of motor, proprioception and fine touch, with contralateral loss of pain and temperature sensation below the level of injury. It usually follows a penetrating SCI damaging only one half of the spinal cord.

Conus medullaris syndrome

Flaccid paralysis of external anal sphincter, faecal incontinence, bladder distension and incontinence, impotence and saddle or perianal anaesthesia. Weakness in lower limbs may result from injury to adjacent lumbar and sacral nerve roots. Caused by injury at T12-L1 level.

Cauda equina syndrome

Results from injury to the cauda equina, leading to asymmetrical, lower motor neuron lower limb weakness with sensory loss in the territory of affected nerve roots, with bladder and bowel areflexia. Caused by injuries below L1 damaging the lumbosacral nerve roots.

Because of proximity of cauda equina and conus medullaris, a single injury may affect both structures, and classification of the injury to one specific syndrome may not be possible.

ASSOCIATED INJURIES

Overall, in major trauma, the incidence of cervical spine injury (CSI) is 1%–3%; 2%–10% of patients with head injuries have a CSI. The more severe the head injury, the more likely is CSI to be present. Patients with head injuries should be assumed to have a CSI until proved otherwise. Among patients with a cervical SCI, 25% have some degree of head injury, with 2%–3% having a severe injury.[9]

Chest injuries are often present in association with thoracolumbar injuries and are difficult to assess due to inability to take an erect chest X-ray, or presence of a mediastinal haematoma associated with the vertebral injury. Computerised tomography (CT) of the chest may be used to assess other chest injuries, with contrast to exclude aortic injuries. There should be a high index of suspicion of abdominal injuries, as the lack of sensation, hypotension and bradycardia from the SCI may mask the usual presentation.

IMMOBILISATION

If traumatic SCI is suspected, initial management involves manual support of the head in a natural, neutral position, limiting angular movement of the head and spine. Padding under the head (approximately 2 cm) may optimise the neutral position.[15] Semi-rigid cervical collars carry significant risks and, if used at all, should be exchanged for softer collars as soon as possible. Hard spinal boards cause rapid development of pressure injury. This risk can be minimised by transferring the patient off the hard board as soon as feasible, and providing meticulous pressure area care. Of the available hard collars, Miami J and Philadelphia collars restrict cervical movement more than Aspen or Miami J/Occian back. The Miami J and Miami J/Occian back cause the lowest levels of mandibular and occipital pressure.[16] Complications of prolonged immobilisation and spinal precautions include cutaneous pressure ulceration, difficult intubation, potential venous obstruction leading to high intracranial pressure, reduced options for central venous access, higher risk of venous thromboembolism (VTE), increased risk of respiratory infections due to restricted physiotherapy, gastroparesis and an inability to provide optimal oral care.[17]

IMAGING

IS IMAGING REQUIRED?

Some trauma patients may not require cervical spinal imaging and the inherent risks that this entails. Two clinical decision tools are used in this context: The National Emergency X-Radiography Utilization Study

(NEXUS) criteria and the Canadian C-Spine rule (CCCR). NEXUS suggests cervical spine imaging is indicated for patients with trauma unless they meet all of the following criteria[18]:

- No posterior midline cervical spine tenderness
- No evidence of intoxication
- Normal level of alertness
- No focal neurological deficit
- No painful distracting injuries

NEXUS criteria have a very high sensitivity (99.6% for significant injuries) if used as initially intended, although the specificity is only 12.9%. They require there to be no evidence of any intoxication (including even an odour of alcohol), an alert level of consciousness sufficient to allow *three object recall at five minutes*, no focal neurological deficits and there should be no painful distracting injuries. This subjective component includes any long-bone fractures, de-gloving injuries, deep lacerations, visceral injuries, crush injuries, large burns or any injury that causes any acute functional impairment. The Canadian C-Spine rules have a higher degree of sensitivity (100%) and specificity (45%), but were based on a smaller cohort of patients than NEXUS.[18] Again, they only define which patients may be clinically cleared without imaging.

IMAGING MODALITIES

PLAIN RADIOGRAPHS

Adequate, three-view combination (A-P, Lateral and odontoid peg view) plain radiography misses injuries of the spinal column in both alert and obtunded patients, with a pooled sensitivity of detecting significant injuries of 52%.[19] Despite reducing thyroid radiation exposure in comparison to CT, plain radiography has no role in this context, unless other modalities are not available.[20]

DYNAMIC STUDIES (DYNAMIC FLUOROSCOPY OR FLEXION/EXTENSION RADIOGRAPHY)

This imaging modality poorly visualises the relevant anatomy[21] and has a low sensitivity to detect injury.[22] It is labour and resource intensive[23] and has now been superseded by CT and magnetic resonance imaging (MRI).

COMPUTERISED TOMOGRAPHY

CT technology has improved considerably in recent years, with multidetector row CT (MDCT) offering sensitivity of detecting spinal injuries, including ligamentous injury, close to 100%.[24] MDCT is readily available, easily performed as part of a polytrauma evaluation and is more time and cost-effective than plain radiography. However, MDCT may miss some significant and unstable injuries (subsequently detectable by MRI) in approximately 4%, with 0.29% requiring surgical stabilisation. Other disadvantages include significant thyroid radiation exposure and transport of a trauma patient to CT.[17]

MAGNETIC RESONANCE IMAGING

To investigate cord injury, MRI provides superior imaging to any other modality.[25] MRI provides a detailed image of spinal cord, spinal ligaments, intervertebral discs and paravertebral soft tissues. It is the most sensitive screening test available to detect soft tissue and ligamentous injuries that could contribute to instability of the cervical spine[26] and MR angiography may detect associated vertebral artery injury. In the setting of trauma, MRI imaging supplements the information obtained from CT scan, and does not replace the need for a CT.

Timing of MRI is another contentious issue as with time, the MR signal may change due to a decrease in ligamentous oedema. The Eastern Association for the Surgery of Trauma guidelines recommend that MRI should be performed within 72 hours[27]; however, there is only limited evidence that delay between injury and imaging results in a false negative MRI.[28]

AN APPROACH TO IMAGING

There is currently no universal consensus. If there is no neurological deficit but the other conditions of the Canadian C-Spine Rule or NEXUS rules are not met, then high resolution MDCT of the entire spine is indicated. For the obtunded blunt trauma patient who is likely to be un-assessable for a prolonged period, an MRI may follow the MDCT. Following trauma, if there is evidence of any new neurological deficit attributable to a SCI, an urgent MRI should be performed.

Policy for the use of MRI in this context should be discussed at an institutional level, with the knowledge that MDCT alone may miss a small percentage of injuries that would otherwise have required intervention, but the false-positive rate of MRI may result in significant morbidity to patients with no injuries who are kept immobilised.[17]

The risk of vertebral artery injury is high in patients with CSI associated with fracture extending to the transverse foramen, basilar skull fracture, facet joint subluxation/dislocation or co-existing disease like diffuse idiopathic skeletal hyperostosis or ankylosing spondylosis.[29]

INTENSIVE CARE MANAGEMENT OF SPINAL CORD INJURY

PREVENTION OF SECONDARY NEUROLOGICAL INJURY AFTER SPINAL CORD INJURY

Spinal cord compression may occur due to misalignment of spine, oedema or haemorrhage. Incomplete injury with spinal cord compression should be urgently decompressed. Stability is the ability of the spine,

under physiological loads, to limit patterns of displacement, which would result in neurological injury, pain, or deformity.[30] It is affected by fracture morphology and osteo-ligamentous integrity. Most unstable spinal injuries require operative intervention. Where indicated, early surgery within 24 hours of injury is safe, may improve neurological outcome, reduces length of stay in acute care, permits early mobilisation and commencement of deep vein thrombosis prophylaxis and lowers hospital cost.[31] Most spinal surgeons prefer to operate as early as possible in patients with incomplete or cervical SCI.

Many pharmacological agents have been investigated for preventing secondary injury and aid recovery of damaged neurons; however, none of these have proven successful. NASCIS 2[32] and NASCIS 3[33] were the largest trials that investigated the role of corticosteroids after SCI. Both were negative studies, showing no significant difference in motor score between treatment groups at any time. Post-hoc sub-group analysis of this data that suggested improvement in neurological outcome was fundamentally flawed. The lack of evidence for efficacy, and significant adverse effects such as detrimental effects on concomitant head injury, has resulted in decline in steroid use in recent years. Other agents that have been investigated with no evidence of benefit include GM-1 ganglioside, tirilazad, naloxone and nimodipine.

Induced hypothermia has been reported to be beneficial in case reports, but there is not enough evidence to recommend this intervention.[34] Fever may worsen outcome and normothermia should be maintained.

Patients typically spend several weeks to months in the hospital. Early referral to a rehabilitation team specialising in management of SCI should be made so that acute management and rehabilitation may proceed hand in hand.

RESPIRATORY DYSFUNCTION

Respiratory dysfunction is a major cause of morbidity after SCI, especially after cervical SCI. Diaphragm, external intercostals, scalene and sternocleidomastoid are the key muscles of inspiration. Quiet expiration is passive, but forceful expiration and cough requires abdominal muscles, interosseous part of internal intercostals, latissimus dorsi, serratus posterior and inferior, triangularis sterni and quadratus lumborum. The effect of SCI on respiratory function depends upon the NLI. Various effects of cervical SCI on respiratory function are listed in Table 80.3. The diaphragm is innervated by C3-C5. If the NLI is above C5, sternocleidomastoid (innervated by cranial nerve XI and anterior rami of C2, C3), and scalene medius and posterior (innervated by C3-C4) become important muscles for inspiration. The abdominal muscles are innervated by T7-L1, and in higher injuries, cough is generated only by the muscles of upper chest, particularly pectoralis major.[35]

RESPIRATORY MANAGEMENT AFTER CERVICAL SPINAL CORD INJURY

Intubation may be required for respiratory failure, secretion clearance, surgery, decreased level of consciousness or because of other injuries. Almost 75% of patients with cervical SCI will require intubation and mechanical ventilation.[36]

The cervical spine should be immobilised during endotracheal intubation. If time and expertise are available, awake fibre-optic intubation minimises the movement of the neck. Video laryngoscopes may improve the glottic view when the neck is immobilised. Direct laryngoscopy with manual inline stabilisation does not eliminate all movement at the cervical spine, but there is no evidence that it is associated with worse neurological outcome than other intubation techniques.

Table 80.3 Effect of cervical spinal cord injury on respiratory function

Decreased vital capacity	Paralysis of diaphragm and intercostal muscles Distortion of rib cage in inspiration due to paralysed intercostal muscles
Reduced compliance of lungs and chest wall	Spasticity of intercostal muscles Altered articulation of ribs to sternum and vertebrae Low functional residual capacity Atelectasis Possible alteration of surfactant
Increased abdominal compliance	Paralysis of abdominal muscles
Increased bronchial tone and secretions	Sympathetic denervation
Poor cough	Reduced vital capacity Abdominal muscle paralysis
Sleep disordered breathing (develops within 6 months)	Unknown cause Increased adipose tissue around neck Antispasticity drugs

In the initial period after cervical SCI, ventilator settings are dictated by associated injuries and other co-morbidities. For example, in patients with severe traumatic brain injury, normocapnia should be maintained. Once acute issues have resolved, mechanical ventilation should be tailored to SCI. Baseline spirometry should be obtained to allow monitoring of progress.

Tidal volume (V_T) more than 10 mL/kg is often used in patients with cervical SCI. The rationale for high V_T ventilation is to prevent atelectasis and reduce the sensation of 'air hunger' experienced following SCI. This avoids the need for high-level positive end-expiratory pressure (PEEP) that may lower the position of diaphragm to one of mechanical disadvantage. In many spinal centres, V_T of 10–20 mL/kg is used routinely,[37] and in small studies has not resulted in higher incidence of ventilator-induced lung injury.[38] With high V_T, dead-space may have to be incorporated into the circuit to avoid hypocapnia. Another approach is to use more conventional V_T and higher PEEP to prevent atelectasis. Until better quality evidence is available, an individualised approach to ventilator settings should be used.

Extubation after mechanical ventilation in patients with cervical SCI requires careful consideration of several factors (Table 80.4), with failure likely to result in reintubation followed by tracheostomy. Extubation failure is commonly due to retained secretions, inadequate cough and sputum plugs. Patients may benefit from extubation to non-invasive ventilation directly, which may be required for several days. A variety of non-invasive ventilation interface devices should be available and nasal skin should be protected from developing pressure ulcers. Aggressive chest physiotherapy and assisted coughing are required to clear secretions.

Table 80.4 Checklist prior to extubation

1.	No further procedure or imaging outside ICU anticipated in next 24 h
2.	No significant hypoxia or reversible respiratory pathology
3.	Ability to tolerate non-invasive ventilation
4.	No contraindication for the assist cough or chest physiotherapy (e.g. rib fractures, major laparotomy)
5.	Minimal respiratory secretions
6.	Negative inspiratory force >20 cm H_2O
7.	Vital capacity >10 mL/kg
8.	Presence of cuff leak (particularly after spinal fixation by anterior approach)
9.	Airway plan and equipment ready for re-intubation

ICU, Intensive care unit.

The tracheostomy rate after cervical SCI varies between 20% and 60%. Complete injuries above C5 usually require tracheostomy.[39] A high NLI, complete SCI, associated facial fractures, thoracic trauma and emergency intubation are associated with need for tracheostomy. Percutaneous tracheostomy is as safe as surgical tracheostomy.[40] Early tracheostomy may reduce the duration of mechanical ventilation and intensive care unit (ICU) length of stay and it does not increase the risk of wound or implant infection even after anterior spinal fixation.[41]

Weaning from mechanical ventilation after cervical SCI may take considerable time. In some centres, high-level tetraplegics are cared for in chronic respiratory care facilities rather than the ICU. It is important that a long-term weaning strategy is agreed upon and adhered to by all members of the multidisciplinary team. Accurate neurological assessment, progressive ventilator-free breathing, adequate rest periods with controlled ventilation, and secretion control with aggressive physiotherapy are associated with successful weaning.[42] Inspiratory muscle training uses an inspiratory resistor to increase strength of inspiratory muscles. While more studies are needed to clearly delineate the role of inspiratory muscle training in weaning of patients with cervical SCI, its use makes physiological sense and is being used increasingly.[43] It should be remembered that most patients with cervical SCI ventilate more easily when supine compared to being upright, as their abdominal contents can push the diaphragm up into a position of better mechanical advantage in supine position. An abdominal binder may be used in the sitting position, which also helps in this regard.

Inhaled anticholinergics and beta-2 agonists reduce airway resistance but have not been shown to improve success of weaning. Anabolic steroids like oxandrolone do not improve respiratory function but may cause hepatotoxicity and dyslipidaemia. Phrenic nerve or direct diaphragmatic pacing systems are occasionally used for respiratory support in high-level tetraplegics.

The NLI is the strongest predictor of successful weaning.[44] Patients with complete injuries at or above C3 are likely to need permanent ventilation. Early identification of patients who cannot be weaned helps reduce their ICU length of stay and expedites the arrangements for equipment and care personnel required for home ventilation or transfer to a chronic respiratory care facility. Overall, approximately 2% of patients with SCI, mostly with complete injures at C1-C4, require life-long ventilation.[45]

CARDIOVASCULAR DYSFUNCTION AFTER SPINAL CORD INJURY

The heart receives its sympathetic innervation from the upper thoracic segments via the superior, middle

and inferior cervical ganglions. Vasomotor tone of the peripheral vasculature is also controlled by segmental sympathetic innervation. The heart's parasympathetic innervation comes from the vagus, and therefore is not affected by SCI. Following SCI, loss of sympathetic supply and unopposed vagal activity may cause profound vasoplegia combined with bradycardia, resulting in hypotension and neurogenic shock. This occurs in 19% of patients with cervical and 7% of thoracic SCI.[46] Other causes of hypotension, particularly hypovolaemic shock, must be excluded before a diagnosis of neurogenic shock is made. Bradycardia and even asystole may occur during routine ICU procedures like endotracheal suction or repositioning in bed after cervical SCI. This occurs most commonly in the first week and generally resolves within 2–6 weeks after injury.[47]

There is some low-quality evidence that maintaining a higher mean arterial pressure (MAP) following SCI may improve cord perfusion pressure, prevent secondary injury and improve neurological outcome. Much is still unknown about this aspect of treatment, including the ideal MAP to target, optimal duration of blood pressure augmentation, the best vasopressor to use and whether the injury being complete or not is significant. Ongoing trials seek to answer some of these questions. Current guidelines recommend systolic blood pressure should not be less than 90 mm Hg at any time and that an average MAP above 85–90 mm Hg be maintained for 7 days following injury.[48] A recent study noted that, compared to dopamine, noradrenaline was associated with lower intrathecal pressure for same spinal cord perfusion pressure.[49]

CARDIOVASCULAR COMPLICATIONS

Autonomic dysreflexia

AD is a medical emergency characterised by acute hypertension due to severe sympathetic stimulation in patients with injuries above T6. It occurs following the resolution of spinal shock and is a frequent cause for admission to ICU. AD occurs due to dysregulated sympathetic activation leading to intense vasoconstriction below the level of lesion. Compensatory parasympathetic activation leads to bradycardia, vasodilatation and sweating above the NLI.[50] Other symptoms include headache, blurred vision, nausea and nasal congestion. The precipitants, investigations and treatment of precipitating factors are outlined in Table 80.5.

Initial management includes primarily detecting and treating the precipitant, sitting the patient up (to induce an orthostatic hypotensive response), loosening tight clothing and antihypertensives. Sublingual or transdermal glyceryl trinitrate is used initially. Nitrates should be avoided in patients who have taken sildenafil for erectile dysfunction in the preceding 24 hours due to risk of severe and protracted hypotension.[51] Sublingual captopril or oral prazosin may be used in unresponsive patients before intravenous agents such as sodium nitroprusside or glyceryl trinitrate infusions are used. Invasive blood pressure monitoring is required if intravenous agents are used. Some patients may develop chronic, severe AD requiring multiple antihypertensives. It must be remembered that in the setting of chronic hypotension that may follow SCI, systolic blood pressure of even >150 mm Hg may be life threatening,[52] and cause intracerebral haemorrhage or myocardial ischaemia.

Table 80.5 Precipitants, investigations and treatment of autonomic dysreflexia

PRECIPITANT	INVESTIGATION AND TREATMENT
Bladder distension (cause in 75%–85%)	Insert or change bladder catheter
Faecal impaction (cause in 13%–19%)	Digital examination Laxatives Enema Manual dis-impaction
Urinary tract calculi	CT scan of urinary tract Cystoscopy or surgery to remove calculi
Urinary tract infection	Urinary microscopy and culture Appropriate antibiotics
Haemorrhoids or anal fissure	Laxatives Dietary management
Decubitus ulcers, with or without infection	Rule out underlying osteomyelitis Pressure area care Consider plastic surgery Consider antibiotics
Foot disease including ingrown toenails	Nail care
Procedures (e.g. suprapubic catheter insertion, cystoscopy, urodynamic studies)	Spinal anaesthesia may prevent AD
Heterotopic ossification	Bone scintigraphy Measure C reactive protein and creatine kinase Physiotherapy Surgery
Pelvic stimulation (sexual activity, menstruation, labour)	Education Be prepared in peripartum period
Skeletal fractures	High index of suspicion below NLI

AD, Autonomic dysreflexia; *CT,* computerised tomography; *NLI,* neurological level of injury.

From Blackmer J. Rehabilitation medicine: 1. Autonomic dysreflexia. *CMAJ.* 2003;169(9):931–935.

Venous thromboembolism

If inadequate or no prophylaxis is used, VTE following SCI has a very high incidence of up to 100%.[53] With prophylaxis, this incidence has reduced, but 5% of patients with SCI will still develop VTE,[54] and pulmonary embolism remains a leading cause of death. Commencement of adequate VTE prophylaxis is easier if all planned surgical procedures can occur as soon as practicable. The risk of venous thromboembolism increases significantly if prophylaxis is started more than 72 hours after the injury.[55] The Consortium for Spinal Cord Medicine recommends use of low-molecular-weight heparin for thromboprophylaxis after SCI.[56] Low-dose unfractionated heparin (e.g. 5000 units, twice daily) has not been shown to be useful after SCI.[56] The duration of prophylaxis should be at least 8 weeks in patients with limited mobility. If pharmacological VTE prophylaxis is contraindicated, a retrievable inferior vena cava filter should be considered.[57]

GASTROINTESTINAL COMPLICATIONS

Paralytic ileus and acute gastric dilatation are common in the first few days following SCI. Unopposed parasympathetic activity results in stomach hyperacidity, necessitating a proton pump inhibitor for ulcer prophylaxis in early days after the injury.

The upper motor neuron bowel syndrome seen in lesions above the T10 is characterised by increased colonic transit time, increased anal sphincter tone, and impaired sensation of fullness of the rectum, which results in constipation and faecal retention.

Stool softeners (for example, coloxyl) are generally required. Stimulants (for example, Senna) may be used at night time. Rectal stimulation is often necessary, and may be achieved by glycerine suppository, enema or digital stimulation. (The so-called 3-2-1 regimen employs three times a day coloxyl; two tablets of Senna at night time; and rectal stimulation once before the planned time of defaecation.) In patients who can eat, bowel motions should be planned after breakfast, taking advantage of the gastrocolic reflex. Other components of bowel management programs include adequate fluid intake, adequate dietary fibre, abdominal massage and, rarely, surgery (e.g. colostomy) or electrical stimulation. Opioids and other constipating medications should be avoided where possible.[58]

In lower motor neuron bowel syndrome, seen in cauda equina injuries, the external anal sphincter is lax but colonic peristalsis is inhibited, leading to both constipation and overflow incontinence. These patients benefit from increasing stool bulk (with fibre) and usually require manual evacuation.

URINARY TRACT COMPLICATIONS

Most patients with an NLI above L1 experience detrusor overactivity with sphincter dyssynergia. This results from the upper motor neuron lesion causing overactivity of both detrusor and the bladder sphincter. As a result, the detrusor contracts against closed sphincter, leading to high intravesical pressure, vesicoureteral reflux, high residual volume, incontinence, bladder spasm and an increased risk of urinary tract infections. Most patients with complete cervical SCI will require a suprapubic cystostomy, while thoracolumbar injuries may be managed by intermittent self-catheterisation. Detrusor overactivity, leading to bladder spasms, is common. Anticholinergics like oxybutynin (oral or transdermal), tolterodine, or solifenacin are used for treatment. In severe cases, intradetrusor botulinum toxin injection may be required. The anticholinergic side effects of these agents may be significant. Most patients require a combination of two anticholinergic medications.

Following SCI, there is a marked alteration in calcium homeostasis, with potential hypercalcaemia, hypercalciuria and a significant risk of calcium oxalate nephrolithiasis.

MUSCULOSKELETAL COMPLICATIONS

Muscle spasticity is a common but late complication. It develops after resolution of spinal shock and is characterised by increased muscle tone, hyperreflexia and muscle spasms below the NLI. Nociceptive stimuli below the level of injury (e.g. constipation, urinary tract infection) should be ruled out in patients with spasms. The initial treatment is oral baclofen. Its side effects include sedation, fatigue and confusion that may interfere with weaning from mechanical ventilation or participation in rehabilitation program. Intrathecal baclofen, local botulinum toxin, gabapentin, pregabalin and benzodiazepines are also used for severe spasticity.[52] Physiotherapy is needed to preserve a full range of movement and prevent contractures.

SKIN CARE

Pressure ulcers are common due to immobility and lack of sensation. Nearly 30% of patients with SCI develop pressure ulcers during their hospital stay, and half of these occur within the first month.[59] They are a source of significant morbidity and are associated with increased hospital length of stay, life-threatening infections, chronic osteomyelitis and AD. Skin healing in denervated skin is significantly delayed, so prevention is vital. The incidence of pressure areas may be reduced by:

- Twice daily skin inspection to detect early pressure areas
- Scheduled, frequent patient repositioning
- Good bowel and bladder care
- Pressure relieving mattress
- Prevention of accumulation of moisture
- Optimal nutrition
- Patient participation in their skin care programme

PSYCHOSOCIAL SUPPORT

Prolonged supportive care is necessary for both patients and their families to help them accept and adapt to neurological disability. Depression is common after SCI. Major depression should be differentiated from depressed mood. Health care workers may have the tendency to overdiagnose depression and conversely, depressive symptoms may be misinterpreted as somatic symptoms (for example, fatigue). Since many patients require antidepressants for pain and are also on drugs with anticholinergic effects (e.g. tolterodine, oxybutynin), management of depression is complex and specialist psychiatric consultation should be sought.

CHRONIC PAIN

Chronic pain is a frequent complication after SCI that occurs in up to two-thirds of patients. Pain after SCI may be classified as nociceptive pain from stimulation of nociceptors, or neuropathic pain from damage to sensory system itself. Most patients will report onset of chronic pain within 6 months after the injury, and frequently whilst still in ICU. Gabapentinoids (gabapentin and pregabalin) for neuropathic pain have the strongest evidence to support their efficacy.[60] Tricyclic antidepressants such as amitriptyline are effective for neuropathic pain in patients who also have depression. Infusions of opiates, ketamine and lignocaine are effective for neuropathic pain in the short term.[60] Behavioural therapy may be useful in addition to pharmacological treatment. Consultation with a pain specialist should be sought in patients with severe, refractory pain.

READMISSION TO THE INTENSIVE CARE UNIT

Common causes for readmission to the ICU for patients with pre-existing SCI are infections (urinary tract infections, pneumonia), AD, VTE and surgery (commonly after urinary tract procedure for renal stones). Meticulous attention should be given to skin care. All usual medications should be continued if possible. Abrupt withdrawal of baclofen may lower the seizure threshold. Risk of venous thromboembolism may be higher, and thromboprophylaxis should be used as appropriate for the clinical condition. The use of succinylcholine for intubation may precipitate severe hyperkalaemia.

OUTCOMES FOLLOWING SPINAL CORD INJURY

Hospital survival after SCI is now more than 90%, with long-term survival substantially better than it was 40 years ago. Factors predictive of higher mortality include higher NLI, complete SCI, older age and presence of co-morbidities.[61] Depending on the individual circumstances, it may be appropriate to have limitations of treatment for elderly patients with complete and high NLI. Most deaths are now due to respiratory and cardiovascular disease, with a decreasing proportion due to urinary complications. The neurological outcome post SCI is best prognosticated with an accurate neurological assessment using the ASIA impairment scale. Even during the first 24 hours, a reliable exam is highly predictive of outcome. Complete (ASIA A) injuries have the least potential for recovery, with only 7% converting to ASIA B by 1 year and none becoming motor-incomplete. However, 54% of ASIA B patients convert to ASIA C or D by 1 year with much better functional outcomes, and nearly all ASIA C under 50 years of age and all ASIA D patients are expected to be ambulatory on discharge from rehabilitation.[13] In the absence of a clinical exam, an MRI may be used to prognosticate, but is far less reliable. Despite significant disability, functional ability may be surprising to those who only manage the acute phase of SCI. For example, someone with a C5 ASIA A SCI may be able to mobilise with a power wheel chair with hand controls, drive a modified vehicle, have a family and a rewarding career.

The treatment offered to the patient may be influenced by the physician understanding of the outcome, quality and satisfaction with life after SCI. Physicians may imagine the quality of life following SCI to be more negative than it actually is.[62] It is vital that critical management decisions, particularly those related to treatment limitation, are not made in haste.

Acknowledgement

We acknowledge the contribution made by Dr. Pooja Arora, Specialist in Spinal Medicine, at Prince of Wales Hospital, Sydney, Australia.

REFERENCES

1. Amin A, Bernard J, Nadarajah R, et al. Spinal injuries admitted to a specialist centre over a 5-year period: a study to evaluate delayed admission. *Spinal Cord*. 2005;43(7):434–437.
2. New PW. Non-traumatic spinal cord injury: what is the ideal setting for rehabilitation? *Aust Health Rev*. 2006;30(3):353–361.
3. van Leeuwen CM, Post MW, van Asbeck FW, et al. Life satisfaction in people with spinal cord injury during the first five years after discharge from inpatient rehabilitation. *Disabil Rehabil*. 2012;34(1):76–83. [Multicenter Study].
4. Oliver M, Inaba K, Tang A, et al. The changing epidemiology of spinal trauma: a 13-year review from a Level I trauma centre. *Injury*. 2012;43(8): 1296–1300.
5. Hagen EM, Rekand T, Gilhus NE, et al. Traumatic spinal cord injuries – incidence, mechanisms and course. *Tidsskr Nor Laegeforen*. 2012;132(7):831–837.
6. Devivo MJ. Epidemiology of traumatic spinal cord injury: trends and future implications. *Spinal Cord*. 2012;50(5):365–372. [Review].

7. Wyndaele M, Wyndaele JJ. Incidence, prevalence and epidemiology of spinal cord injury: what learns a worldwide literature survey? *Spinal Cord*. 2006;44(9):523–529. [Meta-Analysis Review].
8. Ulbrich EJ, Schraner C, Boesch C, et al. Normative MR cervical spinal canal dimensions. *Radiology*. 2014;271(1):172–182. [Multicenter Study Research Support, Non-U.S. Gov't].
9. Sekhon LH, Fehlings MG. Epidemiology, demographics, and pathophysiology of acute spinal cord injury. *Spine*. 2001;26(24 suppl):S2–S12. [Review].
10. Tator CH, Fehlings MG. Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. *J Neurosurg*. 1991;75(1):15–26. [Research Support, Non-U.S. Gov't Review].
11. Rowland JW, Hawryluk GW, Kwon B, et al. Current status of acute spinal cord injury pathophysiology and emerging therapies: promise on the horizon. *Neurosurg Focus*. 2008;25(5):E2. [Review].
12. Kirshblum SC, Burns SP, Biering-Sorensen F, et al. International standards for neurological classification of spinal cord injury (revised 2011). *J Spinal Cord Med*. 2011;34(6):535–546.
13. Burns AS, Lee BS, Ditunno JF Jr, et al. Patient selection for clinical trials: the reliability of the early spinal cord injury examination. *J Neurotrauma*. 2003;20(5):477–482. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S. Research Support, U.S. Gov't, P.H.S.].
14. Ditunno JF, Little JW, Tessler A, et al. Spinal shock revisited: a four-phase model. *Spinal Cord*. 2004;42(7):383–395. Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S. Research Support, U.S. Gov't, P.H.S. Review.
15. Zideman DA, Singletary EM, De Buck ED, et al. Part 9: first aid: 2015 International Consensus on First Aid Science with Treatment Recommendations. *Resuscitation*. 2015;95:e225–e261. [Review].
16. Tescher AN, Rindflesch AB, Youdas JW, et al. Range-of-motion restriction and craniofacial tissue-interface pressure from four cervical collars. *J Trauma*. 2007;63(5):1120–1126. [Comparative Study Evaluation Studies].
17. Plumb JO, Morris CG. Clinical review: spinal imaging for the adult obtunded blunt trauma patient: update from 2004. *Intensive Care Med*. 2012;38(5):752–771.
18. Stiell IG, Clement CM, McKnight RD, et al. The Canadian C-spine rule versus the NEXUS low-risk criteria in patients with trauma. *N Engl J Med*. 2003;349(26):2510–2518. [Comparative Study Research Support, Non-U.S. Gov't Validation Studies].
19. Holmes JF, Akkinepalli R. Computed tomography versus plain radiography to screen for cervical spine injury: a meta-analysis. *J Trauma*. 2005;58(5):902–905. [Comparative Study Evaluation Studies Meta-Analysis Review].
20. Theocharopoulos N, Chatzakis G, Damilakis J. Is radiography justified for the evaluation of patients presenting with cervical spine trauma? *Med Phys*. 2009;36(10):4461–4470. [Evaluation Studies Research Support, Non-U.S. Gov't].
21. Bolinger B, Shartz M, Marion D. Bedside fluoroscopic flexion and extension cervical spine radiographs for clearance of the cervical spine in comatose trauma patients. *J Trauma*. 2004;56(1):132–136.
22. Padayachee L, Cooper DJ, Irons S, et al. Cervical spine clearance in unconscious traumatic brain injury patients: dynamic flexion-extension fluoroscopy versus computed tomography with three-dimensional reconstruction. *J Trauma*. 2006;60(2):341–345. [Comparative Study Validation Studies].
23. Freedman I, van Gelderen D, Cooper DJ, et al. Cervical spine assessment in the unconscious trauma patient: a major trauma service's experience with passive flexion-extension radiography. *J Trauma*. 2005;58(6):1183–1188.
24. Morris CG, McCoy E. Clearing the cervical spine in unconscious polytrauma victims, balancing risks and effective screening. *Anaesthesia*. 2004;59(5):464–482. [Review].
25. Hogan GJ, Mirvis SE, Shanmuganathan K, et al. Exclusion of unstable cervical spine injury in obtunded patients with blunt trauma: is MR imaging needed when multi-detector row CT findings are normal? *Radiology*. 2005;237(1):106–113.
26. Schoenfeld AJ, Bono CM, McGuire KJ, et al. Computed tomography alone versus computed tomography and magnetic resonance imaging in the identification of occult injuries to the cervical spine: a meta-analysis. *J Trauma*. 2010;68(1):109–113, discussion 113–114. [Comparative Study Meta-Analysis].
27. Como JJ, Diaz JJ, Dunham CM, et al. Practice management guidelines for identification of cervical spine injuries following trauma: update from the eastern association for the surgery of trauma practice management guidelines committee. *J Trauma*. 2009;67(3):651–659.
28. Menaker J, Stein DM, Philp AS, et al. 40-slice multidetector CT: is MRI still necessary for cervical spine clearance after blunt trauma? *Am Surg*. 2010;76(2):157–163. [Comparative Study].
29. Lebl DR, Bono CM, Velmahos G, et al. Vertebral artery injury associated with blunt cervical spine trauma: a multivariate regression analysis. *Spine*. 2013;38(16):1352–1361.
30. White AA, Panjabi MM. *Clinical Biomechanics of the Spine*. 2nd ed. Philadelphia: Lippincott; 1990.
31. Furlan JC, Noonan V, Cadotte DW, et al. Timing of decompressive surgery of spinal cord after traumatic spinal cord injury: an evidence-based examination of pre-clinical and clinical studies. *J Neurotrauma*. 2011;28(8):1371–1399.
32. Bracken MB, Shepard MJ, Collins WF, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord

injury. Results of the Second National Acute Spinal Cord Injury Study. *N Engl J Med*. 1990;322(20): 1405–1411.
33. Bracken MB, Shepard MJ, Holford TR, et al. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. *JAMA*. 1997;277(20):1597–1604.
34. Resnick DKM, Fehlings M, McCormick P. *Hypothermia and human spinal cord injury. Position statement and evidence based recommendations from the AANS/CNS joint section on disorders of the spine and the AANS/CNS Joint Section on Trauma*. <http://www.spinesection.org/hypothermia.php>; 2007.
35. Estenne M, De Troyer A. Cough in tetraplegic subjects: an active process. *Ann Intern Med*. 1990; 112(1):22–28. [Research Support, Non-U.S. Gov't].
36. Velmahos GC, Toutouzas K, Chan L, et al. Intubation after cervical spinal cord injury: to be done selectively or routinely? *Am Surg*. 2003; 69(10):891–894.
37. Peterson WP, Barbalata L, Brooks CA, et al. The effect of tidal volumes on the time to wean persons with high tetraplegia from ventilators. *Spinal Cord*. 1999;37(4):284–288. [Clinical Trial Research Support, U.S. Gov't, Non-P.H.S.].
38. Fenton JJ, Warner ML, Lammertse D, et al. A comparison of high vs standard tidal volumes in ventilator weaning for individuals with sub-acute spinal cord injuries: a site-specific randomized clinical trial. *Spinal Cord*. 2016;54(3):234–238.
39. Berney SC, Gordon IR, Opdam HI, et al. A classification and regression tree to assist clinical decision making in airway management for patients with cervical spinal cord injury. *Spinal Cord*. 2011;49(2):244–250. [Research Support, Non-U.S. Gov't].
40. Ganuza JR, Garcia Forcada A, Gambarrutta C, et al. Effect of technique and timing of tracheostomy in patients with acute traumatic spinal cord injury undergoing mechanical ventilation. *J Spinal Cord Med*. 2011;34(1):76–84.
41. Arora S, Flower O, Murray NP, et al. Respiratory care of patients with cervical spinal cord injury: a review. *Crit Care Resusc*. 2012;14(1):73.
42. Gutierrez CJ, Harrow J, Haines F. Using an evidence-based protocol to guide rehabilitation and weaning of ventilator-dependent cervical spinal cord injury patients. *J Rehabil Res Dev*. 2003; 40(5 suppl 2):99–110.
43. Sheel AW, Reid WD, Townson AF, et al. Effects of exercise training and inspiratory muscle training in spinal cord injury: a systematic review. *J Spinal Cord Med*. 2008;31(5):500–508. [Research Support, Non-U.S. Gov't Review].
44. Chiodo AE, Scelza W, Forchheimer M. Predictors of ventilator weaning in individuals with high cervical spinal cord injury. *J Spinal Cord Med*. 2008; 31(1):72–77.
45. Shavelle RM, DeVivo MJ, Strauss DJ, et al. Long-term survival of persons ventilator dependent after spinal cord injury. *J Spinal Cord Med*. 2006;29(5): 511–519.
46. Guly HR, Bouamra O, Lecky FE. The incidence of neurogenic shock in patients with isolated spinal cord injury in the emergency department. *Resuscitation*. 2008;76(1):57–62.
47. Lehmann KG, Lane JG, Piepmeier JM, et al. Cardiovascular abnormalities accompanying acute spinal cord injury in humans: incidence, time course and severity. *J Am Coll Cardiol*. 1987;10(1):46–52. [Case Reports].
48. Walters BC, Hadley MN, Hurlbert RJ, et al. Guidelines for the management of acute cervical spine and spinal cord injuries: 2013 update. *Neurosurgery*. 2013;60(suppl 1):82–91.
49. Altaf F, Griesdale DE, Belanger L, et al. The differential effects of norepinephrine and dopamine on cerebrospinal fluid pressure and spinal cord perfusion pressure after acute human spinal cord injury. *Spinal Cord*. 2017;55(1):33–38.
50. Blackmer J. Rehabilitation medicine: 1. Autonomic dysreflexia. *CMAJ*. 2003;169(9):931–935.
51. Ishikura F, Beppu S, Hamada T, et al. Effects of sildenafil citrate (Viagra) combined with nitrate on the heart. *Circulation*. 2000;102(20):2516–2521.
52. Rabchevsky AG, Kitzman PH. Latest approaches for the treatment of spasticity and autonomic dysreflexia in chronic spinal cord injury. *Neurother*. 2011;8(2):274–282. [Research Support, Non-U.S. Gov't Review].
53. Ploumis A, Ponnappan RK, Maltenfort MG, et al. Thromboprophylaxis in patients with acute spinal injuries: an evidence-based analysis. *J Bone Joint Surg Am*. 2009;91(11):2568–2576.
54. Jones T, Ugalde V, Franks P, et al. Venous thromboembolism after spinal cord injury: incidence, time course, and associated risk factors in 16,240 adults and children. *Arch Phys Med Rehabil*. 2005; 86(12):2240–2247.
55. Aito S, Pieri A, D'Andrea M, et al. Primary prevention of deep venous thrombosis and pulmonary embolism in acute spinal cord injured patients. *Spinal Cord*. 2002;40(6):300–303.
56. Prevention of venous thromboembolism in individuals with spinal cord injury: clinical practice guidelines for health care providers, 3rd ed.: consortium for spinal cord medicine. *Top Spinal Cord Inj Rehabil*. 2016;22(3):209–240. doi:10.1310/sci2203-209.
57. Roberts A, Young WF. Prophylactic retrievable inferior vena cava filters in spinal cord injured patients. *Surg Neurol Int*. 2010;1:68.
58. Krassioukov A, Eng JJ, Claxton G, et al. Neurogenic bowel management after spinal cord injury: a systematic review of the evidence. *Spinal Cord*. 2010;48(10):718–733. [Research Support, Non-U.S. Gov't Review].
59. van der Wielen H, Post MW, Lay V, et al. Hospital-acquired pressure ulcers in spinal cord injured

patients: time to occur, time until closure and risk factors. *Spinal Cord*. 2016;54(9):726–731.
60. Teasell RW, Mehta S, Aubut JAL, et al. A systematic review of pharmacological treatments of pain following spinal cord injury. *Arch Phys Med Rehabil*. 2010;91(5):816–831.
61. Frankel HL, Coll JR, Charlifue SW, et al. Long-term survival in spinal cord injury: a fifty year investigation. *Spinal Cord*. 1998;36(4):266–274.
62. Gerhart KA, Koziol-McLain J, Lowenstein SR, et al. Quality of life following spinal cord injury: knowledge and attitudes of emergency care providers. *Ann Emerg Med*. 1994;23(4):807–812.

81

Abdominal and pelvic injuries

Sarah McNeilly

Almost 25% of major trauma admissions suffer injury to the abdomen or pelvic contents.[1] Mortality from pelvic injury is nearly 10%, whereas abdominal injuries carry a mortality of 8%.[2,3] Haemorrhage is the most common cause of preventable trauma death.[4,5] Injuries can be divided into blunt or penetrating, with most abdominal and pelvic injuries being caused by blunt trauma. Penetrating aetiologies can account for up to a quarter of cases, depending on the society concerned.[6]

MECHANISMS OF INJURY

BLUNT INJURIES

Road traffic collisions (RTCs) are the most common cause of blunt trauma to the abdomen and pelvis.[7] Other common causes include falls, assaults, sporting accidents and industrial accidents. Associated injuries are frequent, involving the thorax, head and extremities. Seat belts and airbags considerably reduce mortality in RTCs, but airbags can be associated with thoracic injuries, including occult injuries to the great vessels and heart, particularly in decelerating incidents with an unstrained passenger.[8,9]

PENETRATING INJURIES

Stab and gunshot wounds account for most penetrating injuries to the abdomen.

STAB AND LACERATION WOUNDS

Neither entry sites nor implement used accurately predict the nature of deeper injury. With penetrating injury in the thoraco-abdominal area, damage to both thoracic and abdominal organs should be suspected, including damage to the diaphragm. Laparotomy remains the treatment of choice for patients with haemodynamic compromise, peritonism, evisceration or impalement but there is considerable debate on the management of the stable asymptomatic patient. Patients are managed with serial examinations or laparoscopy in some centres.[10,11]

GUNSHOT WOUNDS

Injuries depend on missile calibre, its velocity and trajectory. Both injuries and mortality are substantially greater than with stab wounds. Laparotomy should be performed in all cases with haemodynamic instability, signs of peritonism, associated injuries (or intoxication) that prevent serial abdominal examinations or confirmed rectal, bladder or ureter injuries. A non-operative approach for selected low-risk patients has been shown to be safe but is not yet universally accepted.[12]

INITIAL TREATMENT AND INVESTIGATIONS

RESUSCITATION

Initial assessment and resuscitation of the patient are performed simultaneously. The traditional ABC (airway, breathing, circulation) order of assessment and resuscitation has been replaced by <C>ABC, where <C> stands for 'catastrophic haemorrhage'.[13] This concept originated on the battlefield where there was a high mortality from external peripheral haemorrhage. Essentially, any massive haemorrhage is controlled with compression, tourniquet, haemostatic dressing or splintage before airway and breathing are addressed.

The aim of damage control resuscitation (DCR) is to provide haemostasis, with permissive hypotension to decrease bleeding and regain homeostasis in patients with life-threatening haemorrhage. Resuscitation with blood and blood products and the avoidance of crystalloid aims to treat and control coagulopathy early in the process and has been shown to improve survival.[14,15] (See haemorrhage and coagulopathy section.)

CLINICAL ASSESSMENT AND INITIAL INVESTIGATIONS

An initial primary survey is performed by an experienced clinician with the aim of identifying major life-threatening injuries requiring immediate attention. Mechanism of injury can give important information in terms of likely injury patterns. In crush injuries,

ABSTRACT

Abdominal and pelvic trauma is common and has a mortality of around 10%. Preventable death is often from haemorrhage. Blunt trauma is most common, often from falls and road traffic collisions. These patients require concurrent assessment and management to identify and treat life-threatening injuries. Computed tomography (CT) scanning is the most helpful mode of imaging in detecting abdominal and pelvic injuries, which may be complex and involve multiple organs. In major haemorrhage, damage control resuscitation improves mortality and is continued during a damage control laparotomy to stop bleeding. Increasing numbers of injuries are being treated by angio-embolisation, avoiding the need for laparotomy. On the ICU, management includes further resuscitation often followed by management of a patient with an open abdomen. Complications include haemorrhage, coagulopathy, sepsis and entero-cutaneous fistulae.

KEYWORDS

Abdomen
pelvis
haemorrhage
CT scan
damage control
coagulopathy

abdominal organs are crushed between the abdominal wall and spine or ribs; sudden extreme external compression may also cause the rupture of the hollow viscera. Rapid deceleration causes shearing forces which mean adjacent structures move in opposite directions, tearing at points of fixation such as vascular pedicles and mesenteric attachments.[16]

Physical signs and symptoms of internal injury in the abdomen are often unreliable, especially if the patient has other injuries (particularly head) or is intoxicated.[3] The rectum should be examined for tone, prostatic position, blood and evidence of other injury if the patient can be log-rolled.

Pelvic injuries can be difficult to detect by clinical examination alone. Patients may present with a pelvic binder in situ having been applied in the pre-hospital phase and this should not be removed for examination. If no binder is in situ, but pelvic injury is suspected, then one should be applied as part of the primary survey. The pelvis should not be 'sprung' to look for instability, as this may disrupt clots and cause further haemorrhage.[17] A log-roll should also be avoided if there is suspicion of pelvic fracture.

Pain around the pelvic area or lower back, asymmetry of the lower limbs or pelvis, or bruising around the perineum and scrotum can all indicate a pelvic fracture. Blood at the urethral meatus or haematuria are indications that there are associated urethral or bladder injuries.

Initial investigations should occur simultaneously with the primary survey. Bloods should be sent for full blood count, clotting studies, renal and liver function and group and screen with cross-match if bleeding suspected. Venous blood gas analysis should also be performed to assess for acidaemia and to measure the lactate level. Thromboelastography also provides rapid information on deficiencies in clotting factors, clot strength and clot breakdown, which helps to guide transfusion.[18]

CHOICE OF INVESTIGATIONS

The aim of the initial assessment and investigations of a patient with major trauma should be to rapidly identify and treat life-threatening injuries. The choice of diagnostic investigation should streamline this process. In patients with major haemorrhage, immediate computed tomography (CT) should be considered if they are responding to resuscitation or haemodynamically normal. Other diagnostic imaging (plain X-rays or focused assessment with sonography for trauma [FAST]) should be the minimum needed to direct interventions in those too unstable for CT scan.[19]

PLAIN X-RAYS

Portable plain anteroposterior (AP) X-rays of the chest and pelvis are often performed during the primary survey to exclude life-threatening tension pneumothorax and unstable pelvis fracture, though these are often excluded if the patient is going for immediate CT scan and should not delay this process.[16,19] Plain AP X-ray of the pelvis may appear normal, even with the presence of an unstable pelvic fracture, if there is a well-fitting pelvic binder in situ.

COMPUTED TOMOGRAPHY

In the polytrauma patient, the CT scan has become the imaging of choice to identify the patient's injuries, though this may not occur until after emergency haemostatic interventions such as laparotomy or angioembolisation. It has been shown to be superior to the combination of clinical evaluation and diagnostic peritoneal lavage (DPL) for the diagnosis of important abdominal injuries.[16] Current guidelines from the National Institute for Health and Care Excellence (NICE) recommend a whole-body CT (from vertex to toe on the scanogram and vertex to mid-thigh for the CT scan) in the blunt polytrauma patient.[19]

A single bolus of intravenous contrast agent is used and the use of a multidetector scanner allows the capture of arterial and portal venous phases and a delayed phase if necessary. The arterial phase will demonstrate vascular injury or ongoing arterial bleeding from, for example, a displaced pelvic fracture. Oral contrast is no longer required to help detect abdominal injuries.[3]

With isolated gunshot wound to the abdomen in stable patients, CT scan can aid the decision for conservative management, as the bullet trajectory is shown alongside any organ damage caused. Conversely in stabbings, it is no more sensitive than serial clinical examinations and may add little to the management of the patient.[20]

ULTRASONOGRAPHY

The FAST has become an important part of the primary survey of unstable trauma patients in the resuscitation room.[3] The bedside assessment of the heart, pericardium and abdomen allows the rapid detection of life-threatening conditions, expediting their immediate treatment. More recently, the extended-FAST (E-FAST) has taken over, which includes assessment for pneumothoraces. Ultrasound has shown to be more specific and sensitive for pneumothorax than the plain chest X-ray.[21]

In the stable trauma patient, E-FAST combined with clinical examination has been shown to be adequate in ruling out life-threatening injuries before CT scan, meaning routine plain imaging of the chest and pelvis is unnecessary.[21] In the very early post-injury phase, false negatives may be found when looking for fluid in the peritoneum. It is also poor at identifying retroperitoneal fluid and intra-abdominal organ injury without bleeding.[22] Like most imaging, E-FAST is operator dependent.

Table 81.1 Criteria for positive diagnostic peritoneal lavage

CLINICAL		
Initial aspiration of >10 mL frank blood		
Egress of lavage fluid via chest tube or urinary catheter		
Bile or vegetable material in lavage fluid		
LABORATORY		
	BLUNT INJURY	PENETRATING INJURY
RED CELLS		
Definite	>100 × 10⁹/L	>20 × 10⁹/L
Indeterminate	50–100 × 10⁹/L	5–20 × 10⁹/L
White cells	>0.5 × 10⁹/L	0.5 × 10⁹/L
Amylase	>20 IU/L	>20 IU/L
Alkaline phosphatase	>10 IU/L	>10 IU/L

PERITONEAL LAVAGE

The use of E-FAST and rapid CT scanning has meant that diagnostic peritoneal lavage (DPL) is now rarely indicated.[3] It may still be used if there is no access to either E-FAST or CT scanning. DPL detects intraperitoneal injury with up to 98% accuracy, but its high sensitivity can result in a significant non-therapeutic laparotomy rate.[23]

DPL is unjustified when an indication for laparotomy already exists. It is relatively contraindicated in pregnancy, significant obesity and previous abdominal surgery.

Generally accepted criteria for a positive DPL are shown in Table 81.1.

LAPAROSCOPY

Diagnostic laparoscopy may be useful in the haemodynamically stable patient. It is good for visualising the diaphragm and identifying the need for laparotomy, but may miss specific injuries in blunt abdominal trauma, particularly of the bowel. Surgical expertise is crucial. Laparoscopy appears best suited for the evaluation of equivocal penetrating wounds where it has both a diagnostic and potentially therapeutic role.[10]

MANAGEMENT OF THE UNSTABLE PATIENT

In patients with abdominal or pelvic trauma with haemorrhage, rapid transfer to either theatres or the angiography suite for either a laparotomy or angiography is required. These procedures are both diagnostic and part of the definitive treatment of the patient. Resuscitation should continue throughout this time.

INTERVENTIONAL RADIOLOGY

Angioembolisation is now a widely accepted treatment option for patients with solid organ injury and evidence of active contrast extravasation on CT scan.[24] It is also now the standard of care for patients with retroperitoneal arterial bleeding from pelvic fractures.[25] It allows rapid haemorrhage control in an area which is difficult to access surgically whilst avoiding the need for laparotomy. Stents can also be used to repair damaged vessels.

The interventional radiology suite should have suitable facilities to allow anaesthesia and continued resuscitation of the unstable patient during the procedure. Some centres are now combining an interventional radiology suite and operating theatre to allow simultaneous treatment of multiple injuries with surgery and angioembolisation.[26] This reduces the amount of time taken for resuscitation and definitive treatment of haemorrhage.[27]

LAPAROTOMY

In the unstable patient who requires surgery, all efforts should be made to get the patient to surgery as soon as possible and it may be that imaging such as the CT scan is delayed until after surgery.

Damage control surgery (DCS) is the concept of an abbreviated laparotomy to gain control of haemorrhage and limit contamination rather than definitive treatment of injuries identified. Physiology is prioritised over anatomy and it has been shown to improve survival in critically injured, shocked patients.[28,29] This limited operating time ensures rapid transit to the intensive care unit (ICU) for continued resuscitation, correction/prevention of the lethal triad of acidosis, hypothermia and coagulopathy and a thorough further examination (with imaging if necessary) of the patient to ensure all injuries are identified. Once physiology is normalised the patient can return to theatre in a planned way for definitive treatment of the injuries identified.[30]

In massive haemorrhage, the four quadrants of the abdomen are packed sequentially to control venous and solid organ haemorrhage. Arterial haemorrhage may require occlusion of the aorta to gain control. To minimise contamination, simple bowel perforations may be repaired and more complex injuries may be resected. Primary anastomosis and stoma formation are not done at this point to save time, so the bowel is left in discontinuity. At the end of surgery the abdomen is left open, preventing abdominal compartment syndrome, and as further surgery will be required.

DCS is not without its complications and has been shown to increase morbidity and length of stay.[29] For these reasons, it should be reserved for those who are truly reaching the end of their physiological reserve.

Studies are now beginning to identify the exact physiological parameters and injury patterns that require DCS to prevent patients having this type of surgery unnecessarily.[30]

DAMAGE CONTROL RESUSCITATION

Regardless of the method of haemorrhage control, resuscitation of the patient should start in the pre-hospital phase continuing into the ICU. It is now clear that coagulopathy and hyperfibrinolysis occur early in the disease process of major trauma and these should be addressed early.[14,31] DCR describes the concept of minimising crystalloid administration, permissive hypotension and a balanced transfusion of 1:1:1 of clotting factors:platelets:blood to prevent/correct coagulopathy. This method of resuscitation has been shown to increase survival and reduce the overall amount of blood and blood products required.[15,32–34]

SPECIFIC INJURIES

SPLEEN

Alongside the liver, the spleen is the organ most frequently injured by blunt trauma.[24] Injuries vary from a small subcapsular haematoma to hilar devascularisation or shattered spleen and are graded according to the American Association of Surgery for Trauma (AAST) splenic injury scale (I–V). Associated injuries include fractured left-sided ribs, and injuries to the left hemi-diaphragm, pancreas and bowel. Minor injury to the spleen may have few symptoms and other injuries may mask the symptoms. Minor trauma may cause splenic injury when the spleen is enlarged (e.g. from malaria, lymphoma and haemolytic anaemia).

Management can be conservative or via surgery or interventional radiology. Lower grade injuries in stable patients without active bleeding are managed conservatively, whereas higher grade injuries with evidence of contrast blush on CT scan can be managed extremely successfully with angioembolisation – treatment of the source of haemorrhage can restore haemodynamic stability rapidly.[24] If the patient is haemodynamically unstable and proceeding to theatre for laparotomy, 97% of those with splenic injury end up with a splenectomy, though splenic salvage is technically possible. Benefits of autotransplantation of splenic tissue during splenectomy remain unproven.

Overwhelming post-splenectomy infection by encapsulated organisms, such as *Pneumococcus*, can occur early or late (even years) after splenectomy in 0%–2% of individuals. Current UK guidelines recommend the administration of pneumococcal vaccine, meningococcal conjugate vaccine, annual influenza vaccination and vaccination against *Haemophilus influenza* type B post splenectomy.[35]

LIVER

The liver is commonly injured after blunt abdominal trauma, most frequently from motor vehicle collisions. The potential for massive haemorrhage coupled with multiple possible delayed complications means that the morbidity and mortality rate is high with early death most often caused by massive haemorrhage.[36,37] Diagnosis is made either on CT scan or during laparotomy in those too unstable for CT. Injuries range from small subcapsular haematomas to major parenchymal disruption and laceration of hepatic veins or even hepatic avulsion and are graded according to the AAST liver injury scale (I–V). The most commonly identified injury pattern is lacerations to the liver.[16]

Over 80% of patients with blunt hepatic injury are now managed non-operatively, which is up to 100% successful.[36] In patients with active bleeding from hepatic injury who respond transiently to resuscitation, angioembolisation should be the first-line treatment option. For the more unstable option, a laparotomy with packing is recommended followed by angioembolisation.[38] Follow-up CT scans can show the resolution of injury, which typically takes 2–3 months. Complications from non-operative management include hepatic necrosis (most common), hepatic abscesses and infected hepatic collections, bile leak/biloma, gall bladder infarction, ascites and delayed haemorrhage (5%–12%). The complication rate is higher with higher grades of injury. In the completely asymptomatic patient, management can be conservative with monitoring and serial examinations with the facility for further investigation or treatment if the situation changes.

Some patients will still require laparotomy despite apparently successful embolisation. These are the patients requiring ongoing resuscitation after embolisation. The injuries are likely to be high-grade lacerations and often have significant juxta-hepatic venous injuries and ongoing venous haemorrhage requiring DCS and packing. With the advent of hybrid operating suites, the option of simultaneous operative and non-operative management of these complex patients is possible.[26]

GASTROINTESTINAL TRACT

Injury to the gastrointestinal tract (GIT) is common following penetrating trauma but only occurs in approximately 5% of blunt abdominal trauma.[16] Over 90% of patients with abdominal gunshot wounds have injuries requiring operative management mandating laparotomy, though there may be a small sub-set of patients in whom this is unnecessary.[11,12] Laparoscopy can be used to both identify and treat injuries from penetrating trauma in stable patients when peritoneal violation cannot be excluded.[10] Posterior stab wounds are more challenging as they may damage retroperitoneal structures.

Blunt abdominal injuries include perforation or devascularisation of stomach, duodenum, small intestine, colon and their mesenteries, all of which are difficult to evaluate. Physical signs are often absent or non-specific.[3] E-FAST will identify free fluid in the abdomen, which may be due to an intestinal injury but is unable to differentiate between blood, urine, fluid from the breach of a luminal organ or from a chronic condition such as ascites. It will also not identify retroperitoneal fluid.

CT scan is the imaging of choice to search for injuries to the GIT and its blood supply. There are both specific and non-specific signs on CT scan of injury to the bowel which may be extremely subtle. Some of the specific signs include intramural haematoma, interruption of the bowel wall and extraluminal spillage of enteric contents. Some of the non-specific signs include extraluminal air collection, intraperitoneal fluid, bowel wall thickening, abnormal bowel wall enhancement and abnormal 'intestinal behaviours' (variations in tone, motility, shape and location of intestinal loops).[39]

Mesenteric injury ranges from simple contusions to complete traumatic avulsion. Injury to mesenteric vessels and bleeding may lead to bowel ischaemia and infarction, which may require resection of the affected section of bowel. Infarction of the bowel takes time to develop and may not show up initially on the CT scan. Mesenteric 'fat stranding' is a non-uniform increase in density of parts of the mesenteric fat and represents microhaemorrhagic foci. It is a non-specific sign of injury but should raise suspicions of injury to the mesentery and/or bowel.

Uncomplicated bowel injury can usually be managed by primary repair and anastomosis rather than colostomy. A faecal diversion procedure with delayed repair is indicated in significant peritoneal contamination or severe perineal injury or in DCS for speed.

PANCREAS

Pancreatic injury is relatively uncommon and accounts for up to 2% of all trauma patients. In blunt trauma, the pancreas is compressed against the spinal column, causing crush injury or transection in the region of the neck of the pancreas. It is often associated with injury to other abdominal organs, especially major vascular structures; 50% of penetrating injuries to the pancreas also have a concomitant vascular injury. CT is the most useful initial investigation; however, it is insensitive in detection of pancreatic duct injury, particularly early on. Endoscopic retrograde cholangiopancreatography is the most sensitive method for diagnosing duct injury, though logistically challenging to obtain in trauma patients.[16] Serum amylase levels are neither sensitive nor specific for injury and may be normal on presentation.

Treatment is becoming more conservative, and the use of external drains and distal pancreatectomy has been shown to decrease morbidity and mortality. Minor injuries require simple drainage only, whereas more severe injuries to the body and tail of the pancreas are best managed by distal pancreatectomy. Severe proximal injuries involving the duct or disruption of the head are difficult to manage. There is a move to more conservative management with closed drainage alone. Very complex surgery is required if there is concurrent duodenal injury, though there is no current consensus on what is best and occasionally pancreatico-duodenectomy is required. Mortality in these cases is high. Complications such as pancreatitis, fistula, abscess and pseudocyst are common with late complications of sepsis, multiorgan failure and respiratory failure occurring after more severe injury.[40]

KIDNEY AND URINARY TRACT

Blunt injury to the urinary tract is more common than penetrating injury with up to 10% of patients with blunt abdominal trauma having renal injuries.[41] Haematuria, micro- or macroscopic, after abdominal trauma, is a good indicator of injury to the kidneys or urinary tract.[16] Conversely, injuries to the renovascular pedicle or ureters may not cause any haematuria and its absence does not rule out renal injury.

Like liver and splenic injuries, renal injuries are graded on the AAST scale, with most injuries, even the higher grades, being managed conservatively.[41,42]

CT is the examination of choice, allowing early, accurate detection of renal tract injury. Urinary extravasation may be identified only on a repeat scan 10–20 minutes after contrast injection or on a formal retrograde (CT) cystogram. Stable patients with renal injury are most often managed conservatively, which avoids unnecessary surgery and nephrectomy and preserves renal function. Immediate intervention is needed in those with instability to stop bleeding and repair the kidney if possible. This may be done with interventional radiology, but nephrectomy is often the end result if the patient undergoes laparotomy. Parenchymal collecting system injuries often resolve without intervention but injury to the renal pelvis or proximal ureter avulsion require urgent intervention. Higher grade renal injuries treated conservatively require follow up CT at 48 hours, as there is a high rate of complications such as urinoma and haemorrhage. These may require treatment with ureteric stent, percutaneous drainage or percutaneous nephrostomy.[43]

Bladder injury is commonly associated with pelvic fractures. Blunt injury to patients with a distended bladder can cause isolated intraperitoneal bladder rupture. Over 95% of patients with bladder injury have macroscopic haematuria. Retrograde cystography is the investigation of choice. Intraperitoneal bladder rupture requires operative repair and urinary drainage, as it is unlikely to heal spontaneously and puts the patient at risk of bacterial translocation causing

peritonitis. Patients with uncomplicated extraperitoneal injury of the bladder can be managed conservatively with urinary catheter drainage alone.[43,44]

Urethral trauma is caused by direct blunt trauma or in association with pelvic fractures, particularly those involving the pubic diastasis in males.[17] It should be suspected if there is blood at the urethral meatus, perineal injury or abnormal position of the prostate on rectal examination. If there is suspicion of urethral injury, retrograde urethrography should be performed. One gentle attempt at urethral catheterisation by an experienced operator is acceptable, and if this is unsuccessful, then suprapubic catheterisation should be performed by the urologists in conjunction with pelvic surgeons. The timing of definite repair should be organised in conjunction with any required surgery to repair pelvic fractures.

DIAPHRAGM

Diaphragmatic injury occurs in fewer than 5% of cases of blunt injury, is left-sided in 80% of cases, and is rarely an isolated injury. It should be suspected in any penetrating thoracic or abdominal trauma. Diagnosis can be difficult, with up to 50% of chest X-rays having non-specific findings or no abnormality. CT scan has a sensitivity of 61%–87% and specificity of 72%–100% in diagnosing diaphragmatic injury.[45] Multiplanar reconstruction of the images improves on this accuracy further. Mortality is high (30%–60%) in those that are initially missed and present late with intrathoracic strangulation of a herniated viscus.[46]

If there is radiological suspicion of diaphragmatic injury in the stable patient, a diagnostic laparoscopy should be performed to confirm this.[46] Spontaneous healing does not occur, and all defects over 1 cm should be repaired. The risk of associated injuries means that an abdominal approach is most often used.

BONY PELVIS AND PERINEUM

Pelvic fractures in the younger adult are primarily caused by high-energy blunt trauma such as RTCs or falls from height; in the older adult, they are more likely to be due to low-energy falls from standing. Associated injuries are common, to pelvic organs such as the bladder and urethra but also to elsewhere in the body such as head and thoracic injuries. Injuries may be life-threatening and mortality is up to 34% in patients with pelvic fracture and haemodynamic instability.[17,47] Pelvic injury should be suspected in any high-energy injury and is suggested by pain on movement or in the hips, tenderness in the sacral or suprapubic areas, shortening and/or external rotation of a lower limb, gross haematuria or peri-pelvic ecchymosis.

CT is the best mode of imaging to rapidly identify pelvic fractures, any associated injuries or haemorrhage which may be amenable to interventional radiology. Reconstruction of the images will also aid planning the definitive operative fixation of complex fractures. E-FAST in the resuscitation room may identify any intra-abdominal bleeding but will not show associated retroperitoneal haemorrhage.

Pelvic injury is often graded using the Young and Burgess classification where fractures are classified based on the type of force causing the subsequent injury – lateral compression, anterior-posterior compression or vertical shear. Each of these is then subdivided based on severity of ligamentous disruption. An alternative method of classification is the Tile method.[47]

Patients with anterior-posterior compression fractures ('open-book') are more likely to have massive haemorrhage than those with lateral compression fractures, but haemorrhage is always a potential with pelvic fractures and should be identified and treated early.[48] Time to control of haemorrhage has a direct effect on mortality.[49] The management of these patients is difficult and there is no consensus as to what is the best management of the haemodynamically unstable patient with a pelvic fracture. The application of a temporary pelvic binder is often done in the prehospital phase but should be performed in the emergency department otherwise. It reduces bleeding by approximating fracture sites and preventing clot dislodgement by improving stability. The volume of the pelvis doesn't significantly increase when fractured; therefore, there is no tamponade effect from reducing pelvic volume with the binder as originally thought.[47] Although most bleeding in pelvic fractures is venous rather than arterial, in the unstable patient, arterial bleeding is more common.[47,48] Angiography and selective embolisation is highly effective in controlling arterial bleeding, seen as a contrast blush on CT scan with associated retroperitoneal haematoma.[25] This is the treatment of choice in the unstable patient with a negative E-FAST scan if possible. In the unstable patient with a positive E-FAST and pelvic fracture, laparotomy with pelvic packing is used to tamponade bleeding. This may be coupled with external fixation of the pelvis for mechanical stabilisation, reduction of pelvic volume and reduction of bony bleeding.[49,50]

The majority of patients with a pelvic fracture are haemodynamically normal with a stable fracture and moderate ligamentous disruption. These can be fixed on a non-urgent, planned basis.[50] Early operative stabilisation of complex pelvic fractures is preferred in the ICU and can be done externally, internally or as a combination of both; it facilitates respiratory care, pain control and early mobilisation. There is also growing evidence that operative management of pelvic fractures have a better functional outcome in the long term.[47] Compound pelvic fractures involving the perineum, rectum or vagina require aggressive surgery (which may include diversion of the faecal stream) to avoid high mortality.

Early deaths (in the first 24 hours) are due to haemorrhage, whereas late deaths are more commonly due to the systemic inflammatory response (SIRS) to trauma and multiorgan failure.[50]

TRAUMA IN PREGNANCY

The most common causes of trauma in pregnant women include RTCs, assaults and falls.[51] Women injured during pregnancy pose problems of altered physiology, risk to the gravid uterus and foetus, and potential conflict of priorities between mother and foetus. In general, however, the best treatment for the foetus is to treat the mother optimally, which, with major trauma, is a rapid, systematic evaluation of the patient with concurrent treatment of life-threatening emergencies. It must be remembered that the placental blood flow is dependent on maternal arterial blood pressure and has no autoregulation.

The mother should be placed in a left lateral tilt from the start to prevent aortocaval compression and high-flow oxygen should be given until maternal hypoxaemia, hypovolaemia and foetal distress have been excluded. Altered maternal physiology means that shock can be more difficult to detect:

- Increased maternal blood volume by up to 50% with physiological anaemia due to haemodilution
- Increased cardiac output with increased heart rate, reduced systemic vascular resistance and reduction in mean arterial pressure
- Increased respiratory rate and tidal volume with increased oxygen consumption and reduced functional residual capacity and reduced $PaCO_2$; meaning little respiratory reserve if demand increases due to injury and rapid onset of hypoxia
- The uterus is protected by the pelvis up to 12 weeks of pregnancy, after which it encroaches into the peritoneal cavity, displacing maternal organs and becoming more susceptible to injury
- Increased volume of stomach acid, reduced lower oesophageal sphincter tone and reduced gastrointestinal motility, increasing the risk of aspiration
- Pregnancy-induced changes in the airway, coupled with less respiratory reserve, make rapid sequence induction of anaesthesia and intubation of the trachea more difficult in pregnancy.[52]

When considering imaging, the radiation risk to the foetus should be weighed up against the risk to mother and foetus of missing an injury. Imaging that is the standard of care in a non-pregnant patient with potentially life-threatening injuries should remain the same in the pregnant patient.[51] E-FAST is safe in pregnancy and in addition to detecting free fluid in the abdomen, the condition of the foetus can also be assessed.

The injury pattern can change due to the presence of the gravid uterus. There is upward displacement of bowel with the potential for complex intestinal injuries in penetrating trauma of the upper abdomen. The pelvic vasculature is hypertrophied with potential for massive retroperitoneal haemorrhage in pelvic injury. Similarly, the blood supply to the uterus at term is 600 mL/min, meaning there is potential for massive haemorrhage with direct uterine injury. Placental abruption can occur, which may conceal significant blood loss.

Early involvement of the obstetric team is crucial for management decisions and for ongoing monitoring of the materno-foetal unit. Treatment may be expectant or by caesarean section, depending on the condition of the mother and foetus. Uterine rupture is unusual and will often require hysterectomy. In traumatic cardiac arrest, perimortem caesarean section should commence as soon as possible but within 4 minutes for best outcome of mother and foetus.[53]

Following maternal trauma, there is increased risk to the foetus both in the short and long term, especially with more severe trauma. Placental abruption, foetal distress and foetal loss can all occur, as can premature labour.[53] Continuous cardiotocography (indicated at viable gestations) is recommended for all trauma patients to assess foetal well-being and the Kleihauer–Betke tests to identify foeto-maternal haemorrhage has been used to predict patients at high risk for preterm delivery and adverse perinatal outcomes.[51] All Rhesus negative pregnant women who suffer trauma should receive immunoglobulin because of the immunological risk of even minor foeto-maternal haemorrhage.

COMPLICATIONS

HAEMORRHAGE AND COAGULOPATHY

Haemorrhage from injuries due to major trauma is the most common cause of preventable trauma death.[4,5] Acute traumatic coagulopathy (ATC) occurs in up to 35% of patients by the time they arrive at hospital and is associated with significant tissue injury and shock. Endogenous anticoagulation develops in response to the increasingly more procoagulant vasculature due to damaged endothelium. This anticoagulation is due to autoheparinisation, activation of protein C and hyperfibrinolysis. ATC is then worsened by acidosis and hypothermia. Finally, the administration of fluids such as crystalloids or starches further compounds this by causing a dilutional coagulopathy.[14,28,31,32,50]

Treating the massive haemorrhage and coagulopathy associated with major trauma is challenging. DCR, initially developed in the military, should be commenced in the pre-hospital phase. DCR incorporates permissive hypotension, early treatment of the anticipated ATC with use of blood and blood products and limiting the use of crystalloids and early use of tranexamic acid.[28,33] Evidence shows that DCR improves outcome and reduces complications from DCL and may also reduce the number of patients

requiring DCL who can instead have immediate definitive treatment.[33] Equally as important as the treatment of coagulopathy and shock is haemorrhage control using DCS or angioembolisation.

Permissive hypotension aims to avoid the adverse effects of aggressive fluid resuscitation – dilution of clotting factors, hypothermia, increased intraluminal pressure at the site of injury causing dislodgement of clot – whilst maintaining some tissue perfusion for a short period of time.[50] There is little evidence to say what mean arterial pressure is acceptable in this situation, but European guidelines recommend a systolic blood pressure of 80–100 mm Hg, whereas NICE and others recommend a mean arterial pressure of 50 mm Hg.[19,29,54] Permissive hypotension is contraindicated in the presence of concurrent neurological injury where perfusion and oxygenation of the injured brain or spine takes priority.[50]

To address ATC, transfusion with blood and blood products in a 1:1:1 (plasma:platelets:red cells) compared to a 1:1:2 ratio has been shown to improve haemostasis and lead to fewer deaths due to exsanguination in the first 24 hours, although there was no overall improvement in 24-hour or 30-day mortality.[32] This is now being incorporated into guidelines along with the use of major haemorrhage protocols allowing rapid access to blood and blood products.[14,19,28]

Administration of the antifibrinolytic tranexamic acid within 3 hours of injury has been shown to reduce deaths from bleeding without increasing vascular occlusive events in a large study of patients treated in diverse hospital settings.[34] It is commonly given prehospital now, but should be given as early as possible in the resuscitation room if not.[14,19,28]

As trauma in the elderly is increasing, it must be remembered that patients may also be on long-term anticoagulation which may contribute to haemorrhage. This should be identified early and the agent reversed as soon as possible.

OPEN ABDOMEN FOLLOWING DAMAGE CONTROL SURGERY

After DCS, patients are admitted to the ICU with temporary closure of the abdomen. Once their physiology is normalised, they will return to theatre, often several times, for definitive management of the injuries and closure of the abdomen. An open abdomen puts patients at risk of ischaemia-reperfusion injury to the bowel and acute respiratory distress syndrome associated with this; they are also likely to develop a SIRS.[55]

SEPSIS AND ENTERO-CUTANEOUS FISTULA

Entero-cutaneous fistula (ECF), an abnormal communication between the intra-abdominal GIT and the atmosphere, is a significant problem with high morbidity and mortality.[56] It causes multiple complications including sepsis, fluid loss, electrolyte abnormalities, prolonged ICU and hospital stays and complex wound care issues. They are difficult to manage and usually require operative repair. Predisposing factors include:

- Bowel resection
- Bowel left in discontinuity
- Those administrated a large amount of fluids during the first 24 hours
- Multiple abdominal re-explorations
- Delayed closure of an open abdomen.[57]

Early diagnosis and effective lavage and drainage procedures may reduce the incidence of intra-abdominal sepsis. In the absence of sepsis, prophylactic antibiotics for 24 hours are satisfactory for open abdomens after DCS. Infectious complication rates correlate directly with time to fascial closure.[55]

VENTRAL HERNIA

Up to 80% of patients with an open abdomen go on to develop a ventral hernia after delayed fascial closure. This may be planned if there is no other way to close the abdomen.[56] Large ventral hernias may prolong recovery due to discomfort or loss of function. They may be repaired at a later stage with reconstruction of the abdominal wall.

FLUID LOSS AND ELECTROLYTE IMBALANCE

Patients lose large amounts of fluid from the peritoneal cavity resulting in electrolyte imbalance and dehydration. Fluid management after the initial resuscitation is challenging, as excess fluids may lead to increased complications with bowel wall oedema, anastomosis breakdown and abdominal compartment syndrome. Conversely these patients often require extra fluids due to the open peritoneal cavity and SIRS from the trauma. A goal-directed method of fluid therapy should be used.

MALNUTRITION

These patients are highly catabolic and can lose large amounts of protein through the open abdomen. Malnutrition is particularly common in those that develop ECF.[55,56] Nutritional support is crucial and often challenging. Enteral feeding should be commenced early in those with intact intestinal continuity and no obstruction. In those who do not have intestinal continuity (delayed repair of bowel injuries) or have complex injuries, parenteral nutrition may be required.

RAISED INTRA-ABDOMINAL PRESSURE

Although now less common, abdominal distension with raised intra-abdominal pressure may be seen in

the critically injured as a consequence of haemorrhage, bowel oedema, ileus or surgical packs. This can have severe adverse effects on respiratory, cardiovascular and renal function. Alleviation is by surgical decompression and temporary closure, with or without visceral packing. The abdomen is subsequently closed by staged repair as the distension resolves.[56,58]

VENOUS THROMBOEMBOLISM

Pelvic trauma, postoperative status, higher Injury Severity Score and underlying medical risk factors increase the risk of venous thromboembolism 1.5–3 times greater than trauma patients without such factors.[59] Early initiation of mechanical prophylaxis is usually feasible, as is pharmacological prophylaxis when the risk of injury-associated bleeding has reduced. The use of inferior vena cava filters in trauma patients where pharmacological prophylaxis is contraindicated is increasing and reduces the incidence of pulmonary emboli. It is not yet clear which patients benefit most, as there are significant complications related to these devices.[60]

REFERENCES

1. NSW Institute of Trauma and Injury Management. *Major Trauma in NSW 2015*. Sydney: NSW Agency for Clinical Innovation; 2016.
2. Wang H, Robinson RD, Moore B, et al. Predictors of early versus late mortality in pelvic trauma patients. *Scand J Trauma Resusc Emerg Med*. 2016; 24:27.
3. Diercks DB, Mehrotra A, Nazarian DJ, et al. Clinical policy: critical issues in the evaluation of adult patients presenting to the emergency department with acute blunt abdominal trauma. *Ann Emerg Med*. 2011;57(4):387–404.
4. Kleber C, Giesecke MT, Tsokos M, et al. Trauma-related preventable deaths in Berlin 2010: need to change prehospital management strategies and trauma management education. *World J Surg*. 2013; 37:1154–1161.
5. Vähäaho S, Söderlund T, Tulikoura I, et al. Traumatic deaths at hospital: analysis of preventability and lessons learned. *Eur J Trauma Emerg Surg*. 2014;40: 707–713.
6. Smith J, Caldwell E, D'Amours S, et al. Abdominal trauma: a disease in evolution. *ANZ J Surg*. 2005;75: 790–794.
7. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. *Web-based injury statistics query and reporting system (WISQARS)*. http://www.cdc.gov/injury/wisqars.
8. Crandall CS, Olson LM, Sklar DP. Mortality reduction with air bag and seat belt use in head-on passenger car collisions. *Am J Epidemiol*. 2001; 153(3):219–224.
9. Khouzam RN, Al-Mawed S, Farah V, et al. Next-generation airbags and the possibility of negative outcomes due to thoracic injury. *Can J Cardiol*. 2014; 30:396–404.
10. O'Malley E, Boyle E, O'Callaghan A. Role of laparoscopy in penetrating abdominal trauma: a systematic review. *World J Surg*. 2013;37:113–122.
11. Biffl WL, Leppaniemi A. Management guidelines for penetrating abdominal trauma. *World J Surg*. 2015; 39:1373–1380.
12. Navsaria PH, Nicol AJ, Edu S, et al. Selective nonoperative management in 1106 patients with abdominal gunshot wounds. *Ann Surg*. 2015;261:760–764.
13. Hodgetts TJ, Mahoney PF, Russell MQ, et al. ABC to <C>ABC: redefining the military trauma paradigm. *Emerg Med J*. 2006;23:745–746.
14. Stensballe J, Ostrowski SR, Johansson PI. Haemostatic resuscitation in trauma: the next generation. *Curr Opin Crit Care*. 2016;22:591–597.
15. Cotton BA, Reddy N, Hatch QM, et al. Damage control resuscitation is associated with a reduction in resuscitation volumes and improvement in survival in 390 damage control laparotomy patients. *Ann Surg*. 2011;254(4):598–605.
16. Soto JA, Anderson SW. Multidetector CT of blunt abdominal trauma. *Radiology*. 2012;265(3):678–693.
17. Shivji FS, Quah C, Forward DP. Pelvic fractures. *Surgery*. 2015;33(6):257–263.
18. Abdelfattah K, Cripps MW. Thromboelastography and rotational thromboelastometry use in trauma. *Int J Surg*. 2016;33:196–201.
19. Glen J, Constanti M, Brohi K, et al. Assessment and initial management of major trauma: summary of NICE guidance. *BMJ*. 2016;353:i3051.
20. Inaba K, Okoye OT, Rosenheck R, et al. Prospective evaluation of the role of computed tomography in the assessment of abdominal stab wounds. *JAMA Surg*. 2013;148(9):810–816.
21. Hamada SR, Delhaye N, Kerever S, et al. Integrating eFAST in the initial management of stable trauma patients: the end of the plain film radiography. *Ann Intensive Care*. 2016;6(1):62.
22. Montoya J, Stawicki SP, Evans DC, et al. From FAST to E-FAST: an overview of the evolution of ultrasound-based traumatic injury assessment. *Eur J Trauma Emerg Surg*. 2016;42:119–126.
23. Nagy KK, Roberts RR, Joseph KT, et al. Experience with over 2500 diagnostic peritoneal lavages. *Injury*. 2000;31:479–482.
24. Salcedo ES, Brown IE, Corwin MT, et al. Angioembolization for solid organ injury: a brief review. *Int J Surg*. 2016;33:225–230.
25. Salcedo ES, Brown IE, Corwin MT, et al. Pelvic angioembolization in trauma – indications and outcomes. *Int J Surg*. 2016;33:231–236.
26. Kirkpatrick AW, Vis C, Dubé M, et al. The evolution of a purpose designed hybrid trauma operating room from the trauma service perspective: the RAPTOR (resuscitation with angiography percutaneous treatments and operative resuscitations). *Injury*. 2014;45:1413–1421.
27. Kataoka Y, Minehara H, Kashimi F, et al. Hybrid treatment combining emergency surgery and

intraoperative interventional radiology for severe trauma. *Injury*. 2016;47:59–63.
28. Lamb CM, MacGoey P, Navarro AP, et al. Damage control surgery in the era of damage control resuscitation. *Br J Anaesth*. 2014;113(2):242–249.
29. Ball CG. Damage control surgery. *Curr Opin Crit Care*. 2015;21:538–543.
30. Roberts DJ, Bobrovitz N, Zygum DA, et al. Indications for use of damage control surgery in civilian trauma patients. *Ann Surg*. 2016;265(5): 1018–1027.
31. Davenport R, Manson J, De'Arth J, et al. Functional definition and characterisation of acute trauma coagulopathy. *Crit Care Med*. 2011;39:2652–2658.
32. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets and red blood cells in a 1:1:1 vs 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*. 2015;313(5):471–482.
33. Bellal J, Azim A, Zangbar B, et al. Improving mortality in trauma laparotomy through the evolution of damage control resuscitation: analysis of 1030 consecutive trauma laparotomies. *J Trauma Acute Care Surg*. 2017;82(2):328–333.
34. CRASH-2 trial collaborators, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010; 376:23–32.
35. Hildebrand DR, Ben-Sassi A, Ross NP, et al. Modern management of splenic trauma. *BMJ*. 2014;348: g1864.
36. Green CS, Bulger EM, Kwam SW. Outcomes and complications of angioembolization for hepatic trauma: a systematic review of the literature. *J Trauma Acute Care Surg*. 2016;80(3):529–537.
37. Doklestić K, Stefanović B, Gregorić P, et al. Surgical management of AAST grades III-V hepatic trauma by damage control surgery with perihepatic packing and definitive hepatic repair-single centre experience. *World J Emerg Surg*. 2015;34(10):1–8.
38. Stassen NA, Bhullar I, Cheng JD, et al. Nonoperative management of blunt hepatic injury: an Eastern Association for the Surgery of Trauma practice management guideline. *J Trauma Acute Care Surg*. 2012;73(5 suppl 4):S288–S293.
39. Iaselli F, Mazzei MA, Firetto C, et al. Bowel and mesenteric injuries from blunt abdominal trauma: a review. *Radiol Med*. 2015;120:21–31.
40. Potoka DA, Gaines BA, Leppäniemi A, et al. Management of blunt pancreatic trauma: what's new? *Eur J Trauma Emerg Surg*. 2015;41:239–250.
41. Van der Wilden GM, Velmahos GC, Joseph DK, et al. Successful nonoperative management of the most severe blunt renal injuries: a multicentre study of the research consortium of New England Centres for Trauma. *JAMA Surg*. 2013;148(10): 924–931.
42. Long JA, Fiard G, Descotes JL, et al. High-grade renal injury: non-operative management of urinary extravasation and prediction of long-term outcomes. *BJU Int*. 2012;111:E249–E255.
43. Morey AF, Brandes S, Dugi DD III, et al. Urotrauma: AUA guideline. *J Urol*. 2014;192:327–335.
44. Hornez E, Monchal T, Boddaert G, et al. Penetrating pelvic trauma: initial assessment and surgical management in emergency. *J Visc Surg*. 2016;153:79–90.
45. Bonatti M, Lombardo F, Vezzali N, et al. Blunt diaphragmatic lesions: imaging findings and pitfalls. *World J Radiol*. 2016;8(10):819–828.
46. Mahamid A, Peleg K, Givon A, et al. Blunt traumatic diaphragmatic injury: a diagnostic enigma with potential surgical pitfalls. *Am J Emerg Med*. 2017;35(2):214–217.
47. Wong JM, Bucknill A. Fractures of the pelvic ring. *Injury*. 2017;48(4):795–802.
48. Marzi I, Lustenberger T. Management of bleeding pelvic fractures. *Scand J Surg*. 2014;103:104–111.
49. Scemama U, Dabadie A, Varozuaux A, et al. Pelvic trauma and vascular emergencies. *Diagn Interv Imaging*. 2015;96:717–729.
50. Mauffrey C, Cuellar DO III, Hak DJ, et al. Strategies for the management of haemorrhage following pelvic fractures and associated trauma-induced coagulopathy. *Bone Joint J*. 2014;96-B:1143–1154.
51. Brown S, Mozurkewich E. Trauma during pregnancy. *Obstet Gynecol Clin North Am*. 2013;40: 47–57.
52. Reddy SV, Ahmed SN, Kesavachandra G. Trauma during pregnancy. *J Obstet Anaesth Crit Care*. 2012; 2:3–9.
53. Amorosa LF, Amorosa JH, Wellman DS, et al. Management of pelvic injuries in pregnancy. *Orthop Clin North Am*. 2013;44:301–315.
54. Pieracci FM, Biffl WL, Moore EE. Current concepts in resuscitation. *J Intensive Care Med*. 2012;27:79–96.
55. Griggs C, Butler K. Damage control and the open abdomen: challenges for the nonsurgical intensivist. *J Intensive Care Med*. 2016;31(9):567–576.
56. Huang Y, Li Y. Open abdomen in trauma patients: a double-edged sword. *Mil Med Res*. 2016;3:10.
57. Bradley MJ, DuBose JJ, Scalea TM, et al. Independent predictors of enteric fistula and abdominal sepsis after damage control laparotomy – results from the prospective AAST open abdomen registry. *JAMA Surg*. 2013;148(10):947–954.
58. Balogh ZJ, Lumsdaine W, Moore EE, et al. Post-injury abdominal compartment syndrome: from recognition to prevention. *Lancet*. 2014;384: 1466–1475.
59. Paffrath T, Wafaisade A, Lefering R, et al. Venous thromboembolism after severe trauma: incidence, risk factors and outcomes. *Injury*. 2010;41:97–101.
60. Haut ER, Garcia LJ, Shihab HM, et al. The effectiveness of prophylactic inferior vena cava filters in trauma patients: a systematic review and meta-analysis. *JAMA Surg*. 2014;149(2):194–202.

This page intentionally left blank

Part Twelve
Environmental Injuries

This page intentionally left blank

82

Submersion

Tim Bowles

DEFINITIONS

Drowning was defined by the World Health Organization in 2002 as follows: 'Drowning is the process of experiencing respiratory impairment from submersion/immersion in liquid.'[1] If the victim dies as a result, the event should be referred to as 'fatal drowning'. If the drowning process is interrupted, it should be referred to as 'non-fatal drowning'. The Utstein template can be adopted to provide consistent reporting of drowning events and allow accurate categorisation.[2]

EPIDEMIOLOGY

Drowning causes an estimated 372,000 deaths worldwide per year.[3] Of these, 3700 are reported from the USA (approximately 1.2 deaths per 100,000 population) and 290 (1.4 deaths/100,000 population) from Australia.[4,5] More than 90% of fatal drownings occur in low- or middle-income countries and, worldwide, drowning is the third most common cause of unintentional injury death.[3] In the USA, twice as many non-fatal drownings as fatal ones were recorded in 2009.[4] In Australia, drowning is the leading cause of unintentional injury death in children aged 1–3 years.[6] Males predominate, with peaks at 5 and 20 years of age. Private swimming pools and natural water bodies close to home present the greatest risk to young children.[7] Other sites include bath tubs, fish tanks, buckets, toilets and washing machines. Adolescent drowning tends to occur in rivers, lakes, canals and beaches.[8] Lack of adult supervision commonly contributes to toddler accidents; however, child abuse must also be considered. Alcohol and drug intoxication are associated with up to 40% of adolescent drowning.[9] Other risk factors include epilepsy (18%), trauma (16%) and cardiopulmonary disease (14%).[10]

Among older people who drowned in Australia, 69% had a pre-existing medical condition, most commonly cardiovascular disease, but also dementia, depression, epilepsy and Parkinson's disease. A fall into the water was the most frequent antecedent to drowning among older people, although swimming and watercraft incidents were also common.[11] Hyperventilation prior to underwater swimming suppresses the physiological response to rising carbon dioxide tension, allowing hypoxia to ensue with consequent loss of consciousness and water breathing.[12]

PATHOPHYSIOLOGY

Voluntary apnoea and reflex responses occur upon submersion. The diving response is characterised by apnoea, marked generalised vasoconstriction and bradycardia in response to cold-water stimulus of the ophthalmic division of the trigeminal nerve. Blood is thus shunted preferentially to the brain and heart. In infants the response may be marked,[13] but only 15% of fully clothed adults show a significant response. Although the diving reflex appears to play a powerful role in oxygen conservation in animals, its role in humans is unknown but may be protective.[14]

After airway immersion, breath holding followed by laryngospasm occurs. This causes progressive hypoxia and hypercarbia, eventually resulting in relaxation of airway reflexes and water aspiration.[15] Up to 22 mL/kg of water has been estimated to be the maximal survivable inhaled water volume.[16] This is followed by a phase of secondary apnoea and loss of consciousness. Hypoxaemic death ensues if the person is not retrieved and resuscitated; acute respiratory distress syndrome (ARDS) occurs in up to 72% of symptomatic survivors.[17] Multiple organ dysfunction and cerebral damage may become evident in those who survive to hospital.

SALT- VERSUS FRESH-WATER ASPIRATION

The differences between salt- and fresh-water drowning have traditionally been emphasised. This is largely based on animal data. In canine models, after aspiration of massive volumes of salt water, it was possible to recover by suction or mechanical drainage greater volumes than were initially instilled.[18] The hypertonic salt water was drawing fluid into the pulmonary interstitial space, which was thought to result in

ABSTRACT

Drowning is the process of experiencing respiratory impairment from submersion/immersion in liquid. It is the third most common cause of unintentional injury death, with an international death toll almost two-thirds that of malnutrition and well over half that of malaria. Public health efforts at prevention are now a WHO priority. If early rescue does not occur, the predictable sequence is of water inhalation, triggering acute respiratory distress syndrome (ARDS), followed by hypoxic cardiac arrest. Management is essentially supportive, with non-invasive or invasive ventilation using lung protective strategies, considering the presence of contamination and specific treatment requirements. Associated abnormalities frequently include hypovolaemia and hypothermia; mostly cardiovascular instability resolves with restoration of oxygenation, circulating volume and normothermia. However, co-morbidity, particularly in the older population, is common, and cardiovascular disease should be considered in those who do not improve. Prognostication can be difficult, with assessments in the field often incorrect, and reported survivors despite multiple adverse features.

KEYWORDS

Drowning
submersion
resuscitation
environmental hazards

hypovolaemia, hypernatraemia and haemoconcentration as well as pulmonary oedema.

Conversely, after fresh-water aspiration in dogs, minimal volumes of fluid were retrievable from the lungs.[19] The hypotonic water was absorbed into the circulation. The pulmonary oedema seen was thought to be secondary to removal of surfactant, and hypervolaemia; dilutional hyponatraemia and haemolysis were expected.

More recent animal data and human case series have demonstrated that the tonicity of the fluid aspirated is not clinically relevant.[20] No clinically detectable difference in the patterns of lung injury is seen between salt- and fresh-water drowning; both types reduce pulmonary surfactant quantity and function, causing pulmonary oedema both directly and by the generation of osmotic gradients, and hypoxia by collapse, atelectasis and shunting, resulting in ARDS.

WATER CONTAMINANTS

The incidence of pneumonia complicating submersion injury may be greater than 15% in those who survive long enough.[22] Rivers, lakes and coastal waters are greater reservoirs for microbes than well-kept swimming pools. In fresh water, Gram-negative bacteria predominate along with anaerobes and *Staphylococcus* spp., fungi, algal and protozoan species. *Aeromonas* spp. are ubiquitous water-borne bacteria and can be responsible for severe pneumonia.[22] Infection with oral commensals is common, as is infection with multiple organisms. Although prophylactic antibiotic treatment is not recommended in general,[23] if infection is suspected then broad-spectrum antibiotics with antipseudomonal cover is suggested, with knowledge of local organism spectrum and resistance patterns.[24]

Chemicals in polluted water, such as kerosene,[25] chlorine[26] and particulate matter like sand,[27] can cause severe pulmonary dysfunction.

TEMPERATURE

Victims of submersion may develop primary or secondary hypothermia. If submersion occurs in icy water (<5°C), hypothermia may develop rapidly and provide some protection against hypoxia. Surface cooling is unlikely to produce adequate protective hypothermia before hypoxia ensues.[14] Most reports of survival after prolonged submersion involve small children in icy water and it has been postulated that protective core cooling occurs rapidly due to cold-water aspiration, ingestion and absorption, though the mechanisms remain controversial.[28]

Of more importance in cold-water submersion are the detrimental 'cold-shock' responses.[28] These responses include a 'gasp' followed by uncontrollable hyperventilation and reduction in maximal breath-hold times, vasoconstriction, tachycardia, hypertension and increased myocardial oxygen consumption. These responses may lead to motor dyscoordination and swimming failure as well as cardiac arrhythmia; hence, even strong swimmers may drown quickly in icy waters.[29]

MANAGEMENT

BASIC LIFE SUPPORT

Prompt retrieval from the water is essential, as is immediate on-site resuscitation. As any cardiac arrest is normally secondary to hypoxaemia, five rescue breaths should be administered first, followed by standard basic life support. Delivery of adequate rescue breaths may take prolonged insufflation due to reduced compliance and increased resistance. External cardiac massage in the absence of expired air respiration is unlikely to be successful. Rescue breathing can be performed effectively in the water; chest compressions cannot.[21]

The risk of cervical spine injury is small (<0.5%), and attempted cervical spine immobilisation can compromise effective rescue and resuscitation in the water. Therefore, spinal immobilisation is indicated only in the presence of severe injury or consistent history.[21] Removal from the water can cause concealed hypovolaemia, from prolonged immersion, to present as cardiovascular collapse – the victim should be kept in a horizontal position as far as possible.[21]

Regurgitation of stomach contents and swallowed water is common – if it prevents ventilation completely, the victim can be turned to the side and aspiration attempted using direct suction if available. Rewarming should be commenced immediately with the use of blankets and further heat loss should be avoided. When experienced personnel arrive, bag and mask ventilation and advanced cardiac life support are initiated.

INITIAL HOSPITAL MANAGEMENT

Resuscitation continues on arrival to hospital. Endotracheal intubation and mechanical ventilation are instituted if hypoxaemia is severe despite high-flow oxygen or assisted bag and mask respiration. Ventilatory failure, characterised by increasing respiratory distress and rising carbon dioxide levels, and the presence of an impaired conscious level or severe agitation may also necessitate intubation. Airway management may be complicated by large volumes of gastric regurgitation, significant pulmonary oedema obscuring the view of the larynx, and reduced lung compliance preventing the use of a supraglottic airway. The stomach should be decompressed by insertion of a nasogastric tube if possible but this may be difficult in a hypoxic agitated patient. Early active rewarming is indicated for severe hypothermia, but hyperthermia should be meticulously avoided.[21]

ASSESSMENT

HISTORY

Attempts should be made to elucidate the time and the duration of submersion, the presence of polluted water and likely contaminants, details of any cardiac arrest, delay in resuscitation attempts and the likelihood of alcohol ingestion, drug use, pre-existing medical conditions (particularly seizure disorders) and co-existing trauma. If collateral history is available, any symptoms of illness prior to the submersion event should be elicited to rule out or in a medical cause for the drowning that may require treatment.

EXAMINATION

A thorough physical survey is carried out, concentrating on cardiorespiratory examination, looking particularly for signs of respiratory distress, wheeze, crepitations and peripheral circulatory insufficiency. Neurological status should also be assessed. Signs of primary medical cause of drowning should be sought. A trauma secondary and subsequently tertiary survey should rule out the presence of co-existing traumatic injuries. Clinical deterioration in those with minor symptoms and signs can occur and the patient should be reassessed at frequent intervals.

INVESTIGATIONS

These depend on the clinical circumstances and could include:

- *arterial blood gases/lactate level*
- *plasma biochemistry/serum osmolality*: electrolyte abnormalities are unlikely in sea- or fresh-water drowning. CK should be measured as rhabdomyolysis has been reported[30]
- *haematology*: for haemolysis (for example, total haemoglobin (tHb), free Hb and myoglobin concentrations in the plasma and urine)
- *toxicological assays*: for drug and alcohol levels could be considered
- *chest X-ray, 12-lead electrocardiogram (ECG)*
- *microbiology*: tracheal aspirates or sputum for Gram stain, microscopy and culture
- *trauma imaging*: cervical and/or thoracolumbar spine views; computed tomography (CT) scan of the head and cervical spine if head and neck injury is suspected or the patient is comatose. Imaging of other body areas is dependent upon the clinical likelihood of injury.

ADMISSION CRITERIA

Asymptomatic patients with no clinical findings on cardiorespiratory examination and a normal chest radiograph and blood gas are unlikely to develop ARDS and pneumonia and thus may not require hospital admission.[17,31] All other patients should be admitted to a high-dependency area or intensive care unit for continuous monitoring and rewarming.

RESPIRATORY SUPPORT

Severe agitation or coma mandates intubation and mechanical ventilation; otherwise, oxygenation is initially maintained with high-flow oxygen or continuous positive airway pressure by tight-fitting facemask. Superimposed ventilatory failure may be managed with non-invasive bilevel positive airway pressure assistance. Use of non-invasive ventilation may be complicated by regurgitation of swallowed water; nasogastric decompression should be again considered. The use of bronchodilators may reduce air-flow resistance and the work of breathing if evidence of bronchospasm is present. Given the ARDS pathophysiology after drowning, lung-protective strategies should be employed if mechanical ventilation is required. Selective pulmonary vasodilators such as inhaled nitric oxide or inhaled prostacyclin may be useful in severe refractory hypoxaemia, although evidence for efficacy is lacking. In severe cases, extracorporeal membrane oxygenation has been used in some centres.[32]

Resolution of hypoxaemia may be more rapid than in other causes of ARDS.[33] Care should be taken with very rapid liberation from ventilation within the first 24 hours of the drowning event, as pulmonary oedema related to local pulmonary injury may recur.[34]

CARDIOVASCULAR SUPPORT

Prolonged immersion is associated with hypovolaemia related to hydrostatic pressures. Cautious volume expansion and the use of catecholamine infusion may improve cardiac output and blood pressure. Fluid replacement with isotonic fluids is aimed at restoring adequate end-organ perfusion without compromising respiratory function. Where restoration of oxygenation, normovolaemia and normothermia is not associated with resolution of cardiovascular disturbance, the presence of cardiac depression should be considered. Echocardiography is likely to be informative regarding the presence of global myocardial depression associated with the drowning episode, regional ischaemia, or the presence of vasoplegia. In cases where severe circulatory insufficiency or cardiac arrest is associated with severe hypothermia, cardiopulmonary bypass has been used successfully.[35]

CEREBRAL PROTECTION

No evidence exists suggesting that targeted temperature management is beneficial in general after cardiac arrest associated with drowning. However, the strong suspicion of a cardiac arrest causing the drowning

rather than being the result of it could indicate targeted temperature management to a temperature of 36°C.[36] It should be noted that in children, no benefit was observed in hypothermia as opposed to normothermia after cardiac arrest associated with drowning.[37]

No other specific cerebral protective measures have proven efficacy in post anoxic encephalopathy associated with drowning.[38] Maintenance of an adequate cerebral perfusion pressure (mean arterial pressure >80 mm Hg in adults, 60–70 mm Hg in children) is probably reasonable. Prevention of cerebral venous and thus intracranial hypertension can be achieved by neutral neck positioning, avoiding occlusive endotracheal tube ties and head-up positioning. Avoiding hypocapnia ($PaCO_2$ <30 mm Hg [3.99 kPa]), reducing cerebral metabolic rate with sedation, preventing hypoglycaemia and hyperthermia, and the use of anticonvulsants in those with documented seizures are simple measures that may prevent secondary cerebral injury.

OTHER THERAPIES

There is no role for prophylactic corticosteroid therapy in the prevention of acute lung injury after submersion.[15] Prophylactic antibiotic therapy is unproven and the decision to commence therapy is made on the degree of water contamination, need for mechanical ventilation and severity of respiratory failure in each case.[21] Baseline microbiological studies should be sent prior to commencement of therapy.

PROGNOSIS

A large series demonstrated 44% survival to hospital discharge in those with cardiac arrest secondary to drowning.[39] Moderate to severe brain damage is reported in 33% of survivors.[7] The outcome in children is similar, with 30% having selective deficits and 3% with persistent vegetative state.[40] No difference in mortality between fresh- and salt-water submersion has been documented.[10] Lower core temperatures appear to be associated with a better prognosis, except if this occurs after rescue. However, hypothermia in warm-water immersion and severe hypothermia (<30°C) in cold-water immersion is indicative of prolonged immersion and poor outcome.[29] Box 82.1 lists some factors associated with death or severe neurological impairment. None of these predictors is infallible and survival with normal cerebral function has been noted despite the presence of some or all of these factors.[41]

Box 82.1 Predictors of death or severe neurological impairment after submersion

At site of immersion
- Immersion duration >5 min[42]
- Delay in commencement of CPR >10 min[7]

In the emergency department
- Glasgow Coma Score 3[43]
- Fixed dilated pupils[45]

In the intensive care unit (ICU)
- Glasgow Coma Scale <6 on arrival in ICU[45]
- Arterial pH <7.0 on arrival in ICU[44]
- No spontaneous, purposeful movements and abnormal brainstem function 48 hours after immersion[45]
- Abnormal CT scan within 36 hours of submersion

KEY REFERENCES

3. World Health Organization. *Global Report on Drowning: Preventing a Leading Killer*. Geneva: WHO. http://www.who.int/violence_injury_prevention/global_report_drowning/en/; 2014.
17. van Berkel M, Bierens JJL, Lie RLK, et al. Pulmonary oedema, pneumonia and mortality in submersion victims: a retrospective study in 125 patients. *Intensive Care Med*. 1996;22:101–107.
21. Truhlar A, Deakin CD, Soar J, et al. European resuscitation guidelines for resuscitation 2015: section 4. Cardiac arrest in special circumstances. *Resuscitation*. 2015;148–201.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. van Beeck EF, Branche CM, Szpilman D, et al. A new definition of drowning: towards documentation and prevention of a global public health problem. *Bull World Health Organ*. 2005;83:853–856.
2. Idris AH, Berg RA, Bierens J, et al. Recommended guidelines for uniform reporting of data from drowning: the "Utstein style." *Circulation*. 2003;108: 2565–2574.
3. World Health Organization. *Global Report on Drowning: Preventing a Leading Killer*. Geneva: WHO. http://www.who.int/violence_injury_prevention/global_report_drowning/en/; 2014.
4. National Center for Injury Prevention and Control. *WISQARS leading causes of death reports, 1999–2015*. http://webappa.cdc.gov/sasweb/ncipc/mortrate10_us.html.
5. Franklin RC, Scarr JP, Pearn JH. Reducing drowning deaths: the continued challenge of immersion fatalities in Australia. *Med J Aust*. 2010; 192:123–126.
6. Blum C, Shield J. Toddler drowning in domestic swimming pools. *Inj Prev*. 2000;6:288–290.
7. Orlowski JP. Drowning, near drowning, and ice-water submersions. *Pediatr Clin North Am*. 1987; 34:75–92.
8. Wintemute GJ. Childhood drowning and near drowning in the United States. *Am J Dis Child*. 1990; 144:663–669.
9. Wintemute GJ, Kraus JF, Teret SP, et al. Drowning in childhood and adolescence: a population based study. *Am J Public Health*. 1987;77:830–832.
10. Spilzman D. Near drowning and drowning classification. A proposal to stratify mortality based on the analysis of 1831 cases. *Chest*. 1997;112: 660–665.
11. Mahoney AJ, Peden AE, Franklin RC, et al. Fatal, unintentional drowning in older people: an assessment of the role of preexisting medical conditions. *Healthy Aging Res*. 2017;6(1):e7.
12. Daly MD, Angell-James JE, Elsner R. Role of carotid-body chemoreceptors and their reflex interactions in bradycardia and cardiac arrest. *Lancet*. 1979;1:764–767.
13. Nitta M, Kitamura T, Iwami T, et al. Out-of-hospital cardiac arrest due to drowning among children and adults from the Utstein Osaka Project. *Resuscitation*. 2013;84(11):1568–1573.
14. Gooden BA. Why some people do not drown; hypothermia versus the diving response. *Med J Aust*. 1992;152:629–632.
15. Modell JH. Drowning. *N Engl J Med*. 1993;328: 253–256.
16. Modell JH, Davis JH. Electrolyte changes in human drowning victims. *Anesthesiology*. 1969;30:414–420.
17. van Berkel M, Bierens JJL, Lie RLK, et al. Pulmonary oedema, pneumonia and mortality in submersion victims: a retrospective study in 125 patients. *Intensive Care Med*. 1996;22:101–107.
18. Modell JH, Moya F, Newby EJ, et al. The effects of fluid volume in seawater drowning. *Ann Intern Med*. 1967;67:68–80.
19. Modell JH, Moya F. Effects of volume of aspirated fluid during chlorinated freshwater drowning. *Anesthesiology*. 1966;27:662–672.
20. Orlowski JP, Abulleil MM, Phillips JM. The haemodynamic and cardiovascular effects of near-drowning in hypotonic, isotonic or hypertonic solutions. *Ann Emerg Med*. 1989;10:1044–1049.
21. Truhlar A, Deakin CD, Soar J, et al. European resuscitation guidelines for resuscitation 2015: section 4. Cardiac arrest in special circumstances. *Resuscitation*. 2015;148–201.
22. Ender PT, Dolan MJ, Farmer JC, et al. Near-drowning associated Aeromonas pneumonia. *J Emerg Med*. 1996;14:737–741.
23. Wood C. Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary BET1, prophylactic antibiotics in near drowning. *Emerg Med J*. 2010;27:393–394.
24. Tadie JM, Heming N, Serve E, et al. Drowning associated pneumonia: a descriptive cohort. *Resuscitation*. 2012;83:399–401.
25. Segev D, Szold O, Fireman E, et al. Kerosene-induced severe acute respiratory failure in near-drowning. Reports on four cases and review of the literature. *Crit Care Med*. 1999;27:1437–1440.
26. DeNicola LK, Falk JL, Swanson ME, et al. Submersion injuries in children and adults. *Crit Care Clin*. 1997;13:477–502.
27. Dunagan D, Cox J, Chang MC, et al. Sand aspiration with near drowning. Radiographic and bronchoscopic findings. *Am J Respir Crit Care Med*. 1997;156:292–295.
28. Conn AW, Miyassaka K, Katayama M, et al. A canine study of cold water drowning in fresh versus saltwater. *Crit Care Med*. 1995;23:2023–2036.
29. Golden FS, Tipton MJ, Scott RC. Immersion, near drowning and drowning. *Br J Anaesth*. 1997;79: 214–225.
30. Agar JW. Rhabdomyolysis and acute renal failure after near drowning in cold salt water. *Med J Aust*. 1994;161:686–687.
31. Causey AL, Tilelli JA, Swanson ME. Predicting discharge in uncomplicated drowning. *Am J Emerg Med*. 2000;18:9–11.
32. Thalmann M, Trampitsch E, Haberfellner N, et al. Resuscitation in near-drowning with extracorporeal membrane oxygenation. *Ann Thorac Surg*. 2001;72:607–608.
33. Gregorakos L, Markou N, Psalida V, et al. Near-drowning: clinical course of lung injury in adults. *Lung*. 2009;187(2):93–97.
34. Szpilman D, Biernes JJLM, Handley ASJ, et al. Drowning. *N EngI J Med*. 2012;366:2102–2110.
35. Letsou GV, Kopf GS, Elefteriades JA, et al. Is cardiopulmonary by-pass effective for treatment of hypothermic arrest due to drowning or exposure? *Arch Surg*. 1992;127:525–528.

36. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N EngI J Med*. 2013;369:2197–2206.
37. Moler FW, Hutchison JS, Nadkarni VM, et al. Targeted temperature management after pediatric cardiac arrest due to drowning: outcomes and complications. *Pediatr Crit Care Med*. 2016;17(8): 712–720.
38. Bohn DJ, Biggard WJ, Smith CR, et al. Influence of hypothermia, barbiturate therapy and intracranial pressure monitoring on morbidity and mortality after near drowning. *Crit Care Med*. 1986;14: 529–534.
39. Grmec S, Strnad M, Podgorsek D. Comparison of the characteristics and outcome among patients suffering from out-of-hospital primary cardiac arrest and drowning victims in cardiac arrest. *Int J Emerg Med*. 2009;2(1):7–12.
40. Pearn J. Medical aspects of drowning in children. *Ann Acad Med Singapore*. 1992;21:433–455.
41. Layton AJ, Modell JH. Drowning update. *Anesthesiology*. 2009;110:1390–1401.
42. Orlowski JP. Prognostic factors in pediatric cases of drowning and near-drowning. *JACEP*. 1979;8: 176–179.
43. Christensen DW, Jansen P, Perkin RM. Outcome and acute care hospital costs after warm water near drowning in children. *Pediatrics*. 1997;99:715–721.
44. Frates RC. Analysis of predictive factors in the assessment of warm water near-drowning in children. *Am J Dis Child*. 1981;135:1006–1008.
45. Lavelle JM, Shaw KN. Near drowning: is emergency department cardiopulmonary resuscitation or intensive care unit cerebral resuscitation indicated? *Crit Care Med*. 1993;21:368–373.

83

Burns

Ilanit Z Hené, Jacqueline EHM Vet

INTRODUCTION

The last decades have seen a sustained improvement in survival of patients suffering from thermal injury. The most important development has been the establishment of centralised burn care, which has led to the concept of a multidisciplinary burn team, in which all aspects of care are coordinated in an integrated approach to clinical management. Advances in fluid resuscitation, life support techniques and the prevention of infection have been driven by research.[1] With optimal care, children and young adults with burns of more than 80% of total body surface area (TBSA) now stand a reasonable chance of survival.[1] Improvements in survival have gradually led to a shift of emphasis in burn care towards qualitative aspects, such as rehabilitation and quality of life.

PATHOPHYSIOLOGY

LOCAL EFFECTS

Thermal injury produces complex local and systemic responses.[2] The local inflammatory response results in vasodilatation and an increase in vascular permeability. The changes are immediate and the combination produces extravasation of fluid and plasma protein at the site of injury. In extensive burns, oedema becomes generalised. The greatest rate of oedema formation occurs in the first 8 hours, but further extravasation occurs up to 24 hours post burn. The total amount of oedema formed depends on the extent of injury and the volume of fluid administered. Without fluid replacement, hypovolaemic shock occurs, limiting the extent of extravasation. On the other hand, excessive fluid administration will produce excessive oedema and contributes to enlargement and deepening of the burn area.[3–5]

By 24 hours post burn, oedema formation is largely complete and vascular integrity restored.[6]

The process of deepening of the burn wound beyond the area of heat necrosis following injury is at least partly due to microvascular stasis. Events occurring within minutes and hours of injury include microthrombus formation, neutrophil adherence, fibrin deposition and endothelial swelling.[7,8]

SYSTEMIC EFFECTS

Circulatory effects of burn injury become significant in burns of over 20% TBSA. Changes are rapid and the magnitude is roughly proportional to the extent of burn injury. Cardiac output is reduced immediately following injury due to a combination of hypovolaemia, increased blood viscosity and increased levels of agents with myocardial depressant properties, such as interleukin-1 and tumour necrosis factor alpha.[3]

Continuous secretion of endogenous epinephrine, norepinephrine, vasopressin and angiotensin causes an increase in systemic and pulmonary vascular resistance leading to pulmonary oedema.

Cardiac output recovers gradually during the second post-burn day, reaching supranormal levels by day 3 as the hypermetabolic response to burn injury becomes manifest. Circulatory dynamics are complicated by resorption of oedema fluid and by continuing evaporative fluid loss from the wounds. However, prolonged elevation of renin/angiotensin and antidiuretic hormone is well documented and circulating blood volume may remain subnormal into the second week post burn. Loss of vascular integrity contributes to diminished organ perfusion and translocation of bacteriae in the gut.[9]

METABOLIC EFFECTS

Major burn injury (TBSA >20%) results in a hypermetabolic state, which ensues from around the third post burn day. The state is partly sustained by evaporative and radiant heat loss through the wounds, and energy expenditure can be reduced by increasing the ambient temperature and by the use of occlusive dressings.[10] Other factors known to influence the metabolic rate include pain, fear and anxiety. The effect of catecholamines on wound healing and metabolic rate of protein, fat and glucose metabolism contributes to this hypermetabolic state and ongoing catabolism up until 2 years after the injury.[10,11]

ABSTRACT

In the last couple of decades, outcome of severely burned patients has dramatically progressed thanks to development of centralised burn care, improvement of fluid resuscitation, infection prevention and early excision and grafting of the wounds. Thermal injuries cause local and systemic responses leading to vasodilatation, capillary leakage and a hypermetabolic state. The latter can be attenuated by pharmacological agents, early enteral nutrition, proper analgesia, and in time wound treatment. Frequently occurring complications in the treatment of burn patients include over-resuscitation, infection and Multiple Organ Dysfunction syndrome. The three distinct types of inhalation injury (upper airway injury, lower airway injury and inhalation of toxic gases) can increase morbidity and mortality.

KEYWORDS

Burns
total body surface area
hypermetabolism
burn shock
parkland formula
wound sepsis
wound treatment
inhalation injury
carbon monoxide
hydrogen cyanide

PHARMACOLOGICAL EFFECTS

The pharmacokinetics and pharmacodynamics of many drugs are altered in burn patients. During the first 24 hours, when the cardiac output is depressed and capillary leak is present, distribution and clearance of administered drugs are delayed. Thereafter, increased cardiac output leads to accelerated drug absorption and distribution, while oedema fluid acts as an ill-defined third space and hypoalbuminaemia contributes to elevated free fractions leading to rapid clearance and diffusion in the third space. Antibiotics, like quinolones, β-lactams and aminoglycosides, may therefore fail to reach effective levels at conventional dosages.[12,13] On the other hand, toxic levels may ensue if renal failure supervenes. If possible, therefore, antibiotic administration should be guided by measurement of plasma concentrations and even more so if renal replacement therapy is indicated.

Decreased albumin and increased α_1-glycoprotein levels change the pharmacokinetics of benzodiazepines and opioids due to changes in the free fraction.[14] An increase in peri-junctional acetylcholine receptors significantly alters the pharmacodynamics of muscle relaxants.[15] Patients become relatively insensitive to non-depolarising agents, whereas administration of succinylcholine may give rise to excessive release of potassium and cardiac arrest. The burn wound itself is a significant route of drug absorption as well as drug loss contributing to the altered pharmacodynamics and pharmacokinetics.

CLINICAL MANAGEMENT

FIRST AID

Immediate aid consists of stopping the burn process, followed by the removal of clothing and cooling the wound, preferably with tepid running water, for 10–20 minutes. This provides pain relief and may prevent deepening of the wound.[16]

The initial evaluation of the severely burned patient should follow the principles of the Advanced Trauma Life Support guidelines: assessment and stabilisation of the airway (be aware of spinal cord injuries), breathing, circulation, disability and environment control.[17] Hypothermia should be avoided. Oxygen should be given and patients with burns to the head and neck should be kept in a semi-upright position. Burn injury can only be assessed properly under hospital conditions, and priority should be given to early evacuation of the victim.

GENERAL MANAGEMENT: 0–24 HOURS

On admission, a careful history should be taken of the circumstances of the injury, and of the medical history. The patient should be undressed, weighed and carefully examined to exclude additional (traumatic) injury. The extent and depth of injury are assessed with the aid of printed Lund and Browder charts,[18] or by using the 'rule of nines' (Fig. 83.1).[19] The rule of nines is modified for children (Fig. 83.2). A nasogastric tube and urinary catheter should be inserted in patients requiring resuscitation therapy. Escharotomies may be required for circular burns of the neck, trunk and limbs.

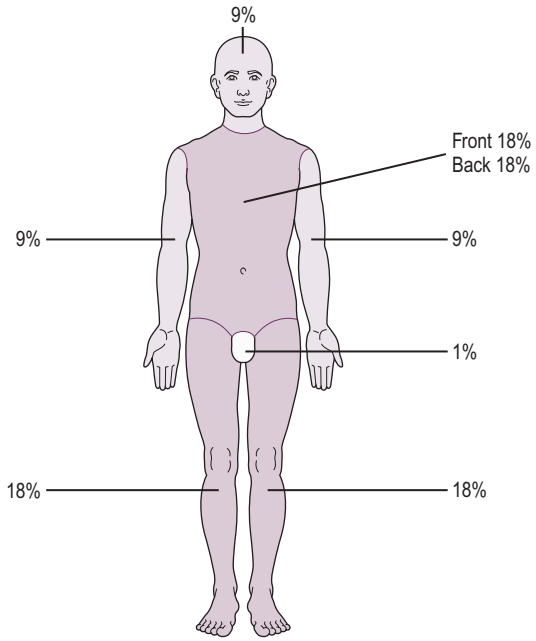


Figure 83.1 'Rule of nine' to estimate body surface area burns in adults.

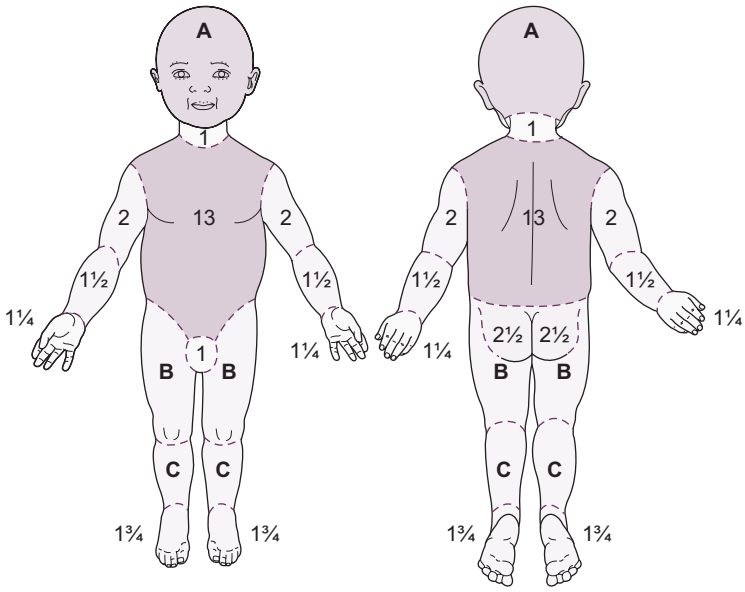
FLUID THERAPY: 0–24 HOURS

Fluid therapy is required for injuries exceeding 15% TBSA (10% in children and frequently in the elderly), preferably by two wide-bore peripheral intravenous (IV) cannulas. The aim is to maintain moderate hypovolaemia to preserve normal organ function utilising as little fluid as possible.

The most widely used resuscitation formula is based on the Parkland Formula,[20] which has been adopted by major training programs such as the Emergency Medicine for Severe Burns:

> *4 mL Ringer-Lactate solution × kg body weight × % TBSA burn in the first 24 hours; of which half should be given in the first 8 hours post burn and the other half in the next 16 hours.*

The formula thus incorporates a faster rate of administration if initial treatment has been delayed. For children, maintenance fluid must be added to compensate for basal needs.



Age	<1 year	1 year	5 years	10 years	15 years	Adult
Area A = ½ of head (%)	9.5	8.5	6.5	5.5	4.5	3.5
Area B = ½ of one thigh (%)	2.75	3.25	4.0	4.25	4.5	4.75
Area C = ½ of one leg (%)	2.5	2.5	2.75	3.0	3.25	3.5

Figure 83.2 Surface area percentages by age.

An increasing concern in recent years has been over-resuscitation in burn patients.[21] Excessive fluid administration increases the risk of circulatory overload in the days following the resuscitation period, resulting in complications such as abdominal or extremity compartment syndrome, deepening of the wounds or multiple organ dysfunction syndrome (MODS).[4,5]

The actual amount of fluid given depends on the clinical condition and the amount of fluid administered can vary widely from what was predicted. Adequacy of resuscitation is monitored by vital signs and a targeted urine output of 0.5–1 mL/kg per hour in adults and 1–2 mL/kg per hour in children. Importantly, this means that the fluid rate should be lowered when the hourly urine output goal has been reached. Requirements are increased in the presence of mechanical ventilation, additional traumatic injury and dehydration (e.g. firefighters, intoxication).

Resuscitation protocols guided by transpulmonary thermodilution (PICCO, PULSION Medical System, Munich, Germany) have been the subject of investigation in the past years. Results show that resuscitation can be achieved with below-normal haemodynamic targets but fluid administration still exceeds the Parkland formula.[22,23] Therefore, transpulmonary thermodilution-guided therapy is not yet incorporated in the standard care of burn resuscitation.

Hypoalbuminaemia develops rapidly and may be extreme. A recent meta-analysis showed that albumin administration may reduce mortality and abdominal compartment syndrome.[24] However, the quality of current evidence is limited and further research needed. In our unit at present, albumin is given to maintain serum albumin above 15 g/L, commencing 12 hours post burn when capillary integrity has been largely restored.

FLUID THERAPY AFTER 24 HOURS

During the second 24 hours, enteral nutritional intake is increased, while the total rate of fluid administration is gradually reduced. At the end of the second day, fluid intake should allow for sufficient urine production, while compensating for evaporative losses through the wounds.

The actual fluid loss through wounds varies widely, and depends on the type of burn and topical wound treatment. A useful formula to obtain a rough estimate for insensible fluid loss per hour is: *(25 + % TBSA) × m^2 body surface area + minimum volume of urine production/h.*

Electrolyte disturbances are common following burn injury and require treatment. Hypernatraemia is often a sign of dehydration, and can be confirmed if the serum urea is elevated. The condition is perilous, especially in the first week post burn, as oliguria and renal failure may develop unexpectedly. The amount of free water given should be increased gradually, particularly in the elderly, to avoid fluid overload. Patients who are in fluid balance may require sodium supplementation to compensate for solute loss in wound exudates.

HAEMOGLOBINURIA/MYOGLOBINURIA

Tissue injury from deep burns, particularly electrical injury, causes the release of myoglobin and haemoglobin from damaged cells. Diagnosis is made on observing discolouration of the urine, from faint pink in mild cases to almost black. Fluid administration should be increased, aiming at a urine output of 1–2 mL/kg per hour to preserve renal function. Additional measures such as mannitol (12.5 g/L resuscitation fluid) to encourage diuresis and bicarbonate to alkalinise the urine have been advocated, but no consensus has been reached.[25]

PAIN THERAPY

During the first 24 hours, pain management is best achieved by incremental doses of an IV opioid. Thereafter, the pain suffered by burn patients may be divided into continuous background pain with breakthrough pain, procedural pain caused by interventions and postoperative pain.[26] The recurring ordeal of dressing changes, physiotherapy exercises and surgical procedures generates apprehension and anxiety, contributes to chronic pain and post-traumatic stress syndrome. In recent years, the advent of slow-release oral opiate medication has greatly improved the administration of analgesia. Procedural pain is best treated with titrated boluses of IV opioids such as remifentanil.[26] Patient-controlled analgesia is effective, although modification of the control button may be necessary for those with bandaged hands. Ketamine in subanaesthetic doses is extremely useful for procedural pain in children and as an adjuvant to opioids in low-dose infusion (0.1–0.2 mg/kg/h) in children and adults. The influence of pain and anxiety on pain perception needs a multidisciplinary approach involving psychological techniques, pain management and a caring environment.[27,28]

NUTRITION

The degree of catabolism is roughly proportional to the extent of injury.[8] In young adults and children with extensive burns, energy expenditure may be doubled. In addition, protein and substantial amounts of trace elements, such as zinc, copper and selenium, are lost in wound exudate.[29] Very early (within 6–12 hours) enteral feeding mitigates the hypermetabolic response and improves outcomes.[29]

Indirect calorimetry is the gold standard to assess energy requirements. In the absence of direct metabolic measurements, the Toronto equation is a well-validated alternative.[29] A high-protein proprietary feed should be supplemented by extra trace elements, vitamins and glutamin.[29]

Patients with extensive burns will require tube feeds, which are generally well tolerated. To minimise interruption of enteral nutrition because of procedures or gastroparesis, post-pyloric feeding is often indicated. PEG tubes are useful when facial burns are present. Adjunctive therapy aimed at promoting anabolism include insulin to maintain normoglycaemia, oxandrolone, and propanolol.[11,26]

WOUND TREATMENT

Treatment of extensive, full-thickness burn wounds by early excision and grafting has been firmly linked to survival.[8] Wound excision should be completed within the first week, before bacterial colonisation and neovascular infiltration of the wound bed develop. These operations are therefore urgent. Successfully grafted wounds will heal within 5 weeks, reducing the time available for bacterial infection to develop, and shortening the period of physiological disturbance. Wounds covered with widely meshed autografts lose large amounts of fluid unless protected by a semipermeable layer, such as allograft or xenograft skin. Autograft donor sites are a further source of fluid loss.

For wounds treated conservatively, the main effort is devoted to the prevention of infection. Topical antimicrobial agents are commonly used, but may have potential side effects (Table 83.1). These compounds change the appearance of the wound and should never be applied until expert wound inspection is complete. A number of biosynthetic materials are currently available, which are designed to improve cosmetic and functional outcome. Despite the use of antiseptic dressings or biosynthetic coverings, there is still a risk of microbial infection developing and unexplained signs of sepsis may necessitate urgent wound revision.

New developments like laser Doppler imaging, electronic mapping and local biomarkers which help to predict whether a burn will spontaneously heal, have the potential to improve outcome.

INFECTION PREVENTION

The most common cause of death in burn injury is MODS caused by sepsis.[30] Infection is facilitated by the skin barrier destruction and the wound presents a favourable medium for bacterial growth. In addition, there is a state of immune dysfunction. Routine surveillance cultures are essential to guide therapy of

Table 83.1 Commonly used topical antimicrobial agents

AGENT	COMMENTS
Silver sulfadiazine (SSD)	The most widely used agent with broad-spectrum cover. Hypersensitivity (rarely) and transient leucopenia have been reported
Cerium nitrate 0.5%	Often added to SSD, and forms a stable eschar. It is reported to bind 'burn toxins'. Methaemoglobinaemia has been reported
Silver nitrate 0.5%	Applied as a soak, and is especially effective against *Pseudomonas*. However, it may increase sodium loss, and potentially can cause methaemoglobinaemia
Mafenide acetate 5%–10%	Effective but short-lived antimicrobial, requiring repeated application. It has good penetration, and its side effects (pain and metabolic acidosis) are less evident with 5% solution
Chlorhexidine	Aqueous solution (0.2%) or 1% gel provides broad-spectrum cover, but is rapidly inactivated, and may cause local pain, and rarely causes hypersensitivity
Nitrofurazone	In polyethylene glycol (PEG) solution it is effective against *Staphylococcus aureus*, but resistance develops early. Side effects include hypersensitivity (common), hyperosmolarity, and renal failure due to PEG absorption has been reported
Povidone iodine	In PEG solution provides broad-spectrum cover, but is rapidly inactivated. It prevents wound maceration. Side effects include occasional hypersensitivity, renal dysfunction due to excessive PEG, metabolic acidosis and rarely dysfunction
Antibiotics	Have been used in solutions, creams, gels and sprays, but selection and development of resistant strains is inevitable, with a risk of systemic toxicity through absorption. Their usage is generally discouraged

burn wound and other infections especially since drug resistance is common.

In an effort to reduce wound colonisation and contamination from cross-infection, barrier nursing of patients with extensive injuries is mandatory. The importance of isolation measures has been stressed, but a significant proportion of patients still become colonised by microorganisms from endogenous reservoirs, which cannot be controlled by barrier nursing alone. Positive experiences have been reported with selective decontamination of the digestive tract but large-scale prospective trials have only been performed in general critical care patients.[31]

SEPSIS

Disruption of wound healing and deepening of the injury together with immune paralysis can easily lead to wound infection and sepsis. However, discrimination between systemic inflammatory response syndrome (SIRS) and sepsis in burns remains arduous. Prodromal signs are common and may include gastrointestinal stasis, increasing positive fluid balance, increasing insulin resistance and increasing pyrexia. As sepsis progresses, clinical deterioration becomes manifest: tachypnoea, circulatory instability, thrombocytopenia and oliguria may herald the onset of multiorgan failure. Leucocyte counts, C-reactive protein levels and procalcitonin are all affected in the acute phase of burns by the SIRS and are unreliable indicators of infection. In the later phase, and for guidance of antibiotic therapy, procalcitonin levels seems to be the most reliable parameter.[32]

INHALATION INJURY

The term inhalation injury includes three distinct types of injury, which often, but not always, occur together. The presence of inhalation injury may increase resuscitation fluid requirements in patients with extensive cutaneous burns.

HEAT INJURY TO THE UPPER AIRWAY

Burns due to the inhalation of hot gases (steam excepted) rarely extend beyond the larynx. The development of mucosal and facial oedema can cause respiratory obstruction, particularly in children.

Facial burn, singed nasal hairs, visible burn to oropharynx and hoarseness are typical features.

If the condition is suspected, early endotracheal intubation is safest, before the procedure is rendered hazardous by oedema formation. However, as mechanical ventilation may aggravate oedema formation, unnecessary intubation should be avoided.

EFFECTS OF SMOKE ON THE RESPIRATORY SYSTEM

Many of the chemicals that are contained in smoke are highly reactive and produce damage to the tracheobronchial tree.[33] Detachment of epithelial cells and the development of tracheobronchial oedema cause airway narrowing and cast formation. Small-airway closure leads to hypoxaemia and respiratory failure. Later, bronchorrhoea and mucosal sloughing

may cause atelectasis and provide a focus for infection. In the absence of a cutaneous injury, the clinical course is usually benign. However, the presence of an extensive skin burn increases the likelihood of acute respiratory distress syndrome; respiratory infection may follow.

There is a history of exposure in a confined space, cough, breathlessness, wheeze, stridor, hypoxaemia, and soot particles in the pharynx. Diagnosis is confirmed by bronchoscopy, which may reveal soot in the bronchial tree, mucosal injury and tracheobronchial oedema.

Treatment is essentially symptomatic. Mild cases may be treated by high-flow oxygen. In severe cases, intubation and ventilatory support are necessary, with positive end-expiratory pressure to maintain small-airway patency. Bronchial toilet by bronchoscopy is recommended on a daily basis to clear debris and to prevent respiratory infection. Endotracheal tubes may become blocked with detritus. As small-airway obstruction is common, ventilation pressures may be adversely affected. Various strategies, such as protective ventilation or high-frequency ventilation, have been advocated to minimise the risks of barotrauma.

Prolonged respiratory assistance may be necessary. The added respiratory requirements of the hypermetabolic state combined with inevitable loss of muscle mass and diaphragmatic atrophy frequently frustrate early weaning efforts. Furthermore, the use of inhaled anticoagulants may improve outcome, although definitive evidence has not been established yet.[34]

INHALATION OF TOXIC GASES

CARBON MONOXIDE

Carbon monoxide (CO), which is released during combustion, is one of the main causes of death following smoke inhalation. The affinity of CO for haemoglobin is 240 times higher than of oxygen. The loss of oxygen transport capacity is dependent on the concentration of inhaled CO and the duration of exposure. In addition, CO binds to intracellular cytochrome systems, inhibiting cellular oxidative processes.[35] The half-life of carboxyhaemoglobin (COHb) is 320 minutes when breathing air, compared to approximately 75 minutes when breathing 100% oxygen.[35]

Carbon monoxide poisoning should be suspected in all cases of exposure to combustion products in a closed space. The classic cherry-red appearance of the CO victim is seldom evident; early signs may be mistaken for inebriation. Symptoms range from a throbbing headache in mild exposure (10%–25% COHb) to weakness, dizziness, confusion and nausea (25%–40% COHb), progressing to collapse, unconsciousness and convulsions (40%–60% COHb). Death is increasingly likely at COHb concentrations of greater than 60%. Patients exposed to high levels of CO may exhibit signs of cardiac instability. Signs of cerebral irritability may persist for days or weeks following apparent recovery.

After exposure, the highest concentration of oxygen available should be administrated. Loss of consciousness is an indication for oxygen delivery via an endotracheal tube. In specific patient groups with severe CO poisoning, hyperbaric oxygen therapy should be considered to reduce long-term cognitive impairment.[35]

HYDROGEN CYANIDE

Hydrogen cyanide toxicity frequently occurs in conjunction with CO inhalation. The cyanide ion binds to metalloproteins, causing cellular asphyxia. Neurological and cardiovascular symptoms can start within seconds to minutes after exposure and the condition can be rapidly fatal. Hydroxycobalamin is the preferred antidote and should be administrated within 2 hours.[36] Be aware that hydroxycobalamin colours urine and skin cherry red. Supportive treatment is as for CO intoxication.

FUTURE PROSPECTS

The outlook for young patients with extensive burn injuries, treated under optimal conditions, is now such that little further progress may be expected in terms of survival alone. Mortality among the elderly does, however, remain high. The major thrust of research is currently directed at improving functional and cosmetic outcome following burns. Although the most visible efforts concern the development of techniques and materials to improve the quality of wound healing, strategies aimed at preventing ventilator-associated morbidity are equally applicable to burn patients, who often require prolonged ventilatory support; new insights into the inflammatory responses may improve the general condition of burn patients, increasing resistance to infection and improving tissue repair. There is growing interest in the psychological effects of thermal trauma, which includes new approaches to the management of pain and mental distress.

In the past, the establishment of burn centres has been largely opportunistic, often depending on the dedication of individual specialists. As the provision of medical services undergoes increasing scrutiny, the organisation of burn care in many countries may be subject to reorganisation. It is of the utmost importance that specialists involved in the field of burn care become actively engaged in this process, in order to guarantee continued quality of care for their population.

REFERENCES

1. Herndon DN, Blakeney PE. Teamwork for total burn care: achievements, directions and hopes. In: Herndon DN, ed. *Total Burn Care*. 4th ed. London, UK: WB Saunders; 2012: [chapter 2].

2. Wilmore DW, Long JM, Mason AD Jr, et al. Catecholamines: mediator of the hypermetabolic response to thermal injury. *Ann Surg*. 1974;180: 653–669.
3. Pham TN, Cancio LC, Gibran NS, et al. American Burn Association practice guidelines burn shock resuscitation. *J Burn Care Res*. 2008;29:257–266.
4. Klein MB, Hayden D, Elson C. The association between fluid administration and outcome following major burn: a multicenter study. *Ann Surg*. 2007; 245(4):622–628.
5. Strang SG, Van Lieshout EM, Breederveld RS, et al. A systematic review on intra-abdominal pressure in severely burned patients. *Burns*. 2014;40:9–16.
6. Shirani KZ, Vaughan GM, Mason AD Jr, et al. Update on current therapeutic approaches in burns. *Shock*. 1996;5:4–16.
7. Tiwari VK. Burn wound: how it differs from other wounds? *Indian J Plast Surg*. 2012;45:364–373.
8. Rowan MP, Cancio LC, Elster EA, et al. Burn wound healing and treatment: review and advancements. *Crit Care*. 2015;19:243.
9. Deitch EA. Intestinal permeability is increased in burn patients shortly after injury. *Surgery*. 1990;107(4): 411–416.
10. Porter C, Tompkins R, Finnerty C, et al. The metabolic stress response to burn trauma: current understanding and therapies. *Lancet*. 2016;388: 1417–1426.
11. Jeschke MG. Postburn hypermetabolism: past, present and future. *J Burn Care Res*. 2016;37(2): 86–96.
12. Jamal JA, Economou CJ, Lipman J, et al. Improving antibiotic dosing in special situations in the ICU: burns, renal replacement therapy and extracorporeal membrane oxygenation. *Curr Opin Crit Care*. 2012; 18(5):460–471.
13. Sime FB. Optimization of dosing regimens and dosing in special populations. *Clin Microbial Infect*. 2015;21:886–893.
14. Blanchet B, Jullien V, Vinsonneau C, et al. Influence of burns on pharmacokinetics and pharmacodynamics of drugs used in the care of burn patients. *Clin Pharmacokinet*. 2008;47(10):635–654.
15. Martyn JAJ, Fukushima Y, Chon JY, et al. Muscle relaxants in burns, trauma, and critical illness. *Int Anesthesiol Clin*. 2006;44:123–143.
16. Wright EH, Harris AL, Furniss D. Cooling of burns: mechanisms and models. *Burns*. 2015;41(5):882–889.
17. ISBI Practice Guidelines Committee; Steering Subcommittee; Advisory Subcommittee. ISBI Practice Guidelines for Burn Care. *Burns*. 2016;42(5): 953–1021.
18. Lund C, Browder N. The estimate of areas of burns. *Surg Gynecol Obs*. 1944;79:352–358.
19. Freshwater MF, Su CT. The second rule of nines: a guide for resuscitation of burn patients. *Ann Plast Surg*. 1979;2(4):298.
20. Baxter CR, Shires T. Physiological response to crystalloid resuscitation of severe burns. *Ann N Y Acad Sci*. 1968;150(3):874–894.
21. Cartotto R, Zhou A. Fluid creep: the pendulum hasn't swung back yet! *J Burn Care Res*. 2010;31(4): 551–558.
22. Sanchez M, Garcia-de-Lorenzo A, Herrero E, et al. A protocol for resuscitation of severe burn patients guided by transpulmonary thermodilution and lactate levels: a 3-year prospective cohort study. *Crit Care*. 2013;17:R176.
23. Guilabert P, Usua G, Martín N. Fluid resuscitation management in patients with burns: update. *Br J Anaesth*. 2016;117(3):284–296.
24. Navickis RJ, Greenhalgh DG, Wilkes MM. Albumin in burn shock resuscitation: a meta-analysis of controlled clinical studies. *J Burn Care Res*. 2016; 37(3):e268–e278.
25. Chavez OL, Leon M, Einav S, et al. Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice. *Crit Care*. 2016;20:135.
26. De Castro RJ, Leal PC, Sakata RK. Pain management in burn patients. *Braz J Anesthesiol*. 2013;63(1): 149–153.
27. Hyland EJ, D'Cruz R, Harvey JG, et al. An assessment of early child life therapy pain and anxiety management: a prospective randomised controlled trial. *Burns*. 2015;41(8):1642–1652.
28. Mahar PD. Frequency and use of pain assessment tools implemented in randomized control trials in the adult burn population: a systematic review. *Burns*. 2012;38:147–154.
29. Rousseau AF, Losser MR, Ichai C. Espen endorsed recommendations: nutritional therapy in major burns. *Clin Nutr*. 2013;32(4):497–502.
30. Brusselaers N, Monstrey S, Vogelaers D, et al. Severe burn injury in Europe: a systematic review of the incidence, etiology, morbidity, and mortality. *Crit Care*. 2010;14(5):R188.
31. López-Rodriquez L, de la Cal MA, García-Hierro P, et al. Selective decontamination attenuates organ dysfunction in critically burn patients. *Shock*. 2016;46(5):492–497.
32. Cabral L, Afreixo V, Almeida L, et al. The use of procalcitonin (PCT) for diagnosis of sepsis in burn patients: a meta-analysis. *PLoS ONE*. 2016;11(12).
33. Enkhbaatar P, Pruitt BA Jr, Suman O, et al. Pathophysiology, research challenges, and clinical management of smoke inhalation injury. *Lancet*. 2016;388(10052):1437–1446.
34. Miller AC, Elamin EM, Suffredini AF. Inhaled anticoagulation regimens for the treatment of smoke inhalation-associated acute lung injury: a systematic review. *Crit Care Med*. 2014;42(2): 413–419.
35. Hampson NB, Piantadosi CA, Thom SR, et al. Practice recommendations in the diagnosis, management, and prevention of carbon monoxide poisoning. *Am J Crit Care Med*. 2012;186(11): 1095–1101.
36. Anseeuw K, Delvau N, Burillo-Putze G, et al. Cyanide poisoning by fire smoke inhalation: a European expert consensus. *Eur J Emerg Med*. 2013; 20(1):2–9.

84

Thermal disorders

Stephen W Lam, Richard Strickland

NORMAL TEMPERATURE REGULATION

Humans are endotherms and maintain a remarkably constant core body temperature (T_c) across an ambient range that may exceed 100°C. In order to do so, humans produce heat via oxidisation of food substrates or use of stored energy. At equilibrium:

Energy input = external work + stored energy + heat

Broadly speaking, heat production may be obligatory or facultative. Obligatory production is continuous and arises from processes essential for cell survival. The major components are the basal metabolic rate and the specific dynamic action of food. Facultative production is intermittent and arises from non-shivering thermogenesis in small amounts of brown adipose tissue, from shivering thermogenesis in skeletal muscle and as a by-product of physical activity. If environmental temperature exceeds mean skin temperature, then heat will be gained from the environment; this generally occurs when ambient temperature exceeds 35°C. Heat is lost by radiation, conduction, convection, and vaporisation of water from sweat and the respiratory tract. These mechanisms are limited by high ambient temperature or humidity. A very small amount of heat is lost in urine and stool.

The body may be visualised as having two thermal compartments, an outer shell comprising the skin and subcutaneous fat, and an inner core. The shell acts to protect the core and provide 'feed-forward' signals that allow the body to respond to potential thermal loads.[1] Current models of thermoregulation suggest T_c is maintained in an interthreshold zone or balance point by a series of relatively autonomous thermoeffector loops dependent on a common variable, T_c.[1,2] Whilst there is evidence for central reciprocal cross inhibition of thermoeffector loops, the concept of a centrally regulated set point has been replaced.

Temperature sensing occurs in skin, tissues of the deep core and centrally, providing afferent input to thermoeffector loops. In the dermis and epidermis, temperature activated transient receptor potential (thermo-TRP) ion channels are found on free ending axons of dorsal root ganglia. Over 30 thermo-TRP channels exist and may be cold (predominant) or heat activated at differing thresholds.[3] Input from these channels travel the dorsal root ganglion to ascend via multiple pathways, including Lamina I of the spinal cord and spinothalamic tract to the brainstem, where fibres for discriminative sensation and homeostatic control diverge.[1] Fibres for homeostatic control project to warm sensitive neurons in the preoptic anterior hypothalamus and cold sensitive neurons in the posterior hypothalamus. Similar afferent inputs are derived from deep thoraco-abdominal musculature, large vessels and many organs. In addition, thermosensitive neurons in the preoptic anterior hypothalamus, circumventricular organs, the midbrain and spinal cord provide central sensory input.

When thermoafferent input reaches a threshold, one or more thermoeffector loops are stimulated, with a resultant heat loss or heat gain response, mediated via behavioural, autonomic or endocrine changes. Behavioural responses, which appear to be driven predominantly by peripheral input, are generally more energy efficient, afford the greatest degree of thermoregulation and often pre-empt significant changes in T_c. If behavioural responses are inadequate or unavailable, as in many intensive care unit (ICU) patients, there is recruitment of autonomic regulation.

Autonomic responses are characterised by a threshold, gain and maximal response (Fig. 84.1). An increase in T_c above 37°C results in a heat loss response comprising cutaneous vasodilatation and sweating, mediated via predominantly cholinergic sympathetic nerves. When accompanied by an appropriate increase in cardiac output (≈3 L/min/°C), vasodilation results in core-to-cutaneous heat transfer and increased heat loss. Skin blood flow may increase from a basal rate of 0.2 L/min up to 8 L/min at T_c ≈39.0°C. Reflexes maintaining blood volume and pressure take precedence over thermoregulation. An inability to increase cardiac output or dehydration will reduce both the gain and maximal response of the vasodilator and sweating thermoeffector loops, respectively.[2,4]

A decrease in T_c initiates heat-preserving responses. At a threshold of 36.8°C, sympathetic adrenergic vasoconstriction occurs, and then non-shivering thermogenesis commences in small amounts of brown adipose tissue. This is of more importance in infants and

ABSTRACT

Thermal disorders can affect almost every system. For each patient, its significance and clinical approach to management depends heavily on factors relating to the condition, its cause, associated complications and co-morbidities. Furthermore, manipulation of temperature carries its own complexities. This chapter encompasses the major issues relating to thermal disorders and temperature management.

KEYWORDS

Thermoregulation
hyperthermia
fever
hypothermia
therapeutic hypothermia
targeted temperature management
therapeutic normothermia
rewarming

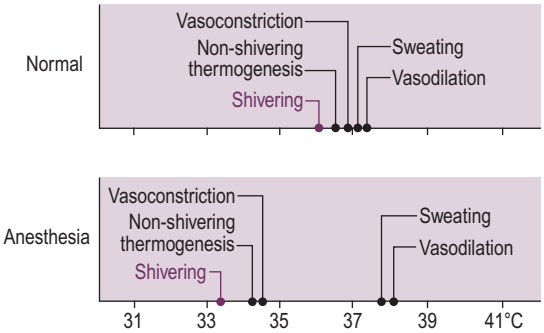


Figure 84.1 A schematic illustrating thermoregulatory thresholds in unanaesthetised and anaesthetised humans. Each response has its own threshold (x intercept) and gain. The interthreshold range is the distance between the first cold response (vasoconstriction) and the first warm response (sweating). *With permission from Sessler DI. Perianaesthetic thermoregulation and heat balance in humans.* FSAEB J. *1993;7:638–644.*

enables heat production by uncoupling proton movement from adenosine triphosphate (ATP) production across the mitochondrial inner membrane.[5] If T_c continues to fall towards 35.5°C, shivering thermogenesis begins, although the threshold and gain are reduced if the substrates for this process are inadequate, as may occur in hypoxaemia or hypoglycaemia.[2] Endocrine response includes increased secretion of cortisol and adrenaline.

The net effect of these mechanisms is maintenance of T_c around 36.9°C ± 0.4°C, with circadian variation of 0.5°C–1.0°C, peaking in the evening and being lowest around 6 AM. T_c is less precisely regulated in young children who may exhibit greater diurnal variation. Whilst T_c is normally maintained in a narrow interthreshold zone, skin temperature may vary widely dependent on ambient temperature and regional cutaneous blood flow. Temperature may vary amongst core organs by as much as 1.5°C during periods of rapid heat loss or gain, as in induction of therapeutic hypothermia (TH) or rewarming from cardiopulmonary bypass. The significance of this is uncertain, although it is worth noting that whilst the balance point at which T_c is normally maintained is close to the upper limit of survival, it is distant from the lower limit.

The ability to regulate temperature diminishes with age. In a thermo-neutral environment, T_c does not change in healthy older adults. When exposed to cold stress, peripheral vasoconstriction and thermogenesis are diminished, both in threshold and maximal response.[6,7] When exposed to heat stress, the elderly exhibit reduced sweat gland output and skin blood flow compared to younger controls.[6] When able, the elderly compensate for diminished autonomic thermoregulation with behavioural thermoregulation; however, this may be impaired when unwell, rendering the elderly prone to thermal insult.[7]

Patients in the ICU are likely to have disturbances of both heat production and heat loss. Anaesthetic agents and opiates significantly reduce the threshold for heat loss response in a dose-dependent manner. Threshold for cutaneous vasoconstriction may fall to 34°C under general anaesthesia (see Fig. 84.1); maximal response is also reduced by some agents, although gain is unaltered.[8,9] Sedative, adrenergic, cholinergic and neuromuscular blocking agents, ambient temperature and exposure, intravenous fluid administration, extracorporeal blood flow, impaired neurological or cardiovascular function, and deficiencies of substrate for thermogenesis are common factors in ICU patients which can affect thermal homeostasis.

FEVER AND HYPERTHERMIA

Hyperthermia results from failure of thermoeffector mechanisms to regulate temperature in the face of uncontrolled endogenous or exogenous heat gain. The primary event is not cytokine mediated and T_c is usually well in excess of 40.0°C. T_c greater than 41°C is usually due to hyperthermia rather than fever.[10]

Fever generally results from a cytokine-mediated change in threshold of thermoeffector loops resulting in regulated thermogenesis and transient elevation in T_c by 1°C–4°C.

Various definitions of fever exist and are acceptable, depending on the desired sensitivity of fever as an indicator of disease. Recognising differences in measurement technique, fever is often defined as a T_c greater than 38.3°C.[11] Fever is common in the ICU with a broad range of aetiologies (Table 84.1).[10] Most are mediated by production of the pro-inflammatory cytokines interleukin-1 (IL-1), IL-6 and tumour necrosis factor alpha (TNFα), which bind to receptors on circumventricular organs and up-regulate phospholipase A_2, resulting in production of prostaglandin E_2 via cyclooxygenase. This in turn stimulates warm sensitive neurons in the preoptic anterior hypothalamus, shifting the threshold of cold sensitive thermoeffectors by as much as 2°C, so inducing vasoconstriction and thermogenesis.[1] As pyrogen levels fall, thermoeffector thresholds return to normal and T_c falls. Fever commonly develops when blood is present in the cerebrospinal fluid (CSF), especially when intraventricular or in large volume.[12]

Mild to moderate fever is a phylogenetically preserved response; however, whether it is beneficial, neutral or harmful is uncertain and may be aetiology dependent.[13,14] There is little evidence to suggest benefit from routine treatment of mild – moderate fever outside the setting of acute brain injury, cardiogenic shock or profound hypoxaemia.[13,14] T_c greater than 38.5°C–40.0°C and the total fever burden, however, is associated with poorer patient outcomes and measures to control T_c should be considered whilst the

Table 84.1 Potential causes of fever in the intensive care unit

- Infection (50%)
- Inflammatory
  - Trauma/Burns/Surgery
  - Pancreatitis
  - Pneumonitis/VILI/ARDS
  - Autoimmune disorders
    - Hypersensitivity reactions (including transplant rejection)
    - Connective tissue disorders
    - Inflammatory bowel disease
    - Hepatitis
    - Myocarditis
    - Vasculitis
    - Neuropathies (GBS)/myopathies
  - Gout
  - Acalculous cholecystitis
  - Granulomatous disease
- Infarction
  - Myocardial
  - Cerebral
  - GIT
  - Pulmonary
  - Other
- Haemorrhage
  - SAH/GIT/other
  - Haematoma reabsorption
- Haematology/oncology
  - Blood product transfusion
  - Malignancy/tumour lysis
  - Radiotherapy
- Endocrine
  - Thyroxtoxicosis
  - Phaeochromocytoma
  - Adrenocorticoid insufficiency
- Seizures
- Drugs
  - Adverse reactions
  - Overdose/withdrawal

ARDS, Acute respiratory distress syndrome; *GBS*, Guillain–Barré syndrome; *GIT*, gastrointestinal tract; *SAH*, subarachnoid hemorrhage; *VILI*, ventilator-induced lung injury.

underlying disorder is treated.[14] Very high T_c can alter enzymatic function and protein folding, disrupting cellular systems including ion channels, surface receptors, mitochondrial electron transport and cytoskeletal elements. Different individuals and cell lines exhibit different resistance to thermal injury. In general, short-term elevation in T_c to 40.0°C is thought to be well tolerated without harm and may provide transient protection from further thermal injury via upregulation of heat shock proteins.[15,16] Beyond this, cellular and organ system dysfunction occurs. These changes represent a spectrum of disease evolution with progressive damage as T_c or exposure duration increase. A T_c greater than 43°C is immediately life threatening. Major organ system effects as core temperature rises are summarised in Table 84.2.

HYPERTHERMIAS

Major causes of hyperthermia are presented in Table 84.3. Important aspects of some are discussed below.

HEAT STROKE

Heat stroke represents the most severe form of heat-related illness. It is characterised by T_c greater than 40.0°C and neurological dysfunction, ranging from restlessness to delirium, seizures and coma.[17] Heat stroke may be classified as either classic (passive) or exertional (active). Classic heat stroke occurs following exposure to high ambient temperatures in those at the extremes of age or with co-morbid disease or medication that affect thermoregulation (Table 84.4). Exertional heat stroke occurs in healthy individuals who undertake strenuous activity in environments with high ambient temperature and humidity, reducing the efficiency of radiative and evaporative heat loss. Whilst the incidence of certain organ dysfunction varies slightly between the two forms, management is the same and they will be discussed together.

The pathogenesis of organ dysfunction in heat stroke has been the subject of much research and our understanding remains incomplete. Cytokine response may be significant, some components of which may be protective. TNFα and IL-6 levels correlate with severity of heat stroke while TNFα and IL-6 double knockout mice exhibit increased heat stroke mortality. Pro- and anti-inflammatory cytokines may be suppressed during onset of hyperthermia, rising 2–4 hours after reaching maximal T_c.[17–19]

Most patients with heat stroke present with delirium or coma, although focal neurology may occur. T_c is usually greater than 40.5°C and patients are vasodilated with evolving distributive shock and multiorgan dysfunction. Sweating is not always present. Disorders that may present in a similar fashion require exclusion (see Table 84.3). Management is essentially supportive. Principles include:

- Resuscitation
  - Recognise the need for alveolar hyperventilation
  - Restore circulating volume with cold 0.9% saline
- Cooling
  - Accurately monitor core temperature (see temperature measurement)
  - Aggressive cooling to T_c less than 39.0°C (Table 84.6)
  - Non-invasive measures that minimise cutaneous vasoconstriction and shivering are usually adequate
- Organ support
  - Particular attention to cardio-respiratory, renal, hepatic, haematological including disseminated intravascular coagulation (DIC), endocrine and neurological function
  - Hypotension usually responds to adequate cooling and volume replacement

Table 84.2 Organ system effects of change in core body temperature

20°C 28°C 30°C 32°C 34°C 35°C ≈ T_C	ORGAN SYSTEM	T_C ≈ 38.3 →	40.0°C 42.0°C INCREASING TIME	44.0°C →
• Cerebral metabolism falls by around 8%/°C • Confusion progresses to coma, hyporeflexia, unreactive pupils • Cerebral electrical activity is absent below 20°C	CNS	Increased $CMRO_2$ and $CMR_{glucose}$ Reduced cerebral blood flow as $PaCO_2$ falls	• Agitation/delirium • Blood–brain barrier injury • Elevated CSF protein/ lymphocytosis	• Coma, seizures • Cerebral oedema • Cortical infarction – especially cerebellum
• Cardiac output halved at 28°C • Reduced contractility • AF with slow ventricular rate at <30°C, VF at <28°C, Asystole at <20°C • Increasing PR, QRS and QT_c intervals (slowed K^+ flux) Osborne J wave below 33°C (height increasing with severity of hypothermia) • Initial increase in heart rate, then progressive fall (HR = 45–55 at 33°C) • Increased contractility ± mild diastolic dysfunction • V_{O_2} falls 8%/°C	CVS	• Tachycardia, vasodilation • Increased stroke volume • Decrease in CVP/SVR • Small decrease MAP • Increase in V_{O_2} ≈10%/°C	• Progressive tachycardia • Reduced stroke volume & MAP Reduced V_{O_2} if acidaemic	• Hypotension/shock • Myocardial infarction
• Pulmonary oedema • Apnoea • Progressive respiratory depression • Depressed cough reflex • Increased bronchial secretions • Reduced mucociliary clearance • Increase in respiratory rate and minute ventilation	Respiratory	Increased minute ventilation – mild respiratory alkalosis	Marked respiratory alkalosis ± metabolic acidosis	• Intravascular thrombosis • Hypoxaemia • ARDS
• Fluid compartment shifting, haemoconcentration, blood viscosity increases ≈2%/°C • Reduced platelet aggregation and adhesion at <35°C (decreased TxA_2 and glycoprotein Ib-IX) • Reduced coagulation factors and platelet adhesion inhibitor (PAI) function at <33°C • Reduction in both tPA and plasminogen activator inhibitor-1 (PAI-1) activity; however, effect appears non-linear and net result is unpredictable • Hypercoagulability and DIC may also result	Haematological	Increased haematocrit if fluid intake inadequate	• Direct activation of endothelium and platelets (increased vWF) • Increased fibrinolysis • Increased endothelial permeability	• Increased circulating TF • Microvascular thrombosis • DIC • Widespread haemorrhage • Endothelial apoptosis

Continued

Table 84.2 Organ system effects of change in core body temperature—cont'd

• Splenic sequestration causing thrombocytopenia and leukopenia • Immune dysfunction (including white blood cells, reduced lymphocyte activation, natural killer cells, cytokines, complement)			Immunological	• Leucocytosis • Increased T & B cell activation, neutrophil/macrophage diapedesis and cytotoxicity • Reduced serum iron	• Leucopenia • Reduced cell mediated cytotoxicity • Lymphoid apoptosis and necrosis	
Acute tubular dysfunction	Reduced ADH and tubular ADH resistance	ANP release and diuresis Increased K^+ Mg^{2+} PO^{4-} excretion	Renal	Reduced renal blood flow	• Tubular necrosis • Glomerular microthrombus and haemorrhage	
Pancreatitis Lactic and ketoacidosis		Reduced GI motility	Gastrointestinal	Reduced splanchnic blood flow	Enterocyte exfoliation – increased musocal permeability	• Bacterial translocation – endotoxaemia • Intestinal infarction • Pancreatic infarction
Reduced drug metabolism			Hepatic		Hepatocyte oedema and fatty infiltration	Haemorrhagic and coagulative necrosis, hepatic failure
Reduced catecholamine and cortisol secretion		• Reduced insulin secretion and insulin resistance • Glycogenolysis • Increased catecholamine and cortisol secretion	Endocrine/metabolic	• Increased cortisol/glucagon secretion • Increased metabolic rate	• Insulin resistance Hyperglycaemia • Hypokalaemia	• Hypoglycaemia • Hyperkalaemia • Adrenal haemorrhage
Loss of shivering, Rhabdomyolysis		Shivering	Musculoskeletal		Rhabdomyolysis	
Vasoconstriction			Skin	Vasodilation (cutaneous blood flow increased up to 8 L/min), Sweat production	Vasodilation Diminishing sweat production	Reduced cutaneous blood flow if CO falls, Anhydrosis

ADH, Antidiuretic hormone; *ANP*, atrial natriuretic peptide; *CMR*, cerebral metabolic rate; *CNS*, central nervous system; *CO*, cardiac output; *CSF*, cerebrospinal fluid; *CVS*, cardiovascular system; *CVP*, central venous pressure; *DIC*, disseminated intravascular coagulation; *GI*, gastrointestinal; *HR*, heart rate; *MAP*, mean arterial pressure; *SVR*, systemic vascular resistance; *TF*, tissue factor, *vWF*, von Willebrand factor.

Table 84.3 Differential diagnosis of hyperthermia

ENVIRONMENTAL HYPERTHERMIA	CNS DISEASE
Heat Stroke	Status epilepticus Hypothalamic stroke Granulomatous disease
DRUGINDUCED HYPERTHERMIA	**INFECTIOUS**
Malignant hyperpyrexia Neuroleptic malignant syndrome Serotonin syndrome Anticholinergic toxicity Sympathomimetic toxicity Salicylate toxicity MAOI toxicity Withdrawal (alcohol, benzodiazepines, baclofen)	Sepsis Encephalitis Meningitis Cerebral abscess Tetanus Malaria Typhoid
ENDOCRINE DISORDERS	**PSYCHIATRIC DISEASE**
Thyrotoxicosis Phaeochromocytoma	Lethal catatonia

CNS, Central nervous system; *MAOI*, monoamine oxidase inhibitor.

Table 84.4 Risk factors for heat stroke

Age
- Extremes of age

Environmental
- High ambient temperature and humidity
- Poor ventilation/lack of air conditioning

Behavioural
- Immobility
- Lack of acclimatisation
- Salt and water deprivation
- Obesity

Underlying conditions
- Cardiovascular disease
- Respiratory disease
- Infection/fever
- Diabetes
- Malnutrition
- Alcoholism
- Hyperthyroidism
- Impaired sweat production

Drugs
- Antihypertensives (ACEI, β-blockers, diuretics)
- Butyrophenones and phenothiazines
- Anticholinergics
- Antiparkinsonians
- Antihistamines
- Tricyclics
- Sympathomimetics

ACEI, Angiotensin-converting enzyme inhibitor.

  - Benzodiazepines are considered first-line agents for treatment of seizure
  - Routine antibiotic prophylaxis is not recommended; however, gastrointestinal (GI) barrier dysfunction can occur and if sepsis is clinically suspected, empirical therapy should cover Gram-negative organisms
  - Insulin receptor expression is downregulated during hyperthermia, so there is a risk of hypoglycaemia after cooling if large initial doses of insulin are used
- Identify and manage precipitants (see Table 84.4)
  - Withhold agents impairing thermoregulation
  - Treat underlying infection, dehydration or endocrine disorders.

The use of dantrolene has been reported in case series; however, it has been found to be ineffective.[20] Use of antipyretics is common, although benefit has not been established and there is an association between the use of paracetamol and incidence of hepatic dysfunction.[17] The normal response to recovery from hyperthermia in mammals is biphasic, with initial hypothermia and then mild hyperthermia prior to restoration of thermal homeostasis. Traditional teaching has been to avoid hypothermia during recovery. In murine models, prevention of hypothermia during recovery was associated with greater hypotension and mortality.[19] It is uncertain whether mild hypothermia should be allowed in humans during treatment for heat stroke.

Heat stroke mortality remains high with an in-hospital mortality of 65% being reported in a large, prospective observational study of classic heat stroke.[21] Those factors strongly associated with death included immobility, psychiatric or cardiovascular disease, T_c and number of organ failures at admission. Survivors often have significant long-term morbidity, predominantly secondary to neurological impairment.

MALIGNANT HYPERTHERMIA

Malignant hyperthermia (MH) is a rare, autosomal dominant, pharmacogenetic myopathy with variable penetrance. It is characterised by a hypermetabolic state and skeletal muscle rigidity that manifests when a susceptible individual is exposed to volatile anaesthetics or depolarising muscle relaxants. The disorder results from abnormal sarcoplasmic calcium flux, and in 70% of cases is linked to a mutation in the ryanodine receptor RYR1. Thirty per cent of individuals with MH do not have RYR1 mutations, and other candidate proteins include Calsequestrin-1 or the dihydropyridine receptor.[22] Upon triggering, the abnormal RYR1 receptor is thought to release excessive calcium into the cytosol, resulting in sustained excitation-contraction coupling. Sustained contraction and increased Ca^{2+}-ATPase activity result in increased aerobic glycolysis; however, muscle blood flow is reduced and eventually metabolism becomes anaerobic, with onset of metabolic acidosis.

Almost all cases are associated with use of a volatile anaesthetic ± succinylcholine.[23] The earliest clinical sign is that of masseter spasm; however, this is neither specific nor sensitive. Hypercarbia disproportional to minute ventilation, sinus tachycardia and a rapidly rising temperature are the cardinal features, associated with generalised muscular rigidity in 40%.[23] These usually occur within 2 hours of exposure. In the ICU, early diagnosis may be difficult as hypercarbia and tachycardia are common, although if out of keeping with the clinical situation or associated with other features such as muscular rigidity, the diagnosis of MH should be considered. Fortunately, the incidence of MH is extremely low if volatiles are avoided. Less common signs include tachypnoea, cyanosis, diaphoresis, cola-coloured urine, bleeding and ventricular dysrhythmias.

Triggering agents should be avoided in those with a history or family history of MH. If MH is suspected, immediate management includes the following:

- Cease triggering agents, flush circuits of volatile anaesthetics. Increase minute ventilation.
- Give dantrolene 2.5 mg/kg intravenous rapidly. Repeat 5–10 minutely until hypercarbia and temperature respond. Maximal initial dose 10 mg/kg (median required 6 mg/kg)[21]
- Treat hyperkalaemia/metabolic acidosis with bicarbonate
- Cool the patient to T_c 36°C–38°C
- Identify and treat complications
  - Cardiac arrhythmias
    - Correct hyperkalaemia and acidosis
    - Do not use calcium channel antagonists as these may cause severe hyperkalaemia and cardiac arrest with high-dose dantrolene
  - Rhabdomyolysis
  - DIC.

All cases should be appropriately monitored until resolution. Dantrolene should be continued at 1 mg/kg 4–6 hourly for 24–48 hours. Failure to respond should prompt a search for an alternate diagnosis. Suspected cases should be referred to an MH screening centre. Testing usually includes a caffeine/halothane contracture test and genetic screening of relatives of confirmed cases for RYR1 mutations. Outcome of MH is good with mortality less than 10%. Additional resources are available from the Malignant Hyperthermia Association of the United States (http://www.mhaus.org/).

NEUROLEPTIC MALIGNANT SYNDROME

Neuroleptic malignant syndrome (NMS) is an idiosyncratic reaction characterised by hyperthermia, muscle rigidity, mental state change and autonomic dysfunction. It typically occurs within a month of introduction or dose increment of an antipsychotic agent (including atypical antipsychotics). Other drugs that antagonise central dopamine transmission or rapid cessation of central dopamine agonist may also precipitate NMS.[24]

NMS is thought to occur as a result of central dopamine antagonism, predominantly at the D2 receptor. In the hypothalamus this results in hyperthermia, whilst mesocortical and nigrostriatal blockade results in mental state change and extrapyramidal symptoms, respectively. It is postulated a loss of central integration gives rise to autonomic instability.[24,25]

The clinical presentation is one of hyperthermia (usually <42°C), 'lead-pipe' rigidity, tachycardia, labile hypertension and delirium or coma. This may be accompanied by hypoventilation, diaphoresis, tremor, incontinence or mutism. Onset is usually over hours to days and the diagnosis requires exclusion of other conditions that may mimic NMS (see Table 84.3). A peripheral leucocytosis is common, and creatine kinase is usually above 1000 IU/L; however, it may be much higher. Acute kidney injury (AKI) and DIC complicate severe cases. Neuroimaging studies and CSF analysis are normal in 95% and electroencephalography (EEG) shows generalised slowing.[25]

Differentiation from other hyperthermias relies predominantly on drug and environmental history, the presence of hypertonia rather than hypotonia (heatstroke) and absence of serotonergic features. If there is clinical suspicion of infection, appropriate cultures including CSF should be performed after neuroimaging. If seizures are suspected, an EEG is required.

Usually only severe NMS requires ICU support. Therapy includes:

- Resuscitation
  - Sedation ± neuromuscular blockade may reduce severity of hyperthermia, rhabdomyolysis and other complications
- Cessation of any potentially causative agent or re-introduction of acutely withdrawn dopamine agonist
- Cooling to maintain T_c less than 39°C
- Supportive care and management of complications with particular attention to
  - Respiratory failure
  - Rhabdomyolysis
  - AKI
  - DIC
  - Arrhythmias
- Potential adjunctive therapies include
  - Benzodiazepines or central α-agonist for agitation
  - Benzodiazepines for seizures or catatonia
  - Bromocriptine 2.5–5 mg enterally 8 hourly
    - Case series suggest reduce extrapyramidal symptoms and mortality
    - May worsen hypotension or psychosis
  - Electroconvulsive therapy (ECT) – case series suggest ECT is safe and effective if NMS is prolonged or psychotic symptoms persist, although most patients were not in the ICU.[26]

Dantrolene has been used in severe cases; however, there is no RYR1 abnormality in NMS, and recent meta-analysis of published cases suggests no benefit.[25] Drug withdrawal and supportive measures are usually adequate and mortality is less than 10%. Psychiatric advice should be sought prior to re-introduction of antipsychotics.

SEROTONIN SYNDROME

A wide range of drugs are associated with the syndrome of serotoninergic toxicity. This includes the selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors, monoamine oxidase inhibitors (MAOIs; including linezolid and methylene blue), lithium, amphetamines, pethidine, fentanyl, tramadol, triptans and St. John's wort. Severe serotonin toxicity only occurs after concurrent use of two or more serotoninergic agents, usually an SSRI and MAOI, and is thought to be mediated predominantly via the $5HT_{2A}$ receptor.[27]

Severe serotonin toxicity presents with altered mental state (agitation, delirium, coma), autonomic stimulation (tachycardia, hyperthermia, diaphoresis, tremor) and neuromuscular excitation (clonus, hyperreflexia, rigidity). Features with greater specificity for serotonin toxicity include hyperreflexia, lower limb or ocular clonus and myoclonus. Rigidity tends to be predominantly lower limb.[27]

Management of severe toxicity involves resuscitation, withdrawal of offending agents, cooling and supportive care. Complications are similar to those observed in the other hyperthermias. Adjunctive therapies are of less importance. These include the $5HT_{2A}$ agonist cyproheptadine, 4–8 mg enterally 6 hourly or chlorpromazine if enteral administration is not possible.

SYMPATHOMIMETIC TOXICITY

Hyperthermia may be precipitated by all centrally acting sympathomimetics by increasing release, inhibiting metabolism or preventing re-uptake of noradrenaline, serotonin and dopamine, usually in a dose-dependent fashion. This results in increased muscle thermogenesis and impaired heat loss. In severe cases, the clinical picture is that of a rapidly progressive hyperthermia with marked delirium or coma, rhabdomyolysis, DIC and multiorgan dysfunction. As with other severe hyperthermias, early and aggressive supportive care is indicated. Most require intubation, neuromuscular blockade and aggressive cooling. Plasma potassium may rise rapidly, necessitating dialysis. There are no specific therapies and whilst dantrolene has been advocated, there is insufficient evidence to support routine use.

ANTIMUSCARINIC TOXICITY

A wide variety of antimuscarinic agents exist. Peripheral toxicity causes tachycardia, cutaneous vasodilatation, mydriasis, urinary retention and impaired sweating. Central toxicity gives rise to tremor, delirium and occasionally seizures. Severe hyperthermia with rhabdomyolysis and DIC may occur; however, this is unusual and most antimuscarinic toxidromes are adequately managed with drug withdrawal, benzodiazepines and passive cooling.

HYPOTHERMIA

DEFINITION AND CLASSIFICATION

Hypothermia is defined as core temperature less than 35°C, and may develop due to abnormal thermoregulation or heat loss overwhelming thermoregulatory capacity. Important causes and contributing factors are summarised in Table 84.5.

Severity is somewhat arbitrarily classified by T_c as[28]

- mild (32°C–35°C)
- moderate (28°C–32°C)
- severe (<28°C)
- profound (<24°C).

Hypothermia may also be classified as unintentional (often referred to as 'accidental'), or intentional (such as in cardiopulmonary bypass [CPB], deep hypothermic arrest and TH). This can be further divided into:

- primary (intact thermoregulation)
- secondary (abnormal thermoregulation)
- tertiary hypothermia (induced for therapeutic purpose, as in TH).

PHYSIOLOGICAL EFFECTS OF HYPOTHERMIA

Hypothermia alters a wide range of molecular and cellular functions, some of which may be exploited for

Table 84.5 Important causes and contributors of hypothermia

Increased heat loss
• Surface conduction, convection, radiation or evaporation
• Vasodilatation, dermatological disruption
Reduced heat production
• Endocrine (diabetic ketoacidosis, hypopituitarism, hypoadrenalism, hypothyroidism)
• Energy reserve (e.g. hypoglycaemia, malnutrition)
• Immobility and reduced neuromuscular activity
• Extremes of age
Impaired or abnormal central thermoregulation
• Central nervous system disorders
• Advanced age
• Pharmacological and toxicological (e.g. alcohol, CNS depressants, psychotropics)
• Uraemia
• Sepsis
• Malignancy

CNS, Central nervous system.

therapeutic purpose. However, prolonged or severe hypothermia causes progressive deterioration in organ function. Table 84.2 provides a summary of the physiological effects of hypothermia.

Manifestations of the normal thermoregulatory response predominate in patients with cold exposure or very mild primary or tertiary hypothermia (generally with T_c above 34°C). Patients with abnormal thermoregulatory capacity (especially those with dysautonomia) may lack some of these features and are therefore more prone to developing secondary hypothermia. There is an increase in catecholamine and cortisol secretion, and sympathetic activation is evident with:

- increase in respiratory rate
- increase in heart rate and contractility
- diastolic cardiac dysfunction
- vasoconstriction with reduced tissue perfusion
- increase in muscle tone and shivering.

The Swiss staging system describes five clinical stages of severity in primary hypothermia as a tool for estimation of T_c where reliable measurement of T_c is not possible. Whilst accuracy is somewhat limited,[29] it remains a useful tool for triage and management decisions in some pre-hospital circumstances[30,31]:

- stage I – clearly conscious and shivering (estimated T_c 32°C–35°C)
- stage II – impaired consciousness without shivering (estimated T_c 28°C–32°C)
- stage III – unconscious, vital signs present (estimated T_c 24°C–28°C)
- stage IV – no (or minimal) vital signs (estimated T_c <24°C)
- stage V – death due to irreversible hypothermia (estimated T_c <13.7°C)

MANAGEMENT OF PATIENTS WITH ABNORMAL CORE TEMPERATURE

CORE TEMPERATURE MEASUREMENT

The temperature of blood perfusing the hypothalamus is considered the reference point for T_c, which can be measured by jugular venous bulb (JVB) catheterisation. This is most accurately approximated by pulmonary artery catheter (PAC) measurements.[32]

During rapid temperature change, JVB temperature is closely approximated by PAC measurements except during, and for around 10 minutes after, rapid infusion of intravenous solution. Lag can be significant from other sites of temperature measurement, depending on the rate and magnitude of change.[32]

Whilst accuracy is temperature dependent, when core temperature is stable, compared with PACs[33–37]:

- the most accurate measurements can be obtained from an oesophageal probe in the lower quarter of the oesophagus (0.11°C ± 0.3°C), or urinary bladder catheter (–0.2°C ± 0.2°C).
- nasopharyngeal, rectal and skin/deep tissue measurements can also be accurate; however, sites such as oral, axillary and tympanic membrane are less reliable, more subject to faults in measurement conditions and technique, and can be inaccurate by more than 0.5°C.

Urinary bladder catheter temperature measurements rely on adequate urine output.[32,37] Oesophageal temperature should be measured at the retro-cardiac region at T8-T9 vertebral level and may be influenced by gas temperature in the trachea.[27,32,36,38]

Brain temperature rather than T_c may be of interest in brain injury and during neuroprotective therapy. However, brain temperature targets are uncertain and guidance from clinical data remains based on measurements of T_c. There may be differences of around 1.5°C between regions of the body and brain, particularly during rapid temperature change or periods of high cerebral metabolism.[12,39] Within the brain itself, cerebral thermo-pooling can occur, with deeper regions warmer than the surface by around 0.5°C–1°C. In brain injury, the brain can be warmer than T_c by as much as 2°C, while brain temperature lower than T_c (inverted temperature gradient) is a poor prognostic sign.[12]

PHARMACOLOGICAL EFFECTS OF ALTERED BODY TEMPERATURE

Much work in this area has been performed on animal models; understanding of drug pharmacology in humans during hypothermia or hyperthermia is limited. Whilst each drug requires characterisation across temperatures, some principles provide guidance.

Febrile patients with systemic inflammatory response syndrome (SIRS) may have high cardiac output with resultant increase in renal and hepatic blood flow. Augmented renal clearance of a number of antimicrobials has been well described in subgroups of ICU patients.[40] Although hepatic blood flow may increase, the acute phase response suppresses expression of many cytokines and the net effect of fever on hepatic clearance in humans is uncertain. In severe hyperthermia, organ dysfunction may significantly alter pharmacokinetics.

In hypothermia, absorption of orally administered drugs is significantly slowed. Bioavailability, dependent upon hepatic extraction, varies between drugs. Effect on volume of distribution (Vd) is variable as tissue blood flow, protein binding and ionisation change. For example, the Vd of midazolam increases by 83% at 33°C, whilst the Vd of pancuronium decreases.[41] Altered ionisation is of significance in drugs with a pKa between 7 and 8 and narrow therapeutic window (e.g. lignocaine). In this setting, pH-stat ventilation may be wise.[41] Hypothermia reduces hepatic blood flow and slows enzyme kinetics, resulting in reduced hepatic and

extrahepatic clearance. Renal flow, glomerular filtration rate (GFR) and tubular secretion are also reduced.[42] In moderate hypothermia, clearance of propofol, morphine and vecuronium are reduced by 10%–25%.[41] Pro-drugs, therefore, have a slower onset, while active drugs and those with active metabolites have prolonged duration of action and increased risk of toxicity.

Pharmacodynamic changes with hypothermia are variable and poorly characterised. Rewarming brings about further kinetic and dynamic alterations. In patients with significant alterations in T_c it seems wise to dose parenterally, avoid pro-drugs and agents with multiple active metabolites, and when possible titrate to a clinical endpoint or undertake temperature-corrected therapeutic drug monitoring.

ACID-BASE AND BLOOD GAS INTERPRETATION

Blood gas analysers are calibrated to perform measurements at 37°C. Deviation in body temperature from 37°C therefore results in a difference between the patient's true values and those derived from the blood gas analyser, which may be clinically significant.

The solubility of a gas is inversely related to the temperature of the solution. Therefore, a hypothermic patient will actually have lower Pa_{O_2} and $PaCO_2$ than the values derived from blood gas analysis performed at 37°C, while the opposite is true in fever and hyperthermia (Henry's Law). The relationship between temperature and gas solubility is non-linear and correction factors are required to calculate true blood gas values in the patient from measurements performed at 37°C.[43]

VENTILATION STRATEGIES

Data on ventilatory strategies are mostly derived from patients undergoing hypothermic CPB and TH following central nervous system injury. It is uncertain whether mechanical ventilation should be adjusted to achieve $PaCO_2$ and pH targets according to the arterial blood gas values measured at 37°C (alpha-stat method), or corrected to the patient's body temperature (pH-stat method).

With theoretical arguments for and against each strategy and no definitive data, alpha-stat is generally favoured with the additional advantage of simplicity.[44–46]

Consideration of pH-stat strategy may be particularly relevant in patients with narrower $PaCO_2$ and/or pH targets. Cerebrovascular reactivity to $PaCO_2$ is preserved, and calculation of the patient's true $PaCO_2$ may be relevant in patients with raised intracranial pressure. Maternal acid-base status may also be particularly relevant to the foetus during pregnancy.[47,48] In post-cardiac arrest patients, new data has raised concerns over possible negative effects of $PaCO_2$ disturbance.[31]

Regardless of ventilation strategy, it should always be noted that measured Pa_{O_2} is not the true patient value if T_c is significantly greater or less than 37°C.

ALPHA-STAT STRATEGY

This strategy is based on the theory that maintaining the pH of neutrality (pN) is important for cellular enzyme function and metabolism. The imidazole group of histidine is an important component of protein acid-base buffering, and has a pN which changes with temperature. Imidazole ionisation fraction (denoted as alpha) remains constant as body temperature changes (if CO_2 content also remains constant), thereby maintaining constant net charge of proteins and maximal ionisation of intracellular metabolic intermediates. When applying alpha-stat theory, $PaCO_2$ is adjusted to meet its target value when measured at 37°C without being corrected for actual patient temperature. Whilst cerebral blood flow is lower (predominantly due to lower $PaCO_2$) in alpha-stat compared with pH-stat management of hypothermic patients, it is thought to match the lower cerebral metabolic rate of hypothermia.

PH-STAT STRATEGY

This strategy is based on the theory that pH should be kept at its target value throughout the range of patient temperatures, and that cerebral blood flow autoregulation continues to react to $PaCO_2$. There is no reference range for temperatures other than 37°C, and the pH-stat approach assumes that values appropriate for 37°C remain so for all temperatures. Use of pH-stat in hypothermic patients requires an increase in CO_2 content, and therefore results in cerebral vasodilatation above the brain's metabolic demand, which may worsen pre-existing intracranial hypertension. It does, however, counteract the leftward shift in oxyhaemoglobin dissociation curve caused by hypothermia.

TRANSCUTANEOUS PULSE OXIMETRY RESPONSE TIMES IN HYPOTHERMIA

In hypothermic patients, the detection of changes in haemoglobin oxygen saturation by transcutaneous pulse oximetry may be significantly slower using finger probes compared with forehead sensors.[49]

HAEMOSTATIC ASSESSMENT

In the same manner as blood gas analysis, common tests of haemostasis such as the thromboelastograph, activated partial-thromboplastin time, and prothrombin and thrombin times are measured with blood samples at 37°C. Hypothermic effects on platelet and coagulation enzyme function are reversible with rewarming and hence laboratory values may be misleading when considering the patient's haemostatic capacity.[27,50] Measurements can be performed at other temperatures with prior calibration of equipment.

MANAGEMENT OF CARDIAC ARREST

No recommendations for modification of standard cardiopulmonary resuscitation (CPR) have been made for fever or hyperthermia.

Severe hypothermia can produce a clinical state which mimics prolonged circulatory arrest and poor prognosis with apnoea, asystole, unreactive pupils and areflexia. However, good outcomes have been achieved with prolonged resuscitation (in excess of 2 hours' CPR) in such patients and therefore efforts should continue until a T_c of at least 35°C is achieved.[31] In a very early report of induced hypothermia in a 51-year-old woman, a rectal temperature of 9°C was reached, with 45 minutes' cardiac standstill before initiation of surface rewarming, which gradually returned spontaneous circulation and apparently normal neurological function.[51]

In circumstances where interruption of CPR is considered potentially beneficial (e.g. to allow transportation to a more favourable environment or facility), 5-minute periods of CPR may be interposed with periods of interruption for up to 5 minutes if estimated T_c is 20°C–28°C, and 10 minutes if T_c is less than 20°C.[31]

Rewarming is important in restoring perfusing cardiac rhythm in patients with ventricular fibrillation (VF) or ventricular tachycardia (VT) and may also resolve atrial arrhythmias, atrioventricular block and bradycardia. Pacing may be hindered by reduced cardiac responsiveness and is generally not considered necessary for bradycardia due to hypothermia.[31,52]

The suggested modification for CPR of hypothermic patients involves[31]:

- withholding drugs until temperature is greater than 30°C, then doubling usual drug intervals until temperature is greater than 35°C,
- delivery of up to 3 shocks using maximum energy for VT or VF, and thereafter withholding further shocks until temperature is greater than 30°C. Rhythms other than VF may revert spontaneously with rewarming.

It is noteworthy that the optimal timing and dose of cardiac arrest drugs is not known for normothermic or hypothermic patients, and the use of vasopressors remains controversial.[53] These recommendations for modifying resuscitation are based on concerns over cardiac unresponsiveness to, and possibly injury from, defibrillation, and reduced effectiveness of drugs or drug toxicity with repeated dosing due to reduced drug metabolism.[31] However, animal studies have found vasoactive drugs and defibrillation to be effective in hypothermia.[52,54] Currently, there is inadequate evidence to support strong recommendations to modify standard CPR algorithms in the setting of hypothermia. Using standard algorithms for defibrillation and vasopressor administration in the presence of hypothermia is considered acceptable.[52]

Whilst there is concern over precipitation of ventricular arrhythmias by patient movement and invasive procedures, it is recommended that hypothermia not delay the performance of life supportive manoeuvres in cardiac arrest.[52]

TEMPERATURE MANAGEMENT AND CONTROL

CONTROLLING HYPERTHERMIA AND FEVER

Severe hyperthermia requires early aggressive pharmacological and physical measures to reduce T_c (Table 84.6). Because the balance point is unaltered in hyperthermia, antipyretic medications are not effective in lowering T_c.

In the case of fever, and especially sepsis, the concept of manipulating T_c is somewhat more controversial. Fever burden, especially T_c above 38.5°C, is associated with worse outcomes in critical illness.[14,55,56] Controlling fever appears to reduce vasopressor requirement in septic shock; however, its net effect on immune function, development of acute lung injury and survival are not certain, with some concerns raised over the use of antipyretic medication in sepsis.[13,55,57–59] Whilst benefit from controlled normothermia in patients with primary neurological injury is yet to be conclusively demonstrated, active measures to treat or prevent pyrexia is recommended in this setting based on the available evidence.[54,60–63]

Paracetamol acts predominantly by central inhibition of cyclooxygenase and results in temperature reduction of 0.3°C–0.4°C, without inducing a counter-regulatory response.[64] Other agents that suppress thresholds for thermogenesis and may be appropriate in the non-ventilated patient include magnesium, opiates, benzodiazepines, clonidine and tramadol.

Control of fever or maintenance of normothermia in the non-sedated, non-intubated patient can be challenging if thermoregulation is intact, with the balance point for T_c often being elevated by endogenous pyrogens or direct hypothalamic insult. The application of physical modes of cooling without pharmacological measures to alter thermoeffector response results in undesired shivering and increased cardio-respiratory workload. In such cases, the risks associated with need for sedation and even intubation and paralysis in order to achieve additional cooling must be weighed against potential benefit of temperature control.

CORRECTING HYPOTHERMIA

TECHNIQUES

The various methods of increasing core temperature are summarised in Table 84.6.

In general, it is considered that:

- for patients with intact autoregulatory thermogenesis and temperature greater than 34°C, passive rewarming alone may be adequate
- Patients with spontaneous circulation and temperature less than 34°C often require addition of active external warming
- Patients with temperature less than 30°C usually require active internal warming.

Table 84.6 Methods of temperature manipulation

CLASSIFICATION		METHOD	RATE OF CHANGE (°C/H)
Passive	Warming	Warm (>24°C) environment Insulating blanket	0.5–1
	Cooling	Cool environment Exposure (removal blankets/clothes)	
Active external	Warming	Warm forced-air blankets Water circulating heating control blanket Radiant heaters Temperature control pads (e.g. Arctic Sun, Medivance Inc., Louisville, Colorado)	1 1 1–2 1.5–3
	Cooling	Wet towels/ice packs Water circulating cooling control blanket Evaporative cooling (fan + tepid mist) Temperature control pads	1 1 1–2 1.5–3
Active internal	Warming	Humidified warm inspired gases Intravascular temperature control catheter (e.g. Alsius CoolGard, Irvine, California; Celsius Control System, Innercool Therapies Inc., San Diego, California) Body cavity lavage isotonic saline (gastric, right pleural 200 mL, peritoneal 10 mL/kg, bladder) Extracorporeal • renal replacement circuit • cardiopulmonary bypass	0.5–1 2–4 2–3 5 10
	Cooling	Cool intravenous fluids (4°C: 30–40 mL/kg) Intravascular temperature control catheter Body cavity lavage isotonic saline (gastric, right pleural 200 mL, peritoneal 10 mL/kg, bladder) Extracorporeal • renal replacement circuit • cardiopulmonary bypass	2–3 2–4 3 5 10

Warming of intravenous fluid (generally to around 40°C) prior to administration is important but is an inefficient means of rewarming. Thoracic lavage has been used successfully in cardiac arrest while gastric and bladder irrigation has a somewhat more limited effect.[27] Extracorporeal techniques are the most effective, and extracorporeal membrane oxygenation or CPB is generally favoured in the setting of cardiac arrest.[27]

TARGET RATES AND POTENTIAL HAZARDS OF REWARMING

Concerns with rewarming from hypothermia can be considered as:

1. Handling of the hypothermic patient and procedural risks of rewarming
2. Physiological effects of rewarming, and
3. Possible neurological injury caused by rapid rewarming.

During rewarming, care should be taken to avoid precipitation of cardiac arrhythmias by sudden movement and invasive intervention; however, this concern should not influence the performance of life-supportive manoeuvres such as intubation and central venous catheterisation, and is very rare at temperatures above 30°C.[36,52]

Vasodilatation often results in the need for intravenous fluid administration. In patients who have become hypothermic due to surface heat loss, the temperature of the peripheral compartment may be lower than the core compartment. Active surface rewarming in these patients may cause peripheral vasodilatation resulting in blood circulating from the cooler peripheral compartment to the core compartment at a lower temperature. This 'core temperature afterdrop' may be mitigated by using active internal rewarming prior to or concurrent with surface rewarming.

Rapid rewarming causes cerebral vasodilatation and loss of cerebral blood flow autoregulation. Intracranial hypertension, if present, may worsen.

Hyperkalaemia may develop due to extracellular shifting. The return of insulin sensitivity may result in potentially detrimental hypoglycaemia and high blood glucose variation.[65,66]

NEUROLOGICAL INJURY AND RATE OF REWARMING

Conceptually, it is reasonable to consider TH used for mitigation of neurological injury separately from unintentional hypothermia where there has not been a primary neurological insult. Whether such a differentiation should actually alter management from a patient outcome perspective, however, is not known at this stage.

REWARMING FROM INTENTIONAL AND THERAPEUTIC HYPOTHERMIA

In studies of hypothermia for neuroprotection from ischaemic, reperfusion, or hypoxic neurological insult including CPB, deep hypothermic arrest, and TH for cardiac arrest there is significant concern that rapid rates of rewarming may cause neurological injury and/or attenuate neuroprotective mechanisms of hypothermia.[67,68] These concerns arise from findings of:

- greater neurological injury and compromise of cerebral blood flow autoregulation by rapid rewarming[69,70]
- a possible association with seizures on rewarming[71,72]
- discrepancy between cerebral and core temperatures during rewarming and possible cerebral rebound hyperthermia[38,39,73]
- findings of better neurocognitive and renal function following slow rather than fast rewarming from CPB.[68,74–76]

In stable patients receiving TH for cardiac arrest, it is broadly recommended that rewarming be conducted at a rate not exceeding 0.5°C/h to achieve a controlled target of 36°C, with avoidance of post TH hyperthermia, which may be harmful.[77]

REWARMING FROM UNINTENTIONAL HYPOTHERMIA

Whether cerebral hypothermia or rapid rewarming can themselves cause neurological injury (in the absence of another primary neurological insult) is not well understood. Apparently complete neurological recovery has been achieved after rewarming from 9°C, despite a period of greater than 45 minutes' cardiac standstill.[51] In severe accidental hypothermia, rates of rewarming around 9°C/h via CPB have resulted in good neurological outcomes.[27]

Where hypothermia is unintentional and in the absence of a primary neurological insult, the risks associated with hypothermia and rapid rewarming should be balanced. As outlined above, maximal rewarming rates using extracorporeal techniques where available are currently favoured in hypothermic cardiac arrest.[27]

Failure to respond adequately to T_c-appropriate rewarming techniques as outlined above should precipitate a careful search for underlying causes of secondary hypothermia, most notably drugs and toxins, endocrinopathy and sepsis. Risk of underlying sepsis was found to be high when rewarming in response to treatment occurred at a rate less than 0.67°C/h, and low when rates greater than 1.67°C/h were achieved.[78]

THERAPEUTIC HYPOTHERMIA AND TARGETED TEMPERATURE MANAGEMENT

POTENTIAL MECHANISMS

Hypothermia is potentially beneficial in a variety of circumstances and is the subject of intense research.

Most mechanisms of potential benefit with TH relate to the modification of temperature-sensitive consequences of cellular injury, with particular focus at present on tissues of the central nervous system in the setting of ischaemia or reperfusion. Traumatic or ischaemia/reperfusion injury results in a cascade of destructive processes ranging from subcellular to systemic levels which can continue for several days and perhaps even weeks.[60] A wide range of these processes are temperature sensitive; however, this varies following an insult. The clinical implications of this variability such as the effect on optimal timing and duration of TH has not been fully elucidated.[27] Table 84.7 lists some of the effects of hypothermia with potential benefit for the central nervous system.

With biological plausibility, positive animal laboratory findings and some positive human trial data, the use of hypothermic range targeted temperature management (TTM), commonly referred to as TH, has been introduced in some circumstances.

Table 84.7 Mechanisms of neuronal benefit with hypothermia

Early mechanisms
• Reduction in cerebral metabolism (≈8% reduction per 1°C fall) and thermo-pooling
• Reduction in mitochondrial dysfunction
• Decreased production of nitric oxide and free radicals
• Decrease in excitatory neurotransmitters and calcium influx
Late mechanisms
• Suppression of ischaemia-induced inflammation
• Mitigation of reperfusion-related DNA injury, lipid peroxidation, and leukotriene production
• Reduced cell membrane leakage and cytotoxic oedema, blood–brain barrier-stabilising effect
• Suppression of seizures
• Reduction in apoptosis (inhibition of caspase activation)

Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet.* 2008;371:1955–1969.

Potential benefit from hypothermia may also be derived from other physiological effects such as those on rate of cerebral metabolism during periods of reduced blood flow, the immune function (in patients with sepsis and septic shock), and reduction of intracranial pressure. Induction of hypothermia for cardio-pulmonary bypass and deep hypothermic arrest in cardiovascular surgery utilises the reduction in cerebral metabolic demand for neuroprotection from ischaemic injury. However, TTM and TH generally refer to the use of hypothermia following an unintended primary neurological injury.

INDICATIONS FOR THERAPEUTIC HYPOTHERMIA

ADULT POST-CARDIAC ARREST TEMPERATURE MANAGEMENT RECOMMENDATIONS

The greatest interest currently is in adult survivors of cardiac arrest. Two landmark clinical trials published in 2002 showed positive outcomes for TH compared with no temperature control for patients who were comatose after achieving return of spontaneous circulation (ROSC) from out-of-hospital pulseless VT or VF cardiac arrest.[79,80] These studies reported no significant difference in complications and therefore potential for harm was thought to be limited if conducted in an appropriate clinical setting. TH was subsequently widely adopted in post-resuscitation management guidelines, although it was acknowledged that the quality of evidence was low and that uncertainties still existed regarding optimal technique/indications and adverse effects other than those reported in these studies.[53,70,81–84]

Nielsen and colleagues subsequently published a large randomised controlled trial in 2013 (the TTM study) which found no significant difference in survival and functional status between normothermic TTM, also referred to as therapeutic normothermia (TN), and TH in adult survivors of out-of-hospital cardiac arrest (OHCA).[85] This international multicentre trial of 939 patients included non-shockable initial cardiac arrest rhythms and also found no significant difference in complications. Whilst this trial brought about significant uncertainty about the benefit of TH over TN, all patients in this trial received TTM and hence the importance of tight temperature control, and especially prevention of fever, remains emphasised.

The core clinical trials outlined above largely set out to investigate the effect of TH; however, interpreted together they perhaps demonstrate more of a benefit in avoidance of post-cardiac arrest fever.[85,86] Therefore, convincing as the experimental animal and laboratory data may be for TH following ischaemia reperfusion, improvement in patient outcomes with TH in clinical practice is yet to be conclusively demonstrated. Potential reasons for this include lack of true benefit, clinical trial methodology and design, ineffectiveness of trialled treatment protocols (patient selection, timing, temperatures, duration, rewarming), and loss of benefit through adverse effects.[87] Whilst these trials reported no difference in the complications studied, more recent data on other factors such as disturbances in $PaCO_2$ and glucose variability which may be brought about by temperature manipulation might in fact be relevant to outcomes.[65,66,77]

The Advanced Life Support Task Force of the International Liaison Committee on Resuscitation (ILCOR) performed an extensive review of the literature published up until December 2014, and made a number of recommendations in 2015 on adult TTM for post-cardiac arrest care. Key points from these and the recommendations made by resuscitation councils in their respective 2015 resuscitation guidelines include[88–90]:

- when TTM is used, a single target temperature value should be prescribed. This value should lie somewhere in the range of 32°C–36°C. The patient's temperature should then be maintained at this value for a period of at least 24 hours.
- It is *strongly* recommended based on *low-quality evidence* that TTM is used for adults who remain unresponsive after achieving ROSC from OHCA with *shockable* initial rhythm (VT or VF).
- Recommendations for the use of TTM is *weak* and based on *very low quality evidence* for
  - **a.** adults who remain unresponsive after achieving ROSC from OHCA with *non-shockable* initial rhythm, and
  - **b.** adults who remain unresponsive after achieving ROSC from in-hospital cardiac arrest (IHCA) of *any* initial rhythm.

PAEDIATRIC POST-CARDIAC ARREST TEMPERATURE MANAGEMENT RECOMMENDATIONS

Data in paediatric patients remaining comatose after achieving ROSC from cardiac arrest is scarce and further studies are awaited. The most important data is from a multicentre prospective randomised study which found no significant difference in primary outcome between TH and TN in OHCA.[91]

Recommendations made by resuscitation councils in 2015 can be summarised as[92,93]:

- For infants and children, it is *strongly recommended* based on moderate quality, non-randomised study evidence that fever be treated after ROSC
- After OHCA, there is a recommendation of *moderate* strength based on moderate quality, randomised study evidence that patients receive either 5 days of TN, or 2 days of TH followed by 3 days of TN
- For IHCA, there is insufficient evidence to recommend one over the other for TN and TH.

NEONATAL HYPOXIC-ISCHAEMIC ENCEPHALOPATHY TEMPERATURE MANAGEMENT RECOMMENDATIONS

Some important recent trial data is also in favour of TH over no temperature control in neonatal hypoxic-ischaemic encephalopathy (HIE).[94]

Recommendations made by resuscitation councils in 2015 can be summarised as[95,96]:

- TH may be considered for neonates born at ≥36 weeks' gestational age with evolving moderate to severe HIE, applied in a manner similar to the major clinical trials with positive outcomes (target 33.5°C–34.5°C, commenced within 6 hours of birth, maintained for 72 hours, rewarmed over at least 4 hours)
- In advanced 'resource-abundant' clinical settings, recommendations are of *moderate* strength that TH be used, based on *high quality evidence* derived from more than one randomized controlled trial (RCT)
- It is still considered reasonable to provide TH in 'resource-limited' clinical environments; however, recommendations for its use in these settings are *weak* and based on *moderate quality* RCT evidence.

OTHER CONDITIONS

TH is also of interest in other conditions, although more supportive data is required to support or refute its use at this stage. These include ischaemic and haemorrhagic cerebrovascular accident, traumatic brain and spinal cord injury, neurosurgery, raised intracranial pressure, liver failure, sepsis and myocardial ischaemia.[97,98]

METHOD OF TH IN ADULTS POST CARDIAC ARREST

Current recommendations on the use of TTM after cardiac arrest in adults are extensively covered in the ILCOR Advisory Statement, upon which the various resuscitation council guidelines have also been largely based. Whilst there is broad agreement on the methodology, it is emphasised that significant uncertainty surrounds almost every aspect of TTM.[88] It is currently recommended that TTM be provided using similar temperature profiles to those used in the major clinical trials outlined above. Important considerations when TH is chosen over TN are summarised below.

- Whilst the indications for TTM have been outlined above, no recommendations exist on which patients should receive TH versus TN. This is decided either in the context of clinical trial protocols or expert consideration on a case-by-case basis.
- A tightly controlled temperature profile over discrete stages of induction, maintenance, reversion, and post TH should be prescribed. The use of imprecise temperature targets and methods of temperature measurement and control is potentially hazardous.[70]
- Since TH seeks to introduce a derangement, it should be performed in a high level ICU with a practice guideline specific for the institution. Outside of this circumstance, it may be reasonable to consider TN as safer than TH.
- Induction of TH is generally carried out as quickly as possible and as soon as possible once the decision for TH has been made.
  - Target temperature should ideally be achieved within 8 hours of ROSC based on earlier trials; however, no absolute time frames have been specified.
  - From a scientific perspective, some destructive processes are only temperature sensitive for a few hours following insult.
  - Rapid achievement of hypothermia also limits shivering, diuresis and electrolyte losses, fluid compartment shifting and haemodynamic fluctuation, as all of these tend to settle at temperatures below 33.5°C.[44]
  - Shivering can increase heat production and oxygen consumption several-fold, but largely settles at temperatures below 34°C. Applying a warm surface in contact with the patient, and the use of alfentanil, fentanyl, pethidine, propofol, dexmedetomidine, clonidine or magnesium are often effective in reducing shivering.
- Methods of rapidly inducing TH include (see Table 84.6):
  - 4°C intravenous crystalloid fluid bolus up to 30 mL/kg over 30 minutes can rapidly lower temperature by around 1°C–1.5°C, but is not sufficient to maintain hypothermia.[79,84] Earlier studies were thought to be encouraging; however, newer data has raised significant concern over safety and its use in the pre-hospital setting is not recommended.[88]
  - surface ice packs or cold air blankets, cooling helmet
  - temperature control devices with external pads (e.g. Arctic Sun) or intravascular catheters (e.g. Alsius CoolGard, Celsius Control System)
  - transnasal evaporative coolant delivery (e.g. RhinoChill, BeneChill, San Diego, California)
  - Temperature control devices use continuous temperature feedback from patient monitoring (such as oesophageal and bladder catheters) or intermittent intravascular temperature measurements (Celsius Control System) to adjust closed loop fluid or catheter temperature. These devices do not involve administration of extra fluid, and use conductive cold or heat between device and skin (surface devices) or blood (intravascular devices). They can achieve cooling rates of up to 2°C/h and are the most precise methods of controlling temperature through all stages of TTM.[89,99–101]

The optimal duration of TH is unknown and may vary between individual cases depending on circumstance and the nature of illness or injury.[27] Current recommendations of greater than 24 hours in adults and 72 hours in neonates are based on the methods used in clinical trials.[88]

Although the optimal rate of rewarming is not known, rewarming is recommended to be tightly controlled at a rate of 0.25–0.5°C/h. Hyperthermia is common following cardiac arrest and is thought to be an important mechanism of secondary neurological damage. Prevention of fever and hyperthermia after neurological insult often requires continued active temperature modulation; however, there is little evidence that this improves patient outcome and the required duration of prevention is not known.[60,77,82]

CLINICAL CONSIDERATIONS DURING THERAPEUTIC HYPOTHERMIA

All of the physiological effects of hypothermia as discussed earlier in this chapter and their implications on patient management should be borne in mind when applying TH. Of particular importance are:

- its effects on potassium and insulin sensitivity/blood glucose
- interpretation of arterial blood gases and acid-base status
- potential masking of fever due to sepsis
- effects on pharmacokinetics and pharmacodynamics
- the use of anticoagulation and thrombolysis
- safety with percutaneous coronary intervention (PCI)
- potential for worsening of cardiac output and arrhythmias
- its implications in pregnant patients
- neurological prognostication following anoxic brain injury.

INSULIN SENSITIVITY AND VENTILATION STRATEGIES

Changes in insulin sensitivity during changes in T_c may contribute to dysglycaemia and increased blood glucose variability, which may be relevant to patient outcomes.[65,66]

Recent data suggests that disturbances in $PaCO_2$ may also be harmful post cardiac arrest, particularly hypocarbia.[31] The current recommendation to maintain normocarbia may therefore have implications on alpha-stat versus pH-stat interpretation of blood gases and ventilation strategies during TH. Alpha-stat management with its associated hypocarbia appears to result in greater jugular venous oxygen desaturation after cardiac arrest; however, data is insufficient at this stage for strong recommendations to be made in favour of either strategy.[102,103]

ANTICOAGULATION AND THROMBOLYSIS DURING THERAPEUTIC HYPOTHERMIA

Bleeding complications have so far not been increased by TH in major clinical trials where patients have received therapeutic anticoagulation and thrombolysis as indicated. Further support for this is emerging in trials combining thrombolysis and TH for stroke.[104] It is currently thought that TH does not significantly increase risk of haemorrhage.[89]

THERAPEUTIC HYPOTHERMIA AND PERCUTANEOUS CORONARY INTERVENTION

Cold skin contact and mild hypothermia can cause vasoconstriction in diseased coronary arteries.[105] There is some suggestion that TH may increase the risk of stent thrombosis; however, results are somewhat mixed in the very limited data available on the impact of TH on complication rates and outcomes in patients receiving PCI.[106–110] It is currently considered safe to provide patients with both TH and PCI.[84]

THERAPEUTIC HYPOTHERMIA IN PATIENTS WITH CARDIOGENIC SHOCK

Hypothermia causes vasoconstriction and uncontrolled shivering increases oxygen consumption and demand. However, hypothermia can also increase contractility and improve haemodynamics.[111–113]

Earlier trials excluded patients with significant shock, whilst there was no difference in mortality between TN and TH amongst patients with mild shock in the TTM study.[79,80,85,110,114]

THERAPEUTIC HYPOTHERMIA IN PREGNANCY

It is currently considered reasonable to use TTM in pregnancy.[31]

There are published cases of TH in pregnancy; however, pregnant patients were excluded in the clinical trials demonstrating benefit with TH. Good maternal outcome with subsequent delivery of apparently normal neonate has been reported following the use of TH at as early as 13 weeks' gestation,[115–117] while foetal demise has also been reported during, but not necessarily as a result of, TH.[118]

The following should be carefully considered regarding TH during pregnancy:

- both hypothermia and rewarming can increase uterine tone and contractions which reduce placental blood flow[119]
- hypothermia shifts maternal haemoglobin-oxygen dissociation curve to the left, reducing placental gas exchange
- maternal acid-base disturbances can further compromise the foetus; temperature should be considered in the interpretation of arterial blood gases, and hypocarbia should be avoided
- normothermic CPB whenever possible is generally favoured during pregnancy, as hypothermic CPB appears to be associated with higher foetal mortality[120–122]

Foetal bradycardia may be associated with foetal distress or hypothermia.[123] Increasing maternal Pa_{O_2} may attenuate foetal bradycardia; however, hyperoxia post cardiac arrest has been found to be associated with increased mortality, possibly due to increased reactive oxygen species in the context of ischaemia-reperfusion injury.[124]

Foetal bradycardia with heart rates around 90–100 beats/min were reported in the case of successful TH in pregnancy.[115]

Maternal hypothermia and alkalaemia decrease foetal Pa_{O_2}.[125] Maternal $PaCO_2$ and pH should ideally be maintained at values normal for gestation. By 12 weeks' gestation, maternal $PaCO_2$ is normally around 32 mm Hg with pH 7.44. Foetal pH is normally around 0.1 less than maternal. In the TH range of 32°C–34°C, corrected values can be estimated by the subtraction of 5 mm Hg per 1°C below 37°C for Pa_{O_2}, subtraction of 2 mm Hg per 1°C below 37°C for $PaCO_2$, and addition of 0.012 per 1°C below 37°C for pH.[43,44]

SEDATION, PARALYSIS AND SEIZURES

Seizures occur in around 36% of patients after ROSC, mostly within the first 24 hours (and therefore coinciding with the period of TH),[126,127] and can result in further brain injury in as soon as 30 minutes.[128,129]

It is not known whether the treatment of seizures impacts patient outcome post cardiac arrest. Nonetheless, based on current understanding of the effects of seizures on brain injury, it is strongly recommended that post-cardiac arrest seizures be treated.[77] The use of paralysis to control shivering during TH may mask seizure activity, and EEG monitoring may need to be considered in paralysed patients.[130,131]

NEUROLOGICAL OUTCOME AND PROGNOSTICATION FOLLOWING THERAPEUTIC HYPOTHERMIA

There is considerable uncertainty about the effect of TH on the reliability of clinical signs as predictors of poor neurological outcome following cardiac arrest. Since findings on clinical examination remain the most important prognosticator, the use of sedatives, muscle-relaxants and the effect of hypothermia on drug metabolism during TH is potentially confounding. The 2006 American Academy of Neurology (AAN) guidelines for neurological prognostication following cardiac arrest appear not to have the same degree of accuracy in patients treated with TH.[53,132–135]

The effects of TH may extend beyond 72 hours from ROSC, which is the minimum recommended interval before neurological prognostication is carried out based on clinical examination.[135] The current level of evidence is considered inadequate to support a specific method of determining with certainty poor neurological prognosis.[53,135] The use of EEG, somatosensory evoked potentials, serum biomarkers (neuron-specific enolase and S-100β) and imaging with computerised tomography and magnetic resonance imaging to supplement clinical examination appears to improve accuracy of predicting poor neurological outcome.[134,135]

REFERENCES

1. Romanovsky AA. Thermoregulation: some concepts have changed. Functional architecture of the thermoregulatory system. *Am J Physiol Regul Integr Comp Physiol*. 2007;292:R37–R46.
2. Mekjavic IB, Eiken O. Contribution of thermal and nonthermal factors to the regulation of body temperature in humans. *J Appl Physiol*. 2006;100: 2065–2072.
3. Caterina MJ. Transient receptor potential ion channels as participants in thermosensation and thermoregulation. *Am J Physiol Regul Integr Comp Physiol*. 2007;292:R64–R67.
4. Donaldson GC, Keatinge WR, Saunders RD. Cardiovascular responses to heat stress and their adverse consequences in healthy and vulnerable human populations. *Int J Hyperthermia*. 2003;19: 225–235.
5. Argyropoulos G, Harper ME. Invited review: uncoupling proteins and thermoregulation. *J Appl Physiol*. 2002;92:2187–2198.
6. Kenny WL, Munce TA. Invited review: aging and human temperature regulation. *J Appl Physiol*. 2003; 95:2598–2603.
7. Van Someren JW. Thermoregulation and aging. *Am J Physiol Regul Integr Comp Physiol*. 2007;292: R99–R102.
8. Sessler DI. Perianaesthetic thermoregulation and heat balance in humans. *FASEB J*. 1993;7:638–644.
9. Sessler DI. Temperature monitoring and perioperative thermoregulation. *Anesthesiology*. 2008; 109:318–338.
10. Niven DJ, Laupland KB. Pyrexia: aetiology in the ICU. *Crit Care*. 2016;20:247–256.
11. O'Gradey NP, Barie PS, Bartlett JG, et al. Practice guidelines for evaluating new fever in critically ill adult patients. *Clin Infect Dis*. 1998;26:1042–1059.
12. Mrozek S, Vardon F, Geeraerts T. Brain temperature: physiology and pathophysiology after brain injury. *Anesthesiol Res Pract*. 2012;2012: Article ID 989487: 13 pages.
13. Gozzoli V, Schöttker P, Suter PM, et al. Is it worth treating fever in intensive care patients? *Arch Intern Med*. 2001;161:121–123.
14. Doyle JF, Schortgen F. Should we treat pyrexia? And how do we do it? *Crit Care*. 2016;20:303–313.
15. Beachy SH, Repasky EA. Toward establishment of temperature thresholds for immunological impact of heat exposure in humans. *Int J Hyperthermia*. 2011;24:344–352.
16. Kregel KC. Invited review: heat shock proteins: modifying factors in physiological stress response and acquired thermotolerance. *J Appl Physiol*. 2002; 92:2177–2186.

17. Bouchama A, Knochel JP. Heat stroke. *N Engl J Med*. 2002;346:1978–1988.
18. Leon LR, Blaha MD, DuBose DA. Time course of cytokine, corticosterone, and tissue injury responses in mice during heat strain recovery. *J Appl Physiol*. 2006;100:1400–1409.
19. Leon LR, Helwig BG. Heat stroke: role of the systemic inflammatory response. *J Appl Physiol*. 2010;109:1980–1988.
20. Bouchama A, Cafege A, DeVol EB, et al. Ineffectiveness of dantrolene sodium in the treatment of heatstroke. *Crit Care Med*. 1991;19:176–180.
21. Argaud L, Ferry T, Le QH, et al. Short and long-term outcomes of heat stroke following the 2003 heat wave in Lyon, France. *Arch Intern Med*. 2007;167:2177–2183.
22. Protasi F, Paolini C, Dainese M. Calsequestrin-1: a new candidate gene for malignant hyperthermia and exertional/environmental heat stroke. *J Physiol*. 2009;587:3095–3100.
23. Larch MG, Gronert GA, Allen GC, et al. Clinical presentation, treatment and complications of malignant hyperthermia in North America from 1987 to 2006. *Anesth Analg*. 2010;110:498–507.
24. Berman BD. Neuroleptic malignant syndrome: a review for neurohospitalist. *Neurohospitalist*. 2011;1(1):441–447.
25. Strawn MD, Keck PE, Caroff SN. Neuroleptic malignant syndrome. *Am J Psychiatry*. 2007;164: 870–876.
26. Trollor JN, Sachdev PS. Electroconvulsive therapy for the treatment of neuroleptic malignant syndrome with psychotic symptoms: a review of reports and cases. *Aust N Z J Psychiatry*. 1999;33(5): 650–659.
27. Isbister GK, Buckley NA, Whyte IM. Serotonin toxicity: a practical approach to diagnosis and treatment. *Med J Aust*. 2007;187(6):361–365.
28. Brown JA, Brugger H, Boyd J, et al. Accidental hypothermia. *N Engl J Med*. 2012;367:1930–1938.
29. Deslarzes T, Rousson V, Yersin B, et al. An evaluation of the Swiss staging model for hypothermia using case reports from the literature. *Scand J Trauma Resusc Emerg Med*. 2016;24:16.
30. Durrer B, Brugger H, Syme D. The medical on-site treatment of hypothermia. ICAR-MEDCOM recommendation. *High Alt Med Biol*. 2003;4:99–103.
31. Truhlář A, Deakin CD, Soar J, et al. European Resuscitation Council guidelines for resuscitation 2015: Section 4. Cardiac arrest in special circumstances. *Resuscitation*. 2015;95:148.
32. Akata T, Setoguchi H, Shirozu K, et al. Reliability of temperatures measured at standard monitoring sites as an index of brain temperature during deep hypothermic cardiopulmonary bypass conducted for thoracic aortic reconstruction. *J Thorac Cardiovasc Surg*. 2007;133:1559–1565.
33. Niven DJ, Gaudet JE, Laupland KB, et al. Accuracy of peripheral thermometers for estimating temperature. A systematic review and meta-analysis. *Ann Intern Med*. 2015;163:768–777.
34. Lawson L, Bridges EJ, Ballou I, et al. Accuracy and precision of non-invasive temperature measurement in adult intensive care patients. *Am J Crit Care*. 2007;16:485–496.
35. Erickson RS, Kirklin SK. Comparison of ear-based, bladder, oral, and axillary methods for core temperature measurement. *Crit Care Med*. 1993;21:1528–1534.
36. Lefrant JY, Muller L, Coussaye JE, et al. Temperature measurement in intensive care patients: comparison of urinary bladder, oesophageal, rectal, axillary, and inguinal methods versus pulmonary artery core method. *Intensive Care Med*. 2003;29:414–418.
37. Fallis WM. Monitoring urinary bladder temperature in the intensive care unit: state of the science. *Am J Crit Care*. 2001;10:38–47.
38. Mekjavic IB, Rempel ME. Determination of esophageal probe insertion length based on standing and sitting height. *J Appl Physiol*. 1990; 69:376–379.
39. Hercus V, Cohen D, Bowring AC. Temperature gradients during hypothermia. *BMJ*. 1959;v1(5135): 1439–1441.
40. Udy A, Roberts JA, Boots RJ, et al. Augmented renal clearance, implications for antibacterial dosing in the critically ill. *Clin Pharm*. 2010;49(1): 1–16.
41. Van den Broek MPH, Groenendaal F, Egberts ACG, et al. Effects of hypothermia on pharmacokinetics and pharmacodynamics, a systematic review of preclinical and clinical studies. *Clin Pharm*. 2010;49(5):277–294.
42. Morales P, Carbery W, Morello A, et al. Alterations in renal function during hypothermia in man. *Ann Surg*. 1957;145(4):488–499.
43. Bacher A. Effects of body temperature on blood gases. *Intensive Care Med*. 2005;31:24–27.
44. Polderman KH, Ingeborg H. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. *Crit Care Med*. 2009;37:1101–1120.
45. Kollmar R, Georgiadis D, Schwab S. Alpha-stat versus pH-stat guided ventilation in patients with large ischemic stroke treated by hypothermia. *Neurocrit Care*. 2009;10:173–180.
46. Aziz KAA, Meduoye A. Is pH-stat or alpha-stat the best technique to follow in patients undergoing deep hypothermic circulatory arrest? *Interact Cardiovasc Thorac Surg*. 2010;10:271–282.
47. Levinson G, Shnider SM, DeLorimier AA, et al. Effects of maternal hyperventilation on uterine blood flow and fetal oxygenation and acid-base status. *Anesthesiology*. 1974;40:340–347.
48. Motoyama EK, Rivard G, Acheson F, et al. The effect of changes in maternal pH and PCO_2 on the PO_2 of fetal lambs. *Anesthesiology*. 1967;28: 891–903.
49. MacLeod DB, Cortinez LI, Keifer JC, et al. The desaturation response time of finger pulse

oximetry during mild hypothermia. *Anaesthesia*. 2005;60:65–71.
50. Douning LK, Ramsay MAE, Swygert TH, et al. Temperature corrected thromboelastography in hypothermic patients. *Anesth Analg*. 1995;81: 608–611.
51. Niazi SA, Lewis FJ. Profound hypothermia in man: report of a case. *Ann Surg*. 1958;147:264–266.
52. Vanden Hoek TL, Morrison LJ, Shuster M, et al. Part 12: cardiac arrest in special situations: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2010;122:S829–S861.
53. Morrison LJ, Deakin CD, Morley PT, et al. Part 8: advanced life support: 2010 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation*. 2010;122: S345–S421.
54. Wira CR, Becker JU, Martin G, et al. Antiarrhythmic and vasopressor medications for the treatment of ventricular fibrillation in severe hypothermia: a systematic review of the literature. *Resuscitation*. 2008;78:21–29.
55. Lee BH, Inui D, Suh GY, et al. Association of body temperature and antipyretic treatments with mortality of critically ill patients with and without sepsis: multi-centered prospective observational study. *Crit Care*. 2012;16:R33.
56. Walter EJ, Carraretto M. The neurological and cognitive consequences of hyperthermia. *Crit Care*. 2016;20:199–207.
57. Jefferies S, Weatherall M, Young P, et al. The effect of antipyretic medications on mortality in critically ill patients with infection: a systematic review and meta-analysis. *Crit Care Resusc*. 2011; 13:125–131.
58. Schortgen F, Clabault K, Katsahian S, et al. Fever control using external cooling in septic shock: a randomized controlled trial. *Am J Respir Crit Care Med*. 2012;185:1088–1095.
59. Rice P, Martin E, He JR, et al. Febrile-range hypothermia augments neutrophil accumulation and enhances lung injury in experimental Gram-negative bacterial pneumonia. *J Immunol*. 2005; 174:3676–3685.
60. Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet*. 2008;371:1955–1969.
61. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. *Crit Care Med*. 2009;37(7):S186–S202.
62. Yenari MA, Hemmen TM. Therapeutic hypothermia for brain ischemia. Where have we come and where do we go? *Stroke*. 2010;41:S72–S74.
63. Karnatovskaia LV, Wartenberg KE, Freeman WD. Therapeutic hypothermia for neuroprotection: history, mechanisms, risks, and clinical applications. *Neurohospitalist*. 2014;4:153–163.
64. Dippel DWJ, van Breda EJ, van Germert HMA, et al. Effect of paracetamol (acetaminophen) on body temperature in acute ischaemic stroke. *Stroke*. 2001;32:1067–1612.
65. Hermanides J, Bosman RJ, Titia M, et al. Hypoglycemia is associated with intensive care unit mortality. *Crit Care Med*. 2010;38:1430–1434.
66. Hermanides J, Titia M, Vriesendorp TM, et al. Glucose variability is associated with intensive care unit mortality. *Crit Care Med*. 2010;38:838–842.
67. Scaravilli V, Bonacina D, Citerio G. Rewarming: facts and myths from the systemic perspective. *Crit Care*. 2012;16(suppl 2):A25.
68. Lu X, Ma L, Sun S, et al. The effects of the rate of postresuscitation rewarming following hypothermia on outcomes of cardiopulmonary resuscitation in a rat model. *Crit Care Med*. 2014; 42:e106–e113.
69. Maxwell WL, Watson A, Queen R, et al. Slow, medium, or fast re-warming following post-traumatic hypothermia therapy? An ultrastructural perspective. *J Neurotrauma*. 2005;22:873–884.
70. Nunnally ME, Jaeschke R, Bellingan GJ, et al. Targeted temperature management in critical care: a report and recommendations from five professional societies. *Crit Care Med*. 2011;39: 1113–1125.
71. Battin M, Bennet L, Gunn AJ. Rebound seizures during rewarming. *Pediatrics*. 2004;114:1369.
72. Legriel S, Troche G, Bedos JP. Status epilepticus after discontinuation of induced hypothermia – an incidental association? *Resuscitation*. 2006; 68:143–146.
73. DeWitt DS, Prough DS. Accurate measurement of brain temperature. *Crit Care Med*. 1998;26:431–432.
74. Grigore AM, Grocott HP, Mathew JP, et al. The rewarming rate and increased peak temperature alter neurocognitive outcome after cardiac surgery. *Anesth Analg*. 2002;94:4–10.
75. Nathan HJ, Wells GA, Munson JL, et al. Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: a randomized trial. *Circulation*. 2001;104:I85–I91.
76. Boodhwani M, Rubens FD, Wozny D, et al. Effects of mild hypothermia and rewarming on renal function after coronary artery bypass grafting. *Ann Thorac Surg*. 2009;87:489–495.
77. Soar J, Callaway CW, Aibiki M, et al. Part 4: advanced life support. 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Resuscitation*. 2015;95:e71–e120.
78. Delaney KA, Vassallo SU, Larkin GL, et al. Rewarming rates in urban patients with hypothermia: prediction of underlying infection. *Acad Emerg Med*. 2006;13:913–921.
79. The Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurological outcome after cardiac arrest. *N Engl J Med*. 2002;346:549–556.
80. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac

arrest with induced hypothermia. *N Engl J Med*. 2002;346:557–563.
81. Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: post-cardiac arrest care. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2010;122(S3):S768–S786.
82. Deakin CD, Nolan JP, Soar J, et al. European Resuscitation Council guidelines for resuscitation 2010. Section 4. Adult advanced life support. *Resuscitation*. 2010;81:1305–1352.
83. Australian Resuscitation Council. *Guideline 11.8: therapeutic hypothermia after cardiac arrest*; 2010. http://www.resus.org.au/.
84. Walters JH, Morley PT, Nolan JP. The role of hypothermia in post-cardiac arrest patients with return of spontaneous circulation: a systematic review. *Resuscitation*. 2011;82:508–516.
85. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med*. 2013;369:2197–2206.
86. Fukuda T. Targeted temperature management for adult out-of-hospital cardiac arrest: current concepts and clinical applications. *J Intensive Care*. 2016;4:30.
87. Polderman KH, Varon J. Interpreting the results of the Targeted Temperature Management Trial in cardiac arrest. *Ther Hypothermia Temp Manag*. 2015;5:73–76.
88. Donnino MW, Andersen LW, Berg KM, et al. Temperature management after cardiac arrest: an advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation and the American Heart Association Emergency Cardiovascular Care Committee and the Council on cardiopulmonary, critical care, perioperative and resuscitation. *Circulation*. 2015;132:2448–2456.
89. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines for post-resuscitation care 2015. Section 5 of the European Resuscitation Council guidelines for resuscitation 2015. *Resuscitation*. 2015;95:202–222.
90. Callaway CW, Soar J, Aibiki M, et al. Part 4: advanced life support. 2015 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation*. 2015;132(suppl 1):S84–S145.
91. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. *N Engl J Med*. 2015;372:1898–1908.
92. de Caen AR, Berg MD, Chameides L, et al. Part 12: pediatric advanced life support. 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132:S526–S542.
93. Maconochie IK, Bingham R, Eich C, et al. European Resuscitation Council guidelines for resuscitation 2015. Section 6. Paediatric life support. *Resuscitation*. 2015;95:223–248.
94. Azzopardi D, Strohm B, Marlow N, et al. Effects of hypothermia for perinatal asphyxia on childhood outcomes. *N Engl J Med*. 2014;371:140–149.
95. Wyllie J, Bruinenberg J, Roehr CC, et al. European Resuscitation Council guidelines for resuscitation 2015. Section 7. Resuscitation and support of transition of babies at birth. *Resuscitation*. 2015;95:249–263.
96. Wyckoff MH, Aziz K, Escobedo MB, et al. Part 13: neonatal resuscitation. 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132:S543–S560.
97. Perman SM, Goyal M, Neumar RW, et al. Clinical applications of targeted temperature management. *Chest*. 2014;145:386–393.
98. Villablanca PA, Rao G, Briceno DF, et al. Therapeutic hypothermia in ST elevation myocardial infarction: a systematic review and meta-analysis of randomised control trials. *Heart*. 2016;102:712–719.
99. Hoedemaekers CW, Ezzahti M, Gerritsen A, et al. Comparison of different cooling methods to induce and maintain normo and hypothermia in ICU patients: a prospective intervention study. *Crit Care*. 2007;11:R91.
100. Gillies MA, Pratt R, Whitely C, et al. Therapeutic hypothermia after cardiac arrest: a retrospective comparison of surface and endovascular cooling techniques. *Resuscitation*. 2010;81:1117–1122.
101. Tomte O, Draegni T, Mangschau A, et al. A comparison of intravascular and surface cooling techniques in comatose cardiac arrest survivors. *Crit Care Med*. 2011;39:443–449.
102. Voicu S, Deye N, Malissin I, et al. Influence of α-stat and pH-stat blood gas management strategies on cerebral blood flow and oxygenation in patients treated with therapeutic hypothermia after out-of-hospital cardiac arrest: a crossover study. *Crit Care Med*. 2014;42:1849–1861.
103. Terman SW, Nicholas KS, Hume B, et al. Clinical practice variability in temperature correction of arterial blood gas measurements and outcomes in hypothermia-treated patients after cardiac arrest. *Ther Hypothermia Temp Manag*. 2015;5:135–142.
104. Hemmen TM, Raman R, Guluma KZ, et al. Intravenous thrombolysis plus hypothermia for acute treatment of ischemic stroke (ICTuS-L). *Stroke*. 2010;41:2265–2270.
105. Nabel EG, Ganz P, Gordon JB, et al. Dilation of normal and constriction of atherosclerotic coronary arteries caused by the cold pressor test. *Circulation*. 1988;77:43–52.
106. Penela D, Magaldi M, Fontanals J, et al. Hypothermia in acute coronary syndrome: brain salvage versus stent thrombosis? *J Am Coll Cardiol*. 2013;61(6):686–687.
107. Oban M, Mayer K, Morath T, et al. The impact of therapeutic hypothermia on on-treatment

platelet reactivity and clinical outcome in cardiogenic shock patients undergoing primary PCI for acute myocardial infarction: results from the ISAR-SHOCK registry. *Thromb Res*. 2015; 136:87–93.
108. Wolfrum S, Pierau C, Radke PW, et al. Mild therapeutic hypothermia in patients after out-of-hospital cardiac arrest due to acute ST-segment elevation myocardial infarction undergoing immediate percutaneous coronary intervention. *Crit Care Med*. 2008;36:1780–1786.
109. Knafelj R, Radsel P, Ploj T, et al. Primary percutaneous coronary intervention and mild induced hypothermia in comatose survivors of ventricular fibrillation with ST-elevation acute myocardial infarction. *Resuscitation*. 2007;74: 227–234.
110. Batista LM, Lima FO, Januzzi JL Jr, et al. Feasibility and safety of combined percutaneous coronary intervention and therapeutic hypothermia following cardiac arrest. *Resuscitation*. 2010;81: 398–403.
111. Zobel C, Adler C, Kranz A, et al. Mild therapeutic hypothermia in cardiogenic shock syndrome. *Crit Care Med*. 2012;40:1715–1723.
112. Schmidt-Schweda S, Ohler A, Post H, et al. Moderate hypothermia for severe cardiogenic shock (COOL Shock Study I&II). *Resuscitation*. 2013;84:319–325.
113. Hovdenes J, Laake JH, Aaberge L, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest: experiences with patients treated with percutaneous coronary intervention and cardiogenic shock. *Acta Anaesthesiol Scand*. 2007; 51:137–142.
114. Annborn M, Bro-Jeppesen J, Nielsen N, et al. The association of targeted temperature management at 33 and 36 with outcome in patients with moderate shock on admission after out-of-hospital cardiac arrest: a post hoc analysis of the Target Temperature Management trial. *Intensive Care Med*. 2014;40:1210–1219.
115. Rittenberger JC, Kelly E, Jang D, et al. Successful outcome utilizing hypothermia after cardiac arrest in pregnancy: a case report. *Crit Care Med*. 2008;36:1354–1356.
116. Chauhan A, Musunuru H, Donnino M, et al. The use of therapeutic hypothermia after cardiac arrest in a pregnant patient. *Ann Emerg Med*. 2012; 60:786–789.
117. Oguayo KN, Oyetayo OO, Stewart D, et al. Successful use of therapeutic hypothermia in a pregnant patient. *Tex Heart Inst J*. 2015;42:367–371.
118. Wible EF, Kass JS, Lopez GA. A report of fetal demise during therapeutic hypothermia after cardiac arrest. *Neurocrit Care*. 2010;13:239–242.
119. Mahli A, Izdes S, Coskun D. Cardiac operations during pregnancy: review of factors influencing fetal outcome. *Ann Thorac Surg*. 2000;69:1622–1626.
120. Regitz-Zagrosek V, Lundqvist CB, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;32:3147–3197.
121. Pomini F, Mercogliano D, Cavalletti C, et al. Cardiopulmonary bypass in pregnancy. *Ann Thorac Surg*. 1996;61:259–268.
122. Chandrasekhar S, Cook CR, Collard CD. Cardiac surgery in the parturient. *Anesth Analg*. 2009;108: 777–785.
123. Jadhon ME, Main EK. Fetal bradycardia associated with maternal hypothermia. *Obstet Gynecol*. 1988;72:496.
124. Kilgannon JH, Jones AE, Shapiro NI, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA*. 2010;303:2165–2171.
125. Levinson G, Shnider SM, DeLorimier AA, et al. Effects of maternal hyperventilation on uterine blood flow and fetal oxygenation and acid-base status. *Anesthesiology*. 1974;40:340–347.
126. Krumholz A, Stern BJ, Weiss HD. Outcome from coma after cardiopulmonary resuscitation: relation to seizures and myoclonus. *Neurology*. 1988;38:401–405.
127. Mani R, Schmitt SE, Mazer M, et al. The frequency and timing of epileptiform activity on continuous electroencephalogram in comatose post-cardiac arrest syndrome patients treated with therapeutic hypothermia. *Resuscitation*. 2012;83:840–847.
128. Holmes GL. Seizure-induced neuronal injury. *Neurology*. 2002;59:S3–S6.
129. Legriel S, Azoulay E, Resche-Rigon M, et al. Functional outcome after convulsive status epilepticus. *Crit Care Med*. 2010;38:2295–2303.
130. Young GB. Neurologic prognosis after cardiac arrest. *N Engl J Med*. 2009;361:605–611.
131. Geocadin RG, Ritzl EK. Seizures and status epilepticus in post cardiac arrest syndrome: therapeutic opportunities to improve outcomes or basis to withhold life sustaining therapies? *Resuscitation*. 2012;83:791–792.
132. Rossetti AO, Oddo M, Logroscino G, et al. Prognostication after cardiac arrest and hypothermia. A prospective study. *Ann Neurol*. 2010;67:301–307.
133. Al Thenayan E, Savard M, Sharpe M, et al. Predictors of poor neurologic outcome after induced mild hypothermia following cardiac arrest. *Neurology*. 2008;71:1535–1537.
134. Sandroni C, Geocadin RG. Neurological prognostication after cardiac arrest. *Curr Opin Crit Care*. 2015; 21:209–214.
135. Sandroni C, Cariou A, Cavallaro F, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. *Resuscitation*. 2014;85: 1779–1789.

85

Electrical safety and injuries

Lester AH Critchley

Patients suffering from the consequences of electrocution and associated burns occasionally require intensive care unit (ICU) management. Patterns of presentation include post cardiopulmonary arrest, coma, blunt trauma and severe burns – either direct or indirect from electrical arcs, flashes or fires. An understanding of the physical concepts behind electrical power supplies and how electrocution occurs helps in determining the extent of these injuries.

Patients and staff in the ICU are at risk of electrocution from faulty electrical equipment. The necessity of direct patient contact with electrical equipment increases this risk, and when therapy involves an invasive contact close to the heart, microshock is an additional hazard. Thus, strict adherence to internationally accepted electrical safety standards is desirable. Faulty electrical equipment can also result in power failures, fires and explosions. The use of mobile phones and related devices near patient equipment can lead to malfunctioning.

PHYSICAL CONCEPTS

Electricity is produced by the movement of negatively charged electrons. A *potential difference* or voltage, measured in volts (V), exists between two points if the number or density of electrons is greater at one point. When these points are connected by a conductor, the potential difference will cause electrons or an *electric current* (*I*), measured in amperes (A), to flow. *Resistance* (*R*), measured in ohms (Ω), opposes this flow of electrons. Resistance is low in a conductor because electrons can move freely from atom to atom. However, resistance is high in an insulator, as electrons are unable to move freely. Voltage, current and resistance are related by Ohm's law:

$$V = I \times R \tag{85.1}$$

If an electric current flows through a resistance, it dissipates energy as heat. The heating effect per second, or *power*, is measured in joules (J)/s or watts (W):

$$\text{power} = V \times I = I^2 \times R \tag{85.2}$$

A current that flows in one direction, such as produced by a battery, is called a *direct current* (*DC*). Electricity to homes, hospitals and factories is supplied as an *alternating current* (*AC*), which flows back and forth at a *frequency* (i.e. cycles per second or hertz [Hz]). Voltage and frequency specifications vary worldwide. This may cause problems when electrical equipment designed to be used in one region is used elsewhere. Voltage specifications range from 100 V (i.e. Japan) to 240 V (i.e. Australia) with 220 V being most commonly supplied (i.e. Britain, most of Europe and Asia). The frequency most commonly supplied is 50 Hz. North America is a notable exception, where the specification is 110–120 V and 60 Hz.

For efficiency, electricity is distributed from the power station using ultra-high voltages. Main power grids carry greater than 1 million volts, which is stepped down by transformers to greater than 10,000 V to supply local powerlines, that are further stepped down to 120–220 V for domestic, commercial and factory use. Accidental contact with these high-voltage supply lines can be fatal if the current returns to ground with the person in its path. High-voltage currents can also flow via ionised air. This is known as electrical arcing and causes surface or flash burns. If an electrical fault occurs in domestic or hospital equipment, the flow of electricity can be re-routed to ground though a bystander who makes contact, resulting in electrocution.

A current flowing in a circuit produces electric and magnetic fields, which induce currents to flow in neighbouring circuits. When this results in a current flowing between the two circuits, it is called coupling. With *capacitive coupling*, high-frequency currents are most easily passed, and the size of the current is greatest when the circuits are in close proximity. *Inductive coupling* can result from the strong magnetic fields produced by heavy-duty electrical equipment such as transformers, electric motors and magnetic resonance imaging (MRI) machines. The most common problem associated with coupling is electrical interference or 'noise'. Monitoring equipment is designed to 'filter' out this noise. However, in certain circumstances,

ABSTRACT

Critical care admissions include victims of electrocution. Most cases (60%) occur in the work place and involve young men, but domestic electrocution (30%) is common. Patterns of injury include coma, blunt trauma from being thrown, and skin and deep tissue burns. Nerves and vascular supplies to limbs are particularly vulnerable. High voltage and lightning strike are a specific form of electrical injury with devastating effects on victims due to severity of burns and tissue damage. Knowledge of how these injuries occur facilitates treatment. Investigations are aimed at diagnosing extent of tissue and organ damage. Faulty medical equipment poses a risk of electrocution to patients and staff. Direct attachment to electrical devices increases the risk, including microshock. International safety codes exist such as IEC 60601. These codes define levels of risk within hospital or health care facilities and recommended levels of internal wiring, isolation and grounding. Regular equipment checks are recommended.

KEYWORDS

Electrocution
microshock
burns
pathophysiology
electrical injuries
lightning
high-tension
safety standards
equipment faults
grounding

such as the use of high-frequency surgical diathermy and magnetic resonance, sufficient amperage can be induced to cause microshock and burns.[1,2] Smaller electromagnetic fields emitted by hand-held devices, such as mobile phones, can affect the programming of microprocessors. Cases of patient equipment malfunctions have been reported.[3]

Static electricity has no free flow of electrons. Insulated objects can become highly charged, usually by repeated rubbing. The charge is dissipated by electrons jumping onto another neighbouring object of a different potential. 'Jumping' electrons ionise and heat the air through which they pass, causing a spark, which may ignite an inflammable liquid or gas. Lightning is a type of static electrical discharge. DCs of 12,000–200,000 A and voltages in the millions are involved; however, flow lasts for only a fraction of a second.[4]

ELECTROPHYSIOLOGICAL CONSIDERATIONS

For a current to flow through the body, the body must complete a circuit. Usually this involves the current flowing from its source to ground through the body, often hand to hand or hand to feet. The pathophysiological effects depend on the size and duration of the current, and this depends on the voltage and electrical resistance of the body. The main pathophysiological effects of current passing through the body are: (1) ventricular fibrillation or asystole, (2) sustained muscle contraction or tetany causing the 'cannot let go' phenomenon and asphyxiation, and (3) dissipation of electrical energy as heat, causing burns, often to deep-seated structures as well as skin. Muscle, blood vessels and nerves act as the main conduits for currents flowing through the body, and offer a very low resistance 500–1000 Ω.[5] Most of the resistance to passage of the current, and thus burning effect, occurs at the skin contact, which can vary enormously. Dry skin has a resistance in excess of 100,000 Ω.[5] However, skin resistance is markedly reduced (to 1000 Ω)[6] if the skin is wet, or if a conductive jelly has been applied. Hence, from Ohm's law, dry skin in contact with 240 V mains supply will result in a harmless 0.24 mA current flowing through the body, whereas moist or wet skin will result in a potentially lethal 240 mA current.

ELECTROCUTION

EPIDEMIOLOGY

Most cases of electrocution occur either in the workplace (about 60%) or at home (about 30%).[6] Most data on the incidence of electrocution come from North America, though significant regional differences exist worldwide.[7,8] Children under 6 years are most at risk from domestic electrocution, but with greater electrical safety awareness and the use of ground fault circuit interrupters (GFCIs), the oral burns once seen from chewing power cords are much less common.[9] Young adult men are the most likely victims of electrocution in the workplace. Powerlines and electrified railway tracks are the most common causes of high-voltage injuries.

CAUSES AND PATTERNS

There are a number of causes of electrocution and each has its own pattern of injuries:

1. *Low-voltage AC with or without loss of consciousness or arrest:* these injuries usually involve exposure to less than 1000 V in the home or office setting
2. *High-voltage AC with or without loss of consciousness or arrest:* these injuries can cause extensive thermal burns and usually are occupation related
3. *DC injury:* these injuries often involve trauma due to the victim being thrown due to violent muscle contraction
4. *Conducted electrical weapons (CEWs) such as Tasers used by the police:* CEWs deliver high-voltage currents, either AC or pulses of DC in the order of 50,000 V. Injuries are due mainly to trauma secondary to the Taser shock[10]
5. *Lightning strike:* this is discussed later.

PATHOPHYSIOLOGY

Pathophysiological processes involved in electrical injuries from an electrical engineer's perspective are well described in a short review article by Bernstein.[11] The extent of injury depends on: (1) the amount of current that passes through the body, (2) the duration of the current, and (3) the tissues traversed by the current (Table 85.1). The extent of injury is most

Table 85.1 Origin and pathophysiological effects of different levels of electrical injury

CURRENT (A)	SOURCE	EFFECTS ON VICTIM
10–100 μA	Earth leakage	Microshock (ventricular fibrillation)
300–400 μA	Faulty equipment	Tingling (harmless)
>1 mA	Faulty equipment	Pain (withdraw)
>10 mA	Faulty equipment	Tetany (cannot let go)
>100 mA	Faulty equipment	Macroshock (ventricular fibrillation)
>1 A	Faulty equipment	Burns and tissue damage
>1000 A	High-tension injury	Severe burns and loss of limbs
>12,000 A	Lightning	Coma, severe burns and loss of limbs

directly related to amperage. However, usually only the voltage involved is known. In general, lower voltages cause less injury, although voltages as low as 50 V have caused fatalities.

TISSUE HEAT INJURY

Currents in excess of 1 A generate sufficient heat energy to cause burns to the skin at entrance and grounding points and occult thermal injury to internal tissues and organs. Small blood vessels and nervous tissue appear to be particularly susceptible.[6]

DEPOLARISATION OF MUSCLE CELLS

An AC of 30–200 mA will cause ventricular fibrillation.[12] Domestic frequencies of 50–60 Hz are most dangerous, being three times more likely to stop the heart than direct or high-frequency current sources. Currents in excess of 5 A cause sustained cardiac asystole, which is the principle used in defibrillation. Apart from ventricular fibrillation, other arrhythmias may occur. Myocardial damage is common and may result in ST and T-wave changes. Global left ventricular dysfunction may occur hours or days later, despite initial minimal electrocardiogram (ECG) changes.[13,14] Myocardial infarction has also been reported.[15] Specific markers of myocardial injury, such as cardiac troponin, should be checked in all suspected cases of electrical injury to the heart.[16]

Tetanic contractions of skeletal muscle occur with currents in excess of 15–20 mA. The threshold is particularly low with ACs at the household frequency of 50–60 Hz. Tetanic contraction will prevent voluntary release of the source of electrocution, the 'cannot let go' phenomenon, and violent muscle contractions may cause fractures of long bones and spinal vertebrae.[6]

VASCULAR INJURIES

Blood vessels may become thrombosed and occluded as a result of the thermal injury. Small vessels are at greater risk, as the blood flow in larger vessels dissipates the heat. Compartment syndromes are seen secondary to tissue oedema, causing tissue ischaemia and necrosis. Affected limbs may require fasciotomy and amputation.[17]

NEUROLOGICAL INJURIES

Neurological injuries may be central or peripheral, and immediate or late in onset. Unconsciousness following electrocution may result from cardiorespiratory arrest, trauma to the head or the direct effect of current passing through the brain. This may be one of the main reasons for admission to the ICU. Monoparesis may occur in affected limbs, and the median nerve is particularly vulnerable.[6,18] Monoparesis may be due to the direct effect of electricity passing through the body or delayed effect due to scar formation. Electrocution to the head may result in unconsciousness, paralysis of the respiratory centre, and late complications such as epilepsy, encephalopathy and Parkinsonism.[6,18] Spinal cord damage resulting in para- or tetraplegia can result from a current traversing both arms and the spine.[6,18] Autonomic dysfunction may also occur, causing acute vasospasm or a late sympathetic dystrophy.[6]

RENAL FAILURE

Direct electrical injury to the kidneys is unusual. However, acute renal failure may result from the myoglobinuria and toxins produced by extensive muscle necrosis.[18]

EXTERNAL BURNS

Victims of high-voltage electrocution can incur extensive superficial or deep external burns from electrical arcs passing over the skin surface, especially from clothes catching fire and heated metal objects such as jewellery. Arc formation requires voltages in excess of 350 V and tracks over the body surface. They can generate extremely high temperatures of up to 5000°C that mainly causes skin burns.[11] Victims can also be burnt by the intense flash caused by the electrical discharge.

OTHER INJURIES

High-voltage and direct current electrocution can cause the victim to fall or be thrown, which may result in traumatic blunt injuries. Thus, it is important to get a reliable witness report of the incidence so that the nature of the patients' injuries is properly understood and nothing is missed, like a fractured cervical spine. All unconscious electrocuted patients should be initially treated with neck and spinal protection. High-voltage injuries can commonly rupture the eardrum and affect hearing.[19] Cataracts may later develop.[20]

MACRO- AND MICROSHOCK

The above domestic/workplace electrocution is known as *macroshock*, and occurs when current flows through the intact skin and body.

In the ICU and other high-level patient care areas, the potential for *microshock* electrocution also exists. Microshock occurs when there is a direct current path to the heart muscle that bypasses the protective electrical resistance of the skin surface. Such a pathway may be provided by saline-filled arterial or venous-pressure-monitoring catheters or transvenous pacemaker wires. The current required to produce ventricular fibrillation in microshock settings is extremely small, in the order of 60 μA.[17] Currents of 1–2 mA are barely

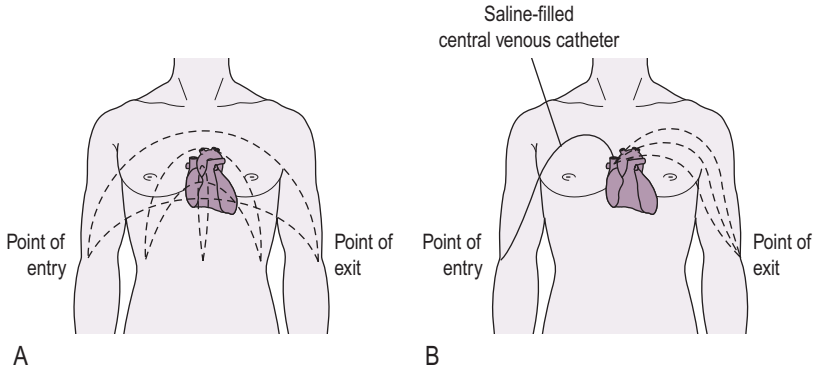


Figure 85.1 Microshock: (a) low current density at the heart; (b) high current density at the heart if there is a conducting pathway, such as a saline-filled catheter.

perceptible and produce tingling of the skin (see Table 85.1). Hence, a lethal microshock may be transmitted to a patient via a staff member who is unaware of the conducted current. Microshock can result from direct contact with faulty electrical equipment, or stray currents from capacitive coupling, or earth leakage. Such small currents are potentially lethal because a high current density is produced at the heart (Fig. 85.1). Patients at risk of microshock require higher levels of electrical safety protection.

HIGH-TENSION AND LIGHTNING STRIKE INJURIES

High-tension electricity (>1000 V) involves voltage much greater than domestic supply, usually many thousands of volts. Sources include powerlines, electrified railway tracks and equipment requiring high internal voltages produced by step-up transformers, although less common today as most high voltage television screens now use liquid crystal technology. Tissue damage is mainly due to the generation of heat, as high-amperage currents are involved. Not only does the current pass through the victim, but electrical arcing may also be involved. Witnesses have described tissues actually exploding.[20]

Lightning injury is a type of high-tension injury. Its incidence depends upon geographical location. Generation of lightning is surprisingly complex and involves a number of steps. The victim of a lightning strike may be hit directly, injured by the side-flash from a nearby object, or electrocuted by ground currents which reroute through the victim's legs.[11]

Victims can be thrown several feet as a result of violent muscular contractions. Electrical arcing of the air causes intense heat, resulting in superficial burns and the clothes igniting. Characteristic entrance and exit site burns are seen, which have a spider-like appearance with redness and blistering. Victims are usually unconscious in the initial phase. However, many victims survive (80%–90%),[4] and good recovery has been reported despite initial hopeless neurological responsiveness (e.g. fixed dilated pupils).[22] Immediate death usually results from cardiorespiratory arrest; asystole is more common than ventricular fibrillation.[4]

MANAGEMENT OF ELECTRICAL INJURIES

Treatment of electrical injuries is mainly supportive. It includes the following.

FIRST AID AND RESUSCITATION

It is imperative to make the immediate environment safe for rescuers. Power sources should be switched off and wet areas avoided where possible. Instinctive attempts to grab the electrocuted victim must be avoided until it is safe to do so. Cardiopulmonary resuscitation is carried out when indicated, and continued even if the prognosis seems hopeless. The neck and spine should be protected because of possible fractures.

INVESTIGATIONS

Investigations are indicated to detect damaged organs. They include ECG, echocardiography, computed tomography (CT) of the head, X-rays of the spine and long bones, haemoglobin, serum electrolytes, cardiac troponin, creatinine kinase and urine myoglobin to assess muscle damage, and nerve conduction studies. Arteriograms may help in the decision to amputate a limb.[17]

HOSPITAL AND INTENSIVE CARE UNIT MANAGEMENT

Management is directed towards treatment of burns, ischaemic and necrotic tissue, and injured organs. The principle of treating electrical burns is complete excision because of the risks of acute renal failure and

sepsis. Fasciotomies and amputations may be necessary. Tetanus toxoid and antibiotics, especially penicillin, are given if indicated.

ELECTRICAL HAZARDS IN THE INTENSIVE CARE UNIT

The ICU has the potential to inflict both macroshock and microshock injuries to staff and patients. Potential sources of these electrical hazards are:

MAJOR ELECTRICAL FAULTS

The casing and insulated wiring of electrical equipment protect against electric shock. Faulty wiring or components, and deterioration of internal insulation, can result in the casing becoming 'live'. Contact with live casing or wires can result in an electric current flowing through the victim to ground. The outcome largely depends on the resistance offered by the body to the current. If it is low, such as in a wet environment, sufficient current can flow to cause death, which is usually due to ventricular fibrillation/asystole or asphyxia from tetanic contraction of respiratory muscles.

MICROSHOCK CURRENTS

EARTH LEAKAGE CURRENTS

Within all pieces of electrical equipment, stray low-amperage electrical currents exist that usually flow to earth, called earth leakage currents. They originate from current leaks across imperfect insulation of wires, capacitive and inductive coupling within the equipment, and coupling from electric and magnetic fields that exist in the working environment, such as the 50–60 Hz mains supply. Normally these currents are small and harmless, but they have the potential to cause microshock.

PACING WIRES AND CENTRAL VENOUS LINES

In certain circumstances, sufficient current to cause microshock can be passed by capacitive and inductive coupling to intracardiac pacing wires and central venous lines. Ventricular fibrillation has been reported from capacitive coupling with thermistor wires in a pulmonary artery catheter.[1]

DIFFERENT EARTH POTENTIALS

Inadequate or faulty earthing can result in separate earthing points being at different resting potentials. If contact is made between the two earthing points, sufficient current can flow to cause microshock.

STAFF–PATIENT CONTACT

Small currents capable of causing microshock can be transmitted unknowingly to a patient by a staff member who simultaneously touches faulty electrical equipment and the patient. If this current returns to earth via an intracardiac connection, a high current density will pass through the heart, resulting in microshock.

INDUCTIVE CURRENTS

Inductive coupling from the strong magnetic fields produced by MRI can cause overheating of wires and equipment. Severe burns have resulted from the use of pulse oximetry during MRI, and specially designed wiring and probes are recommended.[2] Similar problems can exist with any intravascular device containing wires, such as a pulmonary artery catheter. More recently, problems have arisen from the interference caused by personal computers, mobile phones and related devices with patient equipment. Many hospitals have banned the use of such devices in areas where patients are treated.

OTHER RELATED HAZARDS

Electrical equipment has the potential to cause other hazards such as thermal injury, fire and power failures. Preliminary critical incident reports suggest that power failures are the most commonly encountered incidents involving electricity in the ICU. Power failures can be disastrous, as many patients' lives depend on electrically driven 'life support' equipment. One notable emerging hazard is software malfunction, as many newer devices operate using programmable microprocessors. As the intensivist frequently works outside the ICU, they should also be aware of potential electrical hazards outside the ICU.

MEASURES TO PROTECT STAFF AND PATIENTS

EARTHING, FUSES AND CIRCUIT BREAKERS

Earthing reduces the risk of macroshock. The casing in most electrical equipment is connected to ground by a very-low-resistance wire called the earth, which uses the third pin of the electrical socket. If a fault arises, the earth wire offers a low-resistance path to ground. The high-amperage current that results will blow the main fuse or circuit breaker, thus providing protection and warning that a fault is present. However, fuses and circuit breakers do not guarantee patient protection from macroshock and other more sensitive protection strategies are required in patient care locations (see below). Additional protection can be achieved by connecting all the earthing points in a patient care area together by a very-low-resistance wire. This reduces the risk of microshock occurring from earthing points at different potentials, and is commonly used in cardiac protected areas.

ISOLATED POWER SYSTEMS

MAINS ISOLATION

The power supply is isolated from earth using a mains isolation transformer. If contact is made with live faulty circuitry, the risk of electric shock is reduced because stray currents no longer preferentially flow through patient or staff member to earth. Presence of stray earth leakage currents can be detected by using a line isolation monitor. This type of system is particularly useful in wet locations where the body may offer a very low resistance to earth.

INTERNAL ISOLATION

In medical equipment the mains power supply is usually isolated from the patient connection by using internal transformers and photoelectric diodes. The casing is still earthed to protect against faulty circuitry. This method of protection is commonly used in ICU equipment, including most monitoring and patient information systems. Electrical power isolation may limit the use of networks that link patient monitors to printers and information technology systems.

GROUND FAULT CIRCUIT INTERRUPTERS

GFCIs are devices that switch off the electrical supply if small currents are detected flowing to earth. GFCIs are designed to protect against electrocution from faulty electrical equipment. They are commonly incorporated into electrical sockets and require activation. When contact is made with the faulty equipment, an increased current will flow to earth, which trips the system. GFCIs also protect against microshock. A major concern with using GFCIs in critical patient management areas, however, is that power supply to essential life-supporting equipment such as heart–lung machines can be permanently switched off by small-leakage currents.[23,24]

ELECTRICAL SAFETY STANDARDS

Most First-World nations have standards of electrical safety that apply to both the design of medical equipment and their use in health care locations. A number of well-recognised standards exist that can be easily found and uploaded from the Internet. Europe and Great Britain follow the International Electrotechnical Commission Code (IEC) 60601, first published in 1997 and regularly updated, most recently in 2011. The United States follows the National Electric Code, which has a section on Health Care Locations and was most recently updated in 2011. However, since 2013 the Food and Drug Administration (FDA) in the US has used IEC 60601 for approval of new medical equipment. IEC 60601-1 is widely accepted as the benchmark for medical equipment and has become the de facto requirement for medical equipment worldwide. Australia and New Zealand follow similar standards (AS/NZS 3003:2011 and AS/NZS 3200:2010). Hospitals worldwide should establish their own committees to ensure that these standards are applied.

Patient care areas differ in their safety requirements and commonly used classifications are listed below. The ICU should conform to 1(b) and preferably 1(c), as follows:

1. **a.** Unprotected areas, where only routine electrical safety standards are applied
   b. Body-protected areas, where the level of electrical safety is sufficient to minimise the risk of macroshock when the patient is in direct contact with electrical equipment and the skin impedance is reduced or bypassed
   c. Cardiac-protected areas, where the level of electrical safety is sufficient to minimise the risk of direct microshock to the heart
2. Wet locations, where spillage of water and physiological solutions, such as saline and blood, frequently occurs; the US Department of Defense until recently defined wet areas as those used for cystoscopy, arthroscopy and labour/delivery[25]
3. In the past, standards existed for the safe use of inflammable anaesthetic agents.

Currently, the United States only requires GFCIs in wet areas that do not include ICUs and most operating theatres. Other countries, such as Australia, New Zealand and Great Britain, require isolated power systems (IPSs) in operating rooms and ICUs. If cost is not an issue, ideally both internal isolation and GFCIs should be used in 1(a) and 1(b) and wet locations. More stringent controls to protect against microshock are required in 1(c) cardiac-protected locations.

Codes relating to software that run medical devices have recently been introduced. Requirements to make medical equipment more environmentally friendly and provision of safer electrical installations in health care facilities outside the hospital are also being introduced. IEC 60601 now contains over 60 separate codes relating to different medical uses.

EQUIPMENT CHECKS

The purchase of new equipment should be strictly controlled, and circuit diagrams should be provided. All new equipment should be checked that it adheres to the appropriate electrical safety standards, functions properly and for current leaks before it is used in the ICU or other high-risk patient areas. Preventative maintenance of equipment should be done regularly. Dated stickers should be used to show when the equipment was last checked. All faulty equipment must be removed from service, labelled appropriately and recommissioned only after thorough checking.

RESERVE POWER SUPPLIES AND ALARMS

All essential equipment should have a reserve power supply (usually a battery), and alarms that warn of power failure. All hospitals should provide an emergency backup power supply in case of power cuts. Protocol should be in place, or developed, to ensure continuation of ventilation, sedation and other essential life-sustaining therapies in case of complete electrical power failure, or the need to evacuate patients because of fire.

PERSONNEL EDUCATION

Staff should be taught correct ways to handle electrical equipment. Equipment with frayed wires should never be used, plugs should never be tugged, trolleys should never be wheeled over power cords, and two pieces of equipment should never be handled simultaneously. Staff should also respond appropriately to alarms. The increasing use of patient monitoring and information technology systems means that an increasing number of electrical devices are being used at any one time at the patient's bedside, with increasing need for power cords and sockets. Care should be taken when using multiple socket power cables to ensure that their use does not violate electrical safety standards.

KEY REFERENCES

4. Apfelberg DB, Masters FW, Robinson DW. Pathophysiology and treatment of lightning injuries. *J Trauma*. 1974;14:453–460.
5. Bruner JMR. Hazards of electrical apparatus. *Anesthesiology*. 1967;28:396–425.
11. Bernstein T. Electrical injury: electrical engineer's perspective and an historical review. *Ann N Y Acad Sci*. 1994;720:1–10.
18. Solem L, Fischer RP, Strate RG. The natural history of electrical injury. *J Trauma*. 1977;17:487–492.
23. Litt L, Ehrenwerth J. Electrical safety in the operating room: important old wine, disguised new bottles. *Anesth Analg*. 1994;78:417–419.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. McNulty SE, Cooper M, Staudt S. Transmitted radiofrequency current through a flow directed pulmonary artery catheter. *Anesth Analg*. 1994;78: 587–589.
2. Peden CJ, Menon DK, Hall AS, et al. Magnetic resonance for the anaesthetist. Part II. Anaesthesia and monitoring in MR units. *Anaesthesia*. 1992;47: 508–517.
3. Hayes DL, Carrillo RG, Findlay GK, et al. State of the science: pacemaker and defibrillator interference from wireless communication devices. *Pacing Clin Electrophysiol*. 1996;19:1419–1430.
4. Apfelberg DB, Masters FW, Robinson DW. Pathophysiology and treatment of lightning injuries. *J Trauma*. 1974;14:453–460.
5. Bruner JMR. Hazards of electrical apparatus. *Anesthesiology*. 1967;28:396–425.
6. Fontneau NM, Mitchell A. Miscellaneous neurologic problems in the intensive care unit. In: Irwin RS, Cerra FB, Rippe JM, eds. *Intensive Care Medicine*. 4th ed. Philadelphia, PA: Lippincott-Raven; 1999:2127–2135.
7. Spies C, Trohman RG. Narrative review: electrocution and life-threatening electrical injuries. *Ann Intern Med*. 2006;145:531–537.
8. Aghakhani K, Heidari M, Tabatabaee SM, et al. Effect of current pathway on mortality and morbidity in electrical burn patients. *Burns*. 2015;41:172–176.
9. Vorhies JM. Electrical burns of the oral commissure. *Angle Orthod*. 1987;57:2–17.
10. Cushing TA, Wright RK. *Electrical injuries in emergency medicine: treatment and management*. Available Online: http://emedicine.medscape.com/article/770179-overview.
11. Bernstein T. Electrical injury: electrical engineer's perspective and an historical review. *Ann N Y Acad Sci*. 1994;720:1–10.
12. Loughman J, Watson AB. Electrical safety in hospitals and proposed standards. *Med J Aust*. 1971;2:349–355.
13. Lewin RF, Arditti A, Sclarovsky S. Non-invasive evaluation of cardiac injury. *Br Heart J*. 1983;49: 190–192.
14. Jensen PJ, Thomsem PEB, Bagger JP, et al. Electrical injury causing ventricular arrhythmias. *Br Heart J*. 1987;57:279–283.
15. Walton AS, Harper RW, Coggins GL. Myocardial infarction after electrocution. *Med J Aust*. 1988;148:365–367.
16. Karras DJ, Kane DL. Serum markers in the emergency department diagnosis of acute myocardial infarction. *Emerg Med Clin North Am*. 2001;19:321–337.
17. Hunt JL, McManus WF, Haney WP, et al. Vascular lesions in acute electric injuries. *J Trauma*. 1974;14: 461–473.
18. Solem L, Fischer RP, Strate RG. The natural history of electrical injury. *J Trauma*. 1977;17:487–492.
19. Ogren FP, Edmunds AL. Neuro-otologic findings in the lightning-injured patient. *Semin Neurol*. 1995;15:256–262.
20. Watson AB, Wright JS, Loughman J. Electrical thresholds for ventricular fibrillation in man. *Med J Aust*. 1973;1:1179–1182.
21. Burke JF, Quinby WC, Bondoc C, et al. Patterns of high tension electric injury in children and adolescents and their management. *Am J Surg*. 1977;133:492–497.
22. Hanson GC, McIlwaith GR. Lightning injury: two case histories and a review of management. *Br Med J*. 1973;4:271–274.
23. Litt L, Ehrenwerth J. Electrical safety in the operating room: important old wine, disguised new bottles. *Anesth Analg*. 1994;78:417–419.
24. Ehrenwerth J. *Electrical Safety in and Around the Operating Room. ASA Refresher Course in Anesthesia*. Philadelphia, PA: JB Lippincott; 1994:123.
25. Wills JH, Ehrenwerth J, Rogers D. Electrical injury to a nurse due to conductive fluid in an operating room designated as a dry location. *Anesth Analg*. 2010;110:1647–1649.

86

Envenomation

James Tibballs

INTRODUCTION

Envenomations by snakes, spiders, bees, ants, wasps, ticks, jellyfish, octopuses or cone shell snails may threaten life, while envenomation by other creatures may cause serious illness.[1-5] Although this chapter focuses on the management of envenomation in Australia, the principles of management are widely applicable in other countries. Immediate advice on the management of envenomation by Australian creatures may be obtained from the National Poisons Centre (Tel: 131126) but decision making rests with the treating physician.

SNAKES

EPIDEMIOLOGY

Australia is habitat to a large number of venomous terrestrial and marine snakes (Families Elapidae and Hydrophiidae). The genera responsible for the majority of serious illness are brown snakes (*Pseudonaja*), tiger snakes (*Notechis*), taipans (*Oxyuranus*), black snakes (*Pseudechis*) death adders (*Acanthophis*), rough-scaled snake (*Tropidechis carinatus*) and Stephen's banded snake (*Hoplocephalus stephensi*).[1] Most recent deaths have been due to brown snakes and tiger snake envenomation.[6]

The death rate after snakebite is not reliably known, but it appears considerably less in Australia than elsewhere despite the fact that the majority of Australia's snakes are among the most venomous in the world. Approximately 3000 snakebites occur annually in Australia. The mean snake bite death rate in Australia over the last decade was 2.3/annum (Australian Bureau of Statistics).[7] Deaths (1/1000 bites) usually occur because of massive envenomation, snake bite in remote locations, rapid cardiovascular collapse out-of-hospital, or delayed or inadequate antivenom therapy. Approximately 500 victims per annum require antivenom treatment. This morbidity and mortality is a very small contribution to the annual world burden estimated by the World Health Organization at 5 million bites with 2.5 million envenomations, at least 100,000 deaths (1 death/50 bites) and three times that number of limb amputations or severe disability (http://www.who.int/mediacentre/factsheets/fs337/en/).

Death and critical illness from Australian snakebite is due to (1) progressive paralysis leading to respiratory failure, (2) haemorrhage, (3) renal failure, (4) sudden cardiovascular collapse (especially with brown snake bites), or (5) combinations. Renal failure occurs as a consequence of rhabdomyolysis and procoagulant coagulopathy causing microangiopathic haemolytic anaemia (MAHA), hypotension, hypoxaemia and to their combinations.

Snake bite is often 'accidental' when a snake is trodden on or suddenly disturbed. However, many bites occur when humans deliberately interfere with snakes or handle them. At special risk are herpetologists and snake collectors who sustain bites in the course of their work or hobby, but who also develop allergy to venoms and to the antivenoms used in their treatment.[8] Contact with exotic snakes has additional problems of sourcing antivenom and expertise in management.

SNAKE VENOMS

Venoms are complex mixtures of protein toxins that kill the snake's prey and aid its digestion. Many toxins are phospholipases.[1] The main toxins cause paralysis, coagulopathy, rhabdomyolysis and renal failure (Box 86.1).

Paralysis is due to presynaptic and postsynaptic neurotoxins. Presynaptic neurotoxins are phospholipases A_2, which destroy the motor neuron terminal and also cause rhabdomyolysis. Examples are taipoxin in coastal taipan (*Oxyuranus scutellatus*) venom, notexin in mainland tiger snake (*Notechis scutatus*) venom and textilotoxin in common brown snake (*Pseudonaja textilis*) venom.[1] The effect of these toxins, once established, is not responsive to antivenom treatment. Postsynaptic neurotoxins (and presynaptic neurotoxins) are found in venoms of death adders.

Coagulopathy is due either to the procoagulant effect of prothrombin activators (factor Xa-like enzymes) with consumption of clotting factors, or to direct anticoagulants. Coagulopathies expose the victim to the risk of spontaneous haemorrhage.

ABSTRACT

Life-supporting treatment may be required after envenomation by numerous species of Australian snakes including brown, tiger, taipan, death adder and black snakes, which cause paralysis, coagulopathies, rhabdomyolysis and renal failure. Several species of spiders (funnel-web spiders, red-back spiders), several jellyfish (box-jellyfish, Irukandji) and stings of hymenoptera (bees, wasps, ants) also cause life-threatening illness. Blue-ringed octopuses, ticks, cone shells, other jellyfish and stinging fish cause serious illness. Fortunately, Australia has available high-quality antivenoms for most envenomations (all snakes, funnel-web spiders, red-back spiders, box-jellyfish, stone-fish), which, when administered early, can neutralise venom toxins and halt progress of the effects of envenomation but cannot reverse established tissue damage for which time and supportive therapy are required. The antivenom dose for an envenomated snakebite victim is two vials but less or more may be required along with low-dose subcutaneous adrenaline to prevent acute allergic reaction. The treatment of hymenoptera stings is that of anaphylaxis.

KEYWORDS

Envenomation
envenoming
toxin
snake
spider
jellyfish
antivenom
bee
wasp
ant

Box 86.1 Main components of Australian snake venoms

- Neurotoxins
  - Presynaptic and postsynaptic neuromuscular blockers present in all venoms. Cause paralysis
  - Postsynaptic blockers readily reversed by antivenom
  - Presynaptic blockers are more difficult to reverse, particularly if treatment is delayed
  - Some presynaptic blockers are also rhabdomyolysins
- Prothrombin activators
  - Present in brown, tiger, taipan, rough-scaled and Stephen's banded snake venoms
  - Cause procoagulation coagulopathy with possible microangiopathic haemolytic anaemia and acute cardiovascular collapse
  - Intrinsic fibrin(ogen) lysis generates fibrin(ogen) degradation products
  - Significant risk of haemorrhage
- Anticoagulants
  - Present in black snake venoms
  - Prevent blood clotting without consumption of clotting factors
- Rhabdomyolysins
  - Some presynaptic neurotoxins also cause lysis of skeletal and cardiac muscle
  - Apart from loss muscle of mass, may cause myoglobinuria and renal failure

Prothrombin activators are serine proteases which are identifiable in venoms of brown, tiger, taipan, rough-scaled and Stephen's banded snake.[1] With the consumption of platelets and the generation of fibrin(ogen) degradation products by endogenous fibrinolysis, these observations resemble the coagulopathic findings in disseminated intravascular coagulation (DIC) but the phenomenon has also been known as 'defibrination coagulopathy' and 'venom-induced consumption coagulopathy' in which coagulation factors are consumed, serum fibrinogen is depleted and platelets are reduced.

Procoagulant coagulopathy cannot be resolved until venom prothrombin activators have been neutralised with antivenom. However, after circulating venom has been neutralised by antivenom, it may be 4–6 hours or longer before hepatic manufacture of replacement clotting factors can normalise coagulation tests. Procoagulant coagulopathy causes two clinical effects attributable to thromboembolism:

a. MAHA. This is not infrequent and has been observed after brown, taipan, tiger and Stephen's banded snake envenomation.[6,9,10] On blood film, red blood cells are observed as fragmented and haemolysed, and platelets are reduced. Histologically, especially in kidney, capillaries are blocked with fibrin, which damages transiting red blood cells. Renal failure may occur, and support with haemofiltration/dialysis may be needed. The observations resemble those in haemolytic uraemia or thrombotic thrombocytopenic purpura, which are due to deficiency in or antibodies to ADAMST13 (**a** **d**isintegrin **a**nd **m**etalloproteinase with a **th**rombo**s**pondin type 1 motif, member 13) also known as von Willebrand factor (vWf)-cleaving protease, a metalloprotease enzyme that cleaves vWf, a multimeric protein involved in blood coagulation. The absence of breakdown of vWf causes deposition of fibrin and platelets in small blood vessels, especially in the brain and kidney. Plasmapheresis is often undertaken in these conditions to remove the antibody to ADAMST13 and to provide ADAMST13. Activity of ADAMST13 was not reduced in a case of MAHA after a presumed tiger snake bite,[10] but the place of plasmapheresis remains undefined.[9] Haemofiltration/dialysis alone would probably suffice for renal support.

b. Acute cardiovascular collapse. This phenomenon probably explains deaths occurring out-of-hospital, especially after brown snake envenomation.[6,9] The mechanism is probably myocardial ischaemia and/or pulmonary hypertension culminating in transient systemic hypotension, as caused experimentally by brown and tiger snake venoms and their prothrombin activators.[1,11] Indeed, experimentally, thrombus formation within the heart is readily detectible by echocardiography, and embolism to the vasculature system is evident histologically soon after envenomation of dogs with tiger snake prothrombin activator and preventable with heparin.[11] In rats, rapid cardiovascular collapse due to prothrombin activator or release of vasoactive substances by brown snake venom likewise is preventable with antivenom or heparin.[12] Prothrombin activators in venoms gain access to the circulation within minutes after subcutaneous injection. Tachycardia and relatively minor electrocardiogram abnormalities are common. Other causes of hypotension, such as direct cardiac toxicity, are possible.

Anticoagulant coagulopathy occurs after envenomation by black snakes and is amenable to treatment with antivenom.[1]

SNAKE BITE AND ENVENOMATION

Although a bite may be observed, envenomation may not occur because no venom or a small amount of venom is injected; this occurs in about 50% of bites. Bites by Australian snakes may be painful or painless and be unnoticed. This is in marked contrast to bites of many overseas crotalid and viperid snakes, where massive local reaction and necrosis are caused by proteolytic enzymes. In general, Australian snake venoms do not cause extensive damage to local tissues and are usually confined to mild swelling and bruising, and continued slight bleeding from the bite site.

After an Australian snake bite, paired fang marks are often visible but sometimes only scratches or single puncture wounds exist with or without local bruising.

SYMPTOMS AND SIGNS OF ENVENOMATION

Classical symptoms and signs are given in Box 86.2. Sometimes, not all possible symptoms and signs occur. In some cases one symptom or sign may dominate the clinical picture, and in other cases they may wax and wane. These phenomena may be explained by variations in the toxin content of venoms of the same species in different geographical areas, and by variable absorption of different toxins.

Tender or even painful regional lymph nodes are moderately common but are not, *per se*, an indication for antivenom therapy. Lymphadenitis also occurs with bites by mildly venomous snakes that do not cause serious systemic illness.

Occasionally, major or intracranial haemorrhage occurs. In the case of untreated or massive envenomation, rhabdomyolysis may occur. This usually involves all skeletal musculature and sometimes cardiac muscle. The resultant myoglobinuria may cause renal failure.

A high intake of alcohol by adults before snake bite is common, and may confound the cluster of symptoms and signs. Pre-existing treatment with anticoagulant (e.g. warfarin) or disease (e.g. gastrointestinal tract ulceration) may complicate the management of coagulopathy.

Box 86.2 Progressive onset of major systemic symptoms and signs of untreated envenomation

Less than 1 hour after bite
- Headache
- Nausea, vomiting, abdominal pain
- Transient hypotension associated with confusion or loss of consciousness
- Coagulopathy (laboratory testing)
- Regional lymphadenitis

1–3 hours after bite
- Paresis/paralysis of cranial nerves (e.g. ptosis, double vision, external ophthalmoplegia, dysphonia, dysphagia, myopathic facies)
- Haemorrhage from mucosal surfaces and needle punctures
- Tachycardia, hypotension
- Tachypnoea, shallow tidal volume

Greater than 3 hours after bite
- Paresis/paralysis of truncal and limb muscles
- Paresis/paralysis of respiratory muscles (respiratory failure)
- Peripheral circulatory failure (shock), hypoxaemia, cyanosis
- Rhabdomyolysis
- Dark urine (due to myoglobinuria or haemoglobin)
- Renal failure

Note: In massive envenomation or in a child, a critical illness may develop in minutes rather than hours.

SNAKE BITE IN CHILDREN

Snake bite in young children presents additional problems. Envenomation is difficult to diagnose when a bite has not been observed or history is unobtainable. The symptoms of early envenomation may pass unsuspected and the signs, particularly cranial nerve effects, are difficult to elicit. Bite marks may be difficult to distinguish from the effects of everyday minor trauma. Lastly, the onset of the syndrome of envenomation is likely to be more rapid and severe because of the relatively higher ratio of venom to body mass. Presentation may be cardiorespiratory failure. The dose of antivenom is the same as for adults.

IDENTIFICATION OF THE SNAKE

Identification of the snake is helpful but not essential since a venom detection kit (VDK) test is available for snakes of Australia and Papua New Guinea, which guides antivenom selection. If the snake cannot be identified, specific monovalent antivenom, or a combination of monovalent antivenoms or polyvalent antivenom should be administered on a geographical basis (Table 86.1). Nevertheless, identification guides selection of the appropriate antivenom, and provides an insight into the expected syndrome. Administration of the wrong antivenom may endanger a victim's life because a specific monovalent antivenom does not neutralise venoms of other genera. For example, brown snake antivenom does not neutralise venoms of taipans or tiger snakes. On the other hand, tiger snake antivenom neutralises venoms of some black snakes, copperhead snakes, rough-scaled snakes, Stephen's banded snakes and venoms of many lesser venomous species.

Table 86.1 Antivenom and initial dosages when identity of snake uncertain

STATE	ANTIVENOM	UNIT DOSE (VIALS)
Tasmania	Tiger snake	6000 (2)
Victoria	Tiger snake *and* Brown snake	6000 (2) 2000 (2)
New South Wales and Australian Capital Territory; Queensland; South Australia; Western Australia; Northern Territory	Polyvalent	40,000 (2)
Papua New Guinea	Polyvalent	40,000 (2)

Note: (1) If the victim on presentation is critically ill, two to three times these amounts should be given initially. (2) Additional antivenom may be required in the course of management since the absorption of venom toxins may be delayed.

Identification by venom detection kit test

The VDK (Seqirus Australia) is an in vitro test for detection and identification of snake venom at the bite site, in urine, blood or other tissue in cases of snake bite in Australia (and Papua New Guinea). It can be performed at the bedside or in the laboratory. It is an enzyme immunoassay using rabbit antibodies and chromogen and peroxide solutions. A positive result will indicate the type of antivenom to be administered. It detects venom from a range of snake genera including tiger, brown, black, death adder and taipan. Individual species of snake cannot be identified by the test and several genera may yield a positive result in a specified well. The test is very sensitive; it is able to detect venom in concentrations as low as 10 ng/mL, and can yield a visual qualitative result in test wells in approximately 25 minutes. The incidences of false-positive and false-negative tests of the kit are low but not negligible. On occasions, venom may be detected but the patient is asymptomatic and has no signs of envenomation. A decision to administer antivenom should be made only on clinical grounds. A very high concentration of venom in a sample may overwhelm the test and yield a spuriously negative result (Hook effect). If that possibility exists, a diluted sample should be retested.

Identification by physical characteristics

This can be misleading. Not all brown-coloured snakes are brown snakes, not all black-coloured snakes are black snakes and not all banded snakes are tiger snakes. Moreover, brown snakes may have bands and tiger snakes may lack characteristic bands. Non-herpetologists should consult an identification guide with reference to scale patterns to identify a specimen correctly if antivenom therapy is to be based on morphological characteristics alone.

Identification by clinical effects

The appearance of a bite site cannot be used to reliably identify a snake. Likewise, the constellation of symptoms and signs is useful but to a limited degree. For example, paralysis associated with procoagulopathy may be caused by a tiger, taipan, brown, rough-scaled snake, copperhead or Stephen's banded snake, but if rhabdomyolysis also occurs a bite by a brown snake is improbable. Early in the syndrome when procoagulant coagulopathy may be the only clinical effect, it is impossible to distinguish between taipan, brown and tiger snake envenomation. Paralysis associated with anticoagulation may be caused by a black snake or death adder, but if rhabdomyolysis occurs a bite by a death adder is improbable. Paralysis with neither coagulopathy nor rhabdomyolysis may be caused by a death adder bite.

This information is obviously of limited practical importance. It is essential to administer antivenom at the first opportunity when indicated, rather than wait until the full syndrome becomes apparent, to enable an 'educated clinical guess' in selection of the appropriate antivenom by which time the situation may not be amenable to treatment.

MANAGEMENT OF SNAKE ENVENOMATION

The essential management is:

- resuscitation – mechanical ventilation and restoration of blood pressure with intravenous fluids, inotropic and vasoactive agents as needed. Basic cardiopulmonary resuscitation at the scene may be lifesaving.[6]
- application of a pressure-immobilisation first-aid bandage
- administration of antivenom
- performance of investigations.

From a practical point of view, one of three clinical situations usually arises after snake bite. A plan of management for each of these is summarised in Fig. 86.1:

- victim presents with a critical illness
- victim is envenomated but not critically ill
- victim is bitten but clinically does not appear envenomated.

When the envenomated victim is not critically ill, time is available to identify the snake and to administer the specific monovalent antivenom. A pressure-immobilisation bandage should be applied if not already in place, and not removed until antivenom has been administered.

When the victim has been bitten but not apparently envenomated, admission to hospital is advisable with observation, examination and laboratory testing for at least 12 hours.[13] The syndrome of envenomation, particularly neurotoxic signs, may be very slow in onset over numerous hours with an initial period free of symptoms. A test of coagulation should always be performed. If a coagulopathy is present, specific monovalent antivenom should be administered after identification of the species or as indicated by a VDK test. If only a mild coagulopathy is present it may be acceptable to withhold antivenom in the anticipation of spontaneous resolution, but coagulation should be checked at intervals and the victim maintained under surveillance until coagulation is normal.

THE PRESSURE-IMMOBILISATION TECHNIQUE OF FIRST AID

Since at least 95% of snake bites occur on the arms or legs, Sutherland's first-aid pressure-immobilisation technique[14] is applicable in the majority of cases. With this technique, a crêpe (or crêpe-like) bandage, but preferably elasticised, is applied from the fingers or toes up the limb as far as possible, encompassing the bite site. It should be as firm as required for a sprained ankle. Additional immobilisation is applied to the

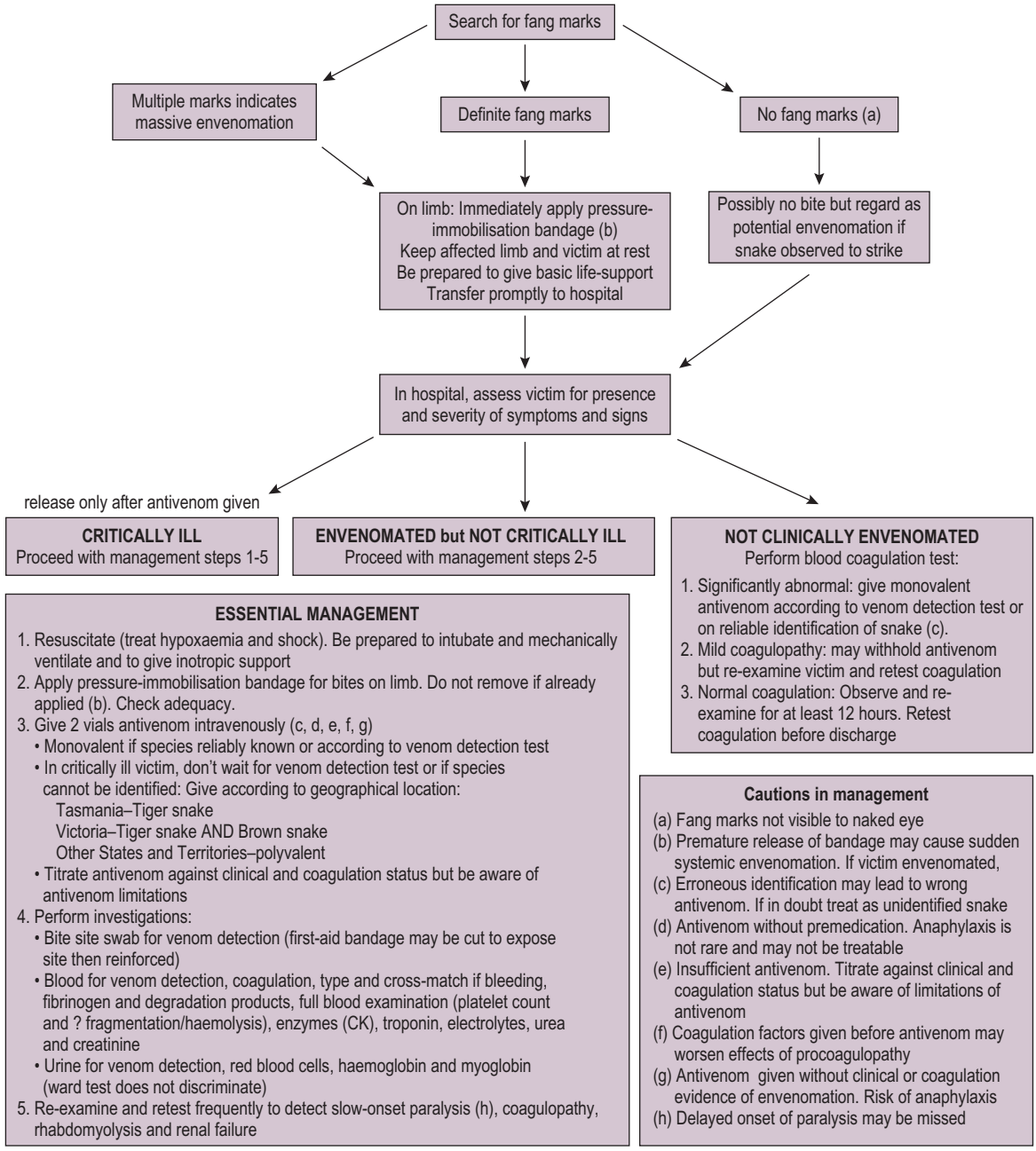


Figure 86.1 Management of snake bite.

entire limb by a rigid splint, with the aim of immobilising joints on either side of the bite site.

Venom is usually deposited subcutaneously. The systemic spread of venom is largely dependent on its absorption by way of the lymphatics[15] or the small blood vessels. Application of a pressure less than arterial to the bitten area when combined with immobilisation of the limb effectively delays the movement of venom to the central circulation. Although it is a first-aid technique designed for use in the field, it should be part of initial management in hospital since it halts further absorption of venom.

Removal of the pressure-immobilisation bandage

Removal in the case of envenomation may precipitate a sudden elevation in blood concentration of venom and collapse of the victim. On the other hand, first aid has not been proven to inactivate venom in humans.

Its removal therefore should be dictated by the circumstance. When an asymptomatic snake-bite victim reaches hospital with the recommended first-aid measures in place, these should not be disturbed until antivenom, appropriate staff and equipment have been assembled. If the victim is symptomatic and antivenom is indicated, the first-aid measures should not be removed until after antivenom has been administered, and reapplied if the victim's condition deteriorates. A swab of the bite site may be obtained by removing the splint temporarily and then cutting a window in the bandage. Thereafter the bandage should be made good and the splint reapplied.

ANTIVENOM

BioCSL Pty Ltd (Parkville, Australia) produces highly purified equine monovalent antivenoms, F(ab')2 fragments of immunoglobulin (Ig)G, against the venoms of the five main terrestrial snakes, including tiger snake, brown snake, black snake, death adder and taipan. A polyvalent antivenom – a mixture of all monovalent antivenoms – is also available. A sea-snake antivenom is also produced from horses immunised with beaked sea snake (*Enhydrina schistosa/Hydrophis zwefeli)* and tiger snake venom.

Antivenom should be administered according to the identity of the snake or if unknown or doubtful, according to the result of a VDK test (Table 86.2). If neither of these criteria can be fulfilled, and if the situation warrants immediate antivenom therapy, the geographical location may be used as a guide since the distribution of many species is known (see Table 86.1). Polyvalent antivenom should not be used when a monovalent antivenom could be used appropriately. For bites by uncommon snakes, when antivenom is indicated, polyvalent antivenom or a monovalent antivenom as indicated by a VDK test should be chosen.

Antivenoms have limitations. Not all toxins in venoms generate antibodies in the immunisation process. Antivenom batches may have different potencies and are manufactured against specific species with less neutralising ability against different species of the same genus or against unrelated species, even when the antivenom chosen is nevertheless appropriate.

Table 86.2 Antivenom and initial dosages when snake identified

SNAKE	ANTIVENOM	UNITS DOSE (VIALS)
Brown snakes	Brown snake	2000 (2)
Chappell Island tiger snake	Tiger snake	12,000 (4)
Copperheads	Tiger snake	3000–6000 (1,2)
Death adders	Death adder	6000 (1)
Mulga (king brown) snake	Black snake	18,000 (1)
Papuan black snake	Black snake	18,000 (1)
Red-bellied black snake	Tiger snake *or* Black snake*	3000 (1) 18,000 (1)
Rough-scaled (Clarence River) snake	Tiger snake	6000 (2)
Sea-snakes	Sea-snake *or* Tiger snake	1000 (1) 3000 (1)
Small-scaled (fierce) snake	Taipan	12,000 (1)
Taipans	Taipan	12,000–36,000 (1–3)
Tasmanian tiger snake	Tiger snake	6000 (2)
Tiger snake	Tiger snake	6000 (2)

*Smaller protein mass tiger snake antivenom preferable. Note: (1) If the victim on presentation is critically ill, two to three times these amounts should be given initially. (2) Additional antivenom may be required in the course of management since the absorption of venom toxins may be delayed.

Dose

In general, the initial dose for envenomation is two vials of an appropriate monovalent antivenom or polyvalent according to whether the identity of the snake is known (see Table 86.2), or unknown (see Table 86.1). Less antivenom may be sufficient for minor envenomation but clinicians should aim to administer two vials at the outset of treatment of envenomation and to administer more antivenom if clinically indicated.

Clinicians should bear in mind the limitations of antivenom treatment: organs and tissues already damaged by venom cannot have function restored by antivenom. Antivenom neutralises accessible toxins and prevents further damage, but time and supportive care are required, for example for nerve terminals and muscle to regenerate after destruction by presynaptic neurotoxins. After bites by species with procoagulant coagulopathic effects, the victim's coagulation status is a useful but not definitive guide to whether more antivenom is required. In the absence of a rapid measurement of exogenous venom procoagulant in blood and of coagulation factors, it is difficult to determine whether continued procoagulant coagulopathy after antivenom administration is due to un-neutralised venom or to the possibility that coagulation factors have not been remanufactured – a process that requires at least 6 hours in the absence of venom.

The neutralisation dose for a particular case is uncertain for numerous reasons. Above all is the fact that the neutralisation dose in humans is unknown. One vial of specific antivenom neutralises in vitro the average yield on 'milking'– a process whereby venom

is harvested by inducing the snake to bite through a latex membrane. Antivenom is tested and doses determined to prevent death in small animals, but the neutralising dose in vivo in humans cannot be extrapolated accurately from such data.

The dose of antivenom required in a particular case is uncertain because the amount of venom injected cannot be determined. Snakes may inject a variable amount of venom.[1] If the amount of venom injected at a bite is greater than the average yield on milking, one vial of antivenom will not be adequate therapy. Moreover, snakes may bite multiple times and absorption of toxins from the bite site is probably a continual process, implying that serial administration of antivenom may be required.

Determination of the neutralisation dose is also confounded by a lack of knowledge of which toxins and to what degree they are neutralised by antivenom antibodies. Moreover, the pharmacokinetics of tissue-bound toxins, penetration of antivenom to tissues and the effect of antivenom on bound toxins in tissues are simply unknown. Victims may present late after envenomation when toxins have already become bound to target tissues and cannot be easily neutralised. Some victims in this circumstance have required mechanical ventilation for many weeks despite large amounts of appropriate antivenom.

The question of neutralising dosing is a controversial issue and excessive doses may have been administered in the past. Arguably, the neutralisation dose should be regarded as the maximum dose beyond which no further improvement is gained with antivenom therapy, but that is very difficult to derive theoretically and in practice in an individual case.

On the basis that a median dose of one vial of antivenom clears the blood of circulating procoagulant toxins, the authors of the Australian Snakebite Study (ASP) of 715 envenomated victims (from 2005 to 2015), proposed that one vial of the relevant antivenom is a sufficient dose for all victims,[6,16] implying that no additional antivenom is indicated. However, the proposition has a number of limitations, including the lack of effect of antivenom on the effects of venom and the use of the median dose derived from all degrees of envenomation. The proposition is also difficult to reconcile with clinical improvement in victims given larger doses, and it is difficult to draw conclusions from the observational evidence of the ASP study, which, although of high quality, is very low or low on any scale of scientific evidence.

According to the ASP study, although less antivenom was used in 2014/2015 compared with 2005 with no differences in mortality, the upper quartile ranges of antivenom doses used in 2014/2015 do not equate to the median dose recommended. In 2014/2015, the upper quartile dose for envenomation by brown snakes was approximately 1.5 vials; for tiger snakes 2.0 vials; and for taipans 1.5 vials (together comprising 61% of envenomations). Only in bites by death adders, mulga snakes and red-bellied black snakes (comprising 23% of envenomations) did the upper quartile range equate to the median dose.

The manufacturers of the antivenoms (bioCSL Pty Ltd)[17] do not support the dosing of one vial and recommend higher doses based on the consensus opinion of an expert committee.

As a general rule, two vials of antivenom would probably suffice, but less or more may be indicated according to the snake involved and the effects on the victim. Undertreatment may be fatal while overtreatment with many vials while unduly expensive is probably not harmful and is attributable to a lack of understanding of the incapability of antivenom to restore established organ dysfunction, and lack of knowledge of the time required for hepatic manufacture of consumed coagulation factors. The consideration of dosing does not relate to adverse reactions, which invariably occur with the first dose of antivenom, nor does it relate to serum sickness, which occurs whatever the dose.[18]

In desperate circumstances of life-threatening envenomation where the patient is seemingly unresponsive to antivenom, it is difficult to differentiate organ dysfunction (which could be reversed) with antivenom and dysfunction (which cannot be reversed), leading to overtreatment.

Administration

The decision to administer antivenom must be based on clinical criteria of envenomation, and not restricted to the result of a VDK test. A positive VDK test of a biological sample confirms a diagnosis of envenomation and the choice of antivenom, but does not imply that antivenom should or should not be given. The VDK test has a false-positive rate and may lead to antivenom being administered to a non-envenomated victim.[6]

If the victim is significantly envenomated, antivenom must be administered as there is no other effective treatment. However, antivenom may be withheld if envenomation is so mild that spontaneous recovery may occur or the consequences of antivenom administration are likely to outweigh the benefit to be gained (e.g. in a herpetologist with minor effects and known to have an allergy to antivenom).

Snake antivenoms must be given by the intravenous route, or in dire circumstances if a vein cannot be cannulated then by the intraosseous route. The large volume of fluid and slow absorption render the intramuscular route useless in emergencies.

A test dose of antivenom to determine allergy should not be done. It is unreliable and a waste of precious time.

Premedication

Antivenom should be preceded by premedication with low-dose subcutaneous epinephrine

(adrenaline), approximately 0.25 mg for an adult and 0.005–0.01 mg/kg for a child, at least 5–10 minutes before commencement of the infusion. In the moribund or critically ill victim, when it is essential to administer antivenom quickly, the epinephrine may be given intramuscularly or even intravenously in smaller doses. However, in general, epinephrine is not recommended by either of those routes because of the risk of intracerebral haemorrhage due to the combination of possible epinephrine-induced hypertension and venom-induced coagulopathy. Although intracerebral haemorrhage has been recorded in the past in association with premedication, all such cases occurred after intravenous epinephrine, and none with subcutaneous epinephrine, which does not cause significant changes in heart rate or blood pressure.[19]

The incidence of all immediate-type reactions and anaphylaxis is about 25% and 10%, respectively,[20] and occasional death after antivenom[21] are sufficient to warrant premedication with epinephrine, which is the only medication proven effective in reducing the incidence of antivenom-induced reactions and their severity.[22,23]

It is not prudent or reasonable to forgo premedication merely on the assumption that if anaphylaxis occurs it will be treatable. Iatrogenic anaphylaxis has a high mortality despite vigorous and expert resuscitation.[24] If an adverse reaction to the first vial of antivenom has not occurred, subsequent vials do not need to be preceded by epinephrine. The reaction rate to polyvalent antivenom is higher than to monovalent antivenoms; they should not be used when a monovalent antivenom or combinations will suffice.

The antihistamine promethazine is ineffective in this setting[25] and indeed contraindicated because it may cause obtundation and hypotension, both of which may exacerbate and confound a state of envenomation. Other drugs, such as steroids and aminophylline, are also not useful in preventing anaphylaxis because their actions, apart from being unproven, are too slow in onset, but steroids are useful for preventing serum sickness.

Infusion

The antivenom may be injected slowly into a running intravenous line or diluted in Hartmann's or other crystalloid solution in approximately 1 in 10 volumes in a burette and administered over 15–30 minutes if the situation is not critical. This method may reduce the risk of an anaphylactoid reaction resulting from its binding with complement. For small children, if multiple vials are required, the dilution may be less to prevent excessive fluid administration. In emergencies the antivenom may be infused quickly in high concentration.

Adverse reactions

Antivenom infusion should be administered in a location equipped and staffed by personnel capable of managing anaphylaxis, which is discussed in detail in Chapter 67. Intramuscular epinephrine is the key treatment in a dose of approximately 0.25–1.00 mg for adults and 10 μg/kg for children. Antivenom therapy should be discontinued temporarily and restarted when the victim's condition is stable.

Lesser degrees of immediate adverse reaction restricted to headache, chest discomfort, fine rash, arthralgia, myalgia, nausea, abdominal pain, vomiting and pyrexia may be managed by temporary cessation of infusion, and the administration of steroids and antihistamine before recommencement.

A delayed hypersensitivity reaction, serum sickness, should be anticipated and patients warned of the symptoms and signs, which usually appear several days to 2 weeks after antivenom administration. Severity may range from a faint rash and pyrexia to serious multisystem disease, including lymphadenitis, polyarthralgia, urticaria, nephritis, neuropathy and vasculitis. The incidence of serum sickness (about 30%) is not dependent on the dose of antivenom administered.[18] Therefore it is reasonable to administer prophylactic treatment, a course of steroids (e.g. prednisolone 1 mg/kg per day for 5 days), to every patient treated with antivenom.

INVESTIGATIONS AND MONITORING

Tests should be performed regularly, interpreted quickly and treated promptly to counter venom effects and its complications. Serial coagulation tests and tests of renal function are especially important. Absorption of venom from the bite site is a continuing process that should be anticipated. Apart from regular monitoring of vital signs and oxygenation, the following are specifically needed:

Bite site

A swab for venom testing should be done. It has the highest likelihood of detecting venom provided the site has not been washed. The bite site may be squeezed to yield venom if it has been washed. A positive result identifies venom but does not prove envenomation.

Urine

Test the urine for venom that may be present when venom in blood has been bound by antivenom and is therefore undetectable. Urine should also be tested for blood and protein. If the urine is pigmented, a distinction should be made between haemoglobinuria and myoglobinuria, which is impossible with simple ward tests. Urine output should be recorded.

Blood

- Coagulation tests should include prothrombin time, activated thromboplastin time, serum fibrinogen and fibrin degradation products.
- A full-blood examination and blood film for haemoglobin level, evidence of haemolysis and

platelet count. A mild elevation in white cell count is expected.
- Electrolytes, urea, creatinine and creatine phosphokinase (isoenzymes and troponin are useful) to monitor rhabdomyolysis and possible renal compromise.

Electrocardiogram

Sinus tachycardia, ventricular ectopy and ST segment and T-wave changes are not uncommon. These effects may be the direct result of venom toxins or from electrolyte disturbances caused by rhabdomyolysis or renal failure.

SECONDARY MANAGEMENT

Coagulation factor and blood transfusion

Although coagulopathy often resolves after several doses of antivenom it does not restore coagulation *per se*; it permits newly manufactured coagulation factors to act unopposed by venom. This is not a failure of antivenom therapy. If haemorrhage is occurring, or if coagulation is not restored after several doses of antivenom over several hours, it is prudent to administer fresh frozen plasma (FFP) and to remeasure coagulation at intervals. FFP 6 hours after antivenom restores the clotting function in most victims.[26] Because regeneration of coagulation factors takes many hours, treatment of isolated coagulopathy entirely with antivenom while waiting for their regeneration exposes the patient to serious haemorrhage. Administration of coagulation factors, such as in the form of FFP, should be preceded by antivenom to neutralise venom prothrombin activator as otherwise consumption coagulopathy may worsen. Platelets and red cell infusion may be required.

Intravenous fluids, rhabdomyolysis and renal protection

After acute resuscitation, administer intravenous fluids in sufficient volume to maintain urine output at about 40 mL/kg per day in an adult and 1–2 mL/kg per hour in a child to prevent tubular necrosis as a consequence of rhabdomyolysis. Life-threatening hyperkalaemia and hypocalcaemia may develop with rhabdomyolysis. Renal failure may also be secondary to MAHA. Haemofiltration or dialysis may be required.

Heparin

Although this anticoagulant has prevented the action of prothrombin activators in animal models of envenomation, it does not improve established consumption coagulopathy. It is not recommended. Instead, the emphasis should be on treating the cause by neutralising venom with antivenom.

Analgesia and sedation

Australian snake bite does not usually cause severe pain but analgesia may be required. However, sedation is required for the mechanically ventilated venom-paralysed victim and analgesia for rhabdomyolysis.

Care of the bite site

Usually no specific care is required. Occasionally the site may blister, bruise, ulcerate or necrose, particularly when a first-aid bandage has been in place for a considerable time or when the bite was by a member of the black snake genus, such as a mulga snake or red-bellied black snake.

Other drugs

Antibiotics are not routinely required but should be considered as for any potentially contaminated wound. Sea-snake bites may cause Gram-negative infections. Tetanus prophylaxis should be reviewed.

SEA-SNAKE BITE

Some sea-snake venoms cause widespread damage to skeletal muscle with consequent myoglobinuria, neuromuscular paralysis or direct renal damage. Many have not been researched. The principles of treatment are essentially the same as for envenomation by terrestrial snakes. The venoms of significant species are neutralised with CSL Ltd beaked sea-snake (*H. zwefeli*, formerly *E. schistosa*) antivenom. If that preparation is not available, tiger snake or polyvalent antivenom should be used. Sea-snake bites are uncommon in Australia and no deaths have been recorded.

UNCOMMON AND EXOTIC SNAKE BITE

Zoo personnel, herpetologists and amateur collectors who catch, maintain or breed species of uncommon Australian snakes or who import or breed exotic (overseas) snakes are at risk, as are personnel in the Australian Quarantine and Inspection Service (AQIS) who encounter exotic species. Specific antivenoms to the venoms of uncommon Australian snakes do not exist, but neutralisation is provided by polyvalent antivenom or by monovalent antivenom, as indicated by the VDK.

Exotic snake antivenoms are maintained by some institutions including Royal Melbourne Hospital (Tel: +61 3 9342 7000), Royal Adelaide Hospital (Tel: +61 8 8222 4000), Ballarat Hospital (Tel: +61 3 5320 4316), Venom Supplies Ltd, Tanunda, South Australia (Tel: +61 8 8563 0001), Australian Reptile Park (Tel: +61 2 4340 1022) and Taronga Zoo (Mosman, Tel: +61 2 9978 4757).

LONG-TERM EFFECTS OF SNAKE BITE

After appropriate timely treatment, recovery is expected but it may be slow, taking many weeks or months, particularly from a critical illness or after delayed presentation involving neurotoxicity,

rhabdomyolysis or renal failure. Isolated neurological or ophthalmic signs may persist. Long-term loss of smell or taste occurs occasionally, especially after bites by black snakes. The psychological effects of snakebite, including depression and post-traumatic stress disorder, may necessitate expert assistance.

SPIDERS

Although several thousand species of spiders exist in Australia, only funnel-web spiders (genera *Atrax, Hadronyche*) and the red-back spider (*Latrodectus hasselti*) have caused death or significant systemic illness. Mouse spiders may also cause significant illness. All spiders have venom but of the numerous other species of spiders in Australia, the bites of relatively few have caused pain and inflammatory signs at the bite site and minor (non-life-threatening) systemic effects. These include members of the families Araneidae (orb-weavers), Clubionidae (sac spiders), Corinnidae (darting spiders), Desidae (lace web spiders, including *Badumna insignis*, black house spider), Lamponidae (white-tail spiders), Lycosidae (wolf spiders), Salticidae (jumping spiders), Sparassidae (huntsman spiders), Zodariidae (spotted or ant spiders) and other Mygalomorphae (trapdoor, mouse and tarantula spiders).[2] Causes for ulcerated skin lesions other than a spider bite should be sought.

FUNNEL-WEB SPIDERS

At least 35 species of the funnel-web genera *Atrax, Hadronyche* and *Illawarra,* inhabit Queensland, New South Wales, Victoria, Tasmania and South Australia,[27] but only species from New South Wales and southern Queensland have caused significant illness and death. Funnel-web spiders are large, dark-coloured and aggressive. A systematic review involving 138 cases identified 77 cases of severe envenomation with 13 deaths, but none occurred after the introduction of antivenom in 1981, and the vast majority (97%) responded to antivenom therapy.[28] All deaths were attributed to the Sydney funnel-web spider (*Atrax robustus*), which inhabits an area within an approximate 160 km radius of Sydney. It may enter houses and seek shelter among clothes or bedding, giving a painful bite when encountered.

Apart from *A. robustus* (Sydney funnel-web), life-threatening illness has been caused by bites from *Hadronyche cerberea* (southern tree funnel-web), *Hadronyche formidabilis* (northern tree funnel-web), *Hadronyche infensa* (Darling Downs funnel-web), *Hadronyche macquariensis* (Port Macquarie funnel-web) and *Hadronyche versuta* (Blue Mountains funnel-web). In contrast to other spiders, male funnel-web spiders have more potent venom than female spiders, but all funnel-web envenomations, irrespective of species and gender, may be treated with funnel-web antivenom.

Bites do not always result in envenomation, but envenomation may be rapidly fatal. The early features of the envenomation syndrome include nausea, vomiting, profuse sweating, salivation and abdominal pain. Life-threatening features are usually heralded by the appearance of muscle fasciculation at the bite site, which quickly involves distant muscle groups. Hypertension, tachyarrhythmias, vasoconstriction, hypersalivation and bronchorrhoea occur. The victim may lapse into coma, develop central hypoventilation and have difficulty maintaining an airway free of secretions. Finally, respiratory failure, pulmonary oedema and severe hypotension culminate in death. The syndrome may develop within several hours but it may be more rapid. Several children have died within 90 minutes of envenomation, and one died within 15 minutes.

The venoms of funnel-web spiders contain hundreds of protein toxins.[2] A family of δ-hexatoxins, comprised of 42–44 residue-peptides with four disulphide bonds creating an inhibitor cystine knot motif, bind to neurotoxin receptor site 3 and exert their effect by slowing inactivation of vertebrate and insect tetrodotoxin-sensitive sodium channels. This action results in massive release of neurotransmitters including acetylcholine at neuromuscular junctions and within the autonomic nervous system and of catecholamines, which may induce acute cardiac failure (Takotsubo cardiomyopathy). The venoms also contain numerous toxins that attack other ion channels in insects but not in humans.

Treatment of envenomation consists of the application of a pressure-immobilisation bandage, intravenous administration of antivenom and support of vital functions, which may include airway support, mechanical ventilation and intensive cardiovascular support, and possibly extracorporeal membrane oxygenation. The antivenom is purified IgG antibody derived from immunisation of rabbits with male *A. robustus* venom, but which is effective against other funnel-web spiders. The appropriate dosing to treat envenomation is not certain but the minimum initial dose of intravenous antivenom for a mild case is 2 ampoules; repeated in 15 minutes if there is no clinical improvement. The dose should be doubled for severe envenomation and thereafter antivenom given according to the clinical status of the victim, but it is uncommon to require more than 6 ampoules of antivenom. In 75 victims requiring antivenom, the median dose administered was 3 ampoules but the range was 1–17.[28] Urgent administration of antivenom is required if any of the following signs are present:

- Muscle fasciculation in the limb involved or remote from the bite, usually first seen in tongue or lips with systemic spread of venom
- Marked salivation or lachrymation
- Piloerection
- Significant tachycardia

- Hypertension in a previously normotensive patient (late in the syndrome the victim may become hypotensive)
- Hypoxaemia, hypoventilation, dyspnoea, pulmonary oedema
- Disorientation, confusion or a depressed level of consciousness.

The venom of Australian mouse spiders (Genus *Missulena*) contains a toxin homologous to the δ-hexatoxins in funnel-web spider venom, and envenomation may be treated if necessary with funnel-web antivenom.[2]

RED-BACK SPIDER

This spider, *L. hasselti*, is distributed throughout Australia and is found outdoors in household gardens in suburban and rural areas. Related species and similar effects of envenomation ('latrodectism') occur in many parts of the world. Red-back spider bite is the most common cause for antivenom administration in Australia. The adult female is identified easily. Its body is about 1 cm in size and has a distinct red or orange dorsal stripe over its abdomen. When disturbed, it gives a pinprick-like bite. However, in contrast to a bite from a snake or funnel-web spider, a bite from a red-back spider is not immediately life threatening, but it may cause severe systemic illness. The bite site becomes inflamed and, during the following minutes to several hours, severe pain exacerbated by movement commences locally and may extend up the limb or radiate elsewhere. The pain may be accompanied by profuse sweating, headache, nausea, vomiting, abdominal pain, fever, hypertension, paranaesthesia and rashes. In a small percentage of cases when treatment is delayed, progressive muscle paralysis may occur over many hours, requiring mechanical ventilation. If untreated, muscle weakness, spasm and arthralgia may persist for months after the bite. No deaths from a red-back spider bite alone have occurred since the availability of antivenom.

The venoms of *Latrodectus* spiders contain numerous toxins; the principle one that affects vertebrates is a protein named α-latrotoxin, which has a molecular mass of approximately 130 kDa. That of *L. hasselti*, α-LTX-Lh1a, comprises 1180 amino acid residues with high homology to others in the genus.[29] As a tetramer or dimer it inserts into the membranes of the nerve endings of neurons, permitting the entry of calcium and the mobilisation of internal calcium stores, which leads to exocytosis of synaptic vesicles and the subsequent release of transmitters.[30] The result of the action of the toxin is the development of a patchy paralysis at the neuromuscular junction and the widespread release of catecholamines.

If the effects of a bite are trivial and confined to the bite site, antivenom may be withheld and analgesia given as required; otherwise, antivenom should be given intramuscularly or intravenously. The antivenom may be given intravenously in cases of refractory pain, but the risk of anaphylaxis may be higher than by the intramuscular route, which is very low (<0.5%). No premedication is recommended but epinephrine should be at hand to treat a severe acute allergic reaction. Several doses of antivenom, several hours apart, may be needed. There is no proven effective first aid, but the application of a cold pack or iced water may help to relieve pain. Bites by *Steatoda* spp. (cupboard spiders) may cause a similar syndrome and can be treated effectively with red-back spider antivenom.[31]

AUSTRALIAN BOX JELLYFISH

The Australian multitentacled box jellyfish, *Chironex fleckeri*, is probably the most venomous creature in the world. It has caused more than 70 deaths in the waters off northern Australia. It has a cuboid bell up to 30 cm in diameter. Numerous tentacles arise from the corners of the bell and trail several metres. It is semitransparent and difficult to see by anyone wading or swimming in shallow water where stings usually occur. The tentacles are lined with millions of nematocysts that, on contact with skin, discharge a threaded barb that pierces subcutaneous tissue, including small blood vessels allowing rapid envenomation. Contact with the tentacles causes severe pain and envenomation, from which death may occur within minutes. Death is probably due to both neurotoxic effects causing apnoea and direct cardiotoxicity, although the precise mode of action of the venom is uncertain. In mechanically ventilated animals, fatal hypotension and cardiac failure occurs rapidly on envenomation, which is probably due to cytolytic poration of cardiac cell membranes, but it is also accompanied by haemolytic hyperkalaemia.[3] The skin that sustains the injury may heal with disfiguring scars and like all jellyfish envenomations it may be subject to recurrent rash of immunogenic origin.[3]

The structures of two of the probable numerous toxins of *C. fleckeri* venom have been determined.[32-36] The *C. fleckeri* toxins CfTX-1 and CfTX-2 cause rapid cardiovascular collapse in rats and have strong haemolytic activity. They have masses 43 and 45 kDa and 436 and 445 amino acid sequences, respectively, and are antigenic to CSL box jellyfish antivenom. They have significant homology with other known protein toxins from other cubozoan and non-cubozoan jellyfish. Additional proteins with pore-forming effects in *C. fleckeri* venom, CfTX-A and CfTX-B, approximately 40 kDa and 42 kDa, respectively, have strong haemolytic activity but minor cardiovascular effects.

First aid is important in the management, which must be administered on the beach, and consists of dousing the skin with acetic acid (vinegar), which inactivates undischarged nematocysts. Adherent tentacles can then be removed. Basic cardiopulmonary

resuscitation may be required on the beach and continued en route to hospital where extracorporeal life support could be considered. Although an ovine antivenom is available and effective in vitro,[3] its effectiveness is doubtful in established critical illness when toxins have already damaged tissues. Several vials should be given in minor illness and up to six vials in critical illness. The prevention of stings is of paramount importance: water must not be entered when this jellyfish is known to be close inshore. Wet suits, clothing and 'stinger suits' offer protection.

Other chirodropid jellyfish, for example, *Chiropsella bronzei* (previously *Chiropsalmus quadrigatus*) may cause a similar but less severe illness and should be treated as for *C. fleckeri* envenomation.[3]

IRUKANDJI SYNDROME

Stings by the carybdeid jellyfish *Carukia barnesi* (Barnes' jellyfish), and by numerous other carybdeid jellyfish may cause a clinical syndrome known as 'Irukandji syndrome'.[37] *C. barnesi* is a small translucent cubozoan jellyfish with a squarish bell a little more than 1 cm in diameter. Single tentacles trail from its four corners. When submerged it is almost invisible.

The sting of *C. barnesi* is mild and marked only by a small area of cutaneous erythema. However, severe general illness may follow with abdominal cramps, hypertension, back pain, nausea and vomiting, limb cramps, chest tightness and marked distress. A sting may result in acute cardiac failure, resembling Takotsubo cardiomyopathy and necessitating mechanical ventilation and inotropic support. The severe syndrome is consistent with endogenous release of catecholamines[38] by toxins acting on sodium channels, and by cytolytic toxins causing pore-formation of cardiac cell membranes. Two deaths attributed to stings were the result of systemic hypertension causing cerebral haemorrhage.

Management of the syndrome includes relief from pain, which is the most important feature in mild to moderate cases. In a case series of 10 victims with Irukandji syndrome, intravenous magnesium salts provided pain relief and a reduction in blood pressure,[39] but these observations were not supported by a randomised trial, which showed that magnesium salts did not influence the required amount of analgesia.[40] Antihypertensive therapy with phentolamine or a 'titratable' nitrate may be required in the initial phase of management but if acute cardiac failure develops, an inotropic agent is required.

Although initially recognised in Australia and typified by the sting of *C. barnesi*, it is being increasingly recognised in victims of stings by similar jellyfish in other oceanic regions. Some protein toxins of *C. barnesi* and a related carybdeid, *Malo kingi*, have molecular mass of 43–46 kDa and have some homologies with cytolytic pore-forming toxins of Chirodropids *C. quadrigatus* and *C. fleckeri* and homologies with ion channel neurotoxins of sea anemones.[4]

AUSTRALIAN PARALYSIS TICK

This tick (*Ixodes holocyclus*) injects a toxin that causes flaccid paralysis after some 3–5 days of feeding on humans. The onset of illness resembles that of Guillain–Barré syndrome. Prompt, careful and entire removal of tick(s) is necessary, followed by a period of observation to ensure that late-onset paralysis does not occur. No antitoxin is available and mechanical ventilation may be required for several days until spontaneous recovery.

BEES, WASPS AND ANTS

Anaphylactic reactions to bee, wasp and ant stings cause approximately the same number of deaths in Australia each year as do snake bites. In the 14-year period from 2000 to 2013, ant, bee and wasp stings caused 17,000 admissions at an annual average of 1200.[7] The 32 arthropod deaths in this period (2–3/annum, 0.11/million population per year) were all due to hymenoptera stings by bees (25), ants (5) and wasps (2). The venoms of these arthropods contain numerous allergenic toxins.[5] The common European honey bee (*Apis mellifera*) is largely responsible. Jumper and bull ants (*Myrmecia* spp.) may also cause anaphylaxis. Refer to Chapter 67 for treatment. Persons who develop reactions to bites should undergo immunotherapy and always carry two doses of injectable epinephrine.[5]

BLUE-RINGED OCTOPUSES

Several species of *Hapalochlaena* inhabit the Australian coastline. When handled, these octopuses bite and inject tetrodotoxin, which is a neurotoxin found in many different species of marine animals. It causes rapid onset of flaccid paralysis. Approximately a dozen deaths have been recorded. The required treatment is mechanical ventilation until spontaneous recovery occurs.

STINGING FISH

Numerous marine and fresh-water fish carry venom in glands attached to stinging spines. The most dangerous is the stonefish (*Synanceia* spp.). When this fish is trodden on, venom is injected. The immediate effect is extreme pain. Several deaths have been recorded, which are presumably due to the known depressive effects of the toxins on cardiovascular and neuromuscular function, and myotoxicity. An antivenom (bioCSL Pty Ltd) is available. Local or regional nerve

blockade may be required for pain relief. Other stinging fish, such as the fresh-water bullrout (*Notesthes robusta*) also cause excruciating pain when their spines are contacted. Immersion of the affected limb in warm-to-hot water provides pain relief.

VENOMOUS CONE SHELLS

Many gastropod molluscs fire a venom-laden harpoon to almost instantaneously immobilise and kill prey. The numerous conotoxins, which are short proteins, stimulate or block neuronal and neuromuscular receptors, causing rapid death. A handful of human deaths have been recorded when shells have been carelessly or unwittingly handled. There is no antivenom. Mechanical ventilation would be required until spontaneous recovery occurs.

KEY REFERENCES

1. Tibballs J. Australian snakebite and treatment. In: Gopalakrishnakone P, Faiz SMA, Gnanathasan CA, et al, eds. *Clinical Toxinology*. Netherlands: Springer; 2018. Available at: https://doi.org/10.1007/978-94-007-6288-6_79-1.
6. Johnston CI, Ryan NM, Page CB, et al. The Australian Snakebite Project, 2005–2015 (ASP-20). *Med J Aust*. 2017;207:119–125.
11. Tibballs J. The cardiovascular, coagulation and haematological effects of tiger snake (*Notechis scutatus*) prothrombin activator and investigation of vasoactive substances. *Anaesth Intensive Care*. 1998;26:536–547.
13. Ireland G, Brown SG, Buckley NA, et al. Changes in serial laboratory test results in snakebite patients: when can we safely exclude envenoming? *Med J Aust*. 2010;193:285–290.
14. Sutherland SK, Coulter AR, Harris RD. Rationalization of first-aid measures for elapid snakebite. *Lancet*. 1979;1:183–186.
16. Isbister GK, Brown SG, Page CB, et al. Snakebite in Australia: a practical approach to diagnosis and treatment. *Med J Aust*. 2013;199:763–768.
17. White J. *A clinician's guide to Australian venomous bites and stings. bioCSL Pty Ltd (Australia)*. 2013.
22. Premawardhena AP, de Silva CE, Fonseka M, et al. Low dose subcutaneous adrenaline to prevent acute adverse reactions to antivenom serum in people bitten by snakes: randomised, placebo controlled trial. *BMJ*. 1999;318:1041–1043.
27. Gray MR. A revision of the Australian funnel-web spiders (Hexathelidae: Atracinae). *Rec Aust Mus*. 2010;62:285–392. doi:10.3853/j.0067-1975.62.2010.1556.
37. Gershwin LA, Richardson AJ, Winkel KD, et al. Biology and ecology of Irukandji jellyfish (Cnidaria: Cubozoa). *Adv Mar Biol*. 2013;66:1–85.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Tibballs J. Australian snakebite and treatment. In: Gopalakrishnakone P, Faiz SMA, Gnanathasan CA, et al, eds. *Clinical Toxinology*. Netherlands: Springer; 2018. Available at: https://doi.org/10.1007/978-94-007-6288-6_79-1.
2. Tibballs J. Spider envenomation in Australia. In: Gopalakrishnakone P, Faiz SMA, Gnanathasan CA, et al, eds. *Clinical Toxinology*. Netherlands: Springer; 2018. Available at: https://doi.org/10.1007/978-94-007-6288-6_68-2.
3. Tibballs J. Australian chirodropid cubozoan jellyfish envenomation. In: Gopalakrishnakone P, Faiz SMA, Gnanathasan CA, et al, eds. *Clinical Toxinology*. Netherlands: Springer; 2018. Available at: https://doi.org/10.1007/978-94-007-6288-6_78-1.
4. Tibballs J. Clinical management of envenomation by Australian carybdeid cubozoan, hydrozoan, and scyphozoan jellyfish. In: Gopalakrishnakone P, Faiz SMA, Gnanathasan CA, et al, eds. *Clinical Toxinology*. Netherlands: Springer; 2018. Available at: https://doi.org/10.1007/978-94-007-6288-6_67-1.
5. Tibballs J. Envenomation by Australian hymenoptera: ants, bees, and wasps. In: Gopalakrishnakone P, Faiz SMA, Gnanathasan CA, et al, eds. *Clinical Toxinology*. Netherlands: Springer; 2018. Available at: https://doi.org/10.1007/978-94-007-6288-6_69-2.
6. Johnston CI, Ryan NM, Page CB, et al. The Australian Snakebite Project, 2005–2015 (ASP-20). *Med J Aust*. 2017;207:119–125.
7. Welton RE, Williams DJ, Liew D. Injury trends from envenoming in Australia, 2000–2013. *Intern Med J*. 2017;47(2):170–176. doi:10.1111/imj.13297.
8. Isbister GK, Brown SG. Bites in Australian snake handlers – Australian snakebite project. *QJM*. 2012;105:1089–1095.
9. Isbister GK, Little M, Cull G, et al. Thrombotic microangiopathy from Australian brown snake (*Pseudonaja*) envenoming. *Intern Med J*. 2007;37:523–528.
10. Ho WK, Verner E, Dauer R, et al. ADAMTS-13 activity, microangiopathic haemolytic anaemia and thrombocytopenia following snake bite envenomation. *Pathology*. 2010;42:200–202.
11. Tibballs J. The cardiovascular, coagulation and haematological effects of tiger snake (*Notechis scutatus*) prothrombin activator and investigation of vasoactive substances. *Anaesth Intensive Care*. 1998;26:536–547.
12. Chaisakul J, Isbister GK, Kuruppu S, et al. An examination of cardiovascular collapse induced by eastern brown snake (*Pseudonaja textilis*) venom. *Toxicol Lett*. 2013;221:205–211.
13. Ireland G, Brown SG, Buckley NA, et al. Changes in serial laboratory test results in snakebite patients: when can we safely exclude envenoming? *Med J Aust*. 2010;193:285–290.
14. Sutherland SK, Coulter AR, Harris RD. Rationalization of first-aid measures for elapid snakebite. *Lancet*. 1979;1:183–186.
15. Howarth DM, Southee AE, Whyte IM. Lymphatic flow rates and first-aid in simulated peripheral snake or spider envenomation. *Med J Aust*. 1994;161:695–700.
16. Isbister GK, Brown SG, Page CB, et al. Snakebite in Australia: a practical approach to diagnosis and treatment. *Med J Aust*. 2013;199:763–768.
17. White J. *A clinician's guide to Australian venomous bites and stings. bioCSL Pty Ltd (Australia)*. 2013.
18. Ryan NM, Kearney RT, Brown SG, et al. Incidence of serum sickness after the administration of Australian snake antivenom (ASP-22). *Clin Toxicol*. 2016;54:27–33.
19. Dassanayake AS, Karunanayake P, Kasturiratne KT, et al. Safety of subcutaneous adrenaline as prophylaxis against acute adverse reactions to anti-venom serum in snakebite. *Ceylon Med J*. 2002;47:48–49.
20. Isbister GK, Brown SG, MacDonald E, et al. Australian Snakebite Project Investigators. Current use of Australian snake antivenoms and frequency of immediate-type hypersensitivity reactions and anaphylaxis. *Med J Aust*. 2008;188:473–476.
21. Williams DJ, Jensen SD, Nimorakiotakis B, et al. Antivenom use, premedication and early adverse reactions in the management of snake bites in rural Papua New Guinea. *Toxicon*. 2007;49:780–792.
22. Premawardhena AP, de Silva CE, Fonseka M, et al. Low dose subcutaneous adrenaline to prevent acute adverse reactions to antivenom serum in people bitten by snakes: randomised, placebo controlled trial. *BMJ*. 1999;318:1041–1043.
23. de Silva HA, Pathmeswaran A, Ranasinha CD, et al. Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo-controlled trial. *PLoS Med*. 2011;8:e1000435.
24. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy*. 2000;30:1144–1150.
25. Fan HW, Marcopito LF, Cardoso JL, et al. A sequential randomised and double blind trial of promethazine prophylaxis against early anaphylactic reactions to antivenom for *Bothrops* snake bites. *BMJ*. 1999;318:1451–1453.
26. Isbister GK, Buckley NA, Page CB, et al. A randomised controlled trial of fresh frozen plasma for treating venom-induced consumption coagulopathy in cases of Australian snakebite (ASP-18). *J Thromb Haemost*. 2013;11:1310–1318.
27. Gray MR. A revision of the Australian funnel-web spiders (Hexathelidae: Atracinae). *Rec Aust Mus*. 2010;62:285–392. doi:10.3853/j.0067-1975.62.2010.1556.
28. Isbister GK, Gray MR, Balit CR, et al. Funnel-web spider bite: a systematic review of recorded clinical cases. *Med J Aust*. 2005;182:407–411.
29. Graudins A, Little MJ, Pineda SS, et al. Cloning and activity of a novel α-latrotoxin from red-back spider venom. *Biochem Pharmacol*. 2012;83:170–183.

30. Luch A. Mechanistic insights on spider neurotoxins. *EXS*. 2010;100:293–315.
31. Isbister GK, Gray M. Effects of envenoming by comb-footed spiders of the genera *Steatoda* and *Achaearanea* (family Theridiidae: Araneae) in Australia. *J Toxicol Clin Toxicol*. 2003;41:809–819.
32. Brinkman D, Burnell J. Partial purification of cytolytic venom proteins from the box jellyfish, *Chironex fleckeri*. *Toxicon*. 2008;51:853–863.
33. Brinkman DL, Burnell JN. Biochemical and molecular characterization of cubozoan protein toxins. *Toxicon*. 2009;54:1162–1173.
34. Brinkman DL, Aziz A, Loukas A, et al. Venom proteome of the box jellyfish *Chironex fleckeri*. *PLoS ONE*. 2012;7:e47866.
35. Brinkman DL, Konstantakopoulos N, McInerney BV, et al. *Chironex fleckeri* (box jellyfish) venom proteins. Expansion of a cnidarian toxin family that elicits variable cytolytic and cardiovascular effects. *J Biol Chem*. 2014;289:4798–4812.
36. Brinkman DL, Jia X, Potriquet J, et al. Transcriptome and venom proteome of the box jellyfish *Chironex fleckeri*. *BMC Genomics*. 2015;16:407.
37. Gershwin LA, Richardson AJ, Winkel KD, et al. Biology and ecology of Irukandji jellyfish (Cnidaria: Cubozoa). *Adv Mar Biol*. 2013;66:1–85.
38. Winkel KD, Tibballs J, Molenaar P, et al. Cardiovascular actions of the venom from the Irukandji (*Carukia barnesi*) jellyfish: effects in human, rat and guinea-pig tissues in vitro and in pigs in vivo. *Clin Exp Pharmacol Physiol*. 2005;32:777–788.
39. Corkeron M, Pereira P, Makrocanis C. Early experience with magnesium administration in Irukandji syndrome. *Anaesth Intensive Care*. 2004;32:666–669.
40. McCullagh N, Pereira P, Cullen P, et al. Randomised trial of magnesium in the treatment of Irukandji syndrome. *Emerg Med Australas*. 2012;24:560–565.

87

Blast and ballistic trauma

Michael C Reade, Peter D (Toby) Thomas

Although still uncommon, the number of mass casualty events involving firearms (e.g. the Paris Bataclan theatre, 2015) and explosions (e.g. Brussels, 2016) has increased in developed countries in recent years, but most deaths still occur in the developing world and therefore are under-reported in Western media.[1] Civilian single-victim firearm attacks and accidental explosions are even more numerous. The principles of managing blast and ballistic trauma are not well appreciated outside the military.[2] Misunderstandings can result in counterproductive planning (e.g. needlessly emptying intensive care units, or failing to understand the requirement for repeated wound surgery over many weeks) and treatment (e.g. needless extensive debridement). This chapter will hopefully remain a curiosity in an otherwise intensely studied book. For the increasing minority who need to read it in detail, perhaps unexpectedly, we hope it provides useful advice.

EPIDEMIOLOGY OF BLAST AND BALLISTIC TRAUMA

Military conflicts result in variable wounding mechanisms, summarised in Table 87.1.[3–5] The trend towards more head and neck wounds in recent conflicts (Table 87.2)[4,6] is attributed to better thoraco-abdominal body armour. The ratio of killed to wounded depends on weapon systems employed, physical surroundings, protective equipment and medical support. The mortality associated with different weapons systems in combat is shown in Table 87.3.[4,7] In modern war, the overall wounded:killed ratio ranges from 2:1 to 13:1,[8] with an average over time of around 4:1.[4,6] Body armour and better medical care are possible explanations for the higher survival (ratio 10:1) of US casualties in Iraq[9] and Afghanistan,[10] although the higher proportion of blast casualties probably also contributed.

Firearms used in a civilian context are more lethal than on the battlefield, with wounded:killed ratios ranging from 0:1 to 1:3,[8] probably because civilian shootings occur at close range with unarmed victims who cannot escape. Higher than expected mortality in war suggests executions rather than combat deaths, and has been used as evidence of war crimes.[8]

The epidemiology of blast trauma conforms to one of five distinct patterns (Table 87.4).[11] Understanding the context of blast provides vital clues to clinical management priorities and to hospital and trauma system planning for these events. For example, few civilian blast survivors (approximately 15%) require surgery, and even fewer (6%–13%) require admission to intensive care.[17]

CAUSES AND TIMING OF DEATH IN BLAST AND BALLISTIC INJURY

Of blast and ballistic trauma deaths, 70% occur due to brain injury or exsanguination within 5 minutes of wounding,[4] and almost none are survivable regardless of treatment. However, most ballistic wounds are not fatal. Of the US combatants who died in the Vietnam War,[6] 25% had potentially correctable surgical causes, and 12% died of infections and other complications. Improvement in hospital care has virtually eliminated the third mortality peak in trauma,[18] leaving pre-hospital care the main target to reduce further preventable mortality. Of the preventable deaths, 60% are due to haemorrhage from extremities, 33% from tension pneumothorax and 6% from airway obstruction.[19] Military personnel are trained to treat these three mechanisms,[20] although these figures can skew training priorities as they report on patients who died rather than those who survived, because comparatively simple interventions (e.g. airway opening) were, in fact, performed correctly.

BLAST TRAUMA

An explosion occurs when a substance rapidly undergoes a chemical or nuclear reaction, releasing energy in the form of a pressure wave, gas (usually) and heat. This chapter discusses 'conventional' rather than the particular effects of nuclear explosions. A *high explosive* produces a supersonic pressure wave, while slower burning (*deflagration*) does not. The first force felt by an affected body is the static pressure wave, depicted in Fig. 87.1. There is no mass movement of gas; rather pressure rapidly increases then becomes

ABSTRACT

Blast wounds by several mechanisms: the blast pressure wave (causing injury at interfaces of different tissue density, such as the lung, ear and bowel), acceleration of projectiles (causing penetrating trauma), physical displacement of the casualty or their surroundings (causing blunt trauma) and miscellaneous effects such as burns and inhalation of toxic gases. Five distinct types of blast (open-air, enclosed-space, underwater, associated with structural collapse and civilian low-explosive blast) cause distinct epidemiological patterns. Ballistic trauma (caused by projectiles) is a component of blast, and also includes wounding by firearms. High- and low-energy transfer wound characteristics determine the extent of tissue injury. Modern principles of treating burn and ballistic trauma build on centuries of experience through the application of evidence-based medicine, and include effective triage; rapid haemorrhage control; early, repeated but minimal debridement; modern ventilator and infection management; and vigilance for predictable late effects, most of which are not within the routine experience of civilian clinicians.

KEYWORDS

War-related injuries
wounds, penetrating
wounds, non-penetrating
blast injuries
ballistics
terrorism
armed conflicts
mass casualty incidents

Table 87.1 Historical variation in combat trauma

CONFLICT	BULLETS %	BLAST/FRAGMENTATION %	OTHER INCL. LAND MINES %
World War I[3]	39	61	—
World War II[3]	10	85	5
Korean War[3]	7	92	1
Vietnam War[3]	52	44	4
Falkland Islands[3]	31.8	55.8	12.4
Yugoslavia 1991–1992[4]	41	2	52
Iraq and Afghanistan[5]	19	77	4

Table 87.2 Historical anatomical wound patterns

CONFLICT	HEAD/NECK %	THORAX %	ABDOMEN %	LIMBS %	OTHER/MULTIPLE
World War I[4,6]	17	4	2	70	7
World War II[4,6]	4	8	4	75	9
Korean War[4,6]	17	7	7	67	2
Vietnam War[4,6]	14	7	5	74	—
Falkland Islands[4,6]	16	15	10	59	—
Yugoslavia 1991–1992[4]	21	9	8	62	23 (also incl. in individual %)
Iraq and Afghanistan[5]	30	6	9	55	—

Table 87.3 Mortality associated with different weapons systems employed in combat

Military rifle bullet	30%–40%
Blast	22%
Blast fragmentation – randomly formed fragments	20% artillery shells; 10% grenades
Blast fragmentation – military preformed fragments	15% artillery shells; 5% grenades

See references 4 and 7.

sub atmospheric. Hard surfaces reflect pressure waves, increasing the transmitted force in enclosed spaces.[11] The second force felt by a body in air is the mass movement of gases liberated by the exploding substance: the 'blast wind', which, near its origin, will contain sufficient thermal energy to cause burns. The momentum of solid objects accelerated by the blast wind can wound well beyond the danger zone of the blast wave or wind.

MECHANISMS OF BLAST INJURY

The classification of blast injury mechanisms is shown in Table 87.5 and Fig. 87.2.

PATHOPHYSIOLOGY OF PRIMARY BLAST INJURY

Primary blast injury is a common cause of death due to military blast,[21] but (except in confined environments or underwater) is uncommon (e.g. 7% in one series)[22] in survivors. If the casualty is close enough to suffer a primary blast injury, secondary and tertiary effects are usually fatal. Civilian low-energy explosive-burn casualties very rarely have primary blast trauma. The exception is 'enhanced' blast mechanisms that cause a prolonged overpressure: most commonly in civilian settings caused by the combustion of air/dust mixtures in grain silos or coal stores, and boiling liquid-expanding vapour explosions (BLEVEs) when gases stored as liquids under pressure explode at temperatures above their boiling points (e.g. liquid petroleum gas bottles in a fire).

The immediate response to a blast to the chest is vagal-mediated hypotension, bradycardia and apnoea. Alternating overpressure and underpressure causes injury due to shear forces, spalling and compression/expansion at the interfaces of tissues of different densities. This especially affects gas-containing organs, of which the ear is the most sensitive. The eardrum can be ruptured (usually inferiorly in the pars tensa) by overpressures of approximately 35 kPa; above 100 kPa rupture is nearly universal. There may be membrane haemorrhage without rupture. Rupture of the

Table 87.4 Epidemiological patterns of blast injury

	OPEN AIR HIGH-EXPLOSIVE BLAST	HIGH-EXPLOSIVE BLAST IN A CONFINED SPACE	HIGH-EXPLOSIVE UNDERWATER BLAST	BLAST CAUSING STRUCTURAL COLLAPSE	CIVILIAN LOW-EXPLOSIVE BLAST
Immediate mortality, % total injured	4 (0–9)	8 (1–14)	Not reliably reported	25 (6–44)	Not reliably reported as incidents usually involve one to two casualties
Any pulmonary effects, % survivors	7 (4–11)	21 (0–46)	84[13]	5 (2–7)	13%[14] (although difficult to separate from the effects of inhalational burn)
Blast lung syndrome, % survivors	5 (3–9)	16 (0–37)	Not specifically reported	1 (0–3)	Not specifically reported; most likely very low
Tympanic membrane rupture, % survivors	5 (0–15)	35 (16–54)	Not reliably reported; most likely very low for patients floating at the surface at the time of the blast	2 (1–4)	0[14]–4[12]
Abdominal injury from blast wave, % survivors	0 (0–2)	3 (0–6)	75[13]	1 (0–6)	0
Penetrating trauma from blast fragmentation	12[16]	15[16]	0	Uncommon, but not reliably reported	Not specifically reported
Blunt trauma (e.g. from falling masonry)	Uncommon, but not reliably reported	Uncommon, but not reliably reported	0	47[15]	Not specifically reported
Burn	10[16]	28[16]	0	2[15]	100[14] – likely to be an overestimate as study was conducted at burn centre – but the true rate is nonetheless high
Summary characteristics	Largest numbers of casualties; smallest proportion of severe injuries, most of which are penetrating blast fragmentation	Highest proportion of survivors with primary blast effects	Mechanism is almost exclusively primary blast-wave injury. Very high incidence of severe blast lung and abdominal injury	Largest number of casualties and immediate fatalities. Blast effects in survivors are rare	Burns are the most common consequence; blast effects are rare

See references 11–16.

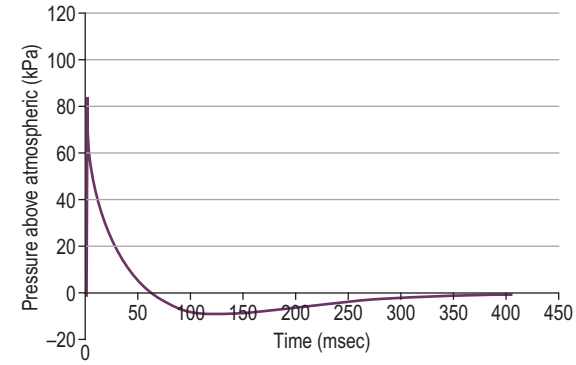


Figure 87.1 (a and b) A blast pressure (Friedlander) wave in air, with the peak overpressure shown diagrammatically in (a) visible as a change in the refractive index of air (marked by *arrows*) in (b). Interactions with surfaces including the ground commonly distort this wave. In many cases this increases the magnitude of the peak pressure at certain positions, resulting in different forces applied to casualties' located similar distances from the blast origin. *Photograph and associated R&D by Dr Fan Zhang, © Her Majesty the Queen in Right of Canada, as represented by the Minister of National Defence, 2016.*

tympanic membrane can cause tinnitus, pain, hearing loss and abnormal vestibular function. One-third of casualties experiencing rupture of the tympanic membrane will have permanent hearing loss.

Tympanic membrane sensitivity to blast led to recommendations it be used as an effective screen for blast injury to other organs, but this is unsupported by clinical experience. Tympanic membrane disruption was present in only 50% of patients with other significant blast injury.[22] Head orientation to the blast is a key determinant of vulnerability.

Blast injury at the alveolar–capillary interface can cause air emboli, pneumothorax, lung contusion, haemothorax, alveolar haemorrhage, mediastinal air and subcutaneous emphysema.[23] As alveoli flood with fluid and cellular debris, the result is 'blast lung' (Fig. 87.3), with hypoxaemia caused by ventilation–perfusion mismatch. Blast lung typically develops over 24–48 hours and takes 7–10 days to resolve. Presentation ranges from mild hypoxaemia to frothy sputum, profound hypoxaemia and subcutaneous emphysema. A chest radiograph will distinguish pneumothorax, haemothorax or pulmonary parenchymal damage from blast or other causes (e.g. inhalation of toxic gases). The effect can appear similar to pulmonary contusion from blunt chest trauma. Arterial air emboli from alveolar–pulmonary venous communications cause most early deaths. Signs of air emboli include cerebral dysfunction such as altered affect, confusion or focal neurological signs. Emboli to the coronary arteries can cause arrhythmias or ischaemia.

Primary abdominal blast injury is rare other than with blast in enclosed spaces and underwater. It most frequently presents late with signs of peritonism indicating visceral rupture. The colon is most commonly affected. Rarely, rupture of the liver or spleen may occur.

The role of primary blast injury in mild traumatic brain injury (mTBI) is unclear. mTBI can cause debilitating symptoms, many of which are shared with post-traumatic stress disorder.[24] Diffusion tensor imaging magnetic resonance imaging (MRI) shows abnormalities in mTBI, but these appear to correlate poorly with clinical signs.[25]

PATHOPHYSIOLOGY OF SECONDARY AND TERTIARY BLAST INJURIES

Secondary blast injuries were more than three times more common than primary blast injuries during Operation Iraqi Freedom[26] and were the commonest cause of death, mainly from penetrating wounds to the head, neck or chest. Survivors of blast fragmentation injuries often have many low-energy superficial wounds ('peppering' or 'battle acne': Fig. 87.4). Up to 80% of military blast casualties will have ocular trauma if they are not wearing eye protection[27] – more than reported in civilian studies – although eye injuries in urban environments containing shattering glass are also common.

Traumatic limb amputation is only partly an effect of the blast wind. Primary blast injury fractures long bones, and the blast wind then detaches the distal portion. This is thought to explain why such amputations are typically not through joints.[28]

MANAGEMENT OF BLAST INJURY

Explosions often cause 'mass casualty' events. Triage should usually be well away from the incident, as placing further explosive devices is a common tactic targeting medical personnel.

EXTREMITY INJURIES

Recent military experience has convincingly demonstrated the value of the pre-hospital windlass arterial tourniquet in stopping life-threating bleeding in both blast and ballistic trauma (Fig. 87.5).

Table 87.5 Mechanisms of blast injury

TYPE OF BLAST INJURY	MECHANISM	EFFECTS
Primary	Static pressure wave, causing barotrauma due to overpressurisation then underpressurisation	Affects mainly air-filled organs: Tympanic membrane rupture 'Blast lung' Hollow viscera rupture (colon) Mild traumatic brain injury (mTBI) Eye (globe rupture, hyphaema, serous retinitis)
Secondary	Effects of projectiles propelled by the explosion	Penetrating injury Soft tissue trauma Traumatic amputation
Tertiary	Effects due to mass movement of air ('blast wind'), either directly or by interaction with the surroundings, incl. collapse of buildings	Blunt and penetrating injury Bone fracture Traumatic amputation Open or closed TBI Crush injury Entrapment
Quaternary	All other effects of blast, including burns, oxygen depletion, creation of dust	Surface and airway burns Inhalation of toxic gases (carbon monoxide, cyanide) Exposure to radiation Asphyxiation

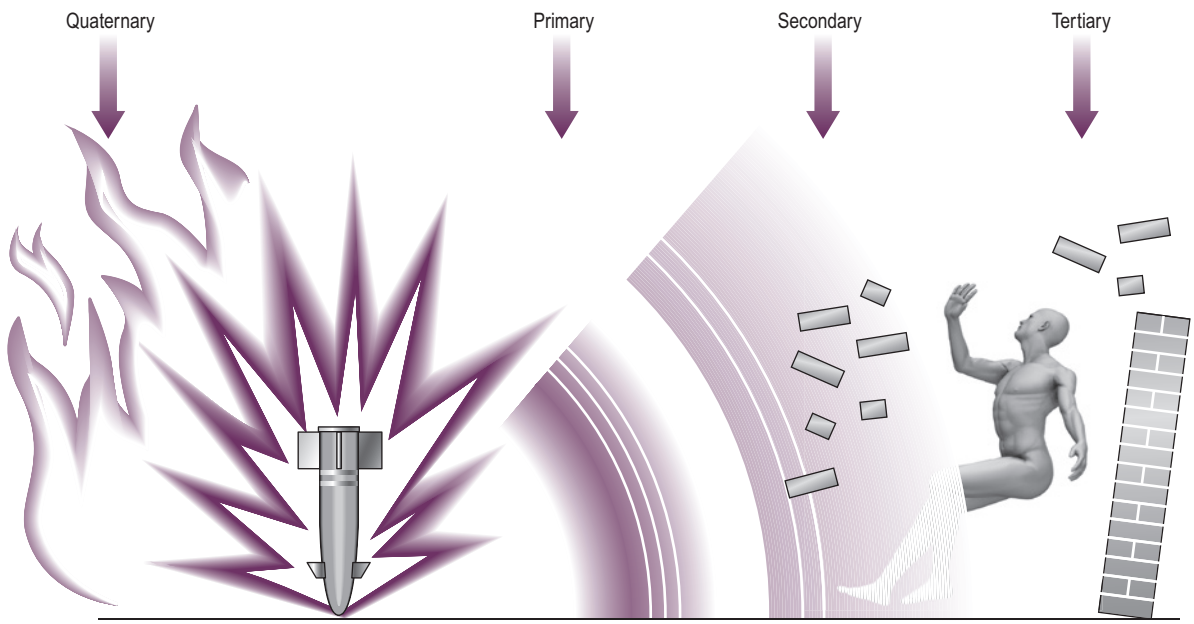


Figure 87.2 Mechanisms of blast injury. *Courtesy of Lieutenant Colonel Anthony Chambers FRACS RAAMC.*

EAR INJURIES

Tympanic membrane rupture is treated conservatively, as most heal spontaneously. About 25% will require delayed surgical closure.

BLAST LUNG

Recommendations for blast lung are mostly extrapolated from those for other causes of acute respiratory distress syndrome, despite the known differences in pathogenic mechanisms. Risk of systematic air embolism increases with mechanical ventilation, suggesting that minimising peak inspiratory pressures and permissive hypercapnia may be useful. Excessive fluid administration should be avoided to minimise contusion. Pumpless arteriovenous extracorporeal oxygenation has been used successfully to transport

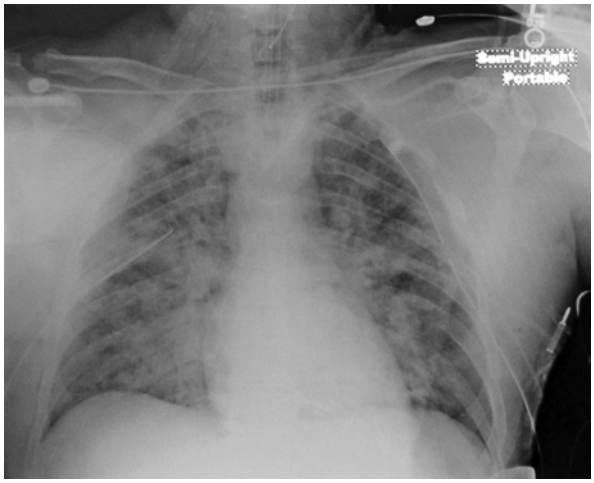


Figure 87.3 Blast lung, showing characteristic perihilar infiltrates. Computed tomography is more sensitive than plain radiography. *Courtesy of Australian Defence Force, Afghanistan, 2012.*

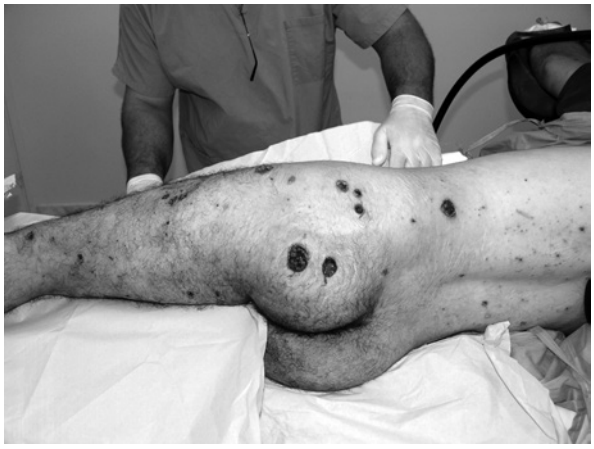


Figure 87.4 'Peppering' or 'battle acne' wounds characteristic of secondary blast injury. *Courtesy of Dr Daron Cunningham, Libya, 2011.*

profoundly hypoxaemic casualties from field hospitals to definitive care.

ABDOMINAL INJURIES

Computed tomography (CT) or focused assessment sonography for trauma (FAST) scanning will guide early management, but clinical suspicion in the days after the injury is even more useful given the likelihood of delayed presentation. Primary anastomosis for blast colorectal injuries is unwise because of the high incidence of leak (30%), so most patients require colonic diversion.[29]

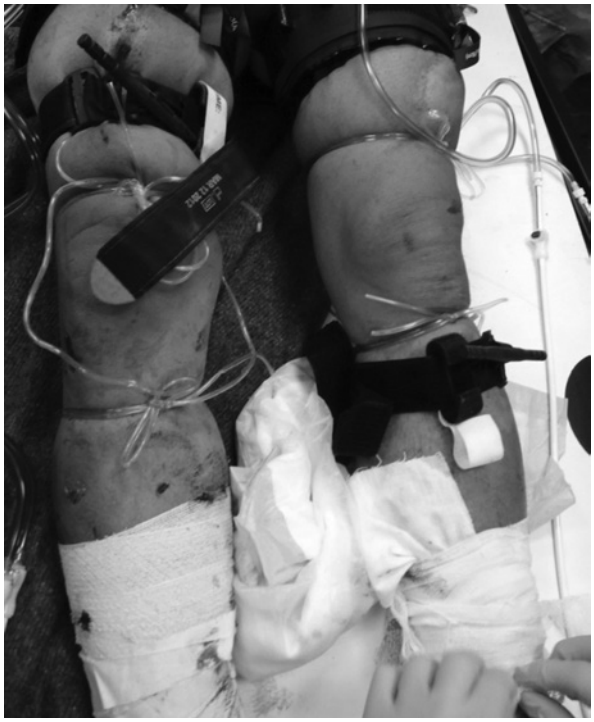


Figure 87.5 Pre-hospital improvised arterial tourniquets, insufficient to stop arterial haemorrhage, supplemented effectively by windlass Combat Application Tourniquets. Note the potential for iatrogenic tissue damage from the improvised devices. In hospital, standard pneumatic tourniquets quickly replace pre-hospital devices. *Courtesy of Australian Defence Force, Afghanistan, 2013.*

TRAUMATIC BRAIN INJURY

Central nervous system blast effects, including diffuse axonal injury, contusion and traumatic subdural haematoma, are all managed according to conventional guidelines.[30] A patient with brief loss of consciousness after blast should have brain CT or MRI if there is persistent headache, vomiting, localising neurological signs or a Glasgow Coma Score less than 15, noting that traumatic brain injury after blast can evolve over 48 hours, with around one-third missed on initial evaluation.[12]

Heterotopic ossification: a late complication of blast injury

Blast considerably accentuates the risk of post-traumatic heterotopic ossification, with an incidence as high as 64% (Fig. 87.6).[31] Heterotopic ossification causes pain, ulceration and loss of function, along with poor fitting of prostheses. Very early low-dose radiotherapy and non-steroidal anti-inflammatory drugs appear effective, but radiotherapy is impractical in the deployed environment and both are accompanied by risk of adverse effects. Surgical excision of extensive lesions remains the only effective treatment.[31]

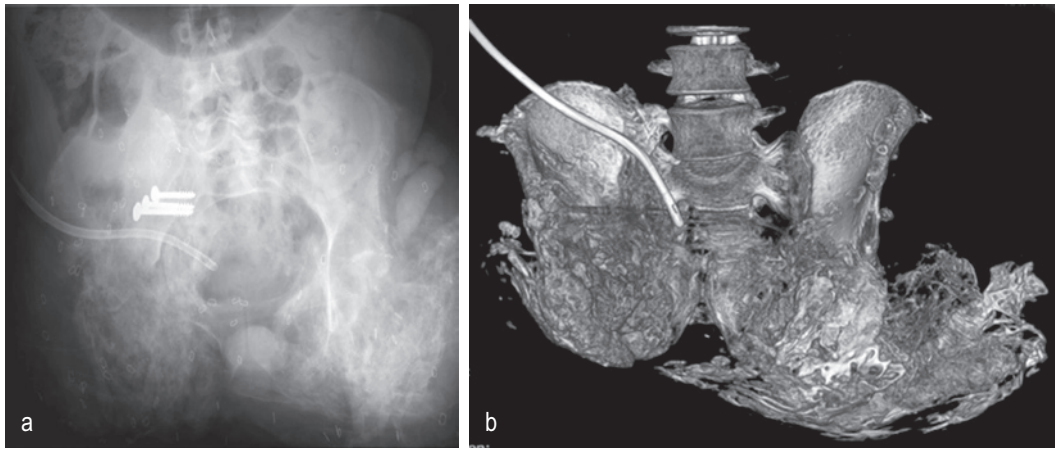


Figure 87.6 (a and b) Radiograph (a) and three-dimensional computed tomography rendering (b) of a patient with severe pelvic heterotopic ossification after bilateral hip disarticulations due to combat-related blast injuries. *From Alfieri KA, Forsberg JA Potter BK. Blast injures and heterotopic ossification.* Bone Joint Res. *2012;8:192–197.*

BALLISTIC TRAUMA

Penetrating ballistic trauma can be caused by fragments energised by explosive devices, or by projectiles from firearms.

BLAST FRAGMENTATION

Casing fragmentation multiplies the range and effect of small blast weapons many times, such as grenades, mines and mortar bombs, producing fragments that optimise range, kinetic energy and dispersion. Larger blast weapons (bombs) rely on their greater energy to create fragments from surrounding rocks or debris. Fragments from casings or surroundings are incorrectly referred to as '*shrapnel*'; blast-fragmentation is correct. The term 'improvised explosive device' (IED) covers a wide range of weapons, from the low-yield 'home made' explosives buried in palm-oil containers that typified much of the post-2001 Afghanistan conflict, to powerful explosive-formed penetrators made from repurposed military munitions used to defeat armour during the post-2003 Iraq insurgency.

BULLETS FROM FIREARMS

A *bullet* is a single projectile shot from a firearm. Modern bullets are attached to *cartridge cases* containing the *percussion cap* or *primer* and *propellant*; the entire structure forms a *round* of *ammunition*. Firearms firing bullets include *rifles* (with a long barrel that is 'rifled' with spiralling grooves inside that make the bullet rotate, increasing gyroscopic stability), *revolvers* (handguns with chambers that rotate to present each round to the barrel) and *pistols* (with short barrels but no rotating chambers). A *shotgun* with a smooth-bored barrel usually fires *shot* (round metal balls) rather than a single formed projectile.

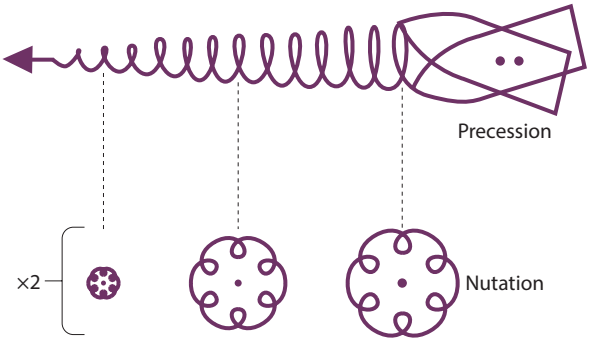


Figure 87.7 Precession and nutation. Both decrease as distance from the barrel increases. *From Volgas DA, Stannard JP, Alonso JE. Ballistics: a primer for the surgeon.* Injury. *2005;36(3):373–379.*

PROJECTILE BALLISTICS

Rapidly expanding propellant gas accelerates the projectile through the firearm barrel. Projectile trajectory is determined by gravity, air friction and pressure resistance, wind, contact with solid objects (causing *ricochets*) and stability in flight. Most bullets in flight have their centre of mass behind their centre of pressure, causing *yaw*; this is opposed by gyroscopic stability, leading to a composite movement of *spin* (rotation around the long axis), *precession* (rotation of the rotational axis) and *nutation* (swaying of the rotational axis as it precesses). During flight, yaw progressively reduces. A bullet is therefore more likely to hit point-on after 100 m of flight than after 3 m (Fig. 87.7).[32,33]

WOUND BALLISTICS

Wound ballistics describe the interaction between a projectile and the biological tissue it hits. The amount of energy that is transferred is determined by the:

- *kinetic energy (KE) of the projectile:* KE = mass × velocity^2/2 × g. The kinetic energy *transferred* to the tissue is mass × (impact velocity – exit velocity)^2/2 × g;
- *rotational energy of the projectile in flight:* usually negligible;
- *shape and impact angle of the projectile:* an aerodynamically shaped bullet will impart more energy if it hits side-on; the degree to which this occurs is determined by its properties in flight, including the distance travelled and whether it has hit anything during flight;
- *projectile deformability and fragmentation;*
- *degree to which the projectile 'tumbles':* a rapid end-over-end motion does not occur; rather, the bullet typically tumbles through 180 degrees and comes to lie base-first. Tumbling is the main reason why full metal jacket exit wounds are often larger than entry wounds; and
- *specific gravity of the tissue hit.*[34]

The terms 'high' and 'low' velocity are not as useful as 'power', incorporating projectile mass, and are even less useful than the concept of energy transfer. Although most rifles are 'high-powered' and most pistols/revolvers 'low-powered', projectile energy is only one determinant of wound magnitude. A 'high-powered' rifle bullet may cause less trauma if it misses ribs and traverses a short path through the chest than a 'low-powered' pistol bullet that fragments after hitting a rib. Notwithstanding this, the kinetic energy of most rifle bullets is many times that from a pistol. Hitting bone, a pistol bullet frequently causes a simple fracture, whereas a rifle bullet causes fragmentation and extensive bone loss.[35] Most individual wounds caused by blast fragmentation (when the patient survives the explosion) are low-energy transfer, but the sum energy transfer (and tissue damage) caused by multiple projectiles over a large body surface area can be substantial.

Further determinants of the effect of the projectile are:

- the function of the tissue affected (e.g. the eye is damaged by minimal energy transfer)
- the ability of the affected tissue to tamponade haemorrhage (e.g. liver bleeds more than muscle).

BULLET DEFORMABILITY

Bullets are typically made of lead or lead–antimony, as high density preserves kinetic energy in flight. Lead bullets melt at velocities of greater than 2000 ft/s (≈600 m/s),[34] necessitating a 'full metal jacket' (a misnomer, as the base of the bullet may have no covering) of a harder substance (e.g. copper/zinc, copper/nickel or steel). Military bullets (according to Third Hague Convention of 1899) must not flatten on contact with the body, thereby avoiding 'unnecessary suffering'. The 'full metal jacket' therefore serves two purposes. By increasing the chance of non-lethal injury, an unintended consequence is to increase combat effect: a wounded enemy soldier consumes more resources than one who is dead. In contrast, hunting rifle bullets have a soft lead or polymer tip, increasing the chance of killing quickly and so reducing suffering. Bullets with hollowed-out points have greater air drag and shorter range, but deform so extensively that exiting the target is unlikely. This is beneficial for police wishing to reduce risk to bystanders.

Doctors are sometimes asked by people concerned with compliance with the laws of armed conflict to classify the type of bullet found in a patient. *Any* bullet can deform and fragment. For example, the North Atlantic Treaty Organisation (NATO) 5.56 mm bullet fragments into two at reproducible wound depths. Finding no intact fully jacketed bullets does not allow this question to be answered.[36]

MECHANISMS OF TISSUE DAMAGE

Bullets cause crushing/laceration, shock waves and cavitation. Crushing and laceration are caused by the direct force of the bullet, and are the principal mechanisms of injury due to 'low-powered' firearms. Shock waves are caused when a 'high-powered' bullet compresses tissues. They cause little damage to most tissues[37] but can rupture gas-filled organs[34] and possibly cause neurological injury.[38] The inertia imparted to tissues by a high-powered bullet causes cavitation: as the tissues continue to move away from the bullet track, subatmospheric pressure sucks in debris. The *temporary cavitation* disrupts cells and their microcirculation, producing dead tissue around the wound track *up to* 30–40× the diameter of the bullet.[34] Cavitation depends on tissue elasticity; for example, liver is more affected than muscle. The temporary cavity collapses to a much smaller permanent cavity, but the size of the permanent cavity is not an indicator of the extent of devitalised tissue. Inelastic gelatine blocks overemphasise the implications of temporary cavitation in many tissues,[39,40] and are additionally misleading by not replicating the effect of passage through tissues of different density upon the bullet track.

MANAGEMENT OF PENETRATING BALLISTIC TRAUMA: BASIC PRINCIPLES

The International Committee of the Red Cross (ICRC) recommends as basic principles: early and thorough wound excision and irrigation; no unnecessary dressing changes; delayed primary closure; antibiotics as

an adjuvant; antitetanus vaccine and immunoglobulin if necessary; no internal bone fixation; and early physiotherapy.[4]

DAMAGE CONTROL SURGERY

Damage control surgery aims to stop haemorrhage, restore blood flow and control wound contamination.[41] Wounds are left packed if necessary, and temporarily closed. Restoration of bowel continuity, definitive debridement and wound closure are all deferred until physiology is optimised. This concept fits well with the ICRC basic principles and, as it requires general rather than specialist surgical expertise, can be performed in small hospitals close to the wounded.

DEFINITIVE MANAGEMENT

In general, re-inspection within 24–48 hours will be required for major wounds, with further debridement if required. This process continues every 48 hours until the wound can be closed. Even apparently clean wounds should not be closed before 4–5 days. Of 16,172 patients in the ICRC database, 41% required two operations, 14% three and 20% four or more.[4] Serial debridement is resource-intensive; in mass casualties or resource-poor environments, the ICRC recognises this approach may be impossible and advises wider initial excisions.[4]

There are exceptions to the 'no primary closure' rule. The head, neck and genitals have such good blood supply that primary closure is possible in all but the most contaminated wounds. Oral mucosa should always be closed primarily if possible. In penetrating brain injury the dura should also be closed, if necessary with a patch of pericranium or muscle aponeurosis.[4] Blood vessels that have been repaired should be covered by viable muscle if possible, with the skin left open.

MANAGEMENT OF SPECIFIC TYPES OF PENETRATING BALLISTIC WOUND

EXTREMITY WOUNDS: WOUNDS THAT DO NOT REQUIRE DEBRIDEMENT

Military[42] and civilian[4] consensus guidelines agree that not all bullet wounds require debridement. Extremities with entry and exit wounds less than 1 cm and no swelling or signs of injury to vital structures can have narrow skin margins excised and the channel irrigated with gravity-fed crystalloid. Wounds that do not penetrate deep fascia require only scrubbing, irrigation, dressings and antibiotics.

EXTREMITY WOUNDS: HOW MUCH TISSUE TO DEBRIDE?

Many published accounts[3,39,43] and the authors' own experiences suggest that surgeons sometimes perform extensive debridement around high-powered bullet tracks in the belief that microvascular tissue damage is more extensive than can be seen. This approach, although once advocated in military texts,[44] ignores empirical studies[43] and the distinction between projectile energy and energy transfer.

In penetrating ballistic trauma, muscle viability was historically assessed using the 'four C's'[7] – *capillary* bleeding when cut, *contracts* when pinched, *colour* of red meat and firm *consistency*. However, apparently dead muscle is often later found to be viable.[39,40,45] Along with substantial consensus,[7,37,39,46] we advocate initial debridement of only tissue and bone that is clearly ischaemic or not attached, with re-inspection and reassessment after 2–3 days. Drawing on experience in Afghanistan and Iraq, detailed consensus recommendations for extremity war wound debridement have been published.[42]

SUPERFICIAL BLAST FRAGMENTATION

There is debate about the optimal management of blast fragmentation penetrating trauma. Historically, military teaching was that all wounds should be surgically debrided, as most fragments carry bacteria. However, few open wounds develop infection,[47] implying that at least some can be managed non-operatively. The smaller superficial wounds in Fig. 87.4 were cleaned with a surgical scrub brush; no infection developed and the resultant scars were smaller than if each perforation had been explored. Published indications for surgical debridement of blast fragmentation wounds derived from case series are listed in Table 87.6.[48,49]

BALLISTIC FRACTURE MANAGEMENT

Bone fragments without any soft tissue attachments should be removed.[35] However, *any* soft tissue attachment makes the assessment of viability difficult, and at initial surgery such fragments should be retained. High-energy transfer fractures and fractures of the proximal tibia and fibula[50] often require fasciotomy to prevent compartment syndrome. Infection risk argues

Table 87.6 Indications for surgical debridement of blast fragmentation wounds

Ordog et al. (1993)[48]	Bowyer (1997)[49]
Presentation >24 h after wounding, without basic cleansing before presentation	Involvement of bone, pleura, peritoneum or major vessels
Wound size >1–2 cm	Wound entry or exit >1–2 cm
Failure to comply with wound care instructions	Evidence of wound cavitation
Factures	Obvious signs of infection Wounds due to buried mines

strongly for plaster, external fixation or traction rather than internal fixation of ballistic fractures.[35,51,52]

ABDOMINAL PENETRATING WOUNDS

Low-energy bullets and blast fragmentation tend to produce discrete injury to abdominal organs. Up to 30% of civilian anterior abdominal and 67% of lower back gunshot wounds can be managed safely without surgery. This approach is increasing in US civilian practice,[53] probably associated with better and more widespread CT imaging; however, it fails in 21% of cases, and failure is associated with increased mortality.[53] High-energy transfer, haemodynamic instability, peritonitis, or lack of reassuring imaging all indicate laparotomy. In the military context, definitive surgery can avert a more prolonged admission for observation. Without comprehensive imaging, it is our practice and that of others[47] to explore all penetrating abdominal wounds. If CT imaging is available, in the light of observational studies,[54] UK military guidelines allow for a selective non-operative approach in the minority of casualties with no peritonitis or haemodynamic instability who can be intensively monitored.

THORAX

Penetrating thoracic injury is either rapidly fatal (e.g. 93% of patients with aortic injuries die before reaching hospital),[55] or managed with simple measures. Of the penetrating thoracic trauma patients who reach medical care, 85% can be successfully managed with intercostal catheter (ICC) drainage alone.[56] An ICC should be placed through a new incision rather than the wound to prevent further haemorrhage. On placement of the ICC, Early Management of Severe Trauma[57] teaching is that greater than 1500 mL initial haemorrhage or greater than 200 mL/h ongoing loss for greater than 2–4 hours necessitates operative thoracotomy. Emergency anterolateral thoracotomy should be considered in patients with penetrating thoracic injuries who arrive pulseless but with electrocardiograph (ECG) activity within the last 6–10 minutes, with the intention of releasing cardiac tamponade, controlling haemorrhage (by cross-clamping the aorta or pulmonary hilum) and allowing internal cardiac massage to 'buy time' for aggressive fluid resuscitation. Thoracic penetrating injury below the level of the nipple, a positive FAST scan or abdominal signs suggests the projectile has traversed the diaphragm.

RETAINED FOREIGN BODIES

Easily accessible projectiles should be surgically removed. However, projectiles buried in healthy tissue (including brain) *unequivocally do not need to be removed*, with some exceptions:

- those lodged in joints or the subarachnoid space, in order to prevent lead arthropathy and systemic toxicity, joint destruction or neural damage;
- those that appear to become the source of systemic infection;
- those lying next to an internal organ (e.g. bronchus, heart), with the risk of subsequent erosion;[40] and
- those causing persistent pain, with the caveat that the psychological effects of a retained projectile are often profound, and this can influence pain perception.

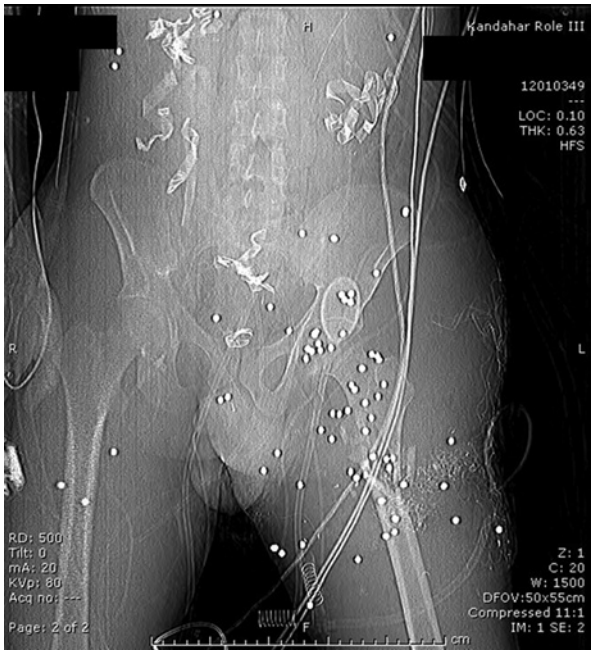


Figure 87.8 Scout computed tomography image showing numerous metallic fragments after blast-fragmentation injury from an improvised explosive device. *Courtesy of Australian Defence Force, Afghanistan, 2012.*

Blood lead levels from projectiles retained in muscle peak at 1 month and in synovial fluid at 6 months.[58] If lead toxicity is the sole indication for projectile removal, the threshold serum levels are 10 µg/dL in children and 40 µg/dL in adults. Projectile removal should be attempted only after chelation with EDTA, dimercaprol, D-penicillamine or dimercaptosuccinic acid.[4]

HELPFUL INVESTIGATIONS

Pre- and intraoperative physical examination is the best single method of evaluating ballistic wounds.[43] However, projectiles often follow unpredictable paths. Radiology can be useful in triage, operative planning and the selection of cases for non-operative management. The extent of blast-fragmentation wounds, such as those in Fig. 87.8, would be almost impossible to assess without radiology. In Iraq and Afghanistan, all patients with substantial ballistic trauma had whole-body CT scanning if it was available, unless operative intervention was immediately required to save life.

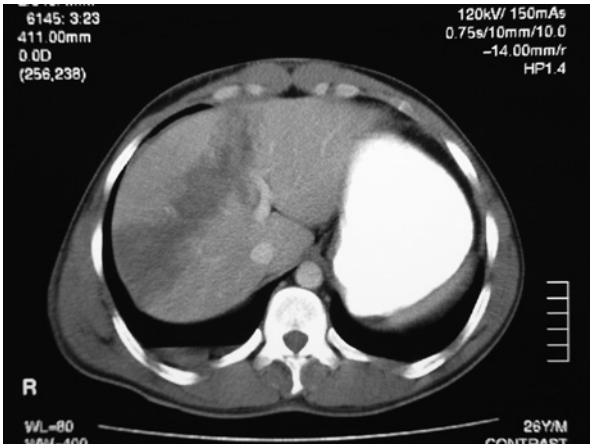


Figure 87.9 Computed tomography image demonstrating the wound track of a 9 mm bullet through the liver. *Courtesy of Dr Daron Cunningham, Cape Town, 2003.*

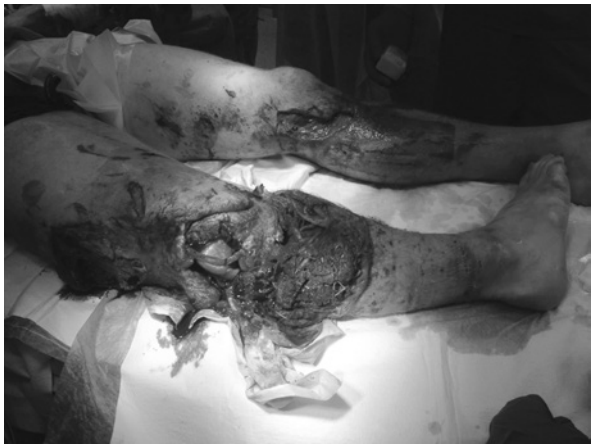


Figure 87.10 Extensive wound contamination and tissue loss due to blast fragmentation from an improvised explosive device. *Courtesy of Australian Defence Force, Afghanistan, 2013.*

Wound paths can be plotted using CT images, allowing surgical planning (Fig. 87.9).

INTERNATIONAL COMMITTEE OF THE RED CROSS WOUND CLASSIFICATION

The ICRC wound classification system[4] categorises disease severity by measuring the size of the entry wound, exit wound and wound cavity, and the involvement of fractures, vital structures and metallic foreign bodies. The result is a grade and type of wound. Unable to capture all aspects of anatomy and physiology and not accounting for multiple wounds, the ICRC system is a poor predictor of outcome, but is nevertheless useful for quantifying the effects of weapon systems.

SPECIAL CASES OF BALLISTIC TRAUMA

LANDMINES AND IMPROVISED EXPLOSIVE DEVICES

Antipersonnel landmines wound by a combination of blast and fragmentation from their casing and from rocks and soil. Buried mines explode upwards through the leg, commonly resulting in traumatic amputation through the midfoot or distal tibia, with debris driven up fascial planes (Fig. 87.10). Wound severity depends on the quantity of explosive, the point of foot contact, the debris near the mine and the footwear.[44] Bounding mines contain two charges: a small explosion propels a tethered casing upwards to 1–2 m, which then explodes propelling fragments 50–100 m. Horizontal spray mines also cause most of their effect by blast fragmentation. Air-dropped 'butterfly' mines rely on primary blast effect to maim when handled. IEDs often mimic the effects of mines, but, being made from anything from artillery shells to household chemicals, their effects are more difficult to predict. All the principles articulated above apply to mine wounds, with particular emphasis on the need to remove soil. Topical negative-pressure dressings are perceived to be particularly useful,[59] but are still not supported by trial evidence.

INCENDIARY DEVICES (NAPALM, WHITE PHOSPHOROUS)

Military forces use white phosphorus and napalm as incendiaries, and white phosphorus is also used to create smokescreens. However, both are effective psychological weapons due to their capacity to inflict severe wounds. Napalm produces an adherent burning gel, invariably producing full-thickness burns involving muscle. A 10% burn typically causes rhabdomyolysis and renal failure.[4] Napalm commonly undergoes incomplete combustion, so carbon monoxide poisoning is common. White phosphorus fragments on explosion and ignites on air contact. Immediate treatment is to scrape off visible particles – for example with a bayonet – followed by keeping the wound moist to exclude air. Dilute (1%) copper sulphate makes white phosphorus safer and easier to remove by turning it black. Alternatively, phosphorus particles glow in low light. Systemically absorbed white phosphorus causes hypocalcaemia and hyperphosphataemia, requiring intravenous calcium.[60]

BEHIND ARMOUR BLUNT TRAUMA

Body armour, consisting of woven textiles and ceramic plates, effectively reduces the lethality of

ballistic trauma. However, rifle bullets larger than 5.56 mm can still kill by the transmission of a force wave.[61] The immediate effects of behind armour blunt trauma (BABT) are vagally mediated apnoea and hypotension,[62] commonly accompanied by pulmonary and myocardial contusion, rib fractures, haemo- and pneumothorax.

INFECTION IN BALLISTIC INJURY

The two requirements for serious wound infection – dead tissue and a deep inoculum of bacteria – are frequently present in ballistic trauma. This is particularly true of military wounds, with typically three to six different bacterial species isolated compared with only one in infected civilian wounds.[35] Bacteria are mainly introduced into gunshot wounds by cavitation, but the bullet is not sterilised by firing and can also lead to infection.[34] Historically, the major causative organisms have been beta-haemolytic streptococci and clostridia. Although 'the best antibiotic is good surgery',[4] infection with both organisms is effectively prevented by prophylactic penicillin. Antibiotics alone may be sufficient for wounds left open with sufficient drainage.[63] US 2011 consensus guidelines for antimicrobial prophylaxis of combat-related wounds, drawing on experience of modern conflict, remain sound.[64] Essential points are summarised in Box 87.1.

Soil potentiates the ability of contamination to cause infection. Wounds contaminated with soil should be thoroughly cleaned, potentially requiring more wound excision than otherwise. Infection is also particularly likely in haematomas,[40] which should be drained. If a wound requires debridement, earlier surgery is associated with less infection. For example, the 10% infection rate in wounds debrided in less than 6 hours after wounding rose to 25% in wounds debrided later.[65]

Box 87.1 Infectious Diseases Society of America and Surgical Infection Society guidelines for the prevention of infections associated with combat-related injuries

IV antibiotic prophylaxis is indicated as soon as possible (ideally <3 h) after wounding.

Cefazolin 2 g IV every 6–8 h (+metronidazole 500 mg IV q8–12 h for oesophageal, abdominal organ, CNS) is appropriate for all wounds except penetrating eye injury, for which Levofloxacin 500 mg IV/PO once daily is recommended.

Alternate agents depend on site of wounding:

- Extremity; thoracic (excl. oesophageal); maxillofacial: Clindamycin (300–450 mg PO TID or 600 mg IV q8 h)
- Oesophageal; abdominal: Ertapenem 1 g IV or moxifloxacin 400 mg IV
- CNS: Ceftriaxone 2 g IV q24 h. Consider adding metronidazole 500 mg IV q8–12 h if gross contamination with organic debris. For penicillin allergic patients, vancomycin 1 g IV q12 h plus ciprofloxacin 400 mg IV q8–12 h

Duration of therapy in the absence of signs of infection: extremity; thoracic – 1–3 days; abdominal – 1 day after definitive washout; maxillofacial – 1 day; CNS: 5 days or until CSF leak is closed, whichever is longer.

Tetanus toxoid and immune globulin should be used as appropriate to immunisation status.

Enhanced Gram-negative coverage with aminoglycoside or fluoroquinolone is not recommended.

Addition of penicillin to prevent clostridial gangrene or streptococcal infection is not recommended.

Redose antimicrobials in the setting of large volume blood produce resuscitation.

Use only topical antimicrobials for burns.

CNS, Central nervous system; *CSF*, cerebrospinal fluid; *IV*, intravenous; *PO*, per os (by mouth); *TID*, ter in die (three times a day).

Hospenthal DR, Murray CK, Andersen RC, et al. Guidelines for the prevention of infections associated with combat-related injuries: 2011 update: endorsed by the Infectious Diseases Society of America and the Surgical Infection Society. *J Trauma*. 2011;71(2 suppl 2):S210–S234.

CONCLUSION

Medical planning and training in the management of ballistic trauma require balancing modern evidence-based medicine with the study of lessons acquired over centuries of conflict. Combatants might be compelled to repeat the mistakes of the past; doctors should not.

Acknowledgements

Commander Ian Young FRACS FAOrthA RAN, Lieutenant Colonel Andrew Higgs FRACS FAOrthA RAAMC, Wing Commander Michael Rudd FRACS RAAFSR and Squadron Leader Daron Cunningham FRACS RAAFSR kindly provided many of the photographs reproduced in this chapter with the permission of the Surgeon-General, Australian Defence Force.

KEY REFERENCES

4. Giannou G, Baldan M. *War surgery: working with limited resources in armed conflict and other situations of violence*. Geneva: International Committee of the Red Cross; 2012.
19. Bellamy RF. The causes of death in conventional land warfare: implications for combat casualty care research. *Mil Med*. 1984;149(2):55–62.
20. *Tactical Combat Casualty Care. Fort Leavenworth, KS, USA: Center for Army Lessons Learned*; 2013. Online. Available: https://publicintelligence.net/call-tactical-combat-casualty-care/.
22. Harrison CD, Bebarta VS, Grant GA. Tympanic membrane perforation after combat blast exposure

in Iraq: a poor biomarker of primary blast injury. *J Trauma*. 2009;67(1):210–211.
42. Guthrie HC, Clasper JC, Kay AR, et al. Initial extremity war wound debridement: a multidisciplinary consensus. *J R Army Med Corps*. 2011;157(2):170–175.
43. Fackler ML. Ballistic injury. *Ann Emerg Med*. 1986;15(12):1451–1455.
64. Hospenthal DR, Murray CK, Andersen RC, et al. Guidelines for the prevention of infections associated with combat-related injuries: 2011 update: endorsed by the Infectious Diseases Society of America and the Surgical Infection Society. *J Trauma*. 2011;71(2 suppl 2):S210–S234.


Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Global IEP. *Terrorism Index*. New York, NY: Institute for Economics and Peace; 2016.
2. Truitt MS, Johnson V, Rivera M, et al. Civilian and military trauma: does civilian training prepare surgeons for the battlefield? *Am Surg*. 2011;77(1): 19–21.
3. Ryan JM, Cooper GJ, Haywood IR, et al. Field surgery on a future conventional battlefield: strategy and wound management. *Ann R Coll Surg Engl*. 1991; 73(1):13–20.
4. Giannou G, Baldan M. *War Surgery: Working With Limited Resources in Armed Conflict and Other Situations of Violence*. Geneva: International Committee of the Red Cross; 2012.
5. Owens BD, Kragh JF Jr, Wenke JC, et al. Combat wounds in operation Iraqi Freedom and operation Enduring Freedom. *J Trauma*. 2008;64(2):295–299.
6. Champion HR, Bellamy RF, Roberts CP, et al. A profile of combat injury. *J Trauma*. 2003;54(suppl 5): S13–S19.
7. Robert P, ed. *The British Military Surgery Pocket Book*. Camberley, UK: British Army; 2004.
8. Coupland RM, Meddings DR. Mortality associated with use of weapons in armed conflicts, wartime atrocities, and civilian mass shootings: literature review. *BMJ*. 1999;319(7207):407–410.
9. Holcomb JB, Stansbury LG, Champion HR, et al. Understanding combat casualty care statistics. *J Trauma*. 2006;60(2):397–401.
10. Bailey JA, Morrison JJ, Rasmussen TE. Military trauma system in Afghanistan: lessons for civil systems? *Curr Opin Crit Care*. 2013;19(6):569–577.
11. Arnold JL, Halpern P, Tsai MC, et al. Mass casualty terrorist bombings: a comparison of outcomes by bombing type. *Ann Emerg Med*. 2004;43(2): 263–273.
12. Bochicchio GV, Lumpkins K, O'Connor J, et al. Blast injury in a civilian trauma setting is associated with a delay in diagnosis of traumatic brain injury. *Am Surg*. 2008;74(3):267–270.
13. Huller T, Bazini Y. Blast injuries of the chest and abdomen. *Arch Surg*. 1970;100(1):24–30.
14. Busche MN, Gohritz A, Seifert S, et al. Trauma mechanisms, patterns of injury, and outcomes in a retrospective study of 71 burns from civil gas explosions. *J Trauma*. 2010;69(4):928–933.
15. Shariat S, Mallonee S, Stidham SS. *Oklahoma City Bombing Injuries. Oklahoma City: Oklahoma State Department of Health*; 1998.
16. Leibovici D, Gofrit ON, Stein M, et al. Blast injuries: bus versus open-air bombings—a comparative study of injuries in survivors of open-air versus confined-space explosions. *J Trauma*. 1996;41(6): 1030–1035.
17. Kosashvili Y, Loebenberg MI, Lin G, et al. Medical consequences of suicide bombing mass casualty incidents: the impact of explosion setting on injury patterns. *Injury*. 2009;40(7):698–702.
18. Gunst M, Ghaemmaghami V, Gruszecki A, et al. Changing epidemiology of trauma deaths leads to a bimodal distribution. *Proc (Bayl Univ Med Cent)*. 2010;23(4):349–354.
19. Bellamy RF. The causes of death in conventional land warfare: implications for combat casualty care research. *Mil Med*. 1984;149(2):55–62.
20. Butler F. *Tactical Combat Casualty Care Handbook, Version 5*. Fort Leavenworth, KS: US Army Center for Army Lessons Learned; 2017. Available at: https://usacac.army.mil/organizations/mccoe/call/publication/17-13.
21. Mellor SG, Cooper GJ. Analysis of 828 servicemen killed or injured by explosion in Northern Ireland 1970-84: the Hostile Action Casualty System. *Br J Surg*. 1989;76(10):1006–1010.
22. Harrison CD, Bebarta VS, Grant GA. Tympanic membrane perforation after combat blast exposure in Iraq: a poor biomarker of primary blast injury. *J Trauma*. 2009;67(1):210–211.
23. Schild HH, Strunk H, Weber W, et al. Pulmonary contusion: CT vs plain radiograms. *J Comput Assist Tomogr*. 1989;13(3):417–420.
24. Bryant RA. Disentangling mild traumatic brain injury and stress reactions. *N Engl J Med*. 2008;358(5): 525–527.
25. Mac Donald CL, Johnson AM, Cooper D, et al. Detection of blast-related traumatic brain injury in U.S. military personnel. *N Engl J Med*. 2011;364(22): 2091–2100.
26. Chambers LW, Green DJ, Gillingham BL, et al. The experience of the US Marine Corps' Surgical Shock Trauma Platoon with 417 operative combat casualties during a 12 month period of operation Iraqi Freedom. *J Trauma*. 2006;60(6):1155–1161.
27. Weichel ED, Colyer MH. Combat ocular trauma and systemic injury. *Curr Opin Ophthalmol*. 2008; 19(6):519–525.
28. Hull JB, Bowyer GW, Cooper GJ, et al. Pattern of injury in those dying from traumatic amputation caused by bomb blast. *Br J Surg*. 1994;81(8): 1132–1135.
29. Duncan JE, Corwin CH, Sweeney WB, et al. Management of colorectal injuries during operation iraqi freedom: patterns of stoma usage. *J Trauma*. 2008;64(4):1043–1047.
30. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma*. 2007;24(suppl 1): S1–S106.
31. Alfieri KA, Forsberg JA, Potter BK. Blast injuries and heterotopic ossification. *Bone Joint Res*. 2012;1(8):192–197.
32. Maiden N. Ballistics reviews: mechanisms of bullet wound trauma. *Forensic Sci Med Pathol*. 2009; 5(3):204–209.
33. Volgas DA, Stannard JP, Alonso JE. Ballistics: a primer for the surgeon. *Injury*. 2005;36(3):373–379.
34. Ordog GJ, Wasserberger J, Balasubramanium S. Wound ballistics: theory and practice. *Ann Emerg Med*. 1984;13(12):1113–1122.
35. Clasper J. The interaction of projectiles with tissues and the management of ballistic fractures. *J R Army Med Corps*. 2001;147(1):52–61.

36. Coupland R. Clinical and legal significance of fragmentation of bullets in relation to size of wounds: retrospective analysis. *BMJ*. 1999;319(7207):403–406.
37. Fackler ML. Gunshot wound review. *Ann Emerg Med*. 1996;28(2):194–203.
38. Courtney M, Courtney A. Comments on Ballistics: a primer for the surgeon. *Injury*. 2008;39(8):964–965.
39. Santucci RA, Chang YJ. Ballistics for physicians: myths about wound ballistics and gunshot injuries. *J Urol*. 2004;171(4):1408–1414.
40. Bellamy RF, Zajtchuk R. *Conventional Warfare: Ballistic, Blast and Burn Injuries*. Washington, DC: Office of the Surgeon General, Department of the Army; 1991.
41. Shapiro MB, Jenkins DH, Schwab CW, et al. Damage control: collective review. *J Trauma*. 2000; 49(5):969–978.
42. Guthrie HC, Clasper JC, Kay AR, et al. Initial extremity war wound debridement: a multidisciplinary consensus. *J R Army Med Corps*. 2011;157(2): 170–175.
43. Fackler ML. Ballistic injury. *Ann Emerg Med*. 1986;15(12):1451–1455.
44. U.S. Department of Defense. *Emergency War Surgery*. Washington, DC: US Government Printing Office; 1975.
45. Fackler ML. War wound treatments. *Br J Surg*. 1989;76(11):1217–1218.
46. Fackler ML, Breteau JP, Courbil LJ, et al. Open wound drainage versus wound excision in treating the modern assault rifle wound. *Surgery*. 1989; 105(5):576–584.
47. Hill PF, Edwards DP, Bowyer GW. Small fragment wounds: biophysics, pathophysiology and principles of management. *J R Army Med Corps*. 2001; 147(1):41–51.
48. Ordog GJ, Sheppard GF, Wasserberger JS, et al. Infection in minor gunshot wounds. *J Trauma*. 1993;34(3):358–365.
49. Bowyer GW. Management of small fragment wounds in modern warfare: a return to Hunterian principles? *Ann R Coll Surg Engl*. 1997;79(3): 175–182.
50. Meskey T, Hardcastle J, O'Toole RV. Are certain fractures at increased risk for compartment syndrome after civilian ballistic injury? *J Trauma*. 2011; 71(5):1385–1389.
51. Rowley D. *War Wounds with Fractures: A Guide to Surgical Management*. Geneva: International Committee of the Red Cross; 1996.
52. Beech Z, Parker P. Internal fixation on deployment: never, ever, clever? *J R Army Med Corps*. 2012; 158(1):4–5.
53. Nabeel ZS, Rushing A, Haut ER, et al. Outcome of selective non-operative management of penetrating abdominal injuries from the North American National Trauma Database. *Br J Surg*. 2012; 99(suppl 1):155–164.
54. Morrison JJ, Clasper JC, Gibb I, et al. Management of penetrating abdominal trauma in the conflict environment: the role of computed tomography scanning. *World J Surg*. 2011;35(1):27–33.
55. Demetriades D, van der Veen BW. Penetrating injuries of the heart: experience over two years in South Africa. *J Trauma*. 1983;23(12):1034–1041.
56. Barker P. Penetrating wounds of the torso. *J R Army Med Corps*. 2001;147(1):62–72.
57. *Advanced Trauma Life Support Student Course Manual*. 10th ed. Chicago, IL: American College of Surgeons; 2018.
58. Manton WI, Thal ER. Lead poisoning from retained missiles. An experimental study. *Ann Surg*. 1986;204(5):594–599.
59. Jeffery SL. Advanced wound therapies in the management of severe military lower limb trauma: a new perspective. *Eplasty*. 2009;9:e28.
60. Chou TD, Lee TW, Chen SL, et al. The management of white phosphorus burns. *Burns*. 2001;27(5): 492–497.
61. Cannon L. Behind armour blunt trauma—an emerging problem. *J R Army Med Corps*. 2001;147(1): 87–96.
62. Sonden A, Rocksen D, Riddez L, et al. Trauma attenuating backing improves protection against behind armor blunt trauma. *J Trauma*. 2009;67(6): 1191–1199.
63. Mellor SG, Cooper GJ, Bowyer GW. Efficacy of delayed administration of benzylpenicillin in the control of infection in penetrating soft tissue injuries in war. *J Trauma*. 1996;40(suppl 3): S128–S134.
64. Hospenthal DR, Murray CK, Andersen RC, et al. Guidelines for the prevention of infections associated with combat-related injuries: 2011 update: endorsed by the Infectious Diseases Society of America and the Surgical Infection Society. *J Trauma*. 2011;71(2 suppl 2):S210–S234.
65. Jackson DS. Sepsis in soft tissue limbs wounds in soldiers injured during the Falklands Campaign 1982. *J R Army Med Corps*. 1984;130(2):97–99.

88

Chemical, biological, radiological and nuclear exposure management

Sophia De Maria

The concept of using toxins to inflict death and destruction has been around for over 2000 years. As far back as around 600 BC, historians report that the Athenian military tainted the water supply of the besieged city of Kirrha with the poisonous hellebore plant, which then rendered its population so weak with diarrhoea they were unable to fight.[1] However, in today's environment, an 'All Hazards' approach opens our thinking to beyond just chemical and biological warfare. CBRN refers to weaponised and non-weaponised chemical, biological, radiological and nuclear materials that can cause great harm and pose significant threat in the wrong hands. In the context of hazardous materials being used as weapons, the aim is to intimidate, incapacitate, or eradicate crops, livestock and personnel. There have been multiple examples of large-scale chemical attacks, the first being the German gas attack with chlorine on 22 April 1915 in Ypres, Belgium, and most recently chemical attacks in Syria, but also the use of mustard and nerve gases in the Iran/Iraq war and the dissemination of Sarin on the Tokyo underground.[2] As health care providers, we are required to treat and care for casualties of chemical, biological, radiological, nuclear and explosive warfare (CBRNE; see Table 88.1).

CLASSIFICATION

Multiple classification systems exist for CBRN agents and are based on physical properties of the agent or physical or clinical effects on the victim.

The all-hazards approach to classifying agents enables most to be categorised into the three following groups:

Damaging: Examples of damaging agents are mustard gas or low-dose radiation. Patients exposed to these agents are unlikely to die from their exposure, but they will require medical attention, which will impact on available medical resources.

Incapacitating: These agents cause a temporary inability to function either mentally or physically.

Lethal: Examples of this type of agent would be nerve agents, cyanide, phosgene, inhaled anthrax and high-dose radiation.

PHYSICAL PROPERTIES

Persistent: This refers to less volatile and viscous agents such as mustard gas and VX nerve agent, as well as dry powder and particulate matter (e.g. anthrax, asbestos and radioactive debris). These agents can remain in the area for up to several weeks, or even years (e.g. radioactive elements and anthrax spores), and have the potential to cause harm via skin contact or inhalation. These agents require formal decontamination procedures, which will vary depending on the agent.

Non-Persistent: These are volatile substances or gases that evaporate and disperse quickly, such as hydrogen cyanide and carbon monoxide. Exposure to these agents can be limited by ambient conditions and extraction from the affected area. However, some chemicals may be absorbed into clothing and equipment; therefore any clothing should be removed to limit ongoing exposure to the patient and any potential exposure to the rescuer.

ROUTES OF EXPOSURE

There are multiple ways that CBRN agents can enter the body and will result in localised or systemic effects, or both.

Inhalation: The agent – gas, vapour, particles and smoke – is breathed in (e.g. cyanide, carbon monoxide, chlorine, anthrax). This route is probably of greatest significance for critical care due to the significant effects on the airway and the lungs.

Ingestion: Agent – liquid, solid – eaten or drunk (cyanide, anthrax, salmonella). Ingestion may result in the affected patient becoming a reservoir of hazardous chemical that may pose an off-gassing hazard

ABSTRACT

Chemical, biological, nuclear and radiological (CBRN) warfare is an ever-increasing threat and is no longer confined to the conventional battlefield, and therefore it is important to be able to recognise and treat the effects of potential agents.

Managing the potential CBRN casualty, or indeed casualties, should follow the <C>AaBC approach, where <C> is catastrophic haemorrhage and 'a' is antidote (or specific treatment), combined with a quick identification of the potential agent to ensure the appropriate antidote/specific treatment is given in a timely manner.

As with all CBRN casualties, the need for careful decontamination and isolation should be carefully evaluated to avoid potentially affecting carers and other patients.

KEYWORDS

Chemical
biological
radiological
nuclear
antidote
warfare
management
symptoms
treatment
clinical

Table 88.1 Examples of confirmed and suspected chemical, biological, radiological and nuclear materials events

TYPES OF OPERATIONS/SCENARIOS	LOCATION	AGENTS
Armed conflict	Western Front (1915–1918) Manchuria (1938–1945) Hiroshima, Nagasaki (1945)	Chlorine, phosgene, mustard, cyanide Plague, anthrax, cholera, typhoid Nuclear detonation
Civil war	Yemen (1967)	Phosgene
Insurgency	Iraq (2007)	Chlorine
Counter-insurgency	Moscow (2002)	Fentanyl analogue
Civil-ethnic conflict	Halabja (1988) Syria (2017)	Mustard, nerve agent, ?cyanide Sarin/sarin-like agent
Terrorism	Tokyo (1995) Eastern US (2001)	Sarin Anthrax
Assassination	London (1978) London (2006) Kuala Lumpur, Malaysia (2017)	Ricin Polonium-210 VX nerve agent
Disease non-battle injury (DNBI)	Bagram (2002)	Norovirus
Humanitarian operations	Zaire (1994)	Cholera
Accidental	Sverdlovsk (1979)	Anthrax

(cyanide salts reacting with stomach acid to produce hydrogen cyanide gas).

Inoculation: Any penetration of the skin to introduce the agent be it liquid or solid (e.g. in 1978, an assassin used an umbrella to fire a ricin-loaded pellet into Georgi Markov, the Bulgarian dissident's leg).[3,4]

Wound: Any contamination that occurs after the skin has been broken, mainly by live biological agents (tetanus, methicillin-resistant *Staphylococcus aureus* [MRSA]).

Transcutaneous: Agent – liquid, solid – which is absorbed through the skin without initially breaking it. This includes VX (nerve agent), mustard gas, acids and alkalis causing blister wounds.

Ocular: Agent – gas, vapour. This may have a localised effect on the eye but have limited or no systemic effect (e.g. low-level nerve gas causing pinpoint pupils).

MANAGEMENT APPROACH

Management of the patient to any CBRN exposure should follow the <C>AaBC approach – Catastrophic haemorrhage, airway, antidote where applicable, breathing and circulation and a 'quick-look' assessment to establish the responsible agent (Table 88.2).

CHEMICAL AGENTS

A chemical weapon or agent is a 'chemical substance which is intended for use in military operations to kill, seriously injure or incapacitate people due to its physiological effects'.[5] These are substances that can be relatively inexpensive to produce and can cause large number of casualties with small quantities of agent.

Chemical agents can be classified according to the mechanism of action in addition to the previously mentioned properties. These include:

Nerve agents: North Atlantic Treaty Organisation (NATO) classified G series and V series.
- G Series: Tabun (GA), sarin (GB), soman (GD) and cyclosarin (GF) – developed in Germany
- V Series: VE, VG, VM and VX – developed in the United Kingdom

Cyanides: Including hydrogen sulphide (previously categorised as 'blood agents')

Vesicants or blistering agents: Mustard gas and Lewisite

Pulmonary agents (previously categorised as 'choking agents'): Chlorine and phosgene.

NERVE AGENTS (SARIN)

Nerve agents are the most lethal chemical warfare agents and are potent, rapid acting organophosphate compounds that bind irreversibly to and inactivate anticholinesterase resulting in a cholinergic (both muscarinic and nicotinic) toxidrome.[6]

SARIN

Sarin (isopropylmethylphosphofluoridate), a potent organophosphate nerve agent, is a colourless, odourless liquid in its pure form at room temperature. Sarin is volatile and water soluble but will cling to clothing and release slowly over 30 minutes.

Table 88.2 Quick-look table of agents and their toxidromes

	CONSCIOUS LEVEL	RESPIRATORY RATE	EYES/PUPILS	SECRETIONS	SKIN	OTHER
Nerve agent	Fitting ↓	↑↑	Pinpoint	↑↑	Sweaty	Fasiculations
Cyanide	Fitting ↓	↑↑/↓	Normal/dilated	Normal	Pink/cyan	Sudden onset
Vesicant	Normal	↑	Normal/red	Normal/↑	Red (delayed)	Mustard (delayed)
Pulmonary agent	Normal	↑↑	Normal/red	↑	Cyan	Pink sputum
Botulinum	Normal	↓	Dilated	↓	Dry	Descending paralysis
MetHb	Agitated	↑	Normal	Normal	Cyan	Chocolate blood
Atropine	Normal	↑	Dilated	↓	Dry	
Opiate	↓	↓	Pinpoint	Normal	Normal	

Table 88.3 Effects of nerve agent

NERVE AGENTS	
Mechanism: Anticholinesterase inhibition leads to over stimulation of the parasympathetic system, motor neurons and the CNS.	
Mild	Eye symptoms: meiosis, red, painful eyes
Moderate	Increased secretions, wheezing, nausea and vomiting, diarrhoea and difficulty breathing
Severe	Muscle weakness, respiratory arrest, seizures, death
Antidotes	Anticholinergics, oximes, diazepam
Other agents	Organophosphates. Treat as above

CNS, Central nervous system.

SYMPTOMS OF EXPOSURE

Symptoms will depend on the route and duration of exposure (see Table 88.3).

The immediate action is to extricate the casualty from the source, remove clothing and decontaminate skin, ideally with a mild alkaline solution. Eyes are irrigated with water or normal saline.

TREATMENT

Direct compromise of the airway can be due to excessive secretions, or to a reduced level of consciousness, and respiratory failure may be due to severe pulmonary oedema (requiring aggressive suctioning), bronchospasm and muscle weakness.

Circulatory collapse from the excessive secretion production may require fluids and vasopressor support.

ANTIDOTE/SPECIFIC TREATMENT

Anticholinergics: To antagonise muscarinic effects. Intravenous (IV) atropine 2 mg (20 micrograms/kg [max 2 mg] in a child) every 3–5 minutes until symptoms subside (skin becomes dry, pupils dilate and bradycardia resolved). Atropine may need to be continued as an infusion for 24 hours.

Oximes: A cholinesterase reactivator at the nicotinic sites. Pralidoxime chloride 30 mg/kg IV over 20 minutes should be started promptly. (Alternative: obidoxime.)

Benzodiazepine: Diazepam 5 mg (any route) for the management of seizures.

CYANIDES

Cyanides asphyxiate by inhibiting cytochrome oxidase and subsequent impairment of aerobic respiration. This leads rapidly to a severe, refractory metabolic (lactic) acidosis.

At room temperature, hydrogen cyanide is a colourless liquid with a boiling point of 26°C. Due to its high volatility, it is difficult to use in warfare outdoors, but can rapidly reach lethal levels in confined spaces. The most important route of poisoning is through inhalation, but skin contact with both liquid and gaseous hydrogen cyanide can result in significant poisoning.

SYMPTOMS OF EXPOSURE

Symptoms typically are signs of significant hypoxia; nausea, vomiting, agitation, tachypnoea, confusion, followed by loss of consciousness, seizures, coma, respiratory arrest and death.

TREATMENT

Initial assessment in the more severe cases may reveal the need for airway and ventilatory support due to

reduced Glasgow Coma Score (GCS) and hypoxic ventilatory failure, and fluids and vasopressors in patients showing signs of circulatory collapse.

The mainstay of treatment is oxygenation and to assist the body's ability to excrete cyanide via the endogenous enzyme rhodanese, and ultimately renal excretion.

ANTIDOTE/SPECIFIC TREATMENT

Oxygen should be administered to all patients with cyanide poisoning.

Dicobalt edetate: (only in confirmed severe cyanide toxicity as it can cause seizures, upper airway oedema, chest pain, hypotension). 300 mg IV over 1 minute, followed by 50 mL of 50% dextrose to protect against toxicity. Second and third doses can be given if no immediate improvement is seen.

Hydroxycobalamin: (a vitamin B12 precursor) will scavenge cyanide to form cyanocobalamin (Vit B12), a non-toxic by product which is then renally cleared[7,8] and will release the cyanide molecule at a slow rate allowing for detoxification by rhodanese. This is considered a safer option, especially in cases of smoke inhalation as it does not cause methemoglobinaemia or hypotension; 5 g IV over 15 minutes and a second dose of 5 g can be given if necessary.

Sodium/amyl nitrite with sodium thiosulphate is an alternative therapy.

VESICANTS/BLISTER AGENTS (MUSTARD GAS)

Vesicants or blister agents are alkylating agents that inhibit glycolysis at the cellular level resulting in cellular necrosis. They are readily absorbed through the eyes and mucous membranes, respiratory tract and skin.

Mustard gas is a yellow oily liquid at room temperature, which evaporates and can penetrate clothing. The effects of mustard gases are typically delayed by 2–4 hours.

SYMPTOMS OF EXPOSURE

The degree of symptoms will depend upon the nature of exposure (gas vs liquid) and the duration of exposure. Contact with mucus membranes results in erythema and subsequent bullae formation, which rupture on contact. Contact with the eyes can cause temporary blindness due to corneal damage, whereas inhalation causes airway burns with possible subsequent obstruction and acute respiratory distress syndrome (ARDS).

TREATMENT

There is no specific antidote for mustard gas exposure and management is supportive.

Inhaled mustard gas can cause respiratory distress/failure requiring ventilatory support due to direct damage to the mucosa, as well as triggering the systemic inflammatory response syndrome (SIRS).

Patient with large burns are treated as any other burn injury with fluid resuscitation, analgesia and addressing any secondary infections.

With mustard burns, vesication may progress for up to 2 weeks after the initial insult[9] and wound healing is protracted, taking at least 12 weeks to heal.

Eye lesions, aided by saline irrigation and topical antibiotics, usually heal in 2 weeks.

PULMONARY AGENTS (CHLORINE AND PHOSGENE)

Pulmonary agents act by direct irritation of the airway mucosa by direct cellular damage (chlorine), or by inflammatory response and free radical formation (phosgene).

The water-soluble chlorine results in predominantly upper airway symptoms but also lung damage with prolonged/high concentration exposure, whereas the low water-soluble phosgene usually exhibits lower airway symptoms rather than upper airway symptoms.

SYMPTOMS OF EXPOSURE

Chlorine

Rapid onset upper airway symptoms, including conjunctivitis, rhinitis and pharyngitis predominate, even when exposed to relatively low concentrations. Airway oedema, laryngospasm and dyspnoea can develop with more prolonged exposure or at higher concentrations.

Phosgene

Symptom onset is usually delayed with lower airway symptoms such as pneumonitis and non-cardiogenic pulmonary oedema presenting 12–24 hours after exposure.

TREATMENT

There is no specific antidote for chlorine or phosgene exposure and treatment is supportive.

The patient may require early intubation if there is evidence of significant upper airway oedema or laryngospasm.

Both chlorine and phosgene exposure result in increased permeability of the alveolar-endothelial membrane leading to non-cardiogenic pulmonary oedema, alveolar collapse and a type 1 respiratory failure pattern. Specific respiratory management includes reducing the closing capacity and alveolar recruitment with continuous positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP). However, both should be used with caution if there are concerns about the haemodynamic stability of the individual, and patients should be adequately volume expanded to maintain venous return.

There may be some role for bronchodilators and inhaled steroids, although systemic steroids are more

controversial with inadequate evidence to support this at present.

The patient may require cardiovascular support, especially if the patient has sustained other injuries.

ANTIDOTE/SPECIFIC TREATMENT

There is no specific antidote treatment for chlorine or phosgene exposure.

BIOLOGICAL AGENTS

Biological weapons achieve their effect by infecting people, animals or plants with a disease causing microorganism or other replicative entity, including viruses, fungi, prions or biological toxins. The extent of the effect depends upon many factors including immunological status of the host population, nutrition and the environment (e.g. sanitation, temperature, water quality, population density).[10]

Biological agents can be classified as:

Live agents: including bacterial, viral, fungal, chlamydial and rickettsial.

Toxin: A toxin can be considered to be a chemically active agent of biological origin. It does not self-replicate and therefore is not transmissible once decontamination has occurred. Biological toxins can be derived from microbes (botulinum), animal (snake and scorpion venom) and plant (ricin and digitalis).

ANTHRAX

In 2001, anthrax spores were disseminated through the United States postal system in envelopes containing threatening notes sent to prominent politicians and media figures. This resulted in five deaths, and anthrax remains the most likely organism to be used in a biological terrorist attack.[11,12]

Bacillus anthracis, the causative agent of anthrax, is a large, Gram-positive, spore forming, aerobic bacillus. The organism readily forms spores, which are highly infectious. Several manifestations of the disease exist, depending on the route of exposure; that is, cutaneous anthrax, gastrointestinal (GI) disease, pulmonary anthrax and anthrax meningitis, and some or all of the forms could present themselves in a mass casualty scenario (e.g. aerosolised spores disseminated over a large urban population by an aircraft). Of these presentations, pulmonary anthrax and anthrax meningitis have the highest mortality.[13]

SYMPTOMS OF EXPOSURE

Pulmonary exposure

Pulmonary exposure is likely to be the primary form of exposure in a mass casualty scenario due to its ease of dissemination. The median incubation period for pulmonary anthrax is 4 days but ranges from 2 to 60 days have been reported. The initial symptoms of infection are non-specific with fever, malaise, non-productive cough, nausea and vomiting, confusion before progressing to respiratory failure and cardiovascular collapse. Chest X-ray (CXR) shows infiltrates, pleural effusion and a widened mediastinum due to lymphadenopathy and haemorrhagic mediastinitis.

Cutaneous exposure

Cutaneous anthrax accounts for greater than 95% of all human cases worldwide and is more often self-limiting than the other forms of anthrax infection.[14] Anthrax eschars are usually seen on the exposed unprotected areas of the body such as upper limbs, face and neck with incubation periods ranging from as little as 9 hours to 3 weeks, with the majority of individuals developing symptoms between 2 and 6 days. The infection starts as a papular lesion accompanied by marked oedema before progressing to the characteristic black eschar, which may take several weeks to fully develop and resolve. Large lesions may require skin grafting, and surgical intervention may be required due to scarring in areas such as the eyelid.

Gastrointestinal exposure

This usually follows ingestion of infected meat and presents with abdominal pain and bloody diarrhoea followed rapidly by cardiovascular collapse and death.

TREATMENT

Immediate severe sepsis management is the mainstay of treatment, including a multidrug therapy regime. Patients may not require airway and ventilator support initially but may progress to ventilatory failure as sepsis progresses.

ANTIDOTE TREATMENT

Ciprofloxacin 400 mg IV 12-hourly plus 1 or 2 of the following;

Penicillin (amoxicillin in pregnant patients and children), rifampicin, vancomycin, imipenem, clindamycin or clarithromycin according to sensitivities and convert to oral dosing as tolerated.

Treatment is prolonged and requires antibiotics for 60 days.

Passive immunisation: Consider immunoglobulins if available and appropriate.

BOTULINUM TOXIN

Botulism is caused by several neurotoxins (types A–G) produced by the anaerobic, Gram-positive bacillus, *Clostridium botulinum.* The botulinum toxins act at four different sites in the body: The neuromuscular junction, autonomic ganglia, and postganglionic parasympathetic and sympathetic nerve endings that release acetylcholine. The neurotoxin acts by direct, irreversible inhibition of receptors at the pre-synaptic surface

of neurons. This prevents the fusion of acetylcholine vesicles with the pre-synaptic membrane and the subsequent release of the acetylcholine.[15] The blockade is most evident clinically in the parasympathetic autonomic nervous system and at the neuromuscular junction. A biological warfare attack with botulinum toxin delivered by aerosol or as an inoculation would be expected to cause symptoms similar to those observed with food-borne botulism.

SYMPTOMS OF EXPOSURE

Patients typically present responsive, afebrile, with a rapidly descending flaccid paralysis with intact sensation. Early signs and symptoms include ptosis, generalised weakness and dizziness. Motor symptoms are usually present in the early stages; cranial nerves (mainly bulbar) are affected first with diplopia, dilated pupils, ptosis, dysphagia, dysphonia and dysarthria. This is followed by a symmetrical, descending flaccid paralysis of the extremities along with weakness of the respiratory muscles with potentially abrupt respiratory failure. Symptoms of parasympathetic inhibition may also be present.

The diagnosis is primarily clinical with confirmation with the mouse inoculation studies and immunoassays. Differential diagnoses include Guillain-Barré syndrome (Miller Fisher variant), myasthenia gravis and tick paralysis.

TREATMENT

Patients should have frequent assessment of gag, cough reflexes, inspiratory force and vital capacity as respiratory failure can be sudden. Mechanical ventilation and supportive therapy may be protracted with nosocomial infections requiring antibiotics (aminoglycosides and clindamycin are contraindicated due to their ability to increase blockade[16,17]).

ANTIDOTE/SPECIFIC TREATMENT

Early administration of the polyvalent antitoxin (types A, B and E) is essential to neutralise circulating toxin, and administration is advised where botulism is a differential diagnosis. Pregnant women, children and immunocompromised patients have been treated with the equine antitoxin safely.

Caution: Hypersensitivity reactions are a problem and may be severe, including anaphylaxis, and should be prepared for prior to administration. All patients should be skin tested for sensitivity.[18]

Contacts with infected patients should be observed closely and treated with antitoxin, a neutralising antibody and the pentavalent toxoid vaccine at the first signs of illness.

PLAGUE

Plague is a zoonotic disease caused by the Gram-negative, coccobacillus *Yersinia pestis* from the *enterobacter* species. Under natural conditions, humans become infected as a result of contact with rodents and their fleas causing bubonic and septicaemic plague. A proportion of bubonic plague patients develop pneumonia, which may then spread by droplets causing primary pneumonic plague. In a bioterrorist scenario, the plague bacillus is likely to be airborne, resulting in multiple casualties with pneumonic plague, which is highly contagious (transmissible).

SYMPTOMS OF EXPOSURE

Pneumonic plague: For primary (inhaled) pneumonic plague, the incubation period is short (2–3 days) and presents with high fever, headache, myalgia, chest pain and cough productive of bloody sputum. The pneumonia progresses rapidly to respiratory failure, circulatory collapse and multiorgan failure. Mortality in untreated patients is 100%. The diagnosis can be confirmed on blood cultures and with antibody testing. CXR shows evidence of bronchopneumonia.

Bubonic plague: Bubonic incubation period is 2–10 days. Onset is acute with high fevers, malaise and tender lymph nodes (buboes). Inguinal lymphadenitis predominates but cervical and axillary lymph nodes can also be affected. The nodes are tender, fluctuant and necrotic.

Septicaemic plague: The bubonic form may spontaneously progress to the septicaemic form with central nervous system (CNS) and respiratory involvement. Mortality in untreated patients in this group is 50% due to circulatory collapse, haemorrhage and peripheral thrombosis.

TREATMENT

Pneumonic plague is highly transmissible and isolation and universal precautions should be implemented. Immediate resuscitation treatment should follow standard sepsis management.

ANTIDOTE/SPECIFIC TREATMENT

Antibiotics for severe infection

Gentamicin 5 mg/kg IV OD
Streptomycin 1 g intramuscularly 12-hourly or
Ciprofloxacin 400 mg IV 12-hourly
add chloramphenicol 25 mg/kg four times per day if evidence of plague meningitis

Antibiotics: Mild infection
Ciprofloxacin 500 mg PO or
Doxycyline 100 mg PO 12-hourly
(Consider ofloxacin and levofloxacin if evidence of resistance to doxycycline.)

SMALL POX

Small pox is an acute viral illness caused by the variola virus, orthopoxvirus. An illness specific to humans, it was a cause of significant morbidity and mortality

in the developing world until recent times. The last recorded case of the natural disease was in Somalia in 1977, and the world was declared free of the disease in 1979 following a global immunisation campaign led by the World Health Organization. The virus now officially exists in only two laboratories in the world, in Russia and the United States. Although there was a human infection case in 1983 (laboratory worker), the appearance of human cases outside of these laboratories would signal the use of the virus as a biological weapon.

Transmission of the virus is by direct contact with an infected case and by the airborne route. The smallpox virus is very stable and can retain its infectivity for long periods outside the body, for example, on clothing.

The disease has been eradicated outside of the laboratory and, as a result, routine immunisation stopped in 1972. A related zoonotic virus, monkeypox, clinically resembles smallpox and has caused sporadic human disease in West and Central Africa.

CLINICAL FEATURES

There is a flu-like prodrome lasting 2–3 days with malaise, fever, rigors and headache. This is followed by the synchronously evolving maculopapular rash progressing to vesicles and then to pustules. The rash tends to involve the face and extremities rather than the trunk. The pustules eventually form crusts and drop off leaving depressed, de-pigmented scars. The patient is contagious from the appearance of the fever until the last scab has healed.

In unvaccinated individuals, the mortality rate is approximately 35%. In a subset of patients, haemorrhagic diathesis and disseminated intravascular coagulation (DIC) develop and has a poor prognosis.

Investigations, such as taking skin, vesicular fluid or pus samples for direct electron microscopy and agar gel immunoprecipitation confirms the diagnosis.

TREATMENT

Small pox is highly transmissible; isolation and universal precautions should be implemented. The mainstay of treatment is supportive and management of secondary sepsis.

ANTIDOTE/SPECIFIC TREATMENT

Active vaccination with the small pox vaccine (vaccinia) should be given within 4 days of exposure, especially in high-risk groups such as pregnancy, HIV infection, chemotherapy, immune disorders and eczema. Also a ring vaccination strategy should be considered as a method of containing any outbreak.[19]

RICIN

Ricin, a glycoprotein toxin extracted from the beans of the castor plant, is one of the most toxic biological agents known, and is of significance as a biological weapon due to its availably worldwide, its ease of production and its extreme pulmonary toxicity. The most notorious case of ricin being used as a weapon was against the Bulgarian broadcaster, Georgi Markov, in London in 1979 who was killed with a ricin-contaminated pellet injected into the back of his leg using a modified umbrella.[4]

The ricin toxin acts by altering the ribosomal mRNA processing and thus inhibiting protein synthesis in eukaryotic cells leading to cell death. The effects of ricin poisoning would depend upon the route, the amount of ricin exposure and the patient's premorbid condition. Ingestion and mastication of three to six castor beans is estimated to be a fatal dose in adults, although most cases of ingestion of the whole castor bean do not result in poisoning as the protective coating of the bean prevents absorption (providing the bean has not been chewed). In addition, ricin is not well absorbed through the GI tract. Inhalation or injection of ricin would result in more rapid onset and severity of toxicity for the equivalent dose.

CLINICAL FEATURES

The clinical picture of ricin toxicity depends on the route of exposure and much of the information is based on animal studies.

Ingestion: All recorded episodes of ingestion have followed a similar clinical picture of rapid onset nausea, vomiting, abdominal cramps and severe diarrhoea followed by cardiovascular collapse and death within 3–4 days.

Inhalation: In mice, the inhalation of ricin resulted in necrotising, suppurative airway lesions and interstitial pneumonia with perivascular and alveolar oedema seen as early as 3 hours post-exposure.

Investigations to confirm ricin toxicity include enzyme-linked immunosorbent assay (ELISA), immunohistology and serology. Other non-specific laboratory findings include: metabolic acidosis, deranged liver and renal function, haematuria and leucocytosis.

TREATMENT

Treatment is supportive, which may include respiratory support, fluids and seizure prevention.

ANTIDOTE/SPECIFIC TREATMENT

An antitoxin is currently under development.

RADIATION AND NUCLEAR HAZARDS

Radiological and nuclear hazards can be either intentional (e.g. 'dirty bomb') or accidental (e.g. a radioactive source has been abandoned at a waste dump/disused medical facility). In the case of intentional exposure, this can either be in the form of an explosive

device where the patient may suffer contaminated traumatic injuries, or a covert radioactive source left in a public place causing significant irradiation without causing any contamination.

The casualty type will depend upon the scenario and will include the following in isolation or combination:

External contamination
Internal contamination
Wound contamination
Irradiation
Combined injuries (irradiation and trauma).

TYPES OF RADIATION

There are four biologically significant types of ionising radiation that may be encountered, including those derived from a nuclear detonation:

Alpha particles: Charged helium nuclei (two protons and two neutrons) are relatively heavy with low penetrating power and are absorbed by the first 20 micrometres of exposed tissue. Alpha particles can therefore be shielded by paper, overalls and mask to prevent internal and wound contamination. However, following ingestion of alpha-emitting radioactive material by ingestion or inhalation, significant damage can occur to the sensitive tissues of the respiratory and GI tract. Ingestion of this type of radiation is associated with cellular damage rather than acute radiation syndrome (ARS).

Beta particles: Energetic electrons emitted from neutron-rich atomic nuclei. Beta particles are significantly smaller than alpha particles and can penetrate skin and cause damage to the epithelial basal stratum. Beta particles can be shielded by layers of plastic or a sheet of metal.

Gamma (high-energy photon) radiation: This radiation is high-energy electromagnetic radiation and is capable of creating ionisation. High-energy photons are highly penetrating and a large fraction may pass through the body without interaction. Dense materials, such as lead or concrete, are used to attenuate gamma radiation.

Neutrons: These are uncharged particles and are usually associated with the nuclear fission process. These particles are highly penetrating and cause significant damage to biological tissue.

Ionising radiation causes its effect by its interaction with DNA. At low levels, radiation causes damage to the DNA increasing the chance of mutation and cancer. At very high levels; that is, levels greater than two sieverts (approx 1000 × the annual background radiation dose in the United Kingdom or approx 100,000 CXR) radiation causes cell death. The most sensitive tissues are those that have the greatest turnover such as bone marrow and GI mucosa. Death following large radiation dose exposure is generally due to coagulopathy or infection. The failure of these systems due to radiation is called ARS.

ARS has been divided into four main phases:

1. An initial 'prodromal phase' occurring during the first few hours after exposure.
2. A 'latent phase', which decreases in time with increasing dose exposure.
3. The 'manifest illness' (clinical) phase involving haematological, GI and neurovascular systems.
4. Recovery or death.

The severity of the symptoms will increase and the duration of each phase will shorten with increasing acute radiation dose.

Diagnosis of ARS is made on a history of significant exposure to radiation, and the fall in circulating lymphocytes can be used as a crude biodosimetry tool to estimate the effective radiation dose received.

SYMPTOMS OF EXPOSURE

Prodromal phase: This phase is characterised by the rapid onset of nausea, vomiting, malaise, headache, and in severe cases, diarrhoea. This is thought to be due to serotonin and histamine release. These symptoms can resolve very quickly and the diagnosis of ARS can be overlooked.

Latent phase: The patient is relatively symptom free during this phase, and the length of this phase depends on the nature of the manifest illness.

Haematopoietic syndrome: the latent phase may vary between 2 and 6 weeks.

GI syndrome: this tends to be shorter, lasting a few days to a week.

Neurovascular syndrome: this is the shortest latent phase lasting only a few hours.

Manifest illness: The manifest illness phase presents with the clinical symptoms associated with the cell death of the major organ system exposed (i.e. bone marrow, GI tract and neurovascular systems). These sub-syndromes are dose dependent.

Haematopoietic: Bone marrow suppression resulting in pancytopaenia will result in:
Haemorrhage (thrombocytopaenia)
Immunosuppression followed by infection (leucopaenia)
Anaemia (reduced red cell count).

The changes in the peripheral blood profile may occur as early as 12 hours post-irradiation although the exact time sequence of depression of various cell lines will vary. The onset of clinical effects range from 10 days to 6–8 weeks post-exposure and death occurs from overwhelming infection and/or haemorrhage.

GI: The main symptoms encountered are nausea, vomiting, loss of appetite, abdominal pains and after a short latent period of a few days to a week, progress

to the characteristic severe fluid losses secondary to haemorrhage and diarrhoea. GI syndrome has a poor prognosis as it is almost always accompanied by bone marrow suppression. The mucosal damage of the GI tract allows the translocation of gut bacteria causing a bacteraemia, which is compounded by the accompanying immunosuppression. Survival is possible with aggressive sepsis and fluid management, and haemorrhage control.

Neurovascular: This syndrome occurs with high, acute doses of radiation and has a short latent phase varying from a few hours to 1–3 days. It presents with symptoms of dizziness, headache followed by a steadily decreasing level of consciousness with eventual coma and death. This rapid and invariably fatal deterioration is due to increased microvascular membrane permeability leading to cerebral oedema, hypotension and cerebrovascular insufficiency. Seizures may or may not occur and there may be little or no evidence of raised intracranial pressure. Due to the high doses of radiation required to cause this syndrome, individuals close enough to a nuclear detonation to be exposed to this dose would generally be located well within the 100% lethality radius for blast and thermal effects.[20]

Cutaneous: This encompasses effects from localised skin exposure through to effects from whole body irradiation. Damage to the skin can present in three ways:

Cutaneous syndrome from whole body irradiation

Local radiation due to close contact with gamma radiation

Beta burns.

Skin changes usually happen within a few hours of irradiation and consist of redness, itching followed by blistering and ulceration of the irradiated site. Large doses can cause permanent hair loss, damage to sebaceous and sweat glands, atrophy and fibrosis. Cutaneous changes are usually seen at radiation doses associated with both haematopoietic and GI syndromes.

TREATMENT

Treatment of any forms of irradiation exposure follows the <C>AaBC principle with sepsis management for neutropaenic patients, blood products such as cytokine (stimulation) therapy and transfusions and eventually cell stem transplant as clinically indicated. Survival from the haematopoietic syndrome will be based on early diagnosis, replacement therapy, infection prevention and bone marrow regeneration.

Acknowledgement

I would like to take this opportunity to acknowledge and thank Dr Steve Bland for his assistance and guidance on this chapter.

REFERENCES

1. Mayor A. *Greek Fire, Poison Arrows & Scorpion Bombs: Biological and Chemical Warfare in the Ancient World. Woodstock*, NY: Overlook; 2003.
2. Okumura T, Takasu N, Ishimatsu S, et al. Report on 640 victims of the Tokyo subway sarin attack. *Ann Emerg Med*. 1996;28(2):129–135. PubMed PMID: 8759575.
3. https://nsarchive.wordpress.com/2010/07/16/document-friday-the-poisonous-umbrella-and-the-assassination-of-georgi-markov/.
4. Paploucas M, Paploucas C, Stergioulas A. Ricin and the assassination of Georgi Markov. *Pak J Biol Sci*. 2008;11(19):2370–2371.
5. Evison D, Hinsley D, Rice P. Chemical weapons. *BMJ*. 2002;324:332–335.
6. Sidell FR, Borak J. Chemical warfare agents: II. Nerve agents. *Ann Emerg Med*. 1992;21:865–871.
7. DesLauriers CA, Burda MA, Whal M. Hydroxycobalamin as a cyanide antidote. *Am J Ther*. 2006; 13(2):161–165.
8. Hall A, Saiers J, Baud F. Which cyanide antidote? *Crit Rev Toxicol*. 2009;39(7):541–552.
9. Rice P. Sulphur mustard injuries of the skin: pathophysiology and management. *Toxicol Rev*. 2003; 22(2):111–118.
10. WHO. *Health Aspects of Chemical and Biological Weapons*. Geneva: WHO; 2003.
11. Inglesby TV, O'Toole T, Henderson DA, et al. Anthrax as a biological weapon, 2002. Updated recommendations for management. *JAMA*. 2002;287: 2236–2252.
12. Kaur M, Singh S, Bhatnagar R. Anthrax vaccines. Present state and future prospects. *Expert Rev Vaccines*. 2013;12(8):955–970.
13. Bower WA, Hendricks K, Pillai S, et al. Clinical frameworks and medical countermeasure use during an anthrax mass casualty incident. CDC Recommendations. *MMWR Recomm Rep*. 2015; 64(4):1–22.
14. Turnbull P, Cosivi O. *Anthrax in Humans and Animals*. 4th ed. Geneva: WHO; 2008:43.
15. Brin MF. Botulinum toxin. Chemistry, pharmacology, toxicity and immunology. *Muscle Nerve Suppl*. 1997;6:S146–S168.
16. Arnon SS. Botulinum toxin as a biological weapon: medical and public health management. *JAMA*. 2001;285:1059–1070.
17. Schulze J, Toepfer M, Schroff KC, et al. Clindamycin and nicotinic neuromuscular transmission. *Lancet*. 1999;354:1792–1793.
18. Black R, Gunn R. Hypersensitivity reactions with botulinum antitoxin. *Am J Med*. 1980;69: 567–570.
19. Kretzschmar M, van den Hof S, Wallinga J, et al. Ring vaccination and smallpox control. *Emerg Infect Dis*. 2004;10(5):832–841. doi:10.3201/eid1005.030419.
20. Bland S. *Medical Management of CBRN Casualties*. North Atlantic Treaty Organisation, Allied Medical Publication; 2017.

Part Thirteen

Pharmacologic Considerations

This page intentionally left blank

89

Pharmacokinetics, pharmacodynamics and drug monitoring in acute illness

Christine Chung

PHARMACOKINETICS

The basic terms used in pharmacokinetics (PK) include bioavailability (F), target (desired) plasma concentration (C_p), volume of distribution (V_d), clearance (Cl) and half-life ($t_{1/2}$).

Bioavailability is the fraction of the administered dose that reaches the systemic circulation[1] and is dependent on many variables including absorption (see later). The value of F for the intravenous (IV) route is usually 1 unless the drug in question is a prodrug (i.e. requires metabolism to its active form). For an oral dosage form, F would also be less than 1 in the majority of cases as a certain percentage of the drug can be lost at each stage of the journey from the gastrointestinal tract to its site of metabolism. For example, bioavailability of digoxin tablets is 0.63 and the liquid 0.75.[2] Therefore, strictly speaking, converting from an oral to an IV dose requires a 20%–30% reduction to provide an equivalent amount of drug. In practice, it is recommended that the dose is reduced by 25%. C_p is the desired plasma concentration.[1]

ABSORPTION

In order for a drug molecule to be absorbed, it is required to cross a membrane. Membranes are comprised of a phospholipid bilayer, with a hydrophilic exterior and a hydrophobic core. Fat-soluble drugs use passive diffusion to cross the membrane barrier. Extremely small water-soluble molecules gain entry through narrow aqueous membrane channels. The majority of water-soluble drugs travel by other mechanisms (e.g. via an active transport process facilitated by an energy source, i.e. adenosine triphosphate [ATP]).[3]

Unionised molecules pass freely through membranes; ionised molecules do not.

Therefore, lipid-soluble drugs, such as phenytoin, can be easily absorbed from the gastrointestinal tract whereas large, water-soluble and polar drugs, such as gentamicin, cannot (Fig. 89.1).

Enteral

The majority of drugs used in critical care are administered via the IV route. There are occasions, however, where an essential drug exists only in the oral form. How much is absorbed via the enteral route is governed by many factors such as:

- site of drug absorption in the gastrointestinal tract; that is, whether it can be accessed (e.g. small bowel obstruction) or if its absorptive capacity is compromised by hypoperfusion in septic shock, for example
- delayed gastric emptying may increase the absorption for drugs absorbed in the acidic environment of the stomach. Conversely, basic drugs usually absorbed in the small intestine may be reduced due to increased degradation in the stomach prior to delivery
- apical drug transporters (e.g. P-glycoprotein/multidrug resistance protein-1 that return drugs back to the intestinal lumen) limit bioavailability[4] but are also affected by systemic inflammatory conditions, such as sepsis, in an unpredictable manner
- whether the pH of the stomach is optimal (e.g. bioavailability of atazanavir is significantly reduced by agents used for stress ulcer prophylaxis. Proton pump inhibitors reduce atazanavir's solubility by raising the pH of the stomach.[5] Weak basic drugs, such as atazanavir, require a low pH for absorption)
- presence of enteral feed that may significantly reduce the efficacy of certain drugs (e.g. phenytoin is best administered in the middle of a 4-hour rest period from enteral feed)[6]
- presence of other drugs that may bind and reduce bioavailability if administered at the same time (e.g. ciprofloxacin and ferrous fumarate)[7]
- formulation of drug administered (e.g. liquid vs tablet)
- gut transit time (e.g. profuse diarrhoea may lead to reduced time for absorption and potentially therapeutic failure)
- gut integrity and perfusion (often reduced in the critically ill)
- extent of first-pass metabolism (see metabolism), which can significantly reduce the amount of drug reaching the systemic circulation or lead to drug toxicity if the liver is failing.[8]

Intramuscular and subcutaneous

The effects of drugs given via intramuscular (IM) or subcutaneous (SC) routes can be erratic and unpredictable

ABSTRACT

Pharmacokinetics (PK) describes a drug's journey through the body. It is the study of a drug's absorption, distribution, metabolism and excretion over time. Pharmacodynamics (PD) is the physiological effect of a drug on the body. The relationship between the two can be used to individualise dosing regimens by predicting how a drug will behave in a given patient.

Manufacturer's dosing ranges are often based on the PK-PD of a normal patient population. While there may be guidance on dosing in special populations (e.g. liver and renal failure) there is rarely advice on dosing in the critically ill.

The effect of critical illness on PK and PD is complex, variable and often unpredictable. Optimisation of treatment remains a therapeutic challenge with drugs that do not have measurable parameters to determine dosing. As a patient improves or deteriorates clinically, drug regimens require adjustment to maximise benefit while minimising adverse toxic effects. The aim of this chapter is to provide the reader with the basic principles of PK and PD to aid in their understanding of drug dosing in the intensive care unit patient.

KEYWORDS

Pharmacokinetics
pharmacodynamics
critical illness
intensive care
absorption
distribution
metabolism
excretion
augmented renal clearance
therapeutic drug monitoring

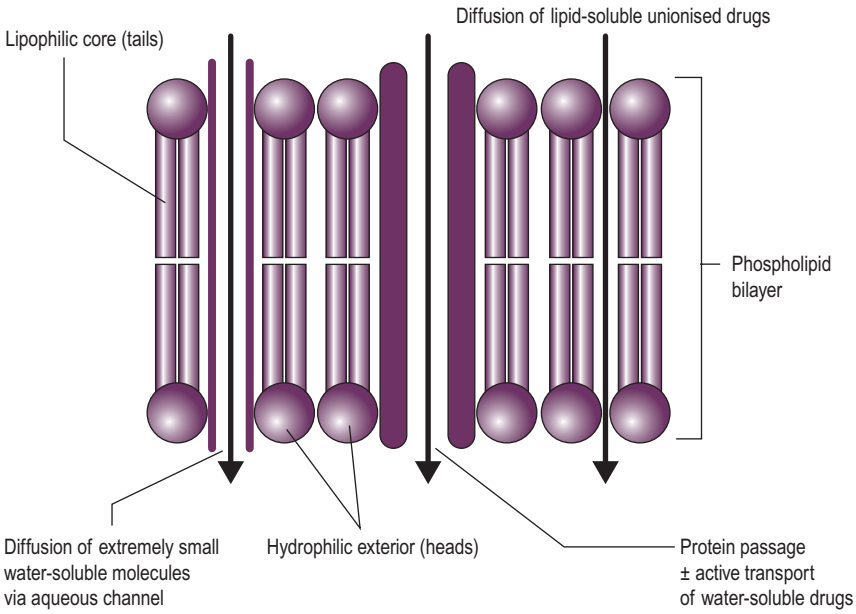


Figure 89.1 Diagram of a membrane.

depending on local blood flow to tissues, adipose and muscle mass. Muscle perfusion is often significantly reduced in patients with haemorrhagic shock making it an undesirable route of administration if rapid systemic effects are required; for example, anti-Factor Xa levels can be severely reduced in patients who are administered SC low-molecular-weight heparin that can predispose them to a venous thromboembolic events; SC oedema as a consequence of aggressive fluid resuscitation in sepsis can also reduce bioavailability of drugs administered via this route.

Local blood flow into adipose tissues is approximately 5% of cardiac output compared to approximately 70% for lean tissues.[9] Therefore obese patients have reduced peripheral perfusion and lower SC adipose tissue concentrations of drugs (see effects of obesity on PK).

Also, patients with a coagulopathy may be at increased risk of bleeding from the IM injection site.

Intravenous

The IV route is the most common form of drug administration in the intensive care unit (ICU) as it usually guarantees 100% bioavailability. However, several factors can still affect drug efficacy:

- drug–drug incompatibility when drugs of very different pHs are administered via the same IV line (e.g. propofol [near neutral pH] and atracurium [acidic pH])[10]
- drug–diluent incompatibility when a very acidic drug (e.g. amiodarone) is diluted with sodium chloride 0.9% (near neutral pH)[11] or a very basic drug (e.g. furosemide) is diluted with dextrose 5% (weakly acidic).[12]

The resultant salt-formed precipitates can lead to line occlusion, loss of drug efficacy and possible danger of systemic embolisation.

- Temperature and light can lead to degradation of, for example, parenteral nutrition,[13] or sodium nitroprusside to cyanide ions,[14] which explains the need for an opaque covering
- Too much diluent (e.g. amiodarone diluted beyond 0.6 mg/L comes out of solution, leading to loss of efficacy).[11]

DISTRIBUTION

Volume of distribution (V_d) is the theoretical volume of fluid into which the total drug administered would have to be diluted to produce the same concentration in plasma. It is unrelated to volume of the body or its fluid compartments but rather to its distribution.[15] V_d is increased by factors decreasing plasma drug concentration[1]:

- reduced protein binding (increased drug available for tissue binding)
- increased tissue binding
- increase in body fat (for fat-soluble drugs)
- oedema, ascites, effusion fluid (for water-soluble drugs)
- sepsis (endothelial damage and increased capillary permeability where fluid leaks into the interstitial space for water-soluble drugs)

- positive-pressure mechanical ventilation (for water-soluble drugs).

Decreased V_d results from the opposite of the above.

Calculation of V_d:

$$V_d = \frac{A}{C} \quad (89.1)$$

where V_d = apparent volume of distribution (L), A = total amount of drug in organ (mg), C = plasma concentration of drug (mg/L).

For example, gentamicin, a hydrophilic drug with minimal protein binding, has a low V_d similar to the extracellular fluid volume (0.25 L/kg).[16] In a septic, mechanically ventilated patient, the V_d of gentamicin increases as the effective extracellular volume increases, and a larger dose is required to obtain therapeutic levels.[17,18]

Phenytoin, a lipophilic drug, is 90% protein bound with a V_d similar to total body volume (0.65 L/kg).[1] Hypoalbuminaemia in critical illness increases the free, pharmacologically active fraction of phenytoin. This should be taken into account when interpreting phenytoin levels. The latter is normally reported as total serum concentrations that assume normal protein binding.

Morphine extensively binds to tissue and has a high V_d (4 L/kg).[19] Uraemia displaces drugs, such as morphine, from their tissue-binding sites, thereby increasing their plasma concentration while reducing the V_d, and this can lead to toxicity.

A drug with a high V_d will take considerable time to reach organ equilibration (approximately four to five times the half-life)[1]:

$$t_{1/2} = 0.693 \times V_d / Q \quad (89.2)$$

where Q = organ blood flow.

V_d is used to calculate the *loading dose* (L_d); that is, the dose required to rapidly achieve a desired therapeutic concentration (C_p) of drug:

$$L_d = \frac{V_d \times C_{pss}}{S \times F} \quad (89.3)$$

where C_{pss} = desired plasma concentration at steady state, S = salt factor of drug, F = bioavailability as a fraction.

For example, the L_d of phenytoin sodium for a 70-kg patient via the IV route would be:

$$L_d = \frac{0.65\ \text{L/kg} \times 70\ \text{kg} \times 15\ \text{mg/L}}{0.92 \times 1} = 741.8\ \text{mg}$$

The dose is usually rounded to the nearest easily measurable value (i.e. 750 mg in this case). (**NB:** This differs considerably from the standard 15 mg/kg dose often used in emergency practice where other prior antiepileptic medicines may have been given.)

Critically ill patients sometimes demonstrate subtherapeutic levels of phenytoin despite accounting for the unbound fraction due to hypoalbuminaemia. A possible explanation is that, as there is more of the free fraction available, more is available for metabolism and excretion. Alternatively, reduced hepatic function may lead to accumulation.[20]

METABOLISM

Metabolism can occur using either or both of the following[21]:

- *Phase I reactions* involve addition or exposure of a polar group, for example –OH. Oxidation or reduction reactions in liver microsomes are catalysed by cytochrome P-450 (CYP) enzymes and hydrolysis of esters to alcohol and carboxylic acid by esterases. Phase I metabolism can therefore be affected by reduced oxygenation delivery as a result of hypoperfusion.
- *Phase II reactions:* these increase a drug's hydrophilicity, promoting its renal or biliary excretion. Conjugation or synthesis takes place in the liver or the lung (e.g. glucuronidation, sulphation, acetylation, methylation). The kidney can excrete the drug metabolite by both filtration, and potentially, by active secretion, into the urine. Usually metabolites are less active than their parent compound, are more polar and more readily excreted in bile or urine.

Extensive first-pass metabolism refers to a drug that is significantly metabolised by the liver prior to becoming available to the systemic circulation.

ELIMINATION

CLEARANCE IN AN ORGAN

The liver and the kidney are the main organs involved in drug removal from the body. The liver can either transport a drug from the blood into the bile or metabolise it into another chemical entity (metabolite).

The rate (R) that the liver or kidney can remove drug from the body is usually proportional to the concentration of drug in the blood (C) (first-order kinetics). This proportionality constant is known as the drug's clearance (Cl) (Fig. 89.2).

Clearance is related to the half-life ($t_{1/2}$) of the drug.

Half-life is the time taken for the plasma drug concentration to fall by 50% and is dependent on V_d:

$$t_{1/2} = \frac{0.693 \times V_d}{Cl} \quad (89.4)$$

(Note: alpha $t_{1/2}$ refers to the distribution $t_{1/2}$; beta $t_{1/2}$ refers to the terminal elimination $t_{1/2}$.)

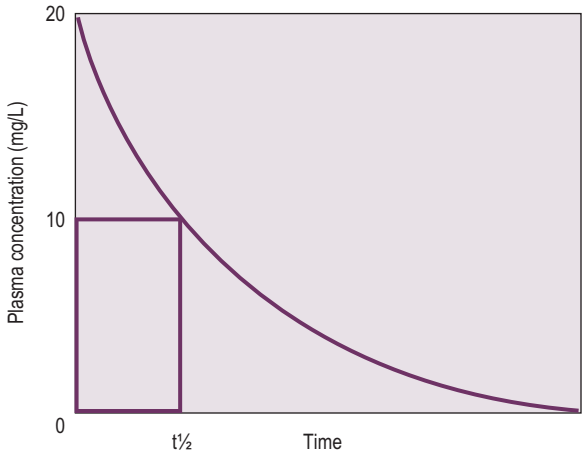


Figure 89.2 First-order elimination graph (plasma drug concentration vs time).

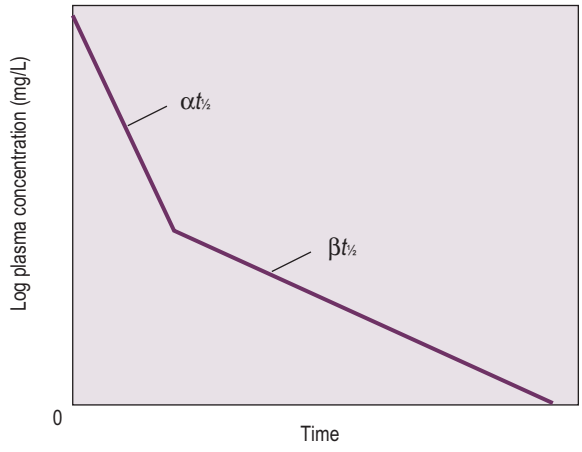


Figure 89.3 Graph of α $t_{1/2}$ and β $t_{1/2}$.

Fig. 89.3 shows the graph of alpha and beta $t_{1/2}$.

Any process that reduces V_d without affecting clearance will shorten $t_{1/2}$ and vice versa.

$t_{1/2}$ can also be expressed as an equation involving the elimination rate constant (fraction of total drug removed per unit time):

$$k = \frac{Cl}{V_d} \quad (89.5)$$

This assumes the drug follows first-order kinetics (i.e. Cl and V_d do not change with dose or concentration).

Caution must be taken with interpreting half-lives with respect to a drug's duration of action. Simply using terminal elimination $t_{1/2}$ to predict the length of drug effect may not be accurate. For example, lipophilic fentanyl exhibits a three-compartment PK model following an IV bolus[22]:

1. *Short-distribution phase:* high concentrations are achieved rapidly in well-perfused organs (brain, kidneys, lungs)
2. *Slower redistribution phase:* in other tissues, skeletal muscle, fat
3. *Elimination phase.*

The terminal $t_{1/2}$ is 3.7 hours, but the duration of action of fentanyl may vary due to 80% protein binding (see effects of hypoalbuminaemia above) and redistribution into body compartments. Hepatic impairment prolongs $t_{1/2}$.

Steady state

$t_{1/2}$ can be used to predict the time for a drug to reach 'steady state' (i.e. when the rate of drug administered equals the rate it is eliminated). Usually this is reached within 4 or 5 half-lives. Similarly, the time taken for a drug to be eliminated from the body would also be 4 to 5 half-lives. A drug that is 90% dependent on metabolic clearance compared with 10% renal will, in hepatic failure, be eliminated primarily by the renal route, but total clearance will still remain at 10% so accumulation will occur.

Hepatic drug clearance

Hepatic drug clearance is affected by blood flow to the liver and the fraction of drug removed as it passes through – that is, the extraction ratio (ER)[23]:

$$\mathrm{ER} = C_{in} - C_{out}/C_{in} \quad (89.6)$$

where C_{in} = concentration in; C_{out} = concentration out.

- *High-extraction drugs (>0.7); for example, morphine:* have significant first-pass metabolism and low oral bioavailability: There is a relative excess of the enzymes that metabolise a drug (i.e. a high intrinsic clearance) and a high proportion of the drug is removed by the liver before reaching the systemic circulation. The rate-limiting step is supply of the drug to the liver. Hepatic clearance therefore depends on hepatic blood flow, which is proportional to cardiac output, and is unaffected by changes in the amount of active enzyme (and therefore enzyme inhibition or enzyme induction) and changes in free fraction of the drug. In advanced sepsis the hepatic blood flow is reduced, but in hyperdynamic sepsis the hepatic perfusion may be spared as blood is diverted to vital organs (see section Renal Drug Clearance). Conversely, in cirrhosis, functional hepatocytes are bypassed when intrinsic clearance falls or portosystemic shunts form, both of which increase drug bioavailability.
- *Intermediate-extraction drugs PKs (0.3–0.7); for example, midazolam:* are more complex to predict. Drugs that fall into this category include those that are normally in the high ER group but alter in this respect when used in patients with hepatic dysfunction. Hepatic

dysfunction and reduced metabolism lead to accumulation of active drug. This is further enhanced if drug metabolites are also active.

- *Low-extraction drugs (<0.3); for example, lorazepam:* have negligible first-pass metabolism and high oral bioavailability: There is a relative deficit of enzymes that metabolise the drug (i.e. a low intrinsic clearance) and the rate-limiting step is enzymatic activity. Hepatic clearance is independent of hepatic blood flow but is influenced by enzyme inhibition or enzyme induction, other competing drugs and changes in free fraction of the drug (the form accessible to the enzyme). Reduced liver perfusion and a fall in ER do not significantly affect drug bioavailability.
- Hepatic dysfunction can reduce the effects of prodrugs that require metabolism to become active.

Box 89.1 lists high and low hepatic extraction drugs.

Zero-order metabolism Most drugs follow first-order PK (i.e. rate of metabolism correlates proportionally with plasma concentration). However, drugs such as phenytoin follow zero-order PK. In this situation metabolism reaches its peak as the enzyme system is saturated and relative clearance falls as plasma concentrations rise. The process is concentration-independent and so an increase in dose will produce a disproportionate rise in plasma levels. The rate of metabolism is constant regardless of the amount of drug present (Fig. 89.4).

Box 89.1 High, intermediate and low extraction ratio drugs

High ER	Intermediate	Low ER
Propranolol	Omeprazole	Lorazepam
Morphine	Codeine	Theophylline
Fentanyl	Amiodarone	Chlordiazepoxide
Propofol	Erythromycin	Phenytoin

ER, Extraction ratio.

Renal drug clearance[24]

Renal clearance of a drug or metabolite is influenced by glomerular filtration, tubular secretion and tubular reabsorption.

Glomerular filtration usually allows the passage of the free but not protein-bound drug into the renal tubules. Drugs that are not subject to tubular secretion or reabsorption therefore have a renal clearance that equals the glomerular filtration rate. Conversely, drugs that undergo active tubular secretion can have higher renal clearances up to a theoretical maximum of renal blood flow. Such drugs are usually charged and can have a high affinity for transporter sites, which allows the passage of even protein-bound drugs. Tubular secretion normally occurs in the proximal tubule and is assumed if clearance rate exceeds calculated filtration rate.

Tubular reabsorption involves the passive diffusion of drugs back across the tubule into the systemic circulation. Such drugs are usually lipophilic and uncharged. The extent of reabsorption is determined by the degree of ionisation and the concentration gradient determined by urine pH and flow rate, respectively. Reabsorption is assumed if the clearance rate is less than the calculated filtration rate (e.g. fluconazole reabsorption is considerable in normal renal function but reduced in acute kidney injury; therefore dose reduction is not necessary, and even an increase may be warranted).

Augmented renal clearance (ARC; C_rCl>/ = 130 mL/min/1.73 m^2) and hepatic clearance can occur as a result of increased cardiac output, and therefore

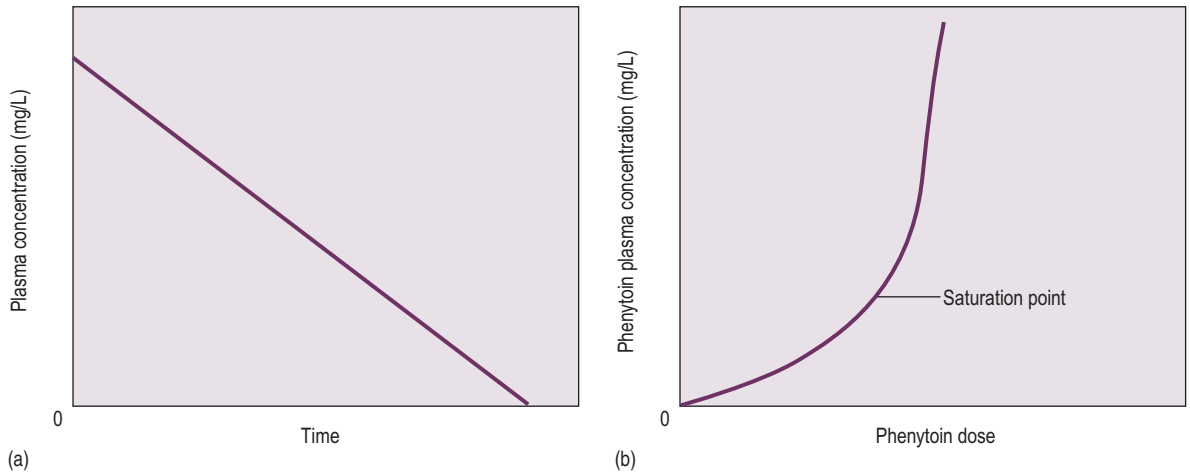


Figure 89.4 (a) Zero-order elimination. (b) Saturation point phenytoin pharmacokinetics.

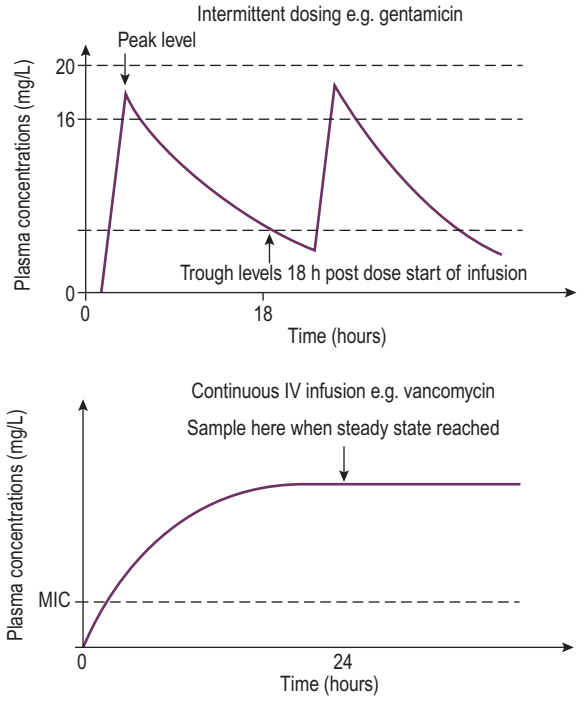


Figure 89.5 Graphs of intermittent drug dosing versus continuous infusion. *MIC*, Minimum inhibitory concentration.

enhanced perfusion to the kidneys and liver by fluid resuscitation, inotropic support or the hyperdynamic phase of sepsis. Unfortunately, this often results in increased metabolism and clearance of drugs. Young (<60 years old) trauma patients with low Sequential Organ Failure Assessment (SOFA) scores (</=4) were particularly susceptible to ARC.[25] Time-dependent antibiotics, which are dosed at intermittent intervals and which rely on the free (unbound) antimicrobial concentration time above the minimum inhibitory concentration (f*T* > MIC) for optimal bactericidal effect, will be at risk of therapeutic failure. The introduction of extended infusions of time-dependent antibiotics has attracted interest from the critical care community. Several studies appear to support its use[26,27] while others are not as convincing,[28,29] and further studies are required. Nevertheless, some ICUs have adopted the practice. The occupancy of an IV line for an extended period of time may be undesirable in a patient with limited IV access.

Fig. 89.5 shows graphs of intermittent dosing versus continuous infusion.

Biliary drug clearance[1,3]

Large molecules can be actively transported by hepatocytes and excreted in the bile either unchanged or conjugated. Conjugated molecules can undergo enterohepatic recirculation (i.e. be hydrolysed by gut bacteria, secreted into the ileum, reabsorbed into the systemic circulation and transported back to the liver via the portal vein). Phenytoin and loperamide are examples of drugs that undergo significant enterohepatic circulation. Biliary obstruction will increase levels of active drug and metabolites excreted via this route.

Other drug clearance routes

Atracurium is an example of a drug that is independent of hepatic or renal clearance and is eliminated via two non-oxidative routes to inactive metabolites[30]:

1. Hydrolysis by non-specific blood esterases in the blood
2. The main route, a non-enzymatic pathway (Hofmann elimination) occurring at physiological pH and body temperature; the elimination rate is increased at higher pH or temperatures and vice versa.

Pulmonary drug clearance[31]

CYP enzymes are also involved in pulmonary metabolism, though the levels of the latter are significantly lower than those in the liver. There is negligible evidence that they substantially contribute to systemic clearance but are first-line defence against pulmonary toxicity.

Pharmacokinetics–pharmacodynamics data on antimicrobials

The majority of PK-pharmacodynamics (PD) in the medical literature focus on the effects of critical illness on antibiotic penetration to their target sites. Plasma levels can be a guide but are not always accurate predictors of tissue interstitial fluid concentrations where most infections occur. Also, therapeutic drug monitoring (TDM) is only performed on antibiotics with a narrow therapeutic range. It is possible for a subtherapeutic drug dose to go unnoticed for some time before clinical manifestations and rising inflammatory markers suggest therapeutic failure. Multiple reviews and studies emphasise the inability to achieve PK-PD target concentrations due to the labile nature of the critically ill. Therefore, it is essential to optimise dosing from the outset and adjust where necessary.

The two main parameters mentioned in all PK-PD literature are the effects of critical illness on V_d and *Cl* of concentration-dependent, time-dependent antibiotics and those that are both.

Examples of such agents are detailed in the table below[32]:

CONCENTRATION DEPENDENT (C_{max}/MIC)	TIME DEPENDENT (f*T* > MIC)	CONCENTRATION AND TIME DEPENDENT ($AUC_{0-24\,h}$/MIC)
Gentamicin	Tazocin	Fluconazole
Amikacin	Meropenem	Linezolid
Daptomycin	Vancomycin	Ciprofloxacin

AUC, Area under the curve; C_{max}, peak concentration; *fT*, free (unbound) antimicrobial concentration; *MIC*, minimum inhibitory concentration.

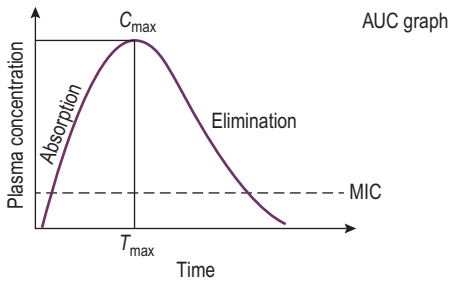


Figure 89.6 Area under the curve (AUC). *MIC*, Minimum inhibitory concentration.

A graph of plasma concentration of drug versus time (area under the curve) is shown in Fig. 89.6.

- C_{max} is the maximum plasma concentration achieved during the time course of the drug.
- T_{max} is the time taken to achieve C_{max}.
- $t_{1/2}$ is the time taken for the plasma level to fall by 50%.
- k is the elimination rate constant.

Concentration-dependent antibiotics are affected by changes in V_d. An increase in V_d will reduce their peak level, often resulting in therapeutic failure. Studies on critically ill septic patients often recommend a higher than the usual recommended dose to achieve PK target levels.

Time-dependent antibiotics are affected by changes in *Cl*. A reduced *Cl* will prolong the fT > MIC but may lead to unnecessarily high peaks and toxic effects.

PRACTICAL APPLICATIONS

REPEAT BOLUS VERSUS INFUSION

Drugs with relatively long half-lives and wide therapeutic indices can be administered by repeat bolus administration (e.g. cefuroxime); those with short half-lives and narrow therapeutic indices (e.g. catecholamines) should be administered in a more predictable and titratable manner by continuous infusion.

OFFSET TIMES

The half-life for some drugs depends on the duration of the infusion (e.g. fentanyl's half-life increases with the duration of continuous infusion). This is particularly evident for drugs with high distribution volumes and with bolus kinetics governed significantly by redistribution rather than clearance. For short infusions, the plasma half-life after the infusion will be less than the terminal elimination half-life. However, as the duration of infusion becomes sufficient to achieve steady state, the half-life upon stopping the infusion will increase until it equals the terminal elimination half-life.[33]

PHARMACOKINETICS–PHARMACODYNAMICS CHANGES IN ORGAN FAILURE

CIRCULATORY FAILURE

Circulatory failure diverts blood flow to essential organs, such as the heart and brain, at the expense of the peripheral tissues. This results in:

- increased levels of drug in the heart and brain
- decreased levels of drug in the peripheries
- reduced renal blood flow and shunting of blood from cortical to juxtamedullary nephrons; glomerular filtration rate (GFR) and tubular excretion fall, decreasing extraction of drugs and renally excreted metabolites
- reduced hepatic blood flow; liver function may be impaired, decreasing the clearance of both highly extracted drugs (reduced delivery to the liver) and poorly extracted drugs (reduced cellular metabolism).

Mechanical ventilation may cause further decline in hepatic perfusion by increasing intrathoracic pressure and therefore decreasing venous return.

The initial effect is a significant decrease in drug V_d and *Cl*. More profound effects are seen in drugs, such as sedatives, that undergo rapid distribution. Fluid and inotropic therapy may briefly alter these effects. In volume overload, there may be an increase in V_d of water-soluble drugs and a prolonged distribution $t_{1/2}$.

HEPATIC FAILURE

Drug dosing in hepatic failure is more difficult to predict compared with renal failure. Derangements in liver function tests do not usually serve as a strict guide for the extent of dose reduction compared with trends in creatinine clearance and other parameters used to estimate renal function.

Absorption

Bioavailability of lipid-soluble drugs is reduced in cholestasis where bile salts are used to enhance their absorption.

Distribution

Patients with ascites may require larger loading doses of water-soluble drugs due to increased V_d.

Hypoalbuminaemia, as a result of catabolism, sepsis, reduced protein intake and synthesis, leads to an increase in the free fraction of highly albumin-bound drugs (e.g. phenytoin). Total serum concentration may appear low or within range but lead to toxic effects if the pharmacologically active free fraction is unaccounted for. Conversely, increased concentrations of α_1-acid glycoprotein (an acute-phase glycoprotein often raised in sepsis), to which phenytoin is 20% bound, can decrease the free fraction.[20] Phenytoin therefore exhibits complex and sometimes unpredictable PK in the critically ill.

Metabolism

See extraction ratio (ER).

Elimination

Cholestasis can reduce elimination of active drug or their metabolites that undergo biliary excretion and enterohepatic circulation. Concomitant renal dysfunction as in hepatorenal syndrome may require a dose reduction of renally excreted drugs.

RENAL FAILURE

Absorption[18]

Uraemia has been linked to reduced gut integrity in animal studies.

Certain drugs used in, for example, chronic renal failure, such as phosphate binders, can reduce the enteral absorption of certain drugs (e.g. ciprofloxacin).

Distribution[18]

Significant fluid retention due to volume resuscitation or reduced diuresis increases the V_d and therefore the distribution $t_{1/2}$ of water-soluble drugs (e.g. gentamicin and beta lactams).

Reduced plasma protein binding of acidic drugs (e.g. amiodarone) can occur. Possible explanations include the displacement of acidic drugs from their albumin-binding sites by endogenous substances that accumulate in renal failure and compete for a position (see Metabolism below).

Plasma protein binding for basic drugs (e.g. epoprostenol) is not usually affected; however, certain interventions, such as haemodialysis, can raise levels of α_1-glycoprotein, an acute-phase protein to which basic drugs usually bind.[23]

Metabolism

Certain drugs that are mainly or completely eliminated from the body by non-renal mechanisms can still accumulate in renal dysfunction; that is, their metabolism is impaired by renal failure. Possible explanations for this include reduced activity of metabolic enzymes.[24]

An accumulation of metabolic products can reduce the protein binding of drugs. For example, uraemia displaces penicillins from their binding sites. The reduced affinity of plasma proteins for phenytoin increases the drug's free fraction. Therefore a non-uraemic patient with a normal free fraction of phenytoin of 0.1 and a total phenytoin level of 7 mg/L will have the same free phenytoin concentration as a uraemic patient with a free fraction of 0.2 and a total phenytoin level of 14 mg/L[1]:

(89.7)

$$C_{paj} = \frac{\text{total phenytoin level (mg/L)}}{0.9 \times (\text{albumin level/normal albumin level}) + 0.1}$$

where C_{padj} = adjusted phenytoin level (free phenytoin concentration), and normal albumin = 40 g/dL.

Elimination

Reduced renal clearance prolongs the terminal elimination $t_{1/2}$.

Renal failure can lead to toxicity if dose adjustments are not made to account for the accumulation of drugs and their active metabolites cleared primarily by the kidneys. Dose can either be reduced, for instance vancomycin (time-dependent bacterial kill), or their dosing intervals increased, for instance gentamicin (concentration-dependent kill). Renal failure usually affects glomerular function more than tubular function, so the excretion of aminoglycosides, which depend more on glomerular filtration, is affected more than that of penicillins, which are dependent on tubular function.

Serum creatinine is usually a poor guide to renal function in the critically ill because creatinine is:

- a by-product of muscle often reduced in critical illness, the elderly or low-weight patients
- influenced by diet (recent protein intake, which can often be insufficient due to variable absorption if administered via the gastrointestinal tract)
- increased or reduced by drugs or disease states without necessarily influencing GFR (e.g. trimethoprim inhibits the renal secretion of creatinine without reducing renal clearance)
- used to calculate C_rCl based on a normal population data of healthy individuals
- usually fluctuating in the critically ill
- a very late marker of renal dysfunction – the GFR has to fall by at least 50% before a significant rise in creatinine is seen; it is better to monitor levels for accumulation of renally cleared drugs (e.g. vancomycin) or electrolytes (e.g. potassium).

Renal replacement therapy drastically alters volumes and clearances of drugs. Effects vary with the mode of dialysis, the filter life, the type of membrane in use and the drugs in question.

RESPIRATORY FAILURE

Insufficient gaseous exchange can disrupt the normal acid-base balance and consequently affect protein binding and V_d. Mechanical ventilation increases intrathoracic pressure, reducing cardiac output, hepatic and renal perfusion. Therefore drugs with a high ER or those that are predominantly renally cleared may be at risk of accumulation. The V_d of water-soluble drugs (e.g. aminoglycosides) and the risk of a stress ulcer are also increased by mechanical ventilation.

EFFECT OF OBESITY ON PHARMACOKINETICS

Total body weight (TBW) is used to guide dosing of lipophilic drugs (e.g. phenytoin) which distribute extensively into adipose tissue. Hydrophilic drugs (e.g. aminoglycosides) have limited distribution into adipose and the increase in lean mass can account up to 40% of excess body weight; therefore adjusted body weight (ABW) is used. To calculate dosing (where IBW = ideal body weight):

$$\text{ABW} = \text{IBW} + 0.4\,(\text{ABW} - \text{IBW}) \quad (89.8)$$

where IBW = ideal body weight.

Decreased metabolism can occur due to hepatic dysfunction caused by fatty liver. An increase in renal clearance of hydrophilic drugs can occur due to the relative increase in kidney size and renal perfusion (Table 89.1).

THERAPEUTIC DRUG MONITORING

TDM is used to guide dosing of drugs with a narrow therapeutic range (i.e. a small therapeutic to toxic window), for example gentamicin, phenytoin and theophylline. Toxicity may be associated with peak drug concentrations (e.g. seizures and arrhythmias from theophylline) or trough concentrations (e.g. ototoxicity from aminoglycosides). Table 89.2 displays examples of drugs with a narrow therapeutic window.[36–38] Hospital laboratories measure total plasma drug concentration. However, it is the unbound drug fraction that is pharmacologically active (see phenytoin).

Regardless of measured concentration, evidence of clinical efficacy or toxicity must be monitored regularly (e.g. altering the maintenance dose of digoxin in a patient with a subtherapeutic level is unnecessary if the ventricular rate is adequately controlled). Conversely, it would be prudent to reload a previously stable epileptic patient presenting with seizures if the phenytoin level is subtherapeutic. If the phenytoin level is therapeutic and the patient's convulsions persist, a neurology review is required. This usually results in the addition of, or a change to, another agent.

Table 89.1 Effect of obesity on dosing and pharmacokinetics

DRUG	EFFECT OF OBESITY ON PK PARAMETER	RECOMMENDED DOSING BASED ON TBW ABW/LBW
Alfentanyl	No effect on V_d ↓Cl and ↑$\beta t_{1/2}$	LBW
Gentamicin	Negligible effect on V_d	ABW
Phenytoin	↑V_d	TBW

ABW, Adjusted body weight; *LBW*, lean body weight; *PK*, pharmacokinetics; *TBW*, total body weight.

SAMPLING TIME FOR DRUG LEVELS

The ideal sampling time for a drug level is either just prior to the next due dose, or once distribution into the tissue is known to be complete. If taken prior to distribution, the levels will be falsely interpreted as higher than expected for the dose administered. For example, an IV loading dose of phenytoin takes at least 2 hours for distribution.[1] A level taken prior to this time would not be a true reflection of the dose administered and subsequent dosing based on the result will be incorrect.

The majority of drug levels are obtained as a 'trough'; that is, a pre-dose level as suggested in the case of phenytoin. Usually, levels should not be taken prior to steady state being reached; for example, it would take approximately 10 days following a formulation change for phenytoin to reach steady state. However, if the patient's PK is suspected not to follow the normal population, as in the case of the critically ill, and if there is a risk of accumulation or underdosing before this time, it would be prudent to sample much sooner so the dose can be promptly optimised.

THE EFFECT OF DRUG INTERACTIONS ON PHARMACODYNAMICS

Multiple drug therapy in the critically ill increases their vulnerability to the effects of drug interactions. It could also be argued that ICU patients are monitored more closely than their counterparts on general wards so any adverse effects are likely to be identified sooner. Nevertheless, if a patient does not demonstrate a normal response to a drug treatment, it may be due to a drug interaction.

The consequence of drug interactions is naturally dependent on the drugs in question. Table 89.3

Table 89.2 Therapeutic drug monitoring in the critically ill

DRUG	THERAPEUTIC CONCENTRATION	TOXIC EFFECTS
Digoxin	1–2 µg/L	Central nervous system and visual disturbances, dizziness, nausea and vomiting[1]
Gentamicin	<1 mg/L (trough)	Nephrotoxicity, ototoxicity[14]
Amikacin	<5 mg/L (trough)	Nephrotoxicity, ototoxicity[33]
Vancomycin	20–25 mg/L (continuous infusion)	Nephrotoxicity, ototoxicity, reversible neutropenia[34]
Phenytoin	10–20 mg/L	Nystagmus, ataxia, dysarthria, cardiovascular collapse[5] Correct for hypoalbuminaemia Caution in uraemia
Theophylline	10–20 mg/L	Arrhythmias, nausea, vomiting[35]

Table 89.3 Examples of drug–drug interactions in intensive care unit patients

DRUG A	DRUG B	INTERACTION	COMMENT
Dexmedetomidine	Amiodarone	Enhanced bradycardic effects when administered with drugs of similar effects	Can result in bradycardia
Midazolam	Amiodarone	Amiodarone is an inhibitor of cytochrome P450 isoenzyme by which midazolam is metabolised	Results in ↑ levels of midazolam
Midazolam	Fluconazole	Fluconazole is an inhibitor of cytochrome P450 isoenzyme by which midazolam is metabolised	Results in ↑ levels of midazolam
Haloperidol	Amiodarone	Both drugs prolong QT interval	Results in ↑ risk of ventricular arrhythmias
Phenytoin	Hydrocortisone	Phenytoin is a potent enzyme inducer	↑ Hydrocortisone metabolism, ↓ therapeutic and adrenal suppressant effects
Amiodarone	Simvastatin	Amiodarone is an inhibitor of cytochrome P450 isoenzyme by which simvastatin is metabolised	↑ Risk of myopathy

provides a few examples of interactions involving commonly used drugs in the ICU.

SUMMARY

The relationship between PK and PD can be used to predict a dosing regimen for a patient. However, wide interpatient variability and the labile nature of the critically ill means careful consideration needs to be applied when formulating an appropriate dose. Best clinical judgement is required. Treatment may need to be individualised and titrated, especially when the outcome does not follow the normal expected clinical response. Levels should be taken to guide dosing in drugs with narrow therapeutic windows, but caution must be taken with interpretation, especially when the clinical symptoms do not correlate with apparently therapeutic readings. For drugs with 'silent' PDs, other markers of therapeutic effect should be sought; for example, a reduction in temperature, C-reactive protein (CRP) and white cell count (WCC) in anti-infectives with a wide therapeutic index. At the same time, the optimising dosage in the ICU should take into account the adverse effects of accumulation if higher doses are used beyond what is normally recommended.

In line with non-drug therapies in the ICU, drug kinetics and dynamics are never simple nor straightforward, and rarely does one dosage regimen fit all. For further advice, please consult your pharmacist.

Acknowledgements

Updated and modified from the chapter in a previous edition by R.N. Upton, J.A. Myburgh and R.G. Morris. Dose regimens are for illustration only and local guidelines should be consulted.

Many thanks to Vanessa Marvin, PharmD for reviewing this chapter prior to submission.

KEY REFERENCES

1. Winter ME. *Basic Clinical Pharmacokinetics*. 5th revised ed. London: Pharmaceutical Press; 2009.
17. Varghese JM, Roberts JA, Lipman J. Pharmacokinetics and pharmacodynamics in critically ill patients. *Curr Opin Anaesthesiol*. 2010;23:472–478.
20. Von Wincklelmann SL, Spriet I, Willems L. Therapeutic drug monitoring of phenytoin in critically ill. *Pharmacotherapy*. 2008;28(11):1391–1400.
21. North-Lewis P. *Drugs and the Liver: A Guide to Drug Handling in Liver Dysfunction*. 1st ed. London, UK: Pharmaceutical Press; 2008.
24. Verbeeck RK, Flora TM. Pharmacokinetics and dosage adjustment in patients with renal dysfunction. *Eur J Clin Pharmacol*. 2009;65:757–773.
28. Abdul-Aziz MH. Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved PKPD and patient outcomes? An observation from the Defining Antibiotic Levels in Intensive care unit patients (DALI) cohort. *J Antimicro Chemother*. 2016;71:196–207.
29. Dulhunty J, Roberts JA, Davis JS, et al. A multicenter randomized trial of continuous versus intermittent β lactam infusion in severe sepsis. *Am J Respir Crit Care Med*. 2015;192(11):1298–1305.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Winter ME. *Basic Clinical Pharmacokinetics*. 5th revised ed. London, UK: Pharmaceutical Press; 2009.
2. Aspen. *Lanoxin tablets and liquid (digoxin)*. UK Summary of Product Characteristics. 2008. Online. Available: http://www.medicines.org.uk/emc/.
3. Struys MM, Kalmar A, De Paepe P. Pharmacokinetic principles. In: Webster NR, Galley HF, eds. *Anaesthesia Science*. Oxford, UK: Blackwell Publishing Ltd; 2006:3–25.
4. Zhou SF. Structure, function and regulation of P-glycoprotein and its clinical relevance in drug disposition. *Xenobiotica*. 2008;38(7–8):802–832.
5. Bristol-Myers Squibb Pharmaceuticals Ltd. *Reyataz (atazanavir)*. UK Summary of Product Characteristics. 2012. Online. Available: http://www.medicines.org.uk/emc/.
6. Pfizer Ltd. *Epanutin (phenytoin) oral suspension*. UK Summary of Product Characteristics. 2012. Online. Available: http://www.medicines.org.uk/emc/.
7. Accord Healthcare Ltd. *Ciprofloxacin tablets*. UK Summary of Product Characteristics. 2009. Online. Available: http://www.medicines.org.uk/emc/.
8. Rowland M, Tozer TN. *Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications*. 4th revised ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010.
9. Rossi M, Nannipieri M, Anselmino M, et al. Subcutaneous adipose tissue blood flow and vasomotion in morbidly obese patients: long term effect of gastric bypass surgery. *Clin Hemorheol Microcirc*. 2011;51:159–167.
10. AstraZeneca UK Ltd. *Diprivan (propofol) 1% emulsion for injection or infusion*. UK Summary of Product Characteristics. 2012. Online. Available http://www.medicines.org.uk/emc/.
11. Hameln Pharmaceuticals Ltd. *Amiodarone hydrochloride 50 mg/ml concentrate for solution for injection*. UK Summary of Product Characteristics. 2010. Online. Available http://www.medicines.org.uk/emc/.
12. Sanofi-Aventis. *Furosemide injection*. UK Summary of Product Characteristics. 2010. Online. Available: http://www.medicines.org.uk/emc/.
13. Austin P, Stroud MA. *Prescribing Adult Intravenous Nutrition*. 1st ed. London, UK: Pharmaceutical Press; 2007.
14. Hospira NZ Ltd. *Sodium nitroprusside injection*. UK Summary of Product Characteristics. 2010. Online. Available: http://www.medicines.org.uk/emc/.
15. Benet LZ, Zia Amir-Hosseini P. Basic principles of pharmacokinetics. *Toxicol Pathol*. 1995;23:115–123.
16. Hospira UK Ltd. *Gentamicin injection*. UK Summary of Product Characteristics. 2011. Online. Available: http://www.medicines.org.uk/emc/.
17. Varghese JM, Roberts JA, Lipman J. Pharmacokinetics and pharmacodynamics in critically ill patients. *Curr Opin Anaesthesiol*. 2010;23:472–478.
18. Eyler RF, Mueller BA. Antibiotic dosing in critically ill patients with acute kidney injury. *Nat Rev Nephrol*. 2011;7:226–235.
19. Amdipharm. *Morphgesic (morphine)*. UK Summary of Product Characteristics. 2011. Online. Available: http://www.medicines.org.uk/emc/.
20. Von Winckelmann SL, Spriet I, Willems L. Therapeutic drug monitoring of phenytoin in critically ill. *Pharmacotherapy*. 2008;28(11):1391–1400.
21. North-Lewis P. *Drugs and the Liver: A Guide to Drug Handling in Liver Dysfunction*. 1st ed. London, UK: Pharmaceutical Press; 2008.
22. Mercury Pharma. *Fentanyl injection*. UK Summary of Product Characteristics. 1999. Online. Available: http://www.medicines.org.uk/emc/.
23. Stenson RE, Constantino RT, Harrison DC. Interrelationships of hepatic blood flow, cardiac output, and blood levels of lidocaine in man. *Circulation*. 1971;43:205–211.
24. Verbeeck RK, Flora TM. Pharmacokinetics and dosage adjustment in patients with renal dysfunction. *Eur J Clin Pharmacol*. 2009;65:757–773.
25. Udy AA, Roberts JA, Boots RJ, et al. Augmented renal clearance: implications for antibacterial dosing in the critically ill. *Clin Pharmacokinet*. 2010;49:1–16.
26. Mattioli F, Fucile C, Del Bono V, et al. Population pharmacokinetics and probability of target attainment of meropenem in critically ill patients. *Eur J Clin Pharmacol*. 2016;72:839–848.
27. Roberts JA, Webb S, Paterson D, et al. A systematic review of the clinical benefits of continuous administration of beta-lactam antibiotics. *Crit Care Med*. 2009;37:2071–2078.
28. Abdul-Aziz MH. Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved PKPD and patient outcomes? An observation from the Defining Antibiotic Levels in Intensive care unit patients (DALI) cohort. *J Antimicro Chemother*. 2016; 71:196–207.
29. Dulhunty J, Roberts JA, Davis JS, et al. A multicenter randomized trial of continuous versus intermittent β lactam infusion in severe sepsis. *Am J Respir Crit Care Med*. 2015;192(11):1298–1305.
30. Actavis UK Ltd. *Atracurium injection*. UK Summary of Product Characteristics. 2009. Online. Available: http://www.medicines.org.uk/emc/.
31. Wijen PAHM, Bekers O, Drent M. Relationship between drug-induced interstitial lung disease and cytochrome P450 polymorphisms. *Curr Opin Pulm Med*. 2010;16:496–502.
32. Chelsea & Westminster Hospital NHS Foundation Trust. *Gentamicin and vancomycin dosing for adult patients with burns and critically ill*. Dr Berge Azadian, Stephen Hughes, Chris Chung.
33. Bailey JM. Context-sensitive half times: what are they and how valuable are they in anaesthesiology? *Clin Pharmacokinet*. 2002;41:793–799.
34. Gous AG, Dance MD, Lipman J, et al. Changes in vancomycin pharmacokinetics in critically ill infants. *Anaesth Intensive Care*. 1995;23:678–682.
35. Shelly MP, Mendel L, Park GR. Failure of critically ill patients to metabolise midazolam. *Anaesthesia*. 1987;42:619–626.

36. Hospira UK Ltd. *Amikacin injection*. UK Summary of Product Characteristics. 2010. Online. Available: http://www.medicines.org.uk/emc/.
37. Wockhardt Ltd. *Vancomycin intravenous infusion*. UK Summary of Product Characteristics. 2008. Online. Available: http://www.medicines.org.uk/emc/.
38. Hameln Pharmaceuticals Ltd. *Aminophylline injection*. UK Summary of Product Characteristics. 2010. Online. Available: http://www.medicines.org.uk/emc/.

90

Poisoning and drug intoxication

Brendan R Murfin, Nicholas A Barrett

Acute poisoning remains one of the commonest medical emergencies, accounting for 5%–10% of hospital medical admissions. Although in the majority of cases the drug ingestion is intentional, the in-hospital mortality remains low (<0.5%).[1] There are specific antidotes available for a small number of poisons and drugs; however, in most intoxication, supportive care is the main management strategy simply allowing time for the intoxicant to be metabolised and excreted. This chapter is a hands-on guide to the general management of acute poisoning and drug intoxication. For more detailed information than can be provided here, please refer to Internet-based information services (e.g. Toxbase in the United Kingdom – http://www.spib.axl.co.uk) or a local/regional/national telephone poisons information service (e.g. National Poisons Information Service in the United Kingdom – 0844 8920111).

Clinical toxicology remains an experience-based specialty; consequently, many recommendations are based on a small literature of case reports or on pharmacological principles rather than on controlled clinical studies. Additionally, a variety of position statements and clinical guidelines have been produced.

GENERAL PRINCIPLES

The general principles of the management of poisoned patients are diagnosis, based on history and clinical features, clinical examination, resuscitation, investigations and continued supportive care. Measures to reduce absorption or enhance elimination, and specific treatments, may be indicated in some cases. In the more acute situations, these actions often have to be carried out simultaneously.

AIRWAY, BREATHING AND CIRCULATION

In acutely poisoned patients who are unconscious, dentures should be removed and the oropharynx cleared of food and vomit. Tracheal intubation and airway protection is almost always necessary when a patient tolerates insertion of an oropharyngeal airway – perhaps the only exception to this rule is patients who have taken gamma hydroxybutyric acid (GHB) or gamma butyrolactone (GBL) where consciousness can be reliably predicted to return within 2–4 hours. Inadequate spontaneous ventilation, determined clinically or by arterial blood gas (ABG) analysis, obviously requires ventilatory support. Venous access should be established, and circulatory assessment must be made. Basic observations, including blood pressure, pulse rate, temperature, peripheral perfusion and urine output, should be recorded.

CLINICAL EXAMINATION

The clinical examination should include looking particularly for needle marks or evidence of previous self-harm. The Glasgow Coma Scale, designed for head-injured patients, is frequently used, but descriptive documentation of the degree of impaired consciousness is much more valuable. In an unconscious patient with no history available, the diagnosis depends upon excluding other common causes of coma (Box 90.1) and circumstantial evidence. Specific attention should be paid to the temperature, pupil size, blood pressure, respiratory and heart rate, as these may help to restrict the list of potential toxins (Box 90.2). Patients should also have a detailed neurological examination, preferably before the administration of any muscle relaxants, documenting the presence/absence of abnormal tone and reflexes, spontaneous/inducible clonus and/or ocular clonus.

INVESTIGATIONS

Important initial investigations include the following:

- *Urinalysis*: keep a sample for later analysis if required. Although rapid reaction dipsticks are available to screen for common drugs of abuse/recreational drugs by immunoassay, their routine use is not recommended owing to false-positive results, detection of metabolites rather than parent drug and/or cross-reactivity with prescription and over-the-counter medicines.
- *Basic biochemistry*: given the dependence on renal elimination for many drugs, acute or chronic renal insufficiency will alter patient management.

ABSTRACT

Poisoning and drug intoxications management remains an important part of emergency and critical care practice. Despite increasing diversity in pharmacopeia and toxin exposures, and limited antidotes, mortality remains low, due predominantly to the deployment of supportive therapies. Data are limited due to the difficulty inherent in developing controlled trials in this field. However, recent developments based on new data and expert work group review has improved our understanding and implementation of protocols and specific managements in many intoxications. These guidelines and commentaries have provided a framework for future review along with easily accessible web-based information available to clinicians at the bedside. This chapter provides a general systematic approach to emergency and supportive management and specific treatments of some common exposures.

KEYWORDS

Poisoning
intoxication
gastric decontamination
enhanced elimination
antidotes
extracorporeal treatments

Box 90.1 Common causes of coma other than acute poisoning

Intracranial bleeds
- Subarachnoid haemorrhage
- Subdural/extradural haematomas

Meningitis or encephalitis
Diabetic comas
Uraemic encephalopathy

Box 90.2 Clinical effects of the common poisons

Convulsions
Tricyclics, isoniazid, lithium, amphetamines, theophylline, carbon monoxide, phenothiazines, cocaine
Skin
Bullae: barbiturates, tricyclics
Sweating: salicylates, organophosphates, amphetamines, cocaine
Pupils
Constricted: opioids, organophosphates
Dilated: hypoxia, hypothermia, tricyclics, phenothiazines, anticholinergics
Temperature
Pyrexia: anticholinergics, tricyclics, salicylates, amphetamines, cocaine
Hypothermia: barbiturates, alcohol, opioids
Cardiac rhythm
Bradycardia: digoxin, beta blockers, organophosphates
Tachycardia: salicylates, theophylline, anticholinergics
Arrhythmias: digoxin, phenothiazines, tricyclics, anticholinergics

- *ABG analysis*: metabolic and/or respiratory acidosis is most common. Aspirin may initially cause a respiratory alkalosis, which in more significant ingestions can be followed by a metabolic acidosis or combined picture of a respiratory alkalosis/metabolic acidosis. Metabolic alkaloses are unusual.
- *Anion gap* = ($[Na^+]$ + $[K^+]$) − ($[Cl^-]$ + $[HCO_3^-]$): it is normally 10–14 mmol/L. Ethanol, methanol, ethylene glycol, metformin, cyanide, isoniazid or salicylates are the most frequent causes of a high anion gap metabolic acidosis in clinical toxicology.
- *Chest X-ray*: inhalation of gastric contents is not uncommon; X-ray changes consistent with aspiration should be sought.
- *Drug levels*: these are rarely helpful except in specific poisonings. They include paracetamol, salicylates, iron, digoxin and lithium. It is important to note that, for most poisonings, drug concentrations guide rather than dictate treatment.

GUT DECONTAMINATION

EMESIS

Ipecacuanha-induced emesis is not recommended.[2] It is ineffective at removing significant quantities of poisons from the stomach, limits the use of activated charcoal (AC) and can increase the risk of aspiration in those patients who have a reduced level of consciousness.

GASTRIC LAVAGE

The joint American and European toxicologists' statement suggests that gastric lavage removes an insignificant amount of poison, and may only propel unabsorbed poison into the small intestine; therefore it is no longer routinely recommended.[3] Additionally, it is important to note that gastric lavage often delays the use of AC, which is likely to have greater benefit with less unwanted effects or risks. Finally, gastric lavage may result in aspiration, particularly in obtunded patients.

ACTIVATED CHARCOAL

AC remains the first-line treatment for most acute poisonings.[4] Owing to its large surface area and porous structure it is highly effective at adsorbing many toxins with few exceptions. Exceptions include elemental metals, pesticides, alcohols including ethanol, strong acids and alkalis, and cyanide. It should be given to all patients who present within 1 hour of ingestion of a potentially toxic amount of a drug or drugs; it should not be given to those patients who are drowsy (unless they have a protected airway). International guidelines recommend administration of AC within 1 hour, so it is vital to rapidly identify those who present after a potentially serious overdose so that it can be given swiftly.[5] Longer than 1 hour it may still be effective if it follows an overdose of a substance that slows gastric emptying (e.g. opioids, anticholinergics, tricyclic antidepressants [TCA]), but this depends on the clinical condition of the patient and the amount ingested.

Repeated doses of AC can increase the elimination of some drugs by interrupting their entero-enteric and enterohepatic circulation.[6] Indications for repeated dose AC are shown in Box 90.3. It should be considered in patients who have ingested a modified or slow-release preparation or significant salicylate ingestions; in these situations multiple doses of AC are being administered to reduce absorption rather than enhance elimination. AC is given in 50 g doses for adults and 0.5–1 g/kg (max 50 g) for children. It commonly causes vomiting; therefore consider giving an antiemetic prior to administration. Multiple doses can be associated with constipation so patients should be given an appropriate laxative. Repeated doses are given at 4-hourly intervals until it is clinically indicated

Box 90.3 Drug intoxications where multiple-dose activated charcoal may be beneficial

Carbamazepine
Theophylline
Digoxin
Quinine
Phenobarbital
Dapsone
Sustained-release preparations

to stop. Obtunded patients with any airway compromise should have their airway secured prior to the use of AC.

WHOLE BOWEL IRRIGATION

This is a method of gut decontamination that is indicated for a limited number of poisons.[7] Whole bowel irrigation involves administration of non-absorbable polyethylene glycol solution to cause a liquid stool and reduce drug absorption by physically forcing contents rapidly through the gastrointestinal (GI) tract. Polyethylene glycol preparations are still occasionally used in surgical units for 'bowel preparation' prior to surgery. It may have a role in treating large ingestions of drugs that are not absorbed by AC. Indications include large ingestions of iron or lithium, ingestion of drug-filled packets/condoms ('body packers'), and large ingestions of sustained-release or enteric-coated drugs (e.g. theophylline or calcium channel blockers). Whole bowel irrigation may lead to significant shifts in fluid and electrolyte composition; hence they should only be considered in patients in whom careful monitoring can be instituted.

ENHANCING DRUG ELIMINATION

In the overwhelming majority of patients who present after an overdose, gut decontamination techniques and supportive care are all that is required. In a limited number of acute poisonings it may be necessary to consider methods to enhance elimination.

URINARY ALKALINISATION

Urinary alkalinisation (previously termed *forced alkaline diuresis*) may be useful for serious poisonings with:

- salicylates
- phenobarbital (with repeated dose AC)
- chlorpropamide
- methotrexate.

Intravenous 8.4% sodium bicarbonate is infused (the joint American and European toxicologists' statement recommends 225 mL over 1 hour in adults) to achieve a urine pH of approximately 7.5–8.5. The term 'urine alkalinisation' emphasises that urine pH manipulation is the prime objective of treatment; the terms 'forced alkaline diuresis' and 'alkaline diuresis' should be discontinued. According to international position statements it should be considered the treatment of choice for moderate to severe salicylate poisoning.[8] Care must be taken to ensure the potassium does not fall rapidly, and the urine pH should be measured every 30 minutes.

EXTRACORPOREAL TECHNIQUES

Numerous extracorporeal techniques are potentially available to aid drug removal in the poisoned patient, as well as correct metabolic and biochemical abnormalities as a result of the poisoning. These include plasmapheresis, haemodialysis, haemofiltration, haemodiafiltration and haemoperfusion. There are limited data on drug clearance by these techniques in the literature and it is not possible to extrapolate from one system to the other. At present, knowledge of the principles of the methods and the kinetics of the drug involved is relied upon.

An international multidisciplinary working party called EXTRIP (EXtracorporeal TReatments In Poisoning) is currently reviewing the role of extracorporeal elimination and have, to date, recommended extracorporeal treatments in severe salicylate, lithium, theophylline, carbamazepine, paracetamol, methanol and select phenytoin poisoning, and advise against the use in tricyclic and digoxin poisoning.[9–16]

Extracorporeal techniques should be considered for specific drugs, in patients with significant renal impairment (and therefore delayed clearance), when there are clinical features or markers of severe toxicity or there is failure to respond to full supportive care coupled with poisoning by a drug that can potentially be removed. The use of extracorporeal techniques is probably worthwhile only if total body clearance is increased by at least 30%. Although some drugs have improved clearance with haemodialysis rather than haemofiltration, ultimately using filtration rates of greater than 50–100 mL/kg per hour is likely to be as effective as other approaches and is widely available in intensive care units. Haemoperfusion is rarely available, but may have a role in hepatically cleared drug poisonings.

LIPID EMULSION THERAPY

Intravenous lipid emulsion (ILE) using 20% Intralipid is now recognised as an effective treatment for local-anaesthetic-induced cardiovascular collapse with a recommended initial dose of 1.5 mL/kg followed by an infusion of 15 mL/kg/h. If cardiovascular instability persists give a repeat bolus dose of 1.5 mL/kg every 5 minutes (two further doses) and increase the rate to 30 mL/kg/h.[17] The maximum cumulative dose is

12 mL/kg.[18] The mechanism for benefit is not entirely clear, but is thought to relate either to the formation of an enlarged lipid sink, which may help to remove the offending drug from target tissues, or as an energy substrate for a shocked myocardium. Based on the lipid sink hypothesis, ILE has been considered a potential treatment for severe acute poisoning from a range of lipophilic drugs. There are an increasing number of case reports where ILE has been used in other poisonings; however, its use is not routinely recommended at this time, outside local anaesthetic toxicity. There have been reports of recurrence of toxicity after initial dosing with ILE, as well as complications such as pancreatitis. For patients with ongoing cardiovascular instability or intractable arrhythmias, measures including extracorporeal support with veno-arterial extracorporeal membrane oxygenation or cardiac bypass should be considered. It is important to remember that the significant lipaemia following ILE therapy may rapidly render the oxygenator non-functional and an urgent oxygenator change may be required if this occurs.

CONTINUED SUPPORTIVE THERAPY

General supportive care of the unconscious unstable patient is required. This includes monitoring and provision of organ support when necessary, as well as fluid balance, correction of electrolytes, initiation of nutritional support and prompt treatment of nosocomial infection. Overall, despite the significant initial physiological disturbance, this group of patients usually has a good outcome.

SPECIFIC THERAPY OF SOME COMMON OR DIFFICULT OVERDOSES

This section emphasises only those features that may aid clinical diagnosis or prognosis. These are always intended to support those measures described under general principles.

AMPHETAMINES INCLUDING 'ECSTASY', 3,4-METHYLENEDIOXY-METHAMPHETAMINE (MDMA)

CLINICAL FEATURES

Symptoms of mild overdose include sweating, dry mouth and anxiety. Although the majority of ecstasy patients are dehydrated, a proportion have hyponatraemia from drinking water to excess; therefore it is important to measure serum sodium and electrolytes early in the patient's management. More severe features include tachycardia, hypertonia, hyperreflexia, hallucinations and hypertension. Supraventricular dysrhythmias may follow with coma, convulsions and the risk of haemorrhagic stroke. A hyperthermic syndrome may develop with hyperpyrexia leading to rhabdomyolysis, metabolic acidosis, acute renal failure, disseminated intravascular coagulation (DIC) and multiple organ failure. Where hyperthermia is suspected it is important that core body temperature (e.g. oesophageal, blood or rectal) is measured to accurately record the degree of hyperthermia.[19]

TREATMENT

AC should be considered up to 1 hour post-ingestion. Benzodiazepines are useful for agitated or psychotic patients and may have a central effect in reducing tachycardia, hypertension and hyperpyrexia. If benzodiazepines fail to control hypertension, other classes of antihypertensives should be started, such as alpha blockers or direct vasodilators. Beta-blockers, even specific ones, should not be used due to the risk of unopposed alpha stimulation and subsequent hypertension or coronary vasospasm developing. In a recent review, this occurred in approximately 1 in 200 patients and although there is no evidence to support this, it may be worth considering drugs with alpha antagonism or mixed alpha/beta antagonism such as labetolol.[20] It should be noted that most patients are fluid-depleted rather than fluid-overloaded, and measurement of sodium concentrations should be undertaken early in fluid resuscitation. Hypertonic saline may rarely need to be considered in severe hyponatraemia, particularly if seizure activity is present. Hyperthermia should be treated in the standard manner, including administration of cold (4°C) IV fluids, general cooling measures and benzodiazepines. For patients whose temperature remains elevated (particularly above 39°C), consider PO/NG (oral/nasogastric) cyproheptadine (a $5HT_{2A}$ antagonist) – the initial dose is 12 mg followed by 2 mg every 2 hours until temperature and other symptoms have settled. Benzodiazepines and cyproheptadine should also be used in those patients with evidence of moderate/severe serotonin toxicity.[21] Additional methods for cooling, such as external and internal cooling devices or those used for maintenance of body temperature post-cardiac arrest, can be considered for rapidly reducing body temperature.

BENZODIAZEPINES

CLINICAL FEATURES

Overdose is common, but clinical features are not usually severe unless complicated by other central nervous system (CNS) depressant drugs (such as alcohol), pre-existing disease or the extremes of age. Toxicity commonly produces drowsiness, dysarthria, ataxia and nystagmus. Paradoxical agitation and confusion can occur less commonly.

TREATMENT

AC can be given if patients present within 1 hour of ingestion, yet supportive treatment is usually all that is required. Flumazenil is a specific antagonist that is not licensed for use in poisoning and may be dangerous

due to the risk of significant cardiovascular (ventricular tachycardia) and neurological (status epilepticus) toxicity, as well as precipitating withdrawal in benzodiazepine-dependent patients.[22] Its use is therefore not recommended.

BETA BLOCKERS

CLINICAL FEATURES

There is a wide variation in the individual response to beta-blocker overdose. Those with cardiac disease are more at risk of complications. Hypotension and bradycardia predominate and are often refractory to standard resuscitation measures. The degree of heart block can range from a prolonged PR interval through to complete heart block and asystole. Cardiogenic shock and pulmonary oedema are not uncommon.[23]

TREATMENT

AC should be considered up to 1 hour post-ingestion and multiple-dose charcoal in patients who have ingested sustained-release preparations. There is limited evidence to support the use of atropine, although it is commonly used in patients who have bradycardia and hypotension. If symptomatic treatment with IV fluids for hypotension fails, glucagon (up to 10 mg IV as an initial bolus) is the next step. Further boluses and/or an infusion may be beneficial in addition to the initial bolus. Further options include hyperinsulinaemic–euglycaemic treatment, as described in the calcium channel blocker section, is indicated. Inotropes/vasopressors and cardiac pacing (higher-voltage capture may be required) can be considered and based on the patient's clinical condition. Other measures including extracorporeal support with veno-arterial extracorporeal membrane oxygenation or cardiac bypass should be considered if the simpler methods are not able to stabilise the patient.[24]

BUTYROPHENONES (INCLUDING HALOPERIDOL)

CLINICAL FEATURES

Drowsiness and extrapyramidal effects are most common. Rarely hypotension, QT prolongation, arrhythmias and convulsions develop. Serious toxicity is uncommon.

TREATMENT

AC should be considered up to 1 hour post-ingestion, otherwise treatment is supportive. Extrapyramidal symptoms can be treated with procyclidine (5–10 mg IV/intramuscularly in adults) or diazepam (10–20 mg in adults). IV lipid emulsion therapy has been reported as a successful strategy in one case report, and although it cannot be recommended for routine use, it may be an option to consider in the event of life-threatening overdose.

CALCIUM CHANNEL BLOCKERS

CLINICAL FEATURES

The cardiac effects of these drugs predominate in overdose, particularly hypotension and atrioventricular block, although reflex tachycardia occurs with nifedipine. Hypotension occurs owing to peripheral vasodilatation and negative inotropy. The therapeutic selectivity of actions is not typically seen in overdose. Severe toxicity may occur in patients who initially appear well, when sustained-release preparations have been ingested.

TREATMENT

AC should be considered up to 1 hour post-ingestion and multiple-dose charcoal in patients who have ingested sustained-release preparations. Treatment remains supportive; however, IV calcium chloride (10 mL of 10% solution) is often given in patients who remain hypotensive despite fluid administration. Further boluses and/or an infusion should be administered as guided by the clinical response. If calcium gluconate is used then administer 30 mL of 10% solution (it has one-third the ionised calcium compared with calcium chloride, and therefore doses should be increased threefold where calcium gluconate is used). In those patients requiring multiple doses and/or an infusion, monitor the serum calcium concentration to ensure it remains below 3 mmol/L. Atropine is often used for bradycardia, and occasionally cardiac pacing may be necessary. In those with persistent hypotension not responding to IV fluids and calcium, the next step, hyperinsulinaemic–euglycaemic therapy, is indicated.[25] An initial bolus of 1 unit/kg of short-acting insulin should be administered with 25–50 mL of 50% dextrose, followed by an infusion of 0.5–2 units/kg/h short-acting insulin; higher doses may be required in severely compromised patients. Careful monitoring of blood glucose and serum potassium should be undertaken, with replacement as necessary. There is anecdotal evidence that increasing glucose requirements suggest that the cardiovascular toxicity is starting to diminish. For patients with ongoing cardiovascular instability or intractable arrhythmias, measures including extracorporeal support with veno-arterial extracorporeal membrane oxygenation or cardiac bypass should be considered.[24]

CARBAMAZEPINE

Absorption is slow and unpredictable; moreover, maximum serum concentrations may not be achieved until 72 hours after ingestion. Carbamazepine undergoes enterohepatic recirculation leading to a prolonged overall half-life and is metabolised to an active metabolite.

CLINICAL FEATURES

Nystagmus, ataxia, tremor and fits are common; however, in severe overdose, fluctuating coma and

severe tachycardia or bradycardia may occur. Plasma concentrations of carbamazepine and the active metabolite can be measured, although they do not correlate well with toxicity. Life-threatening toxicity typically occurs with plasma concentrations greater than 40 mg/L (170 nmol/L).

TREATMENT

Multiple-dose AC is indicated in large ingestions or symptomatic patients, and may help elimination even if initiated several hours after the overdose. Further measures are based on the clinical course. Currently intermittent haemodialysis (IHD) is recommended in severe poisoning with intermittent haemoperfusion (IPF) and continuous renal replacement considered acceptable if IHD is not available.[12]

CARBON MONOXIDE

Haldane first described symptoms of carbon monoxide (CO) toxicity in 1919 and the mechanisms of toxicity remain unclear. Smokers may have up to 10% of their haemoglobin bound to CO (i.e. carboxyhaemoglobin [COHb]), without deleterious effects. Whereas coma and/or COHb levels greater than 40% always indicate serious poisoning, delayed deterioration can occur in their absence. Affinity of CO for haemoglobin is approximately 240 times that of oxygen.

CLINICAL FEATURES

Neurological signs vary from mild confusion through to seizures and coma. A history of loss of consciousness should always be sought and may be the only indicator of significant poisoning. ST segment changes may be present on electrocardiogram (ECG). In the absence of respiratory depression or aspiration, PaO_2 will be normal. It is essential that SaO_2 is measured directly by a co-oximeter, and not calculated. Cherry-pink skin is seen only in textbooks; cyanosis is far more common.

TREATMENT

After basic resuscitative measures, high-flow oxygen (up to 100% if possible) should be administered and continued until the COHb level is less than 5%. This sometimes takes up to 24 hours. Hyperbaric oxygen (HBO), although often used, remains controversial. There have been eight randomised controlled trials of HBO versus normobaric oxygen. Unfortunately, many of these are of poor quality, and it is not possible to show any statistical benefit of HBO in reducing neurological sequelae at 1 month.[26] Considering the frequently encountered logistical difficulties in transferring an unconscious patient to an HBO centre, it cannot be routinely recommended based on the data currently available.

CHLOROQUINE

CLINICAL FEATURES

Hypotension, hypokalaemia, convulsions, ventricular arrhythmias and sudden cardiac arrest may result from severe poisoning. As little as 2 g of chloroquine have been reported to be fatal in adults. Symptoms typically tend to occur very early following ingestion, and normally within 3 hours of ingestion.

TREATMENT

AC should be considered up to 1 hour post-ingestion. In patients who have ingested potentially significant amounts of chloroquine or who have features of significant poisoning, then high-dose diazepam (2 mg/kg over 30 minutes) with inotropic and ventilator support should be considered.[27] Hypokalaemia is common and may be protective in the early stage. Hypokalaemia stems from redistribution into cells, rather than an absolute reduction in potassium. Hypokalaemia is therefore self-correcting and consequently aggressive potassium replacement is not recommended.

COCAINE

CLINICAL FEATURES

The clinical features of acute cocaine toxicity are similar to those seen in the amphetamine toxicity. There is the additional risk of cocaine-related vasospasm, which can lead to ischaemia in any vascular bed, but is of particular significance from a cardiac and cerebral perspective. Cocaine-related myocardial ischaemia is due primarily to coronary artery vasospasm; additional mechanisms included increased myocardial oxygen demand due to increased heart rate, decreased vasodilators (nitric oxide), increased vasoconstrictors (endothelin) and increased platelet aggregation.[28]

TREATMENT

The treatment of the common unwanted effects related to cocaine are the same as those seen with amphetamines. In terms of myocardial ischaemia, there are some differences between the management of this compared with classical atherosclerotic-related ischaemia. Patients should be treated with oxygen and aspirin; low-molecular-weight heparin and glycoprotein IIb/IIIa inhibitors should not be routinely used due to the increased risk of cerebral haemorrhage in significant hypertension. Vasodilators (e.g. S/L, buccal or IV nitrates) should be given early in an attempt to reverse coronary artery vasospasm, although care should be taken if there is a significant tachycardia due to the risk of a reflex tachycardia leading to an increased heart rate. Benzodiazepines should be administered to reduce sympathetic nervous system stimulation, thereby reducing myocardial oxygen demand by reducing the heart rate, as well as potentially causing coronary artery

vasodilatation through peripheral cardiac benzodiazepine receptors. Beta blockers are contraindicated as they can lead to unopposed alpha stimulation leading to worsening hypertension; in addition they can worsen cocaine-related coronary artery vasospasm. Other measures in those who fail to respond include other vasodilators (e.g. calcium channel blockers, alpha blockers) and/or primary angiography and angioplasty/intraluminal drug treatment. For patients with ongoing cardiovascular instability or intractable arrhythmias, measures including extracorporeal support with veno-arterial extracorporeal membrane oxygenation or cardiac bypass should be considered.[24]

CYANIDE

CLINICAL FEATURES

Severe toxicity is rapidly fatal; however, features include coma, respiratory depression, hypotension and metabolic acidosis. More moderate features include brief loss of consciousness, convulsions and vomiting. Rescuers must ensure that they do not get contaminated themselves. Expert advice is usually required in the management of these patients owing to the risk of significant toxicity.

TREATMENT

Inhaled amyl nitrate and 100% oxygen may well have been given at the scene, since it is present in 'cyanide antidote kits'. Following this there are a number of options:

1. Pre-hospital hydroxycobalamin 70 mg/kg or 5 g IV over 15 minutes.
2. In-hospital management of moderate to severe poisoning may require a second dose of 5 g hydroxycobalamin. The ARC suggest a third dose if required.
3. In severe poisoning the addition of sodium thiosulphate 12.5 g at 1.25 g/min is recommended. If signs of poisoning continue, half the original dose may be repeated.[29]
4. Patients with a metabolic acidosis should be given sodium bicarbonate.

DIGOXIN

CLINICAL FEATURES

Toxicity may result from ingestion of as little as 2 mg and lethal doses of >10 mg in adults and >4 mg in children. More commonly toxicity results from taking too high a daily dose and/or a reduction in renal elimination. Any cardiac arrhythmia may occur and adverse effects may be delayed for some hours. Severe poisoning can produce hyperkalaemia and hypotension.

TREATMENT

AC should be considered up to 1 hour post-ingestion and multiple-dose charcoal may be effective by interrupting enterohepatic recirculation of the drug. A digoxin serum level may be helpful although it does not equate to the total body burden. Patients with hyperkalaemia should not be administered calcium gluconate (increased risk of cardiac toxicity); initial management is insulin–dextrose therapy. Those patients with persistent hyperkalaemia (>6.0 to 6.5 mmol/L), along with brady- or tachyarrhythmias associated with hypotension, should be treated with digoxin-specific antibody fragments.[30] Other treatments, particularly where digoxin-specific antibody fragments are not available, may be indicated, but expert advice should be sought in these situations. For patients with ongoing cardiogenic shock or intractable arrhythmias, measures including extracorporeal support with veno-arterial extracorporeal membrane oxygenation or cardiac bypass should be considered.

GAMMA HYDROXYBUTYRIC ACID AND GAMMA BUTYROLACTONE

CLINICAL FEATURES

In moderate to high ingestion, coma, convulsions, bradycardia, hypotension and severe respiratory depression can be seen, and other CNS depressant drugs potentiate the effects. Most patients who present to hospital merely require supportive care, and even those who present in coma are often awake within 2–4 hours; very few require intensive care.[31]

TREATMENT

Management is largely supportive; intubation is often not indicated even in those with significantly reduced levels of consciousness as airways reflexes tend to be maintained.[31] Computed tomography scanning should be considered in those with evidence of head injury, focal neurological signs or failure to wake after 1–2 hours. It is important before discharging a patient to determine whether they are potentially dependent users (daily use) and therefore at risk of withdrawal. Expert advice on the management of these patients should be sought.

IRON

CLINICAL FEATURES

Iron poisoning classically has four phases:

- *phase 1:* initial GI symptoms secondary to direct corrosive action on gastric mucosa
- *phase 2:* latent asymptomatic phase
- *phase 3:* systemic iron toxicity
- *phase 4:* GI strictures several weeks after initial ingestion due to the initial direct GI corrosive effects.

The duration of phases 1 and 2 is dependent on the dose of iron ingested; some patients in very large ingestions may progress straight to a combined phase

1/3 presentation. Serum iron concentration is helpful in patient management.

TREATMENT

In those patients who present with features of severe iron poisoning, deferoxamine (also known as desferrioxamine mesilate) should be commenced at an initial rate of 15 mg/kg/h. The maximum licensed dose is 80 mg/kg/day; however, these patients may require more prolonged treatment and appropriate advice should be sought. For those presenting within 6 hours without severe symptoms, the management can be guided by a serum iron concentration 4–6 hours after ingestion (<55 µmol/L does not require treatment, >90 µmol/L treatment is recommended, 55–90 µmol/L treatment may be required depending on whether the concentration is not falling and/or the clinical condition of the patient). For those presenting more than 6 hours after presentation without severe features, the serum iron concentration is not as helpful in determining the need for treatment; expert advice should be sought for these patients.

ISONIAZID

CLINICAL FEATURES

Severe toxicity is characterised by coma, respiratory depression, hypotension and convulsions resistant to conventional treatments, and may result from doses greater than 80 mg/kg. Protracted convulsions can cause rhabdomyolysis and acute renal failure.

TREATMENT

AC should be considered for large ingestions seen within 1 hour. Management of convulsions is initially benzodiazepines (IV 10–20 mg diazepam, or IV 4 mg lorazepam); those who fail to respond should be treated with 1 g of pyridoxine per gram of isoniazid ingested to a maximum of 5 g. Barbiturates, such as thiopentone, should be used as second line therapy for patients with seizure activity, which does not respond to benzodiazepines. Phenytoin should not be administered, as it is ineffective and isoniazid inhibits the metabolism of phenytoin.

LITHIUM

CLINICAL FEATURES

There are two types of overdose: acute in lithium in naïve individuals/those on treatment, and chronic in those on long-term lithium treatment. For the latter this may be secondary to an intentional overdose or due to other factors such as dehydration or use of interacting drugs (e.g. non-steroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting-enzyme [ACE]-inhibitors, thiazide diuretics). Symptoms of toxicity can be divided as follows:

- *mild:* nausea, vomiting, fine tremor, polyuria, weakness
- *moderate:* confusion, urinary and faecal incontinence, myoclonic twitches/jerks, hypernatraemia, hyperreflexia
- *severe:* coma, renal failure, convulsions, cardiac arrhythmias.

TREATMENT

Lithium concentrations should be measured on arrival in chronic cases and then repeated every 4–6 hours; for acute overdoses, lithium concentrations should be measured 6 hours after ingestion and then every 4–6 hours. Patients should be adequately rehydrated, which may help with any renal impairment. Whole bowel irrigation (see above) should be considered in those who have ingested a potentially toxic amount of lithium. Extracorporeal elimination should be considered in those who have either severe features of lithium toxicity, or a serum lithium concentration of greater than 7.5 mmol/L in acute overdoses or greater than 4 mmol/L in chronic-related toxicity. For patients with ongoing cardiovascular instability or intractable life-threatening arrhythmias, measures including extracorporeal support with veno-arterial extracorporeal membrane oxygenation or cardiac bypass should be considered.[24] Seizure activity should be treated with benzodiazepines (first line) or barbiturates (second line). Phenytoin should not be used for seizure control.

METHANOL AND ETHYLENE GLYCOL

CLINICAL FEATURES

Methanol and ethylene glycol are relatively non-toxic themselves, but their ingestion is a medical emergency because of their metabolism (following a latent period of 12–18 hours) to formic acid and glycolic acid, respectively. These toxic metabolites account for the metabolic acidosis, ocular toxicity, renal failure and mortality that are occasionally seen. Mild features include dizziness, drowsiness and abdominal pain. When treatment is delayed, metabolic acidosis develops with drowsiness, coma and convulsions. The osmolal gap initially is elevated but then falls as the methanol or ethylene glycol is metabolised; the anion gap increases as the toxic metabolites build up.

TREATMENT

AC does not adsorb either methanol or ethylene glycol. The metabolic acidosis should be treated with sodium bicarbonate and the serum electrolytes measured. Ethanol prevents formation of the toxic metabolites and previously it has been the most established treatment; its dosing is complex and it requires 1- to 2-hourly blood ethanol measurement and adjustment of the treatment. Additionally, it can cause significant

CNS depression, necessitating critical care admission. Fomepizole (4-methypyrazole) has now become the antidote of choice; it is a twice-daily weight-based infusion without the need for specific monitoring and is not associated with neurological depression.[32] The initial dose is 15 mg/kg over 30 minutes, followed by a twice-daily infusion of 10 mg/kg for the next four doses and then increased to 15 mg/kg per treatment dose until treatment is no longer required. Ongoing management after initial loading dose often requires the involvement of clinical/medical toxicology services to facilitate ethylene glycol/methanol concentration measurement and interpretation of the results. The EXTRIP work group recommends concurrent extracorporeal treatment for severe methanol poisoning defined by the presence of coma, seizures, new vision deficits, metabolic acidosis pH less than 7.15, persistent metabolic acidosis despite adequate supportive measures and antidotes, a serum anion gap greater than 24 mmol/L or serum methanol levels greater than (1) 700 mg/L (21.8 mmol/L) in the context of fomepizole therapy; (2) greater than 600 mg/L (18.7 mmol/L) in the context of ethanol treatment; and (3) 500 mg/L (15.6 mmol/L) in the absence of alcohol dehydrogenase blocker.[33] It is important to remember with both ethanol and fomepizole that, should extracorporeal treatment be required, not only will the toxic alcohol be removed, but so too will the antidote; modifications to treatment regimens will be required.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

CLINICAL FEATURES

NSAIDs are commonly ingested in an overdose; symptoms tend to be mild and consist with GI symptoms. GI haemorrhage is not commonly reported in an acute overdose of NSAIDs (apart from secondary to Mallory–Weiss tears). Convulsions can occur, but are usually associated with mefenamic acid (up to 10%–15% of patients). Large ingestions of NSAIDs can be associated with metabolic acidosis and/or renal impairment[34] and rarely hepatocellular injury.[35] Patients who do not develop symptoms within 4 hours are unlikely to experience delayed toxicity.

TREATMENT

AC can be given for large ingestions that are seen within 1 hour of the overdose. Convulsions should be treated with a benzodiazepine. Although there is no indication for routine use, those patients with symptoms of GI irritation can be treated with a short course of an oral proton pump inhibitor. Metabolic acidosis should be treated with sodium bicarbonate and other measures as indicated. Supportive care and appropriate investigation are required for patients with renal impairment.

OPIOIDS

CLINICAL FEATURES

Overdose is characterised by pinpoint pupils, drowsiness, shallow breathing and ultimately respiratory failure.

TREATMENT

AC may be effective for oral ingestions; otherwise, treatment is supportive. Naloxone 100–200 µg boluses should be given IV and increased as titrated to clinical response. In patients who fail to respond to 2 mg, alternative diagnoses should be considered. Those who respond may require repeat doses, particularly where a long-acting or sustained/modified release preparation has been ingested; an infusion of naloxone may be required in these patients. Intubation and mechanical ventilation are required if respiratory failure is not rapidly reversed by naloxone.

PARACETAMOL

There is increased metabolism of paracetamol to its toxic metabolite, *N*-acetyl-*p*-benzoquinonimine (NAPQI) as normal conjugation pathways are exceeded. This toxic metabolite irreversibly binds to hepatocytes leading to cell death and release of inflammatory and cytotoxic mediators and further hepatocyte death. The antidote for paracetamol poisoning is *N*-acetylcysteine (NAC). Recent changes the treatment guidelines for paracetamol poisoning in the United Kingdom removed the need for risk assessment and dropped the treatment line used by 25%. All ingestions greater than 75 mg/kg are considered significant. Although IV acetylcysteine administered more than 16 hours after ingestion may not prevent severe liver damage, it should still be given since outcome from paracetamol-induced fulminant hepatic failure is improved. Although severe hepatic injury has a 10% mortality, the majority of patients recover within 1–2 weeks.[36] Patients with fulminant hepatic failure should have an early discussion with a liver transplant centre, as super-urgent transplantation may be required.

CLINICAL FEATURES

Paracetamol poisoning is often asymptomatic in the early stages (the first 24–48 hours); later presentations may be associated with evidence of acute liver injury/failure. Patients with very significant ingestions (initial 4-hour paracetamol concentrations of >800 mg/L) may present in coma with a lactic metabolic acidosis – this is a direct effect of the paracetamol.

TREATMENT

- Those patients who present within an hour – consider AC in significant ingestions.
- Current UK treatment guidelines for single known time-point ingestions are based on a single treatment

line starting at 100 mg/L at 4 hours post-ingestion. Risk stratification is no longer required to determine the need for treatment.
- For those with staggered, supratherapeutic or unknown time of ingestions, treatment is not required for those who have ingested less than 75 mg/kg in the last 24 hours, but it is required for those who have ingested greater than 150 mg/kg (these are based on actual body weight to a maximum of 110 kg). For those who have ingested between 75 and 150 mg/kg, advice should be sought on whether or not treatment is required.
- NAC 150 mg/kg in 200 mL 5% dextrose is infused over 1 hour, followed by 50 mg/kg in 500 mL 5% dextrose over 4 hours and 100 mg/kg in 1 L 5% dextrose over 16 hours (total dose 300 mg/kg in 20 hours). Maximum protective effect is time dependent. An ingestion–treatment interval of less than 10 hours gives the best results.
- In those patients with evidence of liver injury, the last dose (100 mg/kg in 1 L 5% dextrose over 16 hours) is repeated until the patient's condition and biochemical and haematological results are improving.
- Although there is limited evidence, many recommend the use of prolonged NAC in patients with acute kidney injury.
- Expert opinion should be sought early on from a regional centre if liver failure is progressive since liver transplantation may become necessary.

PARAQUAT

In adult humans the lethal dose is 3–6 g (i.e. 15–30 mL of 20% w/v liquid concentrate). The mortality rate in patients ingesting the liquid concentrate is about 45%.[37] The lung is the primary target organ, with the injury being enhanced by oxygen. Peak concentrations are achieved between 0.5 and 2 hours.

CLINICAL FEATURES

Initial symptoms are GI pain and vomiting with corrosive effects on the mouth, pharynx and oesophagus. Dyspnoea and pulmonary oedema follow within 24 hours, progressing to irreversible fibrosis and death. Cardiac, renal and hepatic dysfunctions are common.

TREATMENT

Those treating suspected paraquat-poisoned patients should wear appropriate personal protective equipment to prevent secondary exposure. An urgent qualitative urine test (dithionite spot test) should be undertaken to confirm exposure; a confirmatory plasma concentration should be measured in those where positive as this may guide prognosis. Management is largely supportive: analgesia for oropharyngeal burns and other measures as indicated by the patient's clinical condition. Oxygen therapy can increase the degree and severity of pulmonary fibrosis. Palliative care may be required in those with high paraquat concentrations who fail to respond to treatment. Expert advice should be sought in these patients to determine whether other treatment options including veno-venous extracorporeal membrane oxygenation may be appropriate.

PHENYTOIN

CLINICAL FEATURES

Absorption is slow and unpredictable; moreover, maximum serum concentrations may not be achieved until 72 hours after ingestion. After initial nausea and vomiting, neurological symptoms develop including drowsiness, dysarthria and ataxia, and may ultimately progress to seizures. Cardiovascular toxicity is rare unless the overdose has been given intravenously.

TREATMENT

Most patients require nothing more than supportive measures. There is some evidence from volunteer studies that multi-dose AC can increase the elimination of phenytoin; it is not clear whether this alters the outcome.[38]

SALICYLATES (ASPIRIN)

Moderate toxicity occurs with serum concentrations 500–750 mg/L (3600–5500 µmol/L) and severe toxicity with concentrations greater than 750 mg/L. Serum concentrations alone do not determine prognosis. The elimination half-life increases significantly with increasing concentrations. Small reductions in pH produce large increases in non-ionised salicylate, which then penetrates tissues.

CLINICAL FEATURES

Tinnitus, deafness, diaphoresis, pyrexia, hypoglycaemia, haematemesis, hyperventilation and hypokalaemia may all occur. Coma, hyperpyrexia, pulmonary oedema and acidaemia are reported as more common in fatal cases, which present late.

TREATMENT

Although multiple-dose AC is not recommended by some experts, most medical toxicologists would recommend its use in large ingestions since concretions of salicylates in the stomach can occur with delayed ongoing absorption. Urinary alkalinisation (see above) decreases the amount of non-ionised drug available to enter tissues and should be considered in those with moderate/severe toxicity. Extracorporeal techniques are very effective in removing salicylates and correcting acid-base disturbance.[9]

SELECTIVE SEROTONIN REUPTAKE INHIBITORS OR 5-HT DRUGS

Selective serotonin reuptake inhibitors (SSRIs) include citalopram, fluoxetine, fluvoxamine, paroxetine and

sertraline. These drugs have increasingly replaced the TCA and generally appear to be much safer in overdose.

CLINICAL FEATURES

Drowsiness, tachycardia and mild hypertension are the commonest features. Seizures and coma can occur, as well as a serotonin syndrome in 14% of cases.[39]

TREATMENT

AC should be considered up to 1 hour post-ingestion, otherwise treatment is supportive. Benzodiazepines should be used to treat agitated or hyperthermic patients. There are case reports of cyproheptadine being used to treat severe toxicity with SSRIs.[40] In those with hyperthermia, the advice (as above) for amphetamines should be followed in terms of assessment of the hyperthermia and the appropriate management interventions.

THEOPHYLLINE

CLINICAL FEATURES

Acute theophylline poisoning is potentially very serious and severe poisoning carries a high mortality. Toxic effects such as agitation, tremor, nausea, vomiting and sinus tachycardia become evident at less than 30 mg/L (167 µmol/L). Concentrations greater than 60 mg/L (333 µmol/L) in acute poisoning or greater than 40 mg/L (222 µmol/L) in chronic usage frequently result in seizures, malignant ventricular arrhythmias, severe hypotension and death.[41] A key feature is hypokalaemia, which predisposes to arrhythmias and rhabdomyolysis. Measuring plasma theophylline levels confirms the ingestion and may help in deciding elimination methods; in the majority of poisoned patients they do not aid management. Sustained-release preparations may result in delayed onset and prolonged toxicity.

TREATMENT

Multidose AC should be considered, particularly in those with serum concentrations of greater than 40 mg/L. Although hypokalaemia does occur, there is not a total body depletion of potassium; therefore only potassium concentrations of less than 3 mmol/L should be cautiously replaced; monitor for a rebound hyperkalaemia. Convulsions should be treated with benzodiazepines and cardiac arrhythmias with beta blockers in non-asthmatic patients. Vomiting is often severe, and requires appropriate antiemetic administration. IHD is recommended in severe poisoning and if not available, IPF and continuous renal replacement therapy (CRRT) are acceptable alternatives.[11]

TRICYCLIC ANTIDEPRESSANTS

CLINICAL FEATURES

These drugs remain the leading cause of death from overdose in patients arriving at the emergency department alive and account for up to one-half of all overdose-related adult intensive care admissions.[42] Features include anticholinergic effects such as warm dry skin, tachycardia, blurred vision, dilated pupils and urinary retention. Severe features include respiratory depression, reduced conscious level, cardiac arrhythmias, fits and hypotension. Arrhythmias may be predicted by a QRS duration greater than 100 ms on the ECG; a QRS duration of greater than 160 ms increases risk of seizures. All forms of rhythm and conduction disturbance have been described, and are not necessarily predicted by the ECG.[43] Amoxapine typically causes features of severe poisoning in the absence of QRS widening. Cardiac toxicity is due mainly to quinidine-like actions, slowing phase 0 depolarisation of the action potential. Other mechanisms include impaired automaticity, cholinergic blockade and inhibition of neuronal catecholamine uptake. Toxicity is worsened by acidaemia, hypotension and hyperthermia.

TREATMENT

After supportive care as outlined above, including multiple-dose AC, continuous cardiac monitoring is essential. Increasing arterial pH to ≥7.45 significantly reduces the available free drug and this may be the best way to avoid TCA toxicity. Mild hyperventilation and 8.4% sodium bicarbonate in 50 mmol aliquots achieves this strategy and may improve the outcome.[31] Bicarbonate should probably be given in all cases of QRS prolongation (even in the absence of metabolic acidosis), arrhythmias with associated hypotension or metabolic acidosis; it should also be considered in those with convulsions. If arrhythmias occur, avoid class 1a agents; lidocaine may be best. For patients with intractable arrhythmias, measures including extracorporeal support with veno-arterial extracorporeal membrane oxygenation or cardiac bypass should be considered.[24] Benzodiazepines are the drug of choice for sedation and the treatment of seizures, and may prevent emergence delirium. Extracorporeal treatment is not recommended.[15]

VALPROATE

CLINICAL FEATURES

Most overdoses follow a benign course, with nausea, mild drowsiness and confusion. Coma can occur in large ingestions with cerebral oedema. There is the potential for metabolic derangement, including metabolic acidosis, hypernatraemia, hypoglycaemia and hyperammonaemia.

TREATMENT

Valproate levels are of little value, except to confirm the ingestion. There is poor correlation between the depth of coma and the free or total valproate levels. Supportive management is all that is usually required. Although in therapeutic use, valproate is extensively

protein-bound, with increasing plasma concentrations there is saturation of this binding leading to increased free drug; extracorporeal treatment is now recommended with haemodialysis the first choice and IPF and CRRT are acceptable alternatives.[44] Additionally, in those patients with significant overdoses, associated hepatic dysfunction and hyperammonaemia, consider the use of L-carnitine.

REFERENCES

1. Gunnell D, Ho D, Murray V. Medical management of deliberate drug overdose: a neglected area for suicide prevention? *Emerg Med J*. 2004;21(1):35–38.
2. Höjer J, Troutman WG, Hoppu K, et al. Position paper update: ipecac syrup for gastrointestinal decontamination. *Clin Toxicol*. 2013;51(3):134–139.
3. Benson BE, Hoppu K, Troutman WG, et al. Position paper update: gastric lavage for gastrointestinal decontamination. *Clin Toxicol*. 2013;51(3):140–146.
4. Chyka PA, Seger D, Krenzelok EP, et al. Position paper: single-dose activated charcoal. *Clin Toxicol*. 2005;43(2):61–87.
5. LoVecchio F, Shriki J, Innes K, et al. The feasibility of administration of activated charcoal with respect to current practice guidelines in emergency department patients. *J Med Toxicol*. 2007;3(3):100–102.
6. American Academy of Clinical Toxicology EAoPCaCT. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. *J Toxicol Clin Toxicol*. 1999;37(6):731–751.
7. American Academy of Clinical Toxicology, European Association of Poison Centres and Clinical Toxicologists. Position paper: whole bowel irrigation. *J Toxicol Clin Toxicol*. 2004;42(6):843–854.
8. Proudfoot AT, Krenzelok EP, Vale JA. Position paper on urine alkalinization. *J Toxicol Clin Toxicol*. 2004;42(1):1–26.
9. Juurlink DN, Gosselin S, Kielstein JT, et al. Extracorporeal treatment for salicylate poisoning: systematic review and recommendations from the EXTRIP Workgroup. *Ann Emerg Med*. 2015;66(2):165–181.
10. Decker BS, Goldfarb DS, Dargan PI, et al. Extracorporeal treatment for lithium poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin J Am Soc Nephrol*. 2015;10(5):875–887.
11. Ghannoum M, Wiegand TJ, Liu KD, et al. Extracorporeal treatment for theophylline poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin Toxicol (Phila)*. 2015;53(4):215–229.
12. Ghannoum M, Yates C, Galvao TF, et al. Extracorporeal treatment for carbamazepine poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin Toxicol (Phila)*. 2014;52(10):993–1004.
13. Gosselin S, Juurlink DN, Kielstein JT, et al. Extracorporeal treatment for acetaminophen poisoning: recommendations from the EXTRIP workgroup. *Clin Toxicol*. 2014;52(8):856–867.
14. Anseeuw K, Mowry JB, Burdmann EA, et al. Extracorporeal treatment in phenytoin poisoning: systematic review and recommendations from the EXTRIP (Extracorporeal Treatments in Poisoning) Workgroup. *Am J Kidney Dis*. 2016;67(2):187–197.
15. Yates C, Galvao T, Sowinski KM, et al. Extracorporeal treatment for tricyclic antidepressant poisoning: recommendations from the EXTRIP Workgroup. *Semin Dial*. 2014;27(4):381–389.
16. Mowry JB, Burdmann EA, Anseeuw K, et al. Extracorporeal treatment for digoxin poisoning: systematic review and recommendations from the EXTRIP Workgroup. *Clin Toxicol (Phila)*. 2016;54(2):103–114.
17. The Association of Anaesthetists of Great Britain & Ireland. *Management of Severe Local Anaesthetic Toxicity*; 2010.
18. Ozcan MS, Weinberg G. Intravenous lipid emulsion for the treatment of drug toxicity. *J Intensive Care Med*. 2014;29(2):59–70.
19. Teter CJ, Guthrie SK. A Comprehensive review of MDMA and GHB: two common club drugs. *Pharmacotherapy*. 2001;21(12):1486–1513.
20. Richards JR, Albertson TE, Derlet RW, et al. Treatment of toxicity from amphetamines, related derivatives, and analogues: a systematic clinical review. *Drug Alcohol Depend*. 2015;150:1–13.
21. Ables AZ, Nagubilli R. Prevention, recognition, and management of serotonin syndrome. *Am Fam Physician*. 2010;81(9):1139–1142.
22. Seger DL. Flumazenil – treatment or toxin. *J Toxicol Clin Toxicol*. 2004;42(2):209–216.
23. Shepherd G. Treatment of poisoning caused by beta-adrenergic and calcium-channel blockers. *Am J Health Syst Pharm*. 2006;63(19):1828–1835.
24. Wang GS, Levitan R, Wiegand TJ. Extracorporeal membrane oxygenation (ECMO) for severe toxicological exposures: review of the Toxicology Investigators Consortium (ToxIC). *J Med Toxicol*. 2016;12:95–99.
25. Engebretsen KM, Kaczmarek KM, Morgan J, et al. High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. *Clin Toxicol*. 2011;49(4):277–283.
26. Buckley NA, Isbister GK, Stokes B, et al. Hyperbaric oxygen for carbon monoxide poisoning: a systematic review and critical analysis of the evidence. *Toxicol Rev*. 2005;24(2):75–92.
27. Riou B, Barriot P, Rimailho A, et al. Treatment of severe chloroquine poisoning. *N Engl J Med*. 1988;318(1):1–6.
28. Shanti CM, Lucas CE. Cocaine and the critical care challenge. *Crit Care Med*. 2003;31(6):1851–1859.
29. Anseeuw K, Delvau N, Burillo-Putze G, et al. Cyanide poisoning by fire smoke inhalation: a

European expert consensus. *Eur J Emerg Med*. 2013; 20(1):2–9.
30. Lapostolle F, Borron SW, Verdier C, et al. Digoxin-specific Fab fragments as single first-line therapy in digitalis poisoning. *Crit Care Med*. 2008;36(11):3014–3018.
31. Schep LJ, Knudsen K, Slaughter RJ, et al. The clinical toxicology of gamma-hydroxybutyrate, gamma-butyrolactone and 1,4-butanediol. *Clin Toxicol*. 2012;50(6):458–470.
32. Hovda KE, Jacobsen D. Expert opinion: fomepizole may ameliorate the need for hemodialysis in methanol poisoning. *Hum Exp Toxicol*. 2008;27(7): 539–546.
33. Roberts DM, Yates C, Megarbane B, et al. Recommendations for the role of extracorporeal treatments in the management of acute methanol poisoning: a systematic review and consensus statement. *Crit Care Med*. 2015;43(2):461–472.
34. Smolinske SC, Hall AH, Vandenberg SA, et al. Toxic effects of nonsteroidal anti-inflammatory drugs in overdose. An overview of recent evidence on clinical effects and dose-response relationships. *Drug Saf*. 1990;5(4):252–274.
35. Schmeltzer PA, Kosinski AS, Kleiner DE, et al. Liver injury from nonsteroidal anti-inflammatory drugs in the United States. *Liver Int*. 2016;36:603–609.
36. Chun LJ, Tong MJ, Busuttil RW, et al. Acetaminophen hepatotoxicity and acute liver failure. *J Clin Gastroenterol*. 2009;43(4):342–349.
37. Gawarammana IB, Buckley NA. Medical management of paraquat ingestion. *Br J Clin Pharmacol*. 2011;72(5):745–757.
38. Skinner CG, Chang AS, Matthews AS, et al. Randomized controlled study on the use of multiple-dose activated charcoal in patients with supratherapeutic phenytoin levels. *Clin Toxicol (Phila)*. 2012;50(8):764–769.
39. Isbister GK, Bowe SJ, Dawson A, et al. Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose. *J Toxicol Clin Toxicol*. 2004;42(3): 277–285.
40. McDaniel WW. Serotonin syndrome: early management with cyproheptadine. *Ann Pharmacother*. 2001;35:870–873.
41. Shannon M. Predictors of major toxicity after theophylline overdose. *Ann Intern Med*. 1993;119(12): 1161.
42. Newton EH, Shih RD, Hoffman RS. Cyclic antidepressant overdose: a review of current management strategies. *Am J Emerg Med*. 1994;12(3): 376–379.
43. Harrigan RA, Brady WJ. ECG abnormalities in tricyclic antidepressant ingestion. *Am J Emerg Med*. 1999;17(4):387–393.
44. Ghannoum M, Laliberte M, Nolin TD, et al. Extracorporeal treatment for valproic acid poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin Toxicol (Phila)*. 2015;53(5):454–465.

91

Sedation and pain management in intensive care

Luke E Torre

Despite the widespread use of sedative and analgesic agents in intensive care unit (ICU), the goals of sedation and analgesia are not well established.[1] Having its roots in anaesthesia, ICUs would historically manage patients with full general anaesthesia, including skeletal muscle paralysis and controlled ventilation modes, and this was maintained until the disease process remitted. Sedation and analgesia were considered a necessary adjunct to the management of critically ill patients.

Combinations of opioids and benzodiazepines (BZAs) are commonly used to provide 'sedation' in the ICU. Because high doses of opioids analgesics may result in significant sedation in their own right and are synergistic with sedative agents, the distinction between sedation and analgesia is blurred. This makes the definition and attainment of clear sedation goals elusive.

SEDATION

There has been a paradigm shift in thinking towards sedation practice in ICUs over the past 30 years. A combination of factors has led to this change, notably:

- improved ventilator technology and modes of ventilation allowing synchronised and spontaneous respiration
- improved drug development for sedation and analgesia with pharmacokinetic profiles that allow prompt titration, and pharmacodynamic profiles with fewer side effects
- the development and implementation of sedation scoring systems in the ICU[2]
- the increasing use of percutaneous tracheostomy and/or non-invasive ventilation for patients requiring prolonged ventilation
- the recognition of critical illness polyneuropathy and myopathy and the risk factors associated with it
- the separation and specialisation of intensive care physicians from other domains
- the emerging high-quality evidence in the field of sedation and analgesia in intensive care
- economic pressures and increased demand for finite intensive care resources.

Currently, sedative use in the critically ill should be for one or more of the following purposes:

- a treatment for disease processes such as: seizures, raised intracranial pressure, serotonin syndrome and alcohol withdrawal
- to facilitate tolerance of intensive care therapies such as intubation, mechanical ventilation and active cooling
- to reduce oxygen consumption by reducing patient arousal, activity and anxiety
- to maintain the safety of patient and carers when dealing with the hyperactive delirious patient
- palliation
- procedural sedation.

Sedation of patients in the ICU is an integral part of what health care workers perceive to be care and compassion for the critically ill patient. Presumed benefits of sedative agents include:

- reducing patient anxiety over their illness, the welfare of relatives or the risk of death
- providing adequate rest
- reducing the distress of unpleasant sensations, invasive treatments and monitoring
- blunting awareness of the environment over which the patient has very little control and in which they may be unable to communicate.

Non-pharmacological methods should preferentially be used to help manage these issues. Avoiding potentially distressing situations, allowing adequate access to caring visitors, maintenance of good communication with the patient and a positive outlook by carers will satisfy many of these goals. Small comforts, such as ice chips by mouth, a comfortable mattress, relaxation music and maintaining a daytime/nighttime environment all help this process.

LEVEL AND ASSESSMENT OF SEDATION

Critical to delivery of sedation is an accurate sedation assessment tool. Sedation scoring systems were first introduced in the 1970s.[2] Since that time, several validated scoring systems for critically ill patients have become available. The Ramsay Sedation Scale (RSS)

ABSTRACT

Sedation and analgesia are mainstays of critically ill patient management, but our understanding and use have changed enormously over the decades. Sedation strategies have become tailored, evidence-based treatments, with continual assessment and adjustment aiming to minimise complications and improve patient outcomes. Interest has centred on dexmedetomidine and its possible role in reducing delirium and the role of volatile agents in intensive care units. Pain assessment and treatment continue to improve with the development of critical care specific pain assessment tools. Opioids are the pharmacological cornerstone of treating pain, and newer agents with more favourable pharmacokinetic profiles are in common use. Multimodal analgesia remains the key to optimal pain management. Future work focuses on understanding and improving sleep in critically ill patients.

KEYWORDS

Sedation
analgesia
sedation strategies
dexmedetomidine
benzodiazepines
opioids
propofol
pain
sleep
assessment tools

Table 91.1 Ramsay sedation scale

LEVEL	RESPONSE
AWAKE LEVELS	
1	Patient anxious and agitated or restless or both
2	Patient cooperative, orientated and tranquil
3	Patient responds to commands only
ASLEEP LEVELS	
4	Brisk response to a light glabellar tap or loud auditory stimulus
5	Sluggish response to a light glabellar tap or loud auditory stimulus
6	No response to a light glabellar tap or loud auditory stimulus

Table 91.2 Richmond agitation sedation scale

POINT	PATIENT RESPONSE TO VERBAL AND PHYSICAL STIMULI
+4	Combative – combative, violent, immediate danger to staff
+3	Very agitated – pulls or removes tubes or catheters; aggressive
+2	Agitated – frequent non-purposeful movement, fights ventilator
+1	Restless – anxious, apprehensive but movements not aggressive or vigorous
0	Alert and calm
–1	Drowsy – not fully alert, but has sustained (>10 s) awakening (eye opening/contact) to voice
–2	Light sedation – drowsy, briefly (<10 s) awakens to voice or physical stimulation
–3	Moderate sedation – movement or eye opening (but not eye contact) to voice
–4	Deep sedation – no response to voice but movement or eye opening to physical stimulation
–5	Unarousable – no response to voice or physical stimulation

Siegel MD. Management of agitation in the intensive care unit. *Clin Chest Med*. 2003;24(4):713–722.

and Richmond Agitation Sedation Scale are two of the most popular used worldwide (Tables 91.1 and 91.2). Despite their availability, validation and evidence base, their incorporation into routine management of intensive care patients remains low.[3]

Electroencephalography (EEG), which may be either 'raw' or 'processed', provides a measure of cerebral activity. This monitor is more suitable for assessing depth of anaesthesia and may be difficult to interpret in the encephalopathic patient. Devices using integrated EEG (e.g. bispectral index [BIS]) are available, but further research is required to establish their role in the ICU.[4] Their use is also limited by practical considerations, such as interference due to movement artefact.

SEDATION STRATEGIES

Although the choice of sedative agent(s) must be a conscientious decision based on pharmacokinetic and pharmacodynamic factors relevant to the critically ill patient, it is perhaps of greater importance to decide on the sedation strategy used.

A variety of strategies have been described:

- goal-directed sedation and early goal-directed sedation
- patient-targeted sedation protocols
- daily interruption of sedation
- intermittent sedation
- 'analgosedation', or analgesia-first sedation
- patient-controlled sedation.

The purpose of these strategies should be to achieve a controlled and predetermined level of sedation in the patient. The chosen level of sedation will be intimately linked to the underlying disease process, patients' characteristics and the treatments and interventions they are receiving. The aim of sedation should be documented by the team and conveyed to the bedside nurse, who will have the largest impact on achieving and maintaining the chosen level. Once instituted, the level of sedation should be regularly assessed.

Goal-directed sedation was the first method described in which sedatives are freely adjusted (usually by the bedside nurse) to attain a prescribed level of sedation from a sedation scoring system.[2] A recent focus is on 'early goal-directed sedation', emphasising sedation titration from its commencement in the ICU. This has stemmed from prospective cohort studies showing worse outcomes (including mortality) in patients with deeper levels of initial sedation.[5,6]

Patient-targeted sedation protocols implement two main features: a structured approach to the assessment of patient pain and distress, coupled with an algorithm that directs drug escalation and de-escalation based on the assessments.[7]

Daily interruption of sedation: this strategy uses a similar goal of sedative and analgesic titration to a desired depth of sedation. In contrast to 'patient-targeted sedation protocols', no formal algorithm has been established for drug escalation. However, the risk of excessive sedation is minimised by a daily interruption of both sedative and analgesic infusions until the patient awakens or exhibits distress that mandates drug recommencement, usually with an initial bolus followed by a reduced infusion rate.[7]

Intermittent sedation administration involves use of longer-acting sedative agents, typically lorazepam, given by intermittent bolus titrated via a sedation scoring system.

'Analgosedation', or analgesia-first sedation, is a more modern approach gaining favour in patients, especially where sedation is not a treatment of their disease process. In these patients, opioid analgesia is instituted first, and after pain is adequately controlled, verbal measures are used to calm the patient to a targeted sedation level (e.g. Ramsay score 3–4). Major tranquillisers (e.g. haloperidol) are given for delirium, and only then are sedative agents (e.g. propofol) used for short-term infusion and promptly ceased.[8]

Proposed benefits of the previous sedation strategies include[7–11]:

- shorter duration of mechanical ventilation
- shorter length of ICU and hospital stay
- economic benefit
- less need for diagnostic studies (e.g. computed tomography [CT] scans) to assess impaired conscious state
- less ventilator-associated pneumonia
- a possible mortality benefit.

Criticisms of these strategies include:

- high self-extubation rates
- promotion of myocardial ischaemia
- triggering of a withdrawal syndrome.

Concerns over increased long-term neuropsychological effects (e.g. post-traumatic stress disorder) have been unfounded. Instead, evidence suggests a reduced incidence using such strategies.[12,13]

More holistic, patient care bundles are being introduced that incorporate sedation strategies. For example, the 'ABCDE' bundle combines a daily interruption of sedation, spontaneous breathing trial, delirium assessment and management and early mobilisation package, aiming to reduce the incidence of ICU-acquired delirium and weakness.[14]

SEDATIVE AGENTS

GABA-A RECEPTOR AGONISTS

Gamma-aminobutyric acid (GABA) is a major neurotransmitter in the central nervous system and one that is involved in the complex process of sedation. It binds to the alpha subunit of the GABA-A receptor and, by activation, causes a conformational change that opens the ligand-gated channel, allowing chloride ion influx into the neuron. This hyperpolarises the neuronal membrane and reduces neuronal activity leading to sedation.[15]

The GABA-A receptor agonists used in intensive care are BZAs, propofol and barbiturates. They all share amnesic, hypnotic, anxiolytic and anticonvulsant effects but have no analgesic properties.

Benzodiazepines

BZAs, as a class, are probably the most widely used sedatives in ICUs. BZAs are good anticonvulsant drugs and provide some muscle relaxation. They bind to the gamma subunit of the GABA-A receptor, resulting in a conformational change causing increased opening frequency of the channel.[16] The commonest agents used worldwide are midazolam, lorazepam and diazepam.

These drugs may be given by many routes but most commonly intravenously (IV) or orally (PO). IV administration is by either continuous or intermittent IV infusion (e.g. midazolam in 1 mg/mL, titrated to effect).

Dosage of these agents may vary widely depending on various pharmacokinetic and pharmacodynamic factors such as:

- prior exposure to BZA (increased tolerance)
- age and physiological reserve
- volume status (hypovolaemic patients are more sensitive)
- renal and hepatic dysfunction
- co-administered drugs (e.g. combined with an opioid)
- history of alcohol consumption (increased tolerance).

Although some BZAs (e.g. midazolam) are short-acting, water-soluble agents, there is potential for accumulation of both parent compound and active metabolites in patients with hepatic and/or renal dysfunction. This is especially pertinent in the critically ill, for whom there may be extensive derangement of BZA pharmacokinetic profiles.[17,18] This may result in prolonged sedation with increased length of mechanical ventilation and ICU stay. Therefore there is some difficulty in predetermining suitable dosages. Midazolam 0.02–0.2 mg/kg/h may be suitable, with the level titrated to individual response. Longer-acting agents, such as diazepam, may be given by intermittent IV injection (e.g. diazepam 5–10 mg) as necessary.

BZAs are often combined with opioids in a compound 'sedative' infusion. This allows lower doses of BZA to be used, while benefiting from the opioid effects of respiratory and cough suppression, to facilitate mechanical ventilation and endotracheal tube tolerance.

Flumazenil (flumazepil), the specific BZA antagonist, may be used to reverse the effect of BZAs to counter unwanted acute side effects, such as severe hypotension or respiratory depression, or to allow acute neurological assessment.

Propofol

The IV anaesthetic agent propofol (2,6-di-isopropylphenol) is frequently used for sedation in the ICU. It binds to the beta subunit on the receptor and causes a conformational change to the chloride channel.[16] It gives more profound hypnosis than BZAs, which have a ceiling effect. It is given by continuous IV infusion.

Propofol has a favourable pharmacokinetic profile compared with BZAs, due to rapid hepatic and extrahepatic conjugation reactions to inactive metabolites. Indeed, clearance of propofol exceeds hepatic blood flow. This gives it a relatively short context-sensitive half-time, resulting in rapid offset, particularly after prolonged infusion.

Although propofol has been shown to reduce time on mechanical ventilation compared with BZA (specifically midazolam) sedation, it has not been shown to reduce time in the ICU.[19,20] However, its combination with remifentanil may result in a shorter ICU length of stay compared with the combination of midazolam with either fentanyl or morphine.[21,22]

Caution is required in hypovolaemic patients or those with impaired myocardial function because severe hypotension may result.[23] Doses for ICU sedation are generally much lower than those required for anaesthesia. The diluent in which propofol is delivered is lipid rich and should be considered a source of nutrition and indeed cause of hyperlipidaemia, depending on dosage and duration of therapy. Disodium edetate, present in the propofol solution, does not appear to be harmful in patients receiving long-term infusions of propofol.[24]

There continues to be concern about propofol infusion syndrome (PRIS), particularly in paediatric patients who have developed severe heart failure (preceded by metabolic acidaemia, fatty infiltration of the liver and striated muscle damage) after prolonged, high-dose infusions of propofol.[25] The pathophysiology of this condition remains elusive but may relate to uncoupling of oxidative phosphorylation in mitochondria. There may also be a genetic susceptibility.[26] Caution should therefore be exercised when using propofol for prolonged periods, and infusion rates should be limited to 4 mg/kg/h. Hyperlipidaemia may be a warning sign for development of the syndrome and serum triglyceride monitoring should be considered in patients at risk.[27] Management requires immediate cessation of propofol and cardiovascular supports, which may necessitate extra-corporeal membrane oxygenation (ECMO).[28] The condition, although rare, has a high mortality.

Barbiturates

Thiopentone is reserved for specific indications, such as management of intractable intracranial hypertension, or for the treatment of status epilepticus. It is not commonly used as a general sedative agent due to a long context-sensitive half-time when given by continuous infusion.

VOLATILE ANAESTHETIC AGENTS

The use of volatile anaesthetic agents for sedation in the ICU has been limited by:

- the cost of prolonged administration
- the more complex setup required for the administration of these agents (vaporiser, scavenging apparatus, etc.)
- specific side effects, such as 'halothane' hepatitis; accumulation of fluoride ions and consequent renal dysfunction (sevoflurane [fluoromethyl hexafluoroisopropyl ether] and isoflurane), compound A accumulation and possible renal dysfunction (sevoflurane and absorbent interaction)
- occupational health and safety concerns (e.g. spontaneous miscarriage).

Isoflurane and sevoflurane provide hypnosis, amnesia and, at higher concentrations, immobility of the patient. They have no analgesic properties. Their mechanism of action remains hotly debated. Desflurane, due to its low boiling point, has not yet been successfully incorporated into intensive care ventilator systems.

Volatile agents are useful for short periods of anaesthesia during invasive procedures in the ICU. They have classically been used for longer periods of sedation in acute severe asthma, due to their bronchodilator effect.

Newer vaporiser systems, such as the AnaConDa (Anaesthetic Conserving Device), allow safe administration and recirculation of volatile agent through a standard ICU ventilator. Approximately 90% of the volatile agent is recirculated, greatly reducing cost.[29]

Studies generally show a reduced time to extubation and duration of mechanical ventilation with volatile agents compared with GABA-A agonists, with the time benefit being greater as the duration of sedation increases.[29–31] Other potential advantages include:

- lack of a withdrawal syndrome
- predictable offset independent of renal or hepatic dysfunction
- cardioprotective effects
- no tachyphylaxis
- lower incidence of delirium
- ability to measure and titrate end-tidal volatile concentration.

N-METHYL-D-ASPARTATE RECEPTOR ANTAGONIST

Ketamine acts by blocking *N*-methyl-D-aspartate (NMDA) receptors. It produces a sedative state known as 'dissociative anaesthesia', with the following characteristics:

- mild sedation
- amnesia
- analgesia
- reduced motor activity.

The lack of respiratory and cardiovascular depression at lower doses makes this a relatively safe drug for use in the ICU. Limitations to its use include hallucinations, and delirium during the recovery/withdrawal phase. These may be ameliorated by BZA or dexmedetomidine administration.[32] Ketamine may be used specifically for sedation in severe asthmatics (for its bronchodilator effect), in patients following head injury

(for its effect at the NMDA receptor) or in patients where analgesia is difficult (e.g. extensive burns).[33,34]

MAJOR TRANQUILLISERS

Butyrophenones (e.g. haloperidol and droperidol) and phenothiazines (e.g. chlorpromazine) are very useful agents for the sedation of delirious patients in the ICU. They act via a range of receptors including dopaminergic (D1 and D2), α-adrenergic, histamine, serotonin and cholinergic receptors. Main actions include:

- reduced motor activity
- apathy and reduced initiative
- sedation and drowsiness
- reduced aggression
- antiemetic.

Unwanted effects with these drugs are common and include:

- extrapyramidal effects (dystonia, akathisia and parkinsonism)
- endocrine effects (e.g. lactation)
- anticholinergic effects (e.g. blurred vision, dry mouth, urinary retention, constipation)
- hypotension
- neuroleptic malignant syndrome.

The advantage of major tranquillisers is that they can be used to gain control in difficult situations (e.g. when delirious patients may be a risk to themselves or their carers), without major risk of respiratory depression. They should not be used for long-term sedation, except for the specific treatment of psychosis. Typically, haloperidol, diluted to a 1 mg/mL solution, may be given by repeated IV injection in doses of 1–20 mg/h until the delirious patient is approachable. Repeat dosages would then be titrated to allow easy arousal of the patient. Haloperidol may also be given PO or by intramuscular (IM) injection.

Atypical antipsychotic agents, such as olanzapine and quetiapine, are also efficacious agents for the management of delirious patients.[35] They have a lower side-effect profile than the 'typical' antipsychotics, especially with respect to extrapyramidal side effects. They are usually given PO, although olanzapine may be given as sublingual wafers, a particularly useful route of administration in these patients.

α_2-AGONISTS

Dexmedetomidine is a highly selective α_2-agonist with a half-life of 2 hours. It provides safe analgesia and sedation in the ICU when given as a single agent by IV infusion.[36–39] Although originally licensed in Australia for 24-hour use, longer-duration infusions have been safely administered.[40,41] Compared with BZAs, dexmedetomidine results in less delirium and shorter time to extubation.[42] Furthermore, its use in isolation, or in combination with traditional sedative agents, may be effective in both preventing and treating hyperactive delirium in ICU patients.[14,43–45] This has subsequent benefits on ventilator-free days, ICU length of stay, costs and potentially mortality. Results of future trials in this area are eagerly awaited.

Dexmedetomidine aims to deliver a cooperative, calm and tube-tolerant patient, without respiratory depression.[37] Extubation is usually performed with the agent still infusing to maintain the tranquil cooperative state. Opioid analgesic requirements are fewer compared with GABA agonist sedation.[40]

A loading dose of 1 μg/kg over 10 minutes is recommended in healthy patients, but this should be avoided or attenuated in the critically ill. Infusion rates of 0.2–1.0 μg/kg/h are recommended. Higher rates have been reported, but bradycardia is more frequently seen.[36,41,46] Side effects may be predicted from the mechanism of action and include hypotension and bradycardia.

Clonidine, an established long-acting α_2-agonist, may be used to enhance sedation and analgesia when GABA-A agonists and opioids are used. The usual IV dose range is 50–150 μg, 4–6 hourly.

ANALGESIA

Pain management is a priority in the care of critically ill patients. Skilled use of analgesics in the modern ICU aims to ensure that critically ill patients no longer suffer pain. Pain management relies largely on the use of opioid analgesics together with regional anaesthetic techniques and other adjuncts.

Many patients present to the ICU with painful conditions or undergo painful procedures during their stay. Patients commonly report pain from routine ICU procedures like arterial and central venous cannulation, endotracheal suctioning, insertion of an indwelling urinary catheter or nasogastric tubes and even turning in bed.[47] In addition, other adverse symptoms commonly reported include unsatisfied thirst, difficult sleeping, anxiety, unsatisfied hunger, depression and shortness of breath.[47]

Pain has multiple adverse consequences, such as:

- provoking anxiety
- contributing to lack of sleep
- worsening delirium
- increasing the stress response
- causing respiratory embarrassment due to atelectasis and sputum retention
- causing immobility with venous and gut stasis.

Pain management comprises many modalities in addition to pharmacological methods, including:

- a caring and supportive ICU team, whom the patient can trust
- warm and comfortable surroundings
- attention to pressure areas
- bowel and bladder care
- adequate hydration and amelioration of thirst (e.g. moistening the mouth)

- early tracheostomy where indicated to reduce the discomfort of endotracheal intubation
- supplemental treatments such as acupuncture, acupressure, massage and transcutaneous electrical nerve stimulation (TENS).

Accurate and structured pain assessment is an important part of ICU patient management. For the patient who can communicate, self-reporting remains the gold standard. For those unable to self-report, a variety of pain assessment tools is available, some tailored specifically to critically ill patients. The Behavioural Pain Scale (BPS) (Table 91.3) and Critical-Care Pain Observation Tool (CPOT) (Table 91.4) are well validated in adult ICU patients.[48–52] The use of vital signs and physiological markers alone to assess pain, and response to analgesic administration are unreliable.

OPIOIDS

Opioids remain the mainstay of analgesia in the ICU. The most commonly used agents in the ICU used worldwide include:

- morphine and its analogues (e.g. diamorphine, codeine)

Table 91.3 Behavioural pain scale

ITEM	DESCRIPTION	SCORE
Facial expression	Relaxed	1
	Partially tightened (e.g. brow lowering)	2
	Fully tightened (e.g. eyelid closing)	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with mechanical ventilation	Tolerating movement	1
	Coughing but tolerating ventilation most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

Payen JF, Bru O, Bosson JL, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. *Crit Care Med*. 2001;29(12):2258–2263.

Adapted from Young J, Siffleet J, Nikoletti S, et al. Use of a behavioural pain scale to assess pain in ventilated, unconscious and/or sedated patients. *Intensive Crit Care Nurs*. 2006;22(1):32–39; Elsevier 2006.

Table 91.4 Critical-care pain observation tool

INDICATOR	DESCRIPTION	SCORE	
Facial expression	No muscular tension observed	Relaxed, neutral	0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense	1
	All of the above facial movements plus eyelid tightly closed	Grimacing	2
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movements	0
	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements	Protection	1
	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness	2
Muscle tension Evaluation by passive flexion and extension of upper extremities	No resistance to passive movements	Relaxed	0
	Resistance to passive movements	Tense, rigid	1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid	2
Compliance with ventilator (intubated patients) OR Vocalisation (extubated patients)	Alarms not activated, easy ventilation	Tolerating ventialator or movement	0
	Alarms stop spontaneously	Coughing but tolerating	1
	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator	2
	Talking in normal tone or no sound	Talking in normal tone or no sound	0
	Sighing, moaning	Sighing, moaning	1
	Crying out, sobbing	Crying out, sobbing	2
Total, range			0–8

Adapted from Gelinas C, Fillion L, Puntillo K, Viens C, Fortier M. Validation of the critical-care pain observation tool in adult patients. *Am J Crit Care*. 2006;15(4):420–427.

- semisynthetic and synthetic agents:
  - phenylpiperidine derivatives (e.g. pethidine, fentanyl, sufentanil, remifentanil)
  - methadone
  - thebaine derivatives (e.g. buprenorphine, oxycodone).

The effects of opioids are mediated via the four opioid receptor subtypes; mu, kappa, delta and nociceptin. These are G protein–coupled receptors that inhibit adenyl cyclase to reduce cyclic adenosine monophosphate (cAMP). This results in analgesia mediated at supraspinal, spinal and peripheral nerve endings.[53] The side effects of opioids are well described.

Opioids are titrated to effect by intermittent IV injection, or by continuous infusion. This may be controlled by the nurse (nurse-controlled analgesia [NCA]) or by the patient (patient-controlled analgesia [PCA]). Suitable regimens are 1 mg/mL of morphine, 20 µg/mL of fentanyl or 200 µg/mL of hydromorphone titrated to effect.

NCA is often combined with a BZA such as midazolam to produce a 'sedative/analgesic' infusion for patients on mechanical ventilation (see Sedation section). Opioids can also be administered via the subarachnoid, epidural, transdermal, oral, sublingual and intranasal routes.

In the critically ill, the use of opioids may be complicated by:

- wide interindividual response to similar dosages, especially in debilitated and elderly patients.
- severe hypotension following rapid administration, particularly in hypovolaemic patients
- prolonged duration of action, due to accumulation of parent compound and metabolites (e.g. morphine and its major metabolites morphine-3-glucuronide and morphine-6-glucuronide) in the elderly and in patients with renal and hepatic dysfunction. Use of drugs with shorter half-lives (e.g. fentanyl or sufentanil) or those with organ-independent metabolism (e.g. remifentanil) can reduce this problem
- constipation, often requiring concomitant administration of aperients to promote regular evacuation and prokinetics to prevent gastrostasis and allow enteral feeding
- the development of tolerance
- withdrawal symptoms on cessation or reduction of opioid medication.

Recognition of withdrawal symptoms is not always simple in ICU patients because they may mimic sepsis or delirium. Treatment is by reinstitution of and then slow withdrawal of the opioid. Alternatively, symptoms may be controlled by substitution for a long-acting opioid (e.g. methadone), BZAs or α_2-agonists.

The specific opioid antagonist naloxone has little role to play in the ICU, except for the treatment of severe hypotension, unwanted sedation or respiratory depression following opioid use or overdose. Rapid reversal of opioid effect to facilitate neurological assessment may be another valid use.

REMIFENTANIL

This is a synthetic, selective mu receptor agonist. It undergoes organ-independent hydrolysis by plasma, red blood cell and tissue esterases. It has a reliable context-sensitive half-time of 4 minutes, which makes it particularly attractive for critically ill patients.

Although an analgesic, it is gaining favour as a sedative agent in intensive care because it causes sedation, tube tolerance and a slowed respiratory rate. In addition, its pharmacokinetic profile makes it ideal for rapid neurological assessment. Studies show reduced extubation times and ICU length of stay when compared with traditional opioids.[21,22]

The loading dose is usually 1 µg/kg; however, this should be avoided or attenuated in critically ill patients. Continuous infusion rates of 0.05–0.5 µg/kg/min are usually required, and a starting rate of 0.1 µg/kg/min is recommended. Dosage alterations are usually in increments of 0.025–0.1 µg/kg/min. Due to the short half-life, adequacy of response can be assessed within 20 minutes.

Weaning should also be done by incremental dose reductions due to the risks of rebound hyperalgesia. Adding ketamine during the weaning process may modulate this risk.[54]

SIMPLE ANALGESICS

Paracetamol and other simple analgesics (e.g. salicylates) are particularly effective for:

- musculoskeletal pain
- perioperative pain
- inflammatory conditions
- multimodal analgesia, to reduce opioid requirements.

These drugs are given PO, per rectum (PR) or IV to supplement analgesia in the critically ill (e.g. paracetamol 1 g 4–6-hourly). Paracetamol use is limited by the risk of hepatic dysfunction if used in high dose or for prolonged periods.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

The commonly used non-steroidal anti-inflammatory drugs (NSAIDs) are carboxylic acids (e.g. indometacin [indomethacin], ibuprofen, mefenamic acid) or enolic acids (e.g. piroxicam). NSAIDs are useful for supplemental/multimodal analgesia in the ICU for the conditions listed previously for simple analgesics. They are given PO, PR or by IM injection (e.g. indomethicin 100 mg twice daily PR). Patient selection is paramount in the critically ill due to their serious side effects, including:

- renal dysfunction
- gastrointestinal haemorrhage

- increased bleeding tendency due to platelet inhibition.

The newer cyclooxygenase-2 specific (COX-2) inhibitors, such as valdecoxib and its injectable precursor parecoxib, have a much lower side-effect profile than traditional NSAIDs. This group of drugs should be used for only short periods due to an increased cardiovascular morbidity associated with long-term use.[55] COX-2 inhibitors should be avoided in postoperative cardiac surgical patients due to an increased incidence of thromboembolic complications and sternal wound infection.[56,57]

TRAMADOL

Tramadol is a synthetic, racemic preparation with multiple analgesic actions. The (+) enantiomer is a mu receptor agonist and serotonin reuptake inhibitor, whereas the (–) enantiomer is a norepinephrine reuptake inhibitor.[58] In addition to mu receptor action, which accounts for approximately 30% of its analgesic effect, it also enhances the descending inhibitory pathways involved in pain modulation.[59] It is useful for moderate to severe pain in the postoperative patient in doses of 50–100 mg IV, PO or IM 4-hourly to a maximum of 600 mg/day. Patients are at risk of developing serotonin syndrome while taking tramadol in combination with other proserotonergic agents.[60]

TAPENTADOL

Tapentadol is a centrally acting, synthetic analgesic with mu receptor agonism and norepinephrine reuptake inhibition. It is not a serotonin reuptake inhibitor, does not require metabolic activation and has no active metabolites. It is predominately conjugated by the liver and undergoes minimal cytochrome P450 enzymatic metabolism, thus reducing potential drug interactions.[61,62] It is useful for moderate to severe pain in doses of 50–100 mg IV or PO 4-6 hourly. Despite the relative lack of serotonergic activity compared with tramadol, case reports of serotonin syndrome involving tapentadol in combination with other proserotonergic agents have been reported.[62]

KETAMINE

(See 'NMDA receptor antagonist' earlier.) Ketamine is commonly used as part of multimodal analgesic regimens in surgical patients with severe pain, or if tolerant to opioids. Continuous infusion in a dosage range of 0.1–0.2 mg/kg per hour is recommended.

NITROUS OXIDE

Short-term administration of Entonox (50% nitrous oxide in oxygen) is still useful for analgesia during painful procedures (e.g. burns dressings). This may be given by demand valve (controlled by the patient) or be administered by the medical staff.

LOCAL ANAESTHETICS – REGIONAL ANALGESIA

The use of local anaesthetic techniques in the critically ill patient is limited by:

- pain often emanating from multiple sources and therefore not amenable to a single regional technique
- the requirement for IV sedation/analgesia (for reasons previously outlined), making a regional technique for pain superfluous
- the need to treat pain over a prolonged period, mandating either repetition of the regional block or the placement of an indwelling catheter (e.g. epidural catheter). Indwelling catheters have a defined duration of insertion (usually 3–4 days) due to increasing infection risk
- coagulopathy and thrombocytopenia, frequently seen in this group of patients, making procedures such as epidural injection less safe.

When a regional technique is considered viable, then the following need to be considered:

- the procedure should be carried out by adequately trained personnel
- regional techniques may be time consuming and require additional staff to properly position the patient and assist the proceduralist
- regional techniques carry serious complications (e.g. subarachnoid injection of local anaesthetic or epidural haematoma during placement of epidural catheters), as well as the risk of local anaesthetic toxicity
- good preparation is paramount:
  - informed consent from patient or legal surrogate
  - recent normal coagulation profile or correction of abnormal profile. Platelet counts greater than 75,000/μL are recommended and antiplatelet agents (other than aspirin) should be ceased at an appropriate time interval beforehand
  - the knowledge of and ability to deal with complications
  - experience and knowledge of the drugs being used. Typically ropivacaine 0.2% is used for regional infusions and can be combined with an opioid, such as fentanyl 2–4 μg/mL, for epidural infusion. Recommended maximum bolus doses and continuous infusion rates must be known. For ropivacaine, a single bolus of up to 3 mg/kg is allowed (to a maximum of 300 mg), whereas continuous infusion rates should not exceed 400 μg/kg/h
- adequate training of nursing staff to monitor the level of block in neuraxial techniques, haemodynamic parameters and for possible complications.

Within the previous context, the following blocks may be useful in patients:

- femoral nerve block for hip and femur injuries; 20–40 mL of 0.2% ropivacaine injected intermittently 8–12-hourly into the region of the femoral nerve immediately inferior to the inguinal ligament
- intercostal or paravertebral nerve blocks or catheters for thoracic and upper abdominal injuries or wounds; 20 mL of 0.2% ropivacaine injected into the region of appropriate intercostal nerve – a single injection site has been shown to cover multiple nerve root levels[63]
- brachial plexus or IV regional anaesthesia for isolated upper limb injuries or procedures (e.g. fracture manipulation)
- epidural analgesia for thoracic and abdominal pain (e.g. flail chest, pancreatitis)
- intrapleural analgesia/anaesthesia, applied either via a catheter placed for this purpose or via previously placed intercostal drains.

SLEEP

Although, outwardly, sedated patients resemble the sleep state, there are notable neurophysiological differences. Typically, critically ill patients have shorter periods of sleep, with a distinct reduction of slow-wave 'deep' sleep and rapid eye movement (REM) sleep.[64] Critically ill patients have poor sleep patterns due not only to their primary illness but a host of other factors, including:

- loss of the sleep–wake cycle after prolonged sedation
- pain
- invasive devices and monitoring
- the ICU environment
- nursing duties.

The importance of sleep disturbance in the critically ill on outcome is unknown, but there is concern over its contribution to delirium.[65]

Much of the focus on improving sleep in critically ill patients relies on non-pharmacological measures, addressing the sleep environment and sleep hygiene of the patient. Pharmacological agents such as BZAs may help patients to get to sleep quicker and wake less often but do not seem to improve the quality of physiological sleep.[65]

THE FUTURE

Research into sedation and analgesia in critically ill patients is intensifying. Areas in which future study is focusing include:

- patient-controlled sedation
- target-controlled infusions in intensive care
- automated/semiautomated sedation delivery systems[66]
- melatonergic agents for nocturnal sleep (e.g. ramelteon, valdoxane, melatonin).

KEY REFERENCES

5. Schweickert WD, Kress JP. Strategies to optimize analgesia and sedation. *Crit Care*. 2008;12 (suppl 3):S6.
6. Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet*. 2010;375(9713):475–480.
7. Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000;342(20):1471–1477.
8. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008; 371(9607):126–134.
9. Bucknall TK, Manias E, Presneill JJ. A randomized trial of protocol-directed sedation management for mechanical ventilation in an Australian intensive care unit. *Crit Care Med*. 2008;36(5):1444–1450.
29. Soukup J, Schärff K, Kubosch K, et al. State of the art: sedation concepts with volatile anesthetics in critically ill patients. *J Crit Care*. 2009;24(4):535–544.
43. Reade MC, O'Sullivan K, Bates S, et al. Dexmedetomidine vs. haloperidol in delirious, agitated, intubated patients: a randomised open-label trial. *Crit Care*. 2009;13(3):R75.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Piccolo R, Lipman J, Hon H, et al. Analgesia and sedation in the critically ill – a practical approach. *S Afr J Surg*. 1999;37(1):15–20.
2. Ramsay MA, Savege TM, Simpson BR, et al. Controlled sedation with alphaxalone-alphadolone. *Br Med J*. 1974;2(5920):656–659.
3. Payen JF, Chanques G, Mantz J, et al. Current practices in sedation and analgesia for mechanically ventilated critically ill patients: a prospective multicenter patient-based study. *Anesthesiology*. 2007;106(4):687–695, quiz 891–892.
4. Lu CH, Ou-Yang HY, Man KM, et al. Relative reliability of the auditory evoked potential and bispectral index for monitoring sedation level in surgical intensive care patients. *Anaesth Intensive Care*. 2008;36(4):553–559.
5. Shehabi Y, Bellomo R, Reade MC, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. *Am J Respir Crit Care Med*. 2012;186(8):724–731.
6. Tanaka LM, Azevedo LC, Park M, et al. Early sedation and clinical outcomes of mechanically ventilated patients: a prospective multicentred cohort study. *Crit Care*. 2014;18:R156.
7. Schweickert WD, Kress JP. Strategies to optimize analgesia and sedation. *Crit Care*. 2008;12(suppl 3): S6.
8. Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet*. 2010;375(9713):475–480.
9. Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000;342(20):1471–1477.
10. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008; 371(9607):126–134.
11. Bucknall TK, Manias E, Presneill JJ. A randomized trial of protocol-directed sedation management for mechanical ventilation in an Australian intensive care unit. *Crit Care Med*. 2008;36(5):1444–1450.
12. Strom T, Stylsvig M, Toft P. Long-term psychological effects of a no-sedation protocol in critically ill patients. *Crit Care*. 2011;15(6):R293.
13. Kress JP, Gehlbach B, Lacy M, et al. The long-term psychological effects of daily sedative interruption on critically ill patients. *Am J Respir Crit Care Med*. 2003;168(12):1457–1461.
14. Reade MC, Eastwood GM, Bellomo R, et al. Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: a randomized clinical trial. *JAMA*. 2016; 315(14):1460–1468.
15. Williams DB, Akabas MH. Structural evidence that propofol stabilizes different GABA(A) receptor states at potentiating and activating concentrations. *J Neurosci*. 2002;22(17):7417–7424.
16. Bali M, Akabas MH. Defining the propofol binding site location on the GABAA receptor. *Mol Pharmacol*. 2004;65(1):68–76.
17. Wagner BK, O'Hara DA. Pharmacokinetics and pharmacodynamics of sedatives and analgesics in the treatment of agitated critically ill patients. *Clin Pharmacokinet*. 1997;33(6):426–453.
18. Watling SM, Dasta JF, Seidl EC. Sedatives, analgesics, and paralytics in the ICU. *Ann Pharmacother*. 1997;31(2):148–153.
19. Hall RI, Sandham D, Cardinal P, et al. Propofol vs midazolam for ICU sedation: a Canadian multicenter randomized trial. *Chest*. 2001;119(4): 1151–1159.
20. Walder B, Elia N, Henzi I, et al. A lack of evidence of superiority of propofol versus midazolam for sedation in mechanically ventilated critically ill patients: a qualitative and quantitative systematic review. *Anesth Analg*. 2001;92(4):975–983.
21. Muellejans B, Matthey T, Scholpp J, et al. Sedation in the intensive care unit with remifentanil/propofol versus midazolam/fentanyl: a randomised, open-label, pharmacoeconomic trial. *Crit Care*. 2006; 10(3):R91.
22. Rozendaal FW, Spronk PE, Snellen FF, et al. Remifentanil-propofol analgo-sedation shortens duration of ventilation and length of ICU stay compared to a conventional regimen: a centre randomised, cross-over, open-label study in the Netherlands. *Intensive Care Med*. 2009;35(2): 291–298.
23. Burns AM, Shelly MP, Park GR. The use of sedative agents in critically ill patients. *Drugs*. 1992;43(4): 507–515.
24. Abraham E, Papadakos PJ, Tharratt RS, et al. Effects of propofol containing EDTA on mineral metabolism in medical ICU patients with pulmonary dysfunction. *Intensive Care Med*. 2000;26(suppl 4): S422–S432.
25. Bray RJ. The propofol infusion syndrome in infants and children: can we predict the risk? *Curr Opin Anaesthesiol*. 2002;15(3):339–342.
26. Otterspoor LC, Kalkman CJ, Cremer OL. Update on the propofol infusion syndrome in ICU management of patients with head injury. *Curr Opin Anaesthesiol*. 2008;21(5):544–551.
27. Kam PC, Cardone D. Propofol infusion syndrome. *Anaesthesia*. 2007;62(7):690–701.
28. Fudickar A, Bein B, Tonner PH. Propofol infusion syndrome in anaesthesia and intensive care medicine. *Curr Opin Anaesthesiol*. 2006;19(4):404–410.
29. Soukup J, Schärff K, Kubosch K, et al. State of the art: sedation concepts with volatile anesthetics in critically ill patients. *J Crit Care*. 2009;24(4): 535–544.
30. Mesnil M, Capdevila X, Bringuier S, et al. Long-term sedation in intensive care unit: a randomized comparison between inhaled sevoflurane and

intravenous propofol or midazolam. *Intensive Care Med*. 2011;37(6):933–941.
31. Jerath A, Panckhurst J, Parotto M, et al. Safety and efficacy of volatile anesthetic agents compared with standard intravenous midazolam/propofol sedation in ventilated critical care patients: a meta-analysis and systematic review of prospective trials. *Anesth Analg*. 2016;published ahead of print post author corrections 8th November 2016.
32. Trivedi S, Kumar R, Tripathi AK, et al. A comparative study of dexmedetomidine and midazolam in reducing delirium caused by ketamine. *J Clin Diagn Res*. 2016;10(8):UC1–UC4.
33. Youssef-Ahmed MZ, Silver P, Nimkoff L, et al. Continuous infusion of ketamine in mechanically ventilated children with refractory bronchospasm. *Intensive Care Med*. 1996;22(9):972–976.
34. Kolenda H, Gremmelt A, Rading S, et al. Ketamine for analgosedative therapy in intensive care treatment of head-injured patients. *Acta Neurochir (Wien)*. 1996;138(10):1193–1199.
35. Devlin JW, Roberts RJ, Fong JJ, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. *Crit Care Med*. 2010;38(2):419–427.
36. Venn RM, Bradshaw CJ, Spencer R, et al. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. *Anaesthesia*. 1999;54(12):1136–1142.
37. Venn RM, Hell J, Grounds RM. Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. *Crit Care*. 2000;4(5):302–308.
38. Hall JE, Uhrich TD, Barney JA, et al. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. *Anesth Analg*. 2000;90(3):699–705.
39. Nasraway SA Jr. Use of sedative medications in the intensive care unit. *Semin Respir Crit Care Med*. 2001;22(2):165–174.
40. Shehabi Y, Ruettimann U, Adamson H, et al. Dexmedetomidine infusion for more than 24 hours in critically ill patients: sedative and cardiovascular effects. *Intensive Care Med*. 2004;30(12):2188–2196.
41. Guinter JR, Kristeller JL. Prolonged infusions of dexmedetomidine in critically ill patients. *Am J Health Syst Pharm*. 2010;67(15):1246–1253.
42. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA*. 2009;301(5):489–499.
43. Reade MC, O'Sullivan K, Bates S, et al. Dexmedetomidine vs. haloperidol in delirious, agitated, intubated patients: a randomised open-label trial. *Crit Care*. 2009;13(3):R75.
44. Su X, Meng ZT, Wu XH, et al. Dexmedetomidine for the prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2016;388(10054):1893–1902.
45. Carrasco G, Baeza N, Cabre L, et al. Dexmedetomidine for the treatment of hyperactive delirium refractory to haloperidol in non-intubated ICU patients: a nonrandomized controlled trial. *Crit Care Med*. 2016;44(7):1295–1306.
46. Tan JA, Ho KM. Use of dexmedetomidine as a sedative and analgesic agent in critically ill adult patients: a meta-analysis. *Intensive Care Med*. 2010;36(6):926–939.
47. Nelson JE, Meier DE, Oei EJ, et al. Self-reported symptom experience of critically ill cancer patients receiving intensive care. *Crit Care Med*. 2001;29(2):277–282.
48. Aissaoui Y, Zeggwagh AA, Zekraoui A, et al. Validation of a behavioral pain scale in critically ill, sedated, and mechanically ventilated patients. *Anesth Analg*. 2005;101(5):1470–1476.
49. Mastronardi P, Cafiero T. Rational use of opioids. *Minerva Anestesiol*. 2001;67(4):332–337.
50. Barr J, Fraser GL, Puntillo K, et al. Clincal practice guidelines for the management of pain, agitation and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41(1):263–306.
51. Gélinas C, Fillion L, Puntillo K, et al. Validation of the critical-care pain observation tool in adult patients. *Am J Crit Care*. 2006;15(4):420–427.
52. Payen JF, Bru O, Bosson JL, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. *Crit Care Med*. 2001;29(12):2258–2263.
53. Moran TD, Abdulla FA, Smith PA. Cellular neurophysiological actions of nociceptin/orphanin FQ. *Peptides*. 2000;21(7):969–976.
54. Angst MS, Koppert W, Pahl I, et al. Short-term infusion of the mu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal. *Pain*. 2003;106(1–2):49–57.
55. Lee YH, Ji JD, Song GG. Adjusted indirect comparison of celecoxib versus rofecoxib on cardiovascular risk. *Rheumatol Int*. 2007;27(5):477–482.
56. Ott E, Nussmeier NA, Duke PC, et al. Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. *J Thorac Cardiovasc Surg*. 2003;125(6):1481–1492.
57. Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med*. 2005;352(11):1081–1091.
58. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet*. 2004;43(13):879–923.
59. Budd K, Langford R. Tramadol revisited. *Br J Anaesth*. 1999;82(4):493–495.
60. Torre LE, Menon R, Power BM. Prolonged serotonin toxicity with proserotonergic drugs in the intensive care unit. *Crit Care Resusc*. 2009;11(4):272–275.
61. Afilalo M, Stegmann JU, Upmalis D. Tapentadol immediate release: a new treatment option for acute pain management. *J Pain Res*. 2010;3:1–9.
62. Tayal G, Grewal A, Mittal R, et al. "Tapentadol" – A novel analgesic. *J Anaesth Clin Pharmacol*. 2009;25(4):463–466.

63. Murphy DF. Continuous intercostal nerve blockade. An anatomical study to elucidate its mode of action. *Br J Anaesth*. 1984;56(6):627–630.
64. Bijwadia JS, Ejaz MS. Sleep and critical care. *Curr Opin Crit Care*. 2009;15(1):25–29.
65. Drouot X, Cabello B, d'Ortho MP, et al. Sleep in the intensive care unit. *Sleep Med Rev*. 2008;12(5):391–403.
66. Shaw GM, Chase JG, Rudge AD, et al. Rethinking sedation and agitation management in critical illness. *Crit Care Resusc*. 2003;5(3):198–206.

92

Inotropes and vasopressors

John A Myburgh

INTRODUCTION

The pharmacological support of the failing circulation is a fundamental component of acute medicine with broad applications to patients undergoing resuscitation in the Emergency Department, major surgery under general anaesthesia or in the intensive care unit (ICU).

The principal aim of these drugs is to restore inadequate systemic and regional perfusion to physiological levels.

DEFINITIONS

Inotropic agents are defined as drugs that act on the heart by increasing the velocity and force of myocardial fibre shortening. The consequent increase in contractility results in increased cardiac output and systemic blood pressure.

Vasopressors are broadly considered to be drugs that have a predominantly constrictive action on the peripheral vasculature, both arterial and venous. These drugs are used primarily to increase mean arterial pressure.

The distinction between these two groups of drugs is redundant, despite reference to these in iterations of clinical practice guidelines.

The most commonly used drugs, the catecholamines noradrenaline (norepinephrine) and adrenaline (epinephrine), have both inotropic and protean effects on the venous and arteriolar vasculature.

Given the overlap of pharmacodynamic effects of these drugs, the term 'vasoactive therapy' is a more appropriate description.

Characteristics of the ideal vasoactive drug are shown in Box 92.1.

THE FAILING CIRCULATION

PHYSIOLOGY

Traditionally, cardiac output is discussed in terms of factors that govern cardiac function. These include heart rate and rhythm, preload, myocardial contractility and afterload. Although this perspective is helpful in managing patients whose circulatory function is limited by intrinsic cardiac disease, it is incomplete.

Cardiac output is controlled by venous return to the heart from the peripheral vasculature at an equal rate to that ejected during each cardiac cycle (Fig. 92.1).[1,2]

Blood is pumped from the heart down the aorta by a pressure gradient that is determined by the force of myocardial ejection (contractility) and the impedance to ventricular ejection (afterload). The resultant mean arterial pressure is the major 'afferent' determinant of regional perfusion pressure. Twenty per cent of the blood volume is contained in the arterial ('conducting') vessels.

There is a marked drop in perfusion pressure and flow across the capillary beds to facilitate diffusion of substrates and oxygen. The difference between mean arterial pressure and the pressure in end-capillaries ('efferent' perfusion pressure) determines regional, or organ-specific, perfusion pressure.

Blood enters the venous system and is returned to the heart by a pressure gradient between mean systemic pressure and right atrial pressure. The amount of blood returned to the heart determines the degree of ventricular filling prior to systole (preload) that subsequently determines stroke volume and cardiac output.

Under physiological conditions, the venous ('capacitance') system contains approximately 70% of the total blood volume that acts as a physiological reservoir – the 'unstressed' volume. Under conditions where circulatory demands increase, increased sympathetic tone will cause contraction of this reservoir.[3] The resultant auto-transfusion – the 'stressed' volume – may increase venous return by approximately 30% with consequent increased cardiac output.[4]

Both the arterial and venous systems are integrated under complex neurohormonal influences. These include the adrenergic, renin–angiotensin–aldosterone, vasopressinergic and glucocorticoid systems in addition to local mediators such as nitric oxide, endothelin, endorphins and the eicosanoids.[5]

PATHOPHYSIOLOGY

Circulatory dysfunction or failure may be considered in terms of the major determinants of cardiac output,

ABSTRACT

The pharmacological support of the failing circulation in critically ill patients is directed at restoring and maintaining vital organ perfusion. This is primarily achieved by the administration of intravenous fluids in hypovolaemic patients and augmented by the early and concomitant use of infusions of catecholamines, noradrenaline or adrenaline. These drugs should be used to augment inadequate endogenous responses and are effective at increasing mean arterial pressure, cardiac output and venous return. Current evidence supports the use of these drugs as first-line agents for all forms of shock, although the evidence base is limited. There is little evidence to support the use of synthetic catecholamines or other drugs such as phosphodiesterase inhibitors. Drugs should be titrated to a patient-specific mean arterial pressure and at clinical indices of vital organ function.

KEYWORDS

Inotrope
vasopressor
vasoactive
catecholamines
noradrenaline
norepinephrine
adrenaline
epinephrine
shock
haemodynamic

although there is marked interdependence between these factors.

HEART RATE

Severe bradycardia may reduce both cardiac output and mean arterial pressure if sympathetic tone is compromised. Vasoactive drugs with a positive chronotropic effect increase both the rate and speed of conduction, thereby restoring cardiac output and mean arterial pressure.

Tachycardia is associated with decreased left coronary artery perfusion, due to a reduction of diastolic time when coronary perfusion occurs. This may exacerbate myocardial ischaemia in patients with coronary artery disease, particularly if mean arterial pressure, specifically diastolic blood pressure, is compromised. Drugs that shorten diastolic time or compromise coronary perfusion should be used with caution in susceptible patients.

Box 92.1 The ideal inotrope

- Increases contractility
  - Increases mean arterial pressure
  - Increases cardiac output
  - Improves regional perfusion
- No increase in myocardial oxygen consumption
  - Avoidance of tachycardia
  - Non-arrhythmogenic
  - Maintenance of diastolic blood pressure
- Does not develop tolerance
- Titratable
  - Rapid onset
  - Rapid termination of action
- Compatible with other drugs
- Non-toxic
- Cost effective

PRELOAD

Loss of intravascular blood volume or extracellular fluid is the most common cause of inadequate ventricular preload. This is corrected judiciously with intravenous fluids to maintain and restore normovolaemia. Hypovolaemia must be recognised and treated as soon as possible, preferably before vasoactive therapy is used, although the early use and concomitant use of vasoactive therapy is recommended.[6]

There are other determinants of ventricular preload and venous return. Factors such as loss of muscle tone, positive intrathoracic pressure, loss of atrial contraction (atrial fibrillation) and ablation of sympathetic tone will compromise preload by reducing venous return. Under these circumstances, volume replacement alone

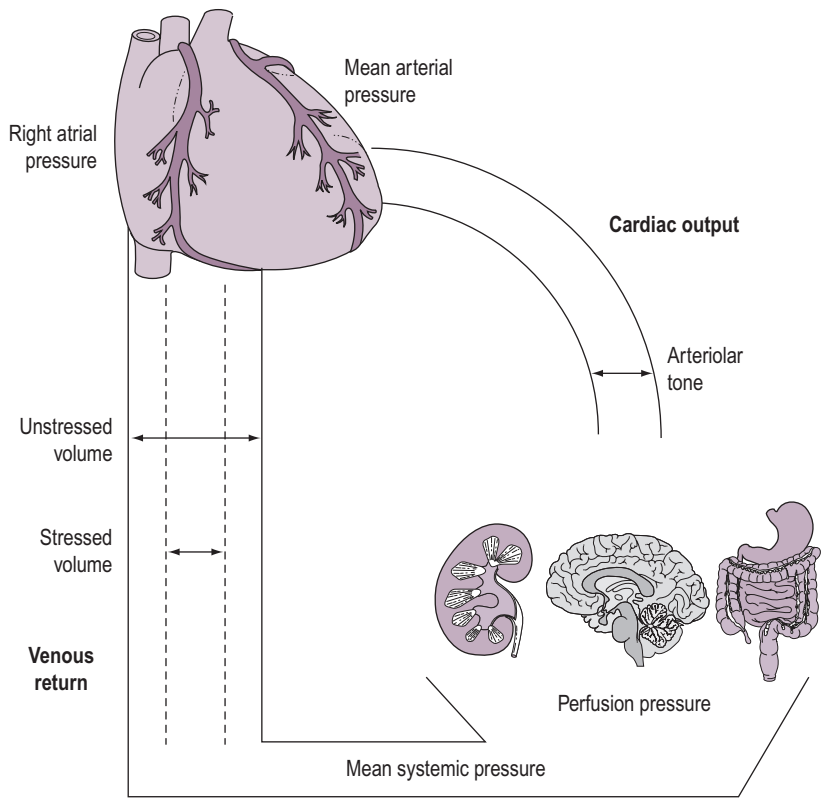


Figure 92.1 Schematic relationship of the determinants of cardiac output and venous return.

may be insufficient to maintain adequate preload, and early, concomitant vasoactive therapy is recommended to augment venous return.

MYOCARDIAL FUNCTION

Myocardial or 'pump' failure may be divided into disorders of systolic ejection (systolic dysfunction) and diastolic filling (diastolic dysfunction).

Systolic dysfunction occurs as a result of reduced effective myocardial contractility. This may be due to primary myocardial factors such as ischaemia, infarction or cardiomyopathy. Myocardial depression of both right and left ventricular function may occur in severe sepsis ('septic cardiomyopathy') or following prolonged infusions of catecholamines ('down-regulation').[7] Increased impedance to ventricular ejection (e.g. hypertensive states) or structural abnormalities (e.g. aortic stenosis or hypertrophic obstructive cardiomyopathy) may cause systolic dysfunction.[8]

Diastolic dysfunction is characterised by reduced ventricular compliance or increased resistance to ventricular filling during diastole. It may be due to mechanical factors, such as structural abnormalities of the ventricle (e.g. restrictive cardiomyopathy), or to impaired diastolic relaxation that occurs with myocardial ischaemia or septic cardiomyopathy. This results in elevated end-diastolic pressure and pulmonary venous congestion. Episodic or 'flash' pulmonary oedema is a common clinical sign of diastolic dysfunction. Tachycardia that shortens diastolic time may exacerbate diastolic failure. Diastolic dysfunction frequently accompanies systolic failure, in both acute and chronic cardiac failure, particularly in elderly patients.[9]

In the presence of systolic dysfunction, adequate stroke volume may be maintained by an increase in left ventricular end-diastolic volume (the Frank–Starling relationship), provided diastolic function is optimal. However, if the loss of effective myocardial mass is critical, the ventricle will be unable to maintain an adequate stroke volume and cardiac output will fall. In this situation, systolic dysfunction usually requires treatment with inotropic agents in order to augment stroke volume, thereby increasing cardiac output and mean arterial pressure.

AFTERLOAD/IMPEDANCE

Disruption or impairment of regulation of the peripheral vasculature may result in circulatory failure. This includes acute sympathetic denervation, such as high quadriplegia, epidural or total spinal anaesthesia ('spinal' shock); distributive failure such as anaphylaxis; or 'vasoplegia' associated with severe sepsis ('vasodilatory' shock).[7,10]

These syndromes are characterised by reduced responsiveness of the peripheral circulation to endogenous or exogenous sympathetic stimulation. This results in pooling in the venous circulation due to the inability to produce a 'stressed' volume.

Management of these conditions has traditionally focused on 'vasoconstrictor' or 'vasopressor' therapy on the arterial circulation, but the predominant vascular lesion is in the venous circulation where haemodynamic monitoring is limited.

CLASSIFICATION

The common cellular mechanism of action of vasoactive agents involves an influence on the release, utilisation or sequestration of intracellular calcium (Fig. 92.2). These agents are divided into two main groups based on whether or not their actions depend upon increases in intracellular cyclic adenosine 3,5-monophosphate (cAMP) and are outlined in Table 92.1.

CATECHOLAMINES

Sympathomimetic amines are the most frequently used vasoactive agents in the ICU and include the naturally occurring catecholamines dopamine, noradrenaline and adrenaline, and the synthetic inotropes dobutamine, isoprenaline and dopexamine.

RECEPTOR BIOLOGY

Catecholamines bind to populations of adrenergic receptors, largely divided into α and β subgroups. Further subgroups of α- (α_{1A}, α_{1B}, α_{2A}, α_{2B}, α_{2C}) and β-receptors (β_1, β_2, β_3) have been identified.[5]

Signal transduction from catecholamine–receptor occupation to the effector cell is modulated by conformational changes in G proteins associated with these receptors. Under the influence of second messengers,

Table 92.1 Classification of inotropes

cAMP DEPENDENT	cAMP INDEPENDENT
Catecholamines	Catecholamines
(β-adrenergic agonists)	(α-adrenergic agonists)
Adrenaline (adrenaline)	Adrenaline (adrenaline)
Noradrenaline (noradrenaline)	Noradrenaline (noradrenaline)
Dopamine	Dopamine
Dobutamine	Digoxin
Dopexamine	Thyroid hormone
Isoprenaline	
Phosphodiesterase inhibitors	
Amrinone	
Milrinone	
Enoximone	
Levosimendan	
Calcium sensitisers	
Levosimendan	
Glucagon	

cAMP, cyclic adenosine monophosphate.

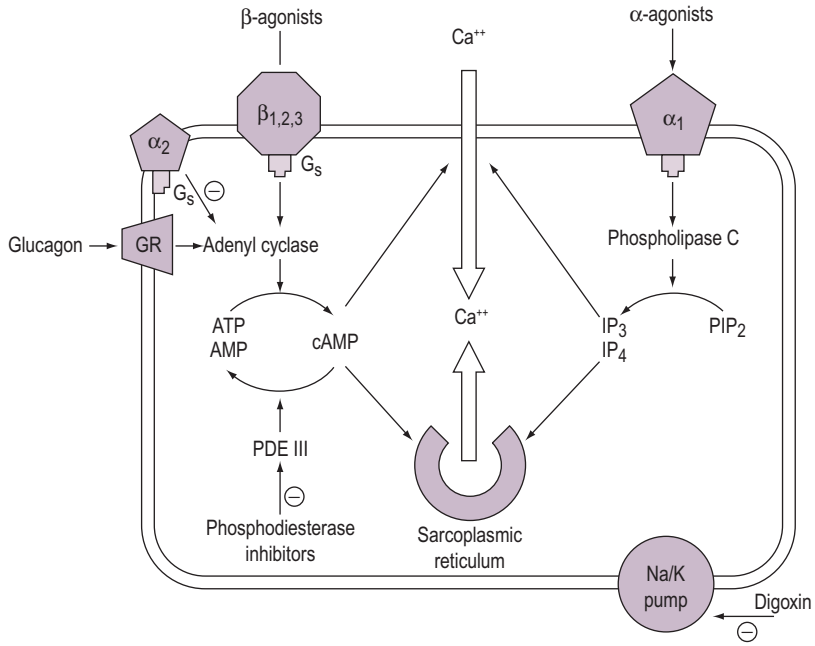


Figure 92.2 Schematic representation of the action of inotropic drugs on intracellular calcium in myocytes. *AMP*, Adenosine monophosphate; *ATP*, adenosine triphosphate; *cAMP*, cyclic AMP; *GR*, glucagon receptor; G_s, G protein complex; *IP3*, inositol phosphate 3; *PDE III*, phosphodiesterase III; *PIP2*, phosphoinositol diphosphate.

such as nitric oxide, endothelin and eicosanoids, conformational changes promote the release of calcium from intracellular stores and membrane calcium permeability. Subsequent phosphorylation of substrate proteins via protein kinases act as third messengers to trigger a cascade of events that lead to specific cardiovascular effects.

β-receptor occupancy predominantly activates adenyl cyclase to increase the conversion of adenosine triphosphate to cAMP. α-receptor occupancy acts independently of cAMP by activation of phospholipase C, which increases inositol phosphates (IP_3 and IP_4) and diacyl glycerol.

This complex agonist–receptor–effector relationship is responsible for teleological, homeostatic mechanisms, such as physiological responses to stress and autoregulation, and may be markedly influenced under pathological conditions. These states produce qualitative changes in the agonist–receptor–effector organ relationship where receptors no longer respond to physiological or pharmacological sympathetic stimulation to the same extent (desensitisation); and quantitative changes, such as reduced receptor density, receptor sequestration and enzymatic uncoupling, may also result in impaired responses (down-regulation).[11]

BIOSYNTHESIS

The biosynthesis and chemical structures of the naturally occurring catecholamines are shown in Fig. 92.3a.

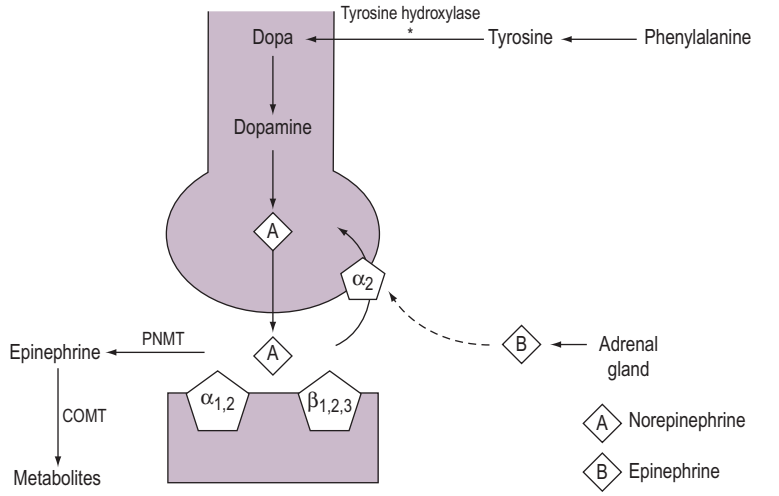
Catecholamines consist of an aromatic ring attached to a terminal amine by a carbon chain. The configuration of each drug is important for determining affinity to respective receptors.

Dopamine is hydroxylated to form noradrenaline that is the predominant peripheral sympathetic chemotransmitter in humans acting at all adrenergic receptors. The release of noradrenaline from sympathetic terminals is controlled by re-uptake mechanisms mediated via α_2-receptors and augmented by adrenaline released from the adrenal gland at times of stress. Noradrenaline is converted to form adrenaline, which is subsequently metabolised in liver and lung.

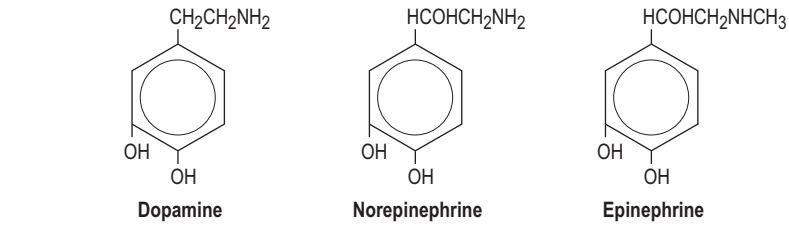
All catecholamines have short biological half-lives (1–2 minutes) and a steady state plasma concentration is achieved within 5–10 minutes after the start of a constant infusion. This allows rapid titration of drug to a clinical end-point such as mean arterial pressure.

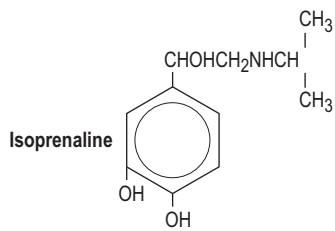
Adrenaline and noradrenaline infusions produce blood concentrations similar to those produced endogenously in shock states, whereas dopamine infusions produce much higher concentrations than those naturally encountered. Dopamine may exert much of its effect by being converted to noradrenaline, thus bypassing the rate-limiting hydroxylation step in catecholamine synthesis.

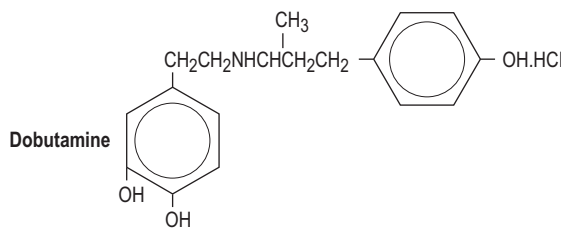
The synthetic catecholamines are primarily derivatives of dopamine (see Fig. 92.3b). These agents are characterised by increased length of the carbon chain

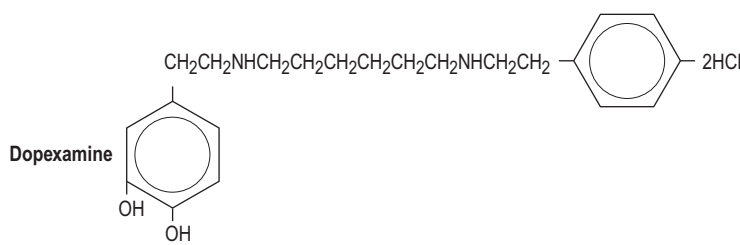


a









b

Figure 92.3 (a) Biosynthesis of catecholamines in sympathetic terminals. *, Rate-limiting step by tyrosine hydroxylase; *COMT*, catechol-*o*-methyl-transferase; *PNMT*, phenethanolamine-*N*-methyltransferase. (b) Chemical structure of endogenous and synthetic catecholamines.

that confers affinity for β-receptors. Dobutamine is a synthetic derivative of isoprenaline. These agents have relatively little affinity for α-receptors due to the configuration of the terminal amine, which differs from the endogenous catecholamines.

Adrenaline, noradrenaline and isoprenaline all have hydroxyl groups on the β-carbon atom of the side chain, and this is associated with 100-fold greater potency than dopamine or dobutamine.

SYSTEMIC EFFECTS

The systemic effects of these agents vary widely between patients and within individuals at different times. The adequacy of response is often unpredictable and depends on the aetiology of circulatory failure and systemic co-morbidities. In some patients, strong 'pressor' responses to small doses may occur characterised by a sharp increase in mean arterial pressure, whereas in others progressively increasing doses of vasoactive drugs are required to attain a targeted mean arterial pressure.

The classification of sympathomimetic agents into α- and β-agonists, based on the above structure–function relationships, is a widely used, albeit crude, predictor of systemic effects.

Adrenaline, noradrenaline and dopamine are predominantly β-agonists at low doses, with increasing α-effects becoming evident as the dose is increased.

The synthetic catecholamines are predominantly β-agonists.

CARDIOVASCULAR

The cardiovascular effects of the catecholamines under physiological conditions are shown in Table 92.2.

Noradrenaline, adrenaline and dopamine increase stroke volume, cardiac output and mean arterial pressure, with little change in heart rate. Dopamine is associated with an increased incidence of dysrhythmias.[12] The effects on the vasculature are similar, primarily increasing venous return without changes in the resistance to venous return and no demonstrable changes in calculated systemic vascular resistance.

Isoprenaline increases cardiac output predominantly by increasing heart rate and by moderate inotropy. This occurs without a significant change in blood pressure due to predominant β_2-receptor-induced venodilatation.

The profile of dobutamine is similar to isoprenaline, although increases in heart rate are not as pronounced. Both of these agents may decrease mean arterial pressure, particularly in hypovolaemic patients, due to reduced venous return caused by venodilatation. The adverse effects of dobutamine and isoprenaline on heart rate and mean arterial pressure may compromise patients with ischaemic heart disease.

In the failing myocardium, particularly in patients with cardiac failure following cardiopulmonary bypass or septic shock, endogenous stores of noradrenaline are markedly reduced.[7] There may be significant desensitisation and down-regulation of cardiac β-receptors. In these situations, α_1- and α_2-receptors have an important role in maintaining inotropy and peripheral vasoresponsiveness.[13] This may be expressed clinically as 'tolerance' or tachyphylaxis to catecholamines, particularly with β-agonists such as dobutamine. This phenomenon may explain the requirement for high doses of catecholamines in refractory shock states. Consequently, the role of β-agonists in patients with severe myocardial failure is questioned.

Catecholamines act predominantly on the venous circulation, primarily restoring and maintaining 'stressed volumes' of the capacitance vessels within teleological limits under pathological conditions. This is important in 'vasodilatory' states such as septic shock.[10]

In clinically used doses, intravenously administered catecholamines have minimal direct vasoconstrictive effects on conducting arterial vessels, including arterial conduits used in cardiac or vascular surgery.

The development of peripheral gangrene in refractory septic shock has been attributed to catecholamine-induced vasoconstriction. There is little evidence to

Table 92.2 Cardiovascular effect of catecholamines

AGENT	β_1 EFFECTS	β_2 EFFECTS	α_1 EFFECTS	α_2 EFFECTS
	+ chronotropy + dromotropy + inotropy	+ inotropy vasodilatation bronchodilatation	+ inotropy vasoconstriction	+ inotropy vasoconstriction
Noradrenaline Adrenaline Dopamine	β effects predominate at low dose; α effects predominate at high dose			
Dobutamine	+	+	(+)	–
Isoprenaline	+	(+)	–	–
Dopexamine	+	+	–	–

+, Stimulation; (+), mild effect; –, no effect.

support this association outside anecdotal reports, as the development of tissue gangrene in these situations primarily occurs as a consequence of intravascular thrombosis caused by sepsis-mediated coagulopathy.

CEREBRAL

Under physiological conditions, catecholamines do not cross the blood–brain barrier. Cerebral blood flow is maintained at a constant rate over a range of perfusion pressure by cerebral autoregulation. Under conditions where the integrity of the blood–brain barrier is altered, such as following traumatic brain injury and aneurysmal subarachnoid haemorrhage, exogenous catecholamines may directly enter the cerebral circulation.

The degree by which these agents directly affect the cerebral circulation following traumatic brain injury is unknown, although there is some evidence suggesting that dopamine has a direct effect causing increased cerebral blood flow and intracranial pressure.[14]

RENAL

The kidney is an efficient autoregulator, maintaining constant glomerular filtration and renal blood flow by neurohormonal mechanisms such as the renin–angiotensin–aldosterone system.[11] All catecholamines increase renal blood flow to a similar extent by increasing cardiac output and mean arterial pressure with a resultant natriuresis. Catecholamine-mediated increases in renal blood flow do not affect glomerular filtration rate.

A natriuresis may also result from the inhibition of cAMP in the renal tubules. This effect has previously been attributed to a specific dopaminergic effect ('low dose' dopamine: 2 μg/kg/minute), although this occurs to a similar extent with adrenaline, noradrenaline and dobutamine. The use of 'renal' dopamine has not been shown to be effective in preventing renal dysfunction in susceptible patients.[15]

METABOLIC

Catecholamine-mediated β-stimulation may result in hyperglycaemia, hypokalaemia and hypophosphataemia, which may need monitoring and correcting.

Adrenaline is associated with the development of hyperlactataemia due to the activation of pyruvate dehydrogenase. Although associated pH may fall to levels around 7.2, the metabolic acidosis is not associated with impaired tissue perfusion or cellular dysoxia. In most patients who are haemodynamically stable, this is a self-limiting phenomenon and is not associated with adverse outcomes.[16,17]

SPLANCHNIC

The splanchnic circulation is more dependent on mean arterial pressure and the duality of the mesenteric and portal systems. Concerns about catecholamine-induced splanchnic vasoconstriction with mesenteric and hepatic ischaemia have not been substantiated.[18]

All catecholamines are equally effective in increasing splanchnic perfusion by improving cardiac output and mean arterial pressure.

PHOSPHODIESTERASE INHIBITORS

Phosphodiesterase (PDE) inhibitors are compounds that cause non-receptor-mediated competitive inhibition of PDE isoenzymes, resulting in increased levels of cAMP (see Fig. 92.2). Importantly, cAMP also affects diastolic heart function through the regulation of phospholamban, the regulatory subunit of the calcium pump of the sarcoplasmic reticulum. This enhances the rate of calcium re-sequestration and associated diastolic relaxation (lusitropy).[19]

For cardiovascular tissue, inhibition of isoenzyme PDE III is responsible for the therapeutic effects. Cardiac effects are characterised by positive inotropy and lusitropy that may be beneficial in patients with reduced ventricular compliance or predominant diastolic failure.[16]

These agents also cause potent vasodilatation with reductions in preload, venous return and afterload as well as a reduction in pulmonary vascular resistance. The term 'inodilation' has been used to describe this dual haemodynamic effect.

Tolerance is not a feature. These agents may have an unsubstantiated role in the management of patients with chronic or subacute cardiac failure by sensitising the myocardium to β-agonists. Other actions include the inhibition of platelet aggregation and the reduction of post-ischaemic reperfusion injury.

The pharmacokinetics of PDE inhibitors are markedly different from catecholamines. Drug half-lives may be prolonged and excretion is predominantly renal. Hypotension may result from vasodilatation, and combined use with catecholamines (e.g. noradrenaline or adrenaline) may be necessary to maintain mean arterial pressure.

PDE inhibitors that have been used in clinical practice include the bipyridine derivatives, amrinone and milrinone; the imidazolones, enoximone and piroximone; and the calcium sensitiser, levosimendan. The cardiovascular effects are similar. Despite the increasing use of PDE inhibitors in critically ill patients, there is little high-quality evidence about the safety and efficacy of these drugs in this patient population.[20]

Milrinone is the most commonly used drug in clinical practice, with the latter exhibiting more inotropic effects than vasodilatation. Enoximone is more rapidly metabolised, but the metabolite is active and its cardiovascular effects persist for some hours.

Levosimendan is a dose-dependent selective PDE inhibitor with a unique action on myocardial calcium metabolism. By increasing myofilament calcium sensitivity throughout the cardiac cycle by binding to cardiac troponin C, associated conformational changes induce improved inotropic and lusitropic function.

Vasodilatation is also induced through adenosine-triphosphate-sensitive potassium channels. Calcium-sensitive actions predominate at low doses, whereas PDE-inhibition effects predominate at higher doses.[21] The half-life of levosimendan is shorter than that of older PDE III inhibitors (approximately 1 hour) and it may be given by infusion. There is emerging evidence that levosimendan is not associated with improved patient-centred outcomes in critically ill patients.[22,23]

HISTORICAL DRUGS

DIGOXIN

Digitalis glycosides have been used for the treatment of heart failure for 200 years and the vagotonic effects used to control the ventricular response in selected supraventricular tachyarrhythmias. Its use in the ICU has been superseded by catecholamines and antiarrhythmics such as amiodarone.

The role of digoxin in acute cardiac failure is limited. It has minimal effects as an inotrope and evaluation of its efficacy is problematic in critically ill patients. The potential for toxicity is increased by hypokalaemia, hypomagnesaemia, hypercalcaemia, hypoxia and acidosis, particularly in patients with an associated acute kidney injury. Toxicity is manifested by dysrhythmias that may assume any form including supraventricular tachyarrhythmias, bradycardia, ventricular ectopy and conduction block at any level.

THYROID HORMONE

Thyroid hormone is required for synthesis of contractile proteins and normal myocardial contraction. It is also a regulator of the synthesis of adrenergic receptors. Its use is limited in critically ill patients, but may have a limited, although unproven, role in haemodynamic support of brain-dead organ donors as a catecholamine-sparing agent.

SELECTIVE VASOPRESSORS

Vascular responsiveness is mediated via adrenergic receptors: α-mechanisms predominantly cause vasoconstriction; β-mechanisms, specifically β_2-receptors, mediate vasodilatation (see Table 92.2).

Noradrenaline, adrenaline and dopamine have variable effects on the peripheral vasculature and should not be regarded principally as vasoconstrictors or vasopressors.

There are few selective 'vasoconstrictors' that predominantly have an unsubstantiated role in vasodilated states such as regional (epidural) anaesthesia or selected patients with acute spinal injury. Their utility in critically ill patients remains limited, although they are widely used in patients undergoing general anaesthesia.

PHENYLEPHRINE AND METARAMINOL

These agents are direct-acting α_2 agonists that are selective vasoconstrictors, both venous and arterial, with minimal β-activity. They have similar pharmacokinetics to catecholamines and may be given by infusion. In patients with normal sympathetic tone, these drugs may cause reflex bradycardia, particularly following bolus administration.

EPHEDRINE

Ephedrine is a synthetic, direct- and indirect-acting, non-catecholamine sympathomimetic that acts on both α- and β-receptors. Duration of action is longer than equivalent doses of adrenaline and it is generally unsuitable as an infusion.

VASOREGULATORY AGENTS

In addition to adrenergic regulation, neurohormonal influences have a regulatory role in maintaining vasomotor tone. These are mediated through the renin–aldosterone–angiotensin axis and local mediators such as vasopressin, corticosteroids, nitric oxide and endothelin.

The response of the neurohumoral system may become blunted in conditions such as severe sepsis, where qualitative and quantitative changes may occur. In this context, failure of vasomotor responsiveness may be considered as part of the multiple organ failure.

VASOPRESSIN

Specific vasopressinergic receptors (V_1, V_2) have been identified in association with sympathetic terminals. Vasopressin is a naturally occurring peptide secreted by the posterior pituitary gland. Reduced serum levels of vasopressin have been demonstrated in septic shock and following cardiopulmonary bypass, suggesting an inflammatory-mediated mechanism. Levels are maintained during cardiogenic shock.[24]

A proportion of patients with severe septic shock requiring high levels of catecholamines to support the circulation may respond to low doses of infused vasopressin (0.04 U/h). However, although vasopressin may improve catecholamine responsiveness in patients with less-severe shock, no benefit in mortality has been demonstrated and there is uncertainty about its use in shock states.[25]

CORTICOSTEROIDS

The role of steroid supplementation in circulatory failure has been studied for over 40 years. Although immunosuppressive or anti-inflammatory doses have been shown to be ineffective, particularly in septic shock, the replacement of 'stress response' doses (approximately 200 mg hydrocortisone per day by

continuous intravenous infusion, or 50 mg 8 hourly) have been shown to improve catecholamine vasoresponsiveness in selected patients with septic shock. However, the role of steroids in shock states remains uncertain, despite two large trials, and they are not routinely recommended.[26] Studies of the potential interaction between corticosteroids and vasopressin have similarly not demonstrated improved survival in patients with septic shock and reduced serum vasopressin levels.[27] In 2017, the ADRENAL trial, conducted in 3500 ICU patients with catecholamine-dependent septic shock demonstrated no significant difference in day-90 mortality in patients who received hydrocortisone or placebo. However, the use of the continuous infusion of hydrocortisone was associated with a reduction in the duration of septic shock, duration of mechanical ventilation and ICU admission, suggesting a potentially beneficial role of hydrocortisone as modulator of vasopressor responsiveness in patients with septic shock.[28]

CLINICAL USES

Currently, there are no definitive studies comparing the efficacy of one inotrope (or combination of inotropes) over another in terms of improving survival.[29]

DRUG SELECTION

In most instances, individual experience and preference determine selection of inotrope(s).

On a pathobiological basis, exogenous catecholamines are used to augment endogenous mechanisms that may be failing at a number of levels. In this context, vasoactive therapy should be regarded as 'cardiovascular neuroendocrine augmentation therapy'.

Noradrenaline or adrenaline are considered as the first-line drug in most causes of circulatory failure. An emerging body of evidence and current clinical practice guidelines, particularly for patients with sepsis confirms this statement.[12,30]

Dopamine predominantly acts as a precursor of noradrenaline and may be used as an alternative to noradrenaline, although it is associated with an increased incidence of arrhythmias.

Prediction of the response of an individual to a catecholamine is problematic as marked inter- and intra-individual variability to the response of vasoactive agents may occur.

The haemodynamic and metabolic response of an agent must be carefully monitored and evaluated. If there is not a satisfactory response, or if undesirable effects are obtained, the dose or agent should be changed.

MONITORING

Accurate monitoring of the circulation is essential in patients with circulatory failure to assess baseline parameters and the response of vasoactive drugs.[31]

Clinical assessment of the circulation remains the cornerstone of monitoring these patients and includes frequent assessment and recording of pulse rate and rhythm, blood pressure, adequacy of peripheral perfusion, skin turgor, level of consciousness and urine output.

The majority of patients with circulatory failure managed in the ICU require haemodynamic monitoring as clinical signs may be masked or influenced by sedation, ventilation or organ failure. As a minimum, all patients receiving vasoactive drugs in all but trivial doses should have accurate monitoring of mean arterial pressure, ideally with an intra-arterial catheter referenced to the aortic root and an assessment of volume status such as central venous pressure.

In selected patients with primary myocardial failure, an assessment of cardiac output may be useful to quantify baseline function and to assess the response of the heart to drug therapy. Measurement of cardiac output may be done non-invasively using transthoracic or transoesophageal echocardiography, or invasively by using a pulmonary catheter, ideally using a continuous cardiac output display system, although the use of these catheters has decreased substantially and is superseded by the use of transthoracic echocardiography.

Derived parameters from pulmonary artery catheters include systemic vascular resistance that is used as a surrogate index of afterload, although this parameter does not reflect afterload, arteriolar tone or venous return. Consequently, systemic vascular resistance should not be used as a criterion for selection of vasoactive drug or as a titratable end-point.

Restoration of reduced tissue perfusion is a primary aim of vasoactive therapy. This may be assessed clinically by improvements in urine output, serum urea and creatinine, reversal of metabolic acidosis and reductions in serum lactate.

DOSAGES AND DRUG ADMINISTRATION

Vasoactive drugs, such as catecholamines or vasopressors, should be administered as a continuous infusion through a dedicated central venous catheter using drug delivery systems such as infusion pumps or syringe drivers.

Infusion lines should be free of injection portals and clearly marked with identifying labels.

Concentrations of infusions should be standardised in accordance with individual unit protocols. Suggested infusion concentrations are shown in Table 92.3.

These infusions in mL/h approximate μg/min. Absolute doses with regard to body weight are not relevant; however, the titrated clinical effect is.

Vasoactive drugs are usually prescribed as a titration against a targeted mean arterial pressure. While a default target mean arterial pressure of 70 mm Hg is frequently used, this should consider the patient's

Table 92.3 Infusion concentrations of commonly used vasoactive drugs

AGENT	INFUSION CONCENTRATION	DOSE
Adrenaline	6 mg/100 mL 5% dextrose	Titrate mL/h (= µg/min)
Noradrenaline	6 mg/100 mL 5% dextrose	Titrate mL/h (= µg/min)
Dopamine	400 mg/100 mL 5% dextrose	Titrate mL/h (approx. µg/kg/min)
Dobutamine	500 mg/100 mL 5% dextrose	Titrate mL/h (approx. µg/kg/min)
Isoprenaline	6 mg/100 mL 5% dextrose	Titrate mL/h (= µg/min)
Milrinone	10 mg/100 mL 5% dextrose	Loading dose: 50 µg/kg over 20 min Infusion: 0.5 µg/kg/min
Levosimendan	25 mg/100 mL 5% dextrose	Loading dose: 24 µg/kg over 10 min Infusion: 0.1 µg/kg/min
Phenylephrine	10 mg/100 mL 5% dextrose	Titrate mL/h (= 100 µg/h)
Metaraminol	100 mg/100 mL 5% dextrose	Titrate mL/h (= mg/h)
Ephedrine	300 mg/100 mL 5% dextrose	Titrate mL/h (= 3 mg/h)
Vasopressin	20 U/20 mL 5% dextrose	2.4 mL/h (0.04 U/min)
Hydrocortisone	100 mg/100 mL 5% dextrose	Loading dose: 100 mg Infusion: 0.18 mg/kg/h

pre-morbid blood pressure, associated co-morbidities and acute illness.[16] In some clinical situations, such as elderly patients with acute-on-chronic kidney injury, a higher mean arterial pressure may be targeted, while in others, such as those with acute intracranial haemorrhage or those following major surgery at risk of secondary haemorrhage, a lower mean arterial pressure may be targeted. These targets must be re-assessed frequently as dictated by the clinical context and trajectory. Increasingly, a lower default mean arterial pressure of 60–65 mm Hg is advocated.

SPECIFIC INDICATIONS

CARDIOPULMONARY RESUSCITATION

Adrenaline has been used for circulatory collapse at least since 1907. The International Liaison Committee on Resuscitation guidelines recommends adrenaline as the first-line vasoactive drug in cardiopulmonary resuscitation.[32] The dose is 1 mg intravenously every 3 minutes.

Adrenaline is recommended as first-line therapy for 'medical pacing' for severe bradyarrhythmias that do not respond to atropine. Isoprenaline has traditionally been used for this purpose; however, its use has been superseded by adrenaline due to concerns about efficacy and lack of α-adrenergic activity.

CARDIOGENIC SHOCK

Theoretically, catecholamine infusions may confer some advantages in cardiogenic shock, particularly in association with acute myocardial infarction. In patients with systolic heart failure, adrenaline, noradrenaline, dopamine and dobutamine have been shown to cause satisfactory short-term effects. This may allow the myocardium time to recover from post-ischaemic 'stunning', particularly after revascularisation. However, no increased long-term survival due to their use has been demonstrated.[29]

The role of PDE inhibitors (e.g. milrinone) and calcium sensitisers (e.g. levosimendan) in acute heart failure may have a potential role in patients with diastolic heart failure, particularly those with associated high impedance states such as aortic stenosis and pulmonary hypertension. Due to their non-adrenergic mechanism of action, these agents may be useful in patients who are 'resistant' to catecholamines. However, recent high-quality randomised, controlled trials have not shown superiority of levosimendan over dobutamine, but showed that levosimendan is associated with increased adverse outcomes, particularly tachyarrhythmias and catecholamine-dependence in patients with septic shock.[22,23]

SEPARATION FROM CARDIOPULMONARY BYPASS

Numerous combinations of catecholamines have been used successfully to wean patients from cardiopulmonary bypass. However, there are no definitive studies demonstrating significant benefits of one catecholamine over another.

Adrenaline and noradrenaline have been found to increase cardiac output with little increase in heart rate or afterload and are often regarded as first-line drugs.

Dobutamine may be associated with vasodilatation and hypotension.

There is no conclusive evidence that the catecholamines, including noradrenaline, cause vasospasm of arterial conduits in clinically used doses.

PDE inhibitors, such as milrinone and levosimendan, either as sole agents or in conjunction with adrenaline or noradrenaline, have been used with variable success driven by local preference, although there is little high-quality evidence that these drugs are superior to catecholamines. PDE inhibitors may have a beneficial role in high impedance states such as in patients with pulmonary hypertension undergoing mitral valve replacement or in those with severe preoperative diastolic heart failure.[33]

Cardiopulmonary bypass may be associated with a systemic inflammatory response syndrome characterised by a hyperdynamic, vasodilated state. Noradrenaline is frequently advocated as a 'vasopressor' agent in this context to restore mean arterial pressure, which may be reduced as a consequence. Although catecholamines may be required to achieve appropriate target mean arterial pressure and cardiac output, caution should be applied if high doses (e.g. >30 μg/min noradrenaline) are required.

RIGHT VENTRICULAR FAILURE

Right ventricular infarction and major pulmonary embolism may be associated with acute right ventricular failure. Right ventricular depression may also occur in severe sepsis. Restoration of preload is critical in these conditions, as the failing right ventricle is particularly susceptible to reductions in preload.

Inotropes, such as noradrenaline and adrenaline, are regarded as first-line drugs in these situations in order to maintain adequate mean arterial pressure so that right coronary artery perfusion, which occurs throughout the cardiac cycle, is maintained.

SEPTIC SHOCK

The cardiovascular effects of the sepsis syndrome and septic shock are complex and range from a hyperdynamic, vasodilated state to one of increasing myocardial failure and paralysis of the peripheral vasculature (vasoplegia). The latter represents inability of the venous circulation to respond to endogenous or exogenous catecholamines with resultant venous pooling.

An increasing body of literature now recommends the use of catecholamines as first-line agents in the treatment of septic shock. The Surviving Sepsis Campaign guidelines recommend that either noradrenaline or adrenaline be used as the first-line choice vasopressor.[30] However, the basis for this recommendation is limited as there is little high-quality evidence to recommend one catecholamine over another. Concerns about adverse metabolic and splanchnic side effects of adrenaline are unsubstantiated, and there is an emerging body of evidence that noradrenaline and adrenaline are equally effective in treating septic shock.[30] There is evidence that dopamine may be associated with adverse outcomes and its use is being questioned in the absence of superiority to noradrenaline or adrenaline.[12]

The efficacy of dobutamine as a sole agent or in combination with noradrenaline in septic shock is questionable and appears to add little to the efficacy of noradrenaline or adrenaline in terms of resolution of shock or mortality.

Doses required to achieve adequate mean arterial pressure in septic shock may vary: noradrenaline or adrenaline infusions (up to 40 μg/min) may be necessary. Patients who develop marked catecholamine dependency, in the absence of other acute remediable causes, such as active infection, may respond to low doses of vasopressin or 'stress response' doses of hydrocortisone, although there is marked interindividual variation in response to these drugs. However, the use of vasopressin in patients with septic shock has not been shown to improve survival apart from a subgroup of patients with less severe shock.[25,34] Similarly, the role of corticosteroids as a catecholamine-sparing agent is recognised, but whether this observation translates to improved patient-centred outcome remains unknown with current evidence.[26]

ANAPHYLAXIS

Adrenaline is the drug of choice for anaphylactic reactions and for life-threatening bronchospasm, as it blocks mediator release and specifically reverses end-organ effects (see Chapter 66).

A dose of 0.1 mg, as 1 mL of 1:10,000 solution, may be injected subcutaneously, intramuscularly or intravenously. Repeated doses or infusions of up to 100 μg/min may be required. A strong, slowing pulse indicates a systemic pressor effect and provides a useful clinical end-point for the rate of infusion. This α-agonist effect is also probably of considerable importance in anaphylaxis, as deaths are frequently due to prolonged refractory hypotension caused by acute biventricular failure. Early intravenous fluid therapy is also important.

CEREBRAL PERFUSION PRESSURE

Augmentation of cerebral perfusion pressure is an important strategy in patients with pathological reductions in cerebral blood flow, such as traumatic brain injury and subarachnoid haemorrhage. Noradrenaline is used to augment cerebral perfusion pressure in these patients, although there is no conclusive evidence to recommend any particular drug over another.[14]

REFERENCES

1. Guyton AC, Lindsay AW, Kaufmann BN. Effect of mean circulatory filling pressure and other peripheral circulatory factors on cardiac output. *Am J Physiol*. 1955;180:463–468.
2. Beard DA, Feigl EO. Understanding Guyton's venous return curves. *Am J Physiol Heart Circ Physiol*. 2011;301(3):H629–H633.

3. Henderson WR, Griesdale DE, Walley KR, et al. Clinical review: Guyton – the role of mean circulatory filling pressure and right atrial pressure in controlling cardiac output. *Crit Care*. 2010;14(6):243.
4. Shen T, Baker K. Venous return and clinical hemodynamics: how the body works during acute hemorrhage. *Adv Physiol Educ*. 2015;39(4):267–271.
5. Hein L. Adrenoceptors and signal transduction in neurons. *Cell Tissue Res*. 2006;326(2):541–551.
6. Harrois A, Hamada SR, Duranteau J. Fluid resuscitation and vasopressors in severe trauma patients. *Curr Opin Crit Care*. 2014;20(6):632–637.
7. Antonucci E, Fiaccadori E, Donadello K, et al. Myocardial depression in sepsis: from pathogenesis to clinical manifestations and treatment. *J Crit Care*. 2014;29(4):500–511.
8. Nazario LR, Marques da SP. Diastolic dysfunction in hypertension. *Hipertens Riesgo Vasc*. 2017;34(3): 128–139.
9. Meschiari CA, Ero OK, Pan H, et al. The impact of aging on cardiac extracellular matrix. *Geroscience*. 2017;39(1):7–18.
10. Rudiger A, Singer M. The heart in sepsis: from basic mechanisms to clinical management. *Curr Vasc Pharmacol*. 2013;11(2):187–195.
11. Lamba S, Abraham WT. Alterations in adrenergic receptor signaling in heart failure. *Heart Fail Rev*. 2000;5(1):7–16.
12. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362(9):779–789.
13. Jensen BC, O'Connell TD, Simpson PC. Alpha-1-adrenergic receptors: targets for agonist drugs to treat heart failure. *J Mol Cell Cardiol*. 2011;51(4): 518–528.
14. Myburgh JA. Driving cerebral perfusion pressure with pressors: how, which, when? *Crit Care Resusc*. 2005;7(3):200–205.
15. Bellomo R, Chapman M, Finfer S, et al. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet*. 2000;356(9248): 2139–2143.
16. Myburgh JA, Higgins A, Jovanovska A, et al. A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med*. 2008;34(12): 2226–2234.
17. Annane D, Vignon P, Renault A, et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. *Lancet*. 2007;370(9588):676–684.
18. De Backer D, Creteur J, Silva E, et al. Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? *Crit Care Med*. 2003;31(6):1659–1667.
19. Movsesian M. New pharmacologic interventions to increase cardiac contractility: challenges and opportunities. *Curr Opin Cardiol*. 2015;30(3):285–291.
20. Koster G, Bekema HJ, Wetterslev J, et al. Milrinone for cardiac dysfunction in critically ill adult patients: a systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. *Intensive Care Med*. 2016;42(9):1322–1335.
21. Farmakis D, Alvarez J, Gal TB, et al. Levosimendan beyond inotropy and acute heart failure: evidence of pleiotropic effects on the heart and other organs: an expert panel position paper. *Int J Cardiol*. 2016;222: 303–312.
22. Gordon AC, Perkins GD, Singer M, et al. Levosimendan for the prevention of acute organ dysfunction in sepsis. *N Engl J Med*. 2016;375(17): 1638–1648.
23. Landoni G, Lomivorotov VV, Alvaro G, et al. Levosimendan for hemodynamic support after cardiac surgery. *N Engl J Med*. 2017;21376:2021–2031.
24. Landry DW, Levin HR, Gallant EM, et al. Vasopressin pressor hypersensitivity in vasodilatory septic shock. *Crit Care Med*. 1997;25(8):1279–1282.
25. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358(9):877–887.
26. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for treating sepsis. *Cochrane Database Syst Rev*. 2015;(12):CD002243.
27. Russell JA, Walley KR, Gordon AC, et al. Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock. *Crit Care Med*. 2009;37(3):811–818.
28. Venkatesh B, Finfer S, Cohen J, et al. Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med*. 2018;378(9):797–808.
29. Gamper G, Havel C, Arrich J, et al. Vasopressors for hypotensive shock. *Cochrane Database Syst Rev*. 2016;(2):CD003709.
30. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017;43(3):304–377.
31. Huygh J, Peeters Y, Bernards J, et al. Hemodynamic monitoring in the critically ill: an overview of current cardiac output monitoring methods. *F1000Res*. 2016;5.
32. Hazinski MF, Nolan JP, Aickin R, et al. Part 1: Executive summary: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation*. 2015;132(16 suppl 1): S2–S39.
33. Raja SG, Rayen BS. Levosimendan in cardiac surgery: current best available evidence. *Ann Thorac Surg*. 2006;81(4):1536–1546.
34. Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: The VANISH randomized clinical trial. *JAMA*. 2016; 316(5):509–518.

93

Vasodilators and antihypertensives

David O'Callaghan, David Antcliffe

Vasodilators are a generic group of drugs that are primarily used in the intensive care unit (ICU) for the management of acute hypertensive states and emergencies. In addition, they have an important role in the management of myocardial ischaemia, systemic and pulmonary hypertension, and cardiac failure.[1,2]

PHYSIOLOGY

Blood pressure is controlled by a complex physiological neurohormonal system involving all components of the cardiovascular system.[3,4] Clinical practice has focused on the arterial circulation as the major regulator of systemic pressure. The importance of venous circulation in determining mean arterial pressure and cardiac output is discussed in Chapter 92.

The role of the peripheral vasculature in the regulation of blood pressure may be conceptually regarded as a balance between vasodilatation and vasoconstriction (Fig. 93.1).[4]

CALCIUM FLUX

The concentration of intracellular ionised calcium is the primary determinant of vascular smooth muscle tone: increases lead to smooth muscle contraction; decreases cause relaxation. Control of calcium influx and efflux is determined by adrenergic receptor occupation and changes in membrane potential, which is mediated through voltage-gated channels (see Chapter 92, Fig. 92.2).

ENDOTHELIAL SYSTEM

The endothelium plays a central role in blood pressure homeostasis by secreting substances such as nitric oxide (NO), prostacyclin and endothelin.[4] These substances are continuously released by the endothelium and are integral in regional autoregulation.[5]

NO is synthesised from L-arginine by NO synthases and diffuses into smooth muscle where it activates guanylate cyclase to increase cyclic guanosine monophosphate (cGMP) resulting in the relaxation of underlying smooth muscle and vasodilatation.

Prostacyclin is synthesised via the arachidonic pathway and has a minor role in the control of vascular tone.

Endothelins are endothelium-derived vasoconstrictor peptides that are associated with increases in vascular smooth muscle intracellular calcium. They bind to endothelin receptors within the vascular smooth muscle causing vasoconstriction, usually in response to shear stresses, tissue hypoxia, angiotensin II and inflammatory mediators (e.g. interleukin-6 and nuclear factor-κB [NF-κB]).

RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

Angiotensinogen is converted by renin to form angiotensin I, which is subsequently converted to angiotensin II by the angiotensin-converting enzyme (ACE). Angiotensin II has a number of effects on blood pressure homeostasis including the release of aldosterone, direct activation of α-adrenergic receptors on vascular smooth muscle and a direct effect in the endothelium. These effects are directed at maintaining blood pressure and are integral in the stress response. ACE also inactivates bradykinins that have predominantly vasodilatory effects, coupled to arachidonic acid synthesis and the generation of prostacyclin.

ADRENERGIC SYSTEM

The sympathetic nervous system is integrally involved with all of the above systems, regulating vascular tone at central, ganglionic and local neural levels. Adrenergic stimulation of β-receptors is associated with vasodilatation; α-receptor stimulation results in vasoconstriction. The vascular effects of the catecholamines and vasopressors are discussed in Chapter 92.

Adrenergic stimulation is the predominant system regulating venous tone[6] via endothelial differences in veins resulting production of less NO and reduced responsiveness to angiotensin II.

ABSTRACT

Vasodilator and antihypertensive medications are drugs commonly used in intensive care to treat a wide variety of clinical conditions. This chapter addresses the underlying physiology of blood pressure control from the role of calcium, the endothelial system and hormonal influences to derangements in this physiology that may lead to hypertension. In this context the mechanisms of action of the most commonly used classes of vasodilators and antihypertensive drugs are also explored. Different clinical situations and pathologies call for specific treatments with the drugs detailed, and in this chapter many of these conditions are reviewed along with current recommendations for treatment.

KEYWORDS

Hypertension
calcium
beta-blockers
ACE inhibitors
alpha-antagonists
ionodilators
aortic dissection
myocardial ischaemia
phaeochromocytoma
pre-eclampsia

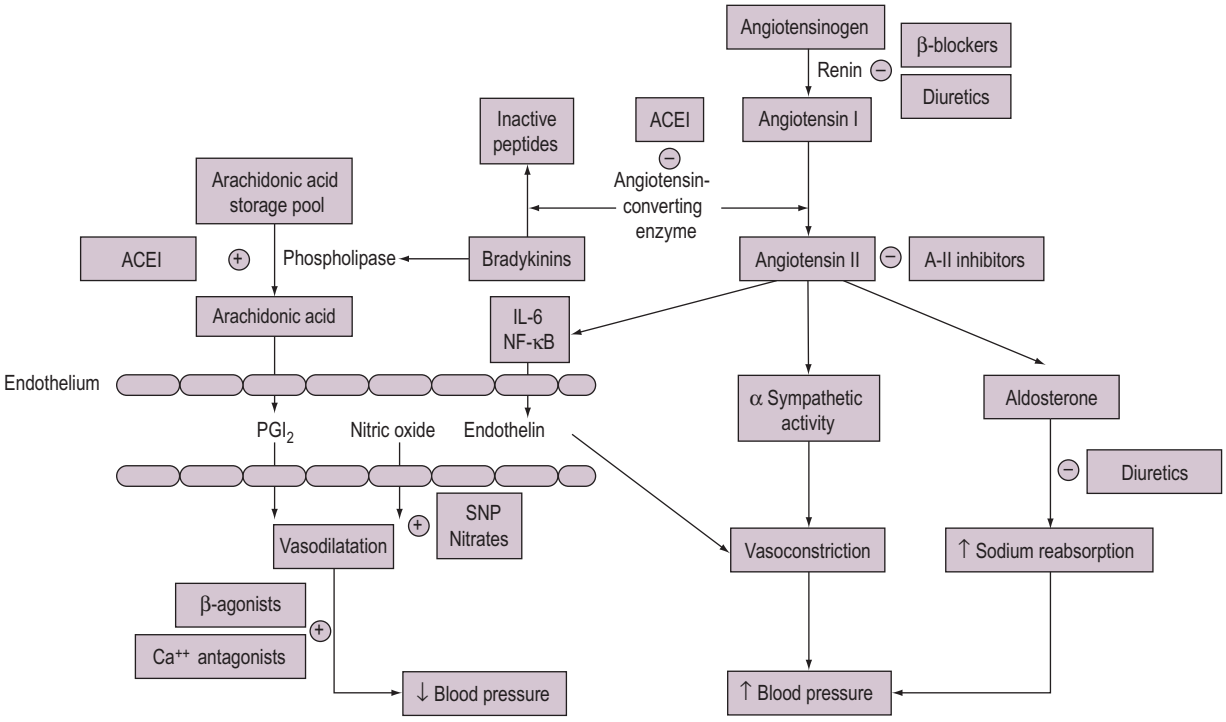


Figure 93.1 Schematic diagram of the neurohormonal factors determining vasomotor tone. Mechanism of action of vasodilators is shown by (–) for inhibition, (+) for stimulation. *A-II*, Angiotensin II; *ACEI*, angiotensin-converting enzyme inhibitors; *IL*, interleukin; *NF*, nuclear factor; *PGI_2*, prostacyclin; *SNP*, sodium nitroprusside.

PATHOPHYSIOLOGY

Hypertensive states develop as a result of impaired or abnormal homeostatic processes, causing an imbalance between vasoconstriction and vasodilation.

Essential hypertension is the most common cause of hypertension and is due to abnormal neurohormonal regulation, particularly exaggerated effects of renin–angiotensin activity.

Secondary causes of hypertension include structural abnormalities such as aortic coarctation or renal artery stenosis; endocrine conditions such as phaeochromocytoma, Cushing syndrome and pregnancy-induced hypertension; and central causes such as raised intracranial pressure.

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers have numerous effects on the cardiovascular system, influencing heart rate, myocardial contractility and vasomotor tone. The entry of calcium through voltage-gated calcium channels is a major determinant of arteriolar, but not venous, tone.[7] Calcium channel blockers are recommended as a first-step treatment for hypertension in Caucasian patients greater than 55 years and Afro-Caribbean patients of any age.[8]

There are three major groups of calcium channel blockers that have different sites of action and therapeutic effects: dihydropyridines (e.g. nifedipine, nimodipine, nicardipine, amlodipine, and felodipine), phenylalkylamines (e.g. verapamil) and benzothiazepines (e.g. diltiazem).

Magnesium is a physiological calcium antagonist, and is used therapeutically as magnesium sulphate.

NIFEDIPINE

Nifedipine is a predominant arteriolar vasodilator, with minimal effect on venous capacitance vessels and no direct depressant effect on heart rate conduction.

It may be administered intravenously, orally or sublingually, and has a rapid onset of action of 2–5 minutes and a duration of action of 20–30 minutes.

Nifedipine can be used to treat angina pectoris, especially that due to coronary artery vasospasm. Peripheral vasodilatation results in decreased systemic blood pressure, often associated with sympathetic stimulation resulting in increased cardiac output and heart rate, which may counter the negative inotropic, chronotropic and dromotropic effects of nifedipine. Nevertheless, nifedipine may be associated with profound hypotension in patients with ventricular dysfunction, aortic stenosis and/or concomitant β-blockade. For this reason, the use of sublingual

nifedipine as a method of treating hypertensive emergencies is no longer recommended.[9]

Nifedipine and related drugs may cause diuretic-resistant peripheral oedema, which is due to the redistribution of extracellular fluid rather than sodium and water retention.

NIMODIPINE

Nimodipine is a highly lipid-soluble analogue of nifedipine. High lipid solubility facilitates entrance into the central nervous system where it causes selective cerebral arterial vasodilatation, which may attenuate cerebral arterial vasospasm following aneurysmal subarachnoid haemorrhage. Improved outcomes have been demonstrated in patients with Grade 1 and 2 subarachnoid haemorrhage.[10] Systemic hypotension may result from peripheral vasodilatation that may compromise cerebral blood flow in susceptible patients. Similarly, cerebral vasodilatation may increase intracranial pressure in patients with reduced intracranial elastance.

The recommended dose following aneurysmal subarachnoid haemorrhage is 60 mg orally 4-hourly, but it can be given at 30 mg 2-hourly to reduce variation in blood pressure. Intravenous nimodipine is not recommended owing to its profound effect on blood pressure.

AMLODIPINE

Amlodipine is an oral preparation that has a similar pharmacodynamic profile to nifedipine. In addition to arteriolar vasodilatory and cardiac effects, amlodipine has been shown to exert specific anti-inflammatory effects in hypertension and diabetic nephropathy, and in modulating high-density lipoprotein (HDL) in patients with hypercholesterolaemia.[11] These effects have seen amlodipine increasingly being used for the treatment of hypertension, and it may have a role in stable critically ill patients with associated comorbidities.

VERAPAMIL

Verapamil predominantly affects the atrioventricular node and is principally used as an antiarrhythmic for the treatment of supraventricular tachyarrhythmias. For this reason, concomitant therapy with β-blockers or digoxin is not recommended.

Verapamil is negatively inotropic and is not as active as nifedipine on smooth muscle; therefore it causes less pronounced decrease in systemic blood pressure. It has a limited role as a vasodilator.[12]

DILTIAZEM

Diltiazem has a similar cardiovascular profile to verapamil, although its vasodilatory properties are intermediate between nifedipine and verapamil. Diltiazem exerts minimal cardiodepressant effects and is less likely to potentiate β-blockers.

MAGNESIUM SULPHATE

Magnesium regulates intracellular calcium and potassium levels by activating membrane pumps and competing with calcium for transmembrane channels. Physiological effects are widespread, affecting cardiovascular, central and peripheral nervous systems and the musculoskeletal junction.[13]

It acts as a direct arteriolar and venous vasodilator causing reductions in blood pressure. Modulation of centrally mediated and peripheral sympathetic tone results in variable effects on cardiac output and heart rate.

Consequently, it has an established role in the treatment of pre-eclampsia and eclampsia,[14] perioperative management of phaeochromocytoma[15] and treatment of autonomic dysfunction in tetanus.[16] It has been proposed as a possible agent for the prevention of secondary ischaemia after aneurysmal subarachnoid haemorrhage; however, evidence of a benefit on outcome is still lacking.[17]

DIRECT-ACTING VASODILATORS

These drugs act directly on vascular smooth muscle and exert their effects predominantly by increasing the concentration of endothelial NO. These drugs are also known as nitrovasodilators.[18]

SODIUM NITROPRUSSIDE

Sodium nitroprusside is a non-selective vasodilator that causes relaxation of arterial and venous smooth muscle. It is comprised of a ferrous ion centre associated with five cyanide moieties and a nitrosyl group. The molecule is 44% cyanide by weight.

It is reconstituted from a powdered form. The solution is light sensitive so it requires protection from exposure to light (e.g. by wrapping administration sets in aluminium foil). Prolonged exposure to light may be associated with an increase in release of hydrogen cyanide, although this is seldom clinically significant.

When infused intravenously, sodium nitroprusside interacts with oxyhaemoglobin, dissociating immediately to form methaemoglobin while releasing free cyanide and NO. The latter is causing the vasodilation.

Dosage is from 0.5 μg/kg/min to 8 μg/kg/min, but should always start at a low infusion rate and build up slowly.

Onset of action is almost immediate with a transient duration, requiring continuous intravenous infusion to maintain a therapeutic effect. Tachyphylaxis can occur and large doses should not be used if the desired

therapeutic effect is not attained, as this may be associated with toxicity.

Sodium nitroprusside produces direct venous and arterial vasodilatation, resulting in a prompt decrease in systemic blood pressure. The effect on cardiac output is variable. Decreases in right atrial pressure reflect pooling of blood in the venous system, which may decrease cardiac output. This may result in reflex tachycardia that may oppose the overall reduction in blood pressure. In patients with left ventricular failure, the effect on cardiac output will depend on initial left ventricular end-diastolic pressure.

Sodium nitroprusside may potentially increase myocardial ischaemia in patients with coronary artery disease by causing an intracoronary steal of blood flow away from ischaemic areas by arteriolar vasodilatation. Secondary tachycardia may also exacerbate myocardial ischaemia.

Due to its non-selectivity, sodium nitroprusside has direct effects on most vascular beds. In the cerebral circulation, sodium nitroprusside is a cerebral vasodilator, leading to increases in cerebral blood flow and blood volume. This may be critical in patients with increased intracranial pressure. Rapid and profound reductions in mean arterial pressure produced by sodium nitroprusside may exceed the autoregulatory capacity of the brain to maintain adequate cerebral blood flow.

Sodium nitroprusside is a pulmonary vasodilator and may attenuate hypoxic pulmonary vasoconstriction, resulting in increased intrapulmonary shunting and decreased arterial oxygen tension. This phenomenon may be exacerbated by associated hypotension.

The prolonged use of large doses of sodium nitroprusside may be associated with toxicity related to the production of cyanide and, to a lesser extent, methaemoglobin.[19]

Free cyanide produced by the dissociation of sodium nitroprusside reacts with methaemoglobin to form cyanmethaemoglobin, or is metabolised by rhodenase in the liver and kidneys to form thiocyanate. A healthy adult can eliminate cyanide at a rate equivalent to a sodium nitroprusside infusion of 2 µg/kg/min or up to 10 µg/kg/min for 10 minutes, although there is marked interindividual variability.

Toxicity should be of concern in patients who become resistant to sodium nitroprusside despite maximum infusion rates and who develop an unexplained lactic acidosis. In high doses, cyanide may cause seizures.

Treatment of suspected cyanide toxicity is cessation of the infusion and administration of 100% oxygen. Sodium thiosulphate (150 mg/kg) converts cyanide to thiocyanate, which is excreted renally. For severe cyanide toxicity, sodium nitrite may be infused (5 mg/kg) to produce methaemoglobin and subsequently cyanmethaemoglobin. Hydroxycobalamin, which binds cyanide to produce cyanocobalamin, may also be administered (5 g over 15 minutes, which may be repeated in severe cases).

GLYCERYL TRINITRATE

Glyceryl trinitrate is an organic nitrate that generates NO through a different mechanism from sodium nitroprusside.

The pharmacokinetics allows glyceryl trinitrate to be given by infusion, with a longer onset and duration of action than sodium nitroprusside. The intravenous dosage can start at 5 µg/min and increase incrementally to 200 µg/min (maximum dose 400 µg/min). Glyceryl trinitrate may also be administered sublingually, orally or transdermally.

Tachyphylaxis is common with glyceryl trinitrate; doses should not be increased if patients no longer respond to standard doses. Glass bottles or polyethylene administration sets are required as glyceryl trinitrate is absorbed into standard polyvinylchloride sets.

The effects on the peripheral vasculature are dose dependent, acting principally on venous capacitance vessels to produce venous pooling and decreased ventricular preload.

Glyceryl trinitrate primarily dilates larger conductance vessels of the coronary circulation, resulting in increased coronary blood flow to ischaemic subendocardial areas, thereby relieving angina pectoris.

Reductions in blood pressure are more dependent on blood volume than with sodium nitroprusside. Precipitous falls in blood pressure may occur in hypovolaemic patients with small doses of glyceryl trinitrate. In euvolaemic patients, reflex tachycardia is not as pronounced as with sodium nitroprusside. At higher doses, arteriolar vasodilatation occurs without significant changes in calculated systemic vascular resistance. More recently, glyceryl trinitrate has been suggested as one approach to improve microcirculatory flow in septic shock, but only after adequate fluid resuscitation.[20]

Glyceryl trinitrate is a cerebral vasodilator and often causes headaches and should be used with caution in patients with known or suspected raised intracranial pressure.

ISOSORBIDE DINITRATE

Isosorbide dinitrate is the most commonly administered oral nitrate for the prophylaxis of angina pectoris. It has a physiological effect that lasts up to 6 hours in doses of 30–120 mg. The mechanism of action is the same as glyceryl trinitrate. Hypotension may follow acute administration, but tolerance to this develops with chronic therapy.[21]

HYDRALAZINE

Hydralazine is a potent, arterioselective, direct-acting vasodilator that acts via the stimulation of cGMP

and the inhibition of smooth muscle myosin light chain kinase.

Following intravenous administration, 5–10 mg, hydralazine has a rapid onset of action, usually within 5–10 minutes. It can alternatively be given by continuous intravenous infusion, initially 200–300 μg/min with maintenance usually 50–150 μg/min, and may be administered orally. The drug is partially metabolised by acetylation, for which there is marked inter-individual variability (35% of the population are slow acetylators). Although this does not have much clinical significance regarding the antihypertensive effects, it is important with respect to toxicity.[21]

Hydralazine causes predominantly arteriolar vasodilatation that is widespread but not uniform. It is associated with direct and reflex sympathetic activity, so that cardiac output and heart rate are increased. Prolonged use of hydralazine stimulates renin release and is associated with sodium and water retention. Consequently, hydralazine is frequently administered with β-blockers and/or diuretics.

Chronic use of hydralazine may be associated with immunological side effects including lupus syndrome, vasculitis, haemolytic anaemia and rapidly progressive glomerulonephritis.

NICORANDIL

Nicorandil has multiple actions. First, it is a potassium channel activator that leads to arteriodilation and improved coronary blood flow. Second, it has nitrate properties that cause venodilation and may also demonstrate cardioprotective effects against ischaemic injury. Third, nicorandil is currently indicated as a second-line treatment for stable angina but its use may be limited by the main side effects of headache, flushing and ulceration.

ALPHA-ADRENERGIC ANTAGONISTS

Several groups of compounds act as α-adrenergic blockers with variable affinity for populations of α-receptors. Physiology and pathophysiology may influence the responsiveness of the drug receptor–effector relationship. Receptor pathobiology is discussed in Chapter 92. Consequently, there may be marked inter- and intraindividual variability in patient response to these drugs.

There are six main groups of α-receptor antagonists: imidazolines (e.g. phentolamine), haloalkylamines (e.g. phenoxybenzamine), prazosin, β-adrenergic antagonists with α-receptor antagonism (labetalol, carvedilol), phenothiazines (chlorpromazine) and butyrophenones (haloperidol).

PHENTOLAMINE

Phentolamine is a non-selective, competitive antagonist at α_1- and α_2-receptors. At low doses, phentolamine causes prejunctional inhibition of norepinephrine (noradrenaline) release (via α_2-receptor inhibition). At higher doses, a more complete α-receptor blockade is achieved, with enhancement of effects of β-agonists due to increased local concentration of norepinephrine produced by α_2-blockade (see Chapter 92, Fig. 92.3a).

Phentolamine is administered intravenously and may be given intermittently or by infusion. Onset is rapid (within 2 minutes), with a duration of action of 10–15 minutes.

Arteriolar and venous vasodilatation reduces systemic blood pressure. Effects on cardiac output are variable, and there is modest reflex sympathetic stimulation without significant increases in heart rate.

PHENOXYBENZAMINE

Phenoxybenzamine is a non-selective, non-competitive, α_1- and α_2-receptor antagonist. Blockade is also produced on histamine, serotonin and acetylcholine muscarinic receptors. Reuptake of norepinephrine is blocked, thereby potentiating the effects of β-agonists.

Phenoxybenzamine is usually administered orally, but may also be given intravenously (taking care to avoid extravasation as it is irritant to tissues). It has a long onset of action and prolonged duration of action (3–4 days). It causes a gradual reduction in systemic blood pressure, without rapid reflex sympathetic activity.

Prolonged use is associated with increased β-adrenergic effects, predominantly increased heart rate, for which combination therapy with β-blockade is used. Phenoxybenzamine is primarily used in the management of phaeochromocytoma, either preoperatively or long term in inoperable patients. It may also be used to control autonomic hyperreflexia in patients with spinal cord transection.[22]

PRAZOSIN

Prazosin is a relatively arterioselective, competitive, α_1-receptor antagonist. It acts postjunctionally and therefore does not inhibit reuptake of norepinephrine. Consequently, it produces less tachycardia for a given reduction in systemic blood pressure.

It is administered orally and usually used for essential or renovascular (hyperreninaemia) hypertension. It is frequently used in combination with β-blockers and diuretics, particularly in patients with renal dysfunction.

LABETALOL

Labetalol is specific competitive antagonist at α_1-, β_1- and β_2-adrenergic receptors. β-blockade effects predominate, with an approximate ratio of α_1:β-receptor blockade of 1:4–7. Labetalol has partial agonist effects on β_2-receptors.

It is administered intravenously (typically 10–50 mg), has a rapid onset of action (5–10 minutes) with a duration of 2–6 hours. It may be given by infusion (usually 15–180 mg/h).

Systemic blood pressure and cardiac output are reduced by a combination of negative inotropy, arterial and venous vasodilatation. Reflex tachycardia is attenuated by β-blockade. These properties make labetalol particularly useful in controlled hypotension during anaesthesia and surgery to reduce bleeding.

Side effects, such as bronchospasm and hyperkalaemia, relate predominantly to β-blockade.

CARVEDILOL

Carvedilol is a non-selective β-blocker with α_1-antagonist activity. Most of the vasodilator activity relates to α_1-antagonism, although at high concentrations it also blocks calcium entry. The ratio of α_1:β-receptor blockade is 1:10. It is administered orally; no intravenous preparation is available.

Studies have demonstrated the slowing of progression of congestive cardiac failure and improved mortality, particularly when used in conjunction with ACE inhibitors in patients with mild to moderate cardiac failure.[23,24] It may also be used in patients who cannot be treated with ACE inhibitors.

HALOPERIDOL AND CHLORPROMAZINE

These drugs act as competitive α-receptor antagonists causing non-selective vasodilatation and blockade of norepinephrine reuptake.

These drugs are primarily used as major tranquillisers or antipsychotics; their effect on the peripheral vasculature should be regarded as a side effect, rather than a specific therapeutic action.

Reduction of systemic blood pressure is variable and may be precipitous, particularly in hypovolaemic patients with high sympathetic drive. These drugs may be useful in neurogenic hypertension, and are not regarded as first-line vasodilators.

INODILATORS

Many inotropic drugs have peripheral vascular effects and these are discussed in more detail in Chapter 92.

At low doses, epinephrine, norepinephrine and dopamine are predominantly β-agonists and can cause both arterial and venous vasodilatation. The response depends on tissue receptor predominance and density. For example, in skeletal muscle, epinephrine causes vasodilation whereas in subcutaneous tissue it is a potent vasoconstrictor; it is for this reason that intramuscular epinephrine is administered in anaphylaxis (the skeletal muscle vasodilation causing rapid systemic absorption) whereas subcutaneous administration will result in little systemic effect.

Dobutamine and isoprenaline are predominantly β-agonists and may cause decreases in mean arterial pressure, particularly in hypovolaemic patients or those with increased sympathetic drive. These agents may have a role in reducing left ventricular afterload in patients with systolic heart failure.

Milrinone is a selective type III phosphodiesterase inhibitor that prevents the breakdown of cyclic adenosine monophosphate (cAMP) within cardiac and vascular tissues. The increased cAMP levels lead to increased levels of intracellular calcium and thus increased contraction of cardiac muscle. Within vascular smooth muscle the cAMP inhibits myosin light chain kinase producing less contraction and thus vascular relaxation.

Levosimendan is a newer calcium sensitiser that leads to a greater ventricular contraction for the same intracellular calcium concentration. It also leads to vasodilatation, mediated by activation of adenosine triphosphate (ATP)-sensitive sarcolemmal and mitochondrial potassium channels. The drug itself has a relatively short half-life, but it has a long-acting active metabolite so that haemodynamic effects may be maintained for up to 7 days.

Both milrinone and levosimendan can lead to marked hypotension, particularly if a bolus dose is given. Therefore in critically ill patients a loading dose is best avoided and any excessive vasodilation may need to be balanced by a low dose of a vasoconstrictor. Usual infusion rates of milrinone are 0.375–0.75 μg/kg/min and levosimendan 0.05–0.2 μg/kg/min.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

ACE inhibition has become a cornerstone in the management of patients with hypertension, cardiac failure and ischaemic heart disease.[25,26] They are now recommended as first-stage treatment for hypertension in Caucasian patients less than 55 years and patients with diabetic nephropathy.[8] These drugs act by non-selective, competitive, irreversible inhibition to the angiotensin I binding site thus reducing conversion to angiotensin II.

There are a very large number of ACE inhibitors on the market with very high penetration into the ambulant patient population. These drugs are administered orally; there are no routinely used parenteral preparations. Consequently, many critically ill patients admitted to the ICU may be taking ACE inhibitors. As a general rule, ACE inhibitors are stopped in most critically ill patients until vital organ (specifically renal) function is stabilised and the patient can take them enterally. Thereafter, doses are gradually increased over time with close monitoring of renal function.

PREPARATIONS

Captopril has a short half-life and therefore may be useful for initiating treatment within the ICU. It is administered orally in increasing doses and intervals to a maximum dose of 50 mg 8-hourly. It may be administered sublingually in acute hypertension (5–25 mg), with an onset of action in 20–30 minutes, and a duration of 4 hours. There are no significant differences in the cardiovascular effects between captopril and other preparations.

Enalapril is a prodrug, activated by hepatic metabolism to enalaprilat, producing a slower and more controlled action. It is administered orally in 5 mg increments to a total of 20 mg twice daily.

Lisinopril has the advantage of single daily dosing and may be useful in stable critically ill patients.

CARDIOVASCULAR EFFECTS

The cardiovascular effects of ACE inhibition are widespread, with effects that influence the peripheral vasculature, cardiac performance, and salt and water homeostasis. Consequently, ACE inhibitors are not principally regarded as vasodilators, although they have both direct and indirect effects on the peripheral vasculature.

Increased production of endothelial vasodilators, such as prostacyclin, and decreased production of endothelin by angiotensin result in generalised venous and arteriolar vasodilatation. This occurs in the absence of reflex sympathetic activity or changes in heart rate, due to the modulation of adrenergic stimulation. Systemic blood pressure is reduced without changes in cardiac output or heart rate.

ACE inhibition is associated with improved myocardial performance following acute myocardial infarction due to left ventricular remodelling and improvement in neurohumoral activation. These drugs have been shown to improve survival following myocardial infarction in patients with left ventricular dysfunction.[27]

'First-dose hypotension' is described in patients receiving ACE inhibitors for the first time. This may occur particularly in patients who are salt- and water-depleted, or those who develop sensitivity to the drug. Drug sensitivity may also present as a sudden decrease in renal function following commencement of the drug.

RENOVASCULAR EFFECTS

ACE inhibitors may cause renal failure, particularly in patients with renovascular disease, hyperreninaemic hypertension and acute kidney injury. The renal effects of ACE inhibitors may be potentiated by diuretics, non-steroidal anti-inflammatory drugs and β-blockers. ACE inhibitors are contraindicated in patients with bilateral renal artery stenosis.

As a rule in intensive care patients, ACE inhibitors are started in suitable patients once renal function has stabilised and the patient no longer requires inotropic support. Initial doses should be low and increased as tolerated.

SIDE EFFECTS AND TOXICITY

In addition to renal dysfunction, ACE inhibitors may be associated with a number of side effects. The most common of these is cough, which is due to the increased production of kinins.[28]

Severe angioneurotic oedema causing upper-airway obstruction may occur with all ACE inhibitors, although this is less common with enalapril and lisinopril. This is due to increased activation of bradykinins. ACE inhibitors are contraindicated in patients with a history of hereditary or idiopathic angioneurotic oedema.[29]

Neutropenia and agranulocytosis are uncommon but potentially lethal side effects in susceptible patients. ACE inhibitors should be avoided in pregnancy due to potential risk of foetal malformation and renal impairment.

ANGIOTENSIN RECEPTOR BLOCKERS

These are a class of antihypertensive drugs that cause irreversible, selective blockade of angiotensin II at AT_1 receptors.[30,31]

Losartan was the prototype, which has been followed by newer compounds such as irbesartan, valsartan and telmisartan. These drugs are oral preparations; there is no parenteral form.

The cardiovascular profile of angiotensin receptor blockers is similar to the ACE inhibitors, but selective blockade of angiotensin II offers several possible advantages over ACE inhibitors. These drugs are long acting and may be given once daily; onset of action is slow, thereby avoiding first-dose hypotension; and side effects, such as cough and angioneurotic oedema, are less common.[32] Angiotensin receptor blockers may be used as an alternative to ACE inhibitors but they should not be combined.[8]

CENTRALLY ACTING AGENTS

These agents modulate adrenergic stimulation at central nervous system and spinal cord level. The vasomotor centre of the medulla mainly controls sympathetic pressor influences, although other brainstem, midbrain and spinal centres have a role.

Most central responses are mediated through α_2-adrenergic receptors, which modulate the release and reuptake of norepinephrine, with subsequent effects on the peripheral vasculature and cardiac function.

CLONIDINE

Clonidine is a centrally acting α_2-agonist that stimulates inhibitory neurons in the vasomotor centre. This results in a reduction in sympathetic outflow from the central nervous system and is associated with negative inotropy and a reduction in heart rate. Systemic blood pressure is reduced by this mechanism, with associated arteriolar and venous vasodilatation. Clonidine has centrally acting analgesic properties, which make it a suitable drug in patients with postoperative hypertension.

Peripherally, it stimulates prejunctional α_2-receptors, thereby decreasing norepinephrine release, but may also have an effect at postjunctional α_1-receptors, causing vasoconstriction. This may present as rebound hypertension following an initial reduction of blood pressure as there is variable duration of the central and peripheral effects.

Clonidine can be administered orally (50–100 µg 8-hourly). It has a rapid onset of action and duration of action of 20–30 minutes.

METHYLDOPA

Methyldopa acts as a centrally acting 'false' transmitter following metabolism to methylnorepinephrine and subsequent stimulation of α_2-receptors leading to reduced sympathetic outflow, although the precise mechanism is not clear.

It has a limited role in hypertensive emergencies, but is useful in accelerated essential, renovascular and pregnancy-induced hypertension.

It is administered orally in doses of 250 mg to 3 g per day, although side effects (e.g. drowsiness and depression) may be minimised if the daily dose is less than 1 g. It may lead to a positive direct Coombs test in 10%–20% of patients.

OTHER ANTIHYPERTENSIVE AGENTS

BETA-ADRENERGIC ANTAGONISTS

β-blockers have been used for the treatment of hypertension for over 30 years and have an increasingly important role in the management of cardiac failure.[33–35] Although no longer recommended as first-step treatment of hypertension, they may be used if ACE inhibitors are poorly tolerated.[8]

In addition to decreasing heart rate and contractility, β-blockers have other neurohumoral effects that affect vascular tone. These relate to the inhibition of renin release from juxtaglomerular cells (see Fig. 93.1) and prejunctional inhibition of norepinephrine, which result in reduction in vascular tone and blood pressure. A central effect of β-blockers has also been proposed.

The mode of action has been described in terms of selectivity to blockade of β-adrenergic receptors (β_1 and/or β_2). While this is an appropriate pharmacological distinction, the clinical activity of these drugs is not as predictable due to mixed populations of β_1- and β_2-receptors in most organs and variable receptor responsiveness in physiological and pathophysiological conditions. Consequently, there is marked interindividual variability in the response to these drugs. In high-enough doses, whether intentionally or due to toxicity, all β-blockers will cause generalised antagonism with resultant therapeutic and toxic effects.

Lipid-soluble β-blockers include propranolol and metoprolol, which are predominantly excreted by the liver; atenolol and sotalol are water-soluble and predominantly renally excreted, warranting caution with these drugs in patients with renal dysfunction.

β-blockers may be given orally or intravenously. As there is significant first-pass metabolism, doses for oral and intravenous administration are markedly different.

Esmolol is an intravenous β-blocker that is rapidly metabolised by red cell esterases and is therefore not dependent on renal or hepatic function. Its rapid onset of action and short duration allow infusion of the drug, making it a useful drug in patients with acute hypertensive states associated with tachycardia. Labetalol and carvedilol are discussed above.

β-blockers are frequently used as adjuncts to vasodilators in the treatment of hypertensive emergencies and states, particularly where reflex tachycardia and sympathetic stimulation occur (e.g. hydralazine, nifedipine and prazosin).

Side effects and toxicity of β-blockers include bradycardia (which may be profound), hypotension, bronchoconstriction (caution in patients who have asthma), aggravation of peripheral vascular ischaemia, hyperkalaemia and masking of the sympathetic response to hypoglycaemia.

DIURETICS

As with β-blockers, diuretics have an established place in the management of hypertension. In addition to their effects on salt and water excretion and the inhibition of aldosterone, direct vasodilatory effects are associated with diuretics such as furosemide and the thiazides.

These drugs have a rapid venodilatory action, which may be due to inhibition of norepinephrine-activated chloride channels on veins. Reductions of blood pressure and right atrial pressure may occur following low doses, and may present before an associated diuresis.

All diuretics should be used with caution in patients with renal dysfunction and avoided if hypovolaemia is present or suspected.

PULMONARY VASODILATORS

Pulmonary vasodilators may be used in the ICU mainly to treat acute right-sided heart failure commonly after cardiac surgery/transplantation. Many of the systemic vasodilators (namely calcium channel blockers, sodium nitroprusside and nitrates) will also have vasodilatory effects within the pulmonary circulation. Specific pulmonary vasodilators may be inhaled or administered intravenously.

NITRIC OXIDE

NO is an endogenous vasodilator. When inhaled it leads to vasodilation in only the ventilated areas of the lung, and rapid combination with haemoglobin prevents systemic vasodilation. This may improve ventilation–perfusion mismatch resulting in an improved oxygenation but controlled trials have not demonstrated any beneficial effect on outcomes in severe acute lung injury and it may have an adverse effect on kidney function.[36] Its use is now mainly confined to the treatment of acute pulmonary hypertension post-cardiac surgery.

NO is oxidated to NO_2 particularly in a high-oxygen environment and therefore NO_2 levels should be carefully monitored. Similarly appropriate scavenging systems must be employed.

Rebound pulmonary hypertension may occur and so NO therapy should be slowly weaned rather than abruptly stopped.

PROSTACYCLIN

Inhaled epoprostenol or iloprost (a prostacyclin derivative) can be used as alternatives to NO, however, although some short-term benefit in oxygenation may be seen there is currently no evidence of improved outcomes with this therapy.[37] Care should be taken to avoid systemic hypotension.

SILDENAFIL

Sildenafil is a phosphodiesterase type 5 inhibitor used in the management of chronic pulmonary hypertension, as well as erectile dysfunction. There are reports of its use for acute pulmonary hypertension within the ICU where it can improve haemodynamics; however, by increasing shunt fraction it might worsen oxygenation when used in acute lung injury.[38]

BOSENTAN

Bosentan is a non-selective endothelin receptor antagonist. Its predominant use is in the treatment of type 1 pulmonary hypertension where it improves exercise capacity and delays clinical worsening. Currently, bosentan has no established role in critical care.

DRUG SELECTION

The clinical use of vasodilators in intensive care is different from their use in ambulatory patients. In the critically ill patient, these drugs are primarily used to control acute rises in mean arterial pressure associated with sympathetic stimulation, or as specific treatment of hypertensive emergencies.[39]

The ideal vasodilator is therefore one that has a rapid and predictable onset of action, allows titration to achieve a desired systemic blood pressure, does not compromise cardiac output, does not cause significant reflex tachycardia and is non-toxic.

The selection of drug to treat hypertensive states will depend on the predominant cause of hypertension and the mechanism of action in the homeostatic pathway (outlined in Fig. 93.1).

There are no large studies investigating optimum therapy in patients presenting with hypertensive emergencies. These conditions occur in a heterogeneous group of patients and drug selection is essentially determined by the underlying pathophysiology, personal preference and experience.[39]

MONITORING

The principles of haemodynamic monitoring in patients receiving vasoactive drugs are outlined in Chapter 92.

Patients with severe hypertension or those receiving infusions or doses of potent vasodilators such as sodium nitroprusside and glyceryl trinitrate must be monitored via an intra-arterial catheter. Non-invasive measurement devices are not rapid or accurate enough and are not recommended in patients with hypertensive emergencies.

As peripheral vasodilators have significant effects on both the arterial and venous systems, the assessment of volume status is important. In the majority of patients, establishing a euvolaemic state is essential before commencing a vasodilator.

DOSAGES AND DRUG ADMINISTRATION

Vasodilators administered via infusion are delivered through a dedicated central venous catheter using infusion pumps or syringe drivers, and are titrated to achieve a target mean arterial pressure. Infusion lines should be free of injection portals and clearly marked with identifying labels. Common drug doses are shown in Table 93.1.

SPECIFIC SITUATIONS

The following is a summary of the clinical uses of the above drugs in hypertensive states commonly encountered in the ICU. Specific pharmacology and physiological effects are discussed above.

Table 93.1 Dose and infusion concentrations of commonly used vasodilators and antihypertensives in intensive care

AGENT	INFUSION/DOSE	CAUTION
Sodium nitroprusside	Diluted in 5% dextrose; range 0.5–8 µg/kg/min	Cyanide toxicity (> total dose 0.5 mg/kg/24 h) Photodegradation Raised intracranial pressure Rebound hypotension Shunt and oxygen desaturation
Glyceryl trinitrate	Diluted in 5% dextrose or 0.9% sodium chloride; range 5–200 µg/min	Drug binding to polyvinylchloride Tachyphylaxis Raised intracranial pressure
Hydralazine	5–10 mg IV bolus IV infusion 50–150 µg/min	Tachycardia Myocardial ischaemia
Phentolamine	1–5 mg IV boluses	Tachycardia
Phenoxybenzamine	Oral: 10 mg/day until postural hypotension	Idiosyncratic hypotension
Prazosin	500 µg, 8-hourly up to 20 mg daily in divided doses	
Nifedipine	Dose depends on preparation	Precipitous hypotension
Amlodipine	5–10 mg oral/day	
Captopril	6.25–75 mg orally, 12-hourly	Caution in renovascular hypertension and renal failure Pregnancy Angioneurotic oedema
Enalapril	5–40 mg oral/day	Caution in renal failure and hypovolaemia
Losartan	25–100 mg oral/day	Caution in renal failure
Clonidine	50–100 µg 8-hourly	May cause rebound hypertension with chronic use
Atenolol	25–50 mg oral b.d.	Caution in poor left ventricular function and asthma Hyperkalaemia Effects potentiated in renal failure
Metoprolol	50–100 mg oral 12-hourly	As for atenolol, safe in renal failure
Esmolol	50–200 µg/kg/min infusion	
Labetalol	15–160 mg/h	

IV, Intravenous.

ACUTE HYPERTENSION

The most common cause of hypertension in intensive care patients is pain or agitation, particularly in postoperative patients. It is important that patients have adequate analgesia and sedation before antihypertensives or vasodilators are used. Other common causes of hypertension include hypothermia, urinary retention, positional discomfort and omission of preadmission antihypertensives, particularly β-blockers and ACE inhibitors. The majority of instances of acute hypertension in the ICU will respond to simple measures.[40]

Sustained hypertension may be treated acutely with incremental doses or infusions of short-acting drugs such as glyceryl trinitrate, sodium nitroprusside, labetalol, hydralazine, nicardipine or clonidine. Infusions of vasodilators may be required if hypertension persists, or if the patient is unable to take longer-acting oral agents such as prazosin or amlodipine. Hypertension associated with tachycardia may be treated with β-blockers.

A hypertensive emergency is an acute rise in blood pressure, usually greater than 180 mm Hg systolic or greater than 120 mm Hg diastolic, which is associated with signs of end-organ damage. Commonly affected organs include the brain (seizures, hypertensive encephalopathy), heart (pulmonary oedema and acute coronary syndromes), kidney, great vessels (aortic dissection) and retina (papiloedema and retinal haemorrhages). In hypertensive emergencies a priority is the rapid control of blood pressure over minutes to hours. Alternatively, a hypertensive urgency is a similar level

of elevation in blood pressure with no evidence of end-organ dysfunction. In this situation blood pressure reduction is less urgent and may be achieved over hours to days.

HYPERTENSIVE ENCEPHALOPATHY

Hypertensive encephalopathy is the presence of signs arising from cerebral oedema caused by a rapidly changed or a severely elevated blood pressure. There may be differences in the degree of hypertension that cause encephalopathy and it may be the rate of increase of blood pressure that is more important than the absolute value. It may present as confusion, visual disturbances, blindness, seizures or stroke. Uncontrolled hypertension is one of the causes of the posterior reversible encephalopathy syndrome (PRES), along with pre-eclampsia, immunosuppressant drugs and sepsis. If not adequately treated, hypertensive encephalopathy may result in intracerebral haemorrhage, coma or death.[41]

Hypertensive encephalopathy may occur in patients with untreated or undertreated hypertension or in association with other diseases such as renal disease (e.g. glomerulonephritis, renovascular disease), thrombotic thrombocytopenic purpura, immunosuppressive therapy, collagen vascular diseases or eclampsia. Consequently, drug treatment will depend on the context in which it occurs. It is also important to rule out other causes of neurological deterioration that may also present with hypertension (e.g. stroke, intracranial haemorrhage or space-occupying lesion).

There is no evidence from randomised, controlled trials to conclude that one therapy is superior to another at improving outcomes. The aim of drug therapy in these patients is to reduce blood pressure in a controlled, predictable and safe way. A blood pressure reduction of 10%–15% in the first hour may be adequate to improve symptoms,[42] and a controlled reduction of less than 25% in the first hours should be a goal.[43] Acutely, short-acting, titratable parenteral drugs are suitable in emergency situations. Assuming there are no absolute contraindications to β-blockers, labetalol and esmolol are ideal drugs to use. Sodium nitroprusside can be used, although it may increase intracranial pressure and reduce cerebral blood flow.[9]

Other agents that are useful in controlling severe hypertension include hydralazine, clonidine and ACE inhibitors (although these must be used cautiously in patients with associated renal dysfunction). Severe drops in blood pressure that might compromise end-organ perfusion have been reported after the use of nifedipine; therefore its use in the emergency setting is not recommended.[9] Combination therapy is often required, although this should be done with caution to minimise additive effects with resultant hypotension.

Patients with hypertensive emergencies are frequently hypovolaemic due to excessive sympathetic stimulation. In the absence of left ventricular failure, judicious fluid replacement may reduce blood pressure and improve renal function, thereby minimising precipitous hypotension that may result following the administration of some drugs. Diuretics are generally avoided in these conditions unless there is evidence of left ventricular failure.[42]

ACUTE STROKE

Acute stroke syndromes frequently occur in the setting of severe hypertension. The reduction of mean arterial pressure must be balanced by the maintenance of adequate cerebral perfusion pressure and cerebral blood flow. Ischaemic brain is vulnerable to critical reductions in cerebral blood flow, while excessive mean arterial pressure may increase the risk of cerebral haemorrhage.[44]

Acutely, blood pressure should be maintained in a normal range until intracranial pathology has been identified by computed tomography scan. Evidence is currently lacking regarding specific targets for blood pressure control in acute stroke. In intracranial haemorrhage intracranial pressure monitoring may be necessary to allow blood pressure to be targeted at maintaining cerebral perfusion pressure; however, if presenting systolic pressure is 150–220 mm Hg reduction to 140 mm Hg is probably safe.[45,46] In acute ischaemic stroke special attention needs to be paid to patients who may be eligible for thrombolysis. In these patients treatment is recommended to reduce systolic blood pressure to less than 185 mm Hg and diastolic pressure to less than 110 mm Hg prior to thrombolysis.[46] In those who do not meet the criteria for thrombolysis guidelines recommend blood pressure reduction only in cases where hypertension is extreme such as systolic blood pressure less than 220 mm Hg or diastolic blood pressure less than 120 mm Hg. Where acute blood pressure reduction is necessary intravenous agents are recommended and current guidelines suggest the use of labetalol or nicardipine.[47] Hypertension in patients with aneurysmal subarachnoid haemorrhage is managed with drugs outlined above.

AORTIC DISSECTION

Aortic dissection is the most dramatic and most rapidly fatal complication of severe hypertension. The aim of medical treatment is to control blood pressure and left ventricular ejection velocity to minimise propagation of the dissection. Blood pressure should be decreased as rapidly as possible to a normal or slightly hypotensive level. Titrations are usually made to achieve systolic blood pressures of 100–120 mm Hg or mean arterial pressure of 55–65 mm Hg with a heart rate

of 60 bpm.[48,49] This will depend on the patient's premorbid blood pressure and the accuracy of blood pressure measurement. It is important to maintain blood pressure at levels compatible with adequate cerebral and renal perfusion.[50]

This is best achieved initially by the use of opioid analgesia and intravenous β-blockers (e.g. esmolol, labetalol or atenolol). Verapamil or diltiazem are suitable alternatives for patients who have a contraindication to β-blockade. Second-line therapy may be with a vasodilator such as sodium nitroprusside or glyceryl trinitrate. However, the use of vasodilators alone should be avoided as this is associated with worsening aortic wall shear stresses and potential worsening of the dissection.

Aortic dissection distal to the left subclavian artery is managed conservatively with antihypertensive therapy. Proximal dissections are managed surgically after acute control of blood pressure.

ACUTE MYOCARDIAL ISCHAEMIA

Myocardial ischaemia in the absence of obstructive coronary atherosclerosis may be precipitated by severe hypertension. This occurs by increased left ventricular wall stress, reduced preload, tachycardia and increased myocardial metabolic demand. Severe ischaemia may result in acute left ventricular failure and pulmonary oedema. These patients should receive a loop diuretic in combination with a titrated vasodilator, such as intravenous glyceryl trinitrate or sodium nitroprusside, to reduce afterload.

PHAEOCHROMOCYTOMA

Tumours of the adrenal medulla secrete catecholamines that result in initial paroxysmal, then sustained, severe hypertension. They may present to the ICU as a hypertensive emergency or perioperatively for surgical ablation.[51]

Acute hypertensive crises associated with phaeochromocytoma are managed with incremental doses or infusions of phentolamine. Untreated patients may be significantly hypovolaemic and may require judicious volume replacement. β-blockers should not be used in the acute setting as these will potentiate unopposed α-adrenergic stimulation.

There is currently no universally accepted method for preparing these patients for surgery.[52] Approaches used may involve α-blockade and β-blockade, or the use of calcium channel antagonists and metyrosine.

Generally, the α-blocking agent phenoxybenzamine is commenced in 10–20 mg increments and continued until blood pressure is controlled. Excessive β-adrenergic effects are treated with β-blockers only after sufficient α-blockade to avoid unopposed α-adrenoreceptor-mediated vasoconstriction and hypertension.[22]

Calcium channel antagonists can also be utilised to facilitate α-blockade,[53,54] and nicardipine has been used in this setting. The exact role of calcium channel antagonists in this context is yet to be fully elucidated but may be to further supplement the effect of α- and β-blockers.

Metyrosine inhibits catecholamine synthesis and may be used as a short-course therapy in the days leading up to surgery. Magnesium sulphate is useful in the perioperative management of phaeochromocytoma. It is given by infusion at 2–4 g/h.[15]

RENAL FAILURE

Renal insufficiency may be a cause or consequence of a hypertensive emergency. Patients on haemodialysis (particularly those receiving erythropoietin therapy) and renal transplant patients (especially those receiving ciclosporin or corticosteroids) commonly present with severe hypertension. In patients with new-onset renal failure accompanying severe hypertension, blood pressure must be controlled without potentiating renal dysfunction. Drugs, such as calcium channel blockers, phentolamine or prazosin, may preserve renal blood flow and are appropriate in these patients. ACE inhibitors and diuretics should be used with caution until renal function has stabilised or improved.

Patients in the recovery phase of acute renal failure are usually hypertensive. This is a normal physiological response and should not be treated unless there is associated myocardial or cerebral ischaemia.[55]

PRE-ECLAMPSIA AND ECLAMPSIA

In addition to delivery of the baby and the placenta, parenteral magnesium sulphate is the treatment of choice to prevent the evolution of pre-eclampsia to eclampsia (seizures and deteriorating encephalopathy).[13] The recommended drugs for the treatment of severe hypertension in critically ill women during pregnancy or soon after birth include labetalol, hydralazine and nifedipine.[56,57]

ACE inhibitors and angiotensin receptor blockers are contraindicated in pregnancy. This is discussed in Chapter 64.

DRUG INTERACTIONS

Severe rebound hypertension may result following abrupt cessation of antihypertensive treatment. Drugs associated with this discontinuation syndrome include clonidine, methyldopa, β-blockers, guanethidine and diuretics. The degree of rebound depends on the rapidity of drug withdrawal, dosage, renovascular and cardiac function. Antihypertensives should be reintroduced according to the status of the patient,

and the degree of hypertension should be managed accordingly.

Interaction between monoamine oxidase inhibitors, other drugs (e.g. indirect sympathomimetics and narcotics) and tyramine-containing foods may result in a hypertensive emergency. This is best managed acutely with α- and/or β-blockers.

REFERENCES

1. Erdmann E. The management of heart failure – an overview. *Basic Res Cardiol*. 2000;95(suppl 1):I3–I7. [Epub 2001/02/24].
2. Metra M, Teerlink JR. Heart failure. *Lancet*. 2017;390(10106):1981–1995. [Epub 2017/05/04].
3. Cohn JN. Left ventricle and arteries: structure, function, hormones, and disease. *Hypertension*. 2001;37(2 Pt 2):346–349. [Epub 2001/03/07].
4. Spieker LE, Flammer AJ, Lüscher TF. The vascular endothelium in hypertension. *Handb Exp Pharmacol*. 2006;176(Pt 2):249–283. [Epub 2006/09/27].
5. Egan K, FitzGerald GA. Eicosanoids and the vascular endothelium. *Handb ExpPharmacol*. 2006;176(Pt 1): 189–211. [Epub 2006/09/27].
6. Magder S, De Varennes B. Clinical death and the measurement of stressed vascular volume. *Crit Care Med*. 1998;26(6):1061–1064. [Epub 1998/07/11].
7. Schulman IH, Zachariah M, Raij L. Calcium channel blockers, endothelial dysfunction, and combination therapy. *Aging Clin Exp Res*. 2005;17(4 suppl): 40–45. [Epub 2006/04/28].
8. National Institute for Health and Clinical Excellence. *Hypertesnion – The Clinical Management of Primary Hypertension. Online*. 2011;http://guidance.nice.org.uk/CG127.
9. Marik PE, Varon J. Hypertensive crises: challenges and management. *Chest*. 2007;131(6):1949–1962. [Epub 2007/06/15].
10. Rinkel GJ, Feigin VL, Algra A, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev*. 2005;(1):CD000277, [Epub 2005/01/28].
11. Zanchetti A, Julius S, Kjeldsen S, et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: an analysis of findings from the VALUE trial. *J Hyperten*. 2006;24(11):2163–2168. [Epub 2006/10/21].
12. De Cicco M, Macor F, Robieux I, et al. Pharmacokinetic and pharmacodynamic effects of high-dose continuous intravenous verapamil infusion: clinical experience in the intensive care unit. *Crit Care Med*. 1999;27(2):332–339. [Epub 1999/03/13].
13. Saris NE, Mervaala E, Karppanen H, et al. Magnesium. An update on physiological, clinical and analytical aspects. *Clin Chim Acta*. 2000;294(1–2): 1–26. [Epub 2000/03/23].
14. Altman D, Carroli G, Duley L, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet*. 2002;359(9321):1877–1890. [Epub 2002/06/12].
15. James MF, Cronjé L. Pheochromocytoma crisis: the use of magnesium sulfate. *Anesth Analg*. 2004;99(3): 680–686. [Epub 2004/08/31]; table of contents.
16. Thwaites CL, Yen LM, Loan HT, et al. Magnesium sulphate for treatment of severe tetanus: a randomised controlled trial. *Lancet*. 2006;368(9545):1436–1443. [Epub 2006/10/24].
17. Dorhout Mees SM, Algra A, Vandertop WP, et al. Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial. *Lancet*. 2012;380(9836):44–49. [Epub 2012/05/29].
18. Vassalle C, Domenici C, Lubrano V, et al. Interaction between nitric oxide and cyclooxygenase pathways in endothelial cells. *J Vasc Res*. 2003;40(5):491–499. [Epub 2003/10/30].
19. Alaniz C, Watts B. Monitoring cyanide toxicity in patients receiving nitroprusside therapy. *Ann Pharmacother*. 2005;39(2):388–389. [Epub 2005/01/13].
20. Spronk PE, Ince C, Gardien MJ, et al. Nitroglycerin in septic shock after intravascular volume resuscitation. *Lancet*. 2002;360(9343):1395–1396. [Epub 2002/11/09].
21. Ferdinand KC. Isosorbide dinitrate and hydralazine hydrochloride: a review of efficacy and safety. *Expert Rev Cardiovasc Ther*. 2005;3(6):993–1001. [Epub 2005/11/19].
22. Prys-Roberts C. Phaeochromocytoma – recent progress in its management. *Br J Anaesth*. 2000; 85(1):44–57. [Epub 2000/08/06].
23. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344(22):1651–1658. [Epub 2001/06/02].
24. Kopecky SL. Effect of beta blockers, particularly carvedilol, on reducing the risk of events after acute myocardial infarction. *Am J Cardiol*. 2006;98(8):1115–1119. [Epub 2006/10/10].
25. Stone PH. Review: ACE inhibitors reduce mortality and cardiovascular endpoints in stable coronary artery disease. *ACP J Club*. 2006;145(2):32. [Epub 2006/09/02].
26. Remuzzi G, Ruggenenti P. Overview of randomised trials of ACE inhibitors. *Lancet*. 2006;368(9535): 555–556. [Epub 2006/08/15].
27. Nickenig G, Ostergren J, Struijker-Boudier H. Clinical evidence for the cardiovascular benefits of angiotensin receptor blockers. *J Renin Angiotensin Aldosterone Sys*. 2006;7(suppl 1):S1–S7. [Epub 2006/09/14].
28. Dicpinigaitis PV. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(1 suppl): 169S–173S. [Epub 2006/01/24].
29. Beltrami L, Zingale LC, Carugo S, et al. Angiotensin-converting enzyme inhibitor-related angioedema: how to deal with it. *Expert Opin Drug Saf*. 2006;5(5):643–649. [Epub 2006/08/16].

30. See S. Angiotensin II receptor blockers for the treatment of hypertension. *Expert Opin Pharmacother*. 2001;2(11):1795–1804. [Epub 2002/02/05].
31. Bhatia V, Bhatia R, Mathew B. Angiotensin receptor blockers in congestive heart failure: evidence, concerns, and controversies. *Cardiol Rev*. 2005;13(6):297–303. [Epub 2005/10/19].
32. Cooper ME, Webb RL, de Gasparo M. Angiotensin receptor blockers and the kidney: possible advantages over ACE inhibition? *Cardiovasc Drug Rev*. 2001;19(1):75–86. [Epub 2001/04/21].
33. Krum H. Guidelines for management of patients with chronic heart failure in Australia. *Med J Aus*. 2001;174(9):459–466. [Epub 2001/06/02].
34. Packer M. Current role of beta-adrenergic blockers in the management of chronic heart failure. *Am J Med*. 2001;110(suppl 7A):81S–94S. [Epub 2001/05/04].
35. Gheorghiade M, Eichhorn EJ. Practical aspects of using beta-adrenergic blockade in systolic heart failure. *Am J Med*. 2001;110(suppl 7A):68S–73S. [Epub 2001/05/04].
36. Adhikari NK, Burns KE, Friedrich JO, et al. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. *BMJ*. 2007;334(7597):779. [Epub 2007/03/27].
37. Dzierba AL, Abel EE, Buckley MS, et al. A review of inhaled nitric oxide and aerosolized epoprostenol in acute lung injury or acute respiratory distress syndrome. *Pharmacotherapy*. 2014;34(3):279–290. [Epub 2014/04/16].
38. Cornet AD, Hofstra JJ, Swart EL, et al. Sildenafil attenuates pulmonary arterial pressure but does not improve oxygenation during ARDS. *Intensive Care Med*. 2010;36(5):758–764. [Epub 2010/02/05].
39. Moser M, Izzo JL Jr, Bisognano J. Hypertensive emergencies. *J Clin Hypertens (Greenwich)*. 2006;8(4):275–281. [Epub 2006/04/06].
40. Slama M, Modeliar SS. Hypertension in the intensive care unit. *Curr Opin Cardiol*. 2006;21(4):279–287. [Epub 2006/06/07].
41. Mabie WC. Management of acute severe hypertension and encephalopathy. *Clin Obstet Gynecol*. 1999;42(3):519–531. [Epub 1999/08/19].
42. Vaughan CJ, Delanty N. Hypertensive emergencies. *Lancet*. 2000;356(9227):411–417. [Epub 2000/09/06].
43. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34(28):2159–2219. [Epub 2013/06/19].
44. Sokol SI, Kapoor JR, Foody JM. Blood pressure reduction in the primary and secondary prevention of stroke. *Curr Vasc Pharmacol*. 2006;4(2):155–160. [Epub 2006/04/14].
45. Morgenstern LB, Hemphill JC 3rd, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2010;41(9):2108–2129. [Epub 2010/07/24].
46. Royal College of Physicians. *National Clinical Guideline for Stroke. Online*. 2016:Available: https://www.rcplondon.ac.uk/guidelines-policy/stroke-guidelines.
47. Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(3):870–947. [Epub 2013/02/02].
48. Morris JH, Mix D, Cameron SJ. Acute aortic syndromes: update in current medical management. *Curr Treat Options Cardiovasc Med*. 2017;19(4):29. [Epub 2017/03/24].
49. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *J Am Coll Cardiol*. 2010;55(14):e27–e129. [Epub 2010/04/03].
50. Ahmad F, Cheshire N, Hamady M. Acute aortic syndrome: pathology and therapeutic strategies. *Postgrad Med J*. 2006;82(967):305–312. [Epub 2006/05/09].
51. Graham GW, Unger BP, Coursin DB. Perioperative management of selected endocrine disorders. *Int Anesthesiol Clin*. 2000;38(4):31–67. [Epub 2000/12/02].
52. Tauzin-Fin P, Sesay M, Gosse P, et al. Effects of perioperative alpha1 block on haemodynamic control during laparoscopic surgery for phaeochromocytoma. *Br J Anaesth*. 2004;92(4):512–517. [Epub 2004/02/10].
53. Ulchaker JC, Goldfarb DA, Bravo EL, et al. Successful outcomes in pheochromocytoma surgery in the modern era. *J Urol*. 1999;161(3):764–767. [Epub 1999/02/18].
54. Lebuffe G, Dosseh ED, Tek G, et al. The effect of calcium channel blockers on outcome following the surgical treatment of phaeochromocytomas and paragangliomas. *Anaesthesia*. 2005;60(5):439–444. [Epub 2005/04/12].
55. Palmer BF. Impaired renal autoregulation: implications for the genesis of hypertension and hypertension-induced renal injury. *Am J Med Sci*. 2001;321(6):388–400. [Epub 2001/06/22].

56. Committee on Obstetric Practice. Committee Opinion No. 692: emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period. *Obstet Gynecol*. 2017; 129(4):e90–e95. [Epub 2017/03/24].

57. National Collaborating Centre for Women's and Children's Health. *Hypertension in pregnancy – the management of hypertensive disorders in pregnancy. Online*. 2011:Available: http://guidance.nice.org.uk/CG107.

This page intentionally left blank

Part Fourteen

Metabolic Homeostasis

This page intentionally left blank

94

Acid–base balance and disorders

Thomas J Morgan

WATER

Water is both solvent medium and active participant in acid–base molecular transactions. At 55.5 M, its concentration dwarfs that of all other players.

WATER DISSOCIATION

Although a major oversimplification, it is useful to model water dissociation as follows:

$$H_2O \leftrightarrow H^+ + OH^-$$

By the Law of Mass Action, at equilibrium $[H^+][OH^-] = Kw\,[H_2O]$, where Kw is the temperature-dependent dissociation constant. The quantitative dominance of $[H_2O]$ allows amalgamation of Kw and $[H_2O]$ as a composite constant K'w. The equilibrium then simplifies further to:

$$[H^+][OH^-] = K'w$$

pH AND ACID–BASE NEUTRALITY

The acidity or alkalinity of aqueous solutions is represented by the pH, which is the negative logarithm of the proton concentration, or more exactly 'activity'. By the Arrhenius definition, neutrality occurs when $[H^+] = [OH^-]$, so that $K'w = ([H^+])^2$ and $pH = 0.5\ pK'w$. Neutral pH at 37°C is 6.8, approximating intracellular pH. The pH in the surrounding extracellular fluid is alkaline, usually exceeding 7.3.

CO_2 PRODUCTION AND ELIMINATION

CO_2 is generated within mitochondria at approximately 200 mL/min and flows down a series of partial pressure gradients to the atmosphere ($P_{CO_2} = 0.3$ mm Hg). The P_{CO_2} in individual tissues is determined by regional CO_2 production, regional blood flow, alveolar perfusion and alveolar ventilation. Typical cell to atmosphere driving pressures are relatively low ($\Delta P_{CO_2} \approx 50$ mm Hg) for several reasons:

- Densely invested tissue microcirculations
- Widespread distribution of carbonic anhydrase, massively accelerating dissolved CO_2/bicarbonate transitions
- Haldane and Hamburger effects, enhancing venous CO_2 transport
- A large continually refreshed interface between pulmonary capillaries and alveolar gas.

In transit to the lungs, CO_2 equilibrates with a series of aqueous environments. All pH values generated *en route* can be computed from the regional PCO_2 plus the concentrations of certain weak acids and electrolytes (see later).

The relationship between arterial P_{CO_2} ($PaCO_2$) and the pH it generates in arterial plasma is a fundamental physiological property of great interest to clinicians (Fig. 94.1). It is frequently disturbed in critical illness.

FACTORS DETERMINING THE $PaCO_2$/pH RELATIONSHIP

The six equations which underpin Peter Stewart's physical chemical analysis of acid–base (Box 94.1) are expressions of the Laws of Mass Action and Mass Conservation and the Principle of Electrical Neutrality.[1] In combination with Gibbs–Donnan effects, they dictate the shape and position of the in vivo $PaCO_2$/pH curve.

Stewart demonstrated that the pH generated by CO_2 in any body fluid can be determined from its partial pressure plus the values of two other independent variables:

1. The total concentration of 'non-volatile' weak acids (A_{tot}), whose acid characteristics arise from variable net negative molecular charges. Protein, the dominant plasma component, has an estimated titratable negative charge of 12–13 mEq/L,[2] mostly from albumin histidine moieties.[3] The normal plasma A_{tot} of approximately 15 mEq/L includes a contribution from inorganic phosphate. Erythrocytic A_{tot} is approximately 60 mEq/L. Haemoglobin is the dominant contributor, with an increment from 2,3 diphosphoglycerate.
2. The strong ion difference (SID), which is the net charge of inorganic and organic chemical entities remaining fully ionised (or quantitatively so) at pH values compatible with life. Strong ions include the cations sodium, potassium, calcium and magnesium and the anions chloride, lactate, acetoacetate and β-hydroxybutyrate. Normal plasma SID

ABSTRACT

The relationship between the partial pressure of carbon dioxide and the pH it generates in biological fluids is fundamental to acid–base diagnosis. In arterial plasma the $PaCO_2$/pH relationship provides a diagnostic framework for primary acid–base disorders and the rules of compensation. Stewart's six equations plus Gibbs–Donnan phenomena define this relationship and allow insights into the Copenhagen and Boston approaches to categorising and quantifying metabolic acid–base abnormalities. Electrical and osmotic gap calculations plus occasional specific assays are necessary adjuncts to complete diagnosis.

KEYWORDS

Acidosis
alkalosis
standard base excess
metabolic
respiratory
Stewart
strong ions

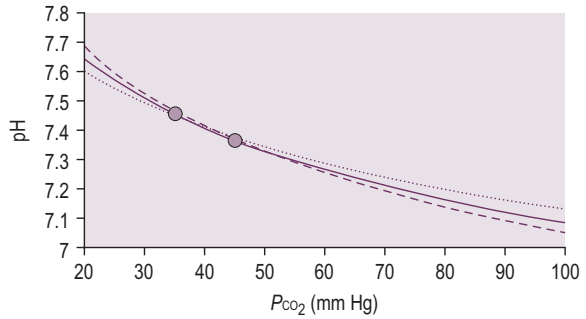


Figure 94.1 P_{CO_2}/pH relationships. The *solid line* shows the normal in vivo $PaCO_2$/pH relationship. The normal $PaCO_2$ range is between the *filled circles*. To the left of the circles there is an increasing acute respiratory alkalosis and to the right an increasing acute respiratory acidosis. The *interrupted curve* represents the normal in vitro whole blood relationship, and the *dotted curve* is the same relationship for separated plasma. A point of commonality exists at P_{CO_2} = 40 mm Hg.

Box 94.1 Stewart's six equations

$[H^+] \times [OH^-] = K'w$
$[H^+] \times [A^-] = Ka \times HA$
$[HA] + [A^-] = A_{tot}$
$[H^+] \times [HCO_3^-] = Kc \times P_{CO_2}$
$[H^+] \times [CO_3^{2-}] = Kd \times [HCO_3^-]$
$SID + [H^+] - [HCO_3^-] - [CO_3^{2-}] - [A^-] - [OH^-] = 0$

K values are known dissociation constants. See text for descriptions of SID, A_{tot} and K'w. The equations can be expressed as a single fourth order polynomial.

is +42 mEq/L. Erythrocyte SID is approximately +57 mEq/L.

ISOLATED CHANGES IN STRONG ION DIFFERENCE AND A_{tot}

A falling SID or a rising A_{tot} reduce pH, forcing equilibria towards metabolic acidosis. Conversely, a rising SID or a falling A_{tot} promote metabolic alkalosis.

SEVERAL STEWART MODEL CAVEATS

- The Stewart approach is a reductionist mathematical analysis. It is not a complete mechanistic breakdown of acid–base physical chemistry.[4] Nevertheless, its concepts provide insights into the physiological basis of Boston and Copenhagen diagnostic 'schools'[5] and serve as a research framework.[6]
- By modelling separated plasma, Stewart disregarded in vivo Gibbs–Donnan ionic traffic within the interstitium–plasma–erythrocyte (IPE) complex.[7] These phenomena cause plasma SID to vary with P_{CO_2}. Predictions of the in vivo dependence of plasma SID on P_{CO_2}[8] have been confirmed by measurements during cardiopulmonary bypass.[9] However, the SID of the overall IPE complex (SID_{IPE})[7] can still be modelled as CO_2 independent.
- The in vivo $PaCO_2$/pH relationship is thus more correctly a function of SID_{IPE} and A_{totIPE}.
- Stewart ignored the 'polyprotic' nature of individual proteins and phosphate by modelling all non-volatile weak acids in each compartment with a single anionic form (A^-), a single conjugate base form (HA) and a universal K_A value. More detailed modelling[2,3] is yet to improve on his original equations as descriptors of the ex vivo plasma P_{CO_2}/pH relationship.[10]
- Siggaard-Andersen[11] and others[12] reject the Stewart model out of hand, despite its utility. They emphasise the 'bystander' status of strong ions and regard SID as a convenient inverse quantification of the 'buffer base', defined as the total concentration of bicarbonate and non-bicarbonate 'buffers'. They assign all molecular acid–base transactions to the buffer base, with excited state water bridges providing intermolecular conduits for proton exchange.[13]

HOW ACID–BASE DISTURBANCES AFFECT THE $PaCO_2$/pH RELATIONSHIP

- Acute respiratory disturbances are primary alterations in $PaCO_2$ which move data points along the acute $PaCO_2$/pH curve without shifting it. Movement is to the left in respiratory alkalosis and to the right in respiratory acidosis (see Fig. 94.1).
- Metabolic disturbances (altered SID and/or A_{tot}) shift the entire curve. The shift is up in metabolic alkalosis and down in metabolic acidosis (Fig. 94.2).

TEMPERATURE CORRECTION OF BLOOD GAS DATA – 'ALPHA-STAT' VERSUS 'pH-STAT' APPROACHES

Blood gas analysers measure exclusively at 37°C. Temperature 'correction' is a software manipulation of plasma pH and gas tension measurements to values that correspond to the patient's core temperature. Advocates of the 'pH-stat' approach monitor these temperature-corrected pH and $PaCO_2$ values, whereas 'alpha-stat' enthusiasts track uncorrected values as measured at 37°C. Both manage patients according to normothermic reference ranges.

The pH-stat approach has similarities to the endothermic physiology of hibernating mammals, whereas the alpha-stat approach mimics the physiology of ectothermic (cold-blooded) animals. Many intensivists

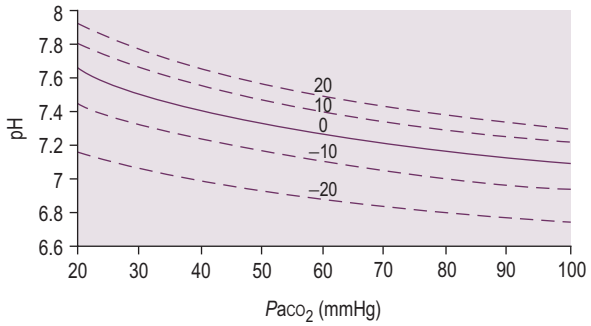


Figure 94.2 $PaCO_2$/pH curve shifts and associated standard base excess (SBE) values (mEq/L). Alterations in metabolic acid–base status shift the curve down in metabolic acidosis (SBE increasingly negative) or up in metabolic alkalosis (SBE increasingly positive).

have adopted the alpha-stat approach, the rationale of which is as follows:

- 'Alpha' is the ratio of protonated to total imidazole on histidine moieties in protein molecules. A value of 0.55 is considered best for intracellular enzyme function.
- Healthy normothermic acid–base status ($PaCO_2$ = 40 mm Hg, arterial plasma pH = 7.4) implies a neutral intracellular pH of 6.8.
- However, neutral pH varies with temperature. For example, at room temperature neutral pH = 7.0.
- Keeping intracellular pH neutral at any temperature maintains alpha at 0.55, due to temperature induced changes in imidazole dissociation. It also facilitates intracellular 'trapping' of metabolic intermediates.
- The alpha-stat goal is therefore to maintain intracellular pH neutrality at any core temperature.
- In alpha-stat theory, this goal is achieved provided $PaCO_2$ and arterial pH measured at 37°C are maintained within normothermic reference ranges.
- This is due to simultaneous alterations in K'w and CO_2 solubility as blood temperature resets to 37°C in the analyser thermostat.
- Although most commonly applied in induced hypothermia, similar arguments apply in fever, the usual intensive care unit scenario.

The main practical difference between the methods is that the pH-stat approach necessitates higher $PaCO_2$ values in hypothermia and lower values in fever. Clinical evidence for either approach is limited, with neither clearly superior.

RENAL PARTICIPATION IN ACID–BASE

Conventional descriptions of renal acid–base handling are framed in terms of filtered HCO_3^- resorption, new HCO_3^- generation and proton excretion. Proton excretion is facilitated by titration of urinary buffers at low pH, especially the $HPO_4^{2-}/H_2PO_4^-$ system (titratable acidity), and by upregulation of distal tubular NH_3 production to facilitate luminal proton 'trapping' as NH_4^+.[14]

The physical chemical explanation is simpler. $[H^+]$ and $[HCO_3^-]$ balance sheets cannot apply because these dependent variables increase and decrease according to PCO_2, SID and A_{tot}. Feedback loops acting through tubular ionophores simply modulate extracellular SID via urinary SID.[4,15,16] Upregulation or downregulation of NH_3 production ensures sufficient NH_4^+ for variable insertion as a urinary substitute for the strong cation Na^+.[17,18] Responses are rapid.[19] Unless there is proteinuria, the kidneys can modify A_{tot} only via phosphate balance, which is a different concept from that of 'titratable acidity'.

ACID–BASE ASSESSMENT

By convention acid–base disorders are categorised as respiratory ($PaCO_2$) or metabolic (non – $PaCO_2$). $PaCO_2$ is the undisputed index of respiratory acid–base status. Two 'schools', Boston and Copenhagen,[20] have formed around the identification and quantification of metabolic acid–base disturbances.

QUANTIFYING METABOLIC ACID–BASE STATUS – THE TWO 'SCHOOLS'

Standard base excess (SBE) is the Copenhagen flagship.[11] SBE integrates SID_{IPE} and A_{totIPE} effects on plasma pH while remaining independent of $PaCO_2$.[21] Boston devotees estimate metabolic acid–base status indirectly by applying empiric plasma bicarbonate-based 'rules of thumb'.[22]

BASE EXCESS, STANDARD BASE EXCESS AND 'WHOLE BODY' BASE EXCESS

In 1960 Siggaard-Andersen and colleagues introduced 'base excess' (BE), calculated by inserting pH, P_{CO_2} and haemoglobin measurements into an 'alignment nomogram' constructed from in vitro experimental data. BE was set at zero at any haemoglobin concentration when pH = 7.4, P_{CO_2} = 40 mm Hg (both at 37°C). If pH ≠ 7.4 or P_{CO_2} ≠ 40 mm Hg, BE could be defined as the concentration of titratable hydrogen ion which returns the pH of ex vivo blood to 7.4 while P_{CO_2} is maintained at 40 mm Hg.

Seventeen years later Siggaard-Andersen published the Van Slyke equation[23] to replace the empiric nomogram. The equation computes BE as $(\Delta[HCO_3^-] + \Delta[A^-])$, in other words as the deviation from the normal buffer base concentration in ex vivo whole blood. On independent evaluation, the Van Slyke equation accurately quantifies metabolic (non-respiratory) acid–base status in blood in vitro.[24] Because buffer base and SID are

quantitatively interchangeable, BE would be expressed in Stewart parlance as the offset in whole blood SID (SID_{PE} excess).

It quickly became clear that like plasma SID, BE loses independence from the partial pressure of carbon dioxide in vivo due to trans-membrane ionic shifts throughout the IPE space. By this mechanism a change in $PaCO_2$ forces BE in the opposite direction. Siggaard-Andersen's solution was to extend the whole blood model to the total IPE space by recalculating BE at a haemoglobin concentration of approximately 48 g/L.[7,11] This is SBE.

SBE is an easily grasped quantitative index of in vivo metabolic acid–base status. It is demonstrably independent of $PaCO_2$[21] and can act as a therapeutic target referenced to the IPE (extracellular plus erythrocytic) space. A useful formula is:

$$SBE = 0.93 \times ([HCO_3^-] + 14.84 \times (pH - 7.4) - 24.4),$$

with SBE and $[HCO_3^-]$ values in mEq/L.

A typical SBE reference range is −3.0 mEq/L to +3.0 mEq/L.

If SBE < −3.0 mEq/L:

- There is a metabolic acidosis, either primary or as compensation for a primary respiratory alkalosis.
- The SBE value quantifies the increase in SID_{IPE} needed to return the downshifted $PaCO_2$/pH curve to the normal position (see Fig. 94.2).
- This is approximately the required dose of sodium bicarbonate in mmol per litre of extracellular fluid (more exactly per litre of I+P+E fluid, approximately 25% of body weight).

If SBE > 3.0 mEq/L:

- There is a metabolic alkalosis, either primary or as compensation for a respiratory acidosis.
- The SBE value is the decrease in SID_{IPE} needed to return the upshifted curve to the normal position.
- Conceptually, it approximates the dose of corrective HCl required per litre of 'extracellular' (I+P+E) fluid.

With blood gas analysis, an extended electrolyte panel and off the shelf iterative software it is now possible to calculate 'whole body' BE, partitioned into 10 components including 'unknown species'.[25]

BICARBONATE-BASED APPROACH – THE BOSTON 'RULES OF THUMB'

Followers of the Boston 'school' match the plasma $[HCO_3^-]$ against the $[HCO_3^-]$ deemed appropriate for the measured $PaCO_2$, using 'rules of thumb'[22] derived from clinical and experimental data (Table 94.1). An offset denotes a metabolic acid–base disturbance.

Some drawbacks:

- The need for bedside 'mental gymnastics'.[20]
- Progressive inaccuracy above $PaCO_2$ values of 80 mm Hg. This is because the equations are linear approximations of non-linear events.
- To convert the $[HCO_3^-]$ offset to a quantitative therapeutic target, the 'apparent bicarbonate space' must first be calculated based on empiric algorithms derived from animal experiments.[26]

Table 94.1 Compensation – mechanisms and rules

DISORDER	COMPENSATION	SIMPLE RULES	BOSTON RULES
Uncompensated respiratory acidosis and alkalosis	Nil	SBE − 3.0 to + 3.0	Respiratory acidosis: $HCO_3^- = 24 + 0.1 \times (PaCO_2 - 40)$ Respiratory alkalosis: $HCO_3^- = 24 + 0.2 \times (PaCO_2 - 40)$
Compensated respiratory acidosis and alkalosis	Extracellular SID adjusted by altered urinary SID	pH is normal or $SBE = 0.4 \times (PaCO_2 - 40)$	Respiratory acidosis: $HCO_3^- = 24 + 0.35 \times (PaCO_2 - 40)$ Respiratory alkalosis: $HCO_3^- = 24 + 0.5 \times (PaCO_2 - 40)$
Metabolic acidosis	Hyperventilation reduces $PaCO_2$	$PaCO_2$ = 2 digits after pH decimal point or $PaCO_2 = 40 + SBE$ ($PaCO_2$ rarely < 10 mm Hg)	$PaCO_2 = 1.5 \times (HCO_3^-) + 8$
Metabolic alkalosis	Hypoventilation increases $PaCO_2$	$PaCO_2$ = 2 digits after pH decimal point or $PaCO_2 = 40 + SBE$ ($PaCO_2$ rarely < 60 mm Hg)	$PaCO_2 = 0.9 \times (HCO_3^-) + 9$

mm Hg, Millimeters of mercury; *SBE*, standard base excess; *SID*, strong ion difference.

ACID–BASE DISORDERS – CLASSIFICATION

PRIMARY DISORDERS

Primary acid–base disorders dictate the direction of pH disturbance. They can be respiratory ($PaCO_2$) or metabolic (non-$PaCO_2$). They are designated by the suffix 'osis', whereas the final pH abnormality has the suffix 'aemia'. In acidaemia, plasma pH is <7.35. In alkalaemia, plasma pH is >7.45. Hence we can have an acidaemia or alkalaemia due to a respiratory or metabolic acidosis or alkalosis, respectively. With opposing primary acid–base disturbances, the pH can be normal.

COMPENSATION AND ITS EFFECT ON pH

Compensation is a counterresponse to a primary disorder, reducing the severity of the pH disturbance.

METABOLIC COMPENSATION FOR RESPIRATORY DISTURBANCES

In respiratory acid–base disturbances the kidneys alter urinary SID to reset SID_{IPE} and thus SBE. By this mechanism, sustained hypocarbia and hypercarbia cause a compensatory metabolic acidosis and alkalosis, respectively. Compensation can take 5 days but is ultimately effective. Over the $PaCO_2$ range 25–80 mm Hg, which encompasses most chronic respiratory disturbances, full compensation normalises the arterial pH.[21,27,28]

RESPIRATORY COMPENSATION FOR METABOLIC DISTURBANCES

Respiratory compensation for metabolic disturbances is faster but less effective. A normal pH is never regained. Feedback loops driven by cerebrospinal fluid (CSF) and plasma pH act on central and peripheral chemoreceptors, respectively, which drive alveolar ventilation. $PaCO_2$ is forced in the direction opposing the metabolic pH perturbation.

In severe metabolic acidosis, minute ventilation can increase more than eightfold. The full response to a metabolic acid–base disturbance evolves over 12–24 hours, at first driven entirely by the peripheral chemoreceptors. Paradoxically the central chemoreceptors dampen the initial response because SID equilibration between plasma and CSF is gradual, whereas PCO_2 equilibration is immediate.

ACID–BASE 'SCANNING TOOLS'

ELECTRICAL GAPS (Table 94.2)

Accumulating strong anions reduce SID, causing metabolic acidosis. Other than chloride and L-lactate, they are not measured routinely. However, they can be injurious, especially in poisonings.[29–31] Critical care practitioners use electrical 'gaps' as early warning systems for 'unmeasured' anions. All quantify net unmeasured

Table 94.2 Factors affecting the anion gap, the albumin-corrected anion gap and the strong ion gap

FACTOR	AG	AGc	SIG
[Pi] ⇑	⇑	⇑	No effect
[Pi] ⇓	⇓	⇓	No effect
pH ⇑	⇑	⇑	No effect
pH ⇓	⇓	⇓	No effect
$[Ca^{2+}]$ and $[Mg^{2+}]$ ⇑	⇓	⇓	No effect
$[Ca^{2+}]$ and $[Mg^{2+}]$ ⇓	⇑	⇑	No effect
[Alb] ⇑	⇑	No effect	No effect
[Alb] ⇓	⇓	No effect	No effect
L-Lactate	⇑	⇑	No effect
Unmeasured strong anions (e.g. D-Lactate, ketoacids, salicylate)	⇑	⇑	⇑
Unmeasured weak anions (Polygelinate, myeloma IgA bands)	⇑	⇑	⇑
Unmeasured strong cations (Lithium)	⇓	⇓	⇓
Unmeasured weak cations (THAMH+, myeloma IgG bands)	⇓	⇓	⇓
Chloride overestimation (Bromism, hyperlipidaemia, high bicarbonate)	⇓	⇓	⇓
Sodium underestimation (hypernatraemia)	⇓	⇓	⇓

AG, Anion gap; *AGc*, albumin-corrected anion gap; *Ig*, immunoglobulin; *SIG*, strong ion gap; *THAM*, tris-hydromethyl aminomethane.

plasma ionic charge in mEq/L in accordance with the Principle of Electrical Neutrality

ANION GAP

The plasma anion gap (AG) is calculated as $[Na^+] + [K^+] - [Cl^-] - HCO_3^-]$. $[K^+]$ is often omitted, reducing the typical reference range to 3–13 mEq/L. The AG quantifies [unmeasured anions] − [unmeasured cations], both strong and weak. It is increased by unmeasured anions and reduced by unmeasured cations. In health the AG largely quantifies A^-, the negative charge on albumin and phosphate.

As a scan for unmeasured strong anions, the AG signal has low sensitivity and specificity. It has zero utility when haemodilution causes coincident hypoalbuminaemia.[32]

ALBUMIN-CORRECTED ANION GAP

The albumin-corrected anion gap (AGc) allows for albumin variation by a simple correction appropriate for acidaemia.

$$AGc = AG + 0.25 \times (40 - [albumin]),$$

assuming a normal plasma [albumin] of 40 g/L.

STRONG ION GAP

Strong ion gap (SIG) further extends the AGc calculation to neutralise other 'unwanted' contributors to the gap signal, the trade-off being increased variability. Although not part of 'Stewart' theory, the SIG can be described in Stewart terms as 'apparent' SID (SIDa) minus 'effective' SID (SIDe), where SIDa = $[Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-] -$ [L-lactate], and SIDe = $[A^-] + [HCO_3^-]$. The term 'strong ion gap' is itself a misnomer because unmeasured ions creating the 'gap' can be strong or weak.

BASE EXCESS GAP

BE is partitioned into four physical chemical components using 'Fencl Stewart' methodology.[33] The first three are calculated separately from measured plasma concentrations of sodium, chloride and albumin. The BE gap is then determined by subtracting these elements from an overall BE value, or in subsequent simplifications from SBE.

NET UNMEASURED ANIONS

The 'net unmeasured anions' quantitative approach of the late Peter Lloyd introduces 'polyprotic' modelling of plasma protein and phosphate, after the work of Constable.[2,34] It is successfully embedded in a laboratory diagnostic module in Hawkes Bay Regional Hospital, Hastings, New Zealand,[35] and there is a downloadable app (Quantitative Acid-Base Analyser for Mobile, Version 1.01, June 2014).

IPEUA AND UIX

The 'IPEua' parameter of Wolf and DeLand[7] and Anstey's 'UIX' (unmeasured ion index)[36] both quantify the unmeasured ionic species component of SBE in the corresponding 'IPE' (interstitium, plasma, erythrocyte) dimension, unlike the BE gap and its successors.

'HEAD TO HEAD' EVALUATION

Eight scanning tools were evaluated under the haemodilution stress of cardiopulmonary bypass.[32] Only the AG failed to respond significantly to a mean surge in acetate plus gluconate concentrations of greater than 10 mEq/L. IPEua and UIX performed best, with areas under receiver-operator characteristic curves of 0.88 and 0.87, respectively. Results for other tools were SIG (0.81), AGc (0.79), standard BE gap (0.77), plasma BE gap (0.71), whole blood BE gap (0.70) and AG (0.59).

OSMOLAL GAP

The osmolal gap scans for unmeasured osmotically active molecules. It is calculated as follows:

Osmolal gap
= measured osmolality − calculated osmolality.

The Bhagat formula for calculated osmolality[37] is often preferred:

Calculated osmolality (mOsmol/kg)
$= 1.89\,[Na] + 1.38\,[K] + 1.03\,[urea] + 1.08\,[glucose]$
$+ 7.45$ (all electrolyte concentrations in mmol/L)

The normal osmolal gap is less than 10 mOsmol/kg. Causes of a raised osmolal gap include:

- mannitol
- glycine (trans-urethral resection of prostate syndrome)
- poisonings with alcohols or glycols. acetone and glycerol (ketoacidosis)
- unknown solutes (hyperlactataemia and renal failure)

PRACTICAL CONSIDERATIONS

DIAGNOSTIC SEQUENCE

After taking a history and examining the patient, a set of arterial blood gases and an electrolyte panel should be evaluated. A series of questions can then be addressed:

WHAT IS THE PRIMARY PROCESS?

- The primary process determines the direction of pH change.

Table 94.3 Acid–base status – primary survey

$PaCO_2$ (mm Hg)	pH	PRIMARY PROCESS(ES)
35–45	7.35–7.45	None
>45	7.35–7.45	1. Chronic respiratory acidosis or 2. Respiratory acidosis, metabolic alkalosis
<35	7.35–7.45	1. Chronic respiratory alkalosis or 2. Respiratory alkalosis, metabolic acidosis
<35	<7.35	Metabolic acidosis
>45	<7.35	Respiratory acidosis
35–45	<7.35	Respiratory acidosis, metabolic acidosis
>45	>7.45	Metabolic alkalosis
<35	>7.45	Respiratory alkalosis
35–45	>7.45	Respiratory alkalosis, metabolic alkalosis

- Look first at the $PaCO_2$ and then at the pH it generates.
- If both are normal, a dual metabolic acid–base disturbance is still possible (metabolic alkalosis plus raised AGc acidosis) but uncommon.
- If either or both are abnormal, check whether the direction of pH change is appropriate for the $PaCO_2$:
  - Appropriate: Primary respiratory disorder.
  - Inappropriate: Primary metabolic disorder.
- Nine possible combinations of $PaCO_2$ and pH (Table 94.3) indicate specific acute, chronic or mixed primary processes.
- An abnormal $PaCO_2$ plus a normal pH means one of two things:
  - Two opposing primary acid–base disorders, one respiratory and one metabolic
  - A chronic respiratory disturbance with metabolic compensation.
- A 'normal' $PaCO_2$ combined with an abnormal pH always represents two primary acid–base disturbances (see Table 94.3).

IS THERE COMPENSATION?

- In metabolic acidosis, hypocarbia ($PaCO_2$ < 35 mm Hg) indicates compensation
- In metabolic alkalosis, hypercarbia ($PaCO_2$ > 45 mm Hg) indicates compensation
- In a respiratory acidosis, metabolic alkalosis (SBE > 3 mEq/L) indicates compensation
- In a respiratory alkalosis, metabolic acidosis (SBE < –3 mEq/L) indicates compensation

IS COMPENSATION APPROPRIATE?

- Apply 'rules of thumb' (see Table 94.1)
- Remember:
  - the pH is normal in fully compensated respiratory acid–base disturbances (though this can take days),
  - the pH is never normal in appropriately compensated metabolic acid–base disturbances.
- Identify inappropriate respiratory compensation as a separate acid–base disturbance. For example:
  - If arterial pH = 7.20 and $PaCO_2$ = 20 mm Hg, there is a metabolic acidosis with appropriate respiratory compensation (see Table 94.1).
  - If pH = 7.20 and $PaCO_2$ = 32 mm Hg, there a metabolic acidosis plus an accompanying respiratory acidosis (despite the hypocarbia).
  - If the pH = 7.20 with a $PaCO_2$ = 12 mm Hg, there is a metabolic acidosis plus an added respiratory alkalosis.

IF METABOLIC ACIDOSIS IS PRESENT, HOW SEVERE IS IT?

- Mild: SBE = –4 mEq/L to –9 mEq/L
- Moderate: SBE = –10 mEq/L to –14 mEq/L
- Severe: SBE = < –14 mEq/L

IF METABOLIC ALKALOSIS IS PRESENT, HOW SEVERE IS IT?

- Mild: SBE = +4 mEq/L to +9 mEq/L
- Moderate: SBE = +10 mEq/L to +14 mEq/L
- Severe: SBE = > +14 mEq/L

WHAT IS THE ANION GAP OR PREFERABLY THE ALBUMIN-CORRECTED ANION GAP?

- If either is elevated, look for unmeasured anions
- If the AGc is low or negative, suspect laboratory error, but consider lithium intoxication, immunoglobulin G myeloma and others (see Table 94.2).

IS ANY ALBUMIN-CORRECTED ANION GAP INCREASE ACCOMPANIED BY A SIMILAR REDUCTION IN STANDARD BASE EXCESS OR $[HCO_3^-]$?

- Yes: Single metabolic disorder
- No: Dual metabolic disorders
  - Example 1: AGc = 20 mEq/L and SBE = –15 mEq/L. There is a mixed normal AGc metabolic acidosis and raised AGc metabolic acidosis (common during resolution of diabetic ketoacidosis).
  - Example 2: AGc = 20 mEq/L and the SBE = 0 mEq/L. There is a mixed metabolic alkalosis and raised AGc metabolic acidosis (such as

Table 94.4 Types of renal tubular acidosis

	TYPE 1	TYPE 2	TYPE 4
Mechanism	Impaired distal NH_4^+ secretion	Increased proximal chloride resorption. With other proximal tubular defects = Fanconi syndrome	Reduced aldosterone secretion or sensitivity. Hyperkalaemic suppression of proximal tubular NH_4^+ production
Some causes	Idiopathic, hypercalcuric, Amphotericin B, lithium carbonate, rheumatoid arthritis, Sjögren disease, systemic lupus erythematosis, cirrhosis, renal transplant rejection, obstructive uropathy, primary hyperparathyroidism, hyperglobulinaemia	Genetic, light chain nephropathy, acetazolamide, heavy metals, aminoglycosides, valproate, chemotherapy, renal transplantation, amyloidosis, paroxysmal nocturnal haemoglobinuria	Hyporeninaemia, adrenal insufficiency, angiotensin converting enzyme-inhibitors, non-steroidal anti-inflammatory drugs, cyclosporine, heparin, amiloride, spironolactone, triamterene, pentamidine, diabetes, obstructive uropathy, interstitial nephropathies, renal transplant rejection, analgesic nephropathy
SBE	Can be <–15 mEq/L	–6 to –15 mEq/L	–6 to –8 mEq/L
Plasma $[K^+]$	Usually low	Low	High
Urine pH post frusemide	>5.5	<5.5. (Bicarbonaturia with $NaHCO_3^-$ infusion)	Usually <5.5
Urinary AG	Positive	Negative	Usually positive
Urinary NH_4^+	Reduced	Normal or high	Usually reduced

AG, Anion gap; *SBE*, standard base excess.

hyperlactataemia superimposed on a pre-existing metabolic alkalosis).

IF THE ALBUMIN-CORRECTED ANION GAP IS INCREASED, WHAT IS THE CAUSE?

- Common causes include L-lactate and the ketoanions (β-hydroxybutyrate and acetoacetate). There are several others (Table 94.4).
- If no obvious cause, a coincident raised osmolal gap suggests methanol (unmeasured anion formate) or ethylene glycol toxicity (unmeasured anions glycolate and oxalate).
- If still no obvious cause, perform specific assays (such as plasma D-lactate, salicylate or pyroglutamate and urinary organic anions).

CLINICAL ACID–BASE DISORDERS

METABOLIC ACIDOSIS

The low SID of metabolic acidosis can be due to a narrowed difference between $[Na^+]$ and $[Cl^-]$ (normal AGc, Box 94.2), or an accumulation of other strong anions (elevated AGc, Box 94.2). A normal AGc acidosis is not always hyperchloraemic because $[Cl^-]$ is only important relative to $[Na^+]$.

CLINICAL FEATURES

The adverse effects of acidaemia (Box 94.3) are more evident at low pH (<7.2). Hyperchloraemia may itself

Box 94.2 Causes of metabolic acidosis

NORMAL AGc	RAISED AGc
Saline infusions	L-lactate acidosis
Organic anion excretion	Ketoacidosis
Ketoacidosis	β-hydroxybutyrate, acetoacetate
Glue sniffing (hippurate, benzoate)	Renal failure
Loss high SID enteric fluid	Sulphate, hippurate, other organic anions
Small intestinal, pancreatic, biliary	Phosphate accumulation increases A_{tot}
Urinary/enteric diversions	Ethylene glycol poisoning
High urinary SID	Glycolate, oxalate
Renal tubular acidosis	Methanol poisoning
High urinary SID	Formate
Post hypocapnia	Salicylate overdose
High urinary SID	Salicylate, L-lactate, ketoanions
TPN and NH_4Cl administration	Pyroglutamic acidosis
	Pyroglutamate
	Toluene (glue sniffing)
	Hippurate, benzoate
	Short bowel syndrome
	D-lactate

AGc, Albumin-corrected anion gap; *SID*, strong ion difference; *TPN*, total parenteral nutrition.

Box 94.3 Adverse effects of metabolic acidosis

- Reduced myocardial contractility, tachydysrhythmia and bradydysrhythmia, systemic arteriolar dilatation, venoconstriction, centralisation of blood volume
- Pulmonary vasoconstriction, hyperventilation, respiratory muscle failure
- Reduced splanchnic and renal blood flow
- Increased metabolic rate, catabolism, reduced adenosine triphosphate synthesis, reduced 2,3-diphosphoglycerate synthesis
- Confusion, drowsiness
- Increased inducible nitric oxide synthetase expression, proinflammatory cytokine release
- Hyperglycaemia, hyperkalaemia
- Cell membrane pump dysfunction
- Bone loss, muscle wasting

cause or contribute to some low pH toxicities, such as impairment of renal blood flow, coagulation disorders, and splanchnic and cerebral dysfunction. Specific adverse effects of other strong anions include:

- blindness and cerebral oedema (formate)
- crystalluria, renal failure and ionised hypocalcaemia in ethylene glycol poisoning (oxalate)
- tinnitus, hyperventilation and fever due to uncoupling of oxidative phosphorylation (salicylate)
- artefactual plasma L-lactate elevation by blood gas analysers in ethylene glycol poisoning (glycolate).[38]

Mild acidaemia has potential benefits. For example, the Bohr effect increases tissue oxygen availability, and lowering pH is protective in hypoxic stress models. Mild normal AGc acidosis is common after infusions of low SID fluids such as 0.9% sodium chloride and certain colloids.[6] With respiratory compensation, arterial pH rarely falls to less than 7.3. Net harm is still possible, potentially from chloride itself,[39] but as yet unconfirmed.[40]

RENAL TUBULAR ACIDOSIS[14]

In renal tubular acidosis (RTA), the urinary SID setting is high relative to the SID_{IPE}, with an inadequate nadir following an acid load. The disturbance is in tubular Cl^- handling, either from reduced NH_3 production (types 1 and 4), or excessive Cl^- resorption (type 2). Causes are legion (see Table 94.4).

Apart from treating underlying causes and preventing hypercalcuria, management in types 1 and 2 RTA is based on administering sodium bicarbonate or citrate to increase extracellular SID, and managing hypokalaemia using potassium citrate (not chloride). In type 4 RTA, inciting agents are ceased and adrenal insufficiency treated with mineralocorticoid replacement. Alkali supplements and frusemide are occasionally necessary.

MANAGEMENT OF METABOLIC ACIDOSIS

Management is directed at the underlying cause. Care is required to avoid a sudden reduction in minute ventilation when instituting mechanical ventilation because this can be lethal. For example, an arterial pH of 6.9 and $PaCO_2$ of 10 mm Hg implies maximal hyperventilation. If the $PaCO_2$ is suddenly returned to 'normal' (40 mm Hg), the arterial pH will fall to 6.7. If the $PaCO_2$ rises further to 60 mm Hg, the pH will be 6.6.

ALKALINISING AGENTS – SODIUM BICARBONATE, 'CARBICARB', SODIUM LACTATE AND TRIS-HYDROMETHYL AMINOMETHANE (THAM)

The term 'alkalinising agent' is preferred to 'buffer'. True chemical buffering is a resistance to pH change on addition of an acid or base, whereas an alkalinising agent in clinical practice increases the pH at any given PCO_2. In other words, it increases the SBE (see Fig. 94.2). For example, a $NaHCO_3$ dose of 1 mmol/kg increases SBE approximately 3 mEq/L.

Administration of alkalinising agents is difficult to justify in hyperlactataemia and other organic acidoses. However, it can be appropriate to infuse $NaHCO_3$ in:

- severe normal AGc acidosis
- severe hyperkalaemia
- methanol and ethylene glycol poisoning
- tricyclic and salicylate overdose.

$NaHCO_3$ increases SBE by increasing SID. The active agent is sodium, not bicarbonate. The high CO_2 content (CO_{2tot} approximately 1028 mmol/L in a 1 M solution) creates two problems:

- The need for CO_2 impermeable containers during autoclaving and storage
- Potential for paradoxical intracellular respiratory acidosis.

Major surges in V_{CO_2} and P_{CO_2} are avoidable unless pulmonary perfusion is massively reduced, such as in cardiac arrest.[4] The key is slow administration (over the course of 30–60 minutes).

The CO_{2tot} of bicarbonate preparations can also be reduced, the tradeoff being a pH rise. In carbicarb ($CO_{2tot} = 750$ mmol/L, $P_{CO_2} = 2$ mm Hg, pH = 9.8), half the monovalent bicarbonate becomes divalent carbonate. However, complete elimination of bicarbonate as NaOH causes unacceptable alkalinity (pH of 1 M solution = 14), with local haemolysis and endothelial damage likely on peripheral administration. Sodium lactate (0.167 M, pH 6.9) is an alternative, provided lactate metabolism is efficient. Note that lactate is replaced by bicarbonate on metabolism to pyruvate. It does not 'generate' bicarbonate directly.[4]

A weak base (Btot) can offset A_{tot} to increase SBE without changing SID. THAM is tromethamine or tris buffer, a weak base with a pKa of 7.7 at 37°C. Because THAM is CO_2 'consuming', transient hypocarbia

Box 94.4 Metabolic alkalosis – causes

LOW URINARY SID	ENTERIC LOSSES OF LOW SID FLUID	GAIN OF HIGH SID FLUID
Loop or thiazide diuretics	Pyloric stenosis, vomiting/gastric outlet obstruction, nasogastric suction	$NaHCO_3$ administration
Post hypercapnia	Villous adenoma	Sodium citrate (plasma exchange, stored blood)
Corticosteroids	Laxative abuse	Renal replacement fluids with high SID (>35 mEq/L)
Cushing syndrome		Milk alkali syndrome
Primary mineralocorticoid excess		
Carbenoxolone, Glycyrrhetinic acid (licorice)		
Hypercalcaemia		
Milk alkali syndrome		
Magnesium deficiency		
Bartter and Gitelman syndromes		

SID, Strong ion difference.

coupled with the immediate SBE increase can precipitate sudden apnoea. THAM accumulates in renal impairment and can cause hypoglycaemia, hyperosmolality, coagulation abnormalities and potassium disturbances.

Potential adverse effects of all alkalinising agents include:

- sudden increases in haemoglobin–oxygen affinity
- hyperosmolar states
- reduced $[Ca^{2+}]$ and $[Mg^{2+}]$
- rebound alkalosis following resolution of an organic acidosis.

METABOLIC ALKALOSIS

Metabolic alkalosis has been described as the most common acid–base disturbance in hospital patients. With modern definitions it is often part of a 'mixed' disorder.

CAUSES OF METABOLIC ALKALOSIS (Box 94.4)

Metabolic alkalosis can be precipitated by:

- Low urinary SID (e.g. diuretics).
- Loss of low SID enteric fluid (e.g. small gut fistulae).
- Gain of high SID fluid (e.g. $NaHCO_3$ administration).

CLINICAL FEATURES

A high plasma pH has several adverse effects (Box 94.5). Mortality escalates as the pH rises to greater than 7.55, although how much is causation versus association is unclear.

TREATMENT

Remove the cause. Additional measures to accelerate extracellular SID reduction include:

- Volume repletion with saline or low SID colloid preparations.
- Administering KCl (SID zero) to correct potassium depletion.

Box 94.5 Severe metabolic alkalosis – multisystem effects

Central nervous system
Vasospasm
Seizures
Confusion, drowsiness
Neuromuscular
Weakness, tetany, muscle cramps
Cardiovascular
Arrhythmias – supraventricular and ventricular
Decreased contractility
Respiratory
Decreased alveolar ventilation
Atelectasis, hypoxaemia
Metabolic
Hyperlactataemia
Low [Pi], $[Ca^{++}]$, $[Mg^{++}]$ and $[K^+]$
Hemoglobin–oxygen affinity
Initially increased (until counteracted by increased 2,3-diphosphoglycerate)

- Acetazolamide administration to increase urinary SID.[41]
- HCl via slow administration through a central venous catheter, or indirectly as NH_4Cl, arginine hydrochloride or lysine hydrochloride.
- Renal replacement therapy.

As with metabolic acidosis, care is required when instituting mechanical ventilation. Minute volume settings should be adjusted to prevent extreme alkalaemia.

RESPIRATORY ACIDOSIS

CAUSES (Table 94.5)

The risk is increased when CO_2 production is high and when ventilation is inefficient (large alveolar or apparatus dead space, respiratory muscle disadvantage due to hyperinflation or increased work of breathing).

Table 94.5 Some causes of respiratory acidosis

MECHANISM/AFFECTED SITE	ACUTE	CHRONIC
Respiratory centre suppression	Sedative and narcotic drugs, central nervous system injury and infection brainstem vasculitis or infarction	Obesity hypoventilation syndrome
Airway obstruction	Inhalational injury, Ludwig angina, laryngeal trauma	Obstructive sleep apnoea, vocal cord paresis, subglottic and tracheal stenosis
Mechanical ventilation	'Permissive' hypercarbia	
Neural/neuromuscular	Spinal cord injury, Guillain-Barré syndrome, myaesthenia gravis, muscle relaxants, envenomation, acute poliomyelitis, critical illness myoneuropathy	Phrenic nerve damage, paraneoplastic syndromes, post-polio syndrome
Muscle	Myopathy, low $[K^+]$, high $[Mg^{2+}]$, low [Pi], diaphragmatic injury, shock	Muscular dystrophies, motor neuron disease
Decreased chest wall compliance	Abdominal distension, burns, pneumothorax, large pleural effusions	Obesity, kyphoscoliosis, ankylosing spondylitis
Loss of chest wall integrity/geometry	Flail segment	Thoracoplasty
Increased small airways resistance	Asthma, bronchiolitis	Chronic obstructive pulmonary disease
Deceased lung compliance	Acute lung injury, pneumonia, pulmonary oedema, vasculitis, and haemorrhage	Pulmonary fibrosis

CLINICAL FEATURES

These include:

- The effects of acidaemia (see Box 94.3).
- Central nervous system dysfunction, including asterixis, confusion, drowsiness, fitting and raised intracranial pressure.
- Renal dysfunction. Sympathoadrenal and renin–angiotensin activation reduce renal perfusion, glomerular filtration rate and urine output.

TREATMENT

Management is directed at the underlying cause. Mechanical ventilation, either non-invasive or invasive, may be required.

RESPIRATORY ALKALOSIS

CAUSES

Respiratory alkalosis arises in a number of clinical scenarios (Box 94.6).

Box 94.6 Conditions predisposing to respiratory alkalosis

ACUTE	CHRONIC
Hypoxaemia	Pregnancy
Hepatic failure	High altitude
Sepsis	Chronic lung disease
Asthma	Neurotrauma
Pulmonary embolism	Chronic liver dysfunction
Pneumonia, acute lung injury	
Central nervous system disorders – stroke, infection, trauma	
Drugs – salicylates, selective serotonin reuptake inhibitors	
Opiate and benzodiazepine withdrawal	
Mechanical hyperventilation – intentional or inadvertent	
Pain, anxiety, psychosis	

CLINICAL FEATURES

The multisystem effects of alkalaemia apply, plus the complications of hypoventilation.

TREATMENT

Management should be directed towards the underlying cause.

REFERENCES

1. Kellum JA, Elbers PWG, eds. *Stewart's Textbook of Acid-Base*. Amsterdam: AcidBase.org; 2009.
2. Staempfli HR, Constable PD. Experimental determination of net protein charge and A(tot) and K(a)

of nonvolatile buffers in human plasma. *J Appl Physiol*. 2003;95(2):620–630.
3. Figge J, Mydosh T, Fencl V. Serum proteins and acid-base equilibria: a follow-up. *J Lab Clin Med*. 1992; 120(5):713–719.
4. Morgan TJ, Venkatesh B, Bellomo R. Acid-base physiology: comments on 10 contentious assertions. *Crit Care Resusc*. 2015;17(3):211–213.
5. Kellum JA. Clinical review: reunification of acid-base physiology. *Crit Care*. 2005;9(5):500–507.
6. Morgan TJ. The ideal crystalloid – what is 'balanced'? *Curr Opin Crit Care*. 2013;19(4):299–307.
7. Wolf MB, Deland EC. A comprehensive, computer-model-based approach for diagnosis and treatment of complex acid-base disorders in critically-ill patients. *J Clin Monit Comput*. 2011;25(6):353–364.
8. Morgan TJ. The Stewart approach – one clinician's perspective. *Clin Biochem Rev*. 2009;30(2):41–54.
9. Langer T, Scotti E, Carlesso E, et al. Electrolyte shifts across the artificial lung in patients on extracorporeal membrane oxygenation: interdependence between partial pressure of carbon dioxide and strong ion difference. *J Crit Care*. 2015;30(1):2–6.
10. Anstey CM. Comparison of three strong ion models used for quantifying the acid-base status of human plasma with special emphasis on the plasma weak acids. *J Appl Physiol*. 2005;98(6):2119–2125.
11. Siggaard-Andersen O, Fogh-Andersen N. Base excess or buffer base (strong ion difference) as measure of a non-respiratory acid-base disturbance. *Acta Anaesthesiol Scand Suppl*. 1995;107:123–128.
12. Kurtz I, Kraut J, Ornekian V, et al. Acid-base analysis: a critique of the Stewart and bicarbonate-centered approaches. *Am J Physiol Renal Physiol*. 2008;294(5):F1009–F1031.
13. Gepshtein R, Leiderman P, Genosar L, et al. Testing the three step excited state proton transfer model by the effect of an excess proton. *J Phys Chem A*. 2005; 109(42):9674–9684.
14. Soriano JR. Renal tubular acidosis; the clinical entity. *J Am Soc Nephrol*. 2002;13:2160–2170.
15. Yunos NM, Bellomo R, Story D, et al. Bench-to-bedside review: chloride in critical illness. *Crit Care*. 2010;14(4):226.
16. Masevicius FD, Tuhay G, Pein MC, et al. Alterations in urinary strong ion difference in critically ill patients with metabolic acidosis: a prospective observational study. *Crit Care Resusc*. 2010;12(4): 248–254.
17. Kellum JA. Determinants of plasma acid-base balance. *Crit Care Clin*. 2005;21(2):329–346.
18. Moviat M, Terpstra AM, van der Hoeven JG, et al. Impaired renal function is associated with greater urinary strong ion differences in critically ill patients with metabolic acidosis. *J Crit Care*. 2012;27(3): 255–260.
19. Zazzeron L, Ottolina D, Scotti E, et al. Real-time urinary electrolyte monitoring after furosemide administration in surgical ICU patients with normal renal function. *Anna Intensive Care*. 2016; 6(1):72.
20. Severinghaus JW. Siggaard-Andersen and the 'Great Trans-Atlantic Acid-Base Debate'. *Scand J Clin Lab Invest Suppl*. 1993;214:99–104.
21. Schlichtig R, Grogono AW, Severinghaus JW. Human PaCO2 and standard base excess compensation for acid-base imbalance. *Crit Care Med*. 1998;26(7):1173–1179.
22. Narins RG, Emmett M. Simple and mixed acid-base disorders: a practical approach. *Medicine (Baltimore)*. 1980;59(3):161–187.
23. Siggaard-Andersen O. The Van Slyke equation. *Scand J Clin Lab Invest Suppl*. 1977;37(146):15–20.
24. Morgan TJ, Clark C, Endre ZH. Accuracy of base excess – an in vitro evaluation of the Van Slyke equation. *Crit Care Med*. 2000;28(8):2932–2936.
25. Wolf MB. Comprehensive diagnosis of whole-body acid-base and fluid-electrolyte disorders using a mathematical model and whole-body base excess. *J Clin Monit Comput*. 2015;29(4):475–490.
26. Adrogue HJ, Gennari FJ, Galla JH, et al. Assessing acid-base disorders. *Kidney Int*. 2009;76(12): 1239–1247.
27. Martinu T, Menzies D, Dial S. Re-evaluation of acid-base prediction rules in patients with chronic respiratory acidosis. *Can Respir J*. 2003;10(6):311–315.
28. Lim VS, Katz AI, Lindheimer MD. Acid-base regulation in pregnancy. *Am J Physiol*. 1976;231(6): 1764–1769.
29. Kerns W 2nd, Tomaszewski C, McMartin K, et al. Alcohols MSGMfT. Formate kinetics in methanol poisoning. *J Toxicol Clin Toxicol*. 2002;40(2): 137–143.
30. Moreau CL, Kerns W 2nd, Tomaszewski CA, et al. Glycolate kinetics and hemodialysis clearance in ethylene glycol poisoning. META Study Group. *J Toxicol Clin Toxicol*. 1998;36(7):659–666.
31. Peter JV, Rogers N, Murty S, et al. An unusual cause of severe metabolic acidosis. *Med J Aust*. 2006; 185(4):223–225.
32. Morgan TJ, Anstey CM, Wolf MB. A head to head evaluation of 8 biochemical scanning tools for unmeasured ions. *J Clin Monit Comput*. 2017;31:449–457.
33. Gilfix BM, Bique M, Magder S. A physical chemical approach to the analysis of acid-base balance in the clinical setting. *J Crit Care*. 1993;8(4):187–197.
34. Constable PD. A simplified strong ion model for acid-base equilibria: application to horse plasma. *J Appl Physiol*. 1997;83(1):297–311.
35. Lloyd P, Freebairn R. Using quantitative acid-base analysis in the ICU. *Crit Care Resusc*. 2006;8(1): 19–30.
36. Anstey CM. Estimating the net effect of unmeasured ions in human extracellular fluid using a new mathematical model. Part II: practical issues. *Anaesth Intensive Care*. 2010;38(5):870–875.
37. Bhagat CI, Garcia-Webb P, Fletcher E, et al. Calculated vs measured plasma osmolalities revisited. *Clin Chem*. 1984;30(10):1703–1705.
38. Morgan TJ, Clark C, Clague A. Artifactual elevation of measured plasma L-lactate concentra-

tion in the presence of glycolate. *Crit Care Med*. 1999;27(10):2177–2179.
39. Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA*. 2012;308(15):1566–1572.
40. Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. *JAMA*. 2015;314(16):1701–1710.
41. Moviat M, Pickkers P, van der Voort PH, et al. Acetazolamide-mediated decrease in strong ion difference accounts for the correction of metabolic alkalosis in critically ill patients. *Crit Care*. 2006;10(1):R14.

95

Fluid and electrolyte therapy

Anthony Delaney, Simon Finfer

The management of patients' fluid and electrolyte status requires an understanding of body fluid compartments as well as an understanding of water and electrolyte metabolism. These principles will be considered along with the commonly encountered fluid and electrolyte disturbances. Recent evidence for the use of fluid therapy in a number of common clinical scenarios will also be presented.

FLUID COMPARTMENTS (Table 95.1; Fig. 95.1)

TOTAL BODY WATER

In humans, water contributes approximately 60% of body weight, with organs varying in water content (Table 95.2). The variation of the percentage of total body weight as water, between individuals, is largely governed by the amount of adipose tissue. The average water content as a percentage of total body weight is 60% for males and 50% for females. Total body water as a percentage of total body weight decreases with age, due to a progressive loss of muscle mass, causing bone and connective tissue to assume a greater percentage of total body weight (Table 95.3).[1–3]

Total body water is commonly divided into two volumes: the extracellular fluid (ECF) volume and the intracellular fluid (ICF) volume.[2] Sodium balance regulates the ECF volume, whereas water balance regulates the ICF volume. Sodium excretion is normally regulated by various hormonal and physical ECF volume sensors, whereas water balance is normally regulated by hypothalamic osmolar sensors.[4]

EXTRACELLULAR FLUID

ECF is defined as all body water external to the cell, and is commonly subdivided into plasma and interstitial fluid volumes. The ECF is normally 40% of total body water and 25% of total body weight. With acute or chronic illness, ICF volume is reduced, and ECF volume is increased and may even exceed the ICF volume. The ECF volume can be divided into the plasma volume, the ECF volume, and the interstitial volume.

INTRACELLULAR FLUID

ICF is defined as all the body water within cells and, unlike the ECF compartment, is an inhomogeneous, multicompartmental entity, with different pH and ionic compositions depending upon the organ or tissue being considered. The ICF volume is often determined by inference from the difference in measurements of the total body water and ECF spaces. This estimation suffers from the inaccuracies inherent in both ECF and total body water measurements. In general, the ICF is considered to be 60% of total body water and 35% of total body weight.

TRANSCELLULAR FLUID

Fluids in this compartment have a common characteristic of being formed by transport activity of cells. The fluid is extracellular in nature and will be considered as part of the interstitial volume. It may vary from 1 L to 10 L, with larger volumes occurring in diseased states (e.g. bowel obstruction or cirrhosis with ascites), and is formed at the expense of the remaining interstitial and plasma volumes.

WATER METABOLISM

Water balance is maintained by altering the intake and excretion of water. In the healthy state, intake is controlled by thirst. Excretion is controlled by the renal action of antidiuretic hormone (ADH). In health, plasma osmolalities of about 280 mOsm/kg suppress plasma ADH to concentrations low enough to permit maximum urinary dilution.[5] Above this value, an increase in ECF tonicity of about 1%–2% or a decrease in total body water of 1–2 L causes the posterior pituitary to release ADH, which acts upon the distal nephron to increase water reabsorption. Maximum plasma ADH concentrations are reached at an osmolality of 295 mOsm/kg.[5] The osmotic stimulation also changes thirst sensation and, in the conscious ambulant individual, initiates water repletion (drinking), which is more important in preventing dehydration

ABSTRACT

The management of patients' fluid and electrolyte status requires an understanding of body fluid compartments and of water and electrolyte metabolism. Water balance is governed by the thirst mechanism and the secretion of antidiuretic hormone (ADH). Disorders of sodium balance, while they may be due to excess sodium intake or losses, are more commonly due to retention of excess water (due to inappropriate fluid therapy or the syndrome of inappropriate ADH leading to hyponatraemia) or dehydration. Clinicians need to consider the causes of electrolyte disorders, such as hyperkalaemia, after attending to the more life-threatening manifestations of these conditions. There is an emerging body of evidence from high quality randomised clinical trials to guide clinicians prescribing fluid therapy to critically ill patients.

KEYWORDS

Electrolytes
hyopnatraemia
hyperkalaemia
magnesium
fluid therapy

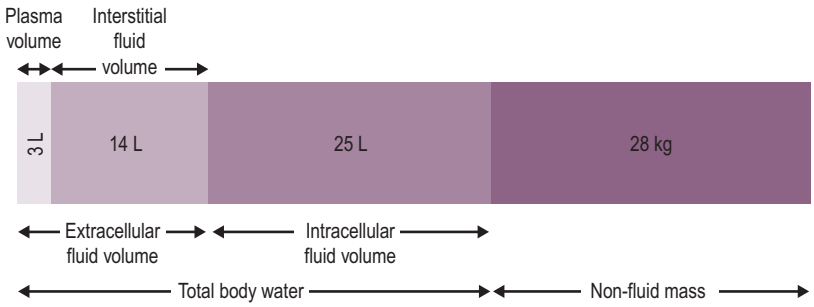


Figure 95.1 Body fluid compartments.

Table 95.1 Body fluid compartments

FLUID COMPARTMENT	VOLUME (mL/kg)	% TOTAL BODY WEIGHT
Plasma volume	45	4.5
Blood volume	75	7.5
Interstitial volume	200	20
Extracellular fluid volume	250	25
Intracellular fluid volume	350	35
Total body fluid volume	600	60

Table 95.2 Water content of various tissues

TISSUE	% WATER CONTENT
Brain	84
Kidney	83
Skeletal muscle	76
Skin	72
Liver	68
Bone	22
Adipose tissue	10

Table 95.3 Water content as a percentage of total body weight

AGE (YEARS)	MALES (%)	FEMALES (%)
10–15	60	57
15–40	60	50
40–60	55	47
>60	50	45

than ADH secretion and action. Thus, in health, the upper limit of the body osmolality (and therefore serum sodium) is determined by the osmotic threshold for thirst, whereas the lower limit is determined by the osmotic threshold for ADH release.[6]

Table 95.4 Drugs affecting antidiuretic hormone secretion

STIMULATE	INHIBIT
Nicotine	Ethanol
Opiate analgesics	Narcotic antagonists
Vincristine	Phenytoin
Barbiturates	
Cyclophosphamide	
Chlorpropamide	
Clofibrate	
Carbamazepine	
Amitriptyline	

Increase in osmolality caused by permeant solutes (e.g. urea) does not stimulate ADH release. ADH may also be released in response to hypovolaemia and hypotension, via the stimulation of low- and high-pressure baroreceptors. ADH release is extremely marked when more than 30% of the intravascular volume is lost. ADH may also be stimulated by pain and nausea, which are thought to act through the baroreceptor pathways.[4] ADH release may also be stimulated by a variety of pharmacological agents (Table 95.4). Renal response to ADH depends upon an intact distal nephron and collecting duct, and a hypertonic medullary interstitium. The capacity to conserve or excrete water also depends upon the osmolar load presented to the distal nephron.[4]

WATER REQUIREMENTS

Water is needed to eliminate the daily solute load, and to replace daily insensible fluid loss (Table 95.5). With a normal daily excretion of 600 mOsm solute, maximal and minimal secretions of ADH will cause urine osmolality to vary from 1200 to 30 mOsm/kg, respectively, and the urine output to vary from 500 mL to 20 L/day, respectively. Skin and lung water losses vary, and may range from 500 mL to 8 L/day depending on physical activity, ambient temperature and humidity.

Table 95.5 Daily fluid balance (for a 70-kg man at rest in a temperate climate)

	INPUT (mL)			OUTPUT (mL)	
	SEEN	UNSEEN		SEEN	UNSEEN
Drink	1000	—	Urine	1000	—
Food	—	650	Skin	—	500
Water of oxidation	—	350	Lungs	—	400
			Faeces	—	100
Total	1000	1000	Total	1000	1000

DISORDERS OF OSMOLALITY

TONICITY

Osmolality is a measure of the number of osmoles per kilogram (Osm/kg) of water. Tonicity is a measure of the effective osmotic pressure gradient when two fluid compartments are separated by a semi-permeable membrane. Tonicity is influenced only by solutes that cannot cross the membrane. The osmolality of the ECF is due largely to sodium salts. Clinical effects of hyperosmolality, due to excess solute, depend upon whether the solute distributes evenly throughout the total body water (e.g. permeant solutes of alcohol or urea) or distributes in the ECF only (e.g. impermeant solutes of mannitol or glucose). With impermeant solutes, hyperosmolality is associated with a shift of fluid from the ICF to the ECF compartment. Hyperosmolality due to increased impermeant solutes is known as hypertonicity. This condition may also be associated with a reduction in the serum sodium concentration (see below).

WATER EXCESS

In a 70-kg man, for every 1 L of excess pure water, ECF increases by 400 mL and ICF increases by 600 mL, on average. The osmolality also decreases by 6–7 mOsm/kg and the serum sodium falls by 3.0–3.5 mmol/L.

WATER DEFICIENCY

In a 70-kg man, for every 1 L of pure water loss, 600 mL is lost from the ICF and 400 mL from the ECF. The osmolality also increases by 7–8 mOsm/kg and the serum sodium rises by 3.5–4.0 mmol/L.

ELECTROLYTES

Chemical compounds in solution may either:

- remain intact (i.e. undissociated), in which case they are called non-electrolytes (e.g. glucose, urea)
- dissociate to form ions, in which case they are called electrolytes. Ions carry an electrical charge (e.g. Na^+, Cl^-). Ions with a positive charge are attracted to a negative electrode or cathode, and hence are called 'cations'. Conversely, ions with a negative charge travel towards a positive electrode or anode and are called 'anions'. Each body water compartment contains electrolytes with different composition and concentration (Table 95.6).

Table 95.6 Electrolyte composition of body fluid compartments

	ICF (mmol/L)	ECF (mmol/L)	
		PLASMA	INTERSTITIAL
Sodium	10	140	145
Potassium	155	3.7	3.8
Chloride	3	102	115
Bicarbonate	10	28	30
Calcium (ionised)	<0.01	1.2	1.2
Magnesium	10	0.8	0.8
Phosphate	105	1.1	1

ECF, Extracellular fluid; *ICF*, intracellular fluid.

Table 95.7 The sodium compartments in a 70-kg man

	TOTAL (mmol)	(mmol/kg)
Total body sodium	4000	58
Non-exchangeable bone sodium	1200	17
Exchangeable sodium	2800	40
Intracellular sodium	250	3
Extracellular sodium	2400	35
Exchangeable bone sodium	150	2

SODIUM

Sodium is the principal cation of the ECF and accounts for 86% of the ECF osmolality. In a 70-kg man, total body sodium content is 4000 mmol (58 mmol/kg) and is divided into a number of compartments (Table 95.7). Normal ECF concentration of sodium varies between

Box 95.1 Common causes of hyponatraemia

1. Spurious result
Isotonic
  Hyperlipidaemia
  Hyperproteinaemia
Hypertonic
  Hyperglycaemia
  Mannitol, glycerol, glycine or sorbitol excess
2. Water retention
Renal failure
Hepatic failure
Cardiac failure
Syndrome of inappropriate ADH secretion
Drugs
Psychogenic polydipsia
3. Water retention and salt depletion
Postoperative, post trauma or patients with excess fluid losses given inappropriate fluid replacement
Adrenocortical failure
Diuretic excess

ADH, Antidiuretic hormone.

134 and 146 mmol/L. The intracellular sodium concentration varies between different tissues, and normally ranges from 3 to 20 mmol/L.

The standard Western society dietary sodium intake is about 150 mmol/day, but the daily intake of sodium varies widely, with urinary losses ranging from less than 1 to greater than 240 mmol/day.[7] Sodium balance is influenced by renal hormonal and ECF physical characteristics. The complete renal adjustment to an altered sodium load usually requires 3–4 days before balance is restored.

HYPONATRAEMIA

Hyponatraemia is defined as serum sodium less than 135 mmol/L and may be classified as isotonic, hypertonic or hypotonic, depending upon the measured serum osmolality (Box 95.1).

Isotonic hyponatraemia

Plasma normally contains 94% water and 7% solids (5.5% proteins, 1% salts and 0.5% lipids). If the solid phase is elevated significantly (e.g. in hyperlipidaemia or hyperproteinaemia), any device that dilutes a specific amount of plasma for analysis will give falsely lower values for all measured compounds. This effect produces 'factitious or pseudo-hyponatraemia' and is associated with a normal measured serum osmolality.[8] The measurement of plasma sodium by an ion-selective electrode is not affected by the volume of plasma 'solids' and therefore 'pseudohyponatraemia' will not occur with this method.[8]

Hypertonic hyponatraemia

In patients who have hypertonicity due to increased amounts of impermeant solutes (e.g. glucose, mannitol, glycerol or sorbitol), a shift of water from the ICF to the ECF occurs to provide osmotic equilibration, thus diluting the ECF sodium. Such resultant hyponatraemia is often associated with an increased measured osmolality. For example, in the presence of hyperglycaemia, for every 3 mmol/L rise in glucose the serum sodium decreases by 1 mmol/L.[9]

Hypotonic hyponatraemia

Hyponatraemia is almost always caused by an excess of total body water, due to excessive hypotonic or water-generating intravenous (IV) fluids (e.g. 1.5% glycine, 0.45% saline or 5% glucose) or to excessive ingestion of water, particularly in the presence of high circulating ADH concentrations. It may rarely be caused by loss of exchangeable sodium or potassium. In the latter circumstances, a loss of approximately 40 mmol of sodium or potassium, without a change in total body water content, is required to lower the serum sodium by 1 mmol/L. As hyponatraemia may be associated with an alteration in both total body water and total body sodium, the ECF may be increased (hypervolaemia), decreased (hypovolaemia) or exhibit no change (isovolaemia).[5]

In health, a fluid intake up to 15–20 L may be tolerated before water is retained and hyponatraemia occurs. In psychogenic polydipsia, if the water intake exceeds the renal capacity to form dilute urine, water retention and hyponatraemia will occur. With this disorder, the plasma osmolality exceeds urine osmolality. In circumstances where ADH is increased (e.g. hypovolaemia, hypotension, pain or nausea), or where renal response to ADH is altered (i.e. in renal, hepatic, pituitary, adrenal or thyroid failure), water retention occurs with lower intakes of fluid.

SPECIFIC CAUSES OF HYPONATRAEMIA

Transurethral resection of prostate syndrome

Clinical features The transurethral resection of prostate (TURP) syndrome consists of hyponatraemia, cardiovascular disturbances (hypertension, hypotension, bradycardia), an altered state of consciousness (agitation, confusion, nausea, vomiting, myoclonic and generalised seizures) and, when using glycine solutions, transient visual disturbances of blurred vision, blindness and fixed dilated pupils, following TURP. It has also been described following endometrial ablation.[10] It may occur within 15 minutes or be delayed for up to 24 hours after surgery,[11] and is usually caused by an excess absorption of the irrigating fluid, which contains 1.5% glycine with an osmolality of 200 mOsm/kg. Hyponatraemic syndromes have also been described when surgical irrigating solutions containing 3% mannitol or 3% sorbitol have been used.

Symptoms usually occur when greater than 1 L of 1.5% glycine or greater than 2–3 L of 3% mannitol or sorbitol have been absorbed.[12]

The excess absorption of irrigating fluid causes an increase in total body water (which is often associated with only a small decrease in plasma osmolality), hyponatraemia (as glycine, sorbitol or mannitol reduces the sodium component of ECF osmolality) and an increase in the osmolar gap.[12,13] When glycine is used, other features include hyperglycinaemia (up to 20 mmol/L; normal plasma glycine concentrations range from 0.15 to 0.3 mmol/L), hyperserinaemia (as serine is a major metabolite of glycine), hyperammonaemia (following deamination of glycine and serine) and metabolic acidosis and hypocalcaemia (due to the glycine metabolites glyoxylic acid and oxalate). Because glycine is an inhibitory neurotransmitter, and as it passes freely into the intracellular compartment when glycine solutions are used, hyperglycinaemia may be more important in the pathophysiology of this disorder than a reduction in body fluid osmolality and cerebral oedema.[14]

Treatment Treatment is largely supportive with the management of any reduction in plasma osmolality being based on the measured plasma osmolality and not the plasma sodium. If the measured osmolality is greater than 260 mOsm/kg and mild neurological abnormalities exist, and if the patient is haemodynamically stable with normal renal function, close observation and reassurance (e.g. the visual disturbances are reversible and will last for less than 24 hours) are usually all that is needed. If the patient exhibits haemodynamic instability or severe and unresolving neurological abnormalities, haemodialysis may be warranted. Hypertonic saline is indicated only if the measured osmolality is less than 260 mOsm/kg and severe non-visual neurological abnormalities exist.[15]

Syndrome of inappropriate antidiuretic hormone secretion

This syndrome is a form of hyponatraemia in which there is an increased concentration of ADH inappropriate to any osmotic or volume stimulus that normally affects ADH secretion.[16] Diagnostic criteria and common causes are listed in Boxes 95.2 and 95.3, respectively.

Clinical features Whereas cerebral manifestations are usually absent when the sodium concentration exceeds 125 mmol/L, progressive symptoms of headache, nausea, confusion, disorientation, coma and seizures may be observed when plasma sodium is below 120 mmol/L, particularly if the decrease in serum sodium concentration occurs rapidly.[17]

Treatment Initial treatment should be fluid restriction with close monitoring of serum sodium. If serum sodium concentration is not increasing with fluid restriction, judicious administration of sodium as IV normal or hypertonic saline may be required. As the true duration and rapidity of onset of hyponatraemia are often unclear, the presence and severity of symptoms may be used as the trigger for active correction of hyponatraemia.[17] The evidence base available to guide therapy is limited and there is consequently no consensus on the optimum rate at which to correct the serum sodium concentration. The major concern is to avoid neurological damage from untreated seizures, cerebral oedema or myelinolysis.[17] In the absence of good evidence, recommended rates at which to increase the sodium concentration vary from 0.5 to 2 mmol/L/h. Unless the treating clinician feels that more rapid correction is indicated, it seems prudent to correct the serum sodium concentration at a slower rather than a faster rate.

Box 95.2 Criteria for the diagnosis of syndrome of inappropriate antidiuretic hormone

- Hypotonic hyponatraemia
- Urine osmolality greater than plasma osmolality
- Urine sodium excretion greater than 20 mmol/L
- Normal renal, hepatic, cardiac, pituitary, adrenal and thyroid function
- Absence of hypotension, hypovolaemia, oedema and drugs affecting ADH secretion
- Correction by water restriction

ADH, Antidiuretic hormone.

Box 95.3 Aetiology of syndrome of inappropriate antidiuretic hormone

Ectopic antidiuretic hormone production by tumours
- Small cell bronchogenic carcinoma
- Adenocarcinoma of the pancreas or duodenum
- Leukaemia
- Lymphoma
- Thymoma

Central nervous system disorders
- Cerebral trauma
- Brain tumour (primary or secondary)
- Meningitis or encephalitis
- Brain abscess
- Subarachnoid haemorrhage
- Acute intermittent porphyria
- Guillain–Barré syndrome
- Systemic lupus erythematosus

Pulmonary diseases
- Viral, fungal and bacterial pneumonias
- Tuberculosis
- Lung abscess

Cerebral salt wasting

Cerebral salt wasting (CSW) is a syndrome occurring in patients with a cerebral lesion and excess renal loss of sodium and chloride.[18] The exact aetiology of the syndrome remains unclear. Although hyponatraemia is not necessary for the diagnosis, the syndrome is commonly associated with hyponatraemia.[19] The diagnosis of CSW is suspected in patients with a cerebral lesion, such as subarachnoid haemorrhage, traumatic brain injury or a cerebral tumour, when there is an elevated urine output, with elevated urinary sodium in the absence of a physiological cause for increased sodium excretion.[19] The syndrome can be differentiated from the syndrome of inappropriate antidiuretic hormone (SIADH), as patients with CSW will have evidence of ECF depletion (e.g. negative fluid balance, tachycardia, increased haematocrit, increased urea, low central venous pressure) as opposed to the SIADH where ECF volume will be normal or slightly expanded.[20] The treatment of patients involves exclusion of other causes of hyponatraemia and increased urine output, replacement of sodium and fluid losses, and possibly fludrocortisone.[21]

SPECIFIC TREATMENTS USED FOR HYPONATRAEMIA

Hypertonic saline

Hypertonic saline, most commonly as 3% saline, is used as a therapy for patients with symptomatic hyponatraemia. Due to the osmolarity (1000 mOsm/L) of 3% saline, it should be given through a central line, and care must be taken to avoid the known complications of its use, including chronic heart failure and central pontine and extrapontine myelinolysis (osmotic demyelination syndrome).[22,23] Careful haemodynamic and electrolyte monitoring throughout saline administration is required.

Although hypertonic saline has been proposed as a therapy for raised intracranial pressure in a number of clinical settings,[24] its use remains controversial.[25] In a recent methodologically sound, randomised, clinical trial, which included 229 patients with severe traumatic brain injury, resuscitation with 250 mL of 7.5% saline was not associated with improved mortality or functional outcomes compared with Hartmann's solution.[26]

Vasopressin receptor antagonists

V_2 receptor antagonists, such as lixivaptan, tolvaptan and OPC-31260, have recently been developed. These agents come from a novel class of non-peptide agents that bind to V_2 receptors in the distal tubule of the kidney and prevent vasopressin-mediated aquaporin mobilisation, and thus promote aquaresis.[27] These agents have been trialled as therapeutic options for the treatment of hyponatraemia in a number of clinical settings, including hyponatraemia associated with heart failure, cirrhosis and SIADH.[27,28] At present the role of V_2 receptor antagonists in the management of hyponatraemia in critically ill patients remains uncertain.

HYPERNATRAEMIA

Hypernatraemia, defined as a serum sodium greater than 145 mmol/L, is always associated with hyperosmolality and may be caused by excessive administration of sodium salts (bicarbonate or chloride), water depletion or excess sodium with loss of water (Box 95.4).

Excessive ingestion of sodium salts is rare, but intravenous infusion of large volumes of sodium-containing fluids is common in the management of hospitalised patients. Hypernatraemia often occurs in the recovery phase of acute illness when spontaneous diuresis or diuretic therapy results in more rapid clearance of free water than sodium. Pure water depletion is uncommon, unless water restriction is applied to a patient who is unconscious or unable to obtain or ingest water, as the thirst response normally corrects water depletion. If it occurs, the serum sodium concentration increases, in association with the loss of both ECF and ICF.

Box 95.4 Causes of hypernatraemia

- Water depletion
  - Extrarenal loss
    - Exposure
    - GIT losses (often with excess saline replacement)
  - Renal loss
    - Osmotic diuresis – urea, mannitol, glycosuria
    - Diabetes insipidus
      - Neurogenic
        - Post-traumatic, fat embolism
        - Metastatic tumours, craniopharyngioma, pinealoma, cysts
        - Meningitis, encephalitis
        - Granulomas (tuberculosis, sarcoid)
        - Guillain–Barré syndrome
        - Idiopathic
      - Nephrogenic
        - Congenital
        - Hypercalcaemia, hypokalaemia
        - Lithium
        - Pyelonephritis
        - Medullary sponge kidney
        - Polycystic kidney
        - Post-obstructive uropathy
        - Multiple myeloma, amyloid, sarcoid
- Salt gain
  - Administration of hypertonic saline, 0.9% saline or sodium bicarbonate

GIT, Gastrointestinal tract.

Clinical features

Hypernatraemia usually produces symptoms if the serum sodium exceeds 155–160 mmol/L (i.e. osmolality >330 mOsm/kg). The clinical features include increased temperature, restlessness, irritability, drowsiness, lethargy, confusion and coma.[29] Convulsions are uncommon. The diminished ECF volume may reduce cardiac output, thereby reducing renal perfusion, leading to pre-renal renal failure.

Treatment

For pure water depletion, this consists of water administration. If IV fluid is required, 5% glucose or hypotonic saline solution (0.45% saline) can be used, as sterile water infusion causes haemolysis. In rare cases, IV sterile water may be used by administering through a central venous catheter.[30] Since rapid rehydration may give rise to cerebral oedema, the change in serum sodium should be no greater than 0.5 mmol/L/h.[29]

POTASSIUM

Potassium is the principal intracellular cation and accordingly (along with its anion) fulfils the role of the ICF osmotic provider. It also plays a major role in the functioning of excitable tissues (e.g. muscle and nerve). As the cell membrane is 20-fold more permeable to potassium than to sodium ions, potassium is largely responsible for the resting membrane potential. Potassium also influences carbohydrate metabolism and glycogen and protein synthesis.

Total body potassium is 45–50 mmol/kg in the male (3500 mmol/70 kg) and 35–40 mmol/kg (2500 mmol/65 kg) in the female; 95% of the total body potassium is exchangeable. As ECF potassium ranges from 3.1 to 4.2 mmol/L, the total ECF potassium ranges from 55 to 70 mmol. About 90% of the total body potassium is intracellular: 8% resides in bone, 2% in ECF water and 70% in skeletal muscle. With increasing age (and decreasing muscle mass), total body potassium decreases.

FACTORS AFFECTING POTASSIUM METABOLISM

The potassium content of cells is regulated by a cell wall pump-leak mechanism. Cellular uptake is by the Na^+/K^+ pump, which is driven by Na^+/K^+ ATPase. Movement of potassium out of the cell is governed by passive forces (i.e. cell membrane permeability and chemical and electrical gradients to the potassium ion).

Acidosis promotes a shift of potassium from the ICF to the ECF, whereas alkalosis promotes the reverse shift. Hyperkalaemia stimulates insulin release, which promotes a shift of potassium from the ECF to the ICF, an effect independent of the movement of glucose. β_2-adrenergic agonists promote cellular uptake of potassium by a cyclic adenine monophosphate (AMP)-dependent activation of the Na^+/K^+ pump, whereas α-adrenergic agonists cause a shift of potassium from the ICF to the ECF.[31] Aldosterone increases the renal excretion of potassium; glucocorticoids are also kaliuretic, an effect that may be independent of the mineralocorticoid receptor.

Normally, mechanisms to reduce the ECF potassium concentration (by increasing renal excretion and shifting potassium from the ECF to the ICF) are very effective. However, mechanisms to retain potassium in the presence of potassium depletion are less efficient, particularly when compared with those of sodium conservation. Even with severe potassium depletion, urinary loss of potassium continues at a rate of 10–20 mmol/day. Metabolic alkalosis also enhances renal potassium loss, by encouraging distal nephron Na^+/K^+, rather than Na^+/K^+ exchange.

HYPOKALAEMIA

Hypokalaemia is defined as a serum potassium of less than 3.5 mmol/L (or plasma potassium less than 3.0 mmol/L). It may be due to decreased oral intake, increased renal or gastrointestinal loss, or movement of potassium from the ECF to the ICF (Box 95.5).

Clinical features

These include weakness, hypotonicity, depression, constipation, paralytic ileus, ventilatory failure, ventricular tachycardias (characteristically Torsades de pointes), atrial tachycardias and even coma.[32] With prolonged and severe potassium deficiency, rhabdomyolysis, thirst and polyuria, due to the development of renal diabetes insipidus, may occur. The electrocardiograph (ECG) changes are relatively non-specific, and include prolongation of the PR interval, T-wave inversion and prominent U-waves.

Treatment

IV or oral potassium chloride will correct hypokalaemia, particularly if it is associated with metabolic alkalosis. If the patient has renal tubular acidosis and hypokalaemia, potassium acetate or citrate may be preferred to potassium chloride. IV administration of potassium should normally not exceed 40 mmol/h, and plasma potassium should be monitored at 1- to 4-hourly intervals.[33] In patients with acute myocardial infarction and hypokalaemia, traditional recommendations were to maintain the serum potassium at ≥4.0 mmol/L,[34] but more recently the need to administer supplemental potassium when the serum potassium is greater than 3.5 mmol/L has been questioned.[35]

HYPERKALAEMIA

Hyperkalaemia is defined as a serum potassium greater than 5.0 mmol/L or plasma potassium greater than 4.5 mmol/L. It may be artefactual (from sampling errors such as in vitro haemolysis); true hyperkalaemia may be due to excessive intake, severe tissue damage, decreased excretion or body fluid compartment shift (Box 95.6).

Box 95.5 Causes of hypokalaemia

Inadequate dietary intake (urine K^+ <20 mmol/L)
Abnormal body losses
- Gastrointestinal (urine K^+ <20 mmol/L)
  - Vomiting, nasogastric aspiration
  - Diarrhoea, fistula loss
  - Villous adenoma of the colon
  - Laxative abuse
- Renal (urine K^+ >20 mmol/L)
  - Conn syndrome
  - Cushing syndrome
  - Bartter syndrome
  - Ectopic ACTH syndrome
    - Small-cell carcinoma of the lung
    - Pancreatic carcinoma
    - Carcinoma of the thymus
- Drugs
  - Diuretics
  - Corticosteroids
  - Carbapenems, amphotericin B, gentamicin
  - Cisplatin
- Renal tubular acidosis
- Magnesium deficiency

Compartmental shift
- Alkalosis
- Insulin
- Na^+/K^+ ATPase stimulation
  - Sympathomimetic agents with β2 effect
  - Methylxanthines
- Barium poisoning
- Hypothermia
- Toluene intoxication
- Hypokalaemic periodic paralysis
- Delayed following blood transfusion (see Chapter 97)

ACTH, Adrenocorticotropic hormone.

Box 95.6 Causes of hyperkalaemia

Collection abnormalities
- Delay in separating RBC
- Specimen haemolysis
- Thrombocythaemia

Excessive intake
- Transiently following blood transfusion (see Chapter 97)
- Exogenous (i.e. IV or oral KCl, massive blood transfusion)
- Endogenous (i.e. tissue damage)
  - Burns, trauma
  - Rhabdomyolysis
  - Tumour lysis

Decrease in renal excretion
- Drugs
  - Spironolactone, triamterene, amiloride
  - Indomethacin
  - Captopril, enalapril
- Renal failure
- Addison disease
- Hyporeninaemic hypoaldosteronism

Compartmental shift
- Acidosis
- Insulin deficiency
- Digoxin overdosage
- Succinylcholine
- Arginine hydrochloride
- Hyperkalaemic periodic paralysis
- Fluoride poisoning

IV, Intravenous; *RBC*, red blood cells.

Clinical features

These include tingling, paraesthesia, weakness, flaccid paralysis, hypotension and bradycardia. The characteristic ECG effects include peaking of the T-waves, flattening of the P-wave, prolongation of the PR interval (until sinus arrest with nodal rhythm occurs), widening of the QRS complex, and the development of a deep S-wave. Finally, a sine wave ECG pattern that deteriorates to asystole may occur at serum potassium levels of 7 mmol/L or greater.

Treatment

This is directed at the underlying cause, and may include dialysis. Rapid management of life-threatening hyperkalaemia may be achieved by[36]:

- Calcium chloride 5–10 mL IV of 10% (3.4–6.8 mmol, which is used to reduce the cardiac effects of hyperkalaemia)
- Sodium bicarbonate, 50–100 mmol IV
- Glucose, 50 g IV with 10–15 units of soluble insulin
- Oral and rectal resonium A, 50 g
- Diuresis with frusemide, 40–80 mg IV
- β-agonists; for example, salbutamol 5–10 mg nebulised.

CALCIUM

Almost all (99%) of the body calcium (30 mmol or 1000 g or 1.5% body weight) is present in bone. A small but significant quantity of ionised calcium exists in the ECF, and is important for many cellular activities including secretion, neuromuscular impulse formation, contractile functions and clotting. Normal daily intake of calcium is 15–20 mmol, although only 40% is absorbed. The average daily urinary loss is 2.5–7.5 mmol. The total ECF calcium of 40 mmol (2.20–2.55 mmol/L) exists in three forms: 40% (1.0 mmol/L) is bound to protein (largely albumin), 47% is ionised (1.15 mmol/L) and 13% is complexed (0.3 mmol/L) with citrate, sulphate and phosphate. The ionised form is the physiologically important form, and may be acutely reduced in alkalosis, which

causes a greater amount of the serum calcium to be bound to protein.[37] The total serum calcium can vary with the serum albumin concentrations. A correction factor can be used to offset the effect of serum albumin on serum calcium: this is 0.02 mmol/L for every 1 g/L increase in serum albumin (up to a value of 40 g/L), added to the measured calcium concentration. For example, if measured serum calcium is 1.82 mmol/L, and serum albumin is 25 g/L, corrected serum calcium = 1.82 + [(40 − 25) × 0.02] mmol/L = 2.12 mmol/L. It has been suggested that ionised calcium, where available, is a better indicator of calcium status in the critically ill.[38]

HYPOCALCAEMIA

Common causes of hypocalcaemia include hypoparathyroidism and pseudohypoparathyroidism, septic shock, acute pancreatitis and rhabdomyolysis.[39] Clinical features of reduced serum ionised calcium include tetany, cramps, mental changes and decrease in cardiac output. Symptomatic hypocalcaemia should be treated with IV calcium, as either calcium chloride or calcium gluconate. It should be remembered that 1 mL of calcium chloride has three times as much elemental calcium as 1 mL of calcium gluconate, and so the former is the preferred formulation in acute situations. Calcium should be administered via a central vein when practical, owing to the risk of tissue damage if extravasated.[39]

HYPERCALCAEMIA

The clinical features of hypercalcaemia include nausea, vomiting, pancreatitis, polyuria, polydipsia, muscular weakness, mental disturbance and ectopic calcification. Some of the common causes of hypercalcaemia include endocrine diseases, such as hyperparathyroidism and thyrotoxicosis, renal failure, malignancy, thiazide diuretics and prolonged immobilisation.[39]

Severe hypercalcaemia (>3.3 mmol/L) or more moderate symptomatic hypercalcaemia will require specific therapy. A cause for the elevated calcium concentration should be sought, and specific treatment may be warranted. General measures include restoration of intravascular volume, followed by the use of a loop diuretic, such as frusemide, to promote calcium excretion. The use of bisphosphonates, such as pamidronate, is recommended for severe hypercalcaemia.[40] Other therapies to consider include corticosteroids, calcitonin and mithramycin.

MAGNESIUM

Magnesium is primarily an intracellular ion that acts as a metallo-coenzyme in numerous phosphate transfer reactions. It has a critical role in the transfer, storage and use of energy.

In humans, the total body magnesium content is 1000 mmol, and plasma concentrations range from 0.70 to 0.95 mmol/L. The daily oral intake is 8–20 mmol (40% of which is absorbed) and the urinary loss, which is the major source of excretion of magnesium, varies from 2.5 to 8 mmol/day.[41]

Box 95.7 Causes of magnesium deficiency

- Gastrointestinal disorders
  - Malabsorption syndromes
  - GIT fistulas
  - Short-bowel syndrome
  - Prolonged nasogastric suction
  - Diarrhoea
  - Pancreatitis
  - Parenteral nutrition
- Alcoholism
- Endocrine disorders
  - Hyperparathyroidism
  - Hyperthyroidism
  - Conn syndrome
  - Diabetes mellitus
  - Hyperaldosteronism
- Renal diseases
  - Renal tubular acidosis
  - Diuretic phase of acute tubular necrosis
- Drugs
  - Aminoglycosides
  - Carbenicillin, ticarcillin
  - Amphotericin B
  - Diuretics
  - Cis-platinum
  - Ciclosporin

GIT, Gastrointestinal tract.

HYPOMAGNESAEMIA

Hypomagnesaemia is caused by decreased intake or increased loss (Box 95.7). Clinical features include neurological signs of confusion, irritability, delirium tremors, convulsions and tachyarrhythmias. Hypomagnesaemia is often associated with resistant hypokalaemia and hypocalcaemia. Treatment consists of IV magnesium sulphate as a bolus of 10 mmol administered over 5 minutes, followed by 20–60 mmol/day.

HYPERMAGNESAEMIA

Hypermagnesaemia is often caused by excessive administration of magnesium salts or conventional doses of magnesium in the presence of renal failure. Clinical features include drowsiness, hyporeflexia and coma, vasodilatation and hypotension, and conduction defects of sinoatrial and atrioventricular nodal block and asystole may occur. Treatment is directed towards increasing excretion of the ion, which may require dialysis. IV calcium chloride may be used for rapidly treating the cardiac conduction defects.[41]

Box 95.8 Causes of hypophosphataemia

Hyperparathyroidism
Vitamin D deficiency
Vitamin-D-resistant rickets
Renal tubular acidosis
Alkalosis
Parenteral nutrition
Alcoholism
Refeeding syndrome

Box 95.9 Causes of hyperphosphataemia

Rhabdomyolysis
Renal failure (acute or chronic)
Vitamin D toxicity
Acidosis
Tumour lysis
Hypoparathyroidism
Pseudohypoparathyroidism
Diphosphonate (bisphosphonate) therapy
Excess intravenous administration

MAGNESIUM THERAPY

There are increasing reports of the use of magnesium as a therapy for a variety of conditions. A randomised, controlled trial of over 10,000 women with pre-eclampsia demonstrated the efficacy of magnesium in the prevention of eclampsia[42]; it is also a recommended treatment for established eclampsia. It has been used to treat atrial fibrillation, to achieve both rate control and reversion to sinus rhythm in a number of settings, including post-cardiac surgery, and in the emergency department.[43,44] Magnesium, given either intravenously or nebulised, may be beneficial for patients with acute severe asthma.[45,46] Magnesium has been investigated for preventing delayed cerebral ischaemia and improving functional outcomes in patients with subarachnoid haemorrhage, but current evidence does not support its routine use for this indication.[47]

PHOSPHATE

While most of the body phosphate exists in bone, 15% is found in the soft tissues as ATP, red blood cell 2,3-DPG, and other cellular structural proteins, including phospholipids, nucleic acids and phosphoproteins. Phosphate also acts as a cellular and urinary buffer.[41]

HYPOPHOSPHATAEMIA

Hypophosphataemia may be caused by a decreased intake, increased excretion or intracellular redistribution (Box 95.8). Although hypophosphataemia is generally symptom-free, clinical features have been described that include paraesthesia, muscle weakness, seizures, coma, rhabdomyolysis and cardiac failure. Hypophosphataemia may be a prominent feature of the refeeding syndrome when it may be accompanied by other electrolyte disturbances such as hypokalaemia and hypomagnesaemia. Treatment consists of close monitoring and replacement as oral or IV sodium or potassium phosphate, 50–100 mmol/24 h.

HYPERPHOSPHATAEMIA

Hyperphosphataemia is usually caused by an increased intake or decreased excretion and is common in both acute and chronic renal failure (Box 95.9). Clinical features include ectopic calcification of nephrocalcinosis, nephrolithiasis and band keratopathy. Treatment may require haemodialysis; otherwise oral aluminium hydroxide and even hypertonic glucose solutions to shift ECF phosphate into the ICF can be used.

FLUID AND ELECTROLYTE REPLACEMENT THERAPY

GENERAL PRINCIPLES

In critical illness many of the body's normal homeostatic mechanisms are deranged and basic life-preserving senses, such as hunger and thirst, may be abolished by disease processes or by treatments such as the use of sedation. As a result, the survival of critically ill patients depends on the administration of appropriate volumes of fluids, and appropriate quantities of electrolytes and nutrition by their medical and nursing attendants. In addition to basal requirements, many critically ill patients have abnormal fluid and electrolyte losses that must be replaced; examples are discussed below.

GASTROINTESTINAL LOSSES

The daily volumes and composition of gastrointestinal tract (GIT) secretions in mmol/L are shown in Table 95.8. Clinical effects of fluid loss from the GIT are largely determined by the volume and composition of the fluid, and therapy is usually directed at replacing the losses. Gastric fluid loss (e.g. from vomiting and nasogastric suction) results in water, sodium, hydrogen ion, potassium and chloride depletion. Hence metabolic alkalosis, hypokalaemia, hypotension and dehydration develop if the saline and potassium chloride losses are not correctly replaced.

Pancreatic and biliary fluid losses (e.g. pancreatic or biliary fistula)

These may result in hyperchloraemic acidosis with hypokalaemia, hypotension and dehydration if the losses of bicarbonate, potassium and saline are not replaced.

Table 95.8 Daily volume and electrolyte composition of gastrointestinal tract secretions

ELECTROLYTES (mmol/L)	VOL. (L)	H^+	Na^+	K^-	CL^-	HCO_3^-
Saliva	0.5–1.0	0	30	20	10–35	0–15
Stomach	1.0–2.5	0–120	60	10	100–120	0
Bile	0.5	0	140	5–10	100	40–70
Pancreatic	0.75	0	140	5–10	70	40–70
Small and large gut	2.0–4.0	0	110	5–10	100	25

Intestinal losses (e.g. fistula or ileostomy losses, diarrhoea and ileus)

These result in hypokalaemia, hypotension and dehydration if the saline and potassium losses are not replaced.

RESUSCITATION FLUIDS

Systemic hypotension is a common feature of acute illness and first-line treatment is usually the administration of intravenous resuscitation fluid. The fluids available to clinicians to maintain or expand intravascular volume include crystalloids, colloid solutions and blood products; the properties of the latter two are discussed in Chapters 97 and 98.

Whether the choice of resuscitation fluid influences patients' outcomes has been the subject of long-running debate. This debate has been fuelled by the conflicting and inconclusive results of a number of meta-analyses.[48,49] Data from clinical trials may help guide clinicians with the choice of resuscitation fluids. The Saline versus Albumin Fluid Evaluation Study, found that saline and albumin produced comparable outcomes in a heterogeneous population of critically ill adult patients,[50] but in patients with traumatic brain injury resuscitation with albumin was associated with a significant increase in mortality.[51] The Crystalloid versus Hydrioxyethyl Starch Trial study demonstrated no advantage to the use of hydroxyethyl starch (HES) compared to saline in a similar population of patients, with a greater proportion of those assigned to HES being treated with renal replacement therapy.[52] The choice of fluid for resuscitation also may be important in patients with severe sepsis. In a trial led by the Scandinavian Critical Care Trials Group[53] patients with severe sepsis who were resuscitated with hydroxylethyl starch 130/0.42 in Ringer's acetate had an increased risk of death compared with those resuscitated only with Ringer's acetate. Although rapid fluid resuscitation remains a strongly recommended treatment for adults with severe sepsis in the developed world, a trial in African children with severe infections has challenged the assumption that this is the correct strategy in all situations. In the Fluid Expansion as Supportive Therapy study, children with severe infections who received 20–40 mL/kg of either normal saline or 5% albumin as fluid boluses had an increased risk of death compared with those who received only maintenance fluids.[54] The relevance of these findings for adult patients and developed world medicine is unclear. Further investigator-initiated trials are currently underway (such as the PLUS study, NCT02721654) and their results may further assist clinicians in developing evidence-based fluid resuscitation strategies.

KEY REFERENCES

51. Myburgh J, Cooper DJ, Finfer S, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med*. 2007;357(9):874–884.
53. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012;367(2):124–134.
54. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med*. 2011;364(26):2483–2495.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Edelman IS, Leibman J. Anatomy of body water and electrolytes. *Am J Med*. 1959;2:725–777.
2. Gamble J. *Chemical Anatomy, Physiology and Pathology of Extracellular Fluid*. Cambridge, MA: Harvard University Press; 1954.
3. Moore FD, Olesen KH, McMurray JD. *Body Composition in Health and Disease*. Philadelphia: WB Saunders; 1963.
4. Bie P. Osmoreceptors, vasopressin, and control of renal water excretion. *Physiol Rev*. 1980;60: 961–1048.
5. Humes HD. Disorders of water metabolism. In: Kokko JP, Tannen RL, eds. *Fluid and Electrolytes*. Philadelphia: WB Saunders; 1986:118–149.
6. Phillips PJ. Water metabolism. *Anaesth Intensive Care*. 1977;5:295–304.
7. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt Cooperative Research Group. *BMJ*. 1988;297: 319–328.
8. Weisberg LS. Pseudohyponatremia: a reappraisal. *Am J Med*. 1989;86:315–318.
9. Katz MA. Hyperglycemia-induced hyponatremia – calculation of expected serum sodium depression. *N Engl J Med*. 1973;289:843–844.
10. Arieff AI, Ayus JC. Endometrial ablation complicated by fatal hyponatremic encephalopathy. *JAMA*. 1993;270:1230–1232.
11. Gravenstein D. Transurethral resection of the prostate (TURP) syndrome: a review of the pathophysiology and management. *Anesth Analg*. 1997; 84:438–446.
12. Hahn RG. Fluid and electrolyte dynamics during development of the TURP syndrome. *Br J Urol*. 1990; 66:79–84.
13. Ghanem AN, Ward JP. Osmotic and metabolic sequelae of volumetric overload in relation to the TURP syndrome. *Br J Urol*. 1990;66:71–78.
14. Jensen V. The TURP syndrome. *Can J Anaesth*. 1991;38:90–96.
15. Agarwal R, Emmett M. The post-transurethral resection of prostate syndrome: therapeutic proposals. *Am J Kidney Dis*. 1994;24:108–111.
16. Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of antidiuretic hormone. *Am J Med*. 1967;42:790–806.
17. Reynolds RM, Padfield PL, Seckl JR. Disorders of sodium balance. *BMJ*. 2006;332:702–705.
18. Cort JH. Cerebral salt wasting. *Lancet*. 1954;266: 752–754.
19. Singh S, Bohn D, Carlotti AP, et al. Cerebral salt wasting: truths, fallacies, theories, and challenges. *Crit Care Med*. 2002;30:2575–2579.
20. Rabinstein AA, Wijdicks EF. Hyponatremia in critically ill neurological patients. *Neurologist*. 2003;9:290–300.
21. Hasan D, Lindsay KW, Wijdicks EF, et al. Effect of fludrocortisone acetate in patients with subarachnoid hemorrhage. *Stroke*. 1989;20:1156–1161.
22. Sterns RH, Riggs JE, Schochet SS Jr. Osmotic demyelination syndrome following correction of hyponatremia. *N Engl J Med*. 1986;314:1535–1542.
23. Martin RJ. Central pontine and extrapontine myelinolysis: the osmotic demyelination syndromes. *J Neurol Neurosurg Psychiatry*. 2004;75(suppl 3):iii, 22–28.
24. Bhardwaj A, Ulatowski JA. Hypertonic saline solutions in brain injury. *Curr Opin Crit Care*. 2004;10: 126–131.
25. White H, Cook D, Venkatesh B. The use of hypertonic saline for treating intracranial hypertension after traumatic brain injury. *Anesth Analg*. 2006;102: 1836–1846.
26. Cooper DJ, Myles PS, McDermott FT, et al. Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. *JAMA*. 2004; 291:1350–1357.
27. Yeates KE, Morton AR. Vasopressin antagonists: role in the management of hyponatremia. *Am J Nephrol*. 2006;26:348–355.
28. Palm C, Pistrosch F, Herbrig K, et al. Vasopressin antagonists as aquaretic agents for the treatment of hyponatremia. *Am J Med*. 2006;119(7 suppl 1): S87–S92.
29. Adrogue HJ, Madias NE. Hypernatremia. *N Engl J Med*. 2000;342:1493–1499.
30. Worthley LI. Hyperosmolar coma treated with intravenous sterile water. A study of three cases. *Arch Intern Med*. 1986;146:945–947.
31. Sterns RH, Cox M, Feig PU, et al. Internal potassium balance and the control of the plasma potassium concentration. *Medicine (Baltimore)*. 1981;60: 339–354.
32. Phelan DM, Worthley LI. Hypokalaemic coma. *Intensive Care Med*. 1985;11:257–258.
33. Stockigt JR. Potassium metabolism. *Anaesth Intensive Care*. 1977;5:317–325.
34. ECC Committee, Subcommittees and Task Forces of the American Heart Association. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 8: stabilization of the patient with acute coronary syndromes. *Circulation*. 2005;112(suppl 24): IV-89–IV-110. Online. Available: http://circ.ahajournals.org/cgi/content/full/112/24_suppl/IV-89.
35. Goyal A, Spertus JA, Gosch K, et al. Serum potassium levels and mortality in acute myocardial infarction. *JAMA*. 2012;307(2):157–164.
36. ECC Committee, Subcommittees and Task Forces of the American Heart Association. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 10.1: life-threatening electrolyte abnormalities. *Circulation*. 2005;112(24 suppl):IV-121–IV-125.
37. Thomas DW. Calcium, phosphorus and magnesium turnover. *Anaesth Intensive Care*. 1977;5:361–371.
38. Slomp J, van der Voort PH, Gerritsen RT, et al. Albumin-adjusted calcium is not suitable for

diagnosis of hyper- and hypocalcemia in the critically ill. *Crit Care Med*. 2003;31:1389–1394.
39. Bushinsky DA, Monk RD. Electrolyte quintet: calcium. *Lancet*. 1998;352:306–311.
40. Ariyan CE, Sosa JA. Assessment and management of patients with abnormal calcium. *Crit Care Med*. 2004;32(4 suppl):S146–S154.
41. Weisinger JR, Bellorin-Font E. Magnesium and phosphorus. *Lancet*. 1998;352:391–396.
42. Altman D, Carroli G, Duley L, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet*. 2002;359: 1877–1890.
43. Davey MJ, Teubner D. A randomized controlled trial of magnesium sulfate, in addition to usual care, for rate control in atrial fibrillation. *Ann Emerg Med*. 2005;45:347–353.
44. Henyan NN, Gillespie EL, White CM, et al. Impact of intravenous magnesium on post-cardiothoracic surgery atrial fibrillation and length of hospital stay: a meta-analysis. *Ann Thorac Surg*. 2005;80:2402–2406.
45. Rowe BH, Bretzlaff JA, Bourdon C, et al. Intravenous magnesium sulfate treatment for acute asthma in the emergency department: a systematic review of the literature. *Ann Emerg Med*. 2000;36: 181–190.
46. Hughes R, Goldkorn A, Masoli M, et al. Use of isotonic nebulised magnesium sulphate as an adjuvant to salbutamol in treatment of severe asthma in adults: randomised placebo-controlled trial. *Lancet*. 2003;361:2114–2117.
47. Dorhout Mees SM, Algra A, Wong GK, et al. Early magnesium treatment after aneurysmal subarachnoid hemorrhage: individual patient data meta-analysis. *Stroke*. 2015;46:3190–3193.
48. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ*. 1998;317:235–240.
49. Vincent JL, Navickis RJ, Wilkes MM. Morbidity in hospitalized patients receiving human albumin: a meta-analysis of randomized, controlled trials. *Crit Care Med*. 2004;32:2029–2038.
50. Finfer S, Bellomo R, Boyce N, et al. SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350:2247–2256.
51. Myburgh J, Cooper DJ, Finfer S, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med*. 2007;357(9):874–884.
52. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367:1901–1911.
53. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012;367(2): 124–134.
54. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *New Engl J Med*. 2011;364(26):2483–2495.

96

Enteral and parenteral nutrition

Richard Leonard

It is standard practice to provide nutritional support to critically ill patients in order to treat pre-existing malnutrition and minimise muscle wasting. However, despite the universality of this practice, the evidence underlying it has often been conflicting and of disappointingly poor quality.[1] These failings lead to the familiar trap of preferring opinion based on an appealing mechanistic theory to objective evidence, exemplified by the apparently ineradicable belief that the enteral route of nutrition offers significant clinical benefits.[2]

The problem persists with the publication of numerous clinical practice guidelines,[3–10] which differ significantly in important areas.[11] Fortunately, both the quantity and the quality of available evidence are improving, offering hope that our present uncertainties may be resolved in the future.

NUTRITIONAL ASSESSMENT

Objective assessment of nutritional status is difficult in the intensive care unit (ICU) because disease processes confound methods used in the general population. Anthropometric measures such as triceps skin-fold thickness and midarm circumference may be obscured by oedema. Voluntary handgrip strength is impractical in unconscious patients. Laboratory measures, including transferrin, pre-albumin and albumin levels, lymphocyte counts, and skin-prick test reactivity, are abnormal in critical illness. Subjective clinical evaluation is better than objective measurement at predicting morbidity.[12] Historical features of malnutrition include weight loss, poor diet, gastrointestinal symptoms, reduced functional capacity and a diagnosis associated with poor intake. Physical signs include loss of subcutaneous fat, muscle wasting, peripheral oedema and ascites.

The problem of subjectivity in nutritional assessment in intensive care has led to attempts to define a group of patients at greater nutritional risk, to whom optimal support may be of most benefit. The observation that an increase in caloric intake was associated with reduced mortality only in patients with a body mass index (BMI) below 25 or above 35[13] led to the development of scoring systems to identify patients at high nutritional risk.[14] The NUTRIC score[15] comprised age, APACHE II and SOFA scores, number of comorbidities, number of days in hospital before admission to the ICU, and interleukin 6 (happily, the modified version[16] dispenses with the need to measure the latter) and has been validated in a general ICU population as identifying a group with worse outcomes. Although the use of nutritional scoring systems is advocated in guidelines, a clinical benefit offered above subjective assessment remains to be demonstrated.

PATIENT SELECTION AND TIMING OF SUPPORT

There are reasonable grounds to believe that it is better to provide nutritional support to critically ill patients than not to do so. This belief is based on the close association between malnutrition, negative nitrogen and calorie balance and poor outcome,[13] and the inevitability of death if starvation continues for long enough. In otherwise healthy humans, this takes several weeks to occur. There is also some direct evidence from one study of jejunal feeding in patients operated on for severe pancreatitis,[17] in which the control group received only intravenous fluids until normal diet resumed. Mortality decreased markedly in the group receiving nutritional support.

Two questions arise from this, relating to the important problem of when nutritional support should start:

- How long is it safe to leave a critically ill patient without nutrition? In other words, which patients need to be fed artificially because they would otherwise be starved for too long, and which can safely wait until they are able to eat?
- If the patient will clearly exceed whatever period is deemed reasonable, is it better to begin feeding immediately? In other words, if we are going to feed, when should we start?

Quite good evidence now supports the early institution of nutritional support, and the trend is both to tolerate much shorter periods without nutrition and to begin feeding more rapidly after initial resuscitation.

ABSTRACT

The evidence base for nutritional support of critically ill patients is at long last improving, although an excess of differing guidelines persists. Feeding should be introduced early, once initial resuscitation is complete, and within 24–48 hours of admission to the intensive care unit (ICU). The route of feeding is largely unimportant, but the enteral route is cheaper and easier to use. The energy and protein requirements of critically ill patients are not known with certainty, and probably vary with the patient's prior nutritional status, and the nature, severity and time-course of the underlying illness. Identification of patients at high nutritional risk, and applying protocolised methods to optimise their nutritional support may improve outcomes. Despite the popularity of research into nutritional adjuncts and techniques, such as intentional underfeeding, aimed at modifying generic disease processes, there is no basis presently for their routine use in unselected intensive care patients.

KEYWORDS

Malnutrition
energy and protein requirements
enteral nutrition
parenteral nutrition
nutritional adjuncts

In 1997, recommendations from a conference sponsored by the US National Institutes of Health, the American Society for Parenteral and Enteral Nutrition and the American Society for Clinical Nutrition suggested that nutritional support be started in any critically ill patient unlikely to regain oral intake within 7–10 days.[18] The basis for this was that, at a typical nitrogen loss of 20–40 g/day, dangerous depletion of lean tissue may occur after 14 days of starvation. Others have suggested a maximum acceptable delay of 3–7 days. Small studies comparing earlier with delayed institution of nutritional support have had conflicting results. A meta-analysis comparing early (first 48 hours after admission to the ICU) with late enteral feeding revealed a reduction in infectious complications.[19] Two subsequent meta-analyses comparing early and delayed enteral feeding both found a reduction in mortality with early support,[20,21] although the authors commented that the total number of patients and the methodological quality of the studies included were both low. Early institution of enteral feeding within 24 hours of ICU admission in patients unlikely to feed orally in that time was an important component of the ACCEPT study guideline (Fig. 96.1).[4] The weight of evidence is presently in favour of this more aggressive approach, and recently issued guidelines endorse this,[9,10] but it cannot be regarded as conclusively proven.[22,23] There have been suggestions that patients with low disease severity and nutrition risk, and those with sepsis, may be adversely affected by aggressive early feeding. The former are unlikely to be significantly represented in the ICU population outside North America, while concerns about the latter were somewhat assuaged by large-scale observational data.[24] The most recent sepsis guidelines reflect this reduced concern.[25]

NUTRITIONAL REQUIREMENTS OF THE CRITICALLY ILL

The optimal doses of energy and protein in critical illness have yet to be determined. A great deal of research effort is currently being directed at this area. Earlier research has been hampered by the linkage between protein and energy provision imposed by the composition of commercially available feeds, and by the fact that in practice the target intake is frequently not achieved.[13,26] Optimal intakes may also vary depending on the nutritional status of the patient, and the nature, severity and stage of the underlying illness. These factors have probably confounded past attempts to define a single best dose in unselected patients.

Some muscle wasting and nitrogen loss are unavoidable in critical illness, despite adequate energy and protein provision.[27] This fact, coupled with a realisation that caloric requirements had previously been overestimated, has led to a historical downward revision of intake, a process which may be continuing.

ENERGY

In 1997, the American College of Chest Physicians published guidelines recommending a daily energy intake of 25 kcal/kg,[3] and this has remained a commonly adopted (although commonly not achieved) target energy intake for critically ill patients.

More recently, concerns have been raised that this standard intake may be excessive. An observational study found lower mortality in those patients who received 9–18 kcal/kg/day than in those with higher and lower intakes.[28] Serendipitously, this is the range within which the actual intake delivered seems to fall. Various mechanisms have been postulated to explain potential harm from higher intake, including suppression of autophagy (an important element of defence against intracellular organisms). There are two main strategies of intentional under-feeding – 'trophic' feeding, whereby a very small volume of feed is provided with the aim of preserving gut mucosal integrity, and 'hypocaloric' feeding, in which around 50% of the standard target is provided. Several studies showed little overall effect, a finding replicated by two recent meta-analyses.[29,30] At present, unequivocal benefits of hypocaloric feeding have yet to be demonstrated in large prospective trials. It remains extremely important to realise that enterally fed patients frequently fail to achieve their target intake, and that significant prolonged under-feeding, with a mounting cumulative caloric deficit, is closely associated with worse outcomes.[13,28,31,32] Very recent observational data continue to demonstrate an association between higher caloric intake and lower mortality in critically ill patients with high NUTRIC scores.[33] Intentional under-feeding, if it has a place at all, may be a strategy more suited to less sick, better nourished patients.

Attempts have also been made to tailor the energy provided to critically ill patients to their individual needs. Two methods are commonly used: indirect calorimetry and predictive equations. Indirect calorimetry is the rather burdensome gold standard; its use may become easier in future with the availability of devices designed for ICU patients. It permits measurement of the resting energy expenditure (REE). This value excludes the energy cost of physical activity, which increases later in the course of an ICU admission.[34] Calorimetry reveals deviations from values predicted by equations,[35] such that two-thirds of patients in one study were being either under- or overfed.[36] Previously, it could not be shown that outcomes are improved by the use of calorimetry,[37] but a more recent study showed a trend towards reduced hospital mortality in the group whose feeding was calorimetrically guided (and who received in consequence a higher caloric intake).[38] Moreover, there are no clear data to relate measured REE to total energy expenditure in the individual patient. Presently, few ICUs use calorimetry.

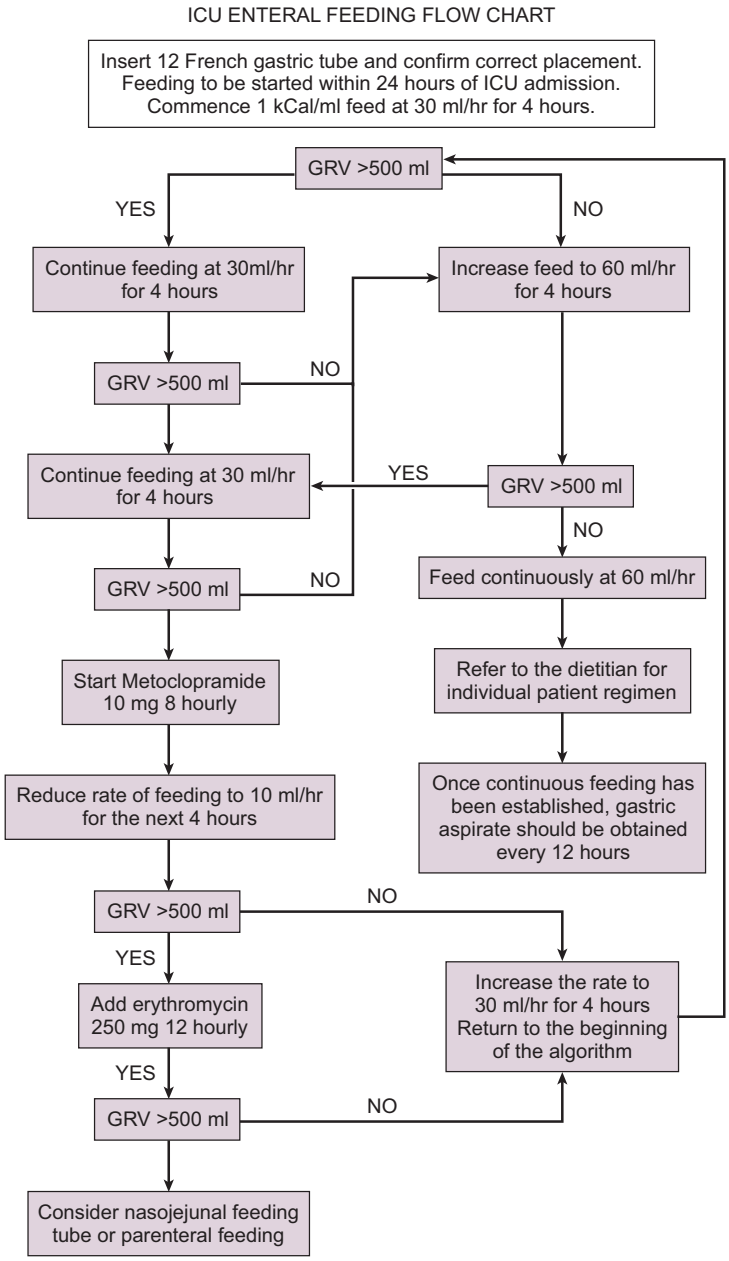


Figure 96.1 Algorithm for intensive care unit (ICU) enteral feeding. *GRV*, Gastric residual volume. *Courtesy of Ella Terblanche, Liesl Wandrag and Jacqui O'Flynn.*

In the absence of a reliable measurement of REE, there exist several equations converting basal metabolic rate predicted from anthropometric data into an estimate of energy expenditure. These rely on correction factors to adjust for variables such as diagnosis, pyrexia and activity. Accepting the general inaccuracy of equations compared with measured energy expenditure, the Penn State formula[39] appears to perform most accurately, except in obese patients.[35]

Despite the popularity of measurements or estimates of energy expenditure, it is not yet clear that their routine use improves outcome. Many ICUs dispense with both and simply aim to deliver 25 kcal/kg/day, in the hope – if not the firm belief – that achieving

somewhat less than this represents an appropriate intake. Increasing the target intake towards 30 kcal/kg/day as the patient recovers and activity increases might then be rational. Nonetheless, the difficulties in interpreting the presently available evidence mean considerable uncertainty attaches to this practice. It may well be that the use of nutritional risk assessment tools to target sicker, more nutritionally compromised individuals with more aggressive regimes tailored to measured REE would represent an improvement on current practice, but this remains to be demonstrated.

PROTEIN

Assessment of nitrogen balance by measuring urinary urea nitrogen is too variable to be useful in estimating protein requirements in the ICU.[40] As there is an upper limit to the amount of dietary protein that can be used for synthesis,[41] there is no benefit from replacing nitrogen lost in excess of this, although mild overprovision appears not to be harmful.[42] The dietary protein requirement for healthy humans is around 0.8 g/kg/day, and for many years the standard recommendation in critical illness was 1 g/kg/day. On the basis of observational studies suggesting reduced mortality and muscle wasting with higher protein intake,[43] recommendations have now been increased to at least 1.2 g/kg/day. Some patients may require up to 2–2.5 g/kg/day, especially those with burns and elderly trauma patients.[9,42] Delivering high-protein intake without also risking excessive energy provision may require use of specialised feed formulae.

MICRONUTRIENTS

Critical illness increases the requirements for vitamins A, E, K, thiamine (B1), B3, B6, vitamin C and pantothenic and folic acids.[44] Thiamine, folic acid and vitamin K are particularly vulnerable to deficiency during total parenteral nutrition (TPN). Renal replacement therapy can cause loss of water-soluble vitamins and trace elements. Deficiencies of selenium, zinc, manganese and copper have been described in critical illness, in addition to the more familiar iron-deficient state. Subclinical deficiencies in critically ill patients are thought to cause immune deficiency and reduced resistance to oxidative stress. Suggested requirements for micronutrients in critically ill patients vary between authors and depending on route of administration; the most comprehensive guidance[44] is reproduced in Tables 96.1 and 96.2. More recent but broadly similar recommendations for some compounds are also available.[45,46]

Commercial preparations of both enteral and parenteral feeding solutions provide standard amounts of micronutrients. Supplementation of intake of certain antioxidant vitamins and trace elements above these levels is discussed below.

Table 96.1 Daily vitamin requirements in critical illness[44]

VITAMIN	FUNCTION	AMOUNT
Vitamin A	Cell growth, night vision	10,000–25,000 IU
Vitamin D	Calcium metabolism	400–1000 IU
Vitamin E	Membrane antioxidant	400–1000 IU
Beta carotene*	Antioxidant	50 mg
Vitamin K	Activation of clotting factors	1.5 µg/kg/day
Thiamine (vitamin B1)	Oxidative decarboxylation	10 mg
Riboflavin (vitamin B2)	Oxidative phosphorylation	10 mg
Niacin (vitamin B3)	Part of NAD, redox reactions	200 mg
Pantothenic acid	Part of coenzyme A	100 mg
Biotin	Carboxylase activity	5 mg
Pyridoxine (vitamin B6)	Decarboxylase activity	20 mg
Folic acid	Haematopoiesis	2 mg
Vitamin B12	Haematopoiesis	20 µg
Vitamin C	Antioxidant, collagen synthesis	2000 mg

*Not strictly a vitamin.

Table 96.2 Daily trace element requirements in critical illness[44]

ELEMENT	FUNCTION	AMOUNT
Selenium	Antioxidant, fat metabolism	100 µg
Zinc	Energy metabolism, protein synthesis, epithelial growth	50 mg
Copper	Collagen cross-linking, ceruloplasmin	2–3 mg
Manganese	Neural function, fatty acid synthesis	25–50 mg
Chromium	Insulin activity	200 mg
Cobalt	B12 synthesis	
Iodine	Thyroid hormones	
Iron	Haematopoiesis, oxidative phosphorylation	10 mg
Molybdenum	Purine and pyridine metabolism	0.2–0.5 mg

Table 96.3 Water and electrolyte requirements per kilogram per day

Water	30 mL
Sodium	1–2 mmol
Potassium	0.7–1 mmol
Magnesium	0.1 mmol
Calcium	0.1 mmol
Phosphorus	0.4 mmol

WATER AND ELECTROLYTES

Water and electrolyte requirements vary widely depending on the patient's condition; typical basal intakes are shown in Table 96.3.

ROUTE OF NUTRITION

When possible, patients should be fed enterally. The advantages over the parenteral route are, however, simply that it is cheaper and easier. Despite the persistent widespread belief that the enteral route offers non-metabolic benefits such as improved gut mucosal integrity and enhanced immune responsiveness, this does not appear to translate into meaningful benefit to patients.

Two hypotheses are commonly advanced in support of the putative superiority of enteral feeding. First, it appears that the lipid contained within TPN is immunosuppressive. Intravenous lipid is known to suppress neutrophil and reticulo-endothelial system function, and a comparison of TPN with and without lipid in critically ill trauma patients showed a lower complication rate in those not receiving lipid.[47] Second, enteral feeding is believed by some to protect against infective complications by improving gut mucosal barrier function and the immune function of gut-associated lymphoid tissue, reducing bacterial translocation and consequent multiple organ failure. However, these theories are based mainly on studies in mice; none of the causal relations they rely upon have been established in humans.

Despite a range of early, small, often poorly designed studies suggesting reductions in infection rates in patients fed enterally, the large recent CALORIES trial demonstrated clearly the absence of any effect of route.[26] While meta-analyses continue to report a reduction in infections with enteral feeding, this effect seems to be based purely on the excessive caloric intake previously associated with parenteral nutrition, rather than the route itself.[8,48] The value of contaminating high quality data from CALORIES with those from earlier, less rigorous studies is far from apparent, and an effect of route alone on clinically significant outcomes is now highly unlikely.

One related area of controversy remains the practice of supplementing partially successful but inadequate enteral intake with intravenous feeding relatively early in the course of an ICU admission. A large multicentre study compared early parenteral supplementation of inadequate enteral intake (within 48 hours of ICU admission) with supplementation delayed until day 8.[49] There was no mortality difference, but patients in the delayed-supplementation group left the ICU earlier and suffered fewer infectious complications. However, interpretation of this study is complicated by the fact that the early-supplementation group received 25–30 kcal/kg/day, raising the possibility that high intake, rather than the route of feeding, was responsible for the increase in infections. The study also used tight glycaemic control. These differences from common practice make it difficult to generalise the findings. It is presently uncertain whether, when and at what dose parenteral feeding should be used to supplement inadequate enteral intake, but very early, aggressive intravenous supplementation does not seem warranted.

ENTERAL NUTRITION

ACCESS

Nasal tubes are preferred to oral, except in patients with a basal skull fracture, in whom there is a risk of cranial penetration. A large-bore (12–14 Fr) nasogastric tube is usually used at first, to provide gastric drainage and permit measurement of gastric residual volumes (see below). Once feeding is established, this can be replaced with a more comfortable fine-bore tube. A stylet is needed to assist in passage of fine-bore tubes. The position of all tubes must be checked before feeding is started, as misplacement is not uncommon and intrapulmonary delivery of feed is potentially fatal. In the United Kingdom, the National Patient Safety Agency has issued guidance recommending daily pH testing of tube aspirate, with X-ray confirmation of correct placement reserved for cases in which pH testing is equivocal or impossible.

Nasojejunal tubes may be beneficial if impaired gastric emptying is refractory to prokinetic agents (see below); their unselective use is not indicated even in patients with mildly elevated gastric residual volumes.[50,51] Spontaneous passage through the pylorus following blind placement is not reliable, but may be increased by the administration of a single dose of erythromycin.[52] Endoscopic or fluoroscopic assistance is needed for truly reliable transpyloric tube placement, although use of electromagnetic guidance systems may obviate the logistic difficulties these traditional methods entail.[53] There are conflicting data on the question of whether nasojejunal feeding reduces the risk of aspiration or ventilator-associated pneumonia,[51,54,55] although a meta-analysis concludes that

it probably does.[8] The tenuous evidence of a clear benefit, coupled with the cost and logistic difficulty of placing them, precludes the routine use of nasojejunal tubes for all patients.

An alternative method of access in those needing long-term enteral feeding is percutaneous gastrostomy, which can be performed endoscopically or radiologically. Percutaneous jejunal access can be obtained either via a gastrostomy or by direct placement during incidental laparotomy.

REGIMEN

Slowly building up the rate of feeding is not proven to avoid symptoms of feed intolerance, such as diarrhoea or high gastric residual volumes. Head-injured patients fed with target intake from the outset have fewer infective complications,[56] and the practice has subsequently been shown to be safe in unselected ICU patients.[57] Nevertheless, it is presently common practice to start delivering around 30 mL/h and build up to the target intake depending on tolerance, as judged by gastric residual volumes. A more aggressive strategy of so-called 'volume-based feeding' (delivering the target volume over 24 hours and catching up for any period of feeding interruption with an increased rate), together with acceptance of higher gastric residual volumes (up to 300 mL) and routine use of prokinetics, results in an increase in the proportion of target intake delivered.[58]

Traditionally, gastric residual volumes are assessed by aspiration of the tube every 4 hours. Values over 150 mL on two successive occasions have been associated with an increased incidence of ventilator-associated pneumonia in one study[59]; in contrast, others have found no link between high residual volumes and the risk of aspiration.[60] Nevertheless, if the residual volume is consistently greater than 200 mL, treatment with prokinetic agents (metoclopramide 10 mg q8h or erythromycin 250 mg q12h intravenously) appears to increase tolerance of feeding, though there is no discernible effect on mortality or morbidity.[52] This is unsurprising in light of two studies showing that it is safe to tolerate gastric residual volumes up to 500 mL[61] or even not to check the volume at all.[62] In refractory cases, a nasojejunal tube often permits successful enteral feeding because small bowel function is resumed quicker than gastric emptying. A nasogastric tube is still needed to drain the stomach. Diarrhoea, abdominal distension, nausea and vomiting may suggest intolerance, even if gastric volumes are low. Absence of bowel sounds is common in ventilated patients and should not be taken to indicate ileus.

Fine-bore tubes should not be aspirated, as this causes them to block. Various folk remedies have been tried for unblocking tubes, including instillation of Coca-Cola, fruit juice and pancreatic enzyme supplements. The instillates should be left in situ for an hour or more.

COMPOSITION

Commercially available enteral feeding solutions vary widely in composition. Polymeric feeds contain intact proteins (derived from whey, meat, soy isolates and caseinates) and carbohydrates in the form of oligo- and polysaccharides. These require pancreatic enzymes for absorption.

Elemental feeds with defined nitrogen sources (amino acids or peptides) are not of benefit when used routinely, but may enable feeding when small bowel absorption is impaired, for instance in pancreatic insufficiency or following prolonged starvation. Lipids are usually provided by vegetable oils consisting mostly of long-chain triglycerides, but some also contain more easily absorbed medium-chain triglycerides. The proportion of non-protein calories provided as carbohydrate is usually two-thirds.

Electrolyte composition varies widely, with sodium- and potassium-restricted formulations available. Vitamins and trace elements are usually added by the manufacturers so that daily requirements are present in a volume containing roughly 2000 kcal. The possible benefits of providing additional doses of some of these substances to critically ill patients are considered below.

COMPLICATIONS

Enteral feeding is an independent risk factor for ventilator-associated pneumonia.[63] Sinusitis due to nasogastric intubation may necessitate changing to an orogastric tube. Fine-bore tubes are vulnerable to misplacement in the trachea or to perforation of the pharynx, oesophagus, stomach or bowel. Percutaneous endoscopic gastrostomy is associated with a high 30-day all-cause mortality in acutely ill patients, in whom it may be best avoided.[64] Other complications include insertion site infection, serious abdominal wall infection and peritonitis. Surgically placed jejunostomies can cause similar problems, and may also obstruct the bowel.

Diarrhoea is common in ICU patients, particularly those being fed enterally. It is often multifactorial and causes considerable distress and morbidity, particularly when the patient is repeatedly soiled with watery stool. Common causes include antibiotic therapy, *Clostridium difficile* infection, faecal impaction and a non-specific effect of critical illness. Malabsorption, lactose intolerance, prokinetic agents, magnesium, aminophylline, quinidine and medications containing sorbitol (for instance, paracetamol syrup and cimetidine) are occasional culprits. Rate of administration of enteral feed also plays a role. Faecal impaction, medication-induced diarrhoea and *C. difficile* infection

must be excluded or treated, while malabsorption may respond to elemental diet. Slowing the rate of feeding sometimes helps; diluting the formula does not. It is unclear whether addition of probiotics or fibre to enteral feed is of benefit in preventing or treating diarrhoea.[8,9]

Metabolic complications include electrolyte abnormalities and hyperglycaemia. Severely malnourished patients are at risk of refeeding syndrome (see below) if nutritional support is begun too rapidly.

PARENTERAL NUTRITION

Parenteral nutritional support is indicated when adequate enteral intake cannot be established within an acceptable time. In some cases, absolute gastrointestinal failure is obvious, whereas in others it becomes apparent only after considerable efforts to feed enterally have failed. As discussed above, there is ample evidence that if enteral feeding cannot be established early, then the parenteral route can safely be used until it can. Nevertheless, the aim in all patients fed intravenously should be to revert to enteral feeding as circumstances permit.

Parenteral feeding solutions may be prepared from their component parts under sterile conditions. Ready-made solutions also exist, but any necessary additions must be made similarly.

In ICU patients, the daily requirements are infused continuously over 24 hours. Careful biochemical and clinical monitoring is important, particularly at the outset (Box 96.1).

Box 96.1 Minimum monitoring during total parenteral nutrition – less stable patients may require more intensive surveillance

Nursing
1. Temperature
2. Pulse
3. Blood pressure
4. Respiratory rate
5. Fluid balance
6. Blood sugar (4-hourly when commencing feed)

Daily (at least)
1. Review of fluid balance
2. Review of nutrient intake
3. Blood sugar
4. Urea, electrolytes and creatinine

Weekly (at least)
1. Full blood picture
2. Coagulation screen
3. Liver function tests
4. Magnesium, calcium and phosphate
5. Weight

As indicated
1. Zinc
2. Uric acid

ACCESS

The major concern with central venous access for TPN is prevention of infection. The following considerations apply.[65]

- *Insertion site:* subclavian lines have lower infection rates than internal jugular or femoral lines. Peripherally inserted central catheters (PICC) also provide safe, convenient access for TPN with low infection rates, and are increasingly used worldwide.
- *Tunnelling* may reduce infection rates in internal jugular lines but apparently not in short-term subclavian lines. It is not recommended for routine use.
- *Expertise* of operator and adequacy of ICU *nurse staffing levels* affect infection rate.
- *Skin preparation:* 2% chlorhexidine in alcohol is the most effective.
- *Sterile technique:* maximal sterile barrier procedures (mask, cap, gown, gloves and large drape) are known to reduce catheter-related bacteraemia rates sixfold. There is a bewildering resistance to use of these precautions outside ICUs.
- *Dressings:* permeable polyurethane transparent dressings are superior to impermeable.
- *Antimicrobial catheters:* catheters coated with either chlorhexidine and silver sulfadiazine or rifampicin and minocycline are several times less likely to cause bacteraemia than standard polyurethane catheters. The duration of the anti-infective effect appears to be longer with the antibiotic-coated catheters (2 weeks vs 1).
- *Scheduled exchange* has not been proven to reduce catheter-related sepsis.
- *Guide-wire exchange* is associated with increased bacteraemia rates, which in routine use outweigh the reduced mechanical complications.

In practice, pre-existing central access is used in the first instance. If a multilumen catheter is used, one lumen should be dedicated to administration of TPN and not used for any other purpose. Three-way taps should be avoided and infusion set changes carried out daily under sterile conditions. For long-term TPN (more than 2 months), specialised catheters with a tunnelled cuff or a subcutaneous port are recommended, although PICC access provides a convenient bridge if already in use.

COMPOSITION

ENERGY

Energy is provided by a combination of carbohydrate and lipid. The optimal balance between the two is unknown; often 30%–40% of non-protein energy is

given as lipid. Alternatively, glucose may be relied upon for almost all the energy, with lipid being infused once or twice a week to provide essential fatty acids.

Glucose is the preferred carbohydrate and is infused as a concentrated solution. Exceeding the body's capacity to metabolise glucose (4 mg/kg/min in the septic patient) can lead to hyperglycaemia, lipogenesis and excess CO_2 production. Endogenous insulin secretion increases to control blood sugar levels. However, many patients require additional insulin, particularly diabetics. This may be infused separately, but when requirements are stable it is more safely added to the TPN solution. Persistent hyperglycaemia is better addressed by reducing the glucose infusion rate than by large doses of insulin.

Lipid provides essential fatty acids (linoleic and linolenic acids) and is a more concentrated energy source than glucose. It may thus avoid the complications of excess glucose administration. However, there are concerns of immunosuppression from lipid infusion, as discussed above. Traditionally, lipid preparations consist of soybean oil emulsified with glycerol and egg phosphatides. Replacement of some or all of the soybean oil with olive-oil- or fish-oil-based lipids or with medium-chain triglycerides has been proposed to offer immunological benefits; however, clear evidence of this has so far been elusive.[66]

NITROGEN

Nitrogen is supplied as crystalline solutions of L-amino acids. Commercially available preparations vary in their provision of conditionally essential amino acids. Glutamine, tyrosine and cysteine are absent from many because of instability.

MICRONUTRIENTS

Vitamin and trace element preparations are added to TPN solutions in appropriate amounts. Thiamine, folic acid and vitamin K are particularly vulnerable to depletion and additional doses may be necessary.

ELECTROLYTES

Amino acid preparations contain varying quantities of electrolytes; additional amounts may need to be added to the solution.

COMPLICATIONS

Parenteral nutrition has the potential for severe complications.

- *Catheter-related sepsis* is addressed above. Other complications of central venous cannulation are discussed elsewhere.
- *Electrolyte abnormalities* include hypophosphataemia, hypokalaemia and hypomagnesaemia, especially in the first 24–48 hours.
- *Hyperchloraemic metabolic acidosis* may result from amino acid solutions with a high chloride content. Replacing some chloride with acetate in the TPN solution will resolve this where necessary.
- *Rebound hypoglycaemia* may occur when TPN is discontinued suddenly. TPN should be weaned over a minimum of 12 hours. If it cannot be continued, an infusion of 10% dextrose should be started and blood sugars closely monitored.
- *Refeeding syndrome* may occur when normal intake is resumed after a period of starvation. It is associated with profound hypophosphataemia, and possibly hypokalaemia and hypomagnesaemia. With the restoration of glucose as a substrate, insulin levels rise and cause cellular uptake of these ions. Depletion of adenosine triphosphate (ATP) and 2,3-diphosphoglyceric acid (2,3-DPG) results in tissue hypoxia and failure of cellular energy metabolism. This may manifest as cardiac and respiratory failure, with paraesthesiae and seizures also reported. Thiamine deficiency may also play a part.
- *Liver dysfunction* is common during TPN. Causes include hepatic steatosis, intrahepatic cholestasis and biliary sludging from gallbladder inactivity. The problems necessitating TPN in the first place may also cause liver dysfunction.
- *Deficiencies* of trace elements and vitamins (especially thiamine, folic acid and vitamin K) may occur.

NUTRITION AND SPECIFIC DISEASES

ACUTE RENAL FAILURE

The advent of continuous renal replacement therapy means that dietary fluid and protein restriction is unnecessary in the ICU. Use of specialised lipid or amino acid formulations in TPN is not supported by evidence, and in general normal nutritional support is appropriate in acute renal failure.

LIVER DISEASE[67]

Energy requirements in ICU patients are not altered by the presence of chronic liver disease. Protein restriction has previously been advocated in patients with chronic hepatic encephalopathy; however, modern practice is to provide a normal protein intake. Hepatic encephalopathy may in part be due to depletion of branched-chain amino acids (BCAAs) permitting increased cerebral uptake of aromatic amino acids, which produce inhibitory neurotransmitters. Neither the routine use of feeds enriched with BCAAs nor intravenous supplementation with BCAAs is indicated.[8,9,22] Thiamine and fat-soluble vitamin deficiencies are common in patients with chronic liver disease.

Acute liver failure reduces gluconeogenesis; hypoglycaemia is a common problem necessitating glucose infusion. Energy and protein requirements are unaltered. BCAAs have not been shown to be superior to standard amino-acid solutions. In patients with

cerebral oedema and severely elevated ammonia levels, brief protein restriction may help.

RESPIRATORY FAILURE

Oxidation of fat produces less carbon dioxide than glucose. There have been attempts to use this to assist in weaning from mechanical ventilation by providing 50% of energy intake as lipid, with mixed results. Avoidance of overfeeding is more important. The supplementation of omega-3 fatty acids in patients with acute respiratory distress syndrome (ARDS) is discussed below.

ACUTE PANCREATITIS

Formerly, TPN was a cornerstone of the management of severe acute pancreatitis to minimise pancreatic stimulation. This has changed with the publication of studies showing both gastric and jejunal feeding to be safe, effective and associated with reductions in infective complications compared with TPN.[68] Elemental feeds and pancreatic enzyme supplements are logical if malabsorption is a problem. Despite the shift towards enteral feeding of patients with pancreatitis, some only can be fed intravenously.

OBESITY

In the absence of calorimetry, the modified Penn State equations specific for the obese[69] are recommended for estimation of energy requirements.[9,70] Although the most recent US clinical practice guideline recommends hypocaloric, high-protein feeding for obese patients, the recommendation is based only on expert consensus, and the supporting evidence is tenuous. If this approach is adopted, the suggested caloric requirement is 11–14 kcal/kg actual body weight/day in patients with a BMI of 30–50, and 22–25 kcal/kg ideal body weight/day in patients with a BMI over 50. High protein intake is emphasised, at 1.2 g/kg actual body weight/day, or 2–2.5 g/kg ideal body weight/day. The benefits of hypocaloric, high-protein feeding in obesity remain to be proven, though, and at present there is insufficient evidence to justify feeding obese patients differently from others.

It is important to note that patients who have undergone some forms of bariatric surgery (especially sleeve gastrectomy and gastric bypass) are at increased risk for micronutrient deficiency, including iron, selenium, copper, zinc, thiamine, folate and vitamins B12 and D.

ADJUNCTIVE NUTRITION

Certain substances have been used as adjuncts to feeding solutions, in attempts to modulate the metabolic and immune responses to critical illness. In general, no conclusive benefit has yet been shown in unselected critically ill patients.

GLUTAMINE

Glutamine serves as an oxidative fuel and nucleotide precursor for enterocytes and immune cells, mainly lymphocytes, neutrophils and macrophages. It also regulates the expression of many genes related to signal transduction and to cellular metabolism and repair. During catabolic illness, glutamine is released in large quantities from skeletal muscle in order to supply these needs. It may then become 'conditionally essential' and hence depleted, particularly given its absence from many parenteral feeding solutions, with potentially adverse effects on gut barrier and immune function. Both enteral and parenteral glutamine supplements have been extensively investigated. Overall, evidence of benefit has remained weak, and comes from old, small, singlecentre studies, which lacked power to inform as to safety.[71] On the other hand, two large, recent, multicentre studies (the REDOXS[72] and MetaPlus[73] studies) found that glutamine supplementation (in the case of MetaPlus combined with antioxidants and fish oils) may be harmful in some groups. Its use is not justified.

SELENIUM

Selenium is necessary in the regulation of glutathione peroxidase, the major scavenging system for oxygen free radicals. Low plasma selenium levels are common in ICU patients, and a number of small studies have shown potential benefits, but these could not be reproduced in well-powered trials.[74,75] Selenium supplementation is not justified.

ANTIOXIDANT VITAMINS

Vitamins A, C and E are also involved in systemic defence against oxidant stress, and have been studied in various doses and combinations with selenium or omega-3 fatty acids. Of the trials not using other adjuncts, only one has shown a reduction in deaths using large enteral doses of vitamins C and E; numbers were relatively small, however, and the control group had a very high mortality rate.[76] In light of the safety concerns arising from the MetaPlus study, routine supplementation with antioxidant vitamins cannot be justified on present evidence.

ARGININE AND IMMUNONUTRITION

Arginine is a non-essential amino acid that acts as a precursor of nitric oxide, polyamines (important in lymphocyte maturation) and nucleotides. Animal studies suggest enhanced cell-mediated immunity and survival when arginine is supplemented. Several

commercially available enteral feeding solutions combine omega-3 fatty acids, arginine, nucleotides and in one case glutamine to produce so-called immune-enhancing diets. There is evidence to support their use following major surgery, but little in general ICU patients. Meta-analysis suggested an increase in mortality when arginine supplementation was given to septic patients,[77] and interim safety assessment of a trial led to its early cessation when this finding was replicated in the subgroup of patients with sepsis.[78]

There has been continued interest in using feeds enhanced with omega-3 fatty acids, often in combination with antioxidant vitamins and borage oil. Some studies have found benefits in patients with ARDS or sepsis. However, these results could not be repeated by other more recent trials,[79–81] and current knowledge does not warrant supplementation with omega-3 fatty acids, alone or in combination with other compounds.

REFERENCES

1. Doig GS, Simpson F, Delaney A. A review of the true methodological quality of nutritional support trials conducted in the critically ill: time for improvement. *Anesth Analg*. 2005;100(2):527–533. PubMed PMID: 15673887. eng.
2. Patel JJ, Hurt RT, McClave SA, et al. Critical care nutrition: where's the evidence? *Crit Care Clin*. 2017;33(2):397–412. PubMed PMID: 28284302.
3. Cerra FB, Benitez MR, Blackburn GL, et al. Applied nutrition in ICU patients. A consensus statement of the American College of Chest Physicians. *Chest*. 1997;111(3):769–778. PubMed PMID: 9118718. eng.
4. Martin CM, Doig GS, Heyland DK, et al. Multicentre, cluster-randomized clinical trial of algorithms for critical-care enteral and parenteral therapy (ACCEPT). *CMAJ*. 2004;170(2):197–204. PubMed PMID: 14734433. eng.
5. Jacobs DG, Jacobs DO, Kudsk KA, et al. Practice management guidelines for nutritional support of the trauma patient. *J Trauma*. 2004;57(3):660–678, discussion 679. PubMed PMID: 15454822. eng.
6. Kreymann KG, Berger MM, Deutz NE, et al. ESPEN guidelines on enteral nutrition: intensive care. *Clin Nutr*. 2006;25(2):210–223. PubMed PMID: 16697087. eng.
7. Singer P, Berger MM, Van den Berghe G, et al. ESPEN Guidelines on parenteral nutrition: intensive care. *Clin Nutr*. 2009;28(4):387–400. [Epub 2009/06/10]; PubMed PMID: 19505748. eng.
8. *2015 Canadian Critical Care Nutrition Clinical Practice Guidelines: Critical Care Nutrition; 2015*. Available from: http://www.criticalcarenutrition.com/cpgs.
9. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr*. 2016;40(2):159–211. PubMed PMID: 26773077.
10. Reintam Blaser A, Starkopf J, Alhazzani W, et al. Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. *Intensive Care Med*. 2017;43(3):380–398. PubMed PMID: 28168570. Pubmed Central PMCID: 5323492.
11. Dhaliwal R, Madden SM, Cahill N, et al. Guidelines, guidelines, guidelines: what are we to do with all of these North American guidelines? *JPEN J Parenter Enteral Nutr*. 2010;34(6):625–643. [Epub 2010/11/26]; PubMed PMID: 21097763. eng.
12. Baker JP, Detsky AS, Wesson DE, et al. Nutritional assessment: a comparison of clinical judgement and objective measurements. *N Engl J Med*. 1982; 306(16):969–972. PubMed PMID: 6801515. eng.
13. Alberda C, Gramlich L, Jones N, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. *Intensive Care Med*. 2009;35(10):1728–1737. PubMed PMID: 19572118.
14. Kondrup J, Rasmussen HH, Hamberg O, et al. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr*. 2003;22(3):321–336. PubMed PMID: 12765673.
15. Heyland DK, Dhaliwal R, Jiang X, et al. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. *Crit Care*. 2011;15(6):R268. PubMed PMID: 22085763. Pubmed Central PMCID: 3388687.
16. Rahman A, Hasan RM, Agarwala R, et al. Identifying critically-ill patients who will benefit most from nutritional therapy: further validation of the 'modified NUTRIC' nutritional risk assessment tool. *Clin Nutr*. 2016;35(1):158–162. PubMed PMID: 25698099.
17. Pupelis G, Selga G, Austrums E, et al. Jejunal feeding, even when instituted late, improves outcomes in patients with severe pancreatitis and peritonitis. *Nutrition*. 2001;17(2):91–94. PubMed PMID: 11240334. eng.
18. Klein S, Kinney J, Jeejeebhoy K, et al. Nutrition support in clinical practice: review of published data and recommendations for future research directions. Summary of a conference sponsored by the National Institutes of Health, American Society for Parenteral and Enteral Nutrition, and American Society for Clinical Nutrition. *Am J Clin Nutr*. 1997;66(3):683–706. PubMed PMID: 9280194. eng.
19. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. *Crit Care Med*. 2001;29(12):2264–2270. PubMed PMID: 11801821. eng.
20. Doig GS, Heighes PT, Simpson F, et al. Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. *Intensive Care*

Med. 2009;35(12):2018–2027. [Epub 2009/09/25]; PubMed PMID: 19777207. eng.
21. Doig GS, Heighes PT, Simpson F, et al. Early enteral nutrition reduces mortality in trauma patients requiring intensive care: a meta-analysis of randomised controlled trials. *Injury*. 2011; 42(1):50–56. [Epub 2010/07/14]; PubMed PMID: 20619408. eng.
22. Doig GS, Simpson F *Evidence-based guidelines for nutritional support of the critically ill: results of a bi-national guideline development conference*. 2005. [Evidence-Based Decision Making Web site.] Available from: http://www.evidencebased.net/files/EBGforNutSupportofICUpts.pdf.
23. Heighes PT, Doig GS, Sweetman EA, et al. An overview of evidence from systematic reviews evaluating early enteral nutrition in critically ill patients: more convincing evidence is needed. *Anaesth Intensive Care*. 2010;38(1):167–174. PubMed PMID: 20191793.
24. Elke G, Wang M, Weiler N, et al. Close to recommended caloric and protein intake by enteral nutrition is associated with better clinical outcome of critically ill septic patients: secondary analysis of a large international nutrition database. *Crit Care*. 2014;18(1):R29. PubMed PMID: 24506888. Pubmed Central PMCID: 4056527.
25. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med*. 2017;45(3):486–552. PubMed PMID: 28098591.
26. Harvey SE, Parrott F, Harrison DA, et al. Trial of the route of early nutritional support in critically ill adults. *N Engl J Med*. 2014;371(18):1673–1684. PubMed PMID: 25271389.
27. Streat SJ, Beddoe AH, Hill GL. Aggressive nutritional support does not prevent protein loss despite fat gain in septic intensive care patients. *J Trauma*. 1987;27(3):262–266. PubMed PMID: 3104621. eng.
28. Krishnan JA, Parce PB, Martinez A, et al. Caloric intake in medical ICU patients: consistency of care with guidelines and relationship to clinical outcomes. *Chest*. 2003;124(1):297–305. PubMed PMID: 12853537. eng.
29. Marik PE, Hooper MH. Normocaloric versus hypocaloric feeding on the outcomes of ICU patients: a systematic review and meta-analysis. *Intensive Care Med*. 2016;42(3):316–323. PubMed PMID: 26556615.
30. Al-Dorzi HM, Albarrak A, Ferwana M, et al. Lower versus higher dose of enteral caloric intake in adult critically ill patients: a systematic review and meta-analysis. *Crit Care*. 2016;20(1):358. PubMed PMID: 27814776. Pubmed Central PMCID: 5097427.
31. Rubinson L, Diette GB, Song X, et al. Low caloric intake is associated with nosocomial bloodstream infections in patients in the medical intensive care unit. *Crit Care Med*. 2004;32(2):350–357. PubMed PMID: 14758147. eng.
32. Villet S, Chiolero RL, Bollmann MD, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. *Clin Nutr*. 2005;24(4):502–509. PubMed PMID: 15899538. eng.
33. Compher C, Chittams J, Sammarco T, et al. Greater protein and energy intake may be associated with improved mortality in higher risk critically ill patients: a multicenter, multinational observational study. *Crit Care Med*. 2017;45(2):156–163. PubMed PMID: 28098623.
34. Plank LD, Hill GL. Sequential metabolic changes following induction of systemic inflammatory response in patients with severe sepsis or major blunt trauma. *World J Surg*. 2000;24(6):630–638. PubMed PMID: 10773114. eng.
35. Frankenfield DC, Coleman A, Alam S, et al. Analysis of estimation methods for resting metabolic rate in critically ill adults. *JPEN J Parenter Enteral Nutr*. 2009;33(1):27–36. PubMed PMID: 19011147.
36. Makk LJ, McClave SA, Creech PW, et al. Clinical application of the metabolic cart to the delivery of total parenteral nutrition. *Crit Care Med*. 1990;18(12):1320–1327. PubMed PMID: 2123141. eng.
37. Saffle JR, Larson CM, Sullivan J. A randomized trial of indirect calorimetry-based feedings in thermal injury. *J Trauma*. 1990;30(7):776–782, discussion 782–783. PubMed PMID: 2116532. eng.
38. Singer P, Anbar R, Cohen J, et al. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. *Intens Care Med*. 2011;37(4):601–609. [Epub 2011/02/23]; PubMed PMID: 21340655. eng.
39. Frankenfield D, Smith JS, Cooney RN. Validation of 2 approaches to predicting resting metabolic rate in critically ill patients. *JPEN J Parenter Enteral Nutr*. 2004;28(4):259–264. PubMed PMID: 15291408.
40. Konstantinides FN, Konstantinides NN, Li JC, et al. Urinary urea nitrogen: too insensitive for calculating nitrogen balance studies in surgical clinical nutrition. *JPEN J Parenter Enteral Nutr*. 1991;15(2):189–193. PubMed PMID: 2051557. eng.
41. Larsson J, Lennmarken C, Martensson J, et al. Nitrogen requirements in severely injured patients. *Br J Surg*. 1990;77(4):413–416. PubMed PMID: 2111195. eng.
42. Hurt RT, McClave SA, Martindale RG, et al. Summary points and consensus recommendations from the international protein summit. *Nutr Clin Pract*. 2017;32(1 suppl):142S–151S. PubMed PMID: 28388374.
43. Weijs PJ, Looijaard WG, Beishuizen A, et al. Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients. *Crit Care*. 2014;18(6):701. PubMed PMID: 25499096. Pubmed Central PMCID: 4279460.

44. Demling RH, DeBiasse MA. Micronutrients in critical illness. *Crit Care Clin*. 1995;11(3):651–673. PubMed PMID: 7552975. eng.
45. Shenkin A. Micronutrients in the severely-injured patient. *Proc Nutr Soc*. 2000;59(3):451–456. PubMed PMID: 10997673.
46. Sriram K, Lonchyna VA. Micronutrient supplementation in adult nutrition therapy: practical considerations. *JPEN J Parenter Enteral Nutr*. 2009;33(5):548–562. [Epub 2009/05/21]; PubMed PMID: 19454751. eng.
47. Battistella FD, Widergren JT, Anderson JT, et al. A prospective, randomized trial of intravenous fat emulsion administration in trauma victims requiring total parenteral nutrition. *J Trauma*. 1997;43(1):52–58, discussion 8–60. PubMed PMID: 9253908. eng.
48. Elke G, van Zanten AR, Lemieux M, et al. Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. *Crit Care*. 2016;20(1):117. PubMed PMID: 27129307. Pubmed Central PMCID: 4851818.
49. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med*. 2011;365(6):506–517. [Epub 2011/07/01]; PubMed PMID: 21714640. eng.
50. White H, Sosnowski K, Tran K, et al. A randomised controlled comparison of early post-pyloric versus early gastric feeding to meet nutritional targets in ventilated intensive care patients. *Crit Care*. 2009;13(6):R187. [Epub 2009/11/26]; PubMed PMID: 19930728. Pubmed Central PMCID: 2811894, eng.
51. Davies AR, Morrison SS, Bailey MJ, et al. A multicenter, randomized controlled trial comparing early nasojejunal with nasogastric nutrition in critical illness. *Crit Care Med*. 2012;40(8):2342–2348. [Epub 2012/07/20]; PubMed PMID: 22809907. eng.
52. Booth CM, Heyland DK, Paterson WG. Gastrointestinal promotility drugs in the critical care setting: a systematic review of the evidence. *Crit Care Med*. 2002;30(7):1429–1435. PubMed PMID: 12130957. eng.
53. Holzinger U, Brunner R, Miehsler W, et al. Jejunal tube placement in critically ill patients: a prospective, randomized trial comparing the endoscopic technique with the electromagnetically visualized method. *Crit Care Med*. 2011;39(1):73–77. [Epub 2010/11/03]; PubMed PMID: 21037470. eng.
54. Acosta-Escribano J, Fernandez-Vivas M, Grau Carmona T, et al. Gastric versus transpyloric feeding in severe traumatic brain injury: a prospective, randomized trial. *Intensive Care Med*. 2010;36(9):1532–1539. [Epub 2010/05/25]; PubMed PMID: 20495781. eng.
55. Hsu CW, Sun SF, Lin SL, et al. Duodenal versus gastric feeding in medical intensive care unit patients: a prospective, randomized, clinical study. *Crit Care Med*. 2009;37(6):1866–1872. [Epub 2009/04/23]; PubMed PMID: 19384225. eng.
56. Taylor SJ, Fettes SB, Jewkes C, et al. Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. *Crit Care Med*. 1999;27(11):2525–2531. PubMed PMID: 10579275. eng.
57. Desachy A, Clavel M, Vuagnat A, et al. Initial efficacy and tolerability of early enteral nutrition with immediate or gradual introduction in intubated patients. *Intensive Care Med*. 2008;34(6):1054–1059. [Epub 2008/01/23]; PubMed PMID: 18210092. eng.
58. Heyland DK, Murch L, Cahill N, et al. Enhanced protein-energy provision via the enteral route feeding protocol in critically ill patients: results of a cluster randomized trial. *Crit Care Med*. 2013;41(12):2743–2753. PubMed PMID: 23982032.
59. Mentec H, Dupont H, Bocchetti M, et al. Upper digestive intolerance during enteral nutrition in critically ill patients: frequency, risk factors, and complications. *Crit Care Med*. 2001;29(10):1955–1961. PubMed PMID: 11588461. eng.
60. McClave SA, Lukan JK, Stefater JA, et al. Poor validity of residual volumes as a marker for risk of aspiration in critically ill patients. *Crit Care Med*. 2005;33(2):324–330. PubMed PMID: 15699835. eng.
61. Montejo JC, Minambres E, Bordeje L, et al. Gastric residual volume during enteral nutrition in ICU patients: the REGANE study. *Intensive Care Med*. 2010;36(8):1386–1393. [Epub 2010/03/17]; PubMed PMID: 20232036. eng.
62. Poulard F, Dimet J, Martin-Lefevre L, et al. Impact of not measuring residual gastric volume in mechanically ventilated patients receiving early enteral feeding: a prospective before-after study. *JPEN J Parenter Enteral Nutr*. 2010;34(2):125–130. PubMed PMID: 19861528.
63. Drakulovic MB, Torres A, Bauer TT, et al. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet*. 1999;354(9193):1851–1858. PubMed PMID: 10584721. eng.
64. Abuksis G, Mor M, Plaut S, et al. Outcome of percutaneous endoscopic gastrostomy (PEG): comparison of two policies in a 4-year experience. *Clin Nutr*. 2004;23(3):341–346. PubMed PMID: 15158297. eng.
65. Fraenkel DJ, Rickard C, Lipman J. Can we achieve consensus on central venous catheter-related infections? *Anaesth Intensive Care*. 2000;28(5):475–490. PubMed PMID: 11094662. eng.
66. Calder PC. Hot topics in parenteral nutrition. Rationale for using new lipid emulsions in parenteral nutrition and a review of the trials performed in adults. *Proc Nutr Soc*. 2009;68(3):252–260. [Epub 2009/05/12]; PubMed PMID: 19426581. eng.
67. Mizock BA. Nutritional support in hepatic encephalopathy. *Nutrition*. 1999;15(3):220–228. PubMed PMID: 10198918. eng.
68. McClave SA, Chang WK, Dhaliwal R, et al. Nutrition support in acute pancreatitis: a systematic

review of the literature. *JPEN J Parenter Enteral Nutr*. 2006;30(2):143–156. [Epub 2006/03/07]; PubMed PMID: 16517959. eng.
69. Frankenfield D. Validation of an equation for resting metabolic rate in older obese, critically ill patients. *JPEN J Parenter Enteral Nutr*. 2011;35(2):264–269. PubMed PMID: 21378256.
70. Choban P, Dickerson R, Malone A, et al. A.S.P.E.N. Clinical guidelines: nutrition support of hospitalized adult patients with obesity. *JPEN J Parenter Enteral Nutr*. 2013;37(6):714–744. PubMed PMID: 23976769.
71. van Zanten AR, Hofman Z, Heyland DK. Consequences of the REDOXS and METAPLUS Trials: the end of an era of glutamine and antioxidant supplementation for critically ill patients? *JPEN J Parenter Enteral Nutr*. 2015;39(8):890–892. PubMed PMID: 25567781.
72. Heyland D, Muscedere J, Wischmeyer PE, et al. A randomized trial of glutamine and antioxidants in critically ill patients. *N Engl J Med*. 2013;368(16):1489–1497. PubMed PMID: 23594003.
73. van Zanten AR, Sztark F, Kaisers UX, et al. High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: a randomized clinical trial. *JAMA*. 2014;312(5):514–524. PubMed PMID: 25096691.
74. Andrews PJ, Avenell A, Noble DW, et al. Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients. *BMJ*. 2011;342:d1542. [Epub 2011/03/19]; PubMed PMID: 21415104. eng.
75. Bloos F, Trips E, Nierhaus A, et al. Effect of sodium selenite administration and procalcitonin-guided therapy on mortality in patients with severe sepsis or septic shock: a randomized clinical trial. *JAMA Intern Med*. 2016;176(9):1266–1276. PubMed PMID: 27428731.
76. Crimi E, Liguori A, Condorelli M, et al. The beneficial effects of antioxidant supplementation in enteral feeding in critically ill patients: a prospective, randomized, double-blind, placebo-controlled trial. *Anesth Analg*. 2004;99(3):857–863. PubMed PMID: 15333422. table of contents, eng.
77. Heyland DK, Novak F, Drover JW, et al. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. *JAMA*. 2001;286(8):944–953. PubMed PMID: 11509059. eng.
78. Bertolini G, Iapichino G, Radrizzani D, et al. Early enteral immunonutrition in patients with severe sepsis: results of an interim analysis of a randomized multicentre clinical trial. *Intensive Care Med*. 2003;29(5):834–840. PubMed PMID: 12684745. eng.
79. Rice TW, Wheeler AP, Thompson BT, et al. Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. *JAMA*. 2011;306(14):1574–1581. [Epub 2011/10/07]; PubMed PMID: 21976613. eng.
80. Grau-Carmona T, Moran-Garcia V, Garcia-de-Lorenzo A, et al. Effect of an enteral diet enriched with eicosapentaenoic acid, gamma-linolenic acid and anti-oxidants on the outcome of mechanically ventilated, critically ill, septic patients. *Clin Nutr*. 2011;30(5):578–584. [Epub 2011/04/09]; PubMed PMID: 21474219. eng.
81. Kagan I, Cohen J, Stein M, et al. Preemptive enteral nutrition enriched with eicosapentaenoic acid, gamma-linolenic acid and antioxidants in severe multiple trauma: a prospective, randomized, double-blind study. *Intensive Care Med*. 2015;41(3):460–469. PubMed PMID: 25672274.

This page intentionally left blank

Part Fifteen

Haematological Management

This page intentionally left blank

97

Blood transfusion and patient blood management

James P Isbister, Craig French

Blood component therapy has a central therapeutic role in clinical medicine; however, blood banking and transfusion medicine have tended to focus on the blood component supply rather than the demand/patient perspective. The clinical focus is 'what is best for the patient?' and not, 'what is best for the blood supply?' This shift from blood product focus to problem-based focus is now referred to as patient blood management (PBM).[1–3] PBM is an evidence-based approach, which, by clinically managing and preserving a patient's blood, aims to optimise patient outcomes.[4] The demand for blood components continues to increase consequent to the greater burden of chronic disease due to ageing of the population, increasing severity of illness, and both a widening range of clinical indications for blood components and newer blood-intensive surgical procedures. This is being tempered by greater focus on clinically appropriate use.

When prescribing blood component therapy, the clinical problem and patient's needs must be accurately identified and clearly understood. Blood component therapy is often required while the basic disease process is corrected (e.g. surgical control for acute haemorrhage, or support for bone marrow suppression until the marrow recovers). Therapy is aimed at controlling the effects of a deficiency (e.g. anaemia, thrombocytopaenia) or preventing secondary complications. Alternatively, the indication is passive immunotherapy (e.g. Rhesus prophylaxis) or high-dosage intravenous immunoglobulin as immunomodulatory therapy.

The role of blood transfusion in a wide range of clinical settings has been critically reassessed, especially in relationship to the labile blood components (red cells, platelet concentrates, fresh frozen plasma, cryoprecipitate). Careful risk assessment and the use of blood conservation techniques have made 'bloodless' surgery possible in most uncomplicated elective surgical settings. Added to the uncertainty about the indications and benefits of allogeneic blood transfusion is the accumulating evidence that blood transfusion is an independent risk factor for poorer clinical outcomes. While transfusions may be lifesaving it is appropriate that there is greater focus on techniques to minimise exposure, transfusion alternatives, and closer attention to the quality and immediate efficacy of blood components.

Traditionally, transfusion has been regarded as the 'default' decision when there is clinical uncertainty. The benefits of transfusion were assumed with little or no evidence to support this assumption and patients were unnecessarily exposed to potential harm.[5,6] Given that the decision-making process for using blood component therapy can be challenging, that indications may be controversial, and that particularly in hemodynamically stable patients the evidence of benefit is uncertain, there are both common sense and scientifically evidence-based reasons to adopt a non-transfusion default position.[7,8] If allogeneic blood component therapy can be avoided, the potential hazards cease to be an issue.

Both evidence-based transfusion medicine and the fact that blood is altruistically donated require that blood is seen as a valuable and unique natural resource that should be conserved and managed appropriately. Blood components should be used as therapy only when there is evidence for potential benefit, when alternatives have been considered, and the potential for harm has been minimised. Potential hazards must be balanced against benefits and wherever possible the benefits and risks should be explained to the patient/relatives.

In considering the use of allogeneic blood transfusion the following questions need to be addressed:

- What is the timeframe of the decision-making process?
- Is it an elective decision?
- What is the most appropriate therapy for the patient?
- Are there alternatives to allogeneic transfusion?
- What component is indicated and where should it be obtained?
- Except for serological compatibility are there any other patient-specific requirements (e.g. irradiated, cytomegalovirus [CMV]-negative)
- How should the component be administered and monitored?
- What are the potential hazards of the blood component therapy?
- Can the risk of adverse effects be avoided or minimised?

ABSTRACT

The administration of blood products to critically ill patients can be lifesaving; however, like all medical interventions the potential risks must be considered together with the benefits. To address this patient blood management (PBM) has been introduced into clinical practice. This chapter provides an overview of PBM as it applies to the critically ill patient: in particular the application of evidence-based clinical practice guidelines, including to those patients with critical bleeding and massive transfusion, is emphasised. Transfusion-related immunomodulation and storage lesion have been associated with adverse patient outcomes. The clinical relevance of recent research in these areas is discussed. Red cell serology (blood type and cross matching) is a highly specialised area: a basic overview for the critical care physician is provided.

KEYWORDS

Blood component therapy
blood transfusion
patient blood management
critical haemorrhage
massive blood transfusion
coagulopathy
hazards of blood transfusion
acute lung injury
blood storage lesion

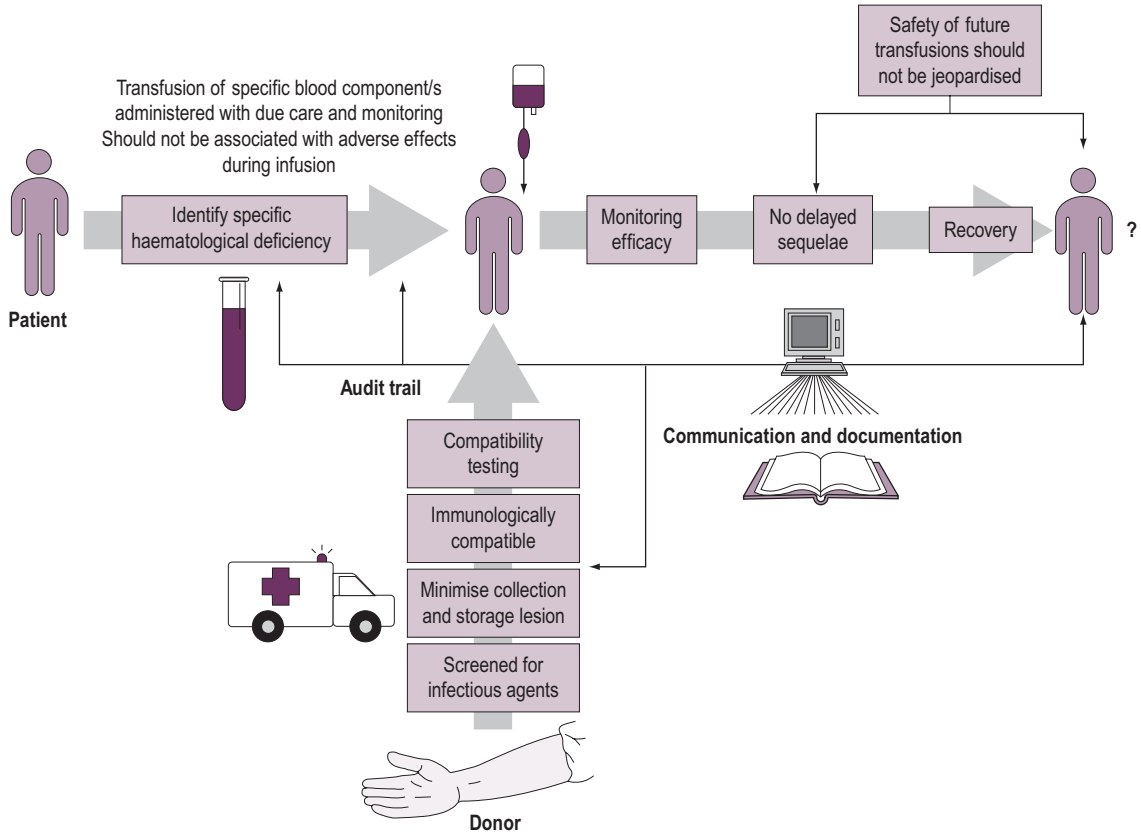


Figure 97.1 What is a safe transfusion?

- Is the patient fully informed of the medical decisions?
- What is the cost of the transfusion therapy?

Safe and effective transfusion requires attention to the following details (Fig. 97.1):

- clearly defined indication and benefits of blood components
- accurate patient identification for blood group compatibility
- identification and careful management of high-risk patients
- appropriate handling, administration and monitoring
- provision of adequate amounts and quality of component(s)
- communication of benefits and risk to the patient/relatives
- the infusion should not be associated with preventable ill effects
- awareness of possible transfusion-related complications
- early diagnosis and prompt action in relation to adverse events of transfusion
- accurate documentation
- input into quality-assurance programmes.

BLOOD STORAGE AND THE STORAGE LESIONS

Blood is altered from the moment of collection and the 'lesions' of collection – anticoagulation, separation, cooling, preservation and storage – compound and progressively increase until the date of expiry.[9] The extent of these changes is determined by collection technique, the specific blood component, the preservative medium, the container, storage time and storage conditions. The threshold storage time for blood components has generally been arbitrarily determined by in vitro studies and assessment of in vivo survival. In the case of red cell concentrates, regulatory standards specify that greater than 75% of transfused cells should survive post-transfusion.

Storage results in quantitative and/or qualitative deficiencies in blood components, which may reduce the immediate efficacy of a transfusion. In parallel with these storage changes is an accumulation of degenerate material (e.g. microaggregates, microparticles and procoagulant material), release of vasoactive agents, cytokine generation and haemolysis.[5] Some are related to the presence of leucocytes and can be minimised by pre-storage leucoreduction.[10] Red cells undergo a change from their biconcave disc shape to spiky

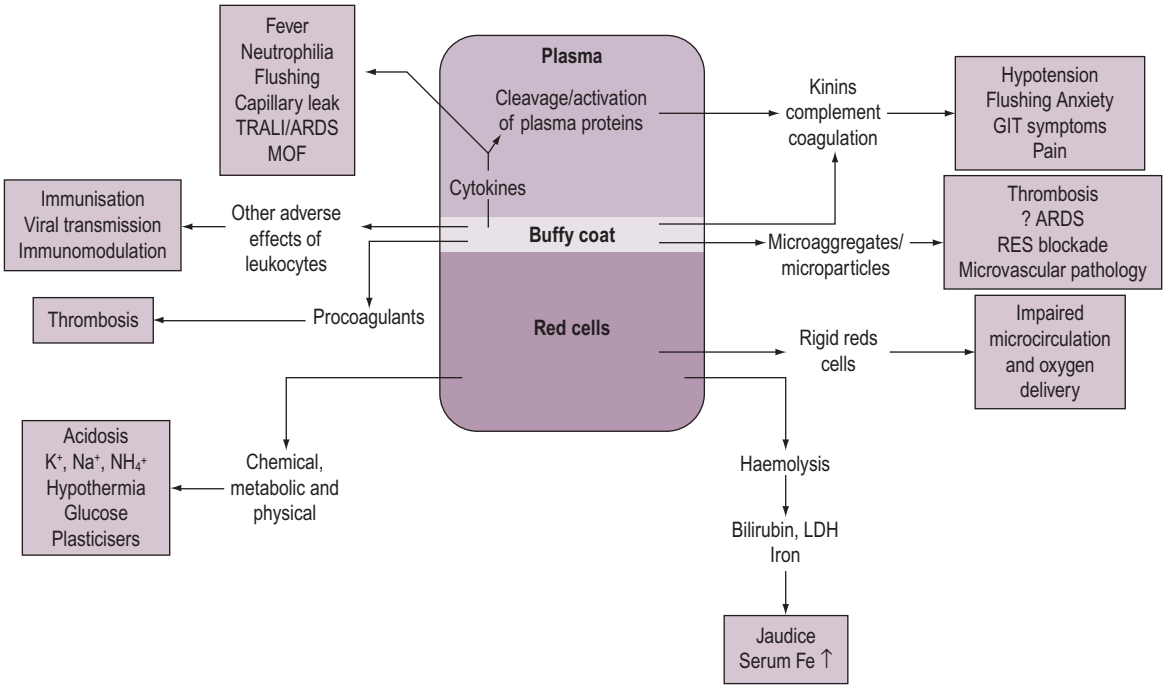


Figure 97.2 The storage lesions. *ARDS*, Adult respiratory distress syndrome; *GIT*, gastrointestinal tract; *LDH*, lactic dehydrogenase; *MOF*, multiorgan failure; *RES*, reticulo-endothelial system; *TRALI*, transfusion-related acute lung injury.

spherocytes (echinocytes) and in so doing lose their flexibility. There are also changes in the red cell membrane resulting in an increased tendency to adhere to endothelial cell surfaces in the microcirculation, especially if there is activation of endothelial cells, for example, in the presence of the systemic inflammatory response (e.g. with shock or sepsis).[11] There is evidence that the immediate post-transfusion function of stored red cells and haemoglobin in delivering oxygen to the microcirculation and unloading is questionable, and several hours are required for red cell oxygen carriage and delivery to return to normal.[12–14] It is important to differentiate between the storage lesion being responsible for failure to achieve clinical/laboratory end-points due to reduced survival and/or qualitative defects in cellular function and the 'toxic' effects of blood storage (Fig. 97.2).

The use of blood filters has been an acknowledgement of the existence of the blood storage lesion and its possible clinical significance. The 170 µm blood-giving filters were first introduced into transfusion medicine to stop the occlusion of blood-giving sets; however, the use of pre-storage leucoreduction filters, and to mitigate the development of the storage lesion in both blood and platelets from its inception, is more logical and scientific. Universal pre-storage leucoreduction is now standard practice in many countries, although it was primarily introduced as a precautionary measure against the possible transmission of variant Creutzfeldt–Jakob disease (vCJD) and not to address the numerous other indications for the removal of leucocytes.[15]

The clinical significance of blood storage lesions remains uncertain. A large body of observational evidence suggest poorer outcome following the administration of older blood.[16–21] Two large, randomised, controlled trials have not demonstrated effect on mortality of the age of transfused red blood cells (RBCs)[22,23]; however, further studies with increased power are required to exclude a clinically significant difference. It is assumed that blood components have been appropriately collected, processed, stored, transported and transfused but, despite much greater attention to standard operating procedures and regulation generally, the quality of the final product cannot be guaranteed.[24] The 'assumed' quality of labile cellular blood products is based on research data and monitoring of standard operating procedures. There is rarely detailed individual product assessment prior to transfusion. It is accepted that the adverse effects of storage increase with time and an arbitrary 'cut-off' is mandated on the basis of research studies. It is reasonable to state, that as a result of improved blood collection, processing, preservation, storage and cold chain management that the clinical use of the labile allogeneic blood components is considerably safer than in the past. However,

questions remain as to efficacy and indications for use.

In relation to the possible clinical significance of the storage lesion, the following should be considered:

- quantitative and qualitative deficiency of blood component
  - failure to achieve anticipated end-points due to reduced quantity and/or quality of the blood product
  - exposure to excessive numbers of donors in achieving efficacy
- physical characteristics
  - hypothermia
  - chemical characteristics
  - citrate toxicity
  - acid–base imbalance
  - glucose
- contamination
  - bacterial resulting in endotoxaemia or septicaemia
  - plasticisers
- accumulation of 'toxic' or degenerate products
  - role of the storage lesion in transfusion-related immunomodulation
  - role of cytokines
  - role of reticuloendothelial system blockade
  - accentuation of free radical pathophysiology due to free iron
- effects of transfusion on laboratory parameters (e.g. elevations in bilirubin, neutrophils, serum iron and lactic dehydrogenase), which may lead to incorrect interpretation
- large-volume transfusions (proportional to storage age) as a risk factor for multiorgan failure (MOF) and adult respiratory distress syndrome (ARDS)
- early hyperkalaemia, late hypokalaemia
- activation and consumption of the haemostatic factors with possible contribution to disseminated intravascular coagulation (DIC) and venous thromboembolism
- non-haemolytic, non-febrile transfusion reactions
- hypotension and circulatory instability due to vasoactive substance (kinins, histamine).

THE ROLE OF LEUCOCYTES AS A 'CONTAMINANT' IN LABILE STORED BLOOD AND THE ROLE OF PRE-STORAGE LEUCOREDUCTION

Leucocytes may be responsible for a wide range of blood component quality and safety issues, but there are difficulties in assessing potential adverse effects.[15] Specific adverse outcomes in some patients have been shown to be due to the presence of leucocytes (e.g. non-haemolytic febrile transfusion reaction, platelet refractoriness and transfusion-associated graft-versus-host disease [TAGVHD]), but this is the minority. In the broader context the overall available evidence – in the absence of adequate large, randomised, clinical trials – suggests that universal pre-storage leucoreduction may reduce transfusion-related morbidity.[25] Leucoreduction of red cell and platelet concentrates potentially minimises the clinical consequences of the immunomodulatory effects of allogeneic transfusion. Hence it may decrease the incidence of recurrence of some cancers, of postoperative infections and of bloodstream infections. In many patients transfusion-related acute lung injury (TRALI) is a multifactorial disorder and in 'at-risk' patients non-leucoreduced blood may be a risk factor. Patients at particular risk include those with trauma, burns, critical bleeding, shock, sepsis and those undergoing cardiopulmonary bypass.[26–29] The quality and function of pre-storage leucoreduced red cell concentrates is better maintained on storage, ensuring better post-transfusion efficacy and survival.[30]

CLINICAL GUIDELINES FOR BLOOD COMPONENT THERAPY

The following is a brief summary of the clinical guidelines for the use of commonly used blood components. The use of specific concentrates or recombinant products is beyond the scope of this book. As alluded to, there is a shift in the current development of clinical practice guidelines from focusing on specific indications for blood components to problem-oriented understanding of the clinical issues (i.e. PBM).[31,32]

RED CELL TRANSFUSIONS

What constitutes the appropriate use of red cell transfusions in acute medicine is contentious because of the difficulties in identifying the benefits of red cell transfusion in many circumstances. Pursuit of the lowest safe haematocrit continues to receive considerable attention, but pushing any aspect of a system to its limits risks 'sailing too close to the wind', which may be appropriate in some situations but potentially hazardous in others.[33,34]

In critically ill patients who are not actively bleeding, a restrictive transfusion strategy should be employed. Guidelines recommend that for most patients red cell transfusion is generally unnecessary when the haemoglobin concentration is greater than 90 g/L.[32] When haemoglobin concentration is in the range 70–90 g/L RBC transfusion is not associated with improved survival. The decision to transfuse should be based on the patient's clinical condition. The transfusion of red cell concentrates is likely to be appropriate when haemoglobin is less than 70 g/L and the anaemia is not reversible with specific therapy; however, lower levels may be acceptable in well-compensated patients, especially in the younger age group.[6] When transfusion is indicated a single unit followed by clinical reassessment is advised.[32]

PLATELET TRANSFUSIONS

Platelet transfusion therapy may benefit patients with platelet deficiency or dysfunction. The following are the indications for platelet transfusions[32]:

PROPHYLAXIS

- In a critically ill patient without bleeding when the platelet count is $<20 \times 10^9$/L
- To maintain the platelet count at $>50 \times 10^9$/L in patients undergoing surgery or invasive procedures
- In qualitative platelet function disorders, depending on clinical features and setting (platelet count is not a reliable indicator for transfusion).

BLEEDING PATIENTS

- In any haemorrhaging patient in whom thrombocytopenia secondary to marrow failure is considered a contributory factor[35]
- When the platelet count is $<50 \times 10^9$/L in the context of massive haemorrhage/transfusion and $<100 \times 10^9$/L in the presence of diffuse microvascular bleeding.

The transfusion of platelet concentrates is not generally considered appropriate:

- when thrombocytopenia is due to immune-mediated destruction
- in thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome
- in uncomplicated cardiac bypass surgery.

FRESH FROZEN PLASMA

There are few specific indications for fresh frozen plasma.[32,36] Its use may be appropriate:

- for the replacement of single-factor deficiencies where a specific or combined factor concentrate is not available
- for treatment of the multiple coagulation deficiencies associated with acute systemic coagulopathies:
  - DIC
  - massive blood transfusion
  - trauma-induced coagulopathy
  - cardiac bypass surgery
  - liver disease
  - peripartum coagulopathies
  - venom-induced coagulopathies.
- for treatment of inherited deficiencies of coagulation inhibitors in patients undergoing high-risk procedures where a specific factor concentrate is unavailable
- for immediate reversal of warfarin-induced anticoagulation in the presence of potentially life-threatening bleeding when prothrombin complex concentrates (PCC) are not available.[37]

The use of fresh frozen plasma is generally not considered appropriate in cases of:

- hypovolaemia
- plasma exchange procedures unless post-exchange invasive procedures are planned or there is a specific indication for replacement
- treatment of immunodeficiency states.

CRYOPRECIPITATE

Cryoprecipitate is prepared from freshly collected plasma and contains factor VIII, fibrinogen, von Willebrand factor, factor XIII and fibronectin. Cryoprecipitate was originally developed for treatment of haemophilia due to factor VIII deficiency, but is now prescribed to treat congenital or acquired hypofibrinogenaemia, usually in the context of liver disease, trauma, DIC, hyperfibrinolysis or massive transfusion.

FIBRINOGEN CONCENTRATE

Fibrinogen concentrate is a freeze-dried preparation derived from human plasma. It is administered intravenously after reconstitution with water for injections. In Australia and New Zealand each vial contains 1 g of human fibrinogen and is approved for use for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenaemia and hypofibrinogenaemia. In critically ill patients the routine use of fibrinogen concentrate is not advised; however, it may be indicated in critical bleeding where hypofibrinogenaemia exists.[32] Research to define the role of fibrinogen concentrate in the bleeding patient is ongoing.

IMMUNOGLOBULIN

Normal human immunoglobulin is available in intramuscular and intravenous forms for the treatment or prevention of infection in patients with proven hypogammaglobulinaemia.[38,39] Intravenous immunoglobulin G is recommended as adjunctive therapy for toxic shock syndrome caused by group A streptococci or *Staphylococcus aureus*[40]; however, the routine use of immunoglobulin therapy in septic shock is not advised. Intravenous immunoglobulin therapy also has a role in therapy of some autoimmune disorders, such as idiopathic thrombocytopenic purpura, autoimmune polyneuropathy and others.

FACTOR CONCENTRATES

There is an increasing number of plasma protein concentrates available for clinical use. Some are prepared from donor plasma and some by recombinant technology. Factor VIII and factor IX concentrates have an established role in the management of haemophilia, but others are in the process of establishing their clinical efficacy and indications. Antithrombin III (ATIII) concentrates are available for thrombophilia due to ATIII

deficiency and have been recommended in other disorders where ATIII may be depleted (e.g. DIC, MOF) but evidence for efficacy is sparse.[41,42] Recombinant human activated protein C has antithrombotic, anti-inflammatory and profibrinolytic properties. Clinical trials of activated protein C in severe sepsis did not demonstrate a consistent beneficial effect.[43] Accordingly its use is no longer recommended.[42]

Recombinant activated factor VII (rFVIIa) was developed for the management of haemophilic patients with coagulation factor inhibitors; rFVIIa has been used 'off label' for controlling haemorrhage in the non-haemophilic setting and there is considerable controversy as to its benefits and risks.[44,45] Patients with uncontrolled critical bleeding and coagulopathy, despite large transfusions and surgical intervention, have significant mortality rates and rFVIIa in these clinical situations has been administered as salvage therapy. While there are a number of case reports and series reporting on the use of rFVIIa in critical life-threatening haemorrhage, controlled studies have not demonstrated evidence for efficacy, and concern exists regarding thrombotic complications. Its routine use is not recommended.[35]

POTENTIAL ADVERSE EFFECTS OF ALLOGENEIC TRANSFUSION

The pathophysiology of blood transfusion reactions can broadly be divided into five categories (Fig. 97.3):

- Reactions may occur due to *immunological differences* between the donor and recipient, resulting in varying degrees of blood component incompatibility. In general, in order for a reaction to occur, the recipient needs to have been previously immunised to a cellular or plasma antigen.[46]
- A wide range of *infectious agents* may be transmitted by allogeneic blood component therapy.
- *Alterations in blood products due to preservation and storage* may result in quantitative and/or qualitative deficiencies in the blood components, which will reduce transfusion efficacy and expose the patient to potentially adverse consequences from storage accumulants in the component.
- *Technical or clerical errors* may result in adverse events in all the above categories.
- *Psychological* – this includes informed consent issues and patient anxiety about compatibility and infectivity.

In terms of causation of an adverse clinical event, the possible role of blood transfusion can be classified into three categories on the basis of probability (Fig. 97.4):

- *Definite – unifactorial – transfusion caused*: the well-understood and reported hazards of transfusion (i.e. immunological, technical, infectious) are generally unifactorial with a 1:1 causal relationship between the blood component transfused (usually a specific individual unit) and the adverse consequence for the patient. ABO blood group incompatibility, transfusion-related infection transmission, TAGVHD and TRALI due to donor leucoagglutinins are examples in this category.
- *Probable – oligofactorial – transfusion related*: some adverse consequences of transfusion result from interaction with other insults, pathophysiology or host factors, but the contribution of the transfusion can usually be specifically identified. Fever, allergic reactions, hypotensive reactions, pulmonary oedema, some cases of TRALI, hyperbilirubinaemia and CMV transmission are examples in this category.

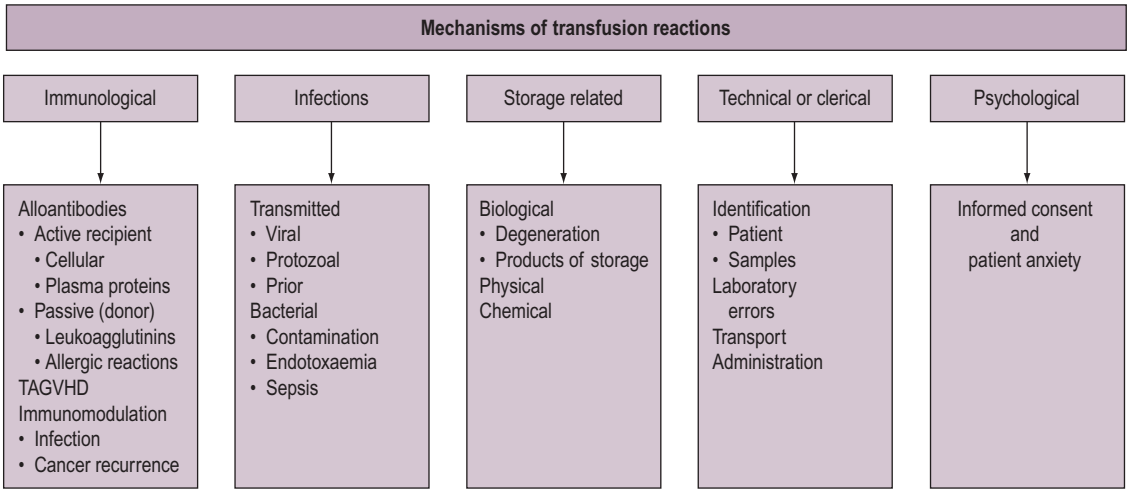


Figure 97.3 Possible mechanisms of adverse effects to blood transfusion. *TAGVHD*, Transfusion-associated graft-versus-host disease.

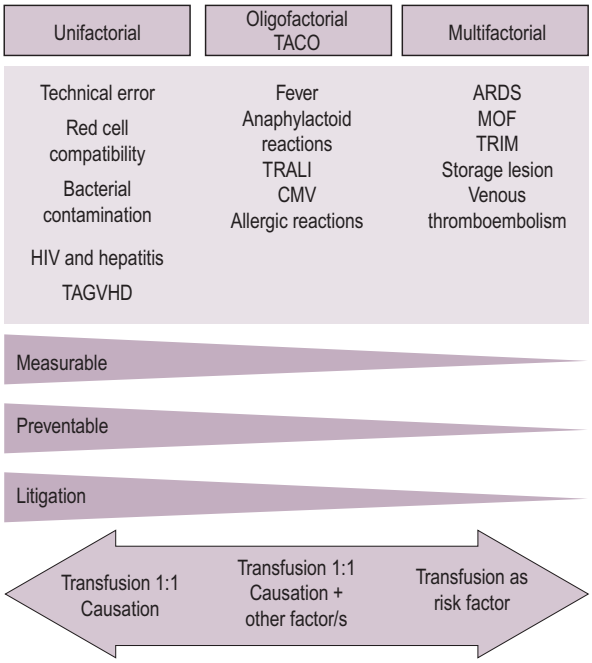


Figure 97.4 Algorithm for analysis for the possibility of a transfusion reaction. *ARDS*, adult respiratory distress syndrome; *CMV*, cytomegalovirus; *HIV*, human immunodeficiency virus; *MOF*, multiorgan failure; *TACO*, transfusion-associated circulatory overload; *TAGVHD*, transfusion-associated graft-versus-host disease; *TRALI*, transfusion-related acute lung injury; *TRIM*, transfusion-induced immunomodulation.

- *Possible – multifactorial – transfusion associated*: transfusion may be a contributor to a complication or poor clinical outcome. In these circumstances it is difficult to implicate transfusion directly in an individual case, nor is it necessarily the major factor. Transfusion-induced immunomodulation (TRIM) and the clinical consequences of storage lesions fall into this category. The role of transfusion being associated with adverse consequences has been established in observational studies, but causation cannot be confidently concluded. Accumulating evidence, in the absence of randomised clinical trials, supports causation, thus demanding a more precautionary approach to allogeneic blood transfusion, examination of alternatives to transfusion and implementation of methods to improve the quality of transfused blood components (especially red cell and platelet concentrates). Universal pre-storage leucoreduction is currently the most important and effective strategy for minimising the clinical impact of TRIM and the blood storage lesions.

Adverse reactions to blood component therapy may present in a wide range of 'guises' and transfusion must always be considered in the differential diagnosis of any unexpected clinical presentation or indeed as a contributory factor to a clinical picture that may have several contributory factors (Fig. 97.5).[47]

PYREXIA

Mild febrile reactions are not usually a matter of concern. The majority of febrile reactions are now considered to be an immunological reaction against one or more of the transfused cellular or plasma components, usually leucocytes.

TRANSFUSION-RELATED INFECTIONS

HEPATITIS

Post-transfusion hepatitis is a potential complication of allogeneic transfusion; donor selection, serological and nucleic acid tests ensure exclusion of infective donors. Hepatitis B and C are now almost totally preventable transfusion-transmitted diseases.

HUMAN IMMUNODEFICIENCY VIRUS

Donor selection, antibody screening and nucleic acid testing of blood donors have almost eliminated transfusion-associated human immunodeficiency virus (HIV) infection.

MONONUCLEOSIS SYNDROMES

The development of swinging pyrexia with varying degrees of peripheral blood atypical mononucleosis, 7–10 days following transfusion, can cause diagnostic confusion. Abnormalities in liver function are common. CMV infection is the commonest cause of this syndrome. When correctly diagnosed CMV is not a serious infection assuming the patient does not have immune compromise.

OTHER TRANSFUSION-TRANSMISSIBLE INFECTIONS

There is an increasing range of agents that have the potential to be transmitted by blood transfusion. The reader is referred to reviews for further information.[47-49]

BACTERIAL CONTAMINATION

Bacterial contamination of stored blood has always been recognised as a potential cause of fulminant endotoxic shock. Although a rare complication, continuing reports of its occurrence, especially in relation to platelet concentrate transfusion, have increased awareness.[50,51] The clinical features of transfusion-related bacterial sepsis in the non-anaesthetised patient include rigors, fever, tachycardia and vascular collapse, with prominent nausea, vomiting and diarrhoea. Anaesthetised patients may have a delayed onset of symptoms (fever, tachycardia, hypotension and cyanosis), followed by DIC, renal failure and sometimes acute lung

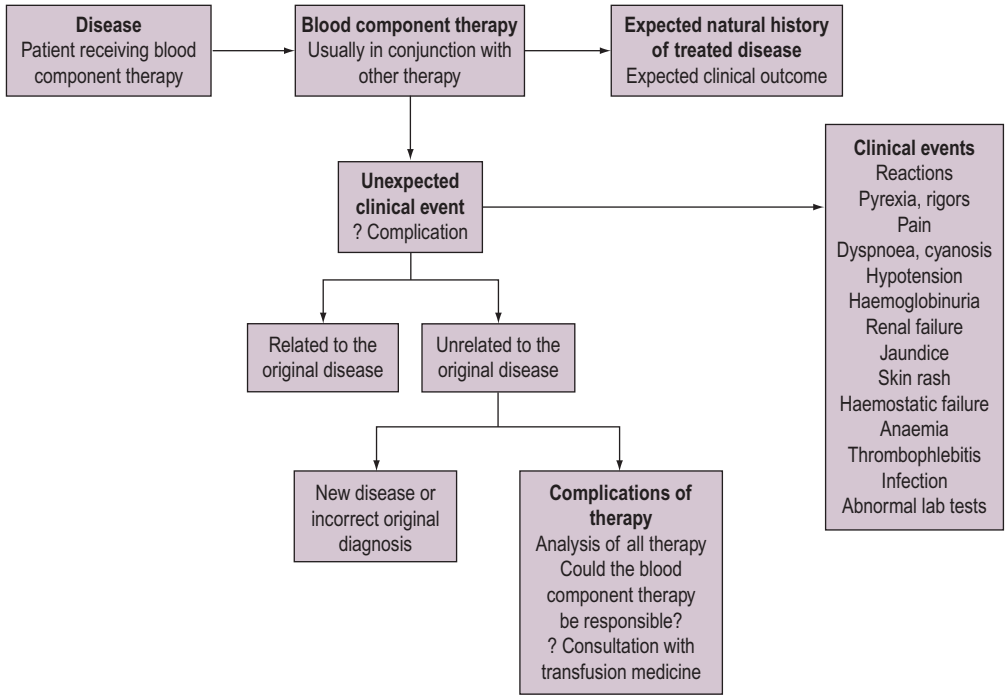


Figure 97.5 Adverse reactions to blood component therapy may be just one of the contributory factors in the differential diagnosis of any unexpected clinical presentation.

injury. The requirement to store platelet concentrates at room temperature increases the risks of bacterial contamination. Pre-release bacterial testing is being more widely advocated as a measure to minimise the problem.

HAEMOLYTIC TRANSFUSION REACTIONS

The most severe acute haemolytic transfusion reactions are due to ABO incompatibility, have an identifiable cause and are avoidable, in contrast to delayed haemolytic reactions that are immune in nature and are difficult to prevent.

INITIAL SYMPTOMS AND SIGNS

The classic symptoms and signs of an acute haemolytic transfusion reaction, typical of ABO incompatibility, include apprehension, flushing, pain (e.g. at infusion site, headache, chest, lumbosacral and abdominal), nausea, vomiting, rigors, hypotension and circulatory collapse.

HAEMOSTATIC FAILURE

Haemorrhagic diathesis due to DIC may be a feature, resulting in severe generalised haemostatic failure, with haemorrhage and oozing from multiple sites.[52] As the responsible transfusion is likely to have been administered for haemorrhage, increasing severity of local bleeding may be the first clue to an incompatible transfusion, especially if the patient is unconscious or anaesthetised in the operating room.

OLIGURIA AND RENAL IMPAIRMENT

Renal impairment may complicate a haemolytic transfusion reaction and its prevention or the appropriate management of established renal failure is important. If circulating volume and urinary output are rapidly restored, established renal failure is unlikely to occur. Death from acute renal failure directly caused by an incompatible blood transfusion is preventable, unless there are other poor prognostic factors.

ANAEMIA AND JAUNDICE

A severe haemolytic transfusion reaction may be suspected from the development of jaundice or anaemia.

ALLERGIC AND ANAPHYLACTOID REACTIONS

Non-cellular blood (plasma and plasma derivatives) components are rarely considered to be a major cause for adverse reactions to transfusion therapy. However, the complexity of plasma and its various components and the effects from component processing results in a broader spectrum of potential adverse effects than is frequently recognised. The antigenic heterogeneity of plasma proteins and the presence of antibodies make the non-cellular components of blood responsible for a range of adverse effects, many of which remain poorly

understood and commonly pass unrecognised in clinical practice.[53]

There has been debate over the years as to the classification of allergic reactions to blood components. Clinical severity may range from minor urticarial reactions or flushing through to fulminant cardiorespiratory collapse and death. Some of these reactions are probably true anaphylaxis, but in others the mechanisms have been less clear and the term 'anaphylactoid' has been used. To avoid implying the mechanism of the reaction, the term 'immediate generalised reaction' has also been used.

The clinical syndromes of immediate reactions have been classified as follows:

- Grade I:
  - skin manifestations
- Grade II:
  - mild to moderate hypotension
  - gastrointestinal disturbances (nausea)
  - respiratory distress
- Grade III:
  - severe hypotension, shock
  - bronchospasm
- Grade IV:
  - cardiac and/or respiratory arrest.

PLASMA AND PLASMA COMPONENTS MAY CAUSE ADVERSE EFFECTS BY SEVERAL PATHOPHYSIOLOGICAL MECHANISMS

Immunological reactions to normal components of plasma may occur in two ways:

- plasma proteins being antigenic to the recipient; they may contain epitopes on their molecules that are different from those on the recipient's functionally identical plasma proteins (e.g. anti-IgA antibodies)
- antibodies in the donor plasma reacting with cellular components of the recipient's blood cells or plasma proteins.

Physicochemical characteristics and contaminants of donor plasma, such as temperature, chemical additives, medications and microorganisms, may be responsible for recipient reactions.

The preparation techniques and storage conditions of blood and blood products may potentially cause adverse reaction through:

- *accumulation of metabolites* or cellular release products
- *plasma activation* (i.e. activation of some of the proteolytic systems). Importantly, the complement and kinin/kininogen systems may generate vasoactive substances and anaphylatoxins that may be responsible for reactions. Some apparently allergic reactions to blood products may be due to vasoactive substances in the infusion. Subjective sensations may be missed in an unconscious patient. Hypotension occurring during rapid infusion of a hypovolaemic patient is likely to be interpreted as further volume loss, particularly with some plasma protein fractions that have been reported as producing a transient fall in blood pressure, and a situation fraught with risk of overload can be produced
- *histamine generation*: histamine levels increase in some stored blood components and levels may be correlated with non-febrile, non-haemolytic transfusion reactions. Histamine release may be stimulated in the patient by plasma components, synthetic colloids and various medications
- *generation of cytokines* during storage may be responsible for non-haemolytic transfusion reactions
- *chemical additives*: there are various chemical additives (ethylene oxide, formaldehyde, drugs, latex) that may be responsible for immunological or non-immunological recipient reactions.

TRANSFUSION-ASSOCIATED GRAFT-VERSUS-HOST DISEASE

Graft-versus-host disease, classically observed in relationship to allogeneic bone marrow transplantation, may occur following a blood transfusion owing to the infusion of immunocompetent lymphocytes precipitating an immunological reaction against the host tissues of the recipient.[54] It is most commonly observed in immunocompromised patients, but may also be seen in recipients of directed blood donation from first-degree relatives, and occasionally where donor and recipient are not related, owing to homozygosity for human leucocyte antigen haplotypes for which the recipient is heterozygous. The syndrome usually occurs 3–30 days post-allogeneic transfusion with fever, liver function test abnormalities, profuse watery diarrhoea, erythematous skin rash and progressive pancytopenia. TAGVHD has be minimised by prestorage leucoreduction but gamma irradiation of blood products is currently the standard of care for the prevention of TAGVHD.[55]

TRANSFUSION-RELATED ACUTE LUNG INJURY

TRALI is a serious complication of blood transfusion and the leading cause of transfusion-related mortality in the United States in FY2015.[56] In the classic plasma neutrophil antibody-mediated form of the disease, symptoms usually arise within hours of a blood transfusion.[57] In contrast to patients with ARDS, recovery usually occurs within 48 hours. The underlying pathophysiology of 'classic' TRALI is due to the presence of leucoagglutinins in donor plasma. When complement is activated, C5a promotes neutrophil aggregation and sequestration in the microcirculation of the lung, causing endothelial damage leading to an interstitial oedema and acute respiratory failure. This classic form of TRALI has been recognised for over five decades, but was thought to be a rare complication of allogeneic plasma transfusion. As leucoagglutinins occur

typically in plasma from multiparous females, male-donor-only fresh frozen plasma is recommended and provided by most blood supply agencies.

It is now accepted that there has been under-recognition and under-diagnosis of TRALI, partly due to a lack of clinical awareness, but also due to a broader understanding of mechanisms by which blood transfusion may cause or be a contributory factor to lung injury.[58] There is also recent experimental evidence supporting a 'two-hit' hypothesis in which patients may be 'primed' by shock, sepsis or extracorporeal circulation making them more susceptible to acute lung injury from blood transfusion.[59]

TRANSFUSION-ASSOCIATED CIRCULATORY OVERLOAD

Transfusion-associated circulatory overload (TACO) is receiving more attention in recent years as many cases of difficult to explain dyspnoea following blood transfusion are caused by circulatory overload.[60] This may be confidently established in some cases, but in others there may be contributing factors, such as pulmonary capillary leak syndromes. Indeed, when there is no identifiable cause for dyspnoea and a definitive transfusion-associated cause of dyspnoea cannot be identified, but suspected, the term transfusion associated dyspnoea (TAD) is used.

TRANSFUSION-RELATED IMMUNOMODULATION

Allogeneic blood transfusion is immunosuppressive having implications in relation to resistance to infection and the likelihood of cancer recurrence.[61–65] Donor leucocytes probably play the most important role in this immunomodulation. TRIM, may be the mechanism by which allogeneic blood transfusion is responsible for poorer clinical outcomes discussed in the next section.

ALLOGENEIC TRANSFUSION AS AN INDEPENDENT RISK FACTOR FOR POORER CLINICAL OUTCOMES

Over the last two decades experimental and clinical studies have identified blood transfusion as an independent risk factor for morbidity and mortality.[66–69] This has been a surprise to many clinicians, health administrators and patients, as it was assumed that blood transfusion can only be of benefit to the bleeding or anaemic patient. This long-standing belief is now being effectively challenged, and debate has moved significantly from a paradigm with a focus on transfusion to one in which the urgent control of critical bleeding, with the avoidance and/or minimisation of blood transfusion.

TRIM is associated with poorer clinical outcomes in a range of clinical settings; however, it is not possible to categorically conclude causation or that pre-storage leucoreduction will eliminate all risk. Accordingly, a precautionary approach should be adopted that is consistent with PBM guidelines, with the modus operandi being to minimise or avoid allogeneic transfusion.[32,70,71]

CRITICAL BLEEDING AND MASSIVE BLOOD TRANSFUSION

For the purpose of this discussion critical bleeding refers to major haemorrhage that is life threatening and is likely to result in massive transfusion. Major haemorrhage is defined as the loss of one blood volume over 24 hours.[72] There is a reappraisal of clinical practice guidelines for the use of blood components in the bleeding patient. The guidelines no longer focus solely on the management of massive blood transfusion, but also stress the importance of the management of critical bleeding and avoiding getting into the massive transfusion coagulopathy quagmire in which the patient can spiral down into the 'triad of death'–coagulopathy, acidosis and hypothermia.[35] Contemporary management of patients with acute haemorrhage challenges some long-standing dogmas. In most patients permissive hypotension and minimal volume resuscitation are considered preferable to aggressive fluid resuscitation until haemorrhage is controlled; however, the optimal blood pressure level remains unknown. Early control of bleeding by compression, tourniquet, packing or surgical control is paramount.

In previously healthy patients who have suffered an acute blood loss of less than 25% of their blood volume, restoring that volume is more important than replacing oxygen-carrying capacity. Intravenous fluid administration may preclude the necessity for allogeneic transfusion, especially when bleeding can be controlled. Intravenous fluids also allow time for transfusion compatibility testing. In the context of acute bleeding and hypovolaemic shock, the haemoglobin level is not the primary indicator for determining the need for allogeneic red cell transfusion. A normal human may survive a 30% deficit in blood volume without fluid replacement, in contrast to an 80% loss of red cell mass if normovolaemia is maintained. Minimisation of allogeneic blood transfusion is important and haemodilution with tolerance of anaemia is now accepted clinical practice. However, there are limits to haemodilution, and not just from the perspective of oxygen-carrying capacity. Marked reduction in blood viscosity is counterproductive as reactive peripheral vasoconstriction to maintain total peripheral resistance results in reduction in functional capillary density in the microcirculation.

In critical bleeding, specific component blood therapy is often required; while lifesaving in this setting transfusion is increasingly being recognised as a two-edged sword and probably a contributory factor to microcirculatory dysfunction and impaired tissue

cellular metabolism. While the evidence base is limited, it is suggested that institutions develop a massive transfusion procedure to guide the initial response to critical bleeding that includes advice regarding the dose, timing and ratio of blood component therapy.[35] Massive transfusion procedures should also include advice regarding their activation; emphasise the importance of early control of bleeding; and facilitate communication and coordination between clinicians, laboratory staff and transfusion service providers. The issue of the optimal ratio of plasma, platelets, and red cells remains controversial. There appears to be a survival advantage associated with decreasing ratios. Data from battlefield studies generated enthusiasm for a 1:1:1 ratio; however, when tested in a multicentre, randomised trial a ratio of 1:1:1 was not superior to a ratio of 1:1:2.[73] This trial provides the best available evidence for the optimal ratio of blood component therapy in the initial response to severe life-threatening bleeding. Failure of haemostasis is common in critically bleeding patients, and is complex and multifactorial in pathogenesis. The importance of avoiding acidosis and hypothermia cannot be overemphasised as the triad of coagulopathy, acidosis and hypothermia has an extremely poor prognosis. Coagulopathy associated with critical bleeding is also related to other aspects of the pathophysiology of the clinical setting. The assumption that there is a 'generic coagulopathy' vaguely referred to as DIC is incorrect and can result in inappropriate therapeutic decisions. DIC refers to a systemic process leading to a consumptive coagulopathy with diffuse microvascular thrombosis. While it is seen following critical bleeding, other causes of coagulopathy are more common. Resuscitation-associated (dilutional) coagulopathy is related to large-volume intravenous fluid (usually crystalloid) administration during the management of haemorrhagic shock.[74] There is also increasing recognition of acute traumatic coagulopathy[75] (ATC) which is driven by the combination of tissue injury, vascular damage and shock. ATC may occur independently of acidosis, hypothermia or haemodilution. Excessive activation of the protein C system and hypofibrinogenaemia secondary to secondary hyperfibrinolysis appears important in its pathogenesis; however, a detailed discussion of ATC is beyond the scope of this chapter and the reader is referred to recent reviews.[75,76] In all circumstances there is activation or inhibition of some aspect of the haemostatic system, and therapy is better informed if the varied mechanisms are understood.

Except for severe abnormalities, haemostatic laboratory parameters correlate poorly with clinical evidence of haemostatic failure. In the massively transfused patient, thrombocytopenia and impaired platelet function are the most consistent significant haematological abnormalities, the correction of which may be associated with control of microvascular bleeding. Coagulation deficiency from massive blood loss is initially confined to factors V and VIII. Activated partial thromboplastin time (APTT), prothrombin time (PT) and fibrinogen assay should be performed, but the urgency of the situation does not usually allow for other specific factor assays. Fibrinogen, the bulk protein of the haemostatic system and essential for effective fibrin clot formation, is receiving greater attention with wider recommendations for replacement using concentrates or cryoprecipitate. Fibrinogen levels less than 1 g/L have generally been the trigger for replacement, but this is being reassessed, especially in the peripartum setting.[77,78]

Frequently, complex tests are required for definitive diagnosis, but the urgency of the situation cannot always await the results, and therapy may be initiated on clinical evidence with minimal laboratory information. A problem with the standard screening tests of coagulation function is that they do not give information about the actual formation of the haemostatic plug, its size, structure or stability. Point-of-care viscoelastic testing assesses clot formation in fresh or citrated whole blood in real time. It appears well suited to the clinical setting of critical bleeding and its use has been advocated to guide blood component therapy.[79]

In ongoing bleeding with associated microvascular oozing, various approaches may be taken. The use of fresh unrefrigerated whole blood (FUWB) is not routinely recommended. It is an 'emotive' subject and has been advocated in some military settings. The provision of fresh whole blood presents logistical, ethical and safety problems. Unscreened blood carries and increased risk of transfusion-transmitted infections and ABO haemolysis. Its use is best limited to clinical trials and situations of life-threatening bleeding where blood component therapy is unavailable or ineffective. As discussed earlier, the routine use of rFVIIa in patients with critical bleeding is not recommended.[35,80] Specialist haematologist advice should be sought prior to its off-label use.

SPECIFIC HAZARDS OF MASSIVE BLOOD TRANSFUSION

Massive blood transfusion may be defined in several ways:

- replacement of the circulating volume in 24 hours
- >4 units of blood in 1 hour with continuing blood loss
- loss of 50% of circulating blood volume within 3–4 hours.

Any patient receiving massive blood component therapy is likely to be seriously ill and have multiple problems. Many adverse effects must be considered in conjunction with the injuries and multiorgan dysfunction. It is not always possible to define the complications caused or aggravated by massive blood transfusion.

CITRATE TOXICITY

A patient responds to citrate infusion by the removal of citrate and the mobilisation of ionised calcium. Citrate is metabolised by the Krebs cycle in all nucleated cells, especially the liver. A marked elevation in the citrate concentration is seen with transfusion exceeding 500 mL in 5 minutes; the level rapidly falls when the infusion is slowed. Citrate metabolism is impaired by hypotension, hypovolaemia, hypothermia and liver disease. Toxicity may also be potentiated by alkalosis, hyperkalaemia, hypothermia and cardiac disease. The clinical significance of a minor depression of ionised calcium remains ill defined, and it is accepted that a warm, well-perfused adult patient with normal liver function can tolerate a unit of blood each 5 minutes without requiring calcium. The rate of transfusion is more significant than the total volume transfused. Common practice is to administer 10% calcium gluconate 1.0 g intravenously following each five units of blood or fresh frozen plasma. Such a practice remains controversial as there is concern regarding calcium homeostasis and cell function in acutely ill patients.

ACID–BASE AND ELECTROLYTE DISTURBANCES

Acid–base

Stored bank blood contains an appreciable acid load and is often used in a situation of pre-existing or continuing metabolic acidosis. The acidity of stored blood is mainly due to the citric acid of the anticoagulant and the lactic acid generated during storage. Their intermediary metabolites are rapidly metabolised with adequate tissue perfusion, resulting in a metabolic alkalosis. Hence the routine use of sodium bicarbonate is unnecessary and is contraindicated. Alkali further shifts the oxygen dissociation curve to the left, provides a large additional sodium load and depresses the return of ionised calcium to normal following citrate infusion. Acid–base estimations should be performed and corrected in the context of the clinical situation. With continuing hypoperfusion, however, metabolism of citrate and lactate will be depressed. In this situation, intravenous bicarbonate and calcium to correct acidosis and low ionised calcium may be considered.

Serum potassium

It is unlikely that the high potassium levels in stored blood have pathological effects in adults. However, hypokalaemia may be a problem 24 hours after transfusion as the transfused cells correct their electrolyte composition and potassium returns into the cells. Thus, although initial acidosis and hyperkalaemia may be an immediate problem with massive blood transfusion, the net result of successful resuscitation is likely to be delayed hypokalaemia and alkalosis. With CPD (citrate–phosphate–dextrose) blood, the acid load and red cell storage lesion are less. Constant monitoring of the acid–base and electrolyte status is essential in such fluctuating clinical situations.

Serum sodium

The sodium content of whole blood and fresh frozen plasma is higher than the normal blood level due to the sodium citrate. This should be remembered when large volumes of plasma are being infused into patients who have disordered salt and water handling (e.g. in renal, liver or cardiac disease).

HYPOTHERMIA

Blood warmed from 4°C to 37°C requires 1255 kJ (300 kcal) – the equivalent heat produced by 1 hour of muscular work – with an oxygen requirement of 62 L. Hypothermia impairs the metabolism of citrate and lactate, shifts the oxygen dissociation curve to the left, increases intracellular potassium release, impairs red cell deformability, delays drug metabolism, masks clinical signs, increases the incidence of arrhythmias, reduces cardiac output and impairs haemostatic function. Thus a thermostatically controlled blood-warming device should be routinely used when any transfusion episode requires the rapid infusion of more than two units of blood.

HYPERBILIRUBINAEMIA

Jaundice is common following massive blood transfusion as a significant amount of transfused stored blood may not survive, resulting in varying degrees of hyperbilirubinaemia. During hypovolaemia and shock, liver function may be impaired, particularly in the presence of sepsis or MOF. An important rate-limiting step in bilirubin transport is the energy-requiring process of transporting conjugated bilirubin from the hepatocyte to the biliary canaliculus. Thus, although an increased load of bilirubin from destroyed transfused red cells may be conjugated, there may be delayed excretion leading to a conjugated hyperbilirubinaemia. This ‘paradoxical’ conjugated hyperbilirubinaemia may be misinterpreted, leading to unnecessary investigations. The effect of resorbing haematoma and the possibility of an occult haemolytic transfusion reaction should also be considered.

BASIC IMMUNOHAEMATOLOGY

Red cell serology is a highly specialised area of knowledge and it is not possible to expect clinicians to have more than a basic working knowledge essential for patient safety. The following is a summary of core knowledge for the clinician.

SALINE AGGLUTINATION

Safe red cell transfusion has revolved around this traditional serological technique. A saline suspension of red cells is mixed with serum and observed for agglutination. Saline agglutination is used for ABO blood grouping and is one of the techniques for compatibility testing of donor blood.

THE DIRECT AND INDIRECT ANTIGLOBULIN TEST

In red cell serology, the antiglobulin test (Coombs test) is used to detect IgG immunoglobulins or complement components. The direct antiglobulin test (DAT) detects immunoglobulin or complement components present on the surface of the red cells circulating in the patient. The result is positive in autoimmune haemolytic anaemia and haemolytic disease of the newborn and during a haemolytic transfusion reaction. The indirect antiglobulin test (IAT) detects the presence of non-agglutinating antibodies in the patient's plasma, usually the IgG type. Antibody screening for atypical antibodies and pre-transfusion compatibility testing are the main applications of the IAT.

REGULAR AND IRREGULAR (ATYPICAL) ANTIBODIES

The regular alloantibodies (isoagglutinins) of the ABO system are naturally occurring agglutinins present in all ABO types (except AB), depending on the ABO group. Group O people have anti-A and anti-B isoagglutinins; group A have anti-B; and Group B have anti-A. Group A cells are the cause of the most common and most dangerous ABO-incompatible haemolytic reactions. Atypical antibodies are not normally present in the plasma, but may be found in some people as naturally occurring antibodies or as immune antibodies. Immune antibodies result from previous exposure due to blood transfusion or pregnancy. Naturally occurring antibodies more frequently react by saline agglutination and, although they may be stimulated by transfusion, are usually of minimal clinical significance. In contrast, many of the immune atypical antibodies are of major clinical significance and their recognition is the raison d'être for pre-transfusion compatibility testing and antenatal antibody screening. Most of the clinically significant immune atypical antibodies are detected by the IAT.

Blood group antigens vary widely in their frequency and immunogenicity. The D antigen of the Rhesus blood group system is common and highly immunogenic. Thus, when a Rh-negative (i.e. D-negative) patient is exposed to D-positive blood there is a high likelihood of forming an anti-D antibody. It is for this reason that the D antigen is taken into account when providing blood for transfusion, in contrast to the numerous other red cell antigens that are less common or less immunogenic. Beyond the Rh (D), and sometimes the Kell (K) blood group antigens, it is not practical, or necessary, to take notice of other blood group antigens unless an atypical antibody is detected during antibody-screening procedures.

THE ANTIBODY SCREEN

On receipt of a blood sample by the transfusion service, the red cells are ABO and Rh D typed, and the serum is screened for atypical antibodies. This screen consists of testing the patient's serum with group O screening cells. The screening panel consists of red cells obtained usually from two group O donors containing all common red cell antigens occurring with a frequency of greater than approximately 2% in the community. If an atypical antibody is detected on the antibody screen, further serological investigations are carried out to identify the specificity of the antibody. These investigations are time-consuming and when possible should be carried out electively.

THE CROSSMATCH (COMPATIBILITY TEST)

The crossmatch is the final compatibility test between the donor cells and the patient's serum. This test tends to be overemphasised, to the detriment of the antibody screen. With sophisticated knowledge of serology the emphasis in the supply of compatible blood is now concentrated on the steps prior to the final compatibility crossmatch.

THE TYPE AND SCREEN SYSTEM

As pre-compatibility testing has assumed the major role in the selection of blood for transfusion, there has been a rethinking of policies relating to the supply of blood for elective transfusions. Whenever elective surgery is planned for a patient who is likely to require blood transfusion, the transfusion service must receive a clotted blood sample well before the anticipated time of surgery. The pre-compatibility testing should be carried out during the routine working hours when facilities are geared for large workloads and enough staff is available to handle all contingencies.

THE PROVISION OF BLOOD IN EMERGENCIES

When quick clinical and laboratory decisions are made under conditions of stress it is frequently difficult for all involved personnel to appreciate the difficulties of others. The decision to give uncrossmatched, partially crossmatched, or to wait for crossmatched compatible blood is not easy, and certain basic serological considerations may clarify for the clinician some of the problems faced by the serologist. Depending upon the degree of urgency and the extent of previous knowledge about the patient's red cell serology, blood can be provided with varying degrees of safety. However, it should be emphasised that when a patient is exsanguinating and likely to die, the giving of ABO-compatible uncrossmatched blood, especially if the antibody screen is negative, is a safe and appropriate therapy.

UNIVERSAL DONOR GROUP O BLOOD

Group O blood under normal circumstances will be ABO compatible with all recipients. The transfusions

should be given as red cell concentrates screened for high-titre A or B haemolysins and used only in extreme emergencies. If the recipient is of childbearing age, every attempt should be made to give Rh-D-negative blood until the patient's blood group is known.

ABO-GROUP-SPECIFIC BLOOD

Transfusion of blood of the correct ABO type circumvents the isoagglutinin problems alluded to above. Simple as this approach may seem, its safety is dependent on meticulous attention to grouping. Previous blood group information, such as a 'bracelet' group or 'unofficial' group written in the patient's records, may be incorrect and there may be considerable risk if blood is administered on the basis of this information.

SALINE-COMPATIBLE BLOOD

The administration of saline-compatible blood is, for practical purposes, the administration of ABO-group-specific blood.

KEY REFERENCES

22. Lacroix J, Hebert PC, Fergusson DA, et al. Age of transfused blood in critically ill adults. *N Engl J Med*. 2015;372(15):1410–1418.
23. Heddle NM, Cook RJ, Arnold DM, et al. Effect of short-term vs. long-term blood storage on mortality after transfusion. *N Engl J Med*. 2016;375(20):1937–1945.
32. National Blood Authority. *Patient Blood Management Guidelines: Module 4 Critical Care*. Canberra, Australia: National Blood Authority; 2012.
35. National Blood Authority. *Patient Blood Management Guidelines: Module 1 Critical Bleeding Massive Transfusion*. Canberra: National Blood Authority; 2011:105.
36. Roback JD, Caldwell S, Carson J, et al. Evidence-based practice guidelines for plasma transfusion. *Transfusion*. 2010;50(6):1227–1239.
39. National Blood Authority. *Criteria for the clinical use of intravenous immunoglobulin in Australia*. Canberra, Australia: National Blood Authority; 2012.
75. Simmons JW, Powell MF. Acute traumatic coagulopathy: pathophysiology and resuscitation. *Br J Anaesth*. 2016;117(suppl 3):iii31–iii43.
76. Davenport R. Pathogenesis of acute traumatic coagulopathy. *Transfusion*. 2013;53(suppl 1):23S–27S.


Acces the complete references list online at http://www.expertconsult.com

REFERENCES

1. Isbister JP. The paradigm shift in blood transfusion. *Med J Aust*. 1988;148(6):306–308.
2. Spahn DR, Holger M, Hofmann A, et al. Patient blood management: the pragmatic solution for the problems with blood transfusions. *Anesthesiolgy*. 2008;109(6):951–953.
3. Thomson A, Farmer S, Hofmann A, et al. Patient blood management – a new paradigm for transfusion medicine? *Vox Sang ISBT Sci Ser*. 2009;4: 423–435.
4. Leahy MF, Hofmann A, Towler S, et al. Improved outcomes and reduced costs associated with a health-system-wide patient blood management program: a retrospective observational study in four major adult tertiary-care hospitals. *Transfusion*. 2017;57(6):1347–1358.
5. Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. *Crit Care Med*. 2008;36(9):1–8.
6. Shander A, Fink A, Javidroozi M, et al. Appropriateness of allogeneic red blood cell transfusion: the international consensus conference on transfusion outcomes. *Transfus Med Rev*. 2011;25(3): 232–246 e53.
7. Isbister JP. Decision making in perioperative transfusion. *Transfus Apher Sci*. 2002;27(1):19–28.
8. Isbister JP. Clinicians as gatekeepers: what is the best route to optimal blood use? *Dev Biol (Basel)*. 2007;127:9–14.
9. Scott KL, Lecak J, Acker JP. Biopreservation of red blood cells: past, present, and future. *Transfus Med Rev*. 2005;19(2):127–142.
10. Sparrow RL, Patton KA. Supernatant from stored red blood cell primes inflammatory cells: influence of prestorage white cell reduction. *Transfusion*. 2004;44(5):722–730.
11. Kriebardis AG, Antonelou MH, Stamoulis KE, et al. Storage-dependent remodeling of the red blood cell membrane is associated with increased immunoglobulin G binding, lipid raft rearrangement, and caspase activation. *Transfusion*. 2007;47(7): 1212–1220.
12. Tinmouth A, Fergusson D, Yee IC, et al. Clinical consequences of red cell storage in the critically ill. *Transfusion*. 2006;46(11):2014–2027.
13. Elfath MD. Is it time to focus on preserving the functionality of red blood cells during storage? *Transfusion*. 2006;46(9):1469–1470.
14. Zubair AC. Clinical impact of blood storage lesions. *Am J Hematol*. 2010;85(2):117–122.
15. Blajchman MA. The clinical benefits of the leukoreduction of blood products. *J Trauma*. 2006;60(suppl6): S83–S90.
16. Karam O, Tucci M, Bateman ST, et al. Association between length of storage of red blood cell units and outcome of critically ill children: a prospective observational study. *Crit Care*. 2010;14(2):R57.
17. Pavenski K, Saidenberg E, Lavoie M, et al. Red blood cell storage lesions and related transfusion issues: a Canadian Blood Services research and development symposium. *Transfus Med Rev*. 2012;26(1):68–84.
18. Hod EA, Zhang N, Sokol SA, et al. Transfusion of red blood cells after prolonged storage produces harmful effects that are mediated by iron and inflammation. *Blood*. 2010;115(21):4284–4292.
19. Eikelboom JW, Cook RJ, Liu Y, et al. Duration of red cell storage before transfusion and in-hospital mortality. *Am Heart J*. 2010;159(5):737–743 e1.
20. Vandromme MJ, McGwin G Jr, Weinberg JA. Blood transfusion in the critically ill: does storage age matter? *Scand J Trauma Resusc Emerg Med*. 2009;17:35.
21. Almac E, Ince C. The impact of storage on red cell function in blood transfusion. *Best Pract Res Clin Anaesthesiol*. 2007;21(2):195–208.
22. Lacroix J, Hebert PC, Fergusson DA, et al. Age of transfused blood in critically ill adults. *N Engl J Med*. 2015;372(15):1410–1418.
23. Heddle NM, Cook RJ, Arnold DM, et al. Effect of short-term vs. long-term blood storage on mortality after transfusion. *N Engl J Med*. 2016;375(20): 1937–1945.
24. Hogman CF, Meryman HT. Red blood cells intended for transfusion: quality criteria revisited. *Transfusion*. 2006;46(1):137–142.
25. van Hilten JA, van de Watering LM, van Bockel JH, et al. Effects of transfusion with red cells filtered to remove leucocytes: randomised controlled trial in patients undergoing major surgery. *BMJ*. 2004;328(7451):1281.
26. Jeschke MG, Chinkes DL, Finnerty CC, et al. Blood transfusions are associated with increased risk for development of sepsis in severely burned pediatric patients. *Crit Care Med*. 2007;35(2):579–583.
27. Zilberberg MD, Carter C, Lefebvre P, et al. Red blood cell transfusions and the risk of acute respiratory distress syndrome among the critically ill: a cohort study. *Crit Care*. 2007;11(3):R63.
28. Vlaar AP, Cornet AD, Hofstra JJ, et al. The effect of blood transfusion on pulmonary permeability in cardiac surgery patients: a prospective multicenter cohort study. *Transfusion*. 2012;52(1):82–90.
29. Gerber DR. Risks of packed red blood cell transfusion in patients undergoing cardiac surgery. *J Crit Care*. 2012;27(6):737.e1–737.e9.
30. Sparrow RL, Healey G, Patton KA, et al. Red blood cell age determines the impact of storage and leukocyte burden on cell adhesion molecules, glycophorin A and the release of annexin V. *Transfus Apher Sci*. 2006;34(1):15–23.
31. Spiess BD. Red cell transfusions and guidelines: a work in progress. *Hematol Oncol Clin North Am*. 2007;21(1):185–200.
32. National Blood Authority. *Patient Blood Management Guidelines: Module 4 Critical Care*. Canberra, Australia: National Blood Authority; 2012.
33. Carson JL, Ferreira G. Transfusion triggers: how low can we go? *Vox Sang*. 2004;87(suppl 2):218–221.
34. Shander A, Javidroozi M, Ozawa S, et al. What is really dangerous: anaemia or transfusion? *Br J Anaesth*. 2011;107(suppl 1):i41–i59.

35. National Blood Authority. *Patient Blood Management Guidelines: Module 1 Critical Bleeding Massive Transfusion*. Canberra: National Blood Authority; 2011:105.
36. Roback JD, Caldwell S, Carson J, et al. Evidence-based practice guidelines for plasma transfusion. *Transfusion*. 2010;50(6):1227–1239.
37. Tran HA, Chunilal SD, Harper PL, et al. An update of consensus guidelines for warfarin reversal. *Med J Australia*. 2013;198(4):198–199.
38. Looney RJ, Huggins J. Use of intravenous immunoglobulin G (IVIG). *Best Pract Res Clin Haematol*. 2006;19(1):3–25.
39. National Blood Authority. *Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia*. Canberra, Australia: National Blood Authority; 2012.
40. Norrby-Teglund A, Muller MP, McGeer A, et al. Successful management of severe group A streptococcal soft tissue infections using an aggressive medical regimen including intravenous polyspecific immunoglobulin together with a conservative surgical approach. *Scand J Infect Dis*. 2005;37(3):166–172.
41. Allingstrup M, Wetterslev J, Ravn FB, et al. Antithrombin III for critically ill patients. *Cochrane Database Syst Rev*. 2016;(2):CD005370.
42. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017;43(3):304–377.
43. Ranieri VM, Thompson BT, Barie PS, et al. Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med*. 2012;366(22):2055–2064.
44. Grottke O, Henzler D, Rossaint R. Activated recombinant factor VII (rFVIIa). *Best Pract Res Clin Anaesthesiol*. 2010;24(1):95–106.
45. Palmason R, Vidarsson B, Sigvaldason K, et al. Recombinant factor VIIa as last-resort treatment of desperate haemorrhage. *Acta Anaesthesiol Scand*. 2012;56(5):636–644.
46. Brand A. Immunological aspects of blood transfusions. *Transpl Immunol*. 2002;10(2–3):183–190.
47. Hendrickson JE, Hillyer CD. Noninfectious serious hazards of transfusion. *Anesth Analg*. 2009;108(3):759–769.
48. Allain JP, Stramer SL, Carneiro-Proietti AB, et al. Transfusion-transmitted infectious diseases. *Biologicals*. 2009;37(2):71–77.
49. *Transfusion-transmissible infections in Australia: 2016 Surveillance Report*. The Kirby Institute and Australian Red Cross Blood Service.
50. Rao PL, Strausbaugh LJ, Liedtke LA, et al; Infectious Diseases Society of America Emerging Infections Network. Bacterial infections associated with blood transfusion: experience and perspective of infectious diseases consultants. *Transfusion*. 2007;47(7):1206–1211.
51. Palavecino E, Yomtovian R. Risk and prevention of transfusion-related sepsis. *Curr Opin Hematol*. 2003;10(6):434–439.
52. Davenport RD. Pathophysiology of hemolytic transfusion reactions. *Semin Hematol*. 2005;42(3):165–168.
53. Gilstad CW. Anaphylactic transfusion reactions. *Curr Opin Hematol*. 2003;10(6):419–423.
54. Kopolovic I, Ostro J, Tsubota H, et al. A systematic review of transfusion-associated graft-versus-host disease. *Blood*. 2015;126(3):406–414.
55. Fast LD. Developments in the prevention of transfusion-associated graft-versus-host disease. *Br J Haematol*. 2012;158(5):563–568.
56. Food and Drug Administration. *Fatalities Reported to FDA Following Blood Collection and Transfusion: Annual Summary for Fiscal Year*; 2016. https://www.fda.gov/downloads/biologicsbloodvaccines/safetyavailability/reportaproblem/transfusiondonationfatalities/ucm598243.pdf.
57. Goldman M, Webert KE, Arnold DM, et al. Proceedings of a consensus conference: towards an understanding of TRALI. *Transfus Med Rev*. 2005;19(1):2–31.
58. El Kenz H, Van der Linden P, Transfusion-related acute lung injury. *Eur J Anaesthesiol*. 2014;31(7):345–350.
59. Tariket S, Sut C, Hamzeh-Cognasse H, et al. Transfusion-related acute lung injury: transfusion, platelets and biological response modifiers. *Expert Rev Hematol*. 2016;9(5):497–508.
60. Alam A, Lin Y, Lima A, et al. The prevention of transfusion-associated circulatory overload. *Transfus Med Rev*. 2013;27(2):105–112.
61. Blajchman MA. Transfusion immunomodulation or TRIM: what does it mean clinically? *Hematology*. 2005;10(suppl 1):208–214.
62. Blumberg N. Deleterious clinical effects of transfusion immunomodulation: proven beyond a reasonable doubt. *Transfusion*. 2005;45(suppl 2):33S–39S, discussion 9S–40S.
63. Raghavan M, Marik PE. Anemia, allogenic blood transfusion, and immunomodulation in the critically ill. *Chest*. 2005;127(1):295–307.
64. Hart S, Cserti-Gazdewich CM, McCluskey SA. Red cell transfusion and the immune system. *Anaesthesia*. 2015;70(suppl 1):38–45, e13–e16.
65. Muszynski JA, Spinella PC, Cholette JM, et al. Transfusion-related immunomodulation: review of the literature and implications for pediatric critical illness. *Transfusion*. 2017;57(1):195–206.
66. Malone DL, Dunne J, Tracy JK, et al. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. *J Trauma*. 2003;54(5):898–905, discussion 7.
67. Isbister JP, Shander A, Spahn DR, et al. Adverse blood transfusion outcomes: establishing causation. *Transfus Med Rev*. 2011;25(2):89–101.
68. Strumper-Groves D. Perioperative blood transfusion and outcome. *Curr Opin Anaesthesiol*. 2006;19(2):198–206.
69. Whitson BA, Huddleston SJ, Savik K, et al. Risk of adverse outcomes associated with blood transfusion after cardiac surgery depends on the amount of transfusion. *J Surg Res*. 2010;158(1):20–27.

70. National Blood Authority. *Patient Blood Management Guidelines: Module 2 Perioperative*. Canberra, Australia: National Blood Authority; 2012.
71. National Blood Authority. *Patient Blood Management Guidelines: Module 3 Medical*. Canberra, Australia: National Blood Authority; 2012.
72. British Committee for Standards in Haematology: Working Group: D, Stainsby SM, Thomas D, et al. Guidelines on the management of massive blood loss. *Br J Haematol*. 2006;135:634–641.
73. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*. 2015;313(5):471–482.
74. Maegele M, Lefering R, Yucel N, et al. Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. *Injury*. 2007;38(3):298–304.
75. Simmons JW, Powell MF. Acute traumatic coagulopathy: pathophysiology and resuscitation. *Br J Anaesth*. 2016;117(suppl 3):iii31–iii43.
76. Davenport R. Pathogenesis of acute traumatic coagulopathy. *Transfusion*. 2013;53(suppl 1): 23S–27S.
77. Wikkelsoe AJ, Afshari A, Stensballe J, et al. The FIB-PPH trial: fibrinogen concentrate as initial treatment for postpartum haemorrhage: study protocol for a randomised controlled trial. *Trials*. 2012; 13:110.
78. Bonnet MP, Basso O. Prohemostatic interventions in obstetric hemorrhage. *Semin Thromb Hemost*. 2012; 38(3):259–264.
79. Hanke AA, Horstmann H, Wilhelmi M. Point-of-care monitoring for the management of trauma-induced bleeding. *Curr Opin Anaesthesiol*. 2017; 30(2):250–256.
80. Lin Y, Moltzan CJ, Anderson DR, et al. The evidence for the use of recombinant factor VIIa in massive bleeding: revision of the transfusion policy framework. *Transfus Med*. 2012;22(6): 383–394.

98

Colloids and blood products

Andrew Lewington, Luke McMenamin

A colloid fluid contains microscopic particles which may be synthetic (e.g. gelatin or starch) or natural (e.g. albumin) suspended in a crystalloid solution, with isotonic saline being most commonly used. The colloidal particles are sufficiently large such that they are retained within the circulation and therefore exert an oncotic pressure across the capillary membrane. In health, the volume-expanding effect of a colloid is superior to that of a crystalloid. Colloids have therefore been used for fluid resuscitation and the expansion of the intravascular volume to restore haemodynamic stability and organ perfusion. However, in critically ill patients or following major surgery the volume-expanding effect of a colloid is reduced (described below) and there has been much debate with respect to the efficacy of colloid fluids versus crystalloid fluids in intravenous fluid resuscitation in theses settings.

The Starling equation has traditionally been used to explain the movement of fluid between the different body compartments, which is determined by the hydrostatic and osmotic forces exerted across semipermeable membranes. The osmotic pressure generated by a solute is proportional to the number of molecules or ions and independent of molecular size. Colloid osmotic pressure (COP) is that exerted by macromolecules and the ultramicroscopic particles (proteins and colloids).[1,2] It can be measured using a membrane transducer system in which the membrane is freely permeable to small ions and water but largely impermeable to the colloid molecules.[3] The membrane pore size and the molecular size distribution of the colloid being studied will dictate the measured value (Figs 98.1 and 98.2).[2,4] The intact vascular barrier is freely permeable to electrolytes and other small osmolytes (glucose, mannitol), but relatively impermeable to macromolecules (see Fig. 98.2). An iso-oncotic colloid or protein preparation has an oncotic pressure equal to that of the human plasma.

More recent experimental findings have challenged the Starling equation and demonstrated that transvascular fluid exchange in humans is not completely explained by this theory. The discovery of the glycocalyx on the surface of the luminal side of all vascular endothelial cells has helped to further our understanding of transvascular fluid exchange.[3] The glycocalyx consists of membrane-bound proteoglycans and glycosaminoglycans (e.g. heparin sulphate and hyaluronic acid), with negatively charged side chains binding plasma proteins. An intact and functional endothelial surface layer (ESL), including the glycocalyx together with the bound plasma proteins (mainly albumin), constitutes the endothelial barrier whose role it is to retain plasma constituents (Fig. 98.3). With new evidence, it is now accepted that the pressure gradient across the anatomical vessel wall appears to be of less importance than previously thought.

In health, the ESL provides an intact barrier with the intravascular osmotic pressure acting as an important determinant of the overall intravascular volume and therefore adequate cardiac preload. During episodes of critical illness, trauma, sepsis, volume overload and major surgery, the ESL is vulnerable to injury from inflammation and/or ischaemia-reperfusion injury, which damages the glycocalyx and impairs the competence of the vascular barrier. In this setting colloidal fluids will pass through the ESL more easily and distribute throughout the interstitial compartment, resulting in a larger volume of distribution and reduced efficacy. This phenomenon helps to explain the clinical challenge of providing adequate intravenous fluid resuscitation to maintain intravascular volume and cardiac preload during critical illness at a time when the ESL is damaged.

Theoretically, an infusion of colloids should expand the pre-existing blood volume by the volume infused, having a volume effect of 100%.[4,5] However, this is not always the case and the volume effect of a colloid is very much context specific.[6] Human studies have demonstrated that nearly 100% of an infused iso-oncotic preparation of human albumin or hydroxyethyl starch remains within the circulatory compartment to maintain normovolaemia during acute blood loss. Whereas when the same fluid is infused into a normovolaemic patient, the volume effect is reduced to 40%, with the remaining fluid directly shifting towards the interstitial space secondary to a marked alteration of the integrity of the ESL.[7] In this scenario it has been proposed that the release of atrial natriuretic peptide-activating metalloproteases may digest the endothelial glycocalyx. This helps to explain the pathophysiological

ABSTRACT

Colloids contain natural or synthetic particles, which are sufficiently large to be retained within the circulation and when infused into a healthy subject have a volume-expanding effect that is superior to that of a crystalloid. However, a greater understanding of the physiology of the endothelial surface layer and how this is disrupted in critical illness in addition to the publication of several studies demonstrating an increased risk of acute kidney injury associated with synthetic colloids (e.g. hydroxyethyl starches) has seen the pendulum swing in favour of crystalloids as first-line resuscitation fluids. Natural colloids such as human albumin 5% may be used for the treatment of hypovolaemia in a wide variety of clinical conditions, but there is currently no evidence that it offers any advantages over less expensive synthetic colloids or crystalloids. Other blood products or plasma derivatives include fresh frozen plasma (FFP), cryoprecipitate, recombinant factor VII, factor IX and immunoglobulin solutions.

KEYWORDS

Colloids
gelatins
hydroxyethyl starch
resuscitation fluids
glycocalyx
blood products
human albumin solution
dextrans
fresh frozen plasma
immunoglobulins

process that underlies the risks associated with the excessive administration of perioperative intravenous fluids during major surgery and the consequences on the ESL.[8]

In comparison to colloids, crystalloids have larger volumes of distribution depending on their composition (Fig. 98.4).[9] With respect to fluid resuscitation, isotonic crystalloids target the whole extracellular compartment, whereas hypotonic crystalloids easily distribute across all body fluid compartments. Colloids or plasma substitutes initially target the intravascular

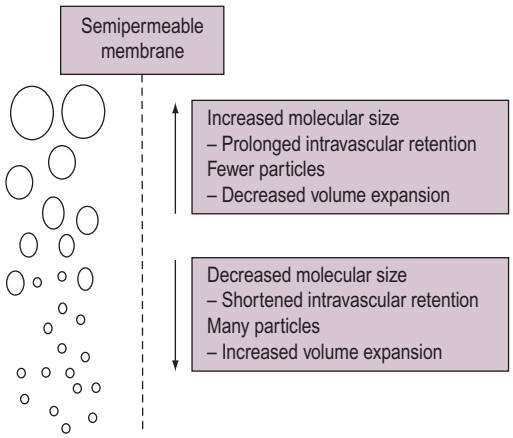


Figure 98.1 Polydispersity of colloid molecular size. *Reproduced with permission from Grocott MPW, Mythen MG. Fluid therapy. In: Goldhill DR, Strunin L, eds.* Clinical Anaesthesiology. *London, UK: Baillière Tindall; 1999:363–381.*

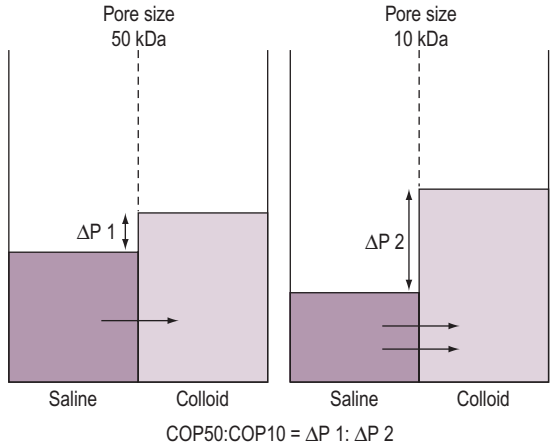


Figure 98.2 Schematic of technique for measurement of the COP50:COP10 ratio. *Reproduced with permission from Grocott MPW, Mythen MG. Fluid therapy. In: Goldhill DR, Strunin L, eds.* Clinical Anaesthesiology. *London, UK: Baillière Tindall; 1999:363–381.*

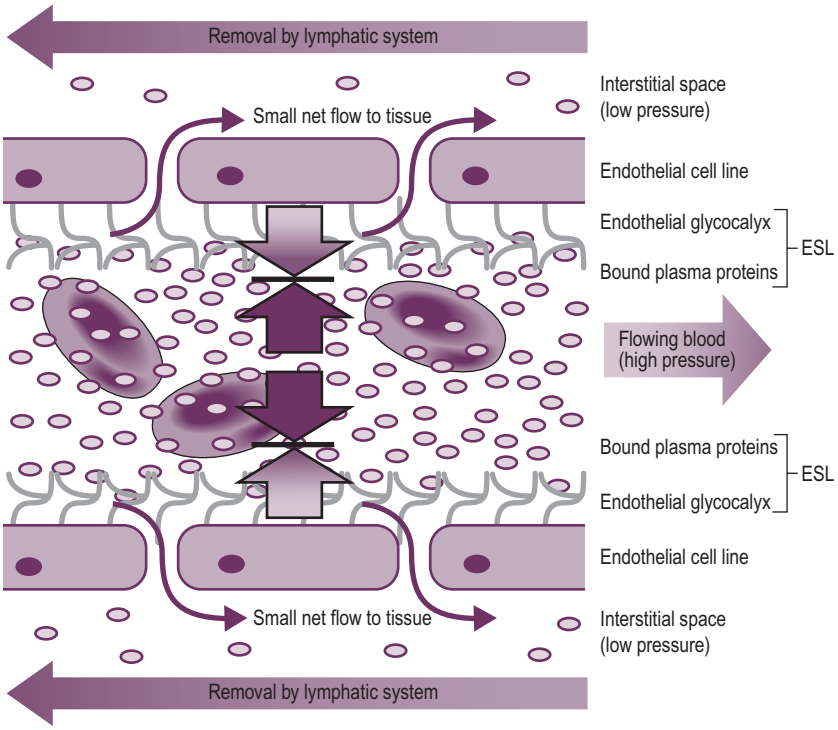


Figure 98.3 The role of the endothelial surface layer (ESL) for fluid homeostasis in steady state: an inwardly directed oncotic gradient across the ESL *(shaded grey arrows)* opposes the hydrostatic force towards the interstitial space *(thick black arrows)*. The net result is only a small fluid flux *(thin black arrows)*, which is removed by the lymphatic system.

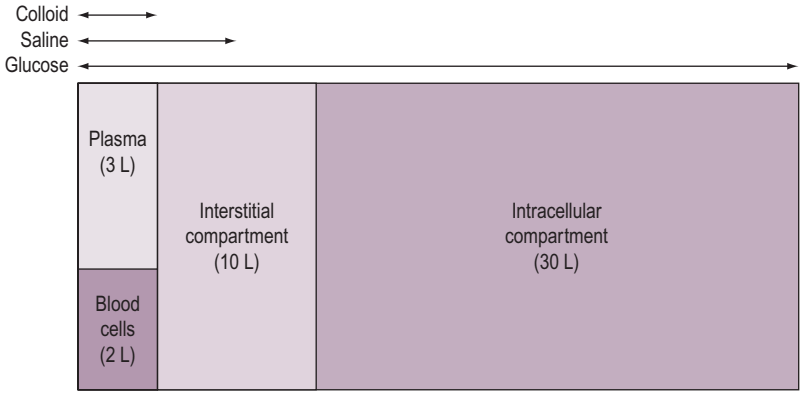


Figure 98.4 Simplified theoretical volumes of distribution of infused isotonic solutions of an ideal colloid, saline and glucose. *Reproduced with permission from Grocott MPW, Mythen MG. Fluid therapy. In: Goldhill DR, Strunin L, eds.* Clinical Anaesthesiology. *London, UK: Baillière Tindall; 1999:363–381.*

compartment. The ideal properties of a colloid would include:

- stable with a long shelf life
- pyrogen, antigen and toxin free
- free from risk of disease transmission
- intravascular volume effect lasts for several hours
- metabolism and excretion do not adversely affect the recipient
- no tissue accumulation
- no direct adverse effects (e.g. acute kidney injury [AKI], coagulopathy).

GELATINS

Gelatin was one of the first synthetic colloids used for intravenous fluid resuscitation. It is produced from the hydrolysis of bovine collagen.[10] The more commonly available preparations are succinylated gelatin (Gelofusine) and urea-linked gelatin–polygeline (Haemaccel) which are suspended in balanced solutions, making them more physiological.[1,2] Gelatins are relatively inexpensive and stable, with long shelf lives. The gelatins' plasma-volume-expanding effect lasts only about 90–120 minutes followed by elimination through the kidneys.[5]

Gelatins have frequently been used as volume expanders in critically ill patients in the intensive care unit (ICU). It is important to note that Haemaccel has a significant calcium content which makes it incompatible with citrated blood if infused through a giving set that has been previously used for this product; however, this does not apply to SAGM (saline–adenine–glucose–mannitol) blood. The reported incidence of reactions to gelatins is low (<0.5%) and range from mild skin rash and pyrexia to life-threatening anaphylaxis. The gelatins appear to have the least impact on haemostasis and it is not clear whether they have any impact over and above simple haemodilution of clotting factors. However, safety evidence from large randomised controlled trials is lacking.

HYDROXYETHYL STARCHES

Hydroxyethyl starches (HES) are produced by hydroxyethyl substitution of amylopectin, a D-glucose polymer obtained from potato or waxy maize.[1,2] The pattern of hydroxyethyl substitution on glucose moieties influences the susceptibility to hydrolysis by non-specific amylases in the blood. The different products are commonly described by their weight-averaged molecular weight (MWw: the number of molecules at each weight times the particle weight divided by the total weight of all the molecules) and their degree of substitution,[1-5] distinguishing hetastarches (0.6–0.7), pentastarches (≈0.5) and tetrastarches (≈0.4). Starch preparations are stable at room temperature and have long shelf lives. The duration of intravascular retention is proportional to MW[2,4,11,12] but is greater than 6 hours even for the 130-kDa tetrastarches. The initial volume effect of iso-oncotic HES preparations (6%) when infused to substitute actual intravascular deficits is close to 100%, irrespective of the generation.[11-13] HES products are associated with an acceptable incidence of adverse events including anaphylactoid reactions. Tissue deposition may result in intractable itching if large volumes of HES are infused over several days.[14] HES products can cause a coagulopathy.[15] In particular, factor VIII (FVIII) levels are reduced and platelet function is impaired, causing a von Willebrand-like syndrome. It is likely that in new-generation HES products some of the side effects are attenuated.[16] However, their safety still needs to be proven.[17-23]

Over recent years there has been much debate regarding the safety of HES in volume resuscitation in the ICU.[24] Numerous trials have investigated the role of HES, in particular in the management of sepsis as summarised in Table 98.1. The Efficacy of Volume

Table 98.1 Trials of hydroxyethyl starches in the management of sepsis and reported effects on kidney function

REFERENCES	RCT TYPE	*n* (HES/CON)	HES FLUID	CONTROL FLUID	KIDNEY PARAMETERS	RRT ()R; 95% CI)
Schortgen et al.[20]	Multicentre	129 (65/64)	6%	3% gelatin	⇑AKI, ⇑ Oliguria, Peak SCr	1.2 ().5–2.0)
Molnár et al.[21]	Single-centre	30 (15/15)	6%	3% gelatin	NR	NR
McIntyre et al.[22]	Multicentre	40 (21/19)	6%	0.9% NS	No difference	3.00 (P.3–31.6)
Brunkhorst et al.[15]	Multicentre	537 (262/275)	10%	Ringer's lactate	⇑AKI	1.95 (1.3–2.9)
Guidet et al.[23]	Multicentre	196 (100/96)	6%	0.9% NS	No difference	NR
Perner et al.[16]	Multicentre	798 (398/400)	6%	Ringer's lactate	⇑AKI	1.35 (1.01–1.8)
Myburgh et al.[17]	Multicentre	7000 (3315/3336)	6%	0.9% NS	⇑RRT	1.21 (1.00–1.45)

AKI, Acute kidney injury; *CON*, control; *HES*, hydroxyethyl starch; *NR*, not reported; *NS*, normal saline; *RCT*, randomised clinical trial; *RRT*, renal replacement therapy.

Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial suggested hyperoncotic preparations of older generations in high dosage should be avoided in haemodynamically stable septic patients due to an increased incidence of AKI.[17] The Scandinavian Starch for Severe Sepsis/Septic Shock (6S) study demonstrated a significantly increased 90-day mortality after HES use, but included 800 septic patients only *after* initial stabilisation.[16] The CHEST study found no difference in mortality and an unaltered renal state (RIFLE) after HES in 7000 ICU patients despite an increase in the use of renal replacement therapy.[17] In 2013 the Cochrane review stated that the use of all HES products increases the risk of AKI and renal replacement therapy in all patient populations and a safe volume of any HES solution has yet to be determined. The report concluded that in most clinical situations it is likely that these risks outweigh any benefits and alternate volume replacement therapies should be used in place of HES products.[18] In the same year the National Institute for Health and Care Excellence (NICE) clinical practice guideline made the recommendation not to use the tetrastarch HES for fluid resuscitation.[19] These recommendations have resulted in the European Health Agency and US Food and Drug Administration restricting the use of HES in patients with critical illness. More clinical studies will be required in the future to address these concerns.

DEXTRANS

Dextrans are polysaccharides biosynthesised commercially from sucrose by the bacterium *Leuconostoc mesenteroides* using the enzyme dextran sucrase.[1,2] This produces a high-molecular-weight dextran that is then cleaved by acid hydrolysis and separated by repeated ethanol fractionation to produce a final product with a relatively narrow MW range. The products are described by their MW – Dextran 40 and Dextran 70 having MWs of 40,000 and 70,000 Da, respectively.

Dextran preparations are stable at room temperature and have long shelf lives. Dextran 70 is used as a plasma substitute for the treatment of hypovolaemia and has an intravascular volume-expanding effect that lasts at least 6 hours. Dextran 40 is used for its effects on microcirculatory flow and blood coagulation in some types of surgery (e.g. vascular, neuro and plastic surgery). The beneficial effects on outcome when Dextran 40 is used as an 'anti-sludging agent' remain controversial. Dextran 40 should not be used as a plasma substitute for the treatment of hypovolaemia as, although it produces an immediate plasma volume expansion as a result of its low MW, it may obstruct kidney tubules and cause AKI.

Dextrans can precipitate true anaphylactic reactions, as antidextran antibodies may be present due to synthesis of dextrans by lactobacilli that occur naturally as gut commensals. Dextran infusion, particularly of the high-molecular-weight products, can also precipitate anaphylactoid reactions. The risk of true anaphylactic reactions can be decreased about 10-fold by pre-treatment with monovalent hapten–dextran. The dextrans are also associated with significant haemostatic derangements which include:

- haemodilution of clotting factors
- reduction in FVIII activity
- increase in plasminogen activation
- increase in fibrinolysis
- reduction in clot strength
- impairment of platelet function.

Red cell aggregation is also reduced with the lower-molecular-weight dextrans. In patients whose haemostatic function is normal prior to infusion, a maximum dose of 1.5 g/kg is often recommended to avoid risk of bleeding complications. The anticoagulant effects of dextrans can be utilised perioperatively

as a prophylaxis against thromboembolism.[1,2] Currently, due to the adverse side-effect profile and the requirement to pretreat with the hapten, dextrans are not commonly used in Europe.

HUMAN ALBUMIN SOLUTION

Naturally occurring human albumin is thought of as an ideal colloid and is commonly the reference solution against which other colloids are judged. Albumin represents the main protein responsible for colloid oncotic pressure and also possesses anti-inflammatory properties by scavenging reactive oxygen species and acts as a buffer for acid-base balance. Human albumin solution is a natural colloid and contains more than 95% albumin with a uniform molecular size (monodispersity), whereas all of the semisynthetic colloids have a distribution of molecular sizes (polydispersity).[2,4] The size–weight relationship is relatively constant, although some colloids can have equivalent MW with different molecular size – succinylated and urea-linked gelatins have almost identical molecular weights but the succinylated product undergoes conformational change due to an increase in negative charge and is physically larger.[4,5]

Human albumin solutions are prepared from human plasma and heat treated to ensure that neither hepatitis nor HIV can be transmitted. It has a relatively short (~1 year) shelf life at room temperature, but a 5-year shelf life at 2°C–8°C. Human albumin 5% (the 4% version is a cost-free by-product of the production of packed red cells, exclusively used in Australia) is used for the treatment of hypovolaemia in a wide variety of clinical conditions. Concentrated salt-poor 20% human albumin is used for the treatment of hypoalbuminaemia in the presence of salt and water overload (e.g. liver failure with ascites). Albumin has putative advantages that include limiting free radical-mediated damage but the importance of a normal serum albumin level remains uncertain.[25-27]

Human-derived colloid has a number of disadvantages. It is an expensive product and concerns have been raised about transmission of infectious agents – such as new-variant Creutzfeldt–Jakob disease (nvCJD) associated with bovine spongiform encephalopathy (BSE) – that are not removed by currently available techniques. Concerns have also been raised by the conclusions of a highly controversial meta-analysis suggesting that the use of human albumin solution may be associated with increased mortality in the critically ill.[27-29] These conclusions were probably unjustified for most collectives except for traumatic brain injury,[30] but there is currently no evidence that the use of human albumin has any advantages over less expensive semisynthetic alternatives[30,31] or indeed crystalloids. However, the latter still applies to all colloids.[30,33,34] The volume effect of 5% human albumin is approximately 90% when used to maintain blood volume during acute blood loss.[32]

FRESH FROZEN PLASMA

Fresh frozen plasma (FFP) contains normal plasma levels of all the clotting factors, albumin and immunoglobulin. A unit is typically 200–250 mL and has a FVIII level of at least 0.7 IU/mL (i.e. 70% of normal levels) and about 0.5 g of fibrinogen. It is kept at a temperature of –18°C or less in order to preserve coagulant levels. FFP is used for the replacement of multiple clotting factor deficiencies (e.g. liver disease, coumarin anticoagulant overdose and coagulopathy associated with massive blood transfusion).[24,35,36] An initial dose of at least 15 mL/kg (four packs for a 70-kg adult) is considered to be appropriate. Physiologically, in a normovolaemic patient, it might be better to correct any clotting factor deficit using a concentrate and then maintain the appropriate level using FFP instead of colloids in the face of ongoing bleeding or other volume deficit. This might decrease the risk of intravascular hypervolaemia, but currently there are no data to support using FFP in this way. FFP should not be used as a plasma volume expander, solely for the treatment of hypovolaemia.

CRYOPRECIPITATE

Cryoprecipitate is prepared by freeze-thaw of FFP, collection of the precipitate and then its resuspension in human plasma. It is a concentrate of FVIII, von Willebrand factor and fibrinogen and contains about 50% of the coagulant factor activity of the original unit (e.g. fibrinogen 250 mg, FVIII 100 IU). Cryoprecipitate is stored at –18°C and remains stable for up to a year.[35] It is indicated in the treatment of coagulation defects, including massive haemorrhage and disseminated intravascular dissemination (DIC), if there is microvascular bleeding associated with a fibrinogen level less than 0.5 g/L. Also, it is, in principle, an alternative to the preferable FVIII or von Willebrand factor concentrates in the treatment of inherited deficiencies of those proteins.[24,36]

FACTOR VIII

Recombinant FVIII is available but concentrates are also still prepared from pools of donor plasma and heat or chemically treated to inactivate HIV-1. It has a shelf life of 2–3 years. Chromatographic concentration results in high-purity FVIII, and the relative merits of high- and intermediate-purity products are being investigated.

Indications are the treatment of haemophilia A.[37] The dosage should carefully follow the recommendations of the respective manufacturers, targeting at plasma activities between 30% and 100%, depending

on the clinical situation. Preferably, the strategy should be planned together with a specialist and will usually lead to a bolus of 25–50 U/kg, which can be repeated, for example, 12-hourly.

FACTOR IX COMPLEX

Factor IX complex (prothrombin complex concentrate, also called 'PPSB') contains the vitamin-K-dependent factors II, VII, IX and X in varying amounts, and is prepared from pools of plasma.[35] It is a freeze-dried preparation reconstituted with water immediately before use. Factor IX complex is mainly used to correct bleeding disorders due to an overdose of the vitamin K antagonistic coumarin anticoagulants in patients who cannot tolerate large volumes of FFP.[35] Purified factor IX concentrates are now available and appear preferable in haemophilia B.

IMMUNOGLOBULINS (GAMMA GLOBULINS)

Human immunoglobulin preparations are pooled from plasma from normal blood donors. It contains antibodies to hepatitis A, measles, mumps, varicella, polio and prevalent bacteria, reflecting the plasma of the donors.[35] Immunoglobulins are indicated in the prevention or treatment of patients with hypogammaglobulinaemia, and may have a role in the treatment of autoimmune diseases, such as thrombocytopenic purpura and myasthenia gravis. Specific immunoglobulins are available for a range of infectious agents including tetanus, hepatitis B, rubella, measles, rabies and varicella zoster. They are made from donor plasma known to contain high levels of the specific IgG antibodies and are used for prophylaxis and treatment in patients who have not been actively immunised. Rhesus-D immunoglobulin is prepared from plasma containing high levels of anti Rh-D antibodies and it prevents sensitisation of Rh-negative mothers to Rh-D positive cells that may enter their circulation. The principal use of Rh-D immunoglobulin is in the prevention of haemolytic disease of the newborn.[38]

KEY REFERENCES

2. Vercueil A, Grocott MP, Mythen MG. Physiology, pharmacology, and rationale for colloid administration for the maintenance of effective hemodynamic stability in critically ill patients. *Transfus Med Rev*. 2005;19:93–109.
7. Chappell D, Jacob M, Hofmann-Kiefer K, et al. A rational approach to perioperative fluid management. *Anesthesiology*. 2008;109:723–740.
9. Jacob M, Chappell D, Hofmann-Kiefer K, et al. The intravascular volume effect of Ringer's lactate is below 20%: a prospective study in humans. *Crit Care*. 2012;16:R86.
11. James MF, Latoo MY, Mythen MG, et al. Plasma volume changes associated with two hydroxyethyl starch colloids following acute hypovolaemia in volunteers. *Anaesthesia*. 2004;59:738–742.


Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Grocott MPW, Mythen MG. Fluid therapy. In: Goldhill DR, Strunin L, eds. *Clinical Anaesthesiology*. London, UK: Baillière Tindall; 1999:363–381.
2. Vercueil A, Grocott MP, Mythen MG. Physiology, pharmacology, and rationale for colloid administration for the maintenance of effective hemodynamic stability in critically ill patients. *Transfus Med Rev*. 2005;19:93–109.
3. Jacob M, Bruegger D, Rehm M, et al. The endothelial glycocalyx affords compatibility of Starling's principle and high cardiac interstitial albumin levels. *Cardiovasc Res*. 2007;73:575–586.
4. Webb AR, Barclay SA, Bennett ED. In vitro colloid osmotic pressure of commonly used plasma expanders and substitutes: a study of the diffusibility of colloid molecules. *Intensive Care Med*. 1989;15:116–120.
5. Lamke LO, Liljedahl SO. Plasma volume changes after infusion of various plasma expanders. *Resuscitation*. 1976;5:93–102.
6. Jacob M, Chappell D, Rehm M. Clinical update: perioperative fluid management. *Lancet*. 2007;369:1984–1986.
7. Chappell D, Jacob M, Hofmann-Kiefer K, et al. A rational approach to perioperative fluid management. *Anesthesiology*. 2008;109:723–740.
8. Corcoran T, Rhodes JE, Clarke S, et al. Perioperative fluid management strategies in major surgery: a stratified meta-analysis. *Anesth Analg*. 2012;114(3):640–651.
9. Jacob M, Chappell D, Hofmann-Kiefer K, et al. The intravascular volume effect of Ringer's lactate is below 20%: a prospective study in humans. *Crit Care*. 2012;16:R86.
10. Davies MJ. Polygeline. *Dev Biol Stand*. 1987;67:129–131.
11. James MF, Latoo MY, Mythen MG, et al. Plasma volume changes associated with two hydroxyethyl starch colloids following acute hypovolaemia in volunteers. *Anaesthesia*. 2004;59:738–742.
12. Rehm M, Orth VH, Weninger E, et al. Acute 'normovolemic' hemodilution with 3.5% polygel (Haemaccel) for patients in the Wertheim–Meigs operation. Blood loss of 87% blood volume without perioperative blood transfusion. *Anaesthesist*. 2001;50:580–584.
13. Jacob M, Rehm M, Orth V, et al. Exact measurement of the volume effect of 6% hydoxyethyl starch 130/0.4 (Voluven) during acute preoperative normovolemic hemodilution. *Anaesthesist*. 2003;52:896–904.
14. Morgan PW, Berridge JC. Giving long persistent starch as volume replacement can cause pruritus after cardiac surgery. *Br J Anaesth*. 2000;85:696–699.
15. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008;358:125–139.
16. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012;12:124–134.
17. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch for fluid resuscitation in intensive care. *N Engl J Med*. 2012;20:1901–1911.
18. Mutter TC, Ruth CA, Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. *Cochrane Database Syst Rev*. 2013;(7):CD007594.
19. *Intravenous Fluid Therapy in Adults in Hospital*. National Institute for Health and Care Excellence (NICE); 2013.
20. Schortgen F, Girou E, Deye N, et al; CRYCO Study Group. The risk associated with hyperoncotic colloids in patients with shock. *Intensive Care Med*. 2008;34(12):2157–2168.
21. Molnár Z, Mikor A, Leiner T, et al; Fluid resuscitation with colloids of different molecular weight in septic shock. *Intensive Care Med*. 2004;30(7):1356–1360.
22. McIntyre LA, Fergusson D, Cook DJ, et al. Canadian Critical Care Trials Group. Fluid resuscitation in the management of early septic shock (FINESS): a randomized controlled feasibility trial. *Can J Anaesth*. 2008;55(12):819–826.
23. Guidet B, Martinet O, Boulain T, et al. Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: the CRYSTMAS study. *Crit Care*. 2012;16(3):R94.
24. Mythen MG, Machin SJ. Derangements of blood coagulation. In: Hanson GC, ed. *Critical Care of the Surgical Patient*. London, UK: Chapman and Hall; 1997:185–194.
25. Halliwell B. Albumin – an important extracellular antioxidant? *Biochem Pharmacol*. 1988;37:569–571.
26. Vincent JL, Navickis RJ, Wilkes MM. Morbidity in hospitalized patients receiving human albumin: a meta-analysis of randomized, controlled trials. *Crit Care Med*. 2004;32:2029–2038.
27. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ*. 1998;317:235–240.
28. Rehm M, Orth V, Kreimeier U, et al. Changes in intravascular volume during acute normovolemic hemodilution and intraoperative retransfusion in patients with radical hysterectomy. *Anesthesiology*. 2000;92(3):657–664.
29. Bunn F, Alderson P, Hawkins V. Colloid solutions for fluid resuscitation. *Cochrane Database Syst Rev*. 2000;(2):CD001319.
30. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350:2247–2256.
31. Stockwell M, Soni N, Riley B. Colloid solutions in the critically ill. A randomized comparison of albumin and polygeline. 1. Outcome and duration of stay in the intensive care unit. *Anaesthesia*. 1992;47:3–6.

32. Stockwell MA, Scott A, Day A, et al. Colloid solutions in the critically ill. A randomised comparison of albumin and polygeline. 2. Serum albumin concentration and incidences of pulmonary oedema and acute renal failure. *Anaesthesia*. 1992;47:7–9.
33. Schierhout G, Roberts I. Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. *BMJ*. 1998;316:961–964.
34. Choi P, Yip G, Quinonez L, et al. Crystalloids vs colloids in fluid resuscitation: a systematic review. *Crit Care Med*. 1999;27:200–210.
35. McClelland DBL, ed. *Handbook of Transfusion Medicine*. London, UK: HMSO; 1989.
36. Mammen EF. Disseminated intravascular coagulation (DIC). *Clin Lab Sci*. 2000;13:239–245.
37. Hambleton J. Advances in the treatment of von Willebrand disease. *Semin Hematol*. 2001;38:7–10.
38. Greenough A. The role of immunoglobulins in neonatal rhesus haemolytic disease. *Biodrugs*. 2001; 15:533–541.

99

Plasmapheresis, therapeutic plasma exchange and intravenous immunoglobulin therapy

Ian Kerridge, David Collins

Blood-letting to remove 'evil humours' has been practiced for over 2000 years. However, although the restoration of 'balance' and the removal of 'noxious' agents from the blood remains the rationale for apheresis, contemporary practice is now based upon an extensive scientific understanding of the pathophysiology of the diseases treated by plasmapheresis and plasma exchange.[1] Exchange transfusions revolutionised the management of haemolytic disease in the newborn, and paved the way for therapeutic plasmapheresis and plasma exchange – the removal of plasma, with replacement by albumin–electrolyte solutions or fresh frozen plasma (FFP). Initially used in the management of hyperviscosity associated with malignant paraproteinaemia, it is now also used in the treatment of more than 100 autoimmune disorders. It is, however, expensive, is not without risk, and its use in many diseases remains a matter of ongoing debate.

Intravenous immunoglobulin (IVIG) – once used purely as replacement therapy for patients with primary humoral immune deficiency – has also become increasingly used as an immunomodulatory agent. Its relevance in this chapter is that it is now being used in many disorders in which plasma exchange is effective, but the convenience and safety of IVIG therapy is preferred as an alternative. The underlying principles in managing autoimmune diseases with IVIG are similar to those of therapeutic plasmapheresis and plasma exchange. The immunomodulatory mechanism of action of IVIG remains controversial and it is likely, as with plasma exchange, that there is more than one mechanism in play. Therapeutic efficacy of IVIG has been established in controlled trials for a range of diseases including idiopathic thrombocytopenic purpura, Kawasaki disease, Guillain–Barré syndrome (GBS), dermatomyositis and others. There is compelling evidence that IVIG can modulate immune reactions of T cells, B cells and macrophages, thus interfering with antibody production and degradation, but also modulating the complement cascade and cytokine networks.

RATIONALE FOR PLASMA EXCHANGE

Theoretically, plasma exchange should be effective to treat any disorder in which there is a pathogenic circulating factor responsible for disease. However, it is increasingly clear that this premise is too simplistic as many other mechanisms contribute to its beneficial effects (Box 99.1). Plasma exchange brings about numerous alterations in the plasma's *milieu interieur* – which may be clinically beneficial or detrimental.

PATHOPHYSIOLOGY OF AUTOIMMUNE DISEASE

Autoimmune disease originates from the breakdown of immunoregulation (i.e. immune tolerance), allowing the immune system to become autoaggressive. Autoimmune diseases with underlying humoral mechanisms result from either a circulating autoantibody against a self-antigen (alone or in combination with an environmental antigen), or circulating immune complexes (which may be deposited in the microcirculation of various organs, resulting in end-organ damage). Cellular and tissue damage are affected by the autoantibody or immune complexes activating the cellular and humoral components of the inflammatory response. The circulating proteolytic systems involved include the complement, coagulation, fibrinolytic and kinin systems. On the cellular side, neutrophils and macrophages are involved, with eosinophils and basophils also playing a part.

Therapy in acute and chronic autoimmune disease aims to minimise irreparable end-organ damage and support patients during the acute illness. This therapy may include:

- non-specific therapy to suppress the effector mechanisms (e.g. corticosteroids, antiplatelet therapy, non-steroidal anti-inflammatory drugs, anticoagulation and depletion of humoral effector mechanisms by plasma exchange or defibrination)

ABSTRACT

Plasmapheresis and therapeutic plasma exchange (TPE) provide effective treatment for over 100 diseases, including those resulting from immunoproliferation with aberrant antibody production, autoimmune disease, immune complex disease and other immune disorders and for the treatment of disease resulting from poisoning, accumulation of toxins or depletion of coagulation factors. Intravenous immunoglobulin (IVIG) – once used purely as replacement therapy for patients with humoral immune deficiency – has also become increasingly used as an immunomodulatory agent. An understanding of the rationale for plasmapheresis, TPE and IVIG, the indications for their use and the adverse consequences that may arise is essential for those working in high acuity care and for those responsible for the care of patients with immune disease.

KEYWORDS

Plasmapheresis
plasma exchange
intravenous immunoglobulin (IVIG)
immune complex disease
autoimmunity

- therapy to reduce the circulating levels of a humoral factor, which is achieved with plasma exchange or an immunoabsorption technique
- specific or broad-spectrum immunosuppressive agents to suppress or block the immune response (e.g. corticosteroids, cytotoxic agents, anti-lymphocyte globulin, high-dose intravenous gamma-globulin therapy)
- therapy directed at altering reticuloendothelial function, which may then have effects on autoantibody and immune complex clearance, or clearance of circulating damaged cells
- IVIG immunomodulatory therapy.

Box 99.1 Rationale for plasma exchange

Removal of circulating toxic factor antibodies
- Monoclonal antibodies
- Autoantibodies
- Alloantibodies

Immune complexes
Chemical drugs
Depletion of mediators of inflammation
Replacement of deficient plasma factor(s)
Potentiation of drug action
Enhanced reticuloendothelial function
Altered immunoregulation
Potentiating effect of plasma exchange on other modes of therapy (e.g. glucocorticoids)

As most disorders are multifactorial, it is unlikely that a single form of therapy will be successful, so a multipronged approach to therapy needs to be based upon analysis of the underlying pathophysiology. The stage of the disease is also important (Fig. 99.1). Clearly, plasma exchange will have a different response when autoantibody production is rising rapidly, compared with a stage when autoantibody has ceased production. Also, immunoregulation is a complex process and therapies may interfere at different points in the immune mechanisms.

In some circumstances, specific and directed therapy may attack the most relevant link in the pathophysiological chain, but overall multiple approaches to

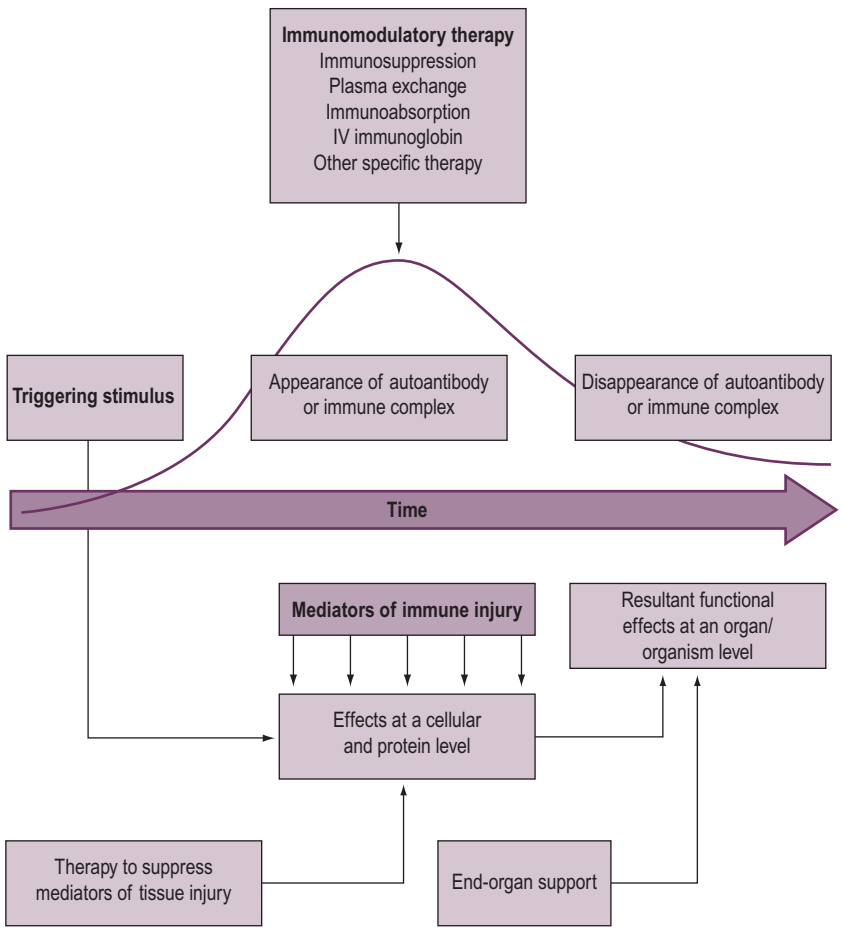


Figure 99.1 The therapy of 'one-hit' autoimmune disease. *IV*, Intravenous.

therapy may be required. In general, plasma exchange is a temporising procedure and concomitant immunosuppressive therapy is required to maintain control. Plasma exchange should generally be regarded as a first step in immunomodulatory therapy, and be restricted to acute or fulminant situations in which autoantibodies or immune complexes are responsible for life-threatening or end-organ-damaging complications. If the humoral factor is only transient ('a one antigen hit' disorder), then no follow-up immunosuppression is required (e.g. acute post-infectious polyneuritis). Increasingly, monoclonal antibody therapy with rituximab (an anti-CD20 antibody) is finding a role in the longer-term management of autoimmune diseases.[2,3]

The recognition of the immunomodulatory effects of IVIG has resulted in an exponential increase in its use in immune and inflammatory disorders – with availability being one of the main drivers of the supply of human-derived plasma products. Indeed, in most of the immune and inflammatory disorders in which plasma exchange has been used, IVIG has been used – often with equal efficacy.[4]

TECHNICAL CONSIDERATIONS

Therapeutic plasmapheresis and plasma exchange are based upon the principle of separation – which can be done by filtration, centrifugation or a combination of both, depending on the equipment available. There are a number of apheresis machines on the market. Filtration plasma exchange is found on a number of dialysis machines and uses a semipermeable membrane with small holes or pores up to 0.2 μm in diameter; this is approximately 30 times the diameter of the pores found in conventional high-flux haemofilter membranes.[5] Blood is pumped into this chamber and the plasma passes through the membrane; this membrane will allow the passage of substances up to 3×10^6 Da, separating substances, such as immunoglobulins, immune complexes and complement factors, from the cellular part of the blood.[5] The plasma is then diverted to a waste bag and the remaining cellular product mixed with replacement fluid and returned to the patient.

Apheresis machines using centrifugation use continuous or intermittent blood flow. The continuous flow machines pump blood through a band centrifuge; applied G-force separates out the blood according to its molecular weight, and the particular product (in this case the plasma) is removed and pumped to the waste bag, with the remaining cellular material being mixed with the replacement fluid and returned to the patient.[6] Intermittent centrifugation uses a Latham bowl, which fills with blood, is centrifuged; the plasma is separated to a waste bag and the cellular products returned to the patient with replacement fluid. This procedure can be carried out through one vein; however, it is a longer procedure than the continuous-flow machines.[6]

The extracorporeal blood is anywhere between 150 mL and 250 mL depending on the machine being used. There is cooling in the extracorporeal circuit, and the replacement fluids will be cool so consideration should be given to maintain body temperature, with a blood warmer and warming blankets.[7]

Good venous access is required for an efficient procedure. Stopping and starting of the machine due to inadequate flow exposes the patient to larger doses of anticoagulant. Peripheral access can be achieved using 18 g or 16 g cannula; however, many patients' veins cannot cope with multiple punctures when a high number of procedures are required, and therefore consideration should be given to a central venous access device (CVAD). There are a number of CVADs available on the market, ranging from semipermanent to the more permanent. A Vas-Cath can be inserted either into the jugular or femoral veins but will have a limited lifespan dependent on the chosen vein, whereas a perma-cath or apheresis Hickman, which are tunnelled after insertion via a central neck vein, will have a longer life and a lower infection risk.

Depending on the reason for plasma exchange, a risk assessment of which access to use should be undertaken to ascertain a suitable device for the patient and the length of treatment. It may, as in the case of thrombotic thrombocytopenic purpura (TTP), be better to start off with peripheral veins for the first couple of treatments until the platelets rise and a more permanent line can be inserted safely and without the use of transfused platelets.[8]

To ensure that the extracorporeal circuit does not clot during plasmapheresis anticoagulation is required. Most apheresis machines use regional anticoagulation, with citrate added as blood enters the apheresis circuit. Pooled plasma also contains citrate so, if used, the amount of citrate returned to the patient is further increased. It should be noted, however, that citrate toxicity can also occur when albumin is used, as this is a calcium-free and calcium avid-binding solution.[7] Although citrate is plasma-bound and relatively short-acting, there will still be some returned to the patient where it is metabolised. Patients with abnormal liver functions will take longer to metabolise the citrate and therefore have an increased risk of citrate toxicity. Citrate toxicity produces hypocalcaemia with symptoms including oral or extremity paraesthesia, light-headedness, tetany, nausea, vomiting and cardiac arrhythmias.[9] The drop in calcium levels occurs within the first 15 minutes of the procedure,[7] therefore attention should be paid to the patient's serum calcium and, if required, supplementation commenced prior to the start of the procedure. Calcium gluconate 10% at a dose of 2 mL per 250 mL of replacement fluid has been recommended; this can be added to the albumin or run as a concurrent infusion.[10,11] Other electrolytes can also become depleted, and should therefore be monitored and replaced as required.[7] Magnesium also binds to

citrate and there can be up to a 60% fall in the blood levels of patients; however, concurrent supplementation is not recommended as routine.[7]

As plasma exchange requires the removal of plasma, this necessitates the use of replacement fluid – which can be 'fresh' plasma (FFP), plasma fractions, albumin, crystalloid or some combination of these. The choice of replacement fluid is made on the basis of the underlying pathology. In TTP, for example, the absence or inhibition of an enzyme, ADAMTS-13 protease and the resultant accumulation of ultra-large von-Willebrand factor leads to the formation of microthrombi and causes the clinical features of the disease, so the replacement fluid should contain ADAMTS-13 enzyme and functional VWF. In contrast, in hyperviscosity states, replacement with colloid alone will be more beneficial.

Occasionally the apheresis circuit is secondary to heart bypass, extracorporeal membrane oxygenation (ECMO) or renal dialysis. The literature is limited but it has been reported as safe.[7] For ECMO and heart bypass, the apheresis practitioner must work closely with the medical staff and perfusionist to ensure the patient's safety. At times the procedure can be managed by undertaking a tandem procedure. This is where an additional device is fitted to the return line of the primary circuit. This line has two ports placed approximately 12 cm apart and allows for the apheresis draw and return lines to be connected. Blood is drawn into the apheresis circuit, processed, plasma drawn off and replacement added. The whole blood is then returned to the patient. The beauty of this procedure is that the ECMO or dialysis needs only to be stopped for the brief time it takes to connect or disconnect the apheresis machine. Consideration is given to the management of the patient's blood pressure and fluid status during the procedure, and these should be corrected as dictated by the patient's condition. Therefore, it is essential that there is good communication between all members of the team and an assessment of the patient's ability to cope with two extracorporeal circuits is made.[12] The majority of apheresis machines will have the capacity to undertake a blood prime of the equipment this will help support the patient's blood volume. Depending on the anticoagulant being used for the primary circuit, the amount of anticoagulant in the apheresis circuit can be reduced. The patient should receive appropriate electrolyte replacement.[13]

INDICATIONS (Box 99.2)

Plasma exchange is most beneficial for immunoproliferative and autoimmune diseases. In some conditions with unclear pathophysiology, the beneficial effects of plasma exchange may be due to infusion of a deficient component in the replacement plasma, rather than removal of a circulating factor.

Box 99.2 Acute diseases in which plasma exchange may be beneficial*

Immunoproliferative diseases with monoclonal immunoglobulins
Hyperviscosity syndrome
Cryoglobulinaemia
Renal failure in multiple myeloma
Autoimmune diseases due to autoantibodies or immune complexes
Goodpasture syndrome
Myasthenia gravis
Guillain–Barré syndrome
Chronic inflammatory demyelinating polyneuropathy (CIDP)
Stiff-man syndrome
Systemic lupus erythematosus
Fulminant antiphospholipid syndrome
Thrombotic thrombocytopenic purpura
Haemolytic uraemic syndrome (HUS)
Rapidly progressive glomerulonephritis
Coagulation inhibitors
Autoimmune haemolytic anaemia
Pemphigus
Paraneoplastic syndromes
Conditions in which replacement of plasma may be beneficial +/– removal of toxins
Disseminated intravascular coagulation
Multiorgan dysfunction syndrome
Overwhelming sepsis syndromes (e.g. meningococcaemia)
Conditions in which the mechanisms are unknown
Reye syndrome
Removal of protein-bound or large-molecular-weight toxins
Paraquat poisoning
Envenomation

*This is an incomplete list and includes only disorders that are relatively common or in which plasma exchange has a definitive role to play.

The American Society for Apheresis (ASFA) has published comprehensive 'Guidelines on the Use of Therapeutic Apheresis in Clinical Practice: Evidence-based approach from the Apheresis Applications Committee of the American Society for Apheresis'.[14] The ASFA guidelines describe four categories of disorder on the basis of a review of the available literature on the efficacy of therapeutic plasma exchange (TPE). These are as follows:

- *Category I*: 'Disorder for which apheresis is accepted as first-line therapy, either as a standalone treatment or in conjunction with other modes of treatment'.
- *Category II*: 'Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment'.
- *Category III*: 'Optimum role of apheresis therapy is not established. Decision-making should be individualised'.

- *Category IV*: 'Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. Internal Review Board approval is desirable if apheresis treatment is undertaken in these circumstances'.

Category I disorders include: myasthenia gravis, GBS, Goodpasture syndrome (anti-glomerular basement membrane [GBM] antibody disease), cryoglobulinaemia, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), sickle cell disease (acute stroke) and Wegener's granulomatosis.

Category II disorders include: multiple sclerosis, neuromyelitis optica, acute disseminated encephalomyelitis, ABO-incompatible solid organ transplantation and catastrophic antiphospholipid syndrome (CAPS).

Category III disorders include: aplastic anaemia, autoimmune haemolytic anaemia, paraneoplastic neurological syndromes, erythrocytosis, acute liver failure, immune complex rapidly progressive glomerulonephritis (RPGN) and sepsis, and multiorgan failure.

Category IV disorders include: dermatomyositis or polymyositis, idiopathic (autoimmune) thrombocytopenia purpura (ITP), rheumatoid arthritis, chronic progressive multiple sclerosis, scleroderma, amyloidosis and inflammatory bowel disease.

MONOCLONAL ANTIBODIES ASSOCIATED WITH IMMUNOPROLIFERATIVE DISEASES

Monoclonal immunoglobulins are a classical feature of multiple myeloma and Waldenström's macroglobulinaemia, but may also be associated with other lymphoproliferative disorders. These monoclonal proteins may be associated with numerous clinical effects, many of which may be reversed by plasma exchange:

- *Hyperviscosity syndrome:* characteristic clinical features of hyperviscosity in association with monoclonal proteins include visual disturbance, neurological dysfunction and hypervolaemia. All are rapidly relieved by plasma exchange.[15]
- *Haemostatic disturbances:* monoclonal proteins may impair haemostasis by adversely affecting platelet function or by inhibitory effects on coagulation factors. Plasma exchange is usually effective in controlling haemorrhage and may be helpful in preparing patients for surgery.
- *Renal failure:* the development of renal failure in the course of multiple myeloma is generally regarded as a sign of poor prognosis. The renal failure is often multifactorial in origin, but some of these factors may be reversible by plasma exchange. Patients presenting acutely with hyperviscosity, dehydration and hypercalcaemia may show recovery of renal function following adequate hydration, alkaline diuresis and plasma exchange.

IMMUNOLOGICAL DISEASES

DISEASES MEDIATED BY SPECIFIC AUTOANTIBODIES

Goodpasture syndrome

In Goodpasture syndrome circulating anti-GBM antibodies can often be demonstrated. The disease classically has a fulminant presentation with rapidly progressive renal failure and life-threatening pulmonary haemorrhage. Early diagnosis and intensive plasma exchange may be necessary to preserve renal function and control pulmonary haemorrhage. Patients who are already in anuric renal failure rarely show improvement in renal function.[16]

Myasthenia gravis

Removal of the acetylcholine receptor autoantibody is often associated with clinical improvement, but the beneficial effects of plasma exchange are usually transient, so the procedure should be used in conjunction with other forms of therapy (see Chapter 58). The major role of plasma exchange is in myasthenic crisis in patients whose condition is resistant to other forms of therapy, and prior to surgery. Therapy can be monitored by acetylcholine receptor autoantibody assays and respiratory function tests. During the procedure patients may transiently deteriorate, owing to a combination of the physical exertion and removal of medication from the circulation. Adequate ventilatory support should be available. IVIG may also be used in myasthenia gravis.[17–19]

Stiff-man syndrome

Stiff-man syndrome is a rare neurological disorder characterised by involuntary axial and proximal limb rigidity and continuous motor unit activity on electromyography. Autoantibodies to glutamic acid decarboxylase are usually demonstrable and plasma exchange is often successful in those in whom autoantibody can be demonstrated, but if negative they are less likely to respond.[20,21]

Autoimmune haematological disorders

Haemostatic failure due to autoantibodies directed against coagulation factors may present a major management problem. Antibodies directed against factor VIII are the commonest, occurring spontaneously or in association with replacement therapy in haemophiliacs. First-line therapy in patients with coagulation factor inhibitors usually requires activated factor VII therapy with recombinant VIIa or appropriate prothrombin concentrates, but plasmapheresis may also be useful in patients who are refractory to first-line therapy or as an adjunct to first-line therapy.[22]

Plasmapheresis may also provide an important part of treatment for patients with CAPS. Although the exact mechanism(s) by which plasmapheresis may assist in the management of CAPS is unknown, including

removal of antiphospholipid antibodies, complement, tumour necrosis factor and cytokines, and restoration of normal levels of antithrombin, protein C and protein S, when used in combination with anticoagulants and steroids it appears to provide the highest likelihood of resolution of thromboses and survival.

IMMUNE COMPLEX DISEASE

Rapidly progressive glomerulonephritis

Immune-complex-induced RPGN may occur by itself or be associated with several systemic disorders (e.g. systemic lupus erythematosus [SLE], polyarteritis nodosa, IgA nephropathy, post-streptococcal infection and Wegener's granulomatosis).[23–25] Plasma exchange may result in improvement in renal function even in patients who present with anuria. The decomplementing and defibrinating effects of plasma exchange may be partly responsible for clinical improvement. The therapeutic role of plasma exchange in RPGN is difficult to assess, but most experienced physicians feel that the procedure leads to a more rapid and complete recovery of renal function in fulminant, rapidly deteriorating cases. However, the ultimate prognosis of the disease depends on adequate immunosuppression to inhibit immune complex formation, or spontaneous disappearance of the inciting antigen.

Systemic lupus erythematosus

In acute life-threatening or organ-damaging relapses of SLE, plasma exchange should be considered if there is rapid deterioration in renal function, cerebritis or acute fulminant lupus pneumonitis.[26]

Cryoglobulinaemia

The various forms of cryoglobulinaemia may be associated with vasculitis or hyperviscosity. If there is an acute fulminant presentation with cutaneous vasculitis, renal failure, and neurological impairment then plasma exchange should be considered an urgent definitive form of therapy.

OTHER IMMUNE-MEDIATED DISEASES

Renal transplant rejection

Humoral mechanisms appear to play a part in hyperacute renal allograft rejection. Plasma exchange +/− IVIG may be useful in tiding patients over episodes of acute graft rejection. However, results of clinical trials have been conflicting.[27,28] General opinion is that plasma exchange helps in a limited number of patients who cannot be currently pre-selected by any clinical or laboratory criteria.

Thrombotic microangiopathies (see also Chapter 100)

The thrombotic microangiopathies describe a number of syndromes characterised by endothelial damage to capillaries and arterioles, leading to disseminated microvascular thrombosis, thrombocytopenia and (often) haemolytic anaemia. They include TTP, haemolytic uraemic syndrome (HUS), atypical HUS, disseminated intravascular coagulation (DIC), CAPS and paediatric thrombocytopenia-associated multiorgan failure (TAMOF).

Thrombotic thrombocytopenic purpura

TTP is a potentially fulminant and life-threatening disorder characterised by platelet microthrombi in small vessels, resulting in microangiopathy. TTP has been linked to a severe deficiency in ADAMTS13 with metalloprotease activity with its target cleavage sequence in vWF. The deficiency of ADAMTS13 may be due either to the presence of an IgG autoantibody inhibitor to this vWF-reducing metalloproteinase or to inherited mutations in ADAMTS13. The clinical syndrome of TTP is manifest by the pentad of thrombocytopenia, microangiopathic haemolytic anaemia, fever, renal dysfunction and neurological abnormalities. Abdominal symptoms, hepatic dysfunction and pulmonary abnormalities may also occur.

TTP used to be a fatal disease in 90% of patients, but dramatic improvement in its outcome has occurred over the past two decades. Plasma exchange has become the cornerstone of the treatment with cryoprecipitate-poor plasma (depleted in vWF).[29,30] It is now possible to achieve remissions in the majority of patients and cures are now common, although unfortunately relapse may occur. The clinical course at relapse is usually milder than the disease at presentation and less-aggressive therapy may be needed.

Haemolytic uraemic syndrome

This syndrome has many similarities to TTP, but in contrast to cerebral TTP, renal involvement is the hallmark of microangiopathy and thrombocytopenia.[31] HUS is commonly categorised into 'typical' and 'atypical' HUS.

Typical HUS, the majority of cases, is commonly associated with infection and diarrhoea (see Chapter 100). Less often, HUS may present insidiously and the cause, which may include chemotherapy, radiotherapy or other medications, may be unclear. TPE is generally not recommended for typical HUS associated with infection – which is often self-limiting and has a mortality of less than 5%. Although it is often tried in adult patients with HUS and in patients with typical HUS of more indeterminate cause – the results are often disappointing.

Atypical HUS is thought to result from genetic mutations in the complement pathway or from acquired autoantibodies against factor H, which result in uncontrolled activation of the alternative complement pathway and direct injury to the microvasculature. In contrast to typical HUS, plasma exchange may be beneficial in patients with atypical HUS, although the optimal therapy for atypical-HUS is now thought

to be eculizumab – a monoclonal antibody that binds with high-affinity to C5 and blocks terminal complement C5a and C5b-9 activity.

Because it is often difficult to distinguish atypical HUS from typical HUS and HUS from TTP, particularly in the acute setting, plasma exchange is often initiated until the results of genetic studies and biomarkers can assist in clarifying the diagnosis.

Inflammatory demyelinating neuropathies and Guillain–Barré syndrome

This acute self-limiting disease in which an acute demyelinating neuropathy occurs (usually following a viral infection) commonly results in admission to the intensive care unit (see Chapter 58). The demyelination is due to post-infectious autoimmunity, with both the cellular and the humoral arms of the immune system attacking myelin. There is now wide experience in the use of plasma exchange and IVIG therapy in GBS, with controlled trials substantiating its benefits of shortening of the illness, and complications. Therapy should be instituted early.[19,32] As GBS also responds to high-dose IVIG, there is debate as to which should be the first line of therapy; as the therapies have comparable efficacy and safety, decisions are usually made on the basis of local logistics and economics.[33] In some cases the onset of recovery after therapy may be delayed, probably due to time for remyelination to occur. Some patients show rapid improvement after plasma exchange, suggesting the presence of neuronal blocking factors. CIDP neuropathy is related to GBS, and plasma exchange and/or IVIG have important roles in treatment, in many cases requiring long-term therapy.

COMPLICATIONS

Plasma exchange is a relatively safe procedure, with a case fatality rate of 3–5 per 10,000 procedures – mainly as a consequence of cardiac arrest, cardiac failure and transfusion-associated acute lung injury (TRALI). Minor complications due to fluid shifts, electrolyte abnormalities and exposure to blood products are common, and for these reasons close supervision by experienced physicians and apheresis operators with a sound understanding of the haemodynamic, biochemical, haematological and immunological effects of plasma exchange is of paramount importance.[34,35]

Assessment prior to commencing the procedure should include vascular access, haemodynamic stability, transfusion history, relevant co-morbidities and concomitant medications.

Potential complications of plasma exchange include: fluid imbalance, reactions to replacement fluids, vasovagal reactions, pyrogenic reactions, hypothermia, embolism (air or microaggregates), hypocalcaemia, anaemia, thrombocytopenia, haemostatic disturbances, hepatitis, hypogammaglobulinaemia and altered pharmacokinetics of drugs.

Plasma exchange can be used for the removal of some drugs in overdose; therefore it will also remove drugs that are being given for therapeutic reasons. Drugs that are likely to be removed are those with a low volume of distribution or high protein binding.[36,37] Consideration should be paid to the timing of drug administration and commencement of the plasma exchange. Other considerations should be the duration of the procedure, the number of procedures and the timing of them, as well as the total volume of plasma removed. Where the level of a particular drug can be measured, this may be required more often to ensure the maintenance of therapeutic levels.

Where patients are receiving continuous infusions affecting sedation or blood pressure, continuous monitoring must occur, and if there are any increases in dose during the apheresis procedure attention should be paid at the end of the procedure to ensure the patient does not receive an excessive dose. The use of the pharmacist in planning apheresis and medication should be considered.[38] If there is any concern that a drug may be removed during the procedure then it should be withheld until completion, or the effects monitored during the procedure and additional doses given as required.[39] Where possible, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers should be stopped 24 hours prior to plasma exchange.[40] This is because these drugs will decrease the patient's ability to activate bradykinin, which, in turn, can lead to flushing, hypotension and respiratory distress.[37]

CIRCULATORY EFFECTS

Any extracorporeal procedure is likely to lead to problems of circulatory instability. Intravascular volume changes, vasovagal reactions, medications and infusion fluids may alone, or in combination, be responsible for circulatory problems. Often the patient will be able to compensate, but if there are pre-existing issues (e.g. altered blood volume, vascular disease or renal failure) then close monitoring is essential. A strict fluid and electrolyte balance should be kept at all times, both during the plasma exchange and as a daily tally.

PLASMA ONCOTIC PRESSURE

Most patients compensate for minor fluctuations in colloid osmotic pressure (COP). Patients who have oedema or local factors predisposing to interstitial fluid accumulation (e.g. raised intracranial pressure, interstitial pulmonary oedema, deep venous thrombosis, and renal impairment) need close attention.

INFECTION

Many patients who are undergoing plasma exchange are already immunosuppressed, either due to their disease or secondary to drug therapy. In patients

requiring recurrent and frequent plasma exchange, attempts should be made to maintain serum immunoglobulin levels. When FFP is not used as replacement fluid, the bacteriocidal and opsonic activities of blood are probably impaired, and it is probably advantageous to infuse at least two units of FFP at the conclusion of the procedure. At the completion of a course of plasma exchange, consideration may need to be given to a dose of intravenous gammaglobulin.

HAEMOSTASIS

Plasma exchange, particularly where albumin is used as the replacement fluid, causes perturbations in the haemostatic system, which may result in either bleeding or thrombosis. The significance of these alterations will depend largely on the volume and frequency of exchange, pre-existing defects in the system, anticoagulation, other risk factors for thrombosis, replacement fluids and invasive procedures.[34]

THE PREGNANT PATIENT

The use of plasma exchange in pregnant patients has been described as safe by many sources. However, there are several considerations to take into account. First is the patient's blood volume, which will increase by 50% from the second trimester; therefore this must be recalculated, and 50% added as the patient's pregnancy progresses, thereby increasing the exchange volume. The patient's position during the procedure needs to be left lateral decubitus, which will move the gravid uterus to take the pressure off the abdominal blood vessels.[41]

Fibrinogen levels rise by 50% in pregnancy and need to be regularly assessed. Blood should be drawn at the commencement of the procedure, and 50% of the predicted lower standard value should be added to the values, and the patient's levels assessed within this range. Because of this change in fibrinogen, an increase in anticoagulant may be required to reduce the risk of clotting within the apheresis circuit. Where a patient has albumin as the replacement therapy, it may be necessary to use FFP towards the end of the procedure to help correct any deficiencies. Assessment of the patient's ionised calcium levels will assist in determining the amount of calcium replacement required. However, the use of a concurrent infusion of calcium gluconate will negate the risk of any citrate toxicity.[42]

Evaluation of the pregnancy by the obstetric team is essential to help maintain the health of mother and child.

REACTIONS TO REPLACEMENT FLUIDS

The rapid infusion of any blood component may be associated with allergic or vasomotor reactions. Plasma exchange is a rather unique situation as blood or blood products and plasma substitutes are being infused at resuscitation rates into normovolaemic, normotensive patients.

Hypotension can occur at any point in the procedure and although plasma exchange will maintain the patient as normovolaemic, there is always the risk of reaction to the exchange fluid or fluid shifts within the patient. Fluid shifts will normally respond to slowing down or halting the procedure and giving a bolus of fluids until there is recovery of the blood pressure.[43] It is helpful to ensure adequate hydration of the patient prior to commencing the procedure as this will also help reduce the risk. It should be noted that many patients have a small drop in their systolic blood pressure within minutes of commencing the procedure. Patients with neurological disorders may also benefit from running the procedure in a positive fluid balance to help counteract a lack of peripheral venous resistance.

Reactions to plasma can be seen as the development of pruritis or urticarial, and necessitate the administration of an antihistamine. If there is chest tightness, acute dyspnoea or hypoxia, and the patient is receiving plasma as the replacement fluid, then consideration should be given to TRALI (see Chapter 97) and appropriate treatment commenced.[10]

Where albumin is the replacement fluid on consecutive days, attention should be paid to coagulation parameters as there may be dilution of clotting factors. In patients with normal liver function, it would be expected that these would return to normal within a few days of ceasing plasma exchange; however, if the patient has had a recent haemorrhage or is pre- or post-surgery then the use of donor plasma may be justified.[7]

EFFECTS OF INTRAVASCULAR PROTEINS

If plasma protein fractions or albumin are being used for replacement fluids, not only will coagulation and complement components be depleted, but various transport and binding proteins in the circulation are significantly reduced. These may have significant effects on drug activity and elimination (e.g. antithrombin III levels may have effects on heparin activity). The effects of corticosteroids may be potentiated after plasma exchange owing to a reduction in binding proteins.

INTRAVENOUS IMMUNOGLOBULIN

IVIG products were originally developed in the 1950s for the treatment of immunodeficiency states. Since then, the immunomodulatory properties of IVIG have led to much broader usage in autoimmune and inflammatory disorders – usually in much higher doses.[44] In many cases the use of IVIG is based upon very limited evidence and much of its use is prescribed

for 'off-label' indications.[45] Consequent shortages of IVIG and concerns regarding its costs have led governments worldwide to attempt to restrict its use to only those conditions in which it has an established or emerging role.

IVIG is a sterile fractionated blood product consisting of concentrated immunoglobulin derived from pooled human plasma from thousands of healthy blood donors. IVIG typically contains more than 95% unmodified IgG (which has intact Fc-dependent effector functions) and trace amounts of IgA and IgM, cytokines, soluble CD4, CD8 and HLA molecules. Because IVIG is derived from large numbers of donors this provides a rich diversity of antibody repertoires and specificities.

A range of IVIG products are available. Although all contain IgG molecules, they may differ with regard to their pH, osmolality, excipient compounds (sucrose/sodium) and, consequently, in their adverse effects. In recent years IVIG preparations have been progressively improved – with the elimination of sugars and the normalisation of salt content and pH, which has significantly reduced the incidence of adverse reactions.[46] At present there is a lack of good comparative data to suggest that one IVIG preparation is superior to another.

IVIG has multiple immunomodulatory and anti-inflammatory activities including: modulation of complement activation with inhibition of generation of membrane attack complex (C5b-9) and subsequent complement-mediated tissue damage, suppression of idiotype antibodies, neutralisation of 'super-antigens', saturation of Fc receptors on macrophages and suppression of various inflammatory mediators including cytokines (TNF-α, IL-1α, IL-6), chemokines, adhesion molecules and metalloproteinases.[47] Importantly, many of these effects extend beyond the half-life of IVIG (IVIG lasts 6–22 days in circulation), suggesting that the immunomodulatory effects of IVIG are not simply due to enhanced passive clearance of autoantibodies or interference with pathogenic autoantibodies.

Box 99.3 Diseases in which intravenous immunoglobulin has an established benefit

- Acquired hypogammaglobulinaemia secondary to haematological malignancies
- Chronic inflammatory demyelinating polyneuropathy
- Guillain–Barré syndrome
- Idiopathic (autoimmune) thrombocytopenia purpura (ITP) in adults
- Inflammatory myopathies
- Kawasaki disease
- Lambert–Eaton myasthenic syndrome
- Multifocal motor neuropathy
- Myasthenia gravis
- Neonatal haemochromatosis
- Primary immunodeficiency diseases
- Stiff-man syndrome
- Graft-versus-host disease
- Acute disseminated encephalomyelitis
- Anti-neutrophil cytoplasmic antibody (ANCA)-positive systemic necrotising vasculitis
- Autoimmune haemolytic anaemia
- Pemphigoid and pemphigus
- Evans syndrome – autoimmune haemolytic anaemia with ITP
- Fetomaternal/neonatal alloimmune thrombocytopenia
- Haemophagocytic syndrome
- ITP in children
- IgM paraproteinaemic neuropathy
- Kidney transplantation
- Multiple sclerosis
- Opsoclonus myoclonus ataxia
- Post-transfusion purpura
- Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency)
- Specific antibody deficiency (including IgG subclasses)
- Toxic epidermal necrolysis/Stevens–Johnson syndrome
- Toxic shock syndrome

INDICATIONS FOR INTRAVENOUS IMMUNOGLOBULIN (Box 99.3)

IVIG has an established role in the treatment of primary immune deficiency and in acquired humoral immunodeficiency states due to haematological malignancies (particularly chronic lymphocytic leukaemia and multiple myeloma) and organ transplantation.[47] It also has an established role in many other conditions associated with autoimmune dysregulation as an immunomodulatory therapy including GBS, idiopathic thrombocytopenic purpura, myasthenia gravis, CIDP and Kawasaki disease. IVIG is often as efficacious as plasmapheresis and so is often recommended as first-line therapy with TPE used for patients who are unresponsive to IVIG and immunosuppressive therapy (generally corticosteroids).[48,49] IVIG is considered as second- or third-line therapy in a number of other conditions in which standard therapies have been ineffective, or are contraindicated and/or where the available evidence is inconclusive. Opinion remains divided as to whether IVIG has any role in sepsis. Despite a biological rationale for its use (based largely on preclinical work demonstrating enhanced bacterial clearance, inhibitory effects on mediators of inflammation and attenuated lymphocyte apoptosis) there is inconsistent evidence regarding its therapeutic efficacy.[50–52]

ADVERSE EFFECTS OF INTRAVENOUS IMMUNOGLOBULIN

Adverse effects occur in 3%–8% of patients. Most are mild and transient, including flushing, fever,

headache, chills, fatigue, nausea, diarrhoea, malaise, myalgia, dyspnoea, back pain, tachycardia and hypotension. Immediate adverse effects can be effectively treated by slowing or temporarily discontinuing the infusion and symptomatic therapy with analgesics, antihistamines and glucocorticoids in more severe reactions. IgA deficiency-related anaphylactic reactions are rare and largely preventable by the identification of patients with IgA deficiency and the use of IgA-depleted immune globulin.

Late adverse effects, including acute renal failure, venous thromboembolism, neutropenia, haemolytic anaemia, arthritis and aseptic meningitis, are also rare. Acute renal failure is generally transient; it usually occurs in dehydrated patients and after the use of sucrose-stabilised products owing to osmotic injury. Thromboembolic complications occur as a result of hyperviscosity, especially in patients who have received a rapid infusion of high-dose IVIG and in those with risk factors including: advanced age, immobilisation, previous venous thromboembolism, hypertension, diabetes mellitus and dyslipidaemia.[53] The blood group antibodies present in IVIG may act as haemolysins and coat red cells with immunoglobulins – resulting in a positive direct antiglobulin test (DAT) and, occasionally, haemolytic anaemia.

KEY REFERENCES

4. Negi VS, Elluru S, Siberil S, et al. Intravenous immunoglobulin: an update on the clinical use and mechanisms of action. *J Clin Immunol*. 2007;27(3):233–245.
7. Balogun RA, Ogunniyi A, Sanford K, et al. Therepeutic apheresis in special populations. *J Clin Apher*. 2010;25:265–274.
14. Szczepiorkowski ZM, Winters JL, Bandarenko N, et al. Guidelines on the use of therapeutic apheresis in clinical practice: evidence-based approach from the apheresis applications committee of the American Society for Apheresis. *J Clin Apher*. 2010;25:83–177.
35. Nguyen TC, Kiss JE, Goldman JR, et al. The role of plasmapheresis in critical illness. *Crit Care Clin*. 2012;28:453–468.
37. Winters JL, ed. *Therapeutic Apheresis: A Physician's Handbook*. 2nd ed. Bethesda, MD: AABB; 2008.
45. Foster R, Suri A, Filate W, et al. Use of intravenous immune globulin in the ICU: a retrospective review of prescribing practices and patient outcomes. *Transfus Med*. 2010;20(6):403–408.
46. Gelfand EW. Intravenous immune globulin in autoimmune and inflammatory diseases. *N Engl J Med*. 2012;367:2015–2025.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Isbister JP. Plasma exchange: a selective form of blood-letting. *Med J Aust*. 1979;2(4):167–173.
2. Scheinberg M, Hamerschlak N, Kutner JM, et al. Rituximab in refractory autoimmune diseases: Brazilian experience with 29 patients (2002–2004). *Clin Exp Rheumatol*. 2006;24(1):65–69.
3. Virgolini L, Marzocchi V. Rituximab in autoimmune diseases. *Biomed Pharmacother*. 2004;58(5):299–309.
4. Negi VS, Elluru S, Siberil S, et al. Intravenous immunoglobulin: an update on the clinical use and mechanisms of action. *J Clin Immunol*. 2007;27(3): 233–245.
5. Lehmann HC, Hartung H-P, Hetzel GR, et al. Plasma exchange in neuroimmunological disorders part 1. *Arch Neurol*. 2006;63(7):930–935.
6. Lambert C, Gericke M, Smith R, et al. Plasma extraction rate and collection efficiency during therapeutic plasma exchange with spectra optia in comparison with haemonetics MCS+. *J Clin Apher*. 2011;26(1):17–22.
7. Balogun RA, Ogunniyi A, Sanford K, et al. Therepeutic apheresis in special populations. *J Clin Apher*. 2010;25:265–274.
8. Duffy SM, Coyle TE. Platelet transfusions and bleeding complications associated with plasma exchange catheter placement in patients with presumed thrombotic thrombocytopenic purpura. *J Clin Apher*. 2013;28(5):356–358.
9. Chhibber V, King KE. Management of the therapeutic apheresis patient. In: McLeod BC, Szczepiorkowski ZM, Weinstein R, et al, eds. *Apheresis: Principles and Practice*. 3rd ed. Bethesda, MD: AABB Press; 2010:229–250.
10. Shemin D, Briggs D, Greenan M. Complications of therapeutic plasma exchange: a prospective study of 1,727 procedures. *J Clin Apher*. 2007;22:270–276.
11. Kankirawatana S, Huang ST, Marques MB. Continuous infusion of calcium gluconate in 5% albumin is safe and prevents most hypocalcemic reactions during therapeutic plasma exchange. *J Clin Apher*. 2007;22:265–269.
12. Farah M, Levin A, Kiaii M, et al. Combination hemodialysis and centrifugal therapeutic plasma exchange: 18 years of Canadian experience. *Hemodial Int*. 2013;17(2):256–265.
13. Zhao Y, Ibrahim H, Bailey JA, et al. Therapeutic plasma exchange performed in tandem with hemodialysis without supplemental calcium in the apheresis circuit. *J Clin Apher*. 2017;32(3): 154–157.
14. Szczepiorkowski ZM, Winters JL, Bandarenko N, et al. Guidelines on the use of therapeutic apheresis in clinical practice: evidence-based approach from the apheresis applications committee of the American Society for Apheresis. *J Clin Apher*. 2010; 25:83–177.
15. Mehta J, Singhal S. Hyperviscosity syndrome in plasma cell dyscrasias. *Semin Thromb Hemost*. 2003; 29(5):467–471.
16. Shah MK, Hugghins SY. Characteristics and outcomes of patients with Goodpasture's syndrome. *South Med J*. 2002;95(12):1411–1418.
17. Zhu KY, Feferman T, Maiti PK, et al. Intravenous immunoglobulin suppresses experimental myasthenia gravis: immunological mechanisms. *J Neuroimmunol*. 2006;176(1–2):187–197.
18. Gajdos P, Chevret S, Toyka K. Intravenous immunoglobulin for myasthenia gravis. *Cochrane Database Syst Rev*. 2006;(2):CD002277.
19. Green DM. Weakness in the ICU: Guillain–Barré syndrome, myasthenia gravis, and critical illness polyneuropathy/myopathy. *Neurologist*. 2005; 11(6):338–347.
20. Shariatmadar S, Noto TA. Plasma exchange in stiffman syndrome. *Ther Apher*. 2001;5(1):64–67.
21. Cantiniaux S, Azulay JP, Boucraut J, et al. Stiff man syndrome: clinical forms, treatment and clinical course. *Rev Neurol*. 2006;162(8–9):832–839.
22. Abshire T, Kenet G. Recombinant factor VIIa: review of efficacy, dosing regimens and safety in patients with congenital and acquired factor VIII or IX inhibitors. *J Thromb Haemost*. 2004;2(6):899–909.
23. Stegmayr BG, Almroth G, Berlin G, et al. Plasma exchange or immunoadsorption in patients with rapidly progressive crescentic glomerulonephritis. A Swedish multi-center study. *Int J Artif Organs*. 1999;22(2):81–87.
24. Rahman T, Harper L. Plasmapheresis in nephrology: an update. *Curr Opin Nephrol Hypertens*. 2006; 15(6):603–609.
25. Jayne DR, Gaskin G, Rasmussen N, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol*. 2007; 18(7):2180–2188.
26. Pagnoux C, Korach JM, Guillevin L. Indications for plasma exchange in systemic lupus erythematosus in 2005. *Lupus*. 2005;14(11):871–877.
27. Lehrich RW, Rocha PN, Reinsmoen N, et al. Intravenous immunoglobulin and plasmapheresis in acute humoral rejection: experience in renal allograft transplantation. *Hum Immunol*. 2005;66(4): 350–358.
28. Rocha PN, Butterly DW, Greenberg A, et al. Beneficial effect of plasmapheresis and intravenous immunoglobulin on renal allograft survival of patients with acute humoral rejection. *Transplantation*. 2003;75(9):1490–1495.
29. Brunskill SJ, Tusold A, Benjamin S, et al. A systematic review of randomized controlled trials for plasma exchange in the treatment of thrombotic thrombocytopenic purpura. *Transfus Med*. 2007; 17(1):17–35.
30. Ozkalemkas F, Ali R, Ozkocaman V, et al. Therapeutic plasma exchange plus corticosteroid for the treatment of the thrombotic thrombocytopenic purpura: a single institutional experience in the southern Marmara region of Turkey. *Transfus Apher Sci*. 2007;36(1):109–115.

31. Noris M, Remuzzi G. Atypical hemolytic–uremic syndrome. *N Engl J Med*. 2009;361(17):1676–1687.
32. Raphael JC, Chevret S, Hughes RA, et al. Plasma exchange for Guillain–Barré syndrome. *Cochrane Database Syst Rev*. 2002;(2):CD001798.
33. Tsai CP, Wang KC, Liu CY, et al. Pharmacoeconomics of therapy for Guillain–Barré syndrome: plasma exchange and intravenous immunoglobulin. *J Clin Neurosci*. 2007;14(7):625–629.
34. Jeffus S, Wehrli G. Blood banking and transfusion medicine for the apheresis medicine practitioner. *J Clin Apher*. 2012;27(3):160–167.
35. Nguyen TC, Kiss JE, Goldman JR, et al. The role of plasmapheresis in critical illness. *Crit Care Clin*. 2012; 28:453–468.
36. Kintzel PE, Eastlund T, Calls KA. Extracorporeal removal of antimicrobials during plasmapheresis. *J Clin Apher*. 2003;18(4):194–205.
37. Winters JL, ed. *Theraputic Apheresis: A Physician's Handbook*. 2nd ed. Bethesda, MD: AABB; 2008.
38. Ibrahim RB, Balogun RA. Medications in patients treated with therapeutic plasma exchange: prescription dosage, timing, and drug overdose. *Semin Dial*. 2012;25(2):176–189.
39. Ibrahim RB, Liu C, Cronin SM, et al. Drug removal by plasmapheresis: an evidence-based review. *Pharmacotherapy*. 2007;27(11):1529–1549.
40. Basic-Jukic N, Kes P, Glavas-Boras S, et al. Complications of therapeutic plasma exchange: experience with 4857 treatments. *Ther Apher Dial*. 2005; 9(5):391–395.
41. Cox JL, Koepsell SA, Shunkwiler SM. Therapeutic plasma exchange and pregnancy: a case report and guidelines for performing plasma exchange in a pregnant patient. *J Clin Apher*. 2017;32(3):154–157.
42. Mokrzycki MH, Balogun RA. Therapeutic apheresis: a review of complications and recommendations for prevention and management. *J Clin Apher*. 2011;26(5):243–248.
43. Khatri BO, Kramer J, Dukic M, et al. Maintenance plasma exchange therapy for steroid-refractory neuromyelitis optica. *J Clin Apher*. 2012;27(4): 183–192.
44. Hughes PD, Cohney SJ. Modifiers of complement activation for prevention of antibody-mediated injury to allografts. *Curr Opin Organ Transplant*. 2011;16(4):425–433.
45. Foster R, Suri A, Filate W, et al. Use of intravenous immune globulin in the ICU: a retrospective review of prescribing practices and patient outcomes. *Transfus Med*. 2010;20(6):403–408.
46. Gelfand EW. Intravenous immune globulin in autoimmune and inflammatory diseases. *N Engl J Med*. 2012;367:2015–2025.
47. Robinson P, Anderson D, Brouwers M, et al. Evidence-based guidelines on the use of intravenous immune globulin for haematologic and neurologic conditions. *Transfus Med Rev*. 2007;21 (2 suppl 1):S3–S8.
48. Patwa HS, Chaudry V, Katzberg H, et al. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2012;78(13):1009–1015.
49. McDaneld LM, Fields JD, Bourdette DN, et al. Immunomodulatory therapies in neurological critical care. *Neurocrit Care*. 2010;12(1):132–143.
50. Shankar-Hari M, Spencer J, Sewell WA, et al. Bench-to-bedside review: immunoglobulin therapy for sepsis – biological plausibility from a critical care perspective. *Crit Care*. 2012;16(2):206.
51. Alejandria MM, Langsang MAD, Dans LF, et al. Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock. *Cochrane Database Syst Rev*. 2002;(1):CD001090.
52. Jurisdictional Blood Committee. *Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia*. 2nd ed. Canberra: Commonwealth of Australia; 2012. Available Online: http://www.nba.gov.au/ivig/index.html.
53. Katz U, Achiron A, Sherer Y, et al. Safety of intravenous immunoglobulin (IVIG) therapy. *Autoimmun Rev*. 2007;6(4):257–259.

100

Haemostatic failure

Chee Wee Tan, Christopher M Ward

Haemostasis is the process whereby blood fluidity and vascular integrity are maintained in the event of vascular injury. Failure of haemostasis is common in critically ill patients and may be complex and multifactorial in pathogenesis. As haemostatic failure may complicate a wide range of medical, surgical and obstetric disorders, definitive diagnosis and specific therapy can significantly impact on outcome. Therapy may need to be initiated on clinical evidence with minimal laboratory information.

NORMAL HAEMOSTASIS

The haemostatic system is tightly controlled, and its role is to initiate clot formation where and when required and in adequate, but not excessive, amounts. There has been a paradigm shift in our understanding of the haemostatic system from one of circulating clotting factors to a more complex process occurring on the surface of activated or damaged cells (Fig. 100.1).[1,2]

The triad of vascular constriction, platelet plugging and fibrin clot formation provides the framework for haemostasis (see Fig. 100.1). Fibrinogen is the bulk protein of the coagulation system and fibrin is the end-product of a cascade of proteolytic activity, whereby precursor coagulation proteins are activated to become potent proteolytic enzymes, which, with the aid of cofactors, produce further activated proteins downstream. Thrombin converts fibrinogen to fibrin soluble monomers, which subsequently polymerise to form the fibrin clot, which is then stabilised by factor XIII. Thrombin generation in small amounts initially occurs in relationship to tissue-factor-bearing cells. This is then transferred to the activated platelet surface where amplification occurs, as highlighted by the cellular model of coagulation.[2]

Following injury, vascular constriction reduces bleeding, and allows time to initiate haemostasis. This is accentuated by vasoconstrictors released in association with platelet plug formation. With large-volume haemorrhage, the consequent systemic hypotension is an important physiological mechanism to minimise blood loss and facilitate stabilisation of the haemostatic plug. Controlled or 'tolerated' hypotension is now accepted as an important aspect of managing critical haemorrhage.[3,4] Vascular endothelial cells play an active role in haemostasis by synthesising substances that act at the membrane surface and/or interact with platelets and the coagulation system (e.g. prostacyclin, antithrombin, plasminogen activator, von Willebrand factor [VWF], thrombomodulin, heparin cofactor II and nitric oxide).[5]

The coagulation system is now thought to be triggered predominantly via the extrinsic pathway in vivo. Damaged tissues expose tissue factor (TF), a membrane-bound protein present in cells surrounding the vascular bed. Factor (F) VII and VIIa (a small amount circulates normally in the blood) then bind TF, activating FX. FXa interacts with the cofactor FVa to form prothrombinase complexes, which generates a small amount of thrombin on the cell surface. FIX is also activated by the TF/VIIa complex; it does not play a significant role in the initiation phase of coagulation, but diffuses across to platelets in the vicinity that have adhered in proximity to the site of the TF-bearing cells. FIXa binds to a specific platelet surface receptor and interacts with cofactor FVIIIa, leading to activation of FX directly on the platelet surface, resulting in the amplification and propagation of coagulation.

VWF is a multimeric glycoprotein (GP) that mediates platelet adhesion to the exposed subendothelium and links the primary vascular/platelet phase to coagulation by being the carrier protein for FVIII. FVIII dissociates from VWF to form a complex on the activated platelet surface with FIXa (tenase complex) to activate FX to FXa. Platelets interact with VWF via GP Ib–IX–V complexes. This results in platelet deceleration along the subendothelium, allowing platelet receptors to bind collagen. Adhesion to collagen and subsequent platelet activation is now thought to be critical in haemostasis and is facilitated by platelet GPVI and GPIa–IIa receptors.[6,7] Recent literature suggests that GPIb–IX–V and GPVI may work in concert to mediate platelet activation, culminating in stable platelet aggregation via the activation of GPIIb–IIIa.[8,9]

Platelet adhesion results in a platelet monolayer over the injured subendothelium, forming a procoagulant surface. Activation of the coagulation cascade results in local generation of thrombin, which binds to

ABSTRACT

Haemostatic failure is encountered increasingly and with greater complexity in the critical care setting with patients with multiple co-morbidities, drug therapies and risk factors that influence the fine balance between haemostasis, thrombosis and major bleeding. This chapter outlines the physiological basis of coagulation and the common factors leading to disordered haemostasis. Clinical and laboratory assessment of primary and secondary haemostasis are discussed, in particular the emergence of point-of-care thromboelastic testing, which provides a global assessment of coagulation and can be used in goal-directed approaches to optimise blood product use and improve clinical outcomes in major bleeding. Management of important congenital and acquired haemostatic disorders are reviewed, including disseminated intravascular coagulation, thrombotic microangiopathies, and bleeding as a result of antiplatelet and anticoagulant therapy, with particular reference to newer agents. Risks and benefits of treatment strategies are discussed.

KEYWORDS

Haemostasis
point-of-care testing
thromboelastography
DOACs
thrombotic microangiopathies
critical bleeding
thrombocytopenia
antiplatelet agents
trauma
reversal agents

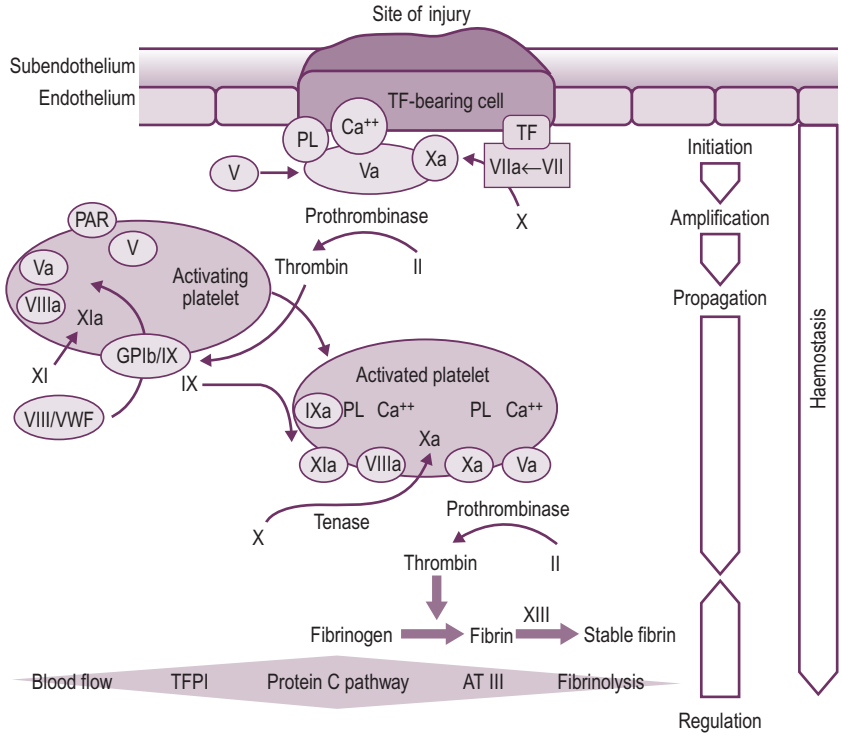


Figure 100.1 The cellular model of coagulation emphasises the interplay between the endothelium, platelets and coagulation factors in the formation of a stable fibrin clot. *AT*, Antithrombin; *PAR*, protease activated receptors; *PL*, phospholipids; *TF*, tissue factor; *TFPI*, tissue factor pathway inhibitor; *VWF*, Von Willebrand factor.

platelet protease-activated receptors (PARs), enhancing intracellular calcium mobilisation and platelet aggregation, resulting in production of a haemostatic plug and further facilitating coagulation. Further clot extension occurs due to platelet recruitment by platelet agonists, such as thrombin, adenosine 5-diphosphate (ADP) and thromboxane A_2, which are released directly from platelets. P-selectin is expressed during activation and plays a role in platelet-to-platelet and platelet-leucocyte interactions.

Parallel to and within the coagulation system are complex feedback mechanisms to guard against inappropriate and excessive activation.[10–12] Several inhibitory proteins, including antithrombin, thrombomodulin, protein C and S, TF pathway inhibitor, together with the fibrinolytic system, are important in this regard. Thrombin itself acts as either a procoagulant or anticoagulant depending on the context. Perturbations in this complex system can produce a wide range of clinical disorders from arterial or venous thrombosis to major bleeding.

SYSTEMIC HAEMOSTATIC ASSESSMENT

Clinical features may localise pathology to either coagulation factors or platelets (see Fig. 100.2). Clinical history is important, especially previous bleeding, family history, co-morbid medical conditions and medications.

Haemostatic system assessment can be broadly divided into laboratory tests of primary haemostasis, specifically platelet number and function, and tests of secondary haemostasis, which assess the integrity of the coagulation cascade (see Fig. 100.2). Point-of-care haemostatic testing is increasing, particularly in the peri-operative assessment of bleeding risk, in critical bleeding and massive blood transfusion, and in the assessment of bleeding risk attributable to anticoagulant and antiplatelet therapy.

TESTS OF PRIMARY HAEMOSTASIS

A full blood count may reveal thrombocytopenia. While a low platelet count ($<50 \times 10^9$/L) can contribute to haemostatic failure, a normal platelet count does not exclude platelet dysfunction as a cause of bleeding. Platelet function tests can be used both for the diagnosis of platelet disorders, and to monitor antiplatelet therapy at point of care.[13,14]

The platelet function analyser (PFA-100, and more recently Innovance PFA-200) has replaced the bleeding time as a commonly used screening test for primary haemostatic defects. In the PFA-100, citrated whole blood

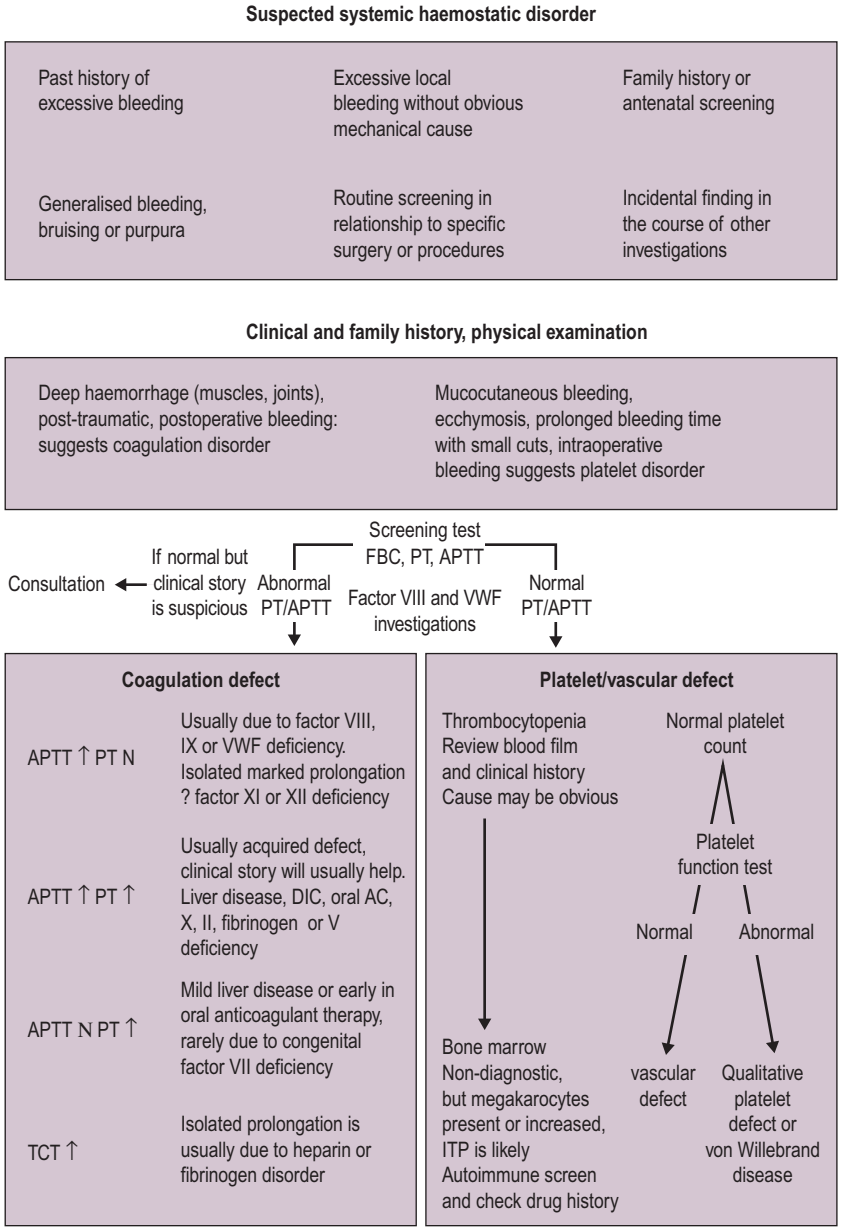


Figure 100.2 Key features of history, examination and laboratory testing involved in the work-up of a patient suspected of a systemic haemostatic disorder. *AC*, Anticoagulants; *APTT*, activated partial thromboplastin time; *DIC*, disseminated intravascular coagulation; *FBC*, full blood count; *ITP*, idiopathic thrombocytopenic purpura; *PT*, prothrombin time; *TCT*, thrombin clotting time; *VWF*, Von Willebrand factor.

is subjected to high shear through a membrane coated with platelet agonists, collagen/epinephrine (adrenaline) or collagen/ADP, resulting in platelet adhesion, aggregation and closure of a membrane aperture.[15] The time to occlude the aperture is the test end-point and is referred to as the closure time. The technique is simple and rapid to perform, but results may be influenced by the platelet count, haematocrit, and ABO blood group. A normal result has a high negative predictive value, and the test is also sensitive to major bleeding disorders such as von Willebrand disease (vWD), Glanzmann thrombasthenia (deficiency in GP IIb/IIIa) and aspirin use. The assay is less sensitive to milder bleeding defects such as platelet storage pool disease, variably prolonged by GP IIb/IIIa antagonists and not affected by clopidogrel.[16] Standard light transmission

aggregometry (LTA) is the gold standard method for diagnosing platelet function defects, but requires technical expertise and hence is less useful in the critical care setting. The recent development of whole blood multiple electrode platelet aggregometry (WBA), such as the Multiplate (Roche), to measure platelet function is promising, as it is a simple and rapid assay with reduced risk of artefactual platelet activation.[17] The use of WBA in assessing platelet response to aspirin and clopidogrel has been published, with results correlating well with LTA.[18,19]

The VerifyNow (Accumetrics) is a point-of-care test that measures platelet aggregation in whole blood, and has been used to gauge response to aspirin, clopidogrel and GP IIb/IIIa antagonists in the setting of percutaneous coronary intervention.[20] Flow cytometry has the advantages of low sample volume and whole blood testing, reflecting physiological conditions.[21,22] The phosphorylation of vasodilator-stimulated phosphoprotein (VASP) is a flow cytometry application used to assess response to clopidogrel.[23]

TESTS OF SECONDARY HAEMOSTASIS

A full blood count, prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen level, D-dimer and thrombin time (TT) provide a broad screen for most clinically significant haemostatic disorders (see Fig. 100.2).[24–26] Based on these results, further specific tests of haemostasis may be performed (e.g. mixing studies, factor assays, platelet function tests and tests of fibrinolytic function).

PROTHROMBIN TIME

The PT is a test of the extrinsic coagulation system. Prolongation may be caused by FVII deficiency, liver disease, vitamin K deficiency or oral anticoagulant therapy. The PT is also expressed as the international normalised ratio (INR), and is used to monitor warfarin use.

ACTIVATED PARTIAL THROMBOPLASTIN TIME

The APTT is a test of the intrinsic coagulation system, and there may be significant variation in test sensitivity and specificity between laboratories. In unselected patients there is poor correlation between the APTT prolongation and bleeding risk. A lupus anticoagulant may prolong the APTT and represent a prothrombotic state, rather than a bleeding tendency. In a patient with a suspected systemic haemostatic defect, an isolated prolongation of the APTT may represent:

- deficiency or inhibitor of FVIII, FIX or FXI
- deficiency in the contact phase of coagulation; that is, FXII and prekallikrein, which importantly does not result in clinically significant bleeding
- prolongation of both APTT and PT may be due to deficiencies of factors X, V, prothrombin or fibrinogen.

THROMBIN CLOTTING TIME

This is a test of the final conversion of fibrinogen to fibrin. Prolongation of thrombin clotting time (TCT) is due to hypofibrinogenaemia, dysfibrinogenaemia, heparin or the generation of fibrin degradation products.

D-DIMER

The D-dimer assay measures cleavage fragments resulting from the proteolytic action of plasmin on fibrin, so is specific for fibrinolysis and a marker of fibrin generation. Apart from venous thrombosis, raised D-dimer can be seen in the postoperative state, trauma, renal impairment, sepsis and importantly, in disseminated intravascular coagulation (DIC) with hyperfibrinolysis.

SPECIFIC COAGULATION FACTOR ASSAYS

Fibrinogen is commonly measured in patients suspected of systemic haemostatic failure, using clottable protein methods, end-point detection techniques or immunochemical tests. The Clauss method is the most common fibrinogen assay used.

Specific factor assays can be performed as secondary tests, after initial screening tests, such as APTT, reveal abnormalities. With an isolated prolonged APTT, a mixing test, in which plasma from normal donors is added to patient sample plasma, can be performed. It will correct APTT prolongation secondary to factor deficiencies, but not due to coagulation factor inhibitors. These include thrombin inhibitors, such as heparin and dabigatran, and acquired FVIII inhibitors. An APTT corrected by a mixing test is further investigated with specific assays for FVIII, FIX and FXI. An isolated PT is investigated in a similar fashion, with FVII deficiency/inhibitor a possible cause.

GLOBAL COAGULATION ASSAYS

The PT and APTT, although useful in detecting coagulation factor deficiencies, have drawbacks. Haemostasis does not just involve coagulation factors, but also cellular components including platelets and endothelial cells, so there is inevitably a limited assessment of coagulation profile via these tests. Global coagulation assays can assess the haemostatic system as a whole, extending coagulation monitoring beyond initial fibrin polymerisation.[27] Point-of-care testing with global coagulation assays offers significant advantages in the critical care setting, including significantly faster turnaround time compared to PT/APTT and assessment of fibrinolytic activity. Global coagulation testing includes whole blood thromboelastography (TEG) (i.e. TEG and ROTEM assays), and thrombin generation tests (TGT). TEG has become more widely used in view of its capacity for real-time coagulation assessment, more so than TGT.

TGTs measure the final step of the coagulation pathway. It informs on both the bleeding risk and

hypercoagulability of a patient, as thrombin has both prothrombotic and fibrinolytic roles. The calibrated automated thrombogram (CAT) assesses thrombin generation by using fluorogenic substrates. As thrombin generation continues beyond fibrin clot formation, it can provide further information on haemostatic capacity. Studies have demonstrated the value of TGT in predicting bleeding in cardiac surgery.[28] TGT parameters responded to fresh frozen plasma (FFP) and fibrinogen concentrate replacement in patients experiencing peri-operative dilutional coagulopathy.[29]

Studies also show that TGT can predict bleeding tendency in patients with mild haemophilia A and FXI deficiency, in whom FXI levels correlate poorly with extent of bleeding.[30,31] More recently, TGT has been used to assess the response to rivaroxaban in patients with anti-phospholipid syndrome.[32] While the use of TGTs are restricted to specialised centres, applications of TGTs are likely to increase in future, particularly with the development of whole blood TGTs.[33]

TEG enables ongoing evaluation of a clot as it forms. In both methods, a sample is placed in a cup, with a pin present in the centre of the cup as the device is operating. In TEG the cup is spinning, whereas in ROTEM it is the pin that rotates. Clot formation results in reduced pin movement, with the information translated into computer tracings, such as that depicted in Fig. 100.3.[34]

Fig. 100.3 illustrates the utility of TEG to provide information on all stages of haemostasis, including fibrinolysis. Measurement of clot strength is gauged by the use of platelet inhibitors, such as abciximab (TEG) or cytochalasin D (ROTEM), hence representing a surrogate marker of fibrinogen levels. TEG has been widely used in cardiac surgery and liver transplantation, and as part of massive transfusion protocols and in trauma settings. Goal-directed approaches towards best-practice use of blood products while optimising clinical outcomes have been recommended by consensus guidelines.[35,36] TEG can play an important role here, establishing initial coagulation status of critically ill patients, triggering early use of appropriate products (including tranexamic acid, fibrinogen, platelets and FXIII), with the resultant changes in haemostatic factors reflected by serial TEG, guiding further blood product administration to improve patient status.[37,38] TEG-platelet mapping assesses clot strength and enables quantification of the extent of inhibition of platelet function by aspirin and ADP antagonists, and has been used to assess bleeding risk prior to surgery.[39]

However, high-quality evidence of global coagulation assays impacting significantly on key clinical outcomes is lacking.[35,40] The greatest benefit has been seen in cardiac surgery.[41] In this area, while use of TEG has resulted in reduction in blood product usage, including red blood cells (RBCs), platelets and especially FFP, benefits, such as reduced mortality and surgical re-exploration rates, have not been consistently demonstrated. Assay standardisation remains an issue.

One of the major benefits of TEG is the capacity to assess fibrinolysis more rapidly, leading to early use of antifibrinolytic therapy. However, critical care physicians should be aware that in major studies, such as the CRASH-2 study, benefits of tranexamic acid extended to all trauma patients who are bleeding or at risk of bleeding.[42,43] Hence therapy should not be delayed while waiting for TEG results nor should it be limited only to patients with hyperfibrinolysis demonstrated on TEG.

While there are limitations with TEG, it provides a more comprehensive assessment of coagulation status when compared to PT/APTT, and its ability to detect and monitor changes in coagulation status at the bedside can lead to the rationalisation of blood product use and early use of therapies shown to improve clinical outcome, such as fibrinogen and tranexamic acid.

CONGENITAL HAEMOSTATIC DEFECTS

Congenital bleeding disorders are rare, but should be suspected in the clinical setting with discrepant or unexpected major bleeding or with abnormal laboratory results (i.e. an isolated prolonged APTT). It is important to identify the defect so that specific replacement therapy can be administered, with dosage guided by regular coagulation factor level monitoring. Congenital bleeding disorders include haemophilia A (FVIII deficiency), haemophilia B (FIX deficiency) and vWD. Haemophilia A and B are characterised by musculoskeletal and soft-tissue bleeding. Apart from specific factor concentrates, antifibrinolytics such as tranexamic acid are useful adjunctive therapy, with desmopressin also effective therapy in mild haemophilia A and certain types of vWD by stimulating endogenous release of FVIII and VWF.

Congenital platelet disorders are also rare, the commonest severe disorder being Glanzmann thrombasthenia, which is a deficiency or dysfunction of GP IIb/IIIa. A history of repeated mucocutaneous bleeding with an abnormal aggregometry result is suggestive of such disorders. Platelet transfusions may be required for acute severe bleeds or in the peri-operative period; recombinant factor VIIa (rFVIIa) is important in cases of platelet transfusion refractoriness. Desmopressin (DDAVP) and antifibrinolytic therapy may also have a role.

ACQUIRED HAEMOSTATIC DISORDERS

Acquired haemostatic disorders also can be broadly divided into platelet defects and coagulation factor abnormalities.

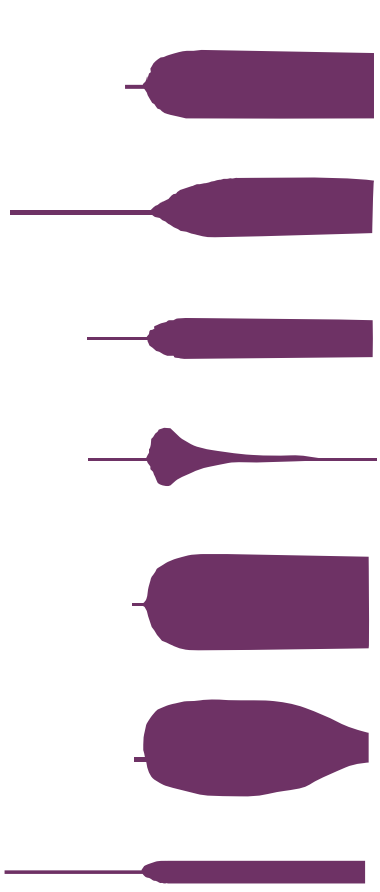


Figure 100.3 Comparative thromboelastograph tracings in normal and pathological states, with measured parameters assessing different aspects of haemostasis. These include: R time, which is the time elapsed until initial fibrin formation; K time gauges the dynamics of clot formation, α-angle assesses the kinetics of fibrin accumulation and cross-linkage, maximum amplitude *(MA)* assesses the effectiveness of platelet–fibrin interactions, while lysis time assesses fibrinolysis. *Modified from Srinivasa V, Gilbertson L, Bhavani-Chankar K. Thromboelastography: where is it and where is it heading?* Int Anesthesiol Clin. *2001;39:35–49.*

QUANTITATIVE PLATELET DEFECTS

DRUG-INDUCED THROMBOCYTOPENIA

The clinical presentation of drug-induced thrombocytopenia ranges from mild to life-threatening bleeding. Drugs with a predilection for inducing thrombocytopenia include quinine, antituberculous drugs, heparin, thiazide diuretics, penicillins, sulfonamides, rifampicin and anticonvulsants.

Heparin-induced thrombocytopenia (HIT) is an important and potentially life-threatening complication of heparin therapy.[44] An immune reaction to heparin typically occurs after 7–10 days of therapy, leading to platelet aggregation and thrombocytopenia. The thrombocytopenia seen in HIT usually does not fall below 20×10^9/L, and platelet count can be normal. HIT is not associated with bleeding, but rather represents a prothrombotic state, manifesting as arterial or venous thrombosis. Medical staff must be vigilant to the possibility of HIT occurring, and to keep heparin therapy as brief as possible. The incidence is less with the use of low-molecular-weight heparin (LMWH). A strong clinical suspicion of HIT (probability of HIT based on four criteria of the 4T score: timing and nadir of thrombocytopenia, the presence of thrombosis, and the possibility of other causes accounting for thrombocytopenia – see Table 100.1) should result in the cessation of heparin, and the commencement of an alternate anticoagulant, such as danaparoid, fondaparinux or argatroban, while awaiting laboratory results.[45]

HIT can be challenging to diagnose in the critical care setting, with many potential causes of thrombocytopenia in the same clinical scenario. Screening tests

Table 100.1 4T score to assess clinical probability of heparin-induced thrombocytopenia; a score of 0–3 represents low probability, 4–5 intermediate and 6–8 high clinical probability of heparin-induced thrombocytopenia

CATEGORY	2 POINTS	1 POINT	0 POINTS
Thrombocytopenia	>50% fall, or nadir ≥20 × 10^9/L	30–50% fall, or nadir 10–19 × 10^9/L	<30% fall, or nadir <10 × 10^9/L
Timing of the decrease in platelet count	Days 5–10, or ≤day 1 with recent heparin (past 30 days)	>Day 10 or timing unclear, or <day 1 if heparin exposure within past 30–100 days	<Day 4 (no recent heparin)
Thrombosis or other sequelae	Proven thrombosis, skin necrosis, or acute systemic reaction after heparin bolus	Progressive, recurrent, or silent thrombosis; erythematous skin lesions	None
Other causes of thrombocytopenia	Non-evident	Possible	Definite

Modified from Lo GK, Juhl D, Warkentin TE, et al. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost*. 2006;4(4):759–765.

for HIT antibodies are available, but these also detect non-pathogenic antibodies, which can commonly occur in the setting of cardiac surgery, resulting in false positive results. Functional HIT assays, such as the serotonin release assay or whole blood aggregometry, which show platelet activation in the presence of heparin and patient serum/plasma, can confirm the diagnosis but are performed only in reference laboratories.[17] A combination of clinical and laboratory criteria is required to assess for HIT.

THROMBOTIC MICROANGIOPATHIES

The thrombotic microangiopathies (TMAs) are disease entities characterised by microvascular endothelial cell injury and formation of platelet microthrombi. They are classically defined by thrombocytopenia, microangiopathic haemolytic anaemia (MAHA) and variable organ involvement. Recent advances in understanding of the pathophysiology of the TMAs have enabled classification into three primary disorders:

- Thrombotic thrombocytopenic purpura (TTP), which is triggered by deficiency of ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), a metalloproteinase that cleaves pro-thrombotic large VWF multimers.
- Shiga toxin-producing *Escherichia coli* haemolytic uraemic syndrome (STEC-HUS), more often seen in the paediatric setting and characterised by gastrointestinal involvement.
- Atypical haemolytic-uraemic syndrome (aHUS), which is driven by dysregulation and uncontrolled activation of the alternative complement pathway and often characterised by renal impairment.

The three entities can be indistinguishable on clinical grounds, and any organ can be impacted by TMAs.[46] However, the lung is almost never involved in TTP, and severe acute renal failure at presentation is unusual in TTP. In fact, a serum creatinine of >150–200 μmol/L and/or a platelet count >30 × 10^9/L makes TTP very unlikely.[47] Platelet counts can be normal or only mildly reduced in aHUS, and the greater the systemic organ involvement, the more likely the offending TMA is aHUS.

Laboratory testing is crucial in determining the precise TMA, with stool culture positivity for STEC definitive for STEC-HUS, and an ADAMTS-13 level of less than 5%–10% is associated with TTP. Hence, aHUS remains a diagnosis of exclusion in the acute setting. Analysis of complement and genetic markers for aHUS are now available and are important for prognosis, but are not required for diagnosis of aHUS acutely.[48]

It is important to determine the specific TMA, as these conditions have significant morbidity and mortality if untreated, and have different management strategies. Plasma exchange and corticosteroids are the mainstay of management for TTP, with rituximab for refractory cases, whereas eculizumab (a monoclonal antibody directed against the complement component C5) is first-line therapy for aHUS.[49,50]

Clinicians should be aware of secondary causes/triggers of TMA, including malignant hypertension, medications such as chemotherapeutic agents, clopidogrel, and calcineurin inhibitors, pregnancy, malignancy, organ transplantation and infections.

IDIOPATHIC THROMBOCYTOPENIC PURPURA

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder where autoantibodies (IgG) are directed against platelets, which are subsequently destroyed by the monocyte–macrophage system, predominantly in the spleen. ITP remains a diagnosis of exclusion. Corticosteroids are first-line therapy in acute episodes, particularly if the platelets are <10 × 10^9/L or with uncontrolled bleeding. High dose dexamethasone (40 mg/day for 4 days) is increasingly used

and has demonstrated efficacy in this setting.[51] Intravenous immunoglobulin is indicated in ITP with major bleeding and/or not responding to corticosteroids, and is particularly useful pre-operatively and in pregnancy. Platelet transfusions should be reserved for life-threatening bleeding and a platelet increment is more likely following a dose of intravenous immunoglobulin. Patients with refractory ITP are treated with thrombopoietin receptor agonists; that is, romiplostim and eltrombopag, splenectomy or rituximab.

THROMBOCYTOPENIA IN CRITICAL CARE SETTINGS

Platelets play an important role in the inflammatory response and a reactive thrombocytosis is usually seen in infection. However, if there is overwhelming sepsis, associated DIC or marrow suppressive influences, including medications, thrombocytopenia can also occur.

QUALITATIVE PLATELET DEFECTS

The most common cause of acquired platelet dysfunction seen in the critical care setting is the use of antiplatelet therapy, which is discussed later in the chapter. Other causes of platelet dysfunction include uraemia, hepatic cirrhosis, multiple myeloma and myeloproliferative disorders.

Platelet dysfunction can also occur in the setting of extracorporeal circulation, especially cardiopulmonary bypass. In this setting, bleeding risk is also impacted by other haemostatic disturbances, including thrombocytopenia and increased fibrinolysis, as well as time on bypass and multiple-valve replacements or re-operations. Key haemostatic measures include ensuring adequate reversal of anticoagulants such as heparin, platelet transfusions and the use of a goal-directed approach to blood product use facilitated by TEG. The use of prothrombin complex concentrate (PCCs) and fibrinogen guided by TEG results have reduced transfusion requirements and thromboembolic events, while improving outcomes, including mortality, in some studies.[52–54]

CRITICAL HAEMORRHAGE AND MASSIVE BLOOD TRANSFUSION

The nature and management of haemostatic defects secondary to acute and/or massive blood loss are explained in greater detail in Chapter 97. TEG is now widely used to facilitate a goal-directed approach in critical bleeding and massive blood transfusion as described earlier in this chapter. Fibrinogen replacement is a key component of resuscitation protocols, with low fibrinogen often occurring early in bleeding/trauma, contributing to the effects of dilutional coagulopathy, and associated with increased mortality.[55] More recent guidelines recommended that fibrinogen be replaced based on results of TEG or if plasma levels less than 1.5–2.0 g/L, with higher levels targeted in specific populations, such as cardiac surgery (3.9 g/L).[35,36] Cryoprecipitate, a source of fibrinogen, has been withdrawn in many countries of the European Union. Fibrinogen concentrates, on the other hand, are virally inactivated and carry a lower risk of transmitting infection, are not blood group specific, and can be stored at room temperature and given without delay owing to thawing. The use of fibrinogen concentrates in a wide variety of clinical settings with high bleeding risk, including aortic aneurysm graft surgery and coronary bypass graft surgery, has resulted in a significant reduction in blood product support (FFP, platelets, RBCs), correction of laboratory abnormalities in coagulation and significant reduction in peri-operative bleeding.[56–58]

FFP and platelet concentrates are often infused to correct significant coagulopathy in massive bleeding. However, the efficacy of FFP has not been established in such settings, including cardiac surgery.[57] FFP also carries the risk of infections, incompatibility reactions, transfusion-related acute lung injury (TRALI) and fluid overload.

Tranexamic acid is now recommended to be administered as early as possible (within 3 hours) in trauma patients with or at risk of major bleeding at a loading dose of 1 g intravenously over 10 minutes, followed by an intravenous infusion of 1 g over 8 hours.[42]

HAEMOSTATIC FAILURE ASSOCIATED WITH LIVER DISEASE

The liver is the production site of nearly all the coagulation factors involved, apart from FVIII and VWF. Bleeding is challenging to evaluate in patients with liver impairment, with prohaemostatic changes (including reduced levels of natural anticoagulants and plasminogen) and antihaemostatic changes (thrombocytopenia, platelet dysfunction, impaired synthesis of clotting factors, excessive fibrinolysis) likely to co-exist. Mild to moderate prolongation of PT does not correlate with bleeding risk. Guidelines have advised assessing FFP use prior to invasive procedures, based on individual patient characteristics.[59,60] FFP also carries the theoretical risk of increasing portal pressure and aggravating bleeding. PCCs are a viable alternative, particularly in patients with fluid overload. Haemostatic defects due to vitamin K deficiency in patients with predominantly cholestatic liver disease may be reversed with vitamin K therapy, without requiring FFP.

Hypofibrinogenaemia/dysfibrinogenaemia are common in patients with liver impairment. As discussed previously, cryoprecipitate or fibrinogen concentrates can be administered in patients with chronic liver disease and bleeding with fibrinogen levels less than 1.5 g/L, or in patients not responding to FFP, as dysfibrinogenaemia is likely to be present.

DISSEMINATED INTRAVASCULAR COAGULATION

DIC is a pathophysiological process characterised by excessive activation of the haemostatic process. Initially, adequate compensation results in defects being demonstrable only in the laboratory tests, but if the initiating disorder is severe the clinical syndrome of uncontrolled acute DIC can result in significant bleeding, which is usually associated with end-organ failure. Secondary fibrinolysis can occur, which may accentuate the bleeding.

PATHOPHYSIOLOGY

DIC is characterised by the initial consumption of clotting factors and platelets within the circulation, resulting in varying degrees of microvascular obstruction due to fibrin deposition (see Fig. 100.4). When significant platelet and coagulation factor consumption occurs, bleeding may become a major feature.

Mechanisms that may inappropriately activate the haemostatic system include:

- activation of the coagulation sequence by the release of tissue thromboplastins into the systemic circulation (e.g. following extensive tissue trauma, during surgery, malignancy and during acute intravascular haemolysis)
- vessel wall endothelial injury causing platelet activation followed by activation of the haemostatic system (e.g. Gram-negative sepsis from endotoxin release, viral infections, extensive burns, prolonged hypotension, hypoxia or acidosis, see Box 100.1).
- induction of platelet activation (e.g. septicaemia, antigen–antibody complexes).

CLINICAL FEATURES

The clinical presentation of DIC varies, with patients showing thrombotic, haemorrhagic, or mixed manifestations in various organ systems. The major clinical problem of acute DIC is bleeding, manifesting as generalised bruising, or bleeding at venepuncture sites and surgical wounds. DIC may occur in association with a wide range of clinical disorders (see Box 100.1).

Box 100.1 Conditions associated with disseminated intravascular coagulation

- Infection
- Bacterial sepsis
- Viral haemorrhagic fevers
- Protozoal (malaria)
- Trauma
- Extensive tissue injury
- Head injury
- Fat embolism
- Malignancy
- Carcinoma
- Leukaemia (especially promyelocytic)
- Immunological disorders
- Transplantation rejection
- Incompatible haemolytic blood transfusion reactions
- Severe allergic reaction
- Drug reactions
- Extracorporeal circulations
- Snake bite envenomation
- Vascular disorders
- Giant haemangioma
- Aortic aneurysm
- Pregnancy associated:
  - Septic abortion
  - Abruptio placentae
  - Eclampsia
  - Amniotic fluid embolism
  - Placenta praevia
- Burns
- Hyperthermia
- Liver disease and acute hepatic necrosis

LABORATORY FINDINGS

Significant DIC can be present despite normal standard coagulation tests. The key tests in diagnosis are those that provide evidence for excessive conversion of fibrinogen to fibrin and its subsequent lysis. Platelet–fibrin clots create a mesh in the microcirculation in which passing red cells may be damaged, resulting in red cell fragmentation and haemolysis. The blood film may demonstrate fragmentation of the red cells (MAHA), but this is more commonly seen in chronic DIC, especially in association with malignancy.

The diagnosis is usually based on a combination of the appropriate clinical picture and laboratory testing of the haemostatic system (Table 100.2). Thrombocytopenia, hypofibrinogenaemia, with prolongation of the APTT, PT and TCT in conjunction with an elevation of fibrin degradation products (D-dimer test), are indicative of DIC. More specialised tests, such as elevation of fibrinopeptide A and reduced levels of antithrombin, add further weight to the diagnosis. To assist in the accurate diagnosis of DIC, the International Society on Thrombosis and Haemostasis (ISTH) has developed a scoring algorithm based on laboratory results (Table 100.3).[61]

In chronic DIC the laboratory findings differ from acute DIC, with often normal or near normal haemostasis testing results. Chronic DIC is a compensated state in which there is increased turnover of each of the haemostatic components. D-dimer is elevated in this setting and red cell fragmentation is often seen on the peripheral blood film.

THERAPY

The most important measure in the management of DIC is treatment of the initiating cause in conjunction with general resuscitation. Transfusion of blood products has the theoretical risk of 'feeding the

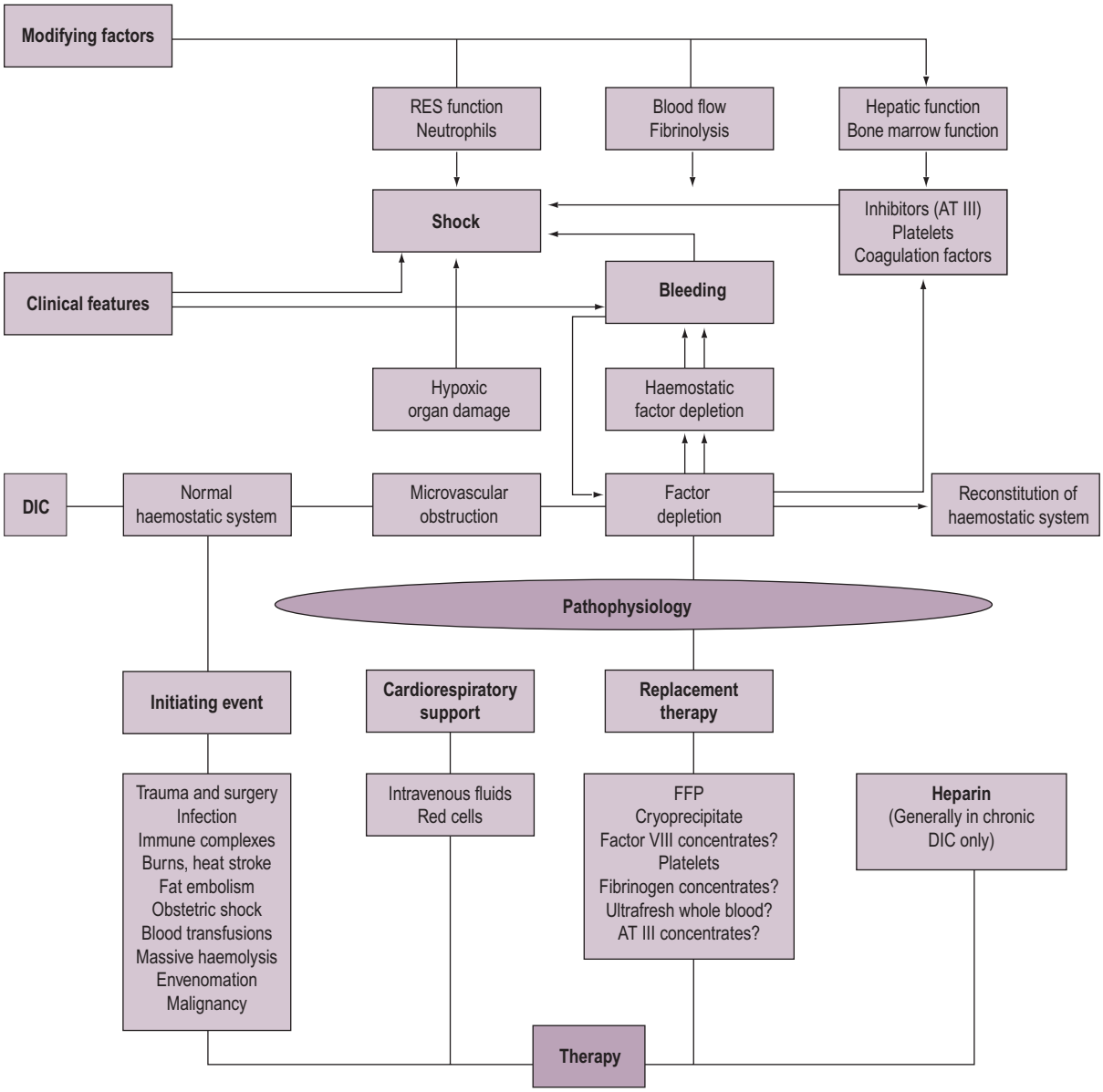


Figure 100.4 The pathophysiology and management of disseminated intravascular coagulation *(DIC)*. *AT*, Antithrombin; *FFP*, fresh frozen plasma; *RES*, reticulo-endothelial system.

fire', providing substrates for microthrombi formation. Hence, blood products should be given only in patients with bleeding/high bleeding risk or prior to major procedures. Local institutions routinely establish laboratory parameters to guide transfusion therapy, usually aiming to maintain fibrinogen levels >1–1.5 g/L and platelet counts >20–30 $\times$ 10^9/L, and PT below 1.5 times normal. Heparin should be used judiciously in the setting of DIC, and can be beneficial in settings where major thrombotic complications have occurred, rather than bleeding. Small doses of unfractionated heparin (UFH) should be used initially. There have also been reports in the literature regarding the use of antithrombin in the setting of DIC, with varying impact on patient mortality.[62]

ANTITHROMBOTIC THERAPY

The landscape of antithrombotic therapy has changed significantly in recent times with the wide availability of direct oral anticoagulants (DOACs), also known as non-vitamin K antagonists (VKA) (NOACs). Recent

Table 100.2 Laboratory test for the diagnosis of acute disseminated intravascular coagulation

ANALYSIS	EARLY	LATE
Platelet count	↓	↓↓
Activated partial thromboplastin time (APTT)	↑	↑↑
Prothrombin time (PT)	↑	↑
Thrombin clotting time (TCT)	↑	↑
Fibrin degradation products (D-dimer assay)	↑	↑↑
Fibrinogen	↓	↓↓
Other coagulation factors II, VII, VIII, X	↓	↓↓
Coagulation inhibitors: antithrombin III, protein C	↓	↓↓↓
Blood film	Usually normal in early stages	Fragmented red cells can be seen in subacute/chronic cases
Supplementary and research tests – prothrombin fragment 1 + 2, thrombin–antithrombin complex (TAT complex), procalcitonin (PCT), plasmin–antiplasmin complexes (PAP complex)	↑	↑

Table 100.3 The ISTH DIC scoring system; a score of ≥5 is indicative of overt DIC

	0 POINTS	1 POINT	2 POINTS
Platelet count ($\times 10^9$/L)	>100	<100	<50
Elevated fibrin-degradation products	No increase	Moderate increase	Strong increase
Prolonged PT (s)	<3	<6	>6
Fibrinogen (g/L)	>1.0	<1.0	

DIC, Disseminated intravascular coagulation; *ISTH*, International Society on Thrombosis and Haemostasis; *PT*, prothrombin time.
From Toh CH, Hoots WK. The scoring system of the Scientific and Standardisation Committee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Haemostasis: a 5-year overview. *J Thromb Haemost.* 2007;5(3):604–606.

consensus guidelines have suggested a preference for DOACs over VKA both in the setting of acute venous thromboembolism (VTE) and stroke prevention in the setting of atrial fibrillation (AF).[63,64] Clinicians must be aware of both the thrombotic and bleeding risks associated with continuing or withholding antithrombotic therapy, and achieve a balance between these risks in a growing number of patients with multiple co-morbidities and both prothrombotic and bleeding tendencies.

With all antithrombotic therapies, the cornerstones of management of major bleeding are investigations for a source of bleeding (i.e. endosocopy for gastrointestinal bleeding), cessation of antithrombotics, and local haemostatic and resuscitation measures. Prohaemostatic agents and reversal strategies also can be pursued depending on the antithrombotic therapy administered.

DIRECT ORAL ANTICOAGULANTS

Unlike VKAs, DOACs target specific coagulation factors, namely FXa (rivaroxaban, apixaban, edoxaban) or thrombin (dabigatran). All DOACs are renally excreted to varying extents. Efficacy and safety of DOACs in the management of VTE and stroke prevention in AF have been demonstrated in large randomised control trials, with similar findings reflected in subsequent real world studies, including the elderly and patients with renal impairment, subpopulations that are particularly at risk of bleeding due to DOACs.[65–68] DOACs offer significant advantages over VKAs, with fixed dosing, and fewer drug and dietary interactions, and they do not require routine laboratory monitoring (Table 100.4). All DOACs have shown a significant reduction in intracranial bleeding rates compared to VKA.

In patients with major bleeding or requiring emergency surgery, PT (for rivaroxaban), and APTT, TT (for dabigatran) can provide useful information on how much drug remains in the patient's circulation and hence contributes to bleeding. While not all laboratory reagents used to measure PT are sensitive to rivaroxaban, a normal PT utilising a rivaroxaban sensitive PT reagent, and a normal APTT, and in particular a normal TT (dabigatran), in this setting would suggest that DOACs are unlikely to be contributing significantly to major bleeding. Drug-specific assays, in the form of modified factor Xa assays for the factor Xa inhibitors, and dilute TT for dabigatran, are now available for DOACs to guide management. As PT and APTT are insensitive to apixaban concentrations,

Table 100.4 Pharmacological properties of new anticoagulants and antiplatelet medications

	DABIGATRAN	RIVAROXABAN	APIXABAN	EDOXABAN	PRASUGREL	TICAGRELOR
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa	Platelet $P2Y_{12}$ receptor	Platelet $P2Y_{12}$, different binding site to ADP
Prodrug	Yes	No	No	No	Yes	No
Elimination half-life	12–14 h	7–13 h	8–13 h	9-11 h	~7 h (active metabolite)	7 h (tigacrelor), 9 h (active metabolite)
Clearance	80%–85% renal	67% renal (33% active, remaining inactive)	~60% hepato-biliary, ~25% renal	50% renal clearance	~70% renal, ~30% hepato-biliary	~60% renal, ~30% hepato-biliary
Cytochrome pathway involvement	—	CYP3A4	CYP3A4	CYP3A4	CYP3A4, CYP2B6 (weak)	CYP3A4, CYP3A5 (less)
Direct antidote	Idrarucizumab	No	No	No	No	No

ADP, Adenosine 5-diphosphate.

an apixaban specific FXa assay is required to gauge drug levels.

Apart from major bleeding and peri-operative care, drug levels are also recommended in patients with renal impairment, in patients with recurrent thrombotic events and when non-compliance is suspected. Standard coagulation testing and drug levels are less critical in patients with normal renal function presenting with bleeding in whom the last dose of DOAC was at least 12 hours prior, as the majority of the DOAC would have been eliminated.

The key advantage of VKA therapy over DOACs was the availability of reversal strategies with vitamin K and PCCs. That is no longer the case, with idrarucizumab now available to reverse effects of dabigatran, and andexanet under development for FXa inhibitors.

Idrarucizumab is a humanised monoclonal antibody fragment with high affinity for dabigatran. It has no intrinsic procoagulant or anticoagulant activity, and is renally excreted. In a large study, idracuzimab given at two 2.5 g intravenous doses (total dose 5 g) no more than 15 minutes apart resulted in rapid and complete reversal of dabigatran activity as gauged by laboratory testing within minutes, an effect that was sustained for greater than 24 hours in nearly all patients.[69] Patients who received idrarucizumab had either life-threatening bleeding or required emergency surgery/high bleeding risk procedures. There were no major safety concerns of the drug, and a recent update of the study confirmed the safety and rapid efficacy of idrarucizumab. Idrarucizumab would now be first-line treatment in dabigatran-related critical bleeding episodes, with haemodialysis an option if the drug was not readily available. Idrarucizumab should not be used for bleeding episodes that can respond to local haemostatic measures or prior to non-emergent surgery.

Andexanet alfa is a recombinant modified human factor Xa protein, which, while catalytically inactive, binds to and sequesters FXa inhibitors, allowing endogenous factor Xa activity to be restored. It is able to reverse the activity of rivaroxaban, apixaban and enoxaparin, and is in the advanced stages of clinical trial development. Until this drug is available, for life-threatening bleeding or bleeding not responding to general haemostatic and resuscitation measures, pro-haemostatic agents such as PCCs, factor VIII inhibitor bypassing activity (FEIBA) or rFVIIa can be used. Tranexamic acid is a useful adjunctive therapy in this setting, particularly for mucosal bleeding.

The key pharmacological properties of the new anticoagulants and new antiplatelet agents are briefly described in Table 100.4.

VITAMIN K ANTAGONISTS

These agents, including warfarin, induce a functional deficiency of the vitamin-K-dependent clotting factors (II, VII, IX and X), hence causing prolongation of PT/INR. Warfarin reversal is indicated for patients with major bleeding/high risk of bleeding. Rapid reversal is achieved with infusion of PCCs (25–50 U/kg) with concurrent administration of intravenous vitamin K. Four-factor PCCs is now first-line treatment in this setting over FFP.[35,70] FFP may still have a role in countries where only three-factor PCC is available. As with bleeding in the setting of DOACs, cessation of anticoagulant and general haemostatic measures are sufficient in most instances.

Vitamin K does not act immediately, with effects seen usually within 6 hours. It accomplishes sustained

reversal, hence its use as a reversal agent needs to be carefully considered in patients at high risk of thrombotic events; that is, patients with mechanical mitral valves, AF $CHADS_2$ score of 5–6, and recent VTE or stroke (<3 months previously).[71] For most surgical interventions or invasive procedures an INR of 1.5 or less is acceptable. This can usually be achieved by temporarily ceasing warfarin. If oral vitamin K is to be given, the injectable form, which can be given both orally and intravenously, is recommended. Doses of up to 5 mg of vitamin K can reverse the INR prolongation without causing significant warfarin resistance when the drug is resumed.

HEPARINS

Heparins act by potentiating the action of antithrombin, a natural anticoagulant. UFH neutralises both thrombin and FXa, unlike the LMWHs, which predominantly neutralise FXa. The anticoagulant effect of UFH is usually measured by prolongation of the APTT. LMWHs do not prolong the APTT and are generally administered on weight basis and are not routinely monitored by a laboratory test. When monitoring is required, a drug-specific anti-Xa assay can be used.

Similar to over-anticoagulation with VKAs, cessation of heparins may be sufficient if bleeding occurs. If major bleeding has occurred, immediate reversal of UFH activity can be achieved with protamine sulphate. Protamine itself can paradoxically act as an anticoagulant in excess doses. Doses of protamine required to neutralise 80%–100% of estimated circulating UFH (e.g. 1 mg of protamine sulphate will neutralise 100 units of heparin given in the previous 2–3 hours) have been suggested.[70] Bleeding on LMWH is more difficult to manage than UFH, owing to the longer effective half-life; protamine also only partially reverses the LMWH effect (1 mg for each 1 mg enoxaparin in previous 8 hours).

ANTIPLATELET AGENTS

Antiplatelet agents are used widely for the treatment of arterial disease, and many of the non-steroidal anti-inflammatory agents (NSAIDs) are also platelet-inhibitory drugs. Aspirin has an irreversible effect on platelet function and platelet function tests may show abnormalities for up to 10 days after medication. Platelet function is usually restored within 24 hours upon cessation of NSAIDs.

$P2Y_{12}$ antagonists include clopidogrel, and newer agents such as prasugrel and ticagrelor. Prasugrel and ticagrelor have a more rapid onset of action than clopidogrel, with antiplatelet effects within 2–4 hours. These drugs inhibit the binding of ADP to its platelet receptor $P2Y_{12}$, thus suppressing ADP-mediated activation of the GP IIb/IIIa complex.

As with aspirin, platelets exposed to $P2Y_{12}$ antagonists are affected for their lifespan (5–10 days) and recovery of normal platelet function occurs as new platelets are produced. $P2Y_{12}$ antagonists are thought to be more potent than aspirin in antiplatelet effect and hence associated with higher bleeding risk.[72] Prasugrel achieves more predictable antagonism of ADP compared with clopidogrel, at the expense of increased bleeding. The bleeding risk is also high with ticagrelor.[73] The bleeding risk associated with antiplatelet agents has also increased with use of dual antiplatelet therapy of increasing duration, particularly with drug-eluting coronary stents and the risk of late in-stent thrombosis.

Clinicians are now regularly confronted with balancing the haemorrhagic risks associated with these agents against the thrombotic risks associated with their discontinuation, either during major bleeding episodes or prior to surgery. As there is no direct reversal agent, bleeding in the setting of antiplatelet therapy is managed mainly by the cessation of drug and general haemostatic measures. Desmopressin has been shown to correct aspirin-induced platelet dysfunction, although clinical outcome data are limited.[74]

Platelet transfusions are often used in acute life-threatening bleeding or prior to emergency surgery in the setting of antiplatelet therapy. However, timing and dosing remain unclear. Platelet transfusions appear to be more effective in reversing platelet dysfunction attributable to aspirin.[75] Ex-vivo studies have demonstrated that correction of clopidogrel-induced abnormal platelet aggregation responses required a higher proportion of donor platelets than aspirin. Platelet transfusions have been reported to be ineffective in reversing the effects of ticagrelor.[76] Platelet function testing with the methods described previously can guide further management. Continuing aspirin in the peri-operative period of most invasive procedures, neuroaxial anaesthesia and coronary artery bypass surgery is reasonable. If bleeding risk is deemed to be too high, clopidogrel and ticagrelor should be withheld for 5 days, and prasugrel for 7 days prior to major surgery.[71]

Normal platelet function is restored more rapidly upon cessation of GP IIb/IIIa inhibitors, more so with tirofiban and eptifibatide (4–8 hours) than abciximab (1–2 days).[70] Hence withdrawal of these drugs is usually sufficient for most bleeding episodes in the absence of thrombocytopenia. Platelet transfusions are recommended with abciximab-associated thrombocytopenia (platelet count $< 10 \times 10^9$/L).

The lack of clear efficacy of platelet transfusions in major bleeding with concurrent antiplatelet therapy was further highlighted by a landmark randomised open-labelled Phase III study (PATCH trial).[77] It showed that platelet transfusions, rather than benefiting patients, were associated with poorer outcomes in patients with stroke due to spontaneous, non-traumatic intracerebral haemorrhage. The trial concluded that platelet transfusions cannot be recommended in this setting.

ACQUIRED COAGULATION INHIBITORS

Major bleeding can be seen with rare inhibitors of coagulation factors. Autoantibodies against FVIII (commonest), IX, X, V and VWF have been reported. Bypassing agents, such as rFVIIa, activated PCCs, such as FEIBA and more recently recombinant porcine FVIII, have been shown to be efficacious in arresting bleeding in this setting, particularly high-titre inhibitors.[78] The other main aim of treatment is antibody eradication. Steroids and cyclophosphamide, as well as rituximab, have been used to achieve this aim. In acute emergencies, particularly in patients with high-titre inhibitors in whom bleeding has not responded to bypass agents, plasmapheresis with an immunoadsorption column can be used.

SUMMARY

While bleeding is complex and often multifactorial in critical care settings, there has been an appreciable advancement in diagnosis and management in the causes of haemostatic failure, both congenital and acquired. Trauma and massive transfusion management strategies are increasingly guided by TEG as part of a goal-directed approach. The increased understanding of pathogenesis of TMAs has resulted in more accurate classification of specific disease subtypes, and emergence of targeted therapies (i.e. eculizumab) for aHUS. Targeted therapies are also often available for congenital bleeding disorders, which are rare but can present for the first time after major surgery or trauma. There are now drug-specific assays for the DOACs, with effective reversal agents now available for dabigatran and emerging for factor Xa inhibitors. Less advances have been made in the management of bleeding in the setting of anti-platelet therapy, with a lack of clear benefits derived from platelet transfusions and no specific reversal agent.

KEY REFERENCES

1. Hoffman M, Monroe DM. Coagulation 2006: a modern view of hemostasis. *Hematol Oncol Clin North Am*. 2007;21(1):1–11.
13. Favaloro EJ, Lippi G, Franchini M. Contemporary platelet function testing. *Clin Chem Lab Med*. 2010; 48(5):579–599.
30. Dargaud Y, Lienhart A, Negrier C. Prospective assessment of thrombin generation test for dose monitoring of bypassing therapy in hemophilia patients with inhibitors undergoing elective surgery. *Blood*. 2010;116(25):5734–5747.
60. Kaatz S, Kouides PA, Garcia DA, et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. *Am J Hematol*. 2012;87(suppl 1): S141–S145.
62. Hook KM, Abrams CS. The loss of homeostasis in hemostasis: new approaches in treating and understanding acute disseminated intravascular coagulation in critically ill patients. *Clin Transl Sci*. 2012;5(1):85–92.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Hoffman M, Monroe DM. Coagulation 2006: a modern view of hemostasis. *Hematol Oncol Clin North Am*. 2007;21(1):1–11.
2. Roberts HR, Hoffman M, Monroe DM. A cell-based model of thrombin generation. *Semin Thromb Hemost*. 2006;32(suppl 1):32–38.
3. Duggan JM. Review article: transfusion in gastrointestinal haemorrhage – if, when and how much? *Aliment Pharmacol Ther*. 2001;15(8):1109–1113.
4. Bickell WH, Wall MJ Jr, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med*. 1994;331(17):1105–1109.
5. Verhamme P, Hoylaerts MF. The pivotal role of the endothelium in haemostasis and thrombosis. *Acta Clin Belg*. 2006;61(5):213–219.
6. Nieswandt B, Pleines I, Bender M. Platelet adhesion and activation mechanisms in arterial thrombosis and ischaemic stroke. *J Thromb Haemost*. 2011;9(suppl 1):92–104.
7. Nuyttens BP, Thijs T, Deckmyn H, et al. Platelet adhesion to collagen. *Thromb Res*. 2011;127(suppl 2): S26–S29.
8. Arthur JF, Gardiner EE, Matzaris M, et al. Glycoprotein VI is associated with GPIb-IX-V on the membrane of resting and activated platelets. *Thromb Haemost*. 2005;93(4):716–723.
9. Gardiner EE, Arthur JF, Shen Y, et al. GPIbα-selective activation of platelets induces platelet signaling events comparable to GPVI activation events. *Platelets*. 2010;21(4):244–252.
10. Tanaka KA, Levy JH. Regulation of thrombin activity-pharmacologic and structural aspects. *Hematol Oncol Clin North Am*. 2007;21(1):33–50.
11. Dahlback B. Blood coagulation and its regulation by anticoagulant pathways: genetic pathogenesis of bleeding and thrombotic diseases. *J Intern Med*. 2005;257(3):209–223.
12. Macias WL, Yan SB, Williams MD, et al. New insights into the protein C pathway: potential implications for the biological activities of drotrecogin alfa (activated). *Crit Care*. 2005;9(suppl 4):S38–S45.
13. Favaloro EJ, Lippi G, Franchini M. Contemporary platelet function testing. *Clin Chem Lab Med*. 2010; 48(5):579–599.
14. Harrison P, Lordkipanidze M. Testing platelet function. *Hematol Oncol Clin North Am*. 2013;27(3): 411–441.
15. Karger R, Donner-Banzhoff N, Müller HH, et al. Diagnostic performance of the platelet function analyzer (PFA-100(R)) for the detection of disorders of primary haemostasis in patients with a bleeding history – a systematic review and meta-analysis. *Platelets*. 2007;18(4):249–260.
16. Michelson AD. Platelet function testing in cardiovascular diseases. *Hematology*. 2005;10(suppl 1): 132–137.
17. Morel-Kopp MC, Tan CW, Brighton TA, et al. Validation of whole blood impedance aggregometry as a new diagnostic tool for HIT. Results of a large Australian study. *Thromb Haemost*. 2012;107(3): 575–583.
18. Ranucci M, Baryshnikova E, Soro G, et al. Multiple electrode whole-blood aggregometry and bleeding in cardiac surgery patients receiving thienopyridines. *Ann Thorac Surg*. 2011;91(1):123–129.
19. Siller-Matula JM, Francesconi M, Dechant C, et al. Personalized antiplatelet treatment after percutaneous coronary intervention: the MADONNA study. *Int J Cardiol*. 2012;167(5):2018–2023.
20. Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA*. 2011;305(11):1097–1105.
21. Cohn RJ, Sherman GG, Glencross DK. Flow cytometric analysis of platelet surface glycoproteins in the diagnosis of Bernard–Soulier syndrome. *Pediatr Hematol Oncol*. 1997;14(1):43–50.
22. Michelson AD. Methods for the measurement of platelet function. *Am J Cardiol*. 2009;103(3 suppl): 20A–26A.
23. Aleil B, Ravanat C, Cazenave JP, et al. Flow cytometric analysis of intraplatelet VASP phosphorylation for the detection of clopidogrel resistance in patients with ischemic cardiovascular diseases. *J Thromb Haemost*. 2005;3(1):85–92.
24. Adams M, Ward C, Thom J, et al. Emerging technologies in hemostasis diagnostics: a report from the Australasian Society of Thrombosis and Haemostasis Emerging Technologies Group. *Semin Thromb Hemost*. 2007;33(3):226–234.
25. Rochon AG, Shore-Lesserson L. Coagulation monitoring. *Anesthesiol Clin*. 2006;24(4):839–856.
26. Soliman DE, Broadman LM. Coagulation defects. *Anesthesiol Clin*. 2006;24(3):549–578, vii.
27. Dargaud Y, Sorensen B, Shima M, et al. Global haemostasis and point of care testing. *Haemophilia*. 2012;18(suppl 4):81–88.
28. Bosch Y, Al Dieri R, ten Cate H, et al. Preoperative thrombin generation is predictive for the risk of blood loss after cardiac surgery: a research article. *J Cardiothorac Surg*. 2013;8:154.
29. Lance MD, Ninivaggi M, Schols S, et al. Perioperative dilutional coagulopathy treated with fresh frozen plasma and fibrinogen concentrate: a prospective randomized intervention trial. *Vox Sang*. 2012;103:25–34.
30. Santagostino E, Mancuso ME, Tripodi A, et al. Severe hemophilia with mild bleeding phenotype: molecular characterization and global coagulation profile. *J Thromb Haemost*. 2010;8(4):737–743.
31. Trossaert M, Regnault V, Sigaud M, et al. Mild hemophilia A with factor VIII assay discrepancy: using thrombin generation assay to assess the bleeding phenotype. *J Thromb Haemost*. 2008;6(3): 486–493.
32. Cohen H, Hunt BJ, Efthymiou M, et al. Rivaroxaban vs warfarin to treat patients with thrombotic anti-phospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomized,

controlled, open-label, phase 2/3, non-inferiority trial. *Lancet Haematol*. 2016;3(9):426–436.
33. Lance MD. A general review of major global coagulation assays: thromboelastography, thrombin generation test and clot waveform analysis. *Thromb J*. 2015;13:1.
34. Srinivasa V, Gilbertson L, Bhavani-Chankar K. Thromboelastography: where is it and where is it heading? *Int Anesthesiol Clin*. 2001;39:35–49.
35. Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: 4th edition. *Crit Care*. 2016;20:100.
36. Kozek-Langenecker SA, Afshari A, Albaladejo P, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol*. 2013;30: 270–382.
37. Schochl H, Nienaber U, Hofer G, et al. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. *Crit Care*. 2010;14:R55.
38. Rea CJ, Foley JH, Ingerslev J, et al. Factor XIII combined with recombinant factor VIIa: a new means of treating severe hemophilia A. *J Thromb Haemost*. 2011;9(3):510–516.
39. Kasivisvanthan R, Abbassi-Ghadi N, Kumar S, et al. Risk of bleeding and adverse outcomes predicted by thromboelastography platelet mapping in patients taking clopidogrel within 7 days of non-cardiac surgery. *Br J Surg*. 2014;101(11):1383–1390.
40. Hunt H, Stanworth S, Curry N, et al. Thromboelastography (TEG) and rotational thromboelastography (ROTEM) for trauma-induced coagulopathy in adult trauma patients with bleeding (review). *Cochrane Database Syst Rev*. 2015;(2):CD010438.
41. Levi M, Hunt BJ. A critical appraisal of point-of-care coagulation testing in critically ill patients. *J Thromb Haemost*. 2015;13(11):1960–1967.
42. CRASH-2 trial collaborators, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomized, placebo-controlled trial. *Lancet*. 2010;376:23–32.
43. Roberts I. Tranexamic acid in trauma: how should we use it? *J Thromb Haemost*. 2015;13(S1):S195–S199.
44. Selleng K, Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia in intensive care patients. *Crit Care Med*. 2007;35(4):1165–1176.
45. Lo GK, Juhl D, Warkentin TE, et al. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost*. 2006;4(4):759–765.
46. Laurence J. Atypical hemolytic uraemic syndrome: making the diagnosis. *Clin Adv Hematol Oncol*. 2012; 10(10 suppl 17):1–12.
47. Coppo P, Schwarzinger M, Buffet M, et al. Predictive features of severe acquired ADAMTS13 deficiency in idiopathic thrombotic microangiopathies: the French TMA reference centre experience. *PLoS ONE*. 2010;5(4):e10208.
48. Campistol JM, Arias M, Ariceta G, et al. An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document. *Nefrologia*. 2015;35:421–447.
49. Sayani FA, Abrams CS. How I treat refractory thrombotic thrombocytopenic purpura. *Blood*. 2015;125(25):3860–3867.
50. Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med*. 2013; 368:2169–2181.
51. Wei Y, Ji XB, Wang YW, et al. High dose dexamethasone vs prednisone for treatment of adult immune thrombocytopenic purpura: a prospective multi-centre randomized trial. *Blood*. 2016;127(3): 296–302.
52. Gorlinger K, Dirkmann D, Hanke AA, et al. First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-centre cohort study. *Anesthesiology*. 2011;115:1174–1189.
53. Bolliger D, Tanaka KA. Roles of thromboelastography and thromboelastometry for patient blood management in cardiac surgery. *Transfus Med Rev*. 2013;27:213–220.
54. National Institute for Health and Care Excellence (NICE). *Detecting, Managing and Monitoring Haemostasis: Viscoelastometric Point-of-Care Testing (ROTEM, TEG and Sonoclot Systems)*. Diagnostic Guidance 13:1–58. NICE: Manchester, UK; 2014. Available at https://www.nice.org.uk/guidance/dg13.
55. Hippala ST, Myllyla GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. *Anesth Analg*. 1995;81(2):360–365.
56. Rahe-Meyer N. Fibrinogen concentrate in the treatment of severe bleeding after aortic aneurysm graft surgery. *Thromb Res*. 2011;128(suppl 1):S17–S19.
57. Morrison GA, Chalmers RT, Solomon C, et al. Fibrinogen concentrate therapy guided by thromboelastometry as an alternative to fresh frozen plasma in major vascular surgery. *J Cardiothorac Vasc Anesth*. 2012;26(4):654–659.
58. Karlsson M, Ternström L, Hyllner M, et al. Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. *Thromb Haemost*. 2009;102(1):137–144.
59. Rockey DC, Caldwell SH, Goodman ZD, et al. Liver biopsy. *Hepatology*. 2009;49(3):1017–1044.
60. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med*. 2011;365(2): 147–156.

61. Toh CH, Hoots WK. The scoring system of the Scientific and Standardisation Committee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Haemostasis: a 5-year overview. *J Thromb Haemost*. 2007;5(3):604–606.
62. Hook KM, Abrams CS. The loss of homeostasis in hemostasis: new approaches in treating and understanding acute disseminated intravascular coagulation in critically ill patients. *Clin Transl Sci*. 2012;5(1):85–92.
63. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149(2):315–352.
64. Kirchnhof P, Benusi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37(38):2893–2962.
65. Van Es N, Coppens M, Schulman S, et al. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from Phase 3 trials. *Blood*. 2014;124: 1968–1975.
66. Eikelboom JW, Weitz JI. "Real world" use of non-vitamin K antagonist oral anticoagulants (NOACs): lessons from the Dresden NOAC registry. *Thromb Haemost*. 2015;113(6):1159–1161.
67. Sardar P, Chatterjee S, Chaudhari S, et al. New oral anticoagulants in elderly adults: evidence from a meta-analysis of randomised trials. *J Am Geriatr Soc*. 2014;62:857–864.
68. Yao X, Abraham NS, Sangaralingham MP, et al. Efficacy and safety of dabigatran, rivaroxaban and apixaban versus warfarin in non-valvular atrial fibrillation. *J Am Heart Assoc*. 2016;5:e00372.
69. Pollack CV, Reilly PA, Eikelboom J, et al. Idrarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373(6):511–520.
70. Makris M, van Veen J, Tait C, et al. Guideline on the management of bleeding in patients on antithrombotic agents. *Br J Haematol*. 2012;160:335–346.
71. Keeling D, Tait RC, Watson H. Peri-operative management of anticoagulation and antiplatelet therapy. *Br J Haematol*. 2016;175:602–613.
72. Sarode R. How do I transfuse platelets to reverse anti-platelet drug effect? *Transfusion*. 2012;52(4):695–701, quiz 694.
73. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045–1057.
74. Reiter RA, Mayr F, Blazicek H, et al. Desmopressin antagonizes the in vitro platelet dysfunction induced by GPIIb/IIIa inhibitors and aspirin. *Blood*. 2003;102(13):4594–4599.
75. Li C, Hirsh J, Xie C, et al. Reversal of the antiplatelet effects of aspirin and clopidogrel. *J Thromb Haemost*. 2012;10:521–528.
76. Godier A, Taylor G, Gaussem P. Inefficiency of platelet transfusion to reverse ticagrelor. *N Engl J Med*. 2015;372(2):196–197.
77. Baharoglu MI, Cordonnier C, Al-Shahi Salman R, et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. *Lancet*. 2016;387(10038):2605–2613.
78. Tarantino MD, Cuker A, Hardesty B, et al. Recombinant porcine sequence factor VIII (rpFVIII) for acquired haemophilia A: practical clinical experience of its use in seven patients. *Haemophilia*. 2017;23(1):25–32.

101

Haematological malignancy

Pascale Gruber, Timothy Wigmore

INTRODUCTION

Haematological malignancies are tumours that involve the bone marrow, blood and lymphoid tissue. They account for 9% of all cancers.[1] Patients with haematological malignancies account for 1.5% of intensive care unit (ICU) admissions.[2]

CLASSIFICATION OF HAEMATOLOGICAL MALIGNANCIES

Traditional descriptive epidemiology divides haematological malignancies into four broad categories: leukaemias, Hodgkin lymphomas, non-Hodgkin lymphomas (NHL) and myelomas, with national and international organisations publishing data in this format.[3–5] The World Health Organization (WHO) subdivides haematological malignancies according to morphology, immunophenotype, and genetic and clinical features.[6–8]

LEUKAEMIA

Over 350,000 people are diagnosed with leukaemia each year worldwide.[3] Presenting features include fatigue, lymphadenopathy, hepatosplenomegaly and general symptoms of bone marrow failure, such as anaemia, bleeding and decreased resistance to infection. The diagnosis of leukaemia is based on peripheral blood and bone marrow demonstrating blast cells, immunophenotyping, cytogenetic and molecular genetic analysis. The severity of disease, the rate of progression and the treatment vary between leukaemias, so precise identification of the specific form of leukaemia is crucial to optimum management.

ACUTE MYELOID LEUKAEMIA

Acute myeloid leukaemia (AML) is characterised by uncontrolled proliferation of immature myeloid precursor cells. The WHO classifies AML into subtypes:

- *AML with characteristic genetic abnormalities:* patients with this subtype have characteristic genetic abnormalities, high rates of remission and generally a good overall prognosis. This category includes patients with translocations t(8:21), inv (16), t(16:16) and acute promyelocytic leukaemias t(15:17). Acute promyelocytic leukaemias (APML), respond well to *all*-trans-retinoic acid (ATRA).[9] In APML the promyelocytes have a classic morphology with dense cytoplasmic granules and Auer rods. The promyelocytes release thromboplastins which results in disseminated intravascular coagulation (DIC).[10]
- *AML with multi-lineage dysplasia:* patients' are often elderly with myelodysplastic syndromes (MDS) and myeloproliferative disease that progress on to developing AML. These patients tend to have a poor overall prognosis.
- *Acute leukaemias of ambiguous lineage:* this is a category of acute leukaemias where both myeloid and lymphoid cells are present or where the blast population does not allow classification in myeloid or lymphoid categories.
- *Therapy-related AML and MDS:* this is a category of patients who have received chemotherapy and/or radiotherapy who then go on to develop AML or MDS.
- *AML not categorised:* includes subtypes of AML that do not fall into the above categories.

ACUTE LYMPHOBLASTIC LEUKAEMIA

Acute lymphoblastic leukaemia (ALL) is a malignant disorder of lymphoid precursor cells, commonly seen in childhood, with a good overall prognosis. ALL induction chemotherapy typically consists of a four- or five-drug regime of prednisolone, vincristine, anthracycline, *L*-asparginase and/or cyclophosphamide.[11,12] Patients with ALL frequently have central nervous system (CNS) involvement, therefore intrathecal chemotherapy or cranio-spinal irradiation is additionally required. Remission is consolidated with further chemotherapy or haematopoietic stem cell transplant (HCT).[10] Prolonged maintenance therapy is often required to eradicate any residual leukaemic cells. A combination of daily methotrexate and 6-mercaptopurine constitutes the basis of most maintenance regimes. Five-year survival is 85%–90% for children and is less in adults.[13]

ABSTRACT

Outcomes for patients with haematological malignancies admitted to the critical care unit have improved over the last decade. This is attributable to improvements in cancer therapy with the use of less cytotoxic chemotherapy; reduced intensity conditioning regimes in patients who are elderly, have co-morbidities or are undergoing repeated transplant; more targeted therapies with the advent of precision medicine; and novel immunotherapies. In addition, advances in intensive care unit (ICU) care, the use of antimicrobial prophylaxis, improved patient selection, closer collaborative working between haematologists and intensivists, and a better understanding of the pharmacokinetics of chemotherapeutic agents in the presence of organ failure have all contributed to improvements in ICU and hospital outcome. However, a number of therapies still require evaluation, such as the impact of newer non-invasive diagnostic and therapeutic techniques, high-flow oxygen therapy, transfusion thresholds, chimeric antigen receptor T-cell therapy and further data on long-term outcomes.

KEYWORDS

Leukaemia
lymphoma
haematopoietic stem cell transplant

CHRONIC LYMPHOCYTIC LEUKAEMIA

Chronic lymphocytic leukaemia (CLL) may be classified as a form of leukaemia or low-grade lymphoma. It is most commonly found in elderly people. Clinical presentation includes fatigue, bone marrow failure, night sweats, lymphadenopathy, painful splenomegaly and autoimmune haemolytic anaemia. The natural history of CLL is variable with a median survival of 8–12 years.[10] Richter's transformation to diffuse large B cell lymphoma (DLBCL) is associated with a poor prognosis (median survival <1 year).[14] First-line treatment is fludarabine, cyclophosphamide and/or rituximab (monoclonal anti-CD20 agent).[15] Alemtuzumab (monoclonal anti-CD52 agent) is useful in refractory CLL.[16]

CHRONIC MYELOID LEUKAEMIA

Chronic myeloid leukaemia (CML) is linked to a translocation of on chromosome 22 and 9 (Philadelphia chromosome) leading to formation of BCR-ABL (a tyrosine protein kinase) causing uncontrolled proliferation in mature and immature white cells.[17] CML typically begins in the *chronic phase*, over several years progresses to an *accelerated phase* and eventually results in *blast crisis*. Patients present with weight loss, splenomegaly, fevers and night sweats. Imatinib (tyrosine kinase inhibitor), results in complete remission in approximately 80% of patients avoiding the need for HCT that was previously the only curative option for CML.[18]

LYMPHOMA

Lymphomas are tumours of B, T or NK lymphoid cells. Worldwide, over 420,000 people are diagnosed with lymphoma each year.[3] Traditionally, lymphomas are divided into Hodgkin lymphomas and NHL. Lymphomas are staged 1–4 according to lymph node spread and are designated A or B depending on the absence or presence of 'B' symptoms – night sweats, fever and weight loss.

HODGKIN LYMPHOMA

Hodgkin lymphoma is common in young people aged between 20 and 30 years. Classic presentation is of cervical lymphadenopathy, fever, night sweats, weight loss and pruritus. Reed-Sternberg cells are characteristic on histology. Choice of combination chemotherapy for Hodgkin lymphoma depends on the patients' age, sex, tumour size and the histological subtype. Radiotherapy may be given for localised or bulky disease.[19] Combination chemotherapy with or without radiotherapy is curative in 75% of newly diagnosed patients with Hodgkin disease.[10]

NON-HODGKIN LYMPHOMAS

NHL is a heterogeneous group of conditions with over 30 subtypes. NHLs are broadly divided into high and low grade. High-grade lymphomas tend to be aggressive but chemo-sensitive, whereas low-grade lymphomas are typically slow growing, indolent and incurable.[10]

Low-grade lymphomas

Low-grade lymphomas encompass follicular lymphoma (most common), mantle cell lymphoma, marginal zone lymphomas and Waldenstrom macroglobinaemia. Clinical presentation, rate of disease progression and treatment modalities vary widely. The disease may continue for years and treatment is not always indicated.

High-grade lymphomas

The most common high-grade lymphoma is DLBCL, accounting for about 30% of new cases of NHL. It typically affects elderly or middle-aged adults. First-line treatment of early-stage DLBCL includes CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisolone) with or without involved field radiotherapy.[20] Early-stage DLBCL is potentially curable with a 5-year survival of 70%–80%.[21] The anti-CD20 antibody, rituximab, has radically changed the prognosis in patients with NHL.[22] Burkitt lymphoma produces fast-growing tumours. There are three distinct variants of Burkitt lymphoma: (1) endemic (African), (2) sporadic and (3) immunodeficiency-associated. These forms differ in their clinical presentation and epidemiology but share the same aggressive nature. Childhood Burkitt lymphoma is highly responsive to combination chemotherapy with a 5-year survival greater than 90%. The risk of tumour lysis syndrome with Burkitt lymphoma is high.[23]

MULTIPLE MYELOMA

Multiple myeloma is a plasma cell malignancy that accounts for 10% of all haematological malignancies.[3] Patients present with bone pain, fractures and bone marrow failure with associated cytopenias. Renal failure is common due to light chain deposition in renal tubules, amyloidosis and hypercalcaemia from bone destruction. Multiple myeloma is not curable, but chemotherapy induces temporary remission. Typically, patients experience repeated episodes of relapse, treatment and remission over several years until the disease can no longer be controlled. Overall 5-year survival for multiple myeloma is around 35%. High-dose chemotherapy with HCT is increasingly being used as it reduces symptoms and increases survival.[24]

TREATMENT OF HAEMATOLOGICAL MALIGNANCIES

Haematological malignancies are treated using chemotherapy, radiotherapy or a combination of both with

the intent of inducing remission or cure. Recently there has been increased interest in the use of chimeric antigen receptor (CAR) T-cell therapy but it is associated with important toxicities.[25] HCT offers the only hope of cure in some conditions, but it is not without risks.

CHEMOTHERAPY

Chemotherapeutic agents, either individually or in combination, are used to induce cure or remission. Recent advances in the understanding of haematological cancers have led to an increase in the variety of chemotherapeutic agents and targeted therapies now available. Those commonly used for treatment of haematological malignancies are outlined in Table 101.1. The goal of *induction therapy* is to achieve remission by reducing the number of leukaemic cells to an undetectable level; the goal of *consolidation therapy* is to eliminate any residual undetectable disease and achieve cure. *Maintenance therapy* is used in ALL and APML to prolong remission. Chemotherapy may also be used as part of a conditioning regimen with or without total body irradiation (TBI) prior to HCT. Administration of some chemotherapeutic agents may result in life-threatening side effects.

IFOSFAMIDE NEUROTOXICITY

Ifosfamide is used in the treatment of lymphomas. It causes reversible neuropsychiatric disorders in 10%–30% of patients including visual or auditory hallucinations, confusion, personality disorders, anxiety, extra-pyramidal symptoms, seizures and coma. Symptoms occur from 2 to 48 hours after infusion, and improve 48 hours after discontinuation of the drug. Risk factors include serum albumin less than 35 mg/dL, hyponatraemia, elevated serum creatinine, previous cisplatin use and bulky abdominal disease. Treatment involves normalisation of serum electrolytes and albumin, benzodiazepines (for seizures) and methylene blue.

RETINOIC ACID SYNDROME

Patients with APML treated with ATRA are at risk of retinoic acid syndrome. Symptoms usually begin within the first 30 days of ATRA therapy and include respiratory failure, fever, weight gain, peripheral oedema, shock, acute kidney injury, cardiac failure, and pericardial and pleural effusions. The condition is potentially life threatening. Management is largely supportive and the discontinuation of ATRA is recommended.[9] There is anecdotal evidence that administration of steroids is beneficial.

IMMUNOTHERAPY

Immunotherapy, particularly with engineered T-cells (specifically CAR T-cells) is showing promising results in a variety of haematological tumours and is likely to become a mainstay of treatment. However, administration is associated with toxicities: anaphylaxis, on target/off tumour effects (such as B-cell aplasia), neurological toxicities (confusion, delirium and seizures) and cytokine release syndrome (CRS). Up to 30% of patients receiving CAR T-cell infusions experience a severe CRS with consequent multiorgan failure. This starts within hours of infusion commencement and may last for several days. Vasopressor support is usually required; invasive ventilation and renal replacement therapy may also be necessary.[25] Other patients experience mild to moderate degrees of CRS and the frequency and potential severity of response mandate administration in an environment with critical care support.

RADIOTHERAPY

Radiotherapy can be used alone or in combination with chemotherapy for lymphoma and myeloma. TBI may be instituted as part of the myeloablative regime in HCT. Side effects include gastrointestinal dysfunction, mucositis, pneumonitis, alopecia and skin irritation (Table 101.1).

HAEMATOPOIETIC STEM CELL TRANSPLANTATION

HCT is potentially curative and has now become the standard treatment for many haematological malignancies. Approximately 50,000–60,000 transplants are carried out per year.[26] ICU admission rates range from 15% to 20% with higher rates reported after allogeneic transplant.[27–29] Prior to HCT, patients must undergo myeloablative conditioning to destroy endogenous bone marrow cells. Typical myeloablative regimes include a combination of busulfan, cyclophosphamide and TBI. Reduced intensity conditioning regimes such as fludarabine and low-dose TBI are reserved for patients who are older, have multiple co-morbidities or have undergone previous transplant. They are less toxic to the bone marrow but are sufficiently immunosuppressive to permit the engraftment of donor cells.

HCT are divided according to the source of the stem cells (peripheral, bone marrow or umbilical cord) and the donor of the cells (autologous or allogeneic). Autologous transplant involves re-infusing harvested peripheral blood taken from the patient during periods of remission. With autologous transplant, patients risk the possibility of re-infusion of their own tumour cells and future disease relapse; however, treatment-related mortality is less than 5%.[30] Allogeneic transplants involve the infusion of donor stem cells (sibling or mixed unrelated donor). Immunosuppression is required to reduce the risk of graft-versus-host disease (GvHD) and graft failure. Treatment-related mortality for allogeneic transplant is much higher due to the

Table 101.1 Common chemotherapeutic agents used in haematological malignancies

CATEGORY	MODE OF ACTION	CHEMOTHERAPEUTIC AGENTS	SIDE EFFECTS
Alkylating agents	Cells directly damage DNA by forming covalent bonds	a. *Alkyl sulfonates* Busulfan	Pulmonary fibrosis Seizures Thromboembolism
		b. *Mustard gas derivatives* Chlorambucil Cyclophosphamide Ifosfamide Melphalan	Haemorrhagic cystitis Neurotoxicity Myelosuppression GI disturbance Hepatotoxicity
		c. *Triazines* Dacarbazine Procarbazine	Myelosuppression GI disturbance
Anti-metabolites	Interferes with DNA and RNA growth by acting as inhibitors of enzymes processing purine and pyrimidines	a. *Folic acid antagonist* Methotrexate	Pneumonitis Myelosuppression Hepatotoxicity
		b. *Purine antagonist* 6-mercaptopurine	Myelosuppression GI disturbance
		c. *Pyrimidine antagonist* Capecitabine Cytarabine Gemcitabine	Myelosuppression Pneumonitis Cardiac arrhythmias GI disturbance
		d. *Adenosine deaminase inhibitor* Fludarabine	Myelosuppression Autoimmune haemolytic anaemia
Antitumour antibiotics	Interfere with enzymes necessary for DNA replication	a. *Anthracyclines* Doxorubicin Daunorubicin	Cardiomyopathy
		b. *Miscellaneous* Bleomycin	Pulmonary fibrosis
Plant alkaloids	Inhibit mitosis by interfering with the assembly of microtubule structure	*Vinca alkaloids* Vinblastine Vincristine	Peripheral neuropathy Hyponatraemia Myelosuppression
Topoisomerase II inhibitors	Interferes with enzymes involved in regulating DNA coiling	Etoposide	Myelosuppression GI disturbance Rash
Tyrosine kinase inhibitors	Binds to the site of tyrosine kinase activity, preventing its activity and causing tumour cell apoptosis	Imatinib	Cardiac failure Pneumonitis Rash Fluid retention
Miscellaneous	Ribonucleotide reductase inhibitor	Hydroxyurea	Myelosuppression Hepatotoxic Nephrotoxic Mucositis
	Binds to retinoic acid receptors involved in cellular growth, proliferation and differentiation	All-trans retinoic acid (ATRA)	Retinoic acid syndrome Headache Hypertriglyceridaemia
	Depletion of cellular asparagine	Asparaginase	Pancreatitis Thromboembolism Myelosuppression

Table 101.1 Common chemotherapeutic agents used in haematological malignancies—cont'd

CATEGORY	MODE OF ACTION	CHEMOTHERAPEUTIC AGENTS	SIDE EFFECTS
Immunotherapy	Monoclonal antibodies to CD20	Rituximab	Fever Muscle and joint pain Cardiotoxicity Hepatotoxicity Nephrotoxicity
	Monoclonal antibodies to CD52	Alemtuzumab	
	Non-specific immunotherapy	Interferon alpha	
	Immunomodulatory agents	Thalidomide Lenalidomide	Thromboembolism Peripheral neuropathy Thrombocytopenia

NOMENCLATURE OF COMMONLY USED COMBINATION CHEMOTHERAPEUTIC REGIMES

CHEMOTHERAPY		HAEMATOLOGICAL MALIGNANCY
FCR	Fludarabine + Cyclophosphamide + Rituximab	CLL
ABVD	Doxorubicin + Bleomycin + Vinblastine + Dacarbazine	HL
BEACOPP	Bleomycin + Etoposide + Doxorubicin + Cyclophosphamide + Vincristine + Procarbazine + Prednisone	HL
R-CVP	Rituximab + Cyclophosphamide + Vincristine + Prednisone	NHL
R-CHOP	Rituximab + Cyclophosphamide + Doxorubicin + Vincristine + Prednisone	NHL
R-FCM	Rituximab + Fludarabine + Cyclophosphamide + Mitoxantrone	NHL
ProMACE–CytaBOM	Prednisone + Doxorubicin (Adriamycin) + Cyclophosphamide + Etoposide – Cytarabine + Bleomycin + Vincristine (Oncovin) + Methotrexate + Leucovorin	NHL
m-BACOD	Methotrexate + Leucovorin + Bleomycin + Doxorubicin (Adriamycin) + Cyclophosphamide + Vincristine (Oncovin) + Dexamethasone	NHL
MACOP-B	Methotrexate + Leucovorin + Doxorubicin (Adriamycin) + Cyclophosphamide + Vincristine (Oncovin) + Prednisone + Bleomycin	NHL
VAD	Vincristine + Doxorubicin (Adriamycin) + Dexamethasone	Multiple myeloma

Note that the above table highlights only some of the commonly used regimes.

CLL, Chronic lymphocytic leukaemia; *GI*, gastrointestinal; *HL*, Hodgkin lymphoma; *NHL*, Non-Hodgkin lymphoma.

National Cancer Institute. Health professional version. <http://www.cancer.gov/cancertopics>.

intensive myeloablative regimens and immunosuppression required.[31]

COMPLICATIONS OF HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Infection

Following HCT, the immune system takes several weeks to recover. The rapidity of recovery is dependent on the type of transplant, the source of the stem cells, the age of the recipient and donor, the myeloablative regimen, the presence of GvHD and the degree of immunosuppression.[32] Most ICU admissions are during the pre-engraftment phase. The period of engraftment is divided into three phases[33]:

1. *Pre-engraftment (<30 days)*. Recipients are neutropenic and susceptible to bacterial infections. The use of novel broad-spectrum antibiotics with excellent Gram-negative coverage has resulted in Gram-positive organisms (*Staphylococcus* spp., *Streptococcus*, *Enterococcus*) being largely responsible for bacteraemias following HCT.
2. *Early post-engraftment* (30–100 days). Cell-mediated immunity is impaired and the recipient is at risk of viral and fungal infections, such as cytomegalovirus (CMV), *Pneumocystis jirovecii* and *Aspergillus* spp.
3. *Late post-engraftment (>100 days)*. Impaired reticuloendothelial, cell-mediated and humoral functions increase recipients' risks of mycobacterial and viral infections.

Historically, CMV infection was a major cause of morbidity and mortality after HCT.[34] CMV antigen surveillance and the use of prophylactic ganciclovir in HCT recipients who are CMV-positive or have received transplants from CMV donors have led to a decrease in the number of CMV infections.[33] Similarly, *P. jirovecii*

Table 101.2 Clinical staging of acute graft-versus-host disease

STAGE	SKIN RASH	LIVER (BILIRUBIN MICROMOL PER LITRE)	GASTROINTESTINAL TRACT (DIARRHOEA IN LITRES PER DAY)
1	Maculopapular rash <25% of BSA	35–50	0.5–1
2	Maculopapular rash 25–50% of BSA	51–102	1–1.5
3	Maculopapular rash >50% of BSA	102–225	>1.5
4	Generalised erythroderma with bullae	>225	Severe abdominal pain with or without ileus

BSA, Body surface area.

Table 101.3 Grading of acute graft-versus-host disease

GRADE	CLINICAL MANIFESTATIONS
I	Stage 1–2 skin, no gut or liver involvement
II	Stage 3 skin, stage 1 gut or stage 1 liver
III	Stage 3 skin, stage 2–4 gut or stage 2–3 liver
IV	Stage 4 skin, stage 4 gut or liver

pneumonia is less common nowadays with the effective use of trimethoprim-sulphamethoxazole or pentamidine prophylaxis. Fungal infections still continue to be problematic with *Aspergillus* spp. and *Candida* spp. predominating. The routine use of azole prophylaxis has reduced the number of *Candida albican* infections but has resulted in the emergence of azole resistant *Candida* species.

Graft-versus-host disease

GvHD occurs when the donor marrow recognises the host tissue as foreign and generates an immune response. The incidence of GvHD is 30%–50% in the post-allogeneic transplant recipient and increases with HLA mismatch, advanced age of the donor and recipient, inadequate immunosuppression and the use of peripheral blood as the stem cell source. Steroids, cyclosporin and/or mycophenolate mofetil are used in the prophylaxis of GvHD. Acute GVHD classically presents 7–28 days post-transplant with a maculopapular skin rash, diarrhoea and/or intrahepatic cholestasis. Acute GvHD is staged and graded according to the number and extent of organ involvement (Tables 101.2 and 101.3).[35]

The diagnosis of acute GvHD is typically confirmed with a skin, rectal or liver biopsy. Treatment of severe acute GvHD involves high-dose pulsed methylprednisolone and/or additional immunosuppressive agents. Gastrointestinal involvement with secretory diarrhoea often necessitates the need for parenteral nutrition and octreotide. The degree of acute GvHD has shown to be predictive of 100-day survival.[36] Chronic GvHD is a multiorgan dysfunction syndrome usually occurring more than 100 days post-transplant. It can be limited or extensive with skin (itchy dry skin, scleroderma), pulmonary (bronchiolitis obliterans), ophthalmic (sicca, keratitis), salivary glands (xerostomia) and neuromuscular (polyneuropathy, polymyositis, myasthenia gravis) involvement, and liver dysfunction (hepatitis, cirrhosis). Treatment is difficult and progression can be limited by increasing the dose of immunosuppression (with a consequent risk of infection).

Graft failure

Graft failure occurs when there is a failure to establish haematological engraftment after HCT. It occurs in less than 5% of patients following allogeneic HCT. Causes of graft failure include inadequate stem cell infusion, infection and GvHD. Graft failure is associated with an increased risk of infection and transplant-related mortality. Management consists of augmentation by granulocyte-colony stimulating factor (G-CSF), stem cell re-infusion or a second HCT.

Diffuse alveolar haemorrhage

Diffuse alveolar haemorrhage (DAH) occurs in 5% of HCT patients. It occurs within 30 days of transplant and is caused by injury to the pulmonary endothelial lining from chemo- and radiotherapy. Age, acute GvHD, intensive myeloablative regimes, TBI and allogeneic transplant are risk factors. Patients typically present with pyrexia, dyspnoea, cough, anaemia and diffuse infiltrates on chest radiographs in the absence of infection. Haemoptysis is rare. Bronchoalveolar lavage (BAL) is bloody, and cytology shows haemosiderin-laden macrophages. Treatment is with high-dose steroids and the response is variable.

Idiopathic pneumonia syndrome

The incidence of idiopathic pneumonia syndrome (IPS) is approximately 7% and it is commonly seen 3 weeks after HCT. Typical presentation is of diffuse infiltrates on chest radiography or computed tomography (CT) scan in the absence of an infective aetiology. Risk factors include allogeneic transplant, GvHD and CMV-positive donor status, pre-transplant radiation, and chemotherapy (busulfan, cyclophosphamide). Treatment is mainly supportive and the mortality is over 70%.

Engraftment syndrome

Engraftment syndrome (also known as capillary leak syndrome) typically presents 4–5 days after autologous HCT with fever, erythematous rash and non-cardiogenic pulmonary oedema. Other features include abnormal liver function tests, transient encephalopathy and multiorgan failure. The underlying pathophysiology is related to the release of pro-inflammatory cytokines and neutrophils. The use of G-CSF increases the prevalence of this syndrome and should it occur, G-CSF should be discontinued immediately. The chest CT scan typically demonstrates bilateral ground-glass opacification. Management is supportive and steroids may be useful.

Veno-occlusive disease

Veno-occlusive disease (VOD) – also known as sinusoidal obstruction syndrome – presents as a triad of painful hepatomegaly, jaundice and ascites 3 weeks following HCT. Other features include weight gain, encephalopathy, bleeding and hepato-renal syndrome. The disease spectrum ranges from a mild, reversible condition to multiorgan failure. Risk factors include myeloablative conditioning regimes (busulfan, cyclophosphamide), pre-existing abnormal liver function tests, intra-abdominal radiotherapy and repeated HCT. The diagnosis is made by hepatic Dopplers showing reversed or reduced portal flow. A transjugular liver biopsy may also help establish the diagnosis. Management and prophylaxis in high-risk patients involves the use of defibrotide, a polydeoxyribonucleotide with antithrombotic, anti-inflammatory and fibrinolytic effects.[37] Severe VOD has a mortality of 85%.

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome is a syndrome characterised by confusion, headache, visual loss and seizures commonly associated with HCT and immunosuppressive agents (e.g. ciclosporin). T2-weighted magnetic resonance imaging characteristically shows diffuse hyper-intensity involving the parieto-occipital white matter. Treatment is targeted at the underlying cause (Fig. 101.1).

Post-transplant lymphoproliferative disorder

Post-transplant lymphoproliferative disorder is a well-recognised but infrequent complication of allogeneic transplant. It is characterised by uncontrolled proliferation of Epstein-Barr virus (EBV)-infected B cells and results in the impairment of T-cell immunity. Risks include previous EBV donor or recipient exposure, aggressive immunosuppression and T-cell depleted transplants. EBV viral load should be monitored regularly. Treatment involves a gradual withdrawal of immunosuppression with the potential risk of GvHD. Intravenous immunoglobulins, anti-B cell monoclonal antibodies, rituximab and infusion of donor T-cells have all been used with variable success.

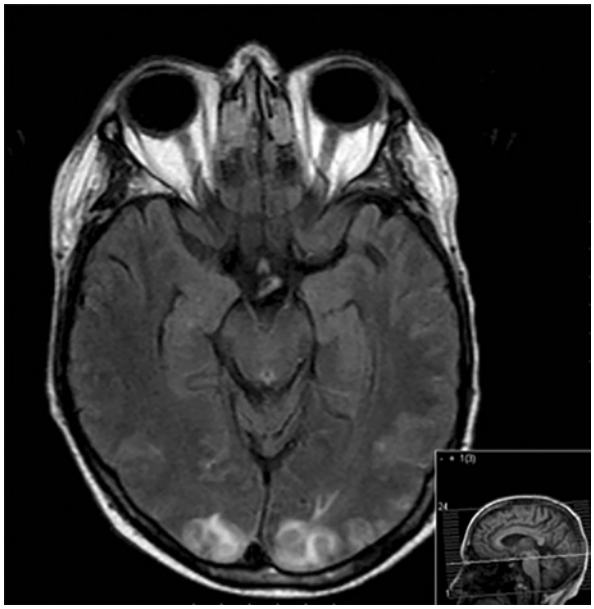


Figure 101.1 Magnetic resonance imaging scan of the brain (T2 with flair) shows high signal bilaterally involving the occipital lobes in keeping with posterior reversible encephalopathy syndrome.

Thrombotic thrombocytopenic purpura

Secondary thrombotic thrombocytopenic purpura (TTP) following HCT is due to endothelial damage from chemotherapy. The classic presentation is of renal failure, fever, thrombocytopenia, fluctuating neurological signs (confusion, mood changes, seizures and drowsiness) and microangiopathic haemolytic anaemia. The blood film typically shows red cell fragments and the haemolysis screen is positive. Treatment is supportive and involves plasmapheresis, broad-spectrum antibiotics and high dose steroids. Haemolytic uraemic syndrome is a similar entity and may be distinguished from TTP by the lack of neurological signs and fever.

PATIENTS WITH HAEMATOLOGICAL MALIGNANCY ON THE INTENSIVE CARE UNIT

Patients with haematological malignancies develop critical illness either due to their underlying cancer or cancer-related treatments such as chemotherapy, radiotherapy or HCT. Outlined below are some common reasons for ICU admission.

ACUTE ONCOLOGICAL EMERGENCIES

A small number of patients are admitted directly to ICU with complications of their haematological malignancy requiring urgent chemotherapy and/or radiotherapy. These include:

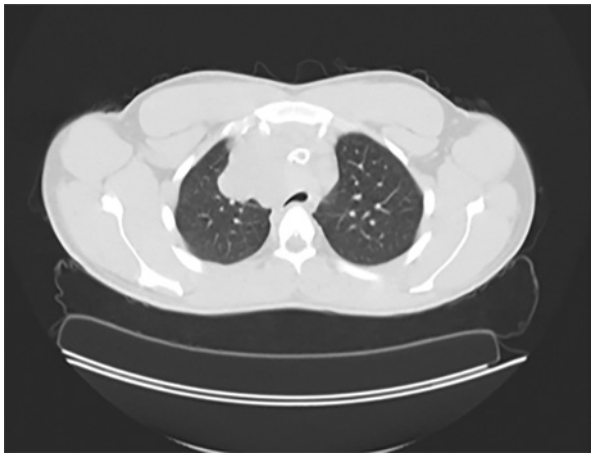


Figure 101.2 Computed tomography scan of the chest showing bulky infiltrative mass (non-Hodgkin lymphomas) extending from the anterior mediastinum to the right paratracheal space with tracheal compression.

1. *CNS involvement.* CNS involvement resulting in focal deficits, seizures, alteration of consciousness or high spinal cord compression is an indication for urgent chemotherapy and/or radiotherapy.
2. *Mediastinal masses and pericardial disease.* Bulky mediastinal masses with compression of trachea, main bronchi or major vessels are often due to NHLs and require urgent chemotherapy and/or radiotherapy to relieve the compression (Fig. 101.2).
3. *DIC.* DIC may be a presenting feature of APML. Specific chemotherapy, such as ATRA and supportive measures, is required.
4. *Hyperviscosity syndromes.* Hyperviscosity syndromes occur with multiple myeloma, leukaemia and Waldenstrom macroglobinaemia. Clinical manifestations include headaches, coma, seizures, visual impairment, retinal haemorrhages, and bleeding. Emergency management is directed at decreasing blood viscosity by plasmapheresis followed by urgent chemotherapy aimed at reducing monoclonal immunoglobulins.
5. *Macrophage activation syndrome (MAS).* MAS, also known as haemophagocytic lymphohistiocytosis, is a recognised presentation of NHL and Hodgkin lymphoma. Typical manifestations of MAS are fever, splenomegaly and at least two cytopenias (anaemia, thrombocytopenia, neutropenia). Shock, acute respiratory distress syndrome and acute kidney injury may also occur. Laboratory findings also include hypoalbuminaemia, hypertriglyceridaemia, hypofibrinogenaemia, hyperferritinaemia (>500 μg/L). Bone marrow findings show activated macrophages phagocytosing platelets, erythrocytes and leukocytes. Steroids and etoposide are the mainstays of treatment.
6. *Hyperleukocytic acute myeloid leukaemia.* Hyperleukocytosis is defined as a total leukocyte count of >100 $\times 10^9$/L. It is typically seen in patients with AML in blast crisis. White cell plugs in the vasculature cause decreased tissue perfusion and result in neurological dysfunction, ischaemia, coagulopathy and respiratory failure.[38] Leukostasis is associated with a high mortality and prompt treatment with chemotherapy and leukapheresis is indicated. Preliminary cytoreduction with hydroxycarbamide or cytarabine before the initiation of intensive chemotherapy is now recommended to prevent uncontrolled tumour lysis syndrome.

In some circumstances, starting chemotherapy in the ICU, even when infection or organ failure is present, may be appropriate to limit disease progression that results in death. Modification chemotherapeutic regimens may be required to limit organ toxicity and the duration of neutropenia. In carefully selected cases of patients given chemotherapy in the ICU, published outcomes have been reasonable with an ICU mortality of 25%–40%.[39,40] The improved outcomes have been attributed to better patient selection, more experience in the administration of chemotherapy in the ICU setting, a greater understanding of optimal chemotherapy dosing in patients with organ failure and better supportive care.[41] In fact, the administration of chemotherapy, in the ICU setting or within the last 3 weeks prior to ICU admission, does not appear to be associated with an increased risk of death.[42]

NEUTROPENIA AND NEUTROPENIC SEPSIS

Neutropenia is defined as an absolute neutrophil count (ANC) of $<1.5 \times 10^9$/L. Severe neutropenia is defined as an ANC $<0.5 \times 10^9$/L. Fever is common in patients with haematological malignancies and differentiating infectious from non-infectious causes of fever is notoriously difficult. Assessment relies on the early identification of a likely source, microbiological surveillance and surrogate information from biomarkers. Severe sepsis and septic shock in patients with haematological malignancies has a reported mortality of 36%–45%.[43,44] High-risk patients are those with significant co-morbidities and prolonged (>7 days) and severe neutropenia. Neutropenic sepsis is potentially fatal if left untreated.[45] Patients with neutropenic sepsis must have antibiotics administered within 1 hour of presentation. A minimum of two sets of blood cultures should be collected from peripheral veins and each lumen of existing central venous catheters. A chest radiograph and culture specimens from sites of suspected infection (sputum, stool, urine) should also be taken. First-line antibiotic treatment is with an anti-pseudomonal β-lactam agent, such as cefepime, a carbapenem (meropenem or imipenem-cilastatin) or piperacillin-tazobactam. Aminoglycosides, fluoroquinolones and/or vancomycin should be added

to the initial regimen in the event of septic shock or if antibiotic resistance is suspected.[46] Vancomycin (or another agent active against Gram-positive cocci) also should be added if there is a suspected catheter-related infection, soft-tissue infection or pneumonia. In ICUs where there is a high incidence of multiresistant organisms, it may be necessary to use a second-line Gram-positive agent such as linezolid. Empirical antifungal therapy should be considered for patients with persistent or recurrent fever. The need for antiviral agents or trimethoprim-sulfamethoxazole should be evaluated.

G-CSF is often used to promote neutrophil recovery in patients with profound neutropenia. Blood cell counts should be obtained daily, and the G-CSF should be discontinued when the white cell count is $>1.0 \times 10^9$/L or the ANC is $>0.5 \times 10^9$/L. Side effects of G-CSF include rash, injection site reaction, bone pain and flu-like symptoms. Finally, environmental precautions should be taken when managing neutropenic patients with meticulous hand hygiene, full barrier precautions (gloves, gowns, and in some cases overshoes and masks) and protective patient isolation. In the United Kingdom, the National Institute for Clinical Excellence has provided comprehensive guidance on the management of neutropenic sepsis following the National Confidential Enquiry into Patient Outcome and Death report (Systemic Anti-Cancer Therapy: For better, for worse? 2008).[47,48]

NEUTROPENIC ENTEROCOLITIS

Patients typically present with abdominal pain, fever and diarrhoea after chemotherapy (especially cytosine arabinoside, vinca alkaloids and doxorubicin). It is caused by a combination of chemotherapy-induced colonic mucosal wall damage, thrombocytopenia-related gastrointestinal bleeding, and colonisation of the bowel by pathogenic bacteria. Complications include bacteraemia, gastrointestinal bleeding and perforation (5%–10%). Abdominal CT scanning may demonstrate pneumoperitoneum or colonic pneumatosis indicating colonic damage with imminent perforation. Bowel-wall thickening on ultrasound scanning may also help to confirm the diagnosis. Management is conservative with bowel rest, parenteral nutrition and antibiotics that target enteric Gram-negative and anaerobic organisms, including *Clostridium difficile*. Surgery may be required in patients with uncontrolled sepsis, bowel perforation or life-threatening gastrointestinal bleeding.

RESPIRATORY FAILURE

Acute respiratory failure is the primary reason for ICU admission in patients with haematological malignancies. The aetiology is commonly infection, although other non-infectious causes including non-cardiogenic pulmonary oedema, acute respiratory distress syndrome, GvHD, DAH, IPS, chemotherapy (methotrexate, bleomycin, fludarabine, gemcitabine) and tumour infiltration of the lung should be considered (Table 101.4). Reported mortality for patients with haematological malignancies who require mechanical ventilation has improved over the last decade, but mechanical ventilation remains a poor prognostic outcome indicator.[49–51] Lung protective ventilation strategies, early use of non-invasive ventilation and high-flow nasal oxygen therapy have all contributed to improvements in

Table 101.4 Causes of respiratory failure in a patient with haematological malignancy

CAUSES	EXAMPLES	
Non-infectious	General	Acute respiratory distress syndrome Aspiration pneumonia Pulmonary leukaemic infiltration Tumour causing upper or lower airway obstruction Non-cardiogenic pulmonary oedema Chemotherapy-induced pulmonary toxicity Pulmonary interstitial fibrosis
	Specific to HCT	Diffuse alveolar haemorrhage syndrome Idiopathic pneumonia syndrome Engraftment syndrome
Infectious	Bacterial	*Pseudomonas*, *Klebsiella*, *Acinetobacter*, *Staphylococcus*, *Enterococcus*, *Streptococcus*, *Legionella*, *Mycoplasma*
	Viral	Influenza, parainfluenza, adenovirus, respiratory syncytial virus, cytomegalovirus, herpes simplex virus, varicella zoster virus
	Fungal	*Candida* spp., *Aspergillus* spp., *Pneumocystis jirovecii*
	Mycobacteria	*Mycobacterium tuberculosis*

HCT, Haematopoietic stem cell transplant.

outcome.[52,53] Routine lung biopsy is no longer recommended and diagnostic BAL is deemed useful in only a select group of patients with the risk that mechanical ventilation may be precipitated.[54]

ACUTE KIDNEY INJURY

Acute kidney injury may be a result of the underlying cancer (monoclonal light chain deposition in multiple myeloma), tumour lysis syndrome, administration of nephrotoxic agents (amphotericin B, foscarnet, aminoglycosides, methotrexate, platin derivatives, cyclophosphamide, cyclosporin), hepato-renal syndrome from VOD or sepsis. In some cases, renal replacement therapy may be required. Studies have shown that the need for renal replacement therapy is an independent predictor of mortality in patients with haematological malignancy.[55,56]

TUMOUR LYSIS SYNDROME

Tumour lysis syndrome is caused by rapid lysis of tumour cells following chemotherapy leading to the release of excessive quantities of intracellular contents into the systemic circulation. The metabolic disturbance is characterised by hyperkalaemia, hyperphosphataemia, hypocalcaemia and hyperuricaemia, which may lead to acute kidney injury and cardiac arrhythmias. It is commonly associated with the acute leukaemias and high-grade lymphomas (e.g. Burkitt lymphoma). Close monitoring of renal function, potassium, calcium, phosphate and urate levels are required in patients with high tumour burden after starting chemotherapy. Allopurinol or rasburicase (a recombinant urate oxidase enzyme) are used as prophylaxis.[57] Treatment includes aggressive fluid hydration, rasburicase and renal replacement therapy.

NEUROLOGICAL DYSFUNCTION

Neurological dysfunction may have a number of aetiologies including infection (bacterial, viral or fungal), bleeding, tumour infiltration, hyperviscosity syndromes (multiple myeloma, Waldenstrom haemoglobinaemia), cerebral infarcts and cerebral venous thrombosis. Some chemotherapy and immunosuppressive agents (methotrexate, cytarabine, 5-fluorouracil, cyclosporin) may present with CNS toxicity and cerebellar syndromes. High-dose cisplatin can cause encephalopathy and optic nerve damage.

GASTROINTESTINAL AND LIVER DYSFUNCTION

Gastrointestinal and liver dysfunction may be associated with chemotherapy (ciclosporin, methotrexate, platinum derivatives), acute GvHD, infection (CMV, EBV, hepatitis, adenovirus, rotavirus, *C. difficile*), VOD and tumour infiltration.

CARDIAC COMPLICATIONS

Cardiac complications, such as cardiac failure, arrhythmias, pericardial effusion, myocarditis or endocarditis, may be the result of the underlying cancer, chemotherapy (anthracyclines, cyclophosphamide, cisplatin) or infection.

PREDICTORS OF MORTALITY IN PATIENTS WITH HAEMATOLOGICAL CANCER

Several studies have looked at predictors of mortality to help identify those patients with haematological malignancy most likely to benefit from ICU care. Neutropenia, autologous transplant and the underlying haematological diagnosis do not seem to correlate with outcome.[58–60] However, advanced age, mechanical ventilation, vasopressor use, GvHD, elevated serum lactate on admission and allogeneic transplants are associated with poorer outcomes.[2,27,29,49,61] The number and severity of organ failures appear to be key determinants of survival.[62] Acute Physiology and Chronic Health Evaluation II scores and Simplified Acute Physiology Score II scores often underestimate mortality in patients with haematological malignancies.[28,63] Several studies have also shown a case-volume relationship demonstrating better outcomes in centres looking after higher numbers of patients with haematological cancers.[64]

OUTCOMES OF PATIENTS WITH HAEMATOLOGICAL MALIGNANCY ADMITTED TO THE INTENSIVE CARE UNIT

Previous studies have reported that patients with haematological malignancies who require intensive care often face a poor prognosis with in-hospital mortality rates of greater than 80% reported in the mid-1990s.[65] However, more recent reports have demonstrated better survival. The largest case series to date has demonstrated an in-hospital mortality of 59%.[2] This reduction in mortality is attributed to improvements in chemotherapeutic regimes, better patient selection, targeted therapies with less organ toxicity and improved ICU care.[66] A joint approach between intensivists and haematologists in the delivery of patient care, early ICU admission of patients at risk of developing organ failure, and effective triaging of patients who are unlikely to benefit from ICU care are also important contributory factors.[66,67] This trend towards lower mortality provides a strong argument against the traditionally held negative perception of patients with haematological malignancy admitted to the ICU and a trigger for change in the way we manage patients with haematological malignancies on the ICU. New recommendations encourage early ICU admission, cytoreductive therapy in patients with hyperleukocytic AML, combination therapy in patients with septic shock, early catheter withdrawal in patients with septic shock of unknown origin, the use of non-invasive diagnostic and therapeutic strategies, 'ICU trials' for appropriate

patients with clear definition of goals of care and early palliative care involvement in patients where ICU care is unlikely to be beneficial (bedridden patients, frail patients, allogenic HCT patients with uncontrolled GvHD).[68]

QUALITY OF LIFE IN CRITICALLY ILL PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES

There are very few studies looking at long-term outcomes and quality of life in critically ill patients with haematological malignancies. A single-centre study followed up 85 patients with haematological malignancies and demonstrated a decline at 3 months and a slight improvement after 1 year with a failure to return to baseline function pre-ICU admission (based on the Euro-QoL-5D Medical Outcomes Study 36-item Short Form Health Survey).[69] Further studies on long-term outcomes are warranted.

REFERENCES

1. Smith A, Howell D, Patmore R, et al. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. *Br J Cancer*. 2011;105(11):1684–1692.
2. Hampshire PA, Welch CA, McCrossan LA, et al. Admission factors associated with hospital mortality in patients with haematological malignancy admitted to UK adult, general critical care units: a secondary analysis of the ICNARC Case Mix Programme Database. *Crit Care*. 2009;13:R137.
3. Ferlay J, Shin HR, Bray F, et al. *GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10 [Internet]*. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr.
4. National Cancer Intelligence Network. *Cancer Incidence by Deprivation England 1995 – 2004*. Available from: http://www.ncin.org.uk.
5. U.S. Cancer Statistics Working Group. *United States Cancer Statistics: 1999–2007 Incidence and Mortality Web-based Report*. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2010. Available from: http://www.cdc.gov/uscs.
6. Jaffe ES, Harris LN, Stein H, et al. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC Press; 2001.
7. Swerdlow SH, Campo E, Harris NL, et al. *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC Press; 2008.
8. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood*. 2002;100(7):2292–2302.
9. Sanz MA, Grimwade D, Tallman MS, et al. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood*. 2009;113(9):1875–1891.
10. National Cancer Institute. *Health professional version*. Available from: http://www.cancer.gov/cancertopics.
11. Larson RA, Dodge RK, Burns CP, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. *Blood*. 1995;85(8):2025–2037.
12. Linker CA, Levitt LJ, O'Donnell M, et al. Treatment of adult acute lymphoblastic leukemia with intensive cyclical chemotherapy: a follow-up report. *Blood*. 1991;78(11):2814–2822.
13. Smith MA, Seibel NL, Altekruse SF, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. *J Clin Oncol*. 2010;28(15):2625–2634.
14. Robertson LE, Pugh W, O'Brien S, et al. Richter's syndrome: a report on 39 patients. *J Clin Oncol*. 1993;11(10):1985–1989.
15. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010;376(9747):1164–1174.
16. Moreton P, Kennedy B, Lucas G, et al. Eradication of minimal residual disease in B-cell chronic lymphocytic leukemia after alemtuzumab therapy is associated with prolonged survival. *J Clin Oncol*. 2005;23(13):2971–2979.
17. Sawyers CL. Chronic myeloid leukemia. *N Engl J Med*. 1999;340(17):1330–1340.
18. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med*. 2006;355(23):2408–2417.
19. Ng AK, Mauch PM. Radiation therapy in Hodgkin's lymphoma. *Semin Hematol*. 1999;36(3):290–302.
20. Coiffier B. State-of-the-art therapeutics: diffuse large B-cell lymphoma. *J Clin Oncol*. 2005;23(26):6387–6393.
21. Coltman CA, Dahlberg S, Jones SE, et al. Southwest Oncology Group Studies in diffuse large cell lymphoma: a subset analysis. In: Kimura K, ed. *Cancer Chemotherapy: Challenges for the Future*. Tokyo, Japan: Excerpta Medica; 1988:194–202.
22. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med*. 2002;346:235–242.
23. Cohen LF, Balow JE, Magrath IT, et al. Acute tumour lysis syndrome. A review of 37 patients with Burkitt's lymphoma. *Am J Med*. 1980;68(4):486–491.
24. Giralt S. Stem cell transplantation for multiple myeloma: current and future status. *Hematology Am Soc Hematol Educ Program*. 2011;2011:191–196.
25. Bonifant CL, Jackson HJ, Brentjens RJ, et al. Toxicity and management in CAR T-cell therapy. *Mol Ther Oncolytics*. 2016;3:16011. doi:10.1038/mto.2016.

26. Gratwohl A, Baldomero H, Aljurf M, et al. Worldwide Network of Blood and Marrow Transplantation. Hematopoietic stem cell transplantation: a global perspective. *JAMA*. 2010;303(16): 1617–1624.
27. Soubani AO, Kseibi E, Bander JJ, et al. Outcome and prognostic factors of hematopoietic stem cell transplantation recipients admitted to a medical ICU. *Chest*. 2004;126:1604–1611.
28. Afessa B, Tefferi A, Hoagland HC, et al. Outcome of recipients of bone marrow transplants who required intensive care unit support. *Mayo Clin Proc*. 1992;67:117–122.
29. Pène F, Aubron C, Azoulay E, et al. Outcome of critically ill allogeneic hematopoietic stem-cell transplantation recipients: a reappraisal of indications for organ failure supports. *J Clin Oncol*. 2006; 24(4):643–649.
30. Jantunen E, Itälä M, Lehtinen T, et al. Early treatment-related mortality in adult autologous stem cell transplant recipients: a nation-wide survey of 1482 transplanted patients. *Eur J Haematol*. 2006; 76(3):245–250.
31. Stewart FM. Indications and relative indications for stem cell transplantation in non-Hodgkin's lymphoma. *Leukemia*. 1993;7(7):1091–1094.
32. van Burik JA, Weisdorf DJ. Infections in recipients of blood and marrow transplantation. *Hematol Oncol Clin North Am*. 1999;13(5):1065–1089.
33. Center for International Blood and Marrow Transplant Research (CIBMTR); National Marrow Donor Program (NMDP); European Blood and Marrow Transplant Group (EBMT); American Society of Blood and Marrow Transplantation (ASBMT); Canadian Blood and Marrow Transplant Group (CBMTG); Infectious Disease Society of America (IDSA); Society for Healthcare Epidemiology of America (SHEA); Association of Medical Microbiology and Infectious Diseases Canada (AMMI); Centers for Disease Control and Prevention (CDC). Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. *Bone Marrow Transplant*. 2009;44(8): 453–558.
34. Meyers JD, Flournoy N, Thomas ED. Risk factors for cytomegalovirus infection after human marrow transplantation. *J Infect Dis*. 1986;153(3):478–488.
35. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft versus host disease in human recipients of marrow from HLA-matched sibling donors. *Transplantation*. 1974;18:295–304.
36. Cahn JY, Klein JP, Lee SJ, et al. Prospective evaluation of 2 acute graft-versus-host (GVHD) grading systems: a joint Société Française de Greffe de Moëlle et Thérapie Cellulaire (SFGM-TC), Dana Farber Cancer Institute (DFCI), and International Bone Marrow Transplant Registry (IBMTR) prospective study. *Blood*. 2005;106(4):1495–1500.
37. Ho VT, Revta C, Richardson PG. Hepatic venoocclusive disease after hematopoietic stem cell transplantation: update on defibrotide and other current investigational therapies. *Bone Marrow Transplant*. 2008;41(3):229–237.
38. Porcu P, Cripe LD, Ng EW, et al. Hyperleukocytic leukemias and leukostasis: a review of pathophysiology, clinical presentation and management. *Leuk Lymphoma*. 2000;39:1.
39. Benoit DD, Depuydt PO, Vandewoude KH, et al. Outcome in severely ill patients with hematological malignancies who received intravenous chemotherapy in the intensive care unit. *Intensive Care Med*. 2006;32:93–99.
40. Wohlfarth P, Staudinger T, Sperr WR, et al. Prognostic factors, long-term survival, and outcome of cancer patients receiving chemotherapy in the intensive care unit. *Ann Hematol*. 2014;93: 1629–1636.
41. Moors I, Pene F, Lengline E, et al. Urgent chemotherapy in hematological patients in the ICU. *Curr Opin Crit Care*. 2015;21:559–568.
42. Vandijck DM, Benoit DD, Depuydt PO, et al. Impact of recent intravenous chemotherapy on outcome in severe sepsis and septic shock patients with hematological malignancies. *Intensive Care Med*. 2008;34:847–855.
43. Williams M, Braun L, Cooper L, et al. Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. *Crit Care*. 2004;8:291–298.
44. Regazzoni CJ, Irrazabal C, Luna CM, et al. Cancer patients with septic shock: mortality predictors and neutropenia. *Support Care Cancer*. 2004;12:833–839.
45. Blot F, Guiguet M, Nitenberg G, et al. Prognostic factors for neutropenic patients in an intensive care unit: respective roles of underlying malignancies and acute organ failures. *Eur J Cancer*. 1997;33: 1031–1103.
46. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52(4):56–93.
47. National Institute for Health and Clinical Excellence. *Neutropenic Sepsis. In Progress*. London: National Institute for Health and Clinical Excellence; 2010. Available from: http://www.nice.org.uk.
48. National Confidential Inquiry in Patient Outcome and Deaths. *For better for worse? A review of the care of patients who died within receiving 30 days of systemic anti-cancer therapy. National Confidential Inquiry in Patient Outcome and Deaths (NCEPOD)* 2008. Available from: http://www.ncepod.org.uk.
49. Kroschinsky F, Weise M, Illmer T, et al. Outcome and prognostic features of intensive care unit treatment in patients with hematological malignancies. *Intensive Care Med*. 2002;28:1294–1300.
50. Afessa B, Azoulay E. Critical care of the hematopoietic stem cell transplant recipient. *Critical Care Clin*. 2010;26(1):133–150.
51. Azevedo LC, Caruso P, Silva UV, et al. Outcomes for patients with cancer admitted to the ICU

requiring ventilatory support: results from a prospective multicenter study. *Chest*. 2014;146:257–266.
52. Hilbert G, Gruson D, Vargas F, et al. Non-invasive continuous positive airway pressure in neutropenic patients with acute respiratory failure requiring intensive care unit admission. *Crit Care Med*. 2000; 28:3185–3190.
53. Mokart D, Geay C, Chow-Chine L, et al. High-flow oxygen therapy in cancer patients with acute respiratory failure. *Intensive Care Med*. 2015;41: 2008–2010.
54. Azoulay E, Mokart D, Lambert J, et al. Diagnostic strategy for hematology and oncology patients with acute respiratory failure: randomized controlled trial. *Am J Respir Crit Care Med*. 2010;182:1038–1046.
55. Hahn T, Rondeau C, Shaukat A, et al. Acute renal failure requiring dialysis after allogeneic blood and marrow transplantation identifies very poor prognosis patients. *Bone Marrow Transplant*. 2003;32:405–410.
56. Gruss E, Bernis C, Tomas JF, et al. Acute renal failure in patients following bone marrow transplantation: prevalence, risk factors and outcome. *Am J Nephrol*. 1995;15:473–479.
57. Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol*. 2008;26(16):2767–2778.
58. Darmon M, Azoulay E, Alberti C, et al. Impact of neutropenia duration on short-term mortality in neutropenic critically ill cancer patients. *Intensive Care Med*. 2002;28:1775–1780.
59. Khassawneh BY, White P Jr, Anaissie EJ, et al. Outcome from mechanical ventilation after autologous peripheral blood stem cell transplantation. *Chest*. 2002;121:185–188.
60. Massion PB, Dive AM, Doyen C, et al. Prognosis of hematologic malignancies does not predict intensive care unit mortality. *Crit Care Med*. 2002; 30:2260–2270.
61. Benoit DD, Vandewoude KH, Decruyenaere JM, et al. Outcome and early prognostic indicators in patients with a hematologic malignancy admitted to the intensive care unit for a life-threatening complication. *Crit Care Med*. 2003;31:104–112.
62. Darmon M, Thiery G, Ciroldi M, et al. Intensive care in patients with newly diagnosed malignancies and a need for cancer chemotherapy. *Crit Care Med*. 2005;33:2488–2493.
63. Lloyd-Thomas AR, Wright I, Lister TA, et al. Prognosis of patients receiving intensive care for life threatening medical complications of haematological malignancy. *Br Med J*. 1988;296:1025–1029.
64. Lecuyer L, Chevret S, Guidet B, et al. Case volume and mortality in haematological patients with acute respiratory failure. *Eur Respir J*. 2008;32:748–754.
65. Tremblay LN, Hyland RH, Schouten BD, et al. Survival of acute myelogenous leukemia patients requiring intubation/ventilatory support. *Clin Invest Med*. 1995;18(1):19–24.
66. Azoulay E, Soares M, Darmon M, et al. Intensive care of the cancer patient: recent achievements and remaining challenges. *Ann Intensive Care*. 2011;1(1):5.
67. Lecuyer L, Chevret S, Thiery G, et al. The ICU trial: a new admission policy for cancer patients requiring mechanical ventilation. *Crit Care Med*. 2007; 35:808–814.
68. Azoulay E, Pene F, Darmon M, et al. Managing critically ill hematology patients: time to think differently. *Blood Rev*. 2015;29:359–367.
69. Oeyen SG, Benoit DD, Annemans L, et al. Long-term outcomes and quality of life in critically ill patients with hematological or solid malignancies: a single center study. *Intensive Care Med*. 2013;39:889–898.

This page intentionally left blank

Part Sixteen

Organ Donation and Transplantation

This page intentionally left blank

102

Organ donation

Stephen J Streat

Transplantation of organs and tissues is established treatment for end-stage organ failure and other conditions.[1,2] Transplant volumes are modestly increasing worldwide because of a number of strategies[3]: live (including altruistic) donors, chains of kidney exchange,[4] donation after circulatory death (DCD), admission of patients to the intensive care unit (ICU) solely for possible organ donation, accepting more organs at a higher risk of failure[1] and from extended category donors, the use of split livers for two recipients[3] and transplanting two kidneys into one recipient.[5] Improving outcomes, despite both increasing recipient co-morbidity and increasing use of organs from extended category and DCD, has led to more patients being offered transplantation. Donation from both live and deceased donors is increasing, but this is slower than the number of potential recipients on waiting lists.

Despite professional condemnation of the practice[6] desperate recipients from wealthy countries continue to take part in 'transplant tourism'[7–9] in poorer countries. Concerns have been expressed about internet-facilitated live donations being potentially vulnerable to commercial exploitation.[10,11] Slow progress continues in alternative approaches to end-stage organ failure, including artificial organs, xenotransplantation and the engineering of organs (and tissues) from stem cells, but no such organ replacement is yet available for clinical use.

The characteristics of deceased donors continue to change, with relative stability in the number of donors after brain death (DBD) in many jurisdictions[12] and ongoing increases in donors after circulatory death (DCD).[13] There are increasingly fewer donors after traumatic brain injury (TBI) and more (often extended-category) donors following (predominantly haemorrhagic) stroke, hypoxic–ischaemic encephalopathy[12] and other non-traumatic conditions. These changes result from better primary prevention of TBI, better treatment of subarachnoid and intracerebral haemorrhage and, in the United States in particular, a lethal epidemic of opioid overdose,[14] together with both changes in ICU admission criteria and end-of-life practice, and more liberal acceptance by transplant services of donors with co-morbidity or potentially reversible organ dysfunction.

Decompressive craniectomy often controls refractory intracranial hypertension[15,16] and thereby reduces the incidence of brain death but has less salutatory effects on long-term functional outcome,[15–17] which may not be acceptable to the patient.

The institution of mechanical ventilatory support in poor-prognosis patients with apparent stroke (to facilitate computed tomography [CT] scanning) has led to more such patients being admitted to ICU 'solely for possible future organ donation', sometimes – but not always – after family agreement to such a course of action. The efficacy of hypothermia,[18] and similar efficacy of targeted temperature management[19] for the amelioration of hypoxic–ischaemic encephalopathy in some populations of patients has led to its use in situations where robust evidence of efficacy is absent (e.g. prolonged asystole after asphyxia). This has contributed to more poor-prognosis patients being admitted to the ICU, including some who later donate organs either through DCD or less often after brain death.

RESPONSIBILITIES OF THE INTENSIVIST

Intensivists are located at the nexus of deceased-donor organ donation in the ICU and almost all are strongly supportive of donation.[20,21] Intensivists must accept, assert and maintain strong leadership and guardianship in deceased-donor organ donation, ensuring that medical, ethical and legal practices are done, and are seen to be done, to the highest standard.[22]

This personal view, shared by some professional societies,[22] is seldom heard in public discourse as advocates for transplant recipients and organ procurement agencies have come to define best practice in deceased-donor organ donation (and its language and metrics) in strictly utilitarian[23] and sometimes insensitive ways. Few intensive care professional societies have independently defined what constitutes best practice in organ donation, but this fact should not facilitate intensivists abrogating their professional responsibility for any aspect of the care of ICU patients and their families. In deceased-donor organ donation this involves the responsibility of caring for the dying patient and their family; identifying the potential for organ donation to occur; determining brain death; liaising with organ

ABSTRACT

Transplantation of organs from both live and deceased donors is increasing, but the number of potential recipients continues to rise. Most of the ongoing increase in deceased donation now comes from donors after circulatory death (DCD). Intensivists are located at the nexus of deceased donation in the intensive care unit and must accept responsibility for leadership and guardianship of it, ensuring that the highest medical, ethical and legal standards are maintained, despite increasingly strident and presumptive societal demands for more donors. Our responsibility includes maintaining expertise in care of the dying patient and their family; identifying of every situation with the potential for donation to occur; determining brain death; liaising with organ donation or procurement agencies; discussing organ donation with the family; maintaining physiological stability and best extracranial organ function until organ retrieval; withdrawing treatment and determining death in DCD; and caring for the family of the deceased irrespective of whether donation took place.

KEYWORDS

Organ donation
donors and donation: deceased
determination of death
brain death
donation after circulatory death
professional ethics

donation or procurement agencies and (if needed) with transplant services; discussing organ donation with the family; maintaining physiological stability and best extracranial organ function until organ retrieval; with drawing treatment and determining death in DCD; and caring for the family of the deceased irrespective of whether organ donation takes place.[22] Intensivists who do not accept these responsibilities should ensure that other colleagues are available to fulfil these roles.

CARE OF THE DYING PATIENT AND THEIR FAMILY

Intensive care staff are familiar with caring for dying patients[24] and their families, including respecting the humanity of the patient, maintaining their dignity and avoiding suffering. These values are made manifest by (inter alia) 'patient comfort care' provided by the nursing staff, continued involvement and attentiveness of the medical staff, good communication with the family and the evident compassion of all ICU staff for the patient and their family.[25]

Patient- and family-centred care requires good communication with the patient (if possible) and the family, within an atmosphere of mutual trust and respect. This is a shared responsibility of the staff and the family but the intensivist should show leadership in establishing rapport during an early meeting (e.g. the morning after admission) with the family of every intensive care patient, particularly for families of patients at high risk of death or disability, where serious issues will be addressed in subsequent meetings as the patient's situation becomes clearer. Family meetings should include an intensivist and nurse, (preferably the 'bedside nurse' looking after the patient), the self-defined family, and if the family wishes, a chaplain, social worker or cultural health worker. The intensivist should accept responsibility for leading the meeting, including being the 'bearer of bad news', and ensure that the nurse is able to be focused on being supportive of the family (while being attentive to whether the intensivist and family appear to share a common understanding). Family meetings should be held in a private room of appropriate size away from the bedside and protected from interruption. The intensivist should convey an accurate account of the sequence of events and the patient's current condition, a realistic prognosis (as far as this is possible) and the immediate treatment plan. Explicit acknowledgment of the shared responsibility of the treating team and the family to act in the best interests of the patient may help in establishing rapport. There must be enough time for family members to speak freely[26] and for their questions to be answered. Before ending the meeting the intensivist should ascertain that the family have expressed all that they want to at this time, that they understand what has been said[25] and agree with the immediate treatment plan. Ensuring that all staff give congruent messages is crucial in maintaining the trust of the family in the treating team. Ideally, one intensivist should speak with the family, but if this is not possible there must be a careful and detailed 'handover' between one intensivist and another about communication with the family. Mutual understanding and trust will help the ICU team and the family work through the most difficult and painful issues, including withdrawal of intensive therapies,[27] and the death of the patient. Discussion of organ donation in the context of such a strong therapeutic relationship becomes (comparatively) straightforward.

Many patients who develop apparent loss of brainstem function do so during a period of active surgical and medical treatment. In these circumstances, formal assessment of brain death should be undertaken after first ensuring that the necessary preconditions for brain death assessment[22] have been met. This includes stopping sedatives, opioids, neuromuscular blockers, hypothermia and other potentially confounding therapies, while maintaining extracranial physiological stability. If preconditions cannot be met for clinical determination of brain death, appropriate imaging showing absent cerebral blood flow should be performed.[22] These actions also preserve the future possibility of organ donation after brain death.

Withdrawal of intensive therapies is common practice in ICUs worldwide.[24,28] Before recommending withdrawal of therapy in the setting of severe brain damage it is essential to establish prognosis to the best possible extent. An unconfounded clinical assessment of central nervous system (CNS) function, imaging (usually CT but increasingly supplemented by magnetic resonance imaging in some conditions; e.g. diffuse axonal injury) and neurophysiology (in particular short-latency somatosensory evoked potentials) all provide important information. During the period of sedative-free CNS assessment, some patients lose apparent brainstem function. If brain death does not occur but devastating brain damage has clearly occurred, those treating the patient (e.g. intensivists, neurosurgeons and others) should achieve a consensus view of prognosis and a recommended treatment plan, which might include withdrawal of intensive treatments (e.g. artificial airway, ventilatory or inotropic support, further neurosurgery). The intensivist should then discuss the prognosis and a recommended plan with the family and facilitate a consensus. Withdrawal of treatment may subsequently occur, either because death is seen to be imminent and inevitable or because the likely survival outcome would not be in accord with the patient's previously expressed wishes or inferred best interests. It is appropriate to withdraw all intensive therapies from such patients, while continuing to provide 'comfort care' to the patient and support to the family.[29] The possibility of future organ donation must not influence the decision to limit or withdraw treatment. Some patients having intensive treatments withdrawn will die within a time frame (e.g. a 'few' hours) that makes DCD a possibility.

Prediction of death after withdrawal of therapy within a time frame that makes DCD possible is necessarily imprecise as some crucial factors (e.g. airway patency after extubation) cannot be prospectively assessed reliably. However, some combination of inadequate airway patency, ventilator-dependence, deep coma and impaired brainstem function[30,31] are strong predictors of earlier death after withdrawal of intensive therapies. Severe cardiopulmonary dysfunction is also predictive but is present in relatively few patients in whom treatment is being withdrawn because of severe brain damage. Organ donation medical specialists with intensive care expertise may assist intensivists in prediction of death within a time frame permitting DCD, and discussion with such professionals is recommended. Where there are no medical reasons why DCD seems not to be potentially feasible, it is appropriate to discuss DCD with the patient's family. However, the possibility of DCD must not be raised by the treating team before the family and the treating team have reached a consensus that treatment will be withdrawn.[22] Increasingly, families of dying patients volunteer that they (or the patient) would wish for organ donation to take place. These views are commonly expressed before the determination of brain death in patients who seem to have lost brainstem function, but can be expressed before then and even prior to a decision that intensive treatments will be withdrawn. The intensivist should sensitively acknowledge these statements and assure the family that this issue will be addressed, without further family prompting, if and when clinical circumstances are appropriate.[22]

IDENTIFICATION OF THE POTENTIAL FOR ORGAN DONATION TO OCCUR

Most ICUs admit ventilated patients with very severe brain damage whose probability of recovery is low, but this practice will identify any (small) sub-group of patients with reversible conditions and then can provide them with the necessary treatment to facilitate their recovery. There are, however, more extreme situations when the chance of acceptable recovery is so remote that neither investigation (CT scanning, usually following intubation and ventilation), active treatment (osmotherapy and emergency surgery) nor admission of the patient to the ICU[32] would usually occur. Some ICUs now routinely admit these patients, either because providing them (and their family) with good end-of-life care in an emergency department is not readily achievable, or solely for the possibility that organ donation might subsequently occur. Some patients have been admitted to the ICU after later deterioration from other wards (e.g. neurology) when possible future organ donation was not considered in the emergency department. 'Routinely' admitting all such patients to the ICU has been called for by some and could probably be expected to increase the number of organs available for transplant,[33] but various ethical, legal and clinical concerns have been raised about such practice.[34–37] Some have suggested that ICU admission should be 'automatic' (i.e. without prior family discussion) for these patients while some intensivists (including this author) admit these patients only with the informed agreement of the family – including an understanding that possible future organ donation is the only reason to admit the patient to the ICU; that organ donation might not be possible; and that the family are prepared to consider organ donation in the near future should clinical circumstances permit it. This is an area within which there is considerable clinical practice variation and no apparent professional consensus on the appropriate extent of transparency in particular.

Organ donation is possible in most situations where brain death has been confirmed or when death occurs very soon after withdrawal of treatment. The rare absolute contraindications to organ donation are when there is an unacceptably high risk of transmission of disease to the recipient (usually because of malignancy or infection), or when the long-term function of all possible donated organs is likely to be unacceptably poor.

Tissue donation (including eyes for corneas and sclera, heart valves and vascular tissue, skin and bone) is also frequently possible in most patients dying in ICUs, including from those who cannot donate organs. Because of the relative benefits and risks to recipients of donated organs and tissues, tissue donation may not be possible in some circumstances where organ donation is acceptable (e.g. low-risk possible food exposure to variant Creutzfeldt-Jakob disease).

Although current haematological or metastatic malignancy remain absolute contraindications to donation, advanced age (e.g. over 80), most treated bacterial sepsis, treated herpes simplex virus encephalitis, positive hepatitis C virus (HCV), hepatitis B virus and even HIV serology, and 'likely cured' malignancies (even some melanoma) are no longer so.[38]

Effective and non-toxic antiviral therapy for HCV has enabled transplantation of organs from HCV-infected donors to HCV-naïve recipients[39] with subsequent curative therapy, despite immunosuppression. Similarly, organs from HIV-positive donors have been transplanted into HIV-positive recipients with acceptable outcomes.[40] Finally, organ-specific relative contraindications to organ donation have reduced as the outcomes of recipients transplanted with donor organs previously considered unacceptable continues to improve. In lung transplantation, for example, some centres accept lungs with severe acute (reversible) dysfunction, and use extra-corporeal membrane oxygenation (ECMO) electively to support the recipient immediately after transplant. As transplant centres have somewhat different acceptance criteria, which themselves continue to change in a more permissive direction, intensivists should discuss possible absolute and organ-specific contraindications to donation

and subsequent transplantation with the appropriate organ donation or procurement agency (who will liaise with transplant services as required) and not decide independently that donation in general or donation of any particular organ is contraindicated on medical grounds. The intensivist should ensure that the information necessary for these decisions is provided.

INFORMATION LIKELY TO BE REQUIRED BY TRANSPLANT TEAMS

- Age, sex, weight, approximate height
- Medical and social history (including co-morbidity, surgery, medication, alcohol, smoking, illicit drug use, tattoos, body piercing, sexual history and allergies)
- Detailed clinical history of fatal illness (including cause of death, history of cardiac arrest, periods of hypotension or hypoxia, evidence of aspiration or sepsis)
- Current clinical status (including physiological parameters and the extent of ventilatory and inotropic support)
- Current investigations (including blood group, arterial blood gases, chest X-ray, electrocardiography, serum urea, creatinine, electrolytes, glucose, bilirubin, transaminases, alkaline phosphatase and γ-glutamyl transpeptidase, prothrombin ratio, activated partial thromboplastin time, haemoglobin, white cell count, platelets and all microbiology results)
- Other investigations may sometimes be required (e.g. echocardiogram, coronary arteriogram, bronchoscopy, additional CT scanning, urinary protein to creatinine ratio, lipase and/or amylase).

In most jurisdictions, an appropriate authority (e.g. a coroner or medical examiner) may legally interdict organ donation under certain circumstances (e.g. homicide) and this issue must also be clarified before donation proceeds. Additional processes may facilitate the agreement of a coroner or medical examiner, including, for example, whole-body CT scanning before organ retrieval, having a forensic pathologist attend the organ retrieval surgery and having the retrieval surgeon provide a detailed record of the organ retrieval surgical findings.

DETERMINATION OF BRAIN DEATH

This is a clinical responsibility of the intensivist and must be carried out according to appropriate codes of practice. Although there are no universal criteria for the determination of brain death, codes of practice around the world are very similar and all require[22,41,42] (at least) these three elements:

1. Establishing the presence of a condition known to produce severe and irreversible structural brain damage
2. Excluding possible confounding factors
3. Determining, by clinical examinations (usually by two independent doctors), that there is profound unresponsive coma and persistent absence of brainstem function.

The clinical examination for the determination of brain death is facilitated by a proforma,[22] which should be included in the medical record. When clinical examination is not possible (e.g. when it is confounded by medications or when brainstem reflexes cannot be examined or, rarely, when testing for apnoea cannot be performed because of very severe respiratory failure), then the absence of cerebral blood flow must instead be demonstrated by reliable imaging.[22] Clinical determination of brain death is possible in patients receiving ECMO if preconditions are fulfilled. Oxygenation can be maintained while establishing that apnoea is present despite hypercarbia by sharply reducing the sweep gas flow and measuring $PaCO_2$ at intervals until after adequate hypercarbia has occurred.[43]

The intensivist should convey the fact of brain death and its medical and legal implications to the family. It can be difficult to accept brain death as death, given the life-like appearance of the skin, the rise and fall of the chest and the warmth of the hands that are preserved by ventilatory and circulatory support. Some family members will accept an offer to view the clinical examination for brain death (with prior careful explanation of the possibility of spinal reflexes), or the cerebral blood flow study when clinical examination is confounded. This may help some to understand and accept the final awful implication of this diagnosis.[44] Intensivists should be open to offering these options. In the absence of organ donation, it is appropriate to remove ventilatory support after brain death when family needs have been met.

DONATION AFTER CIRCULATORY DEATH

DCD, previously known as non-heart-beating donation, is increasing around the world. Kootstra and colleagues from Maastricht[45] described four categories of 'non-heart-beating' donors.

CATEGORIES OF DONATION AFTER CIRCULATORY DEATH

Category I: those who are dead on arrival

Category II: those in whom cardiopulmonary resuscitation is ceased

Category III: those in whom cardiac arrest is expected to occur soon

Category IV: those who have cardiac arrest while brain dead.

In all but Category III the situation is 'uncontrolled'. DCD practice varies considerably worldwide. Almost all DCD donors in the United Kingdom, United States, Canada and Australasia are Category III donors (a

small number are Category IV). Category III donors are also most common in the Dutch experience but donation from Category I and II is increasing.[46] By contrast, in Spain, withdrawal of treatment in the ICU is less common than in Holland or the United Kingdom[47]; most DCD donors are Category I and II,[48] but Category III donors are increasing.

The legal, ethical and medical issues raised by DCD have been widely explored.[22,45,49,50] These include ensuring that there has been a consensus decision to withdraw treatment before organ donation is discussed with the family; estimating the likelihood of death within a timeframe after the withdrawal of treatment that makes donation possible; using agents (e.g. heparin) and procedures (e.g. instrumentation) prior to death that are for 'organ benefit only'; locating where the withdrawal of treatment will take place (ICU, operating room or other location); having the presence of family members there after the withdrawal of treatment; using opioids and sedatives after the withdrawal of treatment; separating clinical responsibility for end-of-life care (including opioids, sedatives and determination of death) from the responsibility for organ procurement; knowing the exact method used for the determination of death; the timing of organ removal after death; knowing the procedure to be followed if the patient does not die within a timeframe where donation is possible; ensuring that the family are fully informed and supported throughout the process; ensuring that all participating personnel are familiar with, and accepting of, DCD procedures; and ensuring that agreed protocols that explicitly address all of these issues are in place. Several national guidelines or recommendations have been produced that address these issues.[22,49,51–56] DCD should take place only after broad clinical, ethical and societal consensus has been achieved and expressed in such a document. Where such a measured process has been followed, DCD has been viewed favourably by both families and hospital staff and has modestly increased the number of organs available for transplant.

DCD after euthanasia was first reported from Belgium,[57] and more recently a combined protocol for euthanasia and DCD has been produced.[58] Demand is growing, apparently inexorably, for legislation sanctioning 'voluntary euthanasia', 'assisted suicide' and – more recently – 'physician-assisted dying' in various jurisdictions including Canada, Australia and New Zealand. Intensivists should be aware that these practices are likely to lead to calls for their involvement in facilitating DCD donation in these circumstances and should prepare a coherent and principled response.[59]

Delayed graft function is more common in recipients of DCD kidney grafts, and long-term graft and recipient outcomes – although similar[60] – may not be quite as good as after a graft from a brain-dead donor.[61] Compared to with DBD liver grafts, lower graft, patient survival and higher rates of biliary complications are commonly reported with DCD liver grafts, but these differences are probably reducing. Recipient and graft outcomes after pancreas[63] and lung transplantation[64] from DCD donors are similar to those after DBD, and similar findings seem likely in DCD heart transplantation[65] although experience remains limited. A number of strategies, in particular ex-vivo normothermic organ perfusion,[66] seem to hold promise for improving the function of many organs (particularly heart, liver and kidney) retrieved after DCD and are likely to soon become more widespread.

DISCUSSION OF ORGAN DONATION WITH THE FAMILY

Organ donation (from deceased donors) is an activity that takes place at the end of life, usually in an ICU. Organ donation is not part of transplantation, which is concerned with the care of patients with end-stage organ failure who may receive organ transplants. Appreciating this distinction allows an analysis of important issues that are not often discussed in transplant-oriented publications. Organ donation fundamentally modifies human rituals at the time of death, even of death in the ICU. Organ removal is an invasive procedure carried out in the operating room. Although done respectfully and with identical surgical processes to those used on living people, it is nevertheless viewed by some as 'mutilating'. Discussion of organ donation is an emotionally intense activity involving a family and a health professional, and requires very clear and sensitive communication. This discussion takes place in the midst of grief – when family members are experiencing the death of a family member. Awareness even of transplantation varies widely in the community and there is even less knowledge of organ donation processes. Some families may not previously have known that organ donation and transplantation occur! Similarly, discussion of and support for organ donation vary widely in the community. There is greater support of 'organ donation in principle' than either individual willingness to donate or willingness to agree to donation on behalf of a family member. Discussion of organ donation among families is promoted as a way of increasing organ donation rates and it may do so. However, some family members hold strong views against organ donation based on personal, spiritual, religious or cultural beliefs.[67] There are utilitarian views about organ donation including the notion that organ donation is the only possible 'positive' outcome that can occur in the setting of brain death[68]; that it is appropriate to refer to dead or dying persons in a utilitarian way as sources of organs for transplant[69]; that organ donation can 'help the next of kin cope with grief'[70]; and that fulfilling the previously expressed wishes of the donor should be the primary or indeed the only[71] consideration. In some jurisdictions these wishes have been deemed legally sufficient for organs

to be retrieved, and are often assumed to be a means of increasing the organ donation rate[72] by excluding the family from the opportunity to prohibit organ donation and 'returning control to the individual'. This assumption may well be erroneous.[73,74] Many countries have defined the status of an individual's wishes about organ donation after their death as constituting legally sufficient 'consent'. However, the validity of the concept of 'consent' can be questioned as the person is dead at the time that the issue is real and because current 'register-based' records of such wishes do not meet accepted standards for informed consent[75] in a personal health care context.[76] Implicit in a 'transplant-oriented' value system is the view that for a family to agree to organ donation is both desirable and of greater moral value ('the right thing to do') than the contrary decision, particularly if organ donation was the previously expressed wish of the dead person. This view, in which close family relationships[77] give no legitimacy to the family to determine what should happen to their loved one after death, is now explicitly acknowledged, practised and advocated by many organ procurement organisations including in the United States and increasingly in the United Kingdom. Similar views are increasingly expressed in Canada, Australia and New Zealand. However, even in countries that legally allow the previously expressed wishes of the deceased to determine whether organ donation may take place, usual practice continues both to involve the family and not to proceed against family objection – accepting that the impact on the deceased's family remains paramount in consent practice.[78]

In many countries, this has resulted in the evolution, exposition and advocacy of strategies to overcome 'refusal to donate'[79] and to thereby achieve 'target conversion rates'. Possible adverse effects of such strategies on family bereavement[80] are not reported by those who advocate for them and whose sole measure of 'quality', 'success' or even 'best practice' in organ donation practice is the proportion of situations in which donation occurs. Intensivists should reflect on their own views on these matters, and be aware of the views of others who might discuss organ donation with family members. Although intensivists continue to most often initiate discussion of organ donation with families in Australasia, this is becoming less common there and in other jurisdictions. Whoever undertakes this discussion should be skilled in communication with grieving people. In Australasian clinical practice, the intensivist has already established a relationship with the family, involving mutual trust and respect, in prior family meetings during the patient's final illness. This relationship naturally allows the intensivist to initiate and facilitate discussion of organ donation. Describing this encounter as 'discussing organ donation' rather than 'obtaining consent' (or 'seeking consent' or even 'persuasion')[81] is not 'organ focused' or coercive in language and enables the intensivist to provide complete and unbiased information and to support the family in their decision making, whatever they might decide about donation.

The intensivist must ensure that the fact of death (in the situation of brain death) is understood. When (Category III) DCD is a possibility, there must be prior consensus agreement by the family and the treating team that treatment must be withdrawn before the option of possible organ donation is raised by the intensivist. The patient is clearly not dead at this time, although death is certainly anticipated to be imminent. This imminent death should also be understood by the family before the option of DCD is offered. There must be sufficient time for the intensivist to inform the family about what organ donation entails (including the subsequent benefits to transplant recipients of those organs), to answer any questions and, if necessary, to facilitate decision making by the family. The discussion may take into account previously expressed wishes, previous family discussions, and the values and beliefs of the patient and family members. Some language is particularly insensitive from the perspective of grieving families and should be avoided[22] (e.g. the use of the term 'harvest'[82] rather than 'organ retrieval' to describe the process of organ retrieval, or 'the body' rather than the person's name to describe the brain-dead person). Increasingly, intensivists are being expected to facilitate the involvement of other people in this discussion – including members of organ procurement agencies and others with specific training about this discussion – with the implicit or explicit aim of 'increasing the consent rate' – to a 'target'. Various models are advocated including 'collaborative requesting', where both ICU staff and others are involved and the 'designated or trained requestor' model wherein ICU staff introduce the 'requestor' and take no part in the discussion of donation. Highly explicit strategic plans have been developed, most notably – but not exclusively – in the United States, to achieve 'target consent rates'. Although such an approach has been reported to 'increase organ donation' in non-randomised time series and other observational studies,[83-85] this was not found in the only randomised controlled trial (RCT) of 'collaborative requesting' so far conducted.[86] 'Repeated requesting' has been reported to increase the number of families who agree to donate and language that is variously persuasive or coercive (e.g. 'fulfilling the deceased's wishes', 'doing what he would have wanted', 'something good may come of this', 'many families take comfort in donation', 'there are many people dying on waiting lists, including in your community') might also achieve that objective. It is increasingly evident that 'conversion-rate'-focused approaches are beginning to dominate the discussion of donation with families, despite – and in the face of – ongoing moral distress in many intensivists, including this author.

The intensivist should facilitate the family spending time at the bedside prior to organ removal if they

wish. Some investigations (e.g. echocardiography or bronchoscopy) may be performed during this time and the family should be informed about these. The intensivist should ensure that the family is offered the opportunity to spend time with the deceased after organ removal.

MAINTENANCE OF EXTRACEREBRAL PHYSIOLOGICAL STABILITY IN BRAIN DEATH

Immediately prior to brain death there is often a limited period of hypertension, tachycardia and occasionally dysrhythmia, mediated by both autonomic activity and catecholamine secretion. Pulmonary oedema, cardiac dysfunction and myocardial injury may develop and may have implications for subsequent heart and lung graft function.[87] Treatment of this temporary sympathetic phenomenon should preferably be with short-acting agents acting only on the circulation (e.g. esmolol). Cardiac arrest rarely occurs during this phase, usually due to tachydysrhythmia, but is often reversible. Hypertension is soon followed by hypotension (which may be profound in the presence of hypovolaemia or cardiac dysfunction) and can lead to cardiac arrest or loss of donor organ viability. Blood pressure (e.g. in adults a mean arterial pressure [MAP] of ~70 mm Hg (9.31 kPa)) should be maintained with inotropic support and volume expansion. Diabetes insipidus soon occurs in most but not all brain-dead persons, which is manifest by brisk hypoosmolar polyuria, leading quickly to hyperosmolality and later to hypovolaemia if untreated.

After loss of cerebral metabolism there is a fall of around 25% in oxygen consumption and carbon dioxide production[88] so that less ventilatory minute volume is necessary for normocarbia. The fall in energy expenditure (heat production) together with the loss of vasomotor tone and loss of possible thermogenesis from shivering exacerbate the risk of hypothermia. Spontaneous movements and spinal motor reflexes commonly persist in brain death[22] and rarely include bizarre movements, which are often reproducible. Family members may be offered the opportunity to view the (perhaps second) clinical examination for brain death and should be warned about the possibility of these responses (which may not have occurred at the first examination) and given a prior explanation of them. These movements and sympathetic circulatory responses can also occur during organ retrieval in the operating room. The use of neuromuscular blockade and other agents (including opioids) is therefore recommended in the operating room.[22]

STRATEGIES FOR MAINTAINING PHYSIOLOGICAL STABILITY

The onset of brain death is usually heralded by rises in intracranial pressure (if measured), hypertension and tachycardia, and progressive loss of brainstem function (coma, pupillary dilatation). These features should initiate preparation for specific support strategies, which include ensuring that central venous access, inotropic support, intravenous access for rapid volume expansion, desmopressin and a source of external heat (e.g. a warming blanket) are all available.

VENTILATORY MANAGEMENT

The aims of ventilatory management are to maintain good oxygenation and normocarbia, to minimise circulatory depression and to maintain, if possible, sufficiently good lung function to allow for future lung donation to occur. Usual pulmonary care including changes of position and sterile endotracheal suctioning must continue. When pulmonary dysfunction is severe, high levels of positive end-expiratory pressure (PEEP) may be required to prevent airway frothing or to provide adequate oxygenation. Establishing that there is apnoea at hypercarbia in such patients may require mechanical hypoventilation prior to apnoea and continuous positive end-expiratory pressure (CPAP) during it. Compared with a conventional ventilatory strategy, the use of a lung-protective strategy (including tidal volumes of 6–8 mL/kg of predicted body weight, PEEP of 8–10 cm H_2O, testing for apnoea on CPAP rather than at zero end-expiratory pressure, and closed-circuit airway suction) has been shown in an RCT[89] to substantially increase both the number of potential lung donors meeting suitability criteria at 6 hours and the number of actual lung donors, with similar 6-month recipient survival. In a matched cohort study, oxygenation impairment remained 2 hours after an apnoea test at zero end-expiratory pressure, but a recruitment manoeuvre immediately after the apnoea test was associated with no such impairment.[90] Although a Pa_{O_2} of more than 300–350 mm Hg (40–46.5 kPa) on 100% oxygen and 5 cm H_2O PEEP was once thought essential for lung donation, more seriously impaired oxygenation (and the use of higher PEEP) have been found acceptable[91] and some transplant centres increasingly use ECMO to electively support recipients of lungs with more serious but reversible impairment with acceptable outcomes.[92]

CIRCULATORY AND METABOLIC MANAGEMENT

The aims of circulatory management are to maintain adequate organ perfusion and arterial pressure without fluid overload or harmful vasoconstriction, and without prejudicing cardiac donation where this might be possible. Reasonable initial haemodynamic goals include normotension (e.g. MAP >70 mm Hg [9.31 kPa]), heart rate of less than 100 beats/min, and central venous pressure of ~8 mm Hg (1.06 kPa). Some inotropic support is usually required. Having established normotension with an inotrope infusion, the haemodynamic response to a volume challenge should be assessed. The choice of inotrope is the subject

of more controversy than evidence. Dobutamine is not recommended. In Australasia norepinephrine (noradrenaline) is preferred and dopamine is seldom used, without apparent harm to organ function in recipients. Low-dose dopamine infusion (4 μg/kg/min) has been shown in an RCT to slightly increase urine volume without effecting serum creatinine and infusion (for ~6 hours in the donor) was associated with a slight reduction in the number of recipients receiving multiple dialyses before renal function recovered.[93] Epinephrine (adrenaline) may have a specific benefit on renal blood flow in brain death,[94] but may also increase glycaemia and thereby osmotic diuresis. Catecholamine infusion may reduce the up-regulation of organ immunogenicity that occurs in brain death and lower the incidence of acute rejection in subsequent recipients of kidney grafts.[95] Although levels of thyroid hormones fall after brain death, this is probably the 'sick euthyroid syndrome' and replacement of the thyroid hormone does not improve the circulation after brain death.[96] Importantly, and highlighting the potential for bias in non-randomised studies in organ donation, this systematic review found that benefit was shown in all 16 separate case series or retrospective audits of the use of thyroid hormones but in none of the seven RCTs.[96] Corticosteroids are often given just prior to organ removal from brain-dead donors and commonly recommended (again on the basis of retrospective analyses) to increase the number of organs, particularly thoracic organs, retrieved and transplanted. Although steroids improved the haemodynamics in an experimental model[97] and in a human RCT,[98] this did not translate into an increased number of organs procured[98] nor did an earlier RCT[99] show any benefit in kidney graft outcomes. Treatment of brain-dead liver donors with high-dose methylprednisolone (~1.6 g over ~14 hours) did not alter the use of fluids and catecholamines compared with a non-steroid group, but it was associated with lower serum levels of inflammatory cytokines in the donors, together with lower recipient transaminase levels in the early post-transplant period and a reduced incidence of acute rejection within 6 months.[100]

Two recent systematic reviews[101,102] of trials of corticosteroids did not find any evidence of benefit. Similarly, two RCTs of the combination of steroid and tri-iodothyronine (T3) did not show beneficial circulatory effects.[103,104] Vasopressin infusion can eliminate or substantially reduce the amount of catecholamine required to support arterial pressure[104,105] without apparent detriment to subsequently transplanted organs. Control of excessive polyuria will minimise the risks of developing hyperosmolality, hypovolaemia or hyperglycaemia secondary to infusion of large amounts of dextrose-containing fluids. Synthetic desmopressin (1-D amino-8 D arginine vasopressin) is commonly given to control diabetes insipidus and appears safe and effective.[106] Control of diabetes insipidus is an essential aspect of rational fluid therapy, and hypovolaemia should be corrected with resuscitation fluids.

The use of so-called 'hormonal resuscitation'[107] (combined use of T3, steroid and vasopressin) continues to increase[108] and continues to be advocated for on the basis of retrospective reports with multiple logistic regression,[109,110] despite no benefit being shown in an RCT in 80 potential cardiac donors.[104] This study did show haemodynamic improvement after brain death occurred with time in both arms of the trial, and that 14/40 hearts initially considered unsuitable for transplant were suitable 6 hours later, suggesting that a determination of unsuitability for heart donation should not be made early after brain death.

Haemoconcentration occurs early after experimental brain death. Crystalloid infusion has been reported to worsen pulmonary function in brain death and somewhat larger volumes will be required than if colloid is used.[111] At least moderate anaemia is well tolerated in brain death, but red cells may be given if needed to maintain packed cell volume at around 0.25 pending organ retrieval. Free water should be given as necessary (1–2 mL/kg/h as 5% dextrose) to maintain serum osmolality in the range of 280–310 mOsm/kg, corresponding to serum sodium below 155 mmol/L. Severe hyperosmolality (probably a marker of inadequate donor care) is associated with poor graft function in subsequent liver recipients.[112] Low-dose insulin infusion is commonly required to prevent hyperglycaemia. Failure to control diabetes insipidus will lead to increased requirements of free water to control serum osmolality, and if large amounts of 5% dextrose are used for this then hyperglycaemia and osmotic diuresis may result. Serum potassium should be kept above 3.5 mmol/L, but correction of hypophosphataemia does not improve haemodynamics in brain death.[113] Oxygen consumption, carbon dioxide production, heat production and glucose oxidation all fall in brain death owing to the loss of cerebral metabolic activity.[88] Hypothermia may readily develop in association with vasoparesis, loss of shivering, exposure to room temperature, warm polyuria and infusion of room temperature intravenous fluids. Core temperature should be kept above the 35–36.5°C required to confirm brain death.[22] Keeping the ambient temperature high (~24°C) and using infusion fluid warmers, heated humidifiers and external warming systems may be required.

AFTERCARE OF THE DONOR FAMILY

Routine aftercare is increasingly recommended[114] for all families of patients who die in ICUs. Aftercare programmes are well received[25] and have the potential to improve the care of subsequent families by revealing areas of inadequate or inappropriate communication. There may be issues specific to organ donation that

need to be addressed, sometimes by way of a family meeting with an intensivist at some later stage. Most organ donation agencies provide donor families with ongoing emotional support (which may extend over many years), provide them with limited anonymous information about the recipients, and accept and facilitate limited anonymous communication (i.e. by letter) between the recipients and the donor families by mutual consent; direct contact is not recommended.[22]

KEY REFERENCES

1. Sayegh MH, Carpenter CB. Transplantation 50 years later – progress, challenges, and promises. *N Engl J Med*. 2004;351(26):2761–2766.
6. International Summit on Transplant Tourism and Organ Trafficking. The declaration of Istanbul on organ trafficking and transplant tourism. *Clin J Am Soc Nephrol*. 2008;3(5):1227–1231.
12. Kramer AH, Baht R, Doig CJ. Time trends in organ donation after neurologic determination of death: a cohort study. *CMAJ Open*. 2017;5(1):E19–E27.
20. Pearson IY, Zurynski Y. A survey of personal and professional attitudes of intensivists to organ donation and transplantation. *Anaesth Intensive Care*. 1995;23:68–74.
21. Bøgh L, Madsen M. Attitudes, knowledge, and proficiency in relation to organ donation: a questionnaire-based analysis in donor hospitals in northern Denmark. *Transplant Proc*. 2005;37(8):3256–3257.
22. Australian and New Zealand Intensive Care Society. *The ANZICS statement on death and organ donation. Melbourne: ANZICS*. Online. Available via: http://www.anzics.com.au/.
23. Manyalich M, Cabrer C, Valero R, et al. Transplant procurement management: a model for organ and tissue shortage. *Transplant Proc*. 2003;35(7):2533–2538.
24. Australian and New Zealand Intensive Care Society. *The ANZICS statement on care and decision-making at the end of life for the critically ill. Melbourne: ANZICS*. Online. Available via: http://www.anzics.com.au/.
25. Cuthbertson SJ, Margetts MA, Streat SJ. Bereavement follow-up after critical illness. *Crit Care Med*. 2000;28:1196–1201.
26. McDonagh JR, Elliott TB, Engelberg RA, et al. Family satisfaction with family conferences about end-of-life care in the intensive care unit: increased proportion of family speech is associated with increased satisfaction. *Crit Care Med*. 2004;32(7):1484–1488.
30. Wind J, Snoeijs MG, Brugman CA, et al. Prediction of time of death after withdrawal of life-sustaining treatment in potential donors after cardiac death. *Crit Care Med*. 2012;40(3):766–769.
31. Rabinstein AA, Yee AH, Mandrekar J, et al. Prediction of potential for organ donation after cardiac death in patients in neurocritical state: a prospective observational study. *Lancet Neurol*. 2012;11(5):414–419.
32. Le Conte P, Riochet D, Labastire L, et al. Identification of potential organ donors of advanced age in EDs. *Am J Emerg Med*. 2012;30(1):170–173.
37. Rady MY, Verheijde JL, McGregor JL. Scientific, legal, and ethical challenges of end-of-life organ procurement in emergency medicine. *Resuscitation*. 2010;81(9):1069–1078.
38. *Transplantation Society of Australia and New Zealand (TSANZ). Clinical guidelines for organ transplantation from deceased donors (Version 1.1 – May 2017*. Available at http://www.tsanz.com.au/organallocationguidelines/documents/ClinicalGuidelinesV1.1May2017.pdf.
41. Wijdicks EF. The diagnosis of brain death. *N Engl J Med*. 2001;344:1215–1221.
44. Tawil I, Brown LH, Comfort D, et al. Family presence during brain death evaluation: a randomized controlled trial. *Crit Care Med*. 2014;42(4):934–942.
45. Kootstra G, Kievit J, Nederstigt A. Organ donors: heartbeating and non-heartbeating. *World J Surg*. 2002;26:181–184.
47. Sprung CL, Cohen SL, Sjokvist P, et al. Ethicus Study Group. End-of-life practices in European intensive care units: the Ethicus Study. *JAMA*. 2003;290(6):790–797.
49. Academy of Medical Royal Colleges. *UK Donation Ethics Committee. An ethical framework for controlled donation after circulatory death*. December 2011. http://aomrc.org.uk/wp-content/uploads/2016/04/Ethical_framework_donation_circulatory_death_1211-3.pdf.
55. Gries CJ, White DB, Truog RD, et al. American Thoracic Society Health Policy Committee. An official American Thoracic Society/International Society for Heart and Lung Transplantation/Society of Critical Care Medicine/Association of Organ and Procurement Organizations/United Network of Organ Sharing Statement: ethical and policy considerations in organ donation after circulatory determination of death. *Am J Respir Crit Care Med*. 2013;188(1):103–109.
66. Morrissey PE, Monaco AP. Donation after circulatory death: current practices, ongoing challenges, and potential improvements. *Transplantation*. 2014;97(3):258–264.
75. Woien S, Rady MY, Verheijde JL, et al. Organ procurement organizations Internet enrolment for organ donation: abandoning informed consent. *BMC Med Ethics*. 2006;7:E14.
80. Kesselring A, Kainz M, Kiss A. Traumatic memories of relatives regarding brain death: request for organ donation and interactions with professionals in the ICU. *Am J Transplant*. 2007;7:211–217.
82. Streat S. No more 'harvesting' of organs. *BMJ*. 2014;349:g6174.
86. The ACRE Trial Collaborators. Effect of 'collaborative requesting' on consent rate for organ

donation: randomised controlled trial (ACRE trial). *BMJ*. 2009;339:b3911.
89. Mascia L, Pasero D, Slutsky AS, et al. Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. *JAMA*. 2010;304(23):2620–2627.
90. Paries M, Boccheciampe N, Raux M, et al. Benefit of a single recruitment maneuver after an apnea test for the diagnosis of brain death. *Crit Care*. 2012;16(4):R116.
93. Schnuelle P, Gottmann U, Hoeger S, et al. Effects of donor pretreatment with dopamine on graft function after kidney transplantation: a randomized controlled trial. *JAMA*. 2009;302(10):1067–1075.
96. Macdonald PS, Aneman A, Bhonagiri D, et al. A systematic review and meta-analysis of clinical trials of thyroid hormone administration to brain dead potential organ donors. *Crit Care Med*. 2012;40(5):1635–1644.
98. Pinsard M, Ragot S, Mertes PM, et al. Interest of low-dose hydrocortisone therapy during brain-dead organ donor resuscitation: the CORTICOME study. *Crit Care*. 2014;18(4):R158.
99. Chatterjee SN, Terasaki PI, Fine S, et al. Pretreatment of cadaver donors with methylprednisolone in human renal allografts. *Surg Gynecol Obstet*. 1977;145:729–732.
100. Kotsch K, Ulrich F, Reutzel-Selke A, et al. Methylprednisolone therapy in deceased donors reduces inflammation in the donor liver and improves outcome after liver transplantation: a prospective randomized controlled trial. *Ann Surg*. 2008;248(6):1042–1050. erratum in: *Ann Surg* 2011; 254(2):391.
101. Dupuis S, Amiel JA, Desgroseilliers M, et al. Corticosteroids in the management of brain-dead potential organ donors: a systematic review. *Br J Anaesth*. 2014;113(3):346–359.
102. D'Aragon F, Belley-Cote E, Agarwal A, et al. Effect of corticosteroid administration on neurologically deceased organ donors and transplant recipients: a systematic review and meta-analysis. *BMJ Open*. 2017;7(6):e014436.
104. Venkateswaran RV, Steeds RP, Quinn DW, et al. The haemodynamic effects of adjunctive hormone therapy in potential heart donors: a prospective randomized double-blind factorially designed controlled trial. *Eur Heart J*. 2009;30(14):1771–1780.


Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Sayegh MH, Carpenter CB. Transplantation 50 years later – progress, challenges, and promises. *N Engl J Med*. 2004;351(26):2761–2766.
2. Dienstag JL, Cosimi AB. Liver transplantation – a vision realized. *N Engl J Med*. 2012;367(16):1483–1485.
3. Abouna GM. Organ shortage crisis: problems and possible solutions. *Transplant Proc*. 2008;40(1): 34–38.
4. Hanto RL, Reitsma W, Delmonico FL. The development of a successful multiregional kidney paired donation program. *Transplantation*. 2008;86(12): 1744–1748.
5. Lucarelli G, Bettocchi C, Battaglia M, et al. Extended criteria donor kidney transplantation: comparative outcome analysis between single versus double kidney transplantation at 5 years. *Transplant Proc*. 2010;42(4):1104–1107.
6. International Summit on Transplant Tourism and Organ Trafficking. The declaration of Istanbul on organ trafficking and transplant tourism. *Clin J Am Soc Nephrol*. 2008;3(5):1227–1231.
7. Ambagtsheer F, Zaitch D, van Swaaningen R, et al. Cross-border quest: the reality and legality of transplant tourism. *J Transplant*. 2012;2012: 391936.
8. Canales MT, Kasiske BL, Rosenberg ME. Transplant tourism: outcomes of United States residents who undergo kidney transplantation overseas. *Transplantation*. 2006;82:1658–1661.
9. Bass D. Kidneys for cash and egg safaris – can we allow 'transplant tourism' to flourish in South Africa? *S Afr Med J*. 2005;95:42–44.
10. Limb M. Concerns raised over organ donation 'matching' website. *BMJ*. 2012;345:e5944.
11. Limb M. Organ matching website says it will operate within the law. *BMJ*. 2012;345:e6030.
12. Kramer AH, Baht R, Doig CJ. Time trends in organ donation after neurologic determination of death: a cohort study. *CMAJ Open*. 2017;5(1):E19–E27.
13. *ANZOD Registry Report 2016 Australia and New Zealand Organ Donation Registry Adelaide, South Australia*. Available at: http://www.anzdata.org.au/anzod/ANZODReport/2016/2016-anzod-full-report-final_v1.0_20170115.pdf.
14. Goldberg DS, Blumberg E, McCauley M, et al. Improving organ utilization to help overcome the tragedies of the opioid epidemic. *Am J Transplant*. 2016;16(10):2836–2841.
15. Cooper DJ, Rosenfeld JV, Murray L, et al. DECRA Trial Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med*. 2011;364(16): 1493–1502.
16. Hutchinson PJ, Kolias AG, Timofeev IS, et al. RESCUEicp Trial Collaborators. Trial of decompressive craniectomy for traumatic intracranial hypertension. *N Engl J Med*. 2016;375(12):1119–1130.
17. Cooper DJ, Nichol A, Hodgson C. Craniectomy for traumatic intracranial hypertension. (Letter). *N Engl J Med*. 2016;375(24):2402.
18. Arrich J, Holzer M, Havel C, et al. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *Cochrane Database Syst Rev*. 2012;(9):CD004128.
19. Nielsen N, Wetterslev J, Cronberg T, et al. TTM Trial Investigators. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med*. 2013;369(23):2197–2206.
20. Pearson IY, Zurynski Y. A survey of personal and professional attitudes of intensivists to organ donation and transplantation. *Anaesth Intensive Care*. 1995;23:68–74.
21. Bøgh L, Madsen M. Attitudes, knowledge, and proficiency in relation to organ donation: a questionnaire-based analysis in donor hospitals in northern Denmark. *Transplant Proc*. 2005; 37(8):3256–3257.
22. Australian and New Zealand Intensive Care Society. *The ANZICS statement on death and organ donation. Melbourne: ANZICS*. Online. Available via: http://www.anzics.com.au/.
23. Manyalich M, Cabrer C, Valero R, et al. Transplant procurement management: a model for organ and tissue shortage. *Transplant Proc*. 2003;35(7): 2533–2538.
24. Australian and New Zealand Intensive Care Society. *The ANZICS statement on care and decision-making at the end of life for the critically ill. Melbourne: ANZICS*. Online. Available via: http://www.anzics.com.au/.
25. Cuthbertson SJ, Margetts MA, Streat SJ. Bereavement follow-up after critical illness. *Crit Care Med*. 2000;28:1196–1201.
26. McDonagh JR, Elliott TB, Engelberg RA, et al. Family satisfaction with family conferences about end-of-life care in the intensive care unit: increased proportion of family speech is associated with increased satisfaction. *Crit Care Med*. 2004; 32(7):1484–1488.
27. Streat S. When do we stop? *Crit Care Resusc*. 2005;7: 227–232.
28. Yaguchi A, Truog RD, Curtis JR, et al. International differences in end-of-life attitudes in the intensive care unit: results of a survey. *Arch Intern Med*. 2005; 165:1970–1975.
29. Henig NR, Faul JL, Raffin TA. Biomedical ethics and the withdrawal of advanced life support. *Annu Rev Med*. 2001;52:79–92.
30. Wind J, Snoeijs MG, Brugman CA, et al. Prediction of time of death after withdrawal of life-sustaining treatment in potential donors after cardiac death. *Crit Care Med*. 2012;40(3): 766–769.
31. Rabinstein AA, Yee AH, Mandrekar J, et al. Prediction of potential for organ donation after

cardiac death in patients in neurocritical state: a prospective observational study. *Lancet Neurol*. 2012;11(5):414–419.
32. Le Conte P, Riochet D, Labastire L, et al. Identification of potential organ donors of advanced age in EDs. *Am J Emerg Med*. 2012;30(1): 170–173.
33. Riad H, Nicholls A, Neuberger J, et al. Elective ventilation of potential organ donors. *BMJ*. 1995;310: 714–718.
34. Manara A, Jewkes C. Intensive care units have good reasons not to do it. *BMJ*. 1995;311: 121–122.
35. *F versus West Berkshire Health Authority*. 1989: 2 All ER 545–51, HL.
36. Watkinson P, McKechnie S, Wilkinson D, et al. Actively delaying death to increase organ donation. *BMJ*. 2012;344:e1179.
37. Rady MY, Verheijde JL, McGregor JL. Scientific, legal, and ethical challenges of end-of-life organ procurement in emergency medicine. *Resuscitation*. 2010;81(9):1069–1078.
38. Transplantation Society of Australia and New Zealand (TSANZ). *Clinical guidelines for organ transplantation from deceased donors (Version 1.1 – May 2017*. Available at http://www.tsanz.com.au/organallocationguidelines/documents/ClinicalGuidelinesV1.1May2017.pdf.
39. Goldberg DS, Abt PL, Blumberg EA, et al. Trial of transplantation of HCV-infected kidneys into uninfected recipients. *N Engl J Med*. 2017;376(24): 2394–2395.
40. Muller E, Barday Z, Mendelson M, et al. Renal transplantation between HIV-positive donors and recipients justified. *S Afr Med J*. 2012;102(6): 497–498.
41. Wijdicks EF. The diagnosis of brain death. *N Engl J Med*. 2001;344:1215–1221.
42. Capron AM. Brain death – well settled yet still unresolved. *N Engl J Med*. 2001;344:1244–1246.
43. Goswami S, Evans A, Das B, et al. Determination of brain death by apnea test adapted to extracorporeal cardiopulmonary resuscitation. *J Cardiothorac Vasc Anesth*. 2013;27(2):312–314.
44. Tawil I, Brown LH, Comfort D, et al. Family presence during brain death evaluation: a randomized controlled trial. *Crit Care Med*. 2014;42(4): 934–942.
45. Kootstra G, Kievit J, Nederstigt A. Organ donors: heartbeating and non-heartbeating. *World J Surg*. 2002;26:181–184.
46. Peters-Sengers H, Homan van der Heide JJ, Heemskerk MBA, et al. Similar 5-year estimated glomerular filtration rate between kidney transplants from uncontrolled and controlled donors after circulatory death – a Dutch cohort study. *Transplantation*. 2017;101(6):1144–1151.
47. Sprung CL, Cohen SL, Sjokvist P, et al. Ethicus Study Group. End-of-life practices in European intensive care units: the Ethicus Study. *JAMA*. 2003;290(6):790–797.
48. de Gracia MC, Osorio JM, Pérez-Villares JM, et al. A new program of kidney transplantation from donors after cardiac death in Spain. *Transplant Proc*. 2012;44(9):2518–2520.
49. Academy of Medical Royal Colleges. *UK Donation Ethics Committee. An ethical framework for controlled donation after circulatory death*. December 2011. http://aomrc.org.uk/wp-content/uploads/2016/04/Ethical_framework_donation_circulatory_death_1211-3.pdf.
50. Haase B, Bos M, Boffa C, et al. Ethical, legal, and societal issues and recommendations for controlled and uncontrolled DCD. *Transpl Int*. 2016;29(7): 771–779.
51. Ridley S, Bonner S, Bray K, et al. Intensive Care Society's Working Group on Organ and Tissue Donation. UK guidance for non-heart-beating donation. *Br J Anaesth*. 2005;95:592–595.
52. Shemie SD, Baker AJ, Knoll G, et al. National recommendations for donation after cardiocirculatory death in Canada: donation after cardiocirculatory death in Canada. *CMAJ*. 2006;175:S1.
53. Bernat JL, D'Alessandro AM, Port FK, et al. Report of a national conference on donation after cardiac death. *Am J Transplant*. 2006;6: 281–291.
54. Reich DJ, Mulligan DC, Abt PL, et al. ASTS Standards on Organ Transplantation Committee. ASTS recommended practice guidelines for controlled donation after cardiac death organ procurement and transplantation. *Am J Transplant*. 2009; 9(9):2004–2011.
55. Gries CJ, White DB, Truog RD, et al. American Thoracic Society Health Policy Committee. An official American Thoracic Society/International Society for Heart and Lung Transplantation/Society of Critical Care Medicine/Association of Organ and Procurement Organizations/United Network of Organ Sharing Statement: ethical and policy considerations in organ donation after circulatory determination of death. *Am J Respir Crit Care Med*. 2013;188(1):103–109.
56. Antoine C, Mourey F, Prada-Bordenave E. Steering committee on DCD program. How France launched its donation after cardiac death program. *Ann Fr Anesth Reanim*. 2014;33(2): 138–143.
57. Ysebaert D, Van Beeumen G, De Greef K, et al. Organ procurement after euthanasia: Belgian experience. *Transplant Proc*. 2009;41(2):585–586.
58. Bollen J, de Jongh W, Hagenaars J, et al. Organ donation after euthanasia: a Dutch practical manual. *Am J Transplant*. 2016;16(7):1967–1972.
59. Allard J, Fortin MC. Organ donation after medical assistance in dying or cessation of life-sustaining treatment requested by conscious patients: the Canadian context. *J Med Ethics*. 2016;pii: medethics-2016-103460.
60. Metcalfe MS, Butterworth PC, White SA, et al. A case control comparison of the results of renal transplantation from heart-beating and

non-heart-beating donors. *Transplantation*. 2001;71: 1556–1559.
61. Lim WH, McDonald SP, Russ GR, et al. Association between delayed graft function and graft loss in donation after cardiac death kidney transplants – a paired kidney registry analysis. *Transplantation*. 2017;101(6):1139–1143.
62. Bohorquez H, Seal JB, Cohen AJ, et al. Safety and outcomes in 100 consecutive donation after circulatory death liver transplants using a protocol that includes thrombolytic therapy. *Am J Transplant*. 2017;17(8):2155–2164. doi:10.1111/ajt.14261.
63. Shahrestani S, Webster AC, Lam VW, et al. Outcomes from pancreatic transplantation in donation after cardiac death: a systematic review and meta-analysis. *Transplantation*. 2017;101(1):122–130.
64. Cypel M, Levvey B, Van Raemdonck D, et al. International Society for Heart and Lung Transplantation. International Society for Heart and Lung Transplantation Donation after Circulatory Death Registry Report. *J Heart Lung Transplant*. 2015;34(10):1278–1282.
65. Dhital KK, Chew HC, Macdonald PS. Donation after circulatory death heart transplantation. *Curr Opin Organ Transplant*. 2017;22(3):189–197.
66. Morrissey PE, Monaco AP. Donation after circulatory death: current practices, ongoing challenges, and potential improvements. *Transplantation*. 2014;97(3):258–264.
67. Chapman JR, Hibberd AD, McCosker C, et al. Obtaining consent for organ donation in nine NSW metropolitan hospitals. *Anaesth Intensive Care*. 1995;23:81–87.
68. Murphy L. Donation – a difficult but most important discussion. *Mich Health Hosp*. 1999;35:20–21.
69. Fisher J. An expedient and ethical alternative to xenotransplantation. *Med Health Care Philos*. 1999;2:31–39.
70. Marck CH, Weiland TJ, Neate SL, et al. Personal attitudes and beliefs regarding organ and tissue donation: a cross-sectional survey of Australian emergency department clinicians. *Prog Transplant*. 2012;22(3):317–322.
71. May T, Aulisio MP, DeVita MA. Patients, families, and organ donation: who should decide? *Milbank Q*. 2000;78:323–336.
72. Spital A. Mandated choice for organ donation: time to give it a try. *Ann Intern Med*. 1996;125: 66–69.
73. Lawlor M, Kerridge I, Ankeny R, et al. Public education and organ donation: untested assumptions and unexpected consequences. *J Law Med*. 2007;14:360–366.
74. Lawlor M, Billson FA. Registering wishes about organ donation may decrease the number of donors. *Med J Aust*. 2007;186:156.
75. Woien S, Rady MY, Verheijde JL, et al. Organ procurement organizations Internet enrolment for organ donation: abandoning informed consent. *BMC Med Ethics*. 2006;7:E14.
76. New Zealand Health and Disability Commissioner. *Code of Health and Disability Services Consumers Rights*. Wellington: Health and Disability Commissioner; 1996. Online. Available: http://www.hdc.org.nz/.
77. Cassell J. *Life and Death in Intensive Care*. Philadelphia: Temple University Press; 2005.
78. Wendler D, Dickert N. The consent process for cadaveric organ procurement: how does it work? How can it be improved? *JAMA*. 2001;285: 329–333.
79. Aldridge A, Guy BS. Deal breakers in the organ donation request process. *Health Mark Q*. 2008;23(4):17–31.
80. Kesselring A, Kainz M, Kiss A. Traumatic memories of relatives regarding brain death: request for organ donation and interactions with professionals in the ICU. *Am J Transplant*. 2007;7:211–217.
81. Siminoff LA, Gordon N, Hewlett J, et al. Factors influencing families' consent for donation of solid organs for transplantation. *JAMA*. 2001;286:71–77.
82. Streat S. No more 'harvesting' of organs. *BMJ*. 2014;349:g6174.
83. Shafer TJ, Wagner D, Chessare J, et al. US organ donation breakthrough collaborative increases organ donation. *Crit Care Nurs Q*. 2008;31(3): 190–210.
84. Simpkin AL, Robertson LC, Barber VS, et al. Modifiable factors influencing relatives' decision to offer organ donation: systematic review. *BMJ*. 2009;338:b991.
85. Lewis VJ, White VM, Bell A. Mehakovic E. Towards a national model for organ donation requests in Australia: evaluation of a pilot model. *Crit Care Resusc*. 2015;17(4):233–238.
86. The ACRE Trial Collaborators. Effect of 'collaborative requesting' on consent rate for organ donation: randomised controlled trial (ACRE trial). *BMJ*. 2009;339:b3911.
87. Deibert E, Aiyagari V, Diringer MN. Reversible left ventricular dysfunction associated with raised troponin I after subarachnoid haemorrhage does not preclude successful heart transplantation. *Heart*. 2000;84:205–207.
88. Bitzani M, Matamis D, Nalbandi V, Vakalos A, Karasakalides A, Riggos D. Resting energy expenditure in brain death. *Intensive Care Med*. 1999;25:970–976.
89. Mascia L, Pasero D, Slutsky AS, et al. Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. *JAMA*. 2010;304(23):2620–2627.
90. Paries M, Boccheciampe N, Raux M, et al. Benefit of a single recruitment maneuver after an apnea test for the diagnosis of brain death. *Crit Care*. 2012;16(4):R116.
91. Gabbay E, Williams TJ, Griffiths AP, et al. Maximizing the utilization of donor organs offered for lung transplantation. *Am J Respir Crit Care Med*. 1999;160:265–271.

92. Hartwig MG, Walczak R, Lin SS, et al. Improved survival but marginal allograft function in patients treated with extracorporeal membrane oxygenation after lung transplantation. *Ann Thorac Surg*. 2012;93(2):366–371.
93. Schnuelle P, Gottmann U, Hoeger S, et al. Effects of donor pretreatment with dopamine on graft function after kidney transplantation: a randomized controlled trial. *JAMA*. 2009;302(10):1067–1075.
94. Ueno T, Zhi-Li C, Itoh T. Unique circulatory responses to exogenous catecholamines after brain death. *Transplantation*. 2000;70:436–440.
95. Schnuelle P, Lorenz D, Mueller A, et al. Donor catecholamine use reduces acute allograft rejection and improves graft survival after cadaveric renal transplantation. *Kidney Int*. 1999;56:738–746.
96. Macdonald PS, Aneman A, Bhonagiri D, et al. A systematic review and meta-analysis of clinical trials of thyroid hormone administration to brain dead potential organ donors. *Crit Care Med*. 2012;40(5):1635–1644.
97. Lyons JM, Pearl JM, McLean KM, et al. Glucocorticoid administration reduces cardiac dysfunction after brain death in pigs. *J Heart Lung Transplant*. 2005;24:2249–2254.
98. Pinsard M, Ragot S, Mertes PM, et al. Interest of low-dose hydrocortisone therapy during brain-dead organ donor resuscitation: the CORTICOME study. *Crit Care*. 2014;18(4):R158.
99. Chatterjee SN, Terasaki PI, Fine S, et al. Pretreatment of cadaver donors with methylprednisolone in human renal allografts. *Surg Gynecol Obstet*. 1977;145:729–732.
100. Kotsch K, Ulrich F, Reutzel-Selke A, et al. Methylprednisolone therapy in deceased donors reduces inflammation in the donor liver and improves outcome after liver transplantation: a prospective randomized controlled trial. *Ann Surg*. 2008;248(6):1042–1050. erratum in: *Ann Surg* 2011; 254(2):391.
101. Dupuis S, Amiel JA, Desgroseilliers M, et al. Corticosteroids in the management of brain-dead potential organ donors: a systematic review. *Br J Anaesth*. 2014;113(3):346–359.
102. D'Aragon F, Belley-Cote E, Agarwal A, et al. Effect of corticosteroid administration on neurologically deceased organ donors and transplant recipients: a systematic review and meta-analysis. *BMJ Open*. 2017;7(6):e014436.
103. Mariot J, Jacob F, Voltz C, et al. Value of hormonal treatment with triiodothyronine and cortisone in brain dead patients. *Ann Fr Anesth Reanim*. 1991;10:321–328.
104. Venkateswaran RV, Steeds RP, Quinn DW, et al. The haemodynamic effects of adjunctive hormone therapy in potential heart donors: a prospective randomized double-blind factorially designed controlled trial. *Eur Heart J*. 2009;30(14):1771–1780.
105. Chen JM, Cullinane S, Spanier TB, et al. Vasopressin deficiency and pressor hypersensitivity in hemodynamically unstable organ donors. *Circulation*. 1999;100:II244–II246.
106. Guesde R, Barrou B, Leblanc I, et al. Administration of desmopressin in brain-dead donors and renal function in kidney recipients. *Lancet*. 1998;352:1178–1181.
107. Malinoski DJ, Patel MS, Daly MC, et al. UNOS Region 5 DMG workgroup. The impact of meeting donor management goals on the number of organs transplanted per donor: results from the United Network for Organ Sharing Region 5 prospective donor management goals study. *Crit Care Med*. 2012;40(10):2773–2780.
108. Callahan DS, Kim D, Bricker S, et al. Trends in organ donor management: 2002 to 2012. *J Am Coll Surg*. 2014;219(4):752–756.
109. Rosendale JD, Kauffman HM, McBride MA, et al. Aggressive pharmacologic donor management results in more transplanted organs. *Transplantation*. 2003;75:482–487.
110. Rosendale JD, Kauffman HM, McBride MA, et al. Hormonal resuscitation yields more transplanted hearts, with improved early function. *Transplantation*. 2003;75:1336–1341.
111. Randell T, Orko R, Hockerstedt K. Peroperative fluid management of the brain-dead multiorgan donor. *Acta Anaesthesiol Scand*. 1990;34:592–595.
112. Totsuka E, Dodson F, Urakami A, et al. Influence of high donor serum sodium levels on early postoperative graft function in human liver transplantation: effect of correction of donor hypernatremia. *Liver Transpl Surg*. 1999;5:421–428.
113. Riou B, Kalfon P, Arock M, et al. Cardiovascular consequences of severe hypophosphataemia in brain-dead patients. *Br J Anaesth*. 1995;74:424–429.
114. Campbell ML, Thill M. Bereavement follow-up to families after death in the intensive care unit. *Crit Care Med*. 2000;28:1252–1253.

103

Liver transplantation

Sarah E Brown, Anish Gupta, Simon Cottam, Julia Wendon

Liver transplantation has revolutionised the care of patients, with both acute and chronic end-stage liver disease. It has become an almost routine procedure, with the majority of patients having a short post-operative intensive care unit (ICU) stay and 1-year survival greater than 90%.[1-4] Indications have widened, and contraindications decreased. As a consequence, the number of patients awaiting transplantation continues to outstrip cadaveric donor rates; waiting times lengthen, and hence patients become critically ill before receiving a transplant, increasing risk and peri-operative complications, and impairing long-term outcome.[5] Innovative strategies have evolved as possible solutions to the lack of cadaveric donor organs, including widening the donor pool to include previously unsuitable donors (so-called marginal donors), paediatric and adult living-related donation, reduced size and splitting techniques and the use of 'non-heart-beating donation'.

PATIENT SELECTION

There are currently relatively few absolute contraindications to liver transplantation and no specific age limitation. Listing requires a multidisciplinary consensus of a 50% chance of 5-year survival once all risks are considered. Donor organs are preciously scarce, and allocation principles must therefore take into account the severity of the recipient's condition and the peri-operative risk profile.

Portopulmonary and hepatopulmonary syndromes (HPS) are now an active indication for transplantation as opposed to a contraindication.[6] These patients are likely to have a more complex postoperative course, especially if graft function is borderline or they develop sepsis. Patients must have the required cardiorespiratory reserve to tolerate the procedure. Guidelines are available with regard to hepatocellular carcinoma and liver transplantation.[7,8] Such patients increasingly, if not inevitably, require disease-modifying treatments, (transarterial chemoembolisation and radio frequency ablation). Periodic imaging of the liver is mandatory to monitor disease progression whilst waiting for a suitable cadaveric donor.

Much work has gone into the development of prognostic tools to allow the accurate prediction of the need and timing for transplantation, and increasingly the system used is the model for end-stage liver disease (MELD). This was initially developed for predicting survival following transjugular intrahepatic portosystemic shunt (TIPS), but has been shown to be equally useful in predicting survival in those awaiting liver transplantation. Survival depends on the physiological reserve of the recipient and the quality of the donor organ. Cardiovascular 'fitness' should remain the key determinant for receiving high-risk donor organs, which are increasingly used in order to match demand. Peri-operative outcome scoring systems are becoming more robust (survival outcomes following liver transplantation [SOFT] and balance of risk score [BAR]), but are still limited to specific types of donor organs and are often disease non-specific.[9,10] Once multiorgan failure has developed in a debilitated patient awaiting transplantation, survival rates decrease to 20%–30% and these patients often require weeks to months of postoperative hospitalisation.[2,11]

Cardiorespiratory function requires detailed assessment prior to listing. There is not one specific test that will determine fitness for transplantation; however, a combination of routine blood tests, computed tomography (CT) imaging, electrocardiography, echocardiography, cardiopulmonary exercise testing and brain imaging – if encephalopathy is a feature – serves as a minimum. CT imaging may uncover underlying pulmonary pathology as well as any coronary calcification (a weak predictor of critical ischaemia).

Cardiopulmonary exercise testing promulgates invaluable information of the cardiac, pulmonary and skeletal muscle-mitochondrial unit. In addition to providing dynamic information on these systems, we are able to gauge the β-adrenoceptor response and the peak oxygen consumption, which has some proven prognostic value.[12] The anaerobic threshold is frequently discussed, but is subject to major limitations – anaemia, smoking, β-blocker therapy, exercise tolerance prior to illness, cirrhotic cardiomyopathy and hepatorenal disease. This test is not validated as a discriminator for accurately determining success in

ABSTRACT

With improvements in immunosuppression and organ allocation systems, liver transplantation has now become a routine procedure, with survival rates at 1 year above 90%. Adults and children with chronic liver disease or multiorgan failure secondary to acute liver failure may be listed for transplantation, with donor organs being retrieved from heart-beating and non-heart-beating donors, as well as living relatives. The management of patients with end-stage liver disease and acute liver failure mandates referral to a specialist centre, where consideration for transplantation can be assessed in a multidisciplinary setting. Increasingly complex patients are able to undergo liver transplantation today, despite the myriad of complications that frequently occur.

KEYWORDS

Liver transplantation
acute liver failure
hepatopulmonary syndrome
hepatorenal syndrome
portopulmonary hypertension
immunosuppression
reperfusion syndrome
paediatric transplantation
acute rejection
viral hepatitis

Table 103.1 Diagnostic criteria for hepatopulmonary syndrome and portopulmonary hypertension

HEPATOPULMONARY SYNDROME	PORTOPULMONARY HYPERTENSION
Chronic liver disease (± cirrhosis)	Portal hypertension
Arterial hypoxaemia	Mean pulmonary artery pressure >25 mm Hg
Pa_{O_2} < 75 mm Hg (10 kPa) or A – a O_2 gradient >20 mm Hg	Pulmonary artery occlusion pressure <15 mm Hg
Intrapulmonary vascular dilatation	Pulmonary vascular resistance >240 dynes/s per cm^{-5}

the peri-operative period, but forms an integral part of each assessment.

Cardiovascular disease is the third commonest cause of death following liver transplantation, after disease recurrence/chronic rejection and malignancy. The risk factors for coronary artery disease require scrupulous investigation prior to listing, particularly as obesity and diabetes may develop post-transplantation, further increasing cardiac risk. Angiography and carotid Doppler studies must form part of the additional work-up in those patients with multiple risk factors.

Obesity is an increasingly common feature in patients listed for transplantation, and non-alcoholic steatohepatitis is the only indication for transplantation that is rising in frequency, soon to be the leading indication. The associated co-morbidities need to be quantified, and the overall risk profile cautiously considered prior to listing. Postoperative complications including infection, wound dehiscence and ventilator dependency are more prevalent, with cardiovascular complications the main cause for mortality. Obese patients with diabetes or coronary artery disease are 40% less likely to reach 5-year survival.[13] However, even transplanted obese patients show a survival benefit over those on the waiting list despite their higher complication rate, and this provides a difficult ethical debate over resource allocation.[14] There are no thresholds in body mass index for listing. Optimisation prior to surgery should focus on controlling medical co-morbidities as well as weight loss and dietary changes.[15]

HEPATIC SYNDROMES

Changes in the cardiovascular system associated with chronic liver disease may contribute to the spectrum of cardiopulmonary disease associated with chronic liver disease and portal hypertension. A hyperdynamic state with high cardiac output, long-standing portal hypertension with the development of collateral flows, together with an imbalance of vasoactive mediators either synthesised or metabolised by the liver, may lead to characteristic changes in both flow and pressure through the pulmonary vasculature. This may be associated with hypoxia and orthodeoxia. Two ends of the spectrum are HPS and portopulmonary hypertension. The two conditions are uncommon but important, as they have vastly different impacts on risk associated with liver transplantation and long-term outcome (Table 103.1). The role of agents used in the management of primary pulmonary hypertension is yet to be examined in a controlled manner in liver disease, but data thus far suggest benefit.

HEPATOPULMONARY SYNDROME

HPS is present in approximately 20% of cirrhotic patients. It can be seen from Table 103.1 that hypoxia is a characteristic finding in this condition. It results from intrapulmonary vascular dilatation at the pre- and post-capillary level, leading to decreased ventilation/perfusion ratios; more uncommonly, anatomical shunt is present with arteriovenous communication. One of the postulated mechanisms of this vasodilatation is overactivity of pulmonary vasculature nitric oxide synthetase; pre-transplant patients have raised levels of exhaled nitric oxide that decrease post-transplant with resolution of the syndrome. Diagnosis is confirmed by contrast-enhanced echocardiography or radionuclide lung perfusion scanning. Medical treatment of the syndrome has been disappointing; indeed, most transplant centres agree that the syndrome is an indication for transplantation in itself, as resolution is reported in up to 85% after transplantation.[16] Risk stratification based on severity is important, as vastly increased peri-transplant mortality is associated with severe hypoxia and high levels of vascular shunt. Severe hypoxia qualifies for MELD exception prioritisation. Mortality overall is 16% at 90 days and 38% at 1 year. Predictors of mortality in this group are severe hypoxia (Pa_{O_2} <6.5 kPa or 50 mm Hg) and shunt fraction greater than 20%.[16] Refractory hypoxia is the indirect cause of death, which may be due to multiorgan failure, intracerebral haemorrhage and sepsis due to bile leaks. Whilst it is true that the recipient's organs are conditioned to function in the chronic preoperative hypoxic state, the liver graft must be protected from hypoxia immediately following transplantation, with a gradual weaning of oxygen levels. Resolution of the syndrome is variable and can take up to 1 year, lending support to the theory that it is vascular remodelling rather than just acute reversal of vasodilatation that reverses hypoxia.[17,18]

PORTOPULMONARY HYPERTENSION

Up to 20% of pre-transplant patients have pulmonary hypertension; this probably constitutes increased flow through the pulmonary vasculature and is not associated with increased resistance. These patients do well after transplantation. A much more ominous syndrome is the presence of pulmonary hypertension with high pulmonary vascular resistance (PVR) (seen in <4%). The aetiology of this syndrome is complex but it is characterised by a hyperdynamic high-flow state with excess central volume and non-embolic pulmonary vasoconstriction. The pathological changes associated with this syndrome match those associated with primary pulmonary hypertension except that cardiac output is high in this group.

In comparison to HPS, there are several differences in terms of response to medical treatment and outcome after transplantation. The response to epoprostenol, a prostaglandin I2 (PGI2) analogue, is encouraging. Decreases in pulmonary artery pressure – but more importantly transpulmonary gradient (TPG) – have been noted, although at least 3 months' treatment seems necessary, suggesting remodelling rather than vasodilatation is the important mechanism. A limiting factor in the treatment may also be progressive thrombocytopenia and splenomegaly. Endothelin receptor antagonists (bosentan, ambrisentan) have been shown to almost normalise PVR in selected patients by blocking the vascular reactivity of the pulmonary vascular bed. Phosphodiesterase inhibitors (sildenafil) increase the availability of nitric oxide within the pulmonary vasculature. These oral agents hold some advantage for outpatient management; however, intravenous prostacyclin remains the treatment of choice in severe cases.[19]

Another difference is the peri-operative risk and post-transplant prognosis. Resolution is not associated with transplantation and progression can be a feature. Peri-operatively, the higher the mean pulmonary artery pressure (MPAP), PVR and TPG, the greater the risk of death, usually due to acute right ventricular decompensation. Right heart pressures need to be closely monitored with pulmonary artery catheterisation preferably commenced pre-operatively to establish prostacylin infusion. Milrinone may be added to gain further control of pulmonary pressures in the peri-operative process. Trans-oesophageal echocardiography (TOE) monitoring provides invaluable assessment of right heart function, and enables more accurate volume replacement during reperfusion. If the MPAP is greater than 35 mm Hg or the PVR is greater than 250 dyne/s per centimetre, mortality reaches 40%. If MPAP is greater than 50 mm Hg some have even suggested delisting or even intraoperative cancellation as the mortality may be as high as 100%.[20] Intravenous pulmonary vasodilators are usually weaned to oral medications which about half the patients will require long term. Resolution in the remaining half occurs over several months.[19]

Table 103.2 Diagnostic criteria for hepatorenal syndrome

Cirrhosis with ascites
Serum creatinine >133 µmol/L (1.5 mg/L)
No improvement in serum creatinine (to <133 µmol/L) after 2 days of diuretic withdrawal and albumin replacement (1 g/kg per day or maximum 100 g/day)
Absence of shock
Absence of nephrotoxic drugs
Absence of renal parenchymal disease

Salerno F, Gerbes A, Gines P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut.* 2007;56: 1310–1318.

HEPATORENAL SYNDROME

Hepatorenal syndrome (HRS) is a potentially reversible cause of renal dysfunction in a small proportion of acute kidney injury (AKI) cases with cirrhosis. Two subtypes exists; type 1 results in acute renal deterioration following a precipitating event (sepsis, post-paracentesis syndrome), whereas type 2 is a progressive form occurring over weeks. It represents an advanced stage of haemodynamic dysfunction, characterised by splanchnic vasodilatation, reduced systemic vascular resistance and reduced effective arterial blood volume. This contraction in central blood volume stimulates a powerful neuroendocrine response mimicking volume depletion and pre-disposing to pre-renal failure (HRS).[21]

The diagnosis is essentially one of exclusion in a patient with cirrhosis (Table 103.2).[22] The prognosis of HRS is poor with the worst survival rates out of all the causes of AKI (3-month survival for type 1 is 20%, and type 2 is 40%). Vasoconstrictor agents, albumin, TIPS and improved antimicrobial therapy have all proven benefits in serving as a bridge to transplantation.

Transplantation is the only treatment for HRS, with normalisation of sodium excretion, serum creatinine and neurohormonal levels occurring within 1 month. The renal vasoconstrictive indices require 12 months before recovering. HRS does increase the complication rate and reduce survival following transplantation, with renal function never recovering in up to 25%. Those on renal replacement therapy for more than 8 weeks prior to transplantation should be offered combined liver–kidney transplantation. Interestingly, the risk of acute rejection for combined liver–kidney grafts is as for liver transplantation, compared to the higher rate of rejection that is seen for renal transplant alone.[22-24]

EXTRACORPOREAL HEPATIC SUPPORT

The liver has metabolic, excretory and synthetic functions; all of which need to be maintained in a patient who has liver failure until either an organ becomes

available or regeneration takes place. Two groups of devices are available; purely mechanical devices provide detoxification whilst bioartificial devices, which require an abundant source of hepatocytes, also provide synthetic and biotransformation activities. Artificial devices include plasma exchange and albumin dialysis, which may incorporate extracorporeal albumin dialysis (MARS [molecular adsorbents recirculating system, Gambro]) or fractionated plasma separation and absorption (Prometheus). Clinical trials are in progress to evaluate the place for these devices. To date, none of these artificial devices have conferred a survival benefit in liver failure in prospective randomised trials, though there has been some success with improvements in neurological status and reduced cerebral oedema.[25-27] Bioartificial devices suffer from limited hepatocyte supply and prospective clinical trials conveying survival benefits, though some early results may prove promising. In addition to efficacy, still to be elucidated is the timescale on which these devices can be used and whether they can bridge the gap to regeneration, thus sparing the patient from transplantation.

PERI-OPERATIVE ASPECTS

OPERATIVE TECHNIQUE

Orthotopic liver transplantation (OLT) involves recipient hepatectomy, revascularisation of the donor graft and biliary reconstruction.

Two main techniques are used in adult liver transplantation – those with vena cava preservation ('piggyback technique') and those using portal bypass (either internal, temporary portocaval shunt or external, veno-venous bypass). The advantages of the piggyback technique include haemodynamic stability during the anhepatic phase, without large volume fluid administration, and the negation of the need for veno-venous bypass with its associated risks and complications. Decreased transfusion requirements, shorter anhepatic time and shorter total operating time are also observed. There is no observed difference in renal function between the two techniques.[28-30] The donor hepatic artery is directly anastomosed, utilising an 'end-to-end' technique, or a conduit is constructed. Portal venous anastomosis must also be undertaken; in most patients this is an end-to-end anastomosis. Portal venous thrombosis is no longer a contraindication to transplantation and these patients may undergo a re-cannulisation procedure or require a jump graft technique. Such conduits and grafts are normally fashioned from donor vessels.

It is imperative that all those caring for the patients are aware of the surgical technique undertaken, as complications may vary. The radiologist must be aware of the technique used to allow appropriate interpretation of subsequent investigations and vascular imaging. This applies not just to the vascular anastomosis but also to the presence of a full graft, a reduced-size graft, a right or left split graft or indeed an auxiliary graft. The biliary anastomosis is normally also undertaken as an end-to-end procedure, the donor bile duct being directly joined to the recipient duct. It is no longer standard for this to be undertaken over a T-tube, but this may be required where there is marked discrepancy between donor and recipient duct size. Some conditions (e.g. extrahepatic biliary atresia, primary sclerosing cholangitis) may preclude end-to-end anastomosis, and formation of choledochojejunostomy may be required.

Split-liver grafts allow one liver to provide an organ for two recipients. Initially comprised of a child receiving the left lateral segment and an adult the remaining liver, nowadays two adults may receive grafts from one liver if the anatomy and size match allow. Such splits may be less than ideal when the recipient has a high MELD score, as is increasingly the case with the prioritisation of sick patients awaiting liver grafts. Such grafts are at increased risk of postoperative complications such as bile leaks and haematoma/collections at the cut surface.[3,31]

Auxiliary liver transplantation is a technique that involves subtotal recipient hepatectomy and implantation of a reduced-size graft. It is a technically difficult procedure, as both portal and arterial supplies have to be constructed de novo. In addition, a duplicate biliary drainage system needs to be constructed. Hepatic venous outflow is anastomosed as usual. In acute liver failure, it has significant potential, since regeneration of the native liver may obviate the need for donor function, potentially allowing withdrawal of immunosuppression. It also has application in the treatment of some hereditary metabolic disorders where adequate metabolic function may be achieved with an auxiliary graft. The major advantage is withdrawal of immunosuppressive therapy if the patient develops severe complications, or when applicable gene therapy becomes available. The disadvantage of auxiliary transplantation in the face of acute liver failure is that the postoperative course is frequently more complicated; reasons are multifactorial, and can be due to the continued presence of a regenerating native liver or due to a smaller donor graft attempting to cope with a critical illness.

Non-heart-beating transplantation (NHBD) has emerged in recent times as a potential way of increasing organs for transplantation.[32,33] The success in renal transplantation has led to exploration of its application in the fields of liver, pancreas and lung retrieval. Most retrievals are undertaken in the context of controlled NHBD (i.e. in the context of planned withdrawal of care). Warm ischaemia can be accurately assessed and cold ischaemia minimised. Early experience with NHBD was associated with inferior survival for patients and grafts, but recent experience suggests

that survival is approaching that for heart-beating donation. There are, however, continuing concerns over biliary and vascular complications. Prolonged cold ischaemia is associated with poor graft function and biliary complications, as are warm ischaemia times of greater than 30 minutes.[34] With regard to postoperative care, an understanding of the pre- and peri-operative factors is essential in anticipating potential complications, initiation of monitoring and proactive management.

Living donor-related transplantation (LDRT) is now a routine undertaking in paediatric liver transplantation. It is becoming increasingly utilised in adult liver transplantation, although its application in countries with good cadaveric donor pools is less established. Adult LDRT using right lobe grafts is an effective procedure with good survival outcomes but is associated with significant complications. From a postoperative perspective the intensive care team may be responsible for the management of both the donor and the recipient. Morbidity rates for donors are significantly higher with the use of a right lobe donation compared with a left lobe graft. Mortality for donors has been reported. Survival rates now reported for living related recipients are good, with rates of 80% at 12 months.[35,36]

Adequate function of undersized transplanted liver grafts is essential to successful outcome. Primary graft non-function is relatively rare and one of the main areas of concern is that of the so-called 'small-for-size syndrome'.[35,37] This was first recognised in the post-transplant setting but also occurs following liver resection. It is still an area under discussion but the clinical entity is that of hyperbilirubinaemia, graft dysfunction, ascites and portal hypertension with associated end-organ dysfunction/failure. There is portal hyperaemia, with portal flow passing into a small liver remnant/graft with associated pathophysiological consequences, and at a histological level there is evidence of arteriolar constriction. In some patients consideration should also be given to the potential compounder of hepatic venous outflow limitation.[38,39] Other factors that predispose to the syndrome are an inappropriate graft weight to recipient, and steatotic grafts. Most management trials have focused on optimising venous outflow and limiting/preventing portal hyperaemia and limiting portal hypertension.[35,40] Animal studies have also examined the role intrahepatic vasodilators with good effect. Management of the syndrome remains controversial but its early consideration allows the clinical team time to consider therapeutic options and interventions.

INTRAOPERATIVE MONITORING

In addition to routine monitors, invasive arterial blood pressure and central venous pressure measurements are invaluable. With modern advances in technology, it has now become routine practice to use some method of cardiac output monitoring. The trends in stroke volume variation and cardiac index can be used as a guide to fluid delivery, and to help gauge requirements for vasopressors and inotropes.

The use of TOE is often reserved for patients with known pulmonary hypertension, though this is gradually being used more frequently to assess fluid status, regional wall motion abnormalities, the presence of intracardiac thrombi and even to locate the position and patency of TIPS.[41,42]

FLUIDS, HAEMORRHAGE AND COAGULATION

There is no consensus on the amount or type of fluid that should be used during liver transplantation. The centrally deplete fluid compartment, if aggressively filled, will rapidly re-distribute to the peripheral and portal circulation, exacerbating haemorrhage.[43] Incremental volume replacement is the key, ideally guided by some form of flow monitoring. Large volumes of crystalloids must be avoided to prevent excessive interstitial oedema. The choice of colloid remains an important topic of debate and ongoing research. The following points should be remembered when deciding which colloid to infuse. Starches with a molecular weight above 200 kDa may predispose to AKI and result in pruritus. Starches may remain within the intravascular compartment for longer than gelatins; however, this effect is questionable with modern, lower molecular weight starches.[44]

OLT may be associated with massive blood loss. The causes are multifactorial and include pre-operative coagulopathy secondary to end-stage liver disease, portal hypertension, surgical technique, adhesions related to previous surgery and intraoperative changes in haemostasis. The degree of clinical coagulopathy is impossible to predict, and relies on the imbalance in anti-haemostatic and pro-haemostatic drivers.[45]

The low-grade fibrinoltyic process in advanced cirrhotics may be exacerbated during surgery, particularly during the anhepatic and re-perfusion stages. Platelet dysfunction, both quantitative and qualitative, is also common, though the impact on haemostasis is variable.[46] The consequences of massive bleeding and replacement are significant, not only in terms of postoperative morbidity and mortality, but also intraoperatively when issues such as acute hypovolaemia, reduced ionised calcium due to citrate accumulation, hyperkalaemia, acidosis and hypothermia become important. Transfusion-related acute lung injury (TRALI) is a potentially devastating complication. It is believed to result from neutrophil antibodies preformed in donor serum. The immunosuppressive effects of large volume blood transfusions are well recognised and pertinent in a group of patients who are already functionally immunosuppressed. In addition to these immediate problems is the risk of transmission of, as yet, unidentified viral infection.

Much effort has gone into reducing the amount of exogenous blood products required intraoperatively. This includes the use of cell salvage techniques with autologous transfusion and frequent testing of haemostasis, utilising both laboratory-based tests and thromboelastography or rotational thromboelastometry. The prophylactic use of tranexamic acid may attenuate the degree of fibrinolysis during the early stages of transplantation. The severe post-reperfusion fibrinolysis often resolves once the donor liver begins to function and seldom requires immediate correction. Optimisation of clot stability with fibrinogen prior to coagulation factor and platelet replacement has led to reduced transfusion requirements in major haemorrhage. Fibrinogen and prothrombin complex concentrates are gaining popularity due to reduced volume load and superior efficacy, though these products are not universally licensed or readily available. They are purified and virally inactivated by nature of the manufacture process, reducing the risks of viral transmission and TRALI.[47] There is a paucity of evidence-based thresholds for platelet transfusion, and the benefits in reducing haemorrhage and improving liver regeneration must be balanced with the adverse risks of ischaemia-reperfusion injury, TRALI and reduced survival.[46] These therapies must be judiciously employed in order to control bleeding at the potential expense of thromboembolic complications which may be as high as 4%.[41]

Although it is assumed that all patients with liver disease are subject to an increased risk of bleeding there are some subgroups that are prothrombotic, as evidenced clinically and with thromboelastography. Patients with pre-operative portal or hepatic venous thrombosis appear to carry a higher incidence of prothrombotic mutations than the general population, and patients with primary biliary cirrhosis and primary sclerosing cholangitis are frequently prothrombotic. Such patients may require anticoagulation in the early postoperative period. Other patient groups such as those with Budd–Chiari syndrome may have a recognised prothrombotic condition with a resultant early requirement for anticoagulation.

Electrolyte disorders are common in advanced liver disease, and careful monitoring of sodium, potassium and calcium levels are paramount. Hyponatraemia is associated with increased mortality in the pre-transplanted patient, and rapid changes in the peri-operative period may lead to further morbidity (although mortality appears comparable).[48] Rapid changes in sodium concentration have been linked to rare cases of central pontine myelinolysis. Calcium is required for haemostasis, and requires supplementation – especially if citrated products have been administered. Life-threatening hyperkalaemia may develop on reperfusion, and must be anticipated and managed immediately. Cell-salvage apparatus can be used to wash the packed red cells to eliminate excess citrate and potassium administration.

POST-REPERFUSION SYNDROME

The post-reperfusion syndrome is a poorly understood phenomenon that occurs after reperfusion of the portal vein through the donor graft. It is characterised by hypotension, bradycardia, vasodilatation, pulmonary hypertension, hyperkalaemia and, in some cases, cardiac arrest. The aetiology is unclear, but a sudden increase in venous return, release of vasoactive substances, and cold potassium-rich preservation fluids are potentially implicated. The syndrome usually resolves within the first 5 minutes of reperfusion with appropriate fluid loading and electrolyte management. However, in approximately 30% of patients it lasts for significantly longer, necessitating the use of inotropes and/or vasopressors. The post-reperfusion syndrome seems more common in organs with longer preservation times and may well be associated with initial poor graft function.

POSTOPERATIVE CARE

The postoperative care of the recipient depends to some extent on pre-operative co-morbidity, the presence of any of the immediate complications listed above, recipient stability during the procedure and lastly the pre-transplant cause of liver failure.

Straightforward recipients who return to the ICU in a stable condition with good graft function may be woken up and weaned immediately. The tracheal tube and some of the invasive monitoring lines should be removed as soon as no longer required to reduce the risk of infection and encourage mobility. Close monitoring of all physiological systems is important in the early postoperative period (Tables 103.3 and 103.4).

Table 103.3 Routine investigation of the post-transplant patient in the intensive care unit

	FBC	LFTs	COAGULATION	DRUG LEVELS	CULTURES	ULTRASOUND
Day 1	√	√	√		As indicated	Routine ultrasound including hepatic artery, hepatic and portal vein flow D1 and D5, and if clinically indicated at other time
Day 2	√	√	√	√	As indicated	
Day 3	√	√	√	√	As indicated	

FBC, Full blood count; *LFTs*, liver function tests.

Table 103.4 Monitoring of graft function in the intensive care unit

PARAMETER		COMMENT
General	Liver perfusion	Characteristics at surgery
	Bile production	Quality ± volume if T-tube in situ
	Haemodynamics	Stabilisation, with cessation of vasopressor requirements
Coagulation	INR/PT	8-hourly for first 24 h, thereafter daily unless indicated. Fall in PT is more important than the actual value. FFP should be withheld to assess graft function although platelets given as indicated
Biochemistry	Glucose	Hypoglycaemia is an ominous sign; 4-hourly for first 24 h Euglycaemia/hyperglycaemia requiring insulin infusion is normal
	Arterial blood gases and lactate	4- to 6-hourly depending on ventilatory requirement. Hyperlactataemia and acid-base disturbance should rapidly resolve. Other causes of base deficit, such as renal tubular acidosis and hyperchloraemia, should be excluded and managed appropriately
	AST	Should fall steadily (50% fall each day). The first measurement may reflect washout and thus the next may be higher. Daily measurements. The initial measurement reflects the degree of preservation injury
	Bilirubin	Early increases may reflect absorption of haematoma and do not reflect graft function. Haemolysis should be considered if the graft is not blood group matched, termed passenger lymphocyte syndrome
	ALP/GGT	Usually normal; increases may reflect biliary complications or cholestasis of sepsis

ALP, Alkaline phosphatase; *AST*, asparate aminotransferase; *FFP*, fresh frozen plasma; *GGT*, gamma-glutamyl transferase; *INR*, international normalised ratio; *PT*, prothrombin time.

EARLY COMPLICATIONS

As with all postoperative surgical intensive care admissions, some complications are applicable to all patients. These include haemorrhagic and pulmonary complications of any prolonged procedure in addition to specific complications pertinent to liver transplantation. These can be subdivided into technical complications, conditions and complications associated with pre-existing liver disease, and complications associated with immunosuppressive agents, graft function and massive transfusion.

CARDIOVASCULAR

End-stage liver disease is characterised by a hyperdynamic circulation, with low systemic vascular resistance, high cardiac index and a proportionately reduced central circulating volume. The majority of patients can be managed with judicious volume loading with or without vasopressors to maintain adequate perfusion pressures. However, in some patients, this state may compensate for degrees of cirrhotic cardiomyopathy, which are characterised by systolic and diastolic dysfunction, electrophysiological abnormalities and a blunted β-adrenoceptor response in the presence of an increased cardiac stress.[49-51] The massive increase in the volume of liver transplants performed in the last decade has revealed cardiac failure as an important cause of morbidity and mortality in the transplant recipient.[52] OLT can impose severe stresses on the cardiovascular system: haemorrhage, third-space loss, impaired venous return due to caval clamping, hypocalcaemia and acidosis all impair myocardial contractility. Reperfusion can also be a time of profound circulatory instability. Rapid fluctuations in filling pressures place the compromised and stressed myocardium at risk of failure. In addition, the impaired exercise tolerance of the pre-transplant recipient may have limited the clinical importance of coronary ischaemia, which becomes pertinent in the post-transplant period.

Haemodynamic changes after OLT are also common; hypertension with an increased systemic vascular resistance is frequent and may be due to the restoration of normal liver function and portal pressure, as well as the hypertensive effect of the calcineurin immunosuppressants. The increased afterload in the early post-transplant period may unmask cardiac dysfunction. Management of myocardial failure post-OLT is largely empirical; diuretics, afterload reduction and positive-pressure ventilation may all be required. In the longer term, control of cardiovascular risk factors is required and many of these patients may over the years return to the intensive care environs with other system failures and considerable burdens of hypertension, coronary ischaemia, diabetes, hyperlipidaemia and renal dysfunction.

PULMONARY

Pulmonary complications are common and occur in 40%–80% of recipients. The presence of pre-operative impairment (e.g. pleural effusions, hypoxaemia, pulmonary hypertension or the HPS) is strongly associated with postoperative complications. Specific conditions related to liver transplantation include

right hemidiaphragm palsy as a result of phrenic nerve damage, which can occur if suprahepatic caval clamping is used intraoperatively. The commonest postoperative problems are pleural effusions, ongoing shunting secondary to the HPS, atelectasis and, over subsequent days, infection. De novo acute lung injury and the acute respiratory distress syndrome are relatively uncommon at this stage. Other complications, such as TRALI and pulmonary oedema, are almost certainly under-recognised and under-reported.

Specific management of portopulmonary syndrome may be required in the postoperative period if right-sided pressures are elevated, to ensure that liver congestion and graft dysfunction do not ensue.[6,50,51] Control of pulmonary pressures may require a variety of therapeutic options, with the treatment options being similar to those utilised in primary pulmonary hypertension. Concern about potential hepatotoxicity needs to be balanced against the need to control right-sided pressures and provide optimal graft function. Similarly, HPS may take a variable time to resolve and hypoxia during this period will require recognition and management.

Respiratory complications are also seen in patients with poor muscle bulk and subsequent weakness. Similarly, the presence of osteoporosis in the pre-transplant patient is frequently associated with postoperative pain and poor cough. The role of adequate analgesia is important, as in all patients, in promoting mobilisation and adequate respiratory function. In general, the management of a protracted respiratory wean follows conventional lines.

NEUROLOGICAL

The quoted incidence of central nervous system (CNS) complications varies widely from 10% to 40% in the published series. Most neurological complications occur within the first month of transplant. The commonest causes relate to the persistence of pre-existing encephalopathy.[53,54] The causes are multiple, including hepatic, metabolic, infectious, vascular and pharmacological. A patient with acute liver failure will remain encephalopathic in the immediate post-transplant period, and is at risk of intracranial hypertension for 48 hours following transplantation, or longer in the face of graft dysfunction. De novo hepatic encephalopathy may develop in patients with severe graft dysfunction and/or primary graft non-function; again the patient is at risk of cerebral oedema. The effects of sepsis, rejection (and its treatment with high-dose steroids), drug therapy (especially the sedatives and analgesics used in the ICU setting) and the presence of renal failure may all contribute to the presence of altered conscious level. The calcineurin inhibitors (CNIs) are particularly associated with seizures and altered conscious level. All such patients will require brain imaging to further define the aetiology of their impaired neurology.

Other possible neurological complications are those of intracerebral haemorrhage. Such bleeds may relate to arteriovenous malformations, may be spontaneous or may be a complication of intracranial pressure monitoring, particularly in patients with acute liver failure. CNS infection normally presents later than the immediate postoperative period, but should always be considered, especially in those patients with a prolonged and complicated postoperative course. All possible infecting agents, including bacterial, viral, fungal and opportunistic, should be considered. Central pontine myelinolysis is a rare but potentially devastating complication associated with rapid sodium shifts. Modern technology and the use of haemofiltration techniques allow tight control of sodium shifts in the majority of patients, and this has become a rare neurological complication.

RENAL DYSFUNCTION

Despite intraoperative efforts, renal dysfunction often progresses and AKI is a relatively common complication, with an incidence of between 25% and 60% and a multifactorial aetiology.[55-58] Risk factors include the presence of pre-transplant co-morbidity (e.g. hypertension, diabetes mellitus, obesity, HRS), severity of underlying liver disease, intraoperative instability, blood product requirement, hepatic ischaemic reperfusion injury, drug toxicity, graft dysfunction and higher risk grafts. The use of higher risk, or marginal, grafts has increased due to the growing demand for organs and a desire to reduce the waiting list mortality. They include grafts from older donors, split or partial grafts, prolonged preservation time (warm and cold ischaemia times), graft steatosis, and NHBD. There is an increased risk of hepatic and extrahepatic complications following transplantation with marginal grafts, with AKI the most common complication.

Mortality in those who require renal replacement is high, graft survival is lower, and there is increased resource utilisation. In order to limit – or avoid – AKI, those with risk factors, or pre-existing renal dysfunction, should have their immunosuppression with nephrotoxic agents, such as CNIs, reduced and interleukin-2 (IL-2) blockers utilised.[59] There must be a balance between the risk of rejection and that of side effects of drug therapies. Mycophenolate mofetil (MMF), a cytotoxic immunosuppressant, may be substituted in the post-transplant course to limit or protect against renal dysfunction.

Intra-abdominal hypertension should always be considered in the post-transplant setting as a potential contributor not only to renal dysfunction but also to cardiorespiratory embarrassment. Early consideration should be given to laparostomy in patients with elevated intra-abdominal pressures and associated organ dysfunction.[60,61]

PRIMARY NON-FUNCTION

This is a spectrum occurring in 2%–23% of cases, which at worst requires urgent retransplantation. It

is characterised by poor graft function from the time of reperfusion, with hyperlactataemia, coagulopathy, metabolic acidosis, hypoglycaemia, hyperkalaemia and a rapid elevation in aminotransferase concentrations, accompanied by a systemic inflammatory response.

A major reason for the initial graft dysfunction is ischaemic injury to the graft, which depends on the type of preservation fluid used, and the duration of cold and warm ischaemia time. The aetiology of primary non-function (PNF) remains unclear.[62]

Vasodilator prostaglandins and antioxidants may have a role in 'rescue therapy', but controlled data are lacking.

SURGICAL PROBLEMS

Anastomotic thromboses are uncommon complications of liver transplantation, but can cause significant morbidity, which may require further invasive procedures and even urgent retransplantation. Hepatic artery thrombosis occurring in the early postoperative period is associated with a similar picture to PNF. Small vessel calibre is a risk factor, and is more prevalent in the paediatric recipient where it has also been associated with prothrombotic states, such as protein C deficiency. Ultrasound is the first-line screening test and is undertaken both routinely in the immediate postoperative period, and if there is a sudden rise in transaminase measurements. If the vessel is not visualised, the patient should proceed to CT angiography. If diagnosed quickly, emergency intervention can be undertaken to re-establish arterial flow; however, emergency retransplantation may be required.

Venous complications, such as portal thrombosis, are even more uncommon, and are usually associated with intraoperative technical difficulty, recurrence of pre-operative disease or undiagnosed thrombophilia. Portal thrombosis is normally associated with portal hypertension and massive ascites, but may also be associated with graft dysfunction, especially in the paediatric population. CT scanning will interrogate the vessels and also provide information on graft perfusion: regional ischemia may be identified, which may have presented as a transaminitis. Treatment is dependent on the severity of the injury but ranges from diuretics to angioplasty, surgical reconstruction or ultimately retransplantation. Regional ischaemia and areas of poor perfusion should be actively sought in patients with a transaminitis and especially in those who had received a reduced size or split-liver graft.

Biliary complications post-liver transplant are relatively common. The bile duct normally receives two-thirds of its arterial supply from the gastroduodenal artery and one-third from the hepatic artery. Post-transplant, the only supply is from the hepatic artery, making it vulnerable to ischaemic injury whether that be at the time of retrieval, reperfusion or post-operatively. The resulting complication depends on the type of biliary anastomosis and the timing of the insult. Strictures are more commonly observed than leaks. Management of biliary complications is, in the first instance, endoscopic, with stent placement and/or balloon dilatation. In patients with a T-tube in situ, cholangiography may be undertaken by that route. Open reconstruction in the early postoperative period is uncommon (Tables 103.5, 103.6 and 103.7). Bile leaks also may be seen in the postoperative period from the cut surface of a split graft. Bile leaks are associated with an increased risk of infection and, potentially, of pseudoaneurysm formation.

Table 103.5 Technical complications of orthotopic liver transplantation

COMPLICATION	COMMENT
ABDOMINAL BLEEDING	
Anastomosis	Immediate
Graft surface (if cut down)	Immediate
General ooze secondary to coagulopathy	Immediate
Pseudo-aneurysm formation	Can present early or late and is usually associated with intra-abdominal sepsis and biliary leaks
VASCULAR COMPLICATIONS	
Hepatic artery thrombosis	Early and late
Portal vein thrombosis	Early and late; there may also be a stenosis of the portal vein rather than thrombosis
Inferior vena caval obstruction	May be infra-, supra- or retrohepatic in site
BILIARY COMPLICATIONS	
Biliary leak	Usually early
Biliary stricture	Usually late
Papillary dysfunction	Late
Roux-en-Y dysfunction	Usually late

ACUTE REJECTION

Acute cellular rejection becomes a risk from approximately 5–7 days post-transplant; the clinical signs of rejection are non-specific and include fever, deterioration in graft function and a rapid rise in serum aminotransferase concentration. Liver biopsy is the only reliable diagnostic tool; however, biopsy may be relatively contraindicated due to coagulopathy. In some circumstances transjugular biopsy offers a solution to

Table 103.6 Biochemical and clinical features of technical problems

COMPLICATION	FEATURES	INVESTIGATION	MANAGEMENT
Hepatic artery thrombosis	Early: rapid rise in transaminase, coagulopathy, graft failure	Ultrasound, angiogram	Thrombectomy, retransplantation
	Differential diagnosis: hyperacute rejection, primary non/dysfunction		
	Late: biliary complications, strictures, sepsis, liver abscess	Ultrasound, angiogram	Angioplasty
Portal vein thrombosis	Early: rapid deterioration in graft function, acute liver failure, ascites, variceal bleeding	Ultrasound, CT, angiography, MRA	Thrombectomy, retransplantation, conservative management
	Late: mildly abnormal LFTs, portal hypertension, varices	Ultrasound, CT, angiography, MRA	

CT, Computed tomography; *LFTs*, liver function tests; *MRA*, magnetic resonance angiography.

Table 103.7 Differential diagnosis of graft dysfunction in intensive care unit

Primary non-function
Preservation injury
Rejection – hyperacute/acute
Vascular complications
Biliary complications
Drug-induced liver dysfunction
Infection – viral, bacterial, fungal
Recurrent disease (normally late)

this problem. The differential diagnosis may be that of sepsis, or problems with vascular integrity; there are some data to suggest that procalcitonin may be of use in the differentiation (Table 103.8). The normal management regime for an episode of acute rejection is that of pulsed methylprednisolone (1 g for 3 days), though approximately 10% will develop steroid-resistant rejection. Antithymocyte globulin, a polyclonal lymphocyte antibody preparation, is often used in liver transplant centres to treat steroid-resistant rejection.

INFECTIOUS COMPLICATIONS

Transplant recipients are uniquely vulnerable to infection with up to 80% developing at least one infection during the first year.[63] Prolonged and technically difficult surgery, large wounds, urinary catheterisation and the need for central venous access postoperatively, combine with conditions attendant to end-stage liver disease, including neutropenia, deficits in the mucocutaneous barrier, diabetes mellitius, uraemia and protein-calorie malnutrition, to increase susceptibility.

Bacterial infections are frequent and represent the most dangerous complication in liver transplant patients. More than one-third of infections occur within the first 30 days and the risk factors include: NHBD, MELD greater than 20, albumin level greater than 2.8 g/L, high intraoperative transfusion requirement (packed red cell >6 U, fresh frozen plasma >12 U), bilioenteric anastomosis and prolonged length of stay (ICU stay >6 days and hospital >21 days).[64] However, compared with a decade ago, the overall incidence is reduced, probably due to improved and patient-tailored immunosuppressive regimens. Sepsis remains an important and life-long complication of liver transplantation, which may require readmission to intensive care.[65,66]

The epidemiology of pathogens is evolving; the incidence of Gram-positive bacterial infection (enterococci and staphylococci) is now more common than Gram-negative sepsis. More concerning is the emergence of multiple antibiotic-resistant bacteria, in particular methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci and extended-spectrum β-lactamase producing Gram-negative organisms. Mortality and graft failure associated with infection caused by these multiply resistant organisms is significantly greater compared with other organisms.[67]

A decline in the incidence of both *Pneumocystis jiroveci* (formerly *P. carinii*) and cytomegalovirus (CMV) infection is probably a result of both modulating immunosuppressive regimens and more effective prophylaxis. Patients should be screened for viral infections, including herpes simplex virus (HSV) and CMV utilising polymerase chain reaction techniques.

Opportunistic fungal infections remain problematic. Candidiasis is the most frequent fungal infection and the leading cause of invasive fungal infection. The gastrointestinal tract is often colonised with *Candida* species and infection can occur secondary to overgrowth and translocation, or as the result of leaks from anastomosis within the alimentary canal. Risk factors for invasive candidiasis include: previous use of prophylactic antibiotics for spontaneous bacterial peritonitis, renal replacement therapy, retransplantation,

Table 103.8 Management of rejection in intensive care

	COMMENT	CHARACTERISTICS	LIVER BIOPSY	DIFFERENTIAL DIAGNOSIS	TREATMENT OPTIONS
Hyperacute rejection	Rare in OLT 1–10 days post-transplant	Rapid deterioration in graft function: AST >1000 Coagulopathy, acidosis	Haemorrhagic necrosis	Primary non-function/ delayed function Hepatic artery thrombosis	Retransplantation Rarely: OKT3, cyclophosphamide, plasmapheresis (unproven)
Acute rejection	30%–70% Occurs at mean of 7–9 days	Often clinically silent apart from fever and RUQ pain High AST and bilirubin Coagulation and acid-base undisturbed	Portal inflammation Endothelitis Bile duct damage	Sepsis Vascular Viral	Methylprednisolone 1 g daily for 3 days

In those who do not respond: Consider diagnosis; if correct, consider tacrolimus if induction agent is ciclosporin A, OKT3 or MMF/sirolimus if other new agents.

AST, Aspartate aminotransferase; *MMF*, mycophenolate mofetil; *OLT*, orthotopic liver transplantation; *RUQ*, right upper quadrant.

Table 103.9 Infection in the intensive care unit

	BACTERIAL	VIRAL	FUNGAL	PROTOZOAL
Aetiology	Wound Nosocomial pneumonia Line sepsis UTI Liver Biliary	HSV CMV EBV Varicella	Candida Aspergillus PCP Cryptococcus	Toxoplasmosis Strongyloides
Timing	Any time	HSV in first few weeks CMV 3–10 weeks EBV from 4 weeks Varicella later All may be earlier in ALF or retransplantation	Usually after 4 weeks	After 3 weeks

ALF, Acute liver failure; *CMV*, cytomegalovirus; *EBV*, Epstein–Barr virus; *HSV*, herpes simplex virus; *PCP*, pneumocystis pneumonia; *UTI*, urinary tract infection.

technically difficult surgery, intraoperative blood transfusion and prolonged ICU stay.[68] *Aspergillius* spp. are the second most common fungal infection, though diagnosis can be difficult, and often involves invasive procedures. Non-invasive serological markers, including 13-b-glucan (BDG) and aspergillus galactomannan, can be used as diagnostic indicators. The use of prophylactic antifungals is now widespread in those with risk factors, but consideration to drug-drug interactions, particularly those with CNIs, is important (Table 103.9).[69]

FEVER

In transplant recipients, 76% of febrile episodes have a documented infectious aetiology, but acute rejection needs to be considered in the differential diagnosis. In the ICU transplant recipient the aetiology is even more likely to be infectious – often nosocomial and bacterial. In one study, pneumonia, catheter-related bacteraemia and the biliary tree were the three most common sources in the ICU population (41%). Viral infections accounted for 9% of febrile episodes, fungal infections 3% and endocarditis 3%. As mentioned above, the epidemiology of pathogens is changing and it is important to have thorough knowledge of local problem pathogens on which to base meaningful antibiotic policy.

These data have implications for the threshold to investigate febrile episodes, suspect bacterial infection and commence appropriate empirical antibiotic therapy. However, it also should be appreciated that immunosuppressed recipients do not always produce a febrile response to infection.

MANAGEMENT OF CYTOMEGALOVIRUS INFECTION AFTER LIVER TRANSPLANTATION

CMV infection is rarely associated with symptomatic illness in healthy hosts, but is a major cause of morbidity and mortality in transplant recipients; it is the single

most common opportunistic infection after solid organ transplantation. In the absence of antiviral prophylaxis the overall incidence of CMV infection after OLT ranges from 23% to 85%, with approximately 50% of those developing clinical disease.

CMV infection most commonly occurs in the first 3 months after OLT, with a peak incidence in the third and fourth week. Infection may be asymptomatic or it may cause a spectrum of illness including fever, thrombocytopenia, neutropenia, pneumonia and hepatitis. The indirect effects of infection probably contribute more to the adverse effects on graft function than direct effects. CMV infection further immunosuppresses the recipient, leading to increased opportunistic fungal infection and also increased risk of Epstein–Barr virus infection which can go on to be associated with post-transplant lymphoproliferative disease. CMV infection is also implicated in increased rejection. In those patients who proceed to transplant who are already receiving immunosuppressive agents, or in those with acute liver failure, CMV disease may present earlier in the clinical course.

The risk of CMV infection post-transplant is dependent on the serological status of both the donor and recipient; the highest risk is associated with donor positive/recipient negative.[70] Proven prophylactic strategies in the high-risk groups include valganciclovir or ganciclovir for 3 months. Currently, intravenous ganciclovir remains the gold standard in the treatment of CMV disease. Therapy will be converted to oral ganciclovir to facilitate discharge from hospital and rehabilitation. There is no evidence to support specific immunoglobulin in addition, but it is frequently added in the management of CMV pneumonitis.[67]

MANAGEMENT OF VIRAL HEPATITIS

Hepatitis C (HCV)-related cirrhosis is the commonest indication for transplantation in both Europe and the United States. Post-transplant, HCV viraemia is universal. Recurrent liver disease, with a more accelerated and aggressive course, is often observed; indeed, 20% are cirrhotic at 5 years post-transplant.[71] Those with histological evidence of recurrence also have a greater incidence of acute rejection. Risk factors for progressive disease post-liver transplantation include donor characteristics (age and donor type), viral characteristics (genotype and viral load), the inflammatory grade of the explanted liver, recipient immune status and immunosuppression regimen. Immunosuppression, especially with steroids, directly increases the HCV RNA serum load. Most transplant programmes therefore convert to single- or double-agent immunosuppression regimens as soon as possible post-transplant.[72] Several strategies to prevent the complications of HCV recurrence post-liver transplant have been attempted: treatment prior to transplant, immediate or peri-operative prophylaxis, early pre-emptive therapy and treatment of established disease. Eradication of the virus prior to transplantation is the ideal approach, and the advent of interferon-free regimens with direct-acting antiviral agents has resulted in sustained virological response reported in 86%–97% of cirrhotic patients across genotypes.[73-76] There is limited evidence to suggest that peri-operative treatment may prevent reinfection of the new graft, and currently there is no established role for this, or early pre-emptive treatment. Studies have shown excellent efficacy of direct-acting antivirals, with or without ribavirin, in the treatment of HCV recurrence post-transplantation, and whilst the side-effect profile is considerably less than the previous interferon-based regimens, drug-drug interactions with CNIs are an important consideration. Retransplantation for HCV recurrence has shown to be a successful possibility should the transplanted liver begin to fail.[77]

Initial results of transplantation for hepatitis B infection were discouraging, largely due to recurrent disease with rapid and fatal progression. The introduction of oral nucleos(t)ide analogues (NA), and effective measures to prevent and treat reinfection, led to a significant improvement in outcomes. Pre-transplantation patients should be treated with NAs, preventing flares and reducing disease progression, and this combined with early post-transplant immunoprophylaxis, with hepatitis G immunoglobulin, has dramatically reduced the re-infection rate to less than 10%. Following transplantation NA therapy must be continued indefinitely. In respect of the modulation of immunosuppression regimens, the comments made with respect to HCV are similarly applicable.

IMMUNOSUPPRESSION

As the field of transplantation evolves, new immunosuppressive regimens and drugs become available. For all combinations, however, there is a balance to be struck between the optimal prevention of rejection and the toxicity and unwanted effects of the drugs. These agents affect T-cell-dependent B-cell activation, targeting different sites in the T-cell activation cascade by inhibiting T-cell activation or causing T-cell depletion. The incidence of acute rejection rises at about 1 week after OLT; it resembles a delayed-type hypersensitivity reaction, and immunosuppressive agents are highly effective at treating it. Chronic rejection occurs over months to years and is characterised by the 'vanishing bile-duct' syndrome, pathological mechanisms are poorly understood and immunosuppressant agents are largely ineffective.[59]

The introduction of CNI immunosuppression revolutionised the outcome of solid organ transplantation, leading to the 1-year survival rates we routinely see today. In most liver transplant programmes, tacrolimus, along with steroids, form the mainstay drugs after liver transplantation, certainly in the early stages.

Tacrolimus is a macrolide compound that inhibits IL-2 and interferon-gamma-production reducing T-cell activation. It is 100 times more potent than ciclosporin A and has become the first-line CNI as it is associated with fewer episodes of acute cellular rejection, steroid-resistant rejection, graft loss and postoperative death. The improvement in short-term survival following the introduction of CNIs has not translated into longer-term survival, with a loss of 7 life years when compared to the non-transplant population. The long-term side effects of CNI immunosuppression, including cardiovascular disease, chronic renal failure and malignancy, contribute significantly to the non-hepatic late deaths post-liver transplantation. Tacrolimus dosing should be individualised and drug levels monitored.

These manifestations of toxicity can be difficult in the management of post-transplant immunosuppression in patients who exhibited encephalopathy or renal dysfunction pre-transplant; the use of agents without nephrotoxic profiles, or strategies to limit the CNI dose (e.g. induction with basiliximab) may be considered in this context. It is usual to have an induction regimen beginning in the peri-operative period; this usually involves a CNI and steroids, which are administered in a high-dose taper regime. With time after transplantation, the required level of immunosuppression decreases and drug doses may be reduced further. Cytotoxic drugs, such as azathioprine or MMF, may also allow further reduction of steroids and CNIs. The long-term effects of immunosuppression have to be considered but are less pertinent in the immediate postoperative period.

Antibodies can be used in patients with pre-existing renal dysfunction, or those at high risk, as a CNI-sparing mechanism, or to minimise steroid use. Basiliximab is a humanised monoclonal antibody against the IL-2 receptor. Blockade of the IL-2 receptor prevents T-cell proliferation. In one study comparing tacrolimus plus steroids to steroid-free tacrolimus plus an IL-2 receptor blocker, graft and patient survival were comparable, but the incidence of biopsy proven acute cellular rejection, diabetes mellitus and CMV infection, were higher in the tacrolimus and steroid group.[78]

Sirolimus is a novel immunosuppressant that has been used extensively in renal transplantation and more recently in liver transplant recipients in whom the CNIs are contraindicated.[59] It resembles tacrolimus structurally, and binds to the same protein, but whereas ciclosporin and tacrolimus act by inhibiting IL-2 gene transcription, sirolimus acts by blocking post-receptor signal transduction and IL-2-dependent proliferation. In addition to its immunosuppressive actions, sirolimus is also an antifungal and antiproliferative agent. Sirolimus lacks neuro- and nephrotoxicity. However, it can raise the intracellular concentrations of ciclosporin A and tacrolimus, indirectly potentiating their toxicity. Hyperlipidaemia has also been noted, although this may be a reflection of the often higher dose steroid regimens used in combination with sirolimus. Because of its antiproliferative effects, sirolimus can also cause thrombocytopenia, neutropenia and anaemia; there have also been concerns about its effects on wound healing. Everolimus is the hydroxyethyl derivative of sirolimus. Its mechanism of action is similar to sirolimus but is secondary to the increased risk of hepatic artery thrombosis, so it should not be used until at least 30 days after liver transplantation. Sirolimus and everolimus also require therapeutic drug-level monitoring, not only because serum concentrations have a high level of intra- and interindividual variability, but also because there are significant interactions with drugs that use the cytochrome P-450 3A system.

Future strategies for limiting the long-term sequelae of immunosuppression hope to utilise the unique hepatic immunological environment, and induce tolerance so that immunosuppression could be withdrawn.

All immunosuppressive regimens should be tailored to individual patient needs and a balance struck between the side effects (short and long term) and the risk of rejection.

READMISSION TO THE INTENSIVE CARE UNIT/LATE COMPLICATIONS

The cause of readmission to the ICU after liver transplantation varies in relation to time after transplantation. Approximately 20% of recipients require readmission, and this correlates with actuarial reduced patient and graft survival. In the period immediately after transplantation, cardiorespiratory failure is the commonest reason for readmission, due to both fluid overload and infection. Indeed, an abnormal pre-discharge chest X-ray is predictive of readmission, as is high central venous pressure and tachypnoea. Other predictors of readmission are age, pre-transplant synthetic function, bilirubin, amount of intraoperative blood products and renal dysfunction. Graft dysfunction, severe sepsis and postoperative care of surgical complications are other important causes of readmission. Bleeding and biliary anastomotic leaks represent the commonest surgical causes for readmission.

LIVER TRANSPLANTATION FOR ACUTE LIVER FAILURE

Acute liver failure is a syndrome associated with an acute onset coagulopathy, jaundice and encephalopathy; the causes are many and the syndrome is notable for its high morbidity and mortality. The acceptance of emergency liver transplantation in selected cases has revolutionised the clinical course, but the outcome is sometimes disappointingly poor, often due to the rapid development of uncontrollable cerebral oedema, sepsis and multiorgan failure.

Table 103.10 King's college hospital prognostic criteria for non-survival among patients with acute liver failure

PARACETAMOL INDUCED	NON-PARACETAMOL INDUCED
pH <7.3 (irrespective of grade of encephalopathy), following volume resuscitation and >24 hours post ingestion	PT >100 s (INR >6.5) irrespective of grade of encephalopathy *or*
or	pH <7.3 following volume resuscitation *or*
PT >100 s (INR > 6.5) *and* creatinine >300 µmol/L in patients with grade III–IV encephalopathy, occurring within a 24-h timeframe	Any three of the following variables (in association with encephalopathy): Age <10 years or >40 years Aetiology: non-A, non-B or drug induced Jaundice to encephalopathy >7 days PT >50 s (INR >3.5) Serum bilirubin >300 µmol/L

INR, International normalised ratio; *PT*, prothrombin time.

There is also a short window of opportunity in listing these patients; despite the highest priority listing they may receive 'marginal' organs or even ABO blood group incompatible organs. Early determination of prognosis and appropriate listing for transplant are clearly important. The King's College Hospital prognostic criteria for non-survival among patients with acute liver failure is a tool used to identify those at high risk while sparing those in whom spontaneous recovery will otherwise occur (Table 103.10). The criteria for paracetamol-induced acute liver failure, and non-paracetamol-induced acute liver failure, were first published in 1989 and were derived from the analysis of patients managed at a single centre between 1973 and 1987.[79] It has been validated both in Europe and the United States. More recently, the advances in the non-transplantation medical management of patients with paracetamol-induced acute liver failure have led to a new novel model being devised that incorporates a dynamic component. Admission data, including age, Glasgow Coma Score, arterial pH and lactate, creatinine, INR, SOFA cardiovascular failure, are used to derive an initial predictive model, with changes to blood lactate levels and INR on day 2 to predict 30-day survival.[80] This model has yet to be prospectively validated but, as with other models in critically ill patients, sequential assessment will provide additional prognostic value.

PAEDIATRIC LIVER TRANSPLANTATION

OLT is the treatment of choice for children with end-stage liver disease. Cholestatic disorders make up the largest indication for transplantation, with extrahepatic biliary atresia plus or minus previous Kasai porto-enterostomy accounting for over 50% of paediatric transplants. Metabolic diseases and primary hepatic tumours are also common indications. As in adult recipients, multisystem effects of end-stage liver disease are common, and the occurrence of liver disease as part of a congenital syndrome (e.g. Alagille's) may warrant invasive pre-operative evaluation of extrahepatic manifestation. Scarce availability of paediatric donors has driven innovations such as reduced size grafts, split-liver techniques and living donor programmes, which have all contributed to expand the pool of available donors and reduce the mortality for those children waiting for suitable organs.

One of the biggest problems associated with paediatric transplantation is the relatively high incidence of vascular complications such as hepatic artery thrombosis, portal vein thrombosis and venous outflow obstruction. Risk factors for these conditions include fulminant hepatic failure, long operation time, donor/recipient age and weight discrepancies, young recipient age, low recipient weight and arterial reconstruction techniques. In order to minimise these often devastating complications, strategies to minimise the risk include delayed primary closure of the abdominal wall, haematocrit maintained at 22%–25% to ensure laminar flow, and the avoidance of platelets and blood components combined with considered use of anticoagulants.

Associated cardiac, pulmonary or renal abnormalities observed in some paediatric syndromes with liver disease may require particular attention and management such as the pulmonary stenosis seen in association with Alagille syndrome.

Ten-year survival rates of 74% (age 12–17 years) to 84% (age 1–5 years) has brought about a new set of challenges relating to complications and management of long-term immunosuppression. The concept of tolerance-inducing immunosuppressive regimens has spurned a number of studies investigating this phenomenon.[81]

REFERENCES

1. Roberts MS, Angus DC, Bryce CL, et al. Survival after liver transplantation in the United States: a disease-specific analysis of the UNOS database. *Liver Transpl*. 2004;10:886–897.
2. Habib S, Berk B, Chang CC, et al. MELD and prediction of post-liver transplantation survival. *Liver Transpl*. 2006;12:440–447.
3. Futagawa Y, Terasaki PI. An analysis of the OPTN/UNOS Liver Transplant Registry. *Clin Transpl*. 2004; 315–329.

4. Burroughs AK, Sabin CA, Rolles K, et al. 3-month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome. *Lancet*. 2006;367:225–232.
5. Fink MA, Berry SR, Gow PJ, et al. Risk factors for liver transplantation waiting list mortality. *J Gastroenterol Hepatol*. 2007;22:119–124.
6. Krowka MJ. Hepatopulmonary syndrome and portopulmonary hypertension: implications for liver transplantation. *Clin Chest Med*. 2005;26:587–597.
7. Mazzaferro V, Bhoori S, Sposito C, et al. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. *Liver Transpl*. 2011;17:S44–S57.
8. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology*. 2001;33:1394–1403.
9. Rana A, Hardy MA, Halazun KJ, et al. Survival outcomes following liver transplantation (SOFT) score: a novel method to predict patient survival following liver transplantation. *Am J Transplant*. 2008;8:2537–2546.
10. Dutkowski P, Oberkofler CE, Slankamenac K, et al. Are there better guidelines for allocation in liver transplantation?: a novel score targeting justice and utility in the Model for End stage Liver Disease era. *Ann Surg*. 2011;254:745–754.
11. Fusai G, Dhaliwal P, Rolando N, et al. Incidence and risk factors for the development of prolonged and severe intrahepatic cholestasis after liver transplantation. *Liver Transpl*. 2006;12:1626–1633.
12. Carlisle JB. Assessing fitness, predicting outcome, and the missing axis. *Br J Anaesth*. 2012;109:35–39.
13. Thuluvath PJ. Morbid obesity and gross malnutrition are both poor predictors of outcome after liver transplantation: what can we do about it? *Liver Transpl*. 2009;15:838–841.
14. Pelletier SJ, Schaubel DE, Wei G, et al. Effect of body mass index on the survival benefit of liver transplantation. *Liver Transpl*. 2007;13:1678–1683.
15. Watt KD. Reducing the load: the evolution and management of obesity and non-alcoholic steatohepatitis before liver transplantation. *Liver Transpl*. 2012;18:S52–S58.
16. Machicao VI, Fallon MB. Hepatopulmonary syndrome. *Semin Respir Crit Care Med*. 2012;33:11–16.
17. Krowka MJ, Plevak D. The distinct concepts and implications of hepatopulmonary syndrome and portopulmonary hypertension. *Crit Care Med*. 2005; 33:470.
18. Schiffer E, Majno P, Mentha G, et al. Hepatopulmonary syndrome increases the postoperative mortality rate following liver transplantation: a prospective study in 90 patients. *Am J Transplant*. 2006; 6:1430–1437.
19. Krowka MJ. Portopulmonary hypertension. *Semin Respir Crit Care Med*. 2012;33:17–25.
20. Krowka MJ. Evolving dilemmas and management of portopulmonary hypertension. *Semin Liver Dis*. 2006; 26:265–272.
21. Moreau R, Lebrec D. Acute kidney injury: new concepts. *Nephron Physiol*. 2008;109:73–79.
22. Salerno F, Gerbes A, Gines P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut*. 2007;56:1310–1318.
23. Ruiz R, Barri YM, Jennings LW, et al. Hepatorenal syndrome: a proposal for kidney after liver transplantation (KALT). *Liver Transpl*. 2007;13: 838–843.
24. Ruiz R, Kunitake H, Wilkinson AH, et al. Long-term analysis of combined liver and kidney transplantation at a single center. *Arch Surg*. 2006;141:735–741.
25. Wai CT, Lim SG, Aung MO, et al. MARS: a futile tool in centres without active liver transplant support. *Liver Int*. 2007;27:69–75.
26. Banares R, Nevens F, Larsen FS, et al. Extracorporeal liver support with the molecular adsorbent recirculating system (MARS) in patients with acute-on-chronic liver failure (AOCLF). The RELIEF trial. *J Hepatol*. 2010;52:S459–S471.
27. Nyberg SL. Bridging the gap. *Liver Transpl*. 2012;18: S10–S14.
28. Reddy KS, Johnston TD, Putnam LA, et al. Piggyback technique and selective use of veno-venous bypass in adult orthotopic liver transplantation. *Clin Transplant*. 2000;14:370–374.
29. Parrilla P, Sanchez-Bueno F, Figueras J, et al. Analysis of the complications of the piggy-back technique in 1112 liver transplants. *Transplant Proc*. 1999; 31:2388–2389.
30. Cabezuelo JB, Ramirez P, Acosta F, et al. Does the standard vs piggyback surgical technique affect the development of early acute renal failure after orthotopic liver transplantation? *Transplant Proc*. 2003;35:1913–1914.
31. Heaton N. Small-for-size liver syndrome after auxiliary and split liver transplantation: donor selection. *Liver Transpl*. 2003;9:S26–S28.
32. Monbaliu D, Van Gelder F, Troisi R, et al. Liver transplantation using non-heart-beating donors: Belgian experience. *Transplant Proc*. 2007;39: 1481–1484.
33. Muiesan P, Girlanda R, Jassem W, et al. Single-center experience with liver transplantation from controlled non-heartbeating donors: a viable source of grafts. *Ann Surg*. 2005;242:732–738.
34. Deshpande R, Heaton N. Can non-heart-beating donors replace cadaveric heart-beating liver donors? *J Hepatol*. 2006;45:499–503.
35. Chan SC, Fan ST, Lo CM, et al. Effect of side and size of graft on surgical outcomes of adult-to-adult live donor liver transplantation. *Liver Transpl*. 2007; 13:91–98.
36. PolidoJr WT, Lee KH, Tay KH, et al. Adult living donor liver transplantation in Singapore: the Asian centre for liver diseases and transplantation experience. *Ann Acad Med Singapore*. 2007;36:623–630.
37. Tucker ON, Heaton N. The 'small for size' liver syndrome. *Curr Opin Crit Care*. 2005;11:150–155.
38. Chan SC, Lo CM, Liu CL, et al. Tailoring donor hepatectomy per segment 4 venous drainage in

right lobe live donor liver transplantation. *Liver Transpl*. 2004;10:755–762.
39. Cheaito A, Craig B, Abouljoud M, et al. Sonographic differences in venous return between piggyback versus caval interposition in adult liver transplantations. *Transplant Proc*. 2006;38:3588–3590.
40. Chan SC, Fan ST, Lo CM, et al. Toward current standards of donor right hepatectomy for adult-to-adult live donor liver transplantation through the experience of 200 cases. *Ann Surg*. 2007;245: 110–117.
41. Sakai T, Matsusaki T, Dai F, et al. Pulmonary thromboembolism during adult liver transplantation: incidence, clinical presentation, outcome, risk factors, and diagnostic predictors. *Br J Anaesth*. 2012;108:469–477.
42. Vannucci A, Johnston J, Earl TM, et al. Intraoperative transoesophageal echocardiography guides liver transplant surgery in a patient with thrombosed transjugular intrahepatic portosystemic shunt. *Anesthesiology*. 2011;115:1389–1391.
43. Moller S, Bendtsen F, Henrikson JH. Effect of volume expansion on systemic hemodynamics and central and arterial blood volume in cirrhosis. *Gastrolenterology*. 1995;109:1917–1925.
44. Awad S, Dharmavaram S, Wearn CS, et al. Effects of an intraoperative infusion of 4% succinylated gelatine (Gelofusine) and 6% starch (Voluven) on blood volume. *Br J Anaesth*. 2012;109:168–176.
45. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *NEJM*. 2011;365:147–156.
46. Pereboom ITA, Lisman T, Porte RJ. Platelets in liver transplantation: friend or foe? *Liver Transpl*. 2008;14:923–931.
47. Ranucci M, Solomon C. Supplementation of fibrinogen in acquired bleeding disorders: experience, evidence, guidelines, and licences. *Br J Anaesth*. 2012; 109:135–137.
48. Yun BC, Kim WR, Biggins SW, et al. Impact of pretransplant hyponatremia on outcome following liver transplantation. *Hepatology*. 2009;49:1610–1615.
49. Cirrhotic cardiomyopathy: multiple reviews. *Liver Transpl*. 2007;13:1060–1061.
50. Lee RF, Glenn TK, Lee SS. Cardiac dysfunction in cirrhosis. *Best Pract Res Clin Gastroenterol*. 2007;21: 125–140.
51. Milani A, Zaccaria R, Bombardieri G, et al. Cirrhotic cardiomyopathy. *Dig Liver Dis*. 2007;39:507–515.
52. Mandell MS, Lindfield J, Tsou MY, et al. Cardiac evaluation of liver transplant candidates. *World J Gastroenterol*. 2008;14:3445–3451.
53. Dhar R, Young GB, Marotta P. Perioperative neurological complications after liver transplantation are best predicted by pre-transplant hepatic encephalopathy. *Neurocrit Care*. 2008;8:253–258.
54. Saner F, Gu Y, Minouchehr S, et al. Neurological complications after cadaveric and living donor liver transplantation. *J Neurol*. 2006;253:612–617.
55. Charlton MR, Wall WJ, Ojo AO, et al. Report of the first international liver transplantation society expert panel consensus conference on renal insufficiency in liver transplantation. *Liver Transpl*. 2009;15:S1–S34.
56. Lebrón Gallardo M, Herrera Gutierrez ME, Seller Pérez G, et al. Risk factors for renal dysfunction in the postoperative course of liver transplant. *Liver Transpl*. 2004;10:1379–1385.
57. O'Riordan A, Wong V, McQuillan R, et al. Acute renal disease, as defined by the RIFLE criteria, post-liver transplantation. *Am J Transplant*. 2007;7:168–176.
58. Rahman S, Davidson BR, Mallett SV. Early acute kidney injury after liver transplantation: predisposing factors and clinical implications. *World J Hepatol*. 2017;9(18):823–832.
59. Perry I, Neuberger J. Immunosuppression: towards a logical approach in liver transplantation. *Clin Exp Immunol*. 2005;139:2–10.
60. Biancofiore G, Bindi ML, Romanelli AM, et al. Renal failure and abdominal hypertension after liver transplantation: determination of critical intra-abdominal pressure. *Liver Transpl*. 2002;8: 1175–1181.
61. Biancofiore G, Bindi ML, Romanelli AM, et al. Postoperative intra-abdominal pressure and renal function after liver transplantation. *Arch Surg*. 2003;138:703–706.
62. Fischer-Frohlich CL, Lauchart W. Expanded criteria liver donors (ECD): effect of cumulative risks. *Ann Transplant*. 2006;11:38–42.
63. Kawecki D, Chmura A, Pacholczyk M, et al. Bacterial infections in the early period after liver transplantation: etiological agents and their susceptibility. *Med Sci Monit*. 2009;15:628–637.
64. Avkan-Oguz V, Ozkardesler S, Unek T. Risk factors for early bacterial infections in liver transplantations. *Transplant Proc*. 2013;45:993–997.
65. Philpott-Howard J, Burroughs A, Fisher N, et al. Piperacillin-tazobactam versus ciprofloxacin plus amoxicillin in the treatment of infective episodes after liver transplantation. *J Antimicrob Chemother*. 2003;52:993–1000.
66. Safdar N, Said A, Lucey MR. The role of selective digestive decontamination for reducing infection in patients undergoing liver transplantation: a systematic review and meta-analysis. *Liver Transpl*. 2004;10:817–827.
67. Patel G, Huprikar S. Infectious complications after orthotopic liver transplantation. *Semin Respir Crit Care Med*. 2012;33:111–124.
68. Husain S, Tollemar J, Dominguez EA. Changes in the spectrum and risk factors for invasive candidiasis in liver transplantation recipients: prospective, multicentre, case-controlled study. *Transplantation*. 2003;75:2023–2029.
69. Cruciani M, Mengoli C, Malena M, et al. Antifungal prophylaxis in liver transplant patients: a systematic review and meta-analysis. *Liver Transpl*. 2006;12:850–858.
70. Limaye AP, Bakthavatsalam R, Kim HW, et al. Impact of cytomegalovirus in organ transplant recipients in the era of antiviral prophylaxis. *Transplantation*. 2006;81:1645–1652.

71. Gringeri E, Vitale A, Brolese A, et al. Hepatitis C virus-related cirrhosis as a significant mortality factor in intention-to-treat analysis in liver transplantation. *Transplant Proc*. 2007;39:1901–1903.
72. Llado L, Xiol X, Figueras J, et al. Immunosuppression without steroids in liver transplantation is safe and reduces infection and metabolic complications: results from a prospective multicenter randomized study. *J Hepatol*. 2006;44:710–716.
73. Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. *Gastroenterology*. 2015;149:649–659.
74. Bourliere M, Bronowicki J, de Ledinghen V, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-ionhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). *Lancet Infect Dis*. 2015;15: 397–404.
75. Gane EJ, Hyland RH, An D, et al. Eficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks in patients with HCV genotype 3 or 6. *Gastroenterology*. 2015;149:1454–1461.
76. Curry MP, O'Leary JG, Bzowej N. Sofosbuvir and velpatasvir for HCV in patients with deompensated cirrhosis. *NEJM*. 2015;373:2618–2628.
77. Ghabril M, Dickson RC, Machicao VI, et al. Liver retransplantation of patients with hepatitis C infection is associated with acceptable patient and graft survival. *Liver Transpl*. 2007;13:1717–1727.
78. Boillot O, Mayer DA, Boudjema K, et al. Corticosteroid-free immunosuppression with tacrolimus following induction with daclizumab: a large randomized control study. *Liver Transpl*. 2005;11:61.
79. O'Grady JG, Alexander GJ, Hayllar KM, et al. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology*. 1989;97:439–445.
80. Bernal W, Wang Y, Maggs J, et al. Development and validation of a dynamic outcome prediction model for paracetamol-induced acute liver failure: a cohort study. *Lancet Gastroenterol Hepatol*. 2016;1: 217–225.
81. Samyn M. Optimising outcomes for pediatric recipients. *Liver Transpl*. 2012;18:S34–S38.

104a

Heart transplantation

Priya Nair, Paul C Jansz, Peter S Macdonald

INTRODUCTION

The first human to human heart transplant was performed in 1967 by Christiaan Barnard at Groote Schuur Hospital in South Africa. It was a surgical success with the donor heart functioning well immediately post-transplant; however, the patient died 18 days later from pneumonia resulting from immunosuppressive therapy. There followed an initial wave of enthusiasm with multiple centres around the world commencing heart transplant programmes. Initial results were poor, however, with high early mortality rates and few long-term survivors. Many institutions abandoned the procedure and only a handful of heart transplant programmes persisted throughout the 1970s. The discovery of cyclosporine and its introduction into clinical transplantation in the late 1970s led to renewed interest in heart transplantation with a rapid growth in transplant activity throughout the 1980s. Since then more than 100,000 heart transplants have been reported to the Registry of the International Society for Heart & Lung Transplantation (ISHLT).[1] Currently, it is estimated that approximately 5000 transplants are performed each year in over 300 countries.[2] The survival rate after heart transplantation has improved steadily over the last two decades and currently approaches 85% at 1 year, 75% at 5 years and 56% at 10 years. Median survival is 12 years. Heart transplantation is now well established as the most effective treatment available for end-stage heart failure.

Heart transplantation is limited by donor organ availability. Historically, the vast majority of deceased donors for heart transplantation were brain dead (DBD). More recently, donation after circulatory death (DCD) has re-emerged as an important source of donor lungs as well as abdominal organs, and in some cardiopulmonary transplant programmes up to one-third of lung transplants are performed from DCD donors.[3] Distant procurement and successful heart transplantation from DCD donors has now been reported by three centres using normothermic ex vivo perfusion.[4–6] Increased utilisation of hearts from DCD donors is anticipated in the years ahead.

Virtually all of the improvement in heart transplant survival over the last 20 years has been during the first few months after transplantation.[2] The improvement in survival can be explained by a number of factors including advances in immunosuppressive therapy with fewer deaths due to uncontrollable rejection or infection, and better patient selection.

THE POTENTIAL HEART DONOR

Of all organs retrieved, the heart is the one most susceptible to the multiple insults that occur during brain death and the subsequent events that occur during donor organ retrieval and transplantation. Studies involving repeated echocardiographic examination of the brain-dead donor have revealed that left ventricular systolic dysfunction is common and that it often improves together with haemodynamic status after a period of aggressive donor management.[7]

In addition to its susceptibility to the adverse consequences of brain death, the heart is the donor organ least tolerant to the obligatory ischaemia reperfusion injury (IRI) that occurs during retrieval and implantation. Data from the ISHLT Registry indicates that as the donor heart ischaemic time (the time from cross clamp of the aorta in the donor to release of the aortic cross clamp in the recipient) increases beyond 3 hours there is a progressive increase in the mortality rate at 1 year post-transplant.[2]

DONOR ELIGIBILITY CRITERIA

Donor eligibility criteria vary between jurisdictions. Those that are currently utilised in Australia and New Zealand are summarised in Table 104a.1.[8] As indicated, donors are subdivided into standard criteria and higher risk donors based on a range of donor characteristics, which, if present, are associated with an increased risk of graft failure and lower survival. Echocardiographic assessment of the donor heart is recommended in all cases. Donor heart dysfunction does not necessarily imply pre-existing disease, but is associated with an increased risk of primary graft failure (PGF).[9,10] In donors with suspected coronary artery disease, coronary angiography is recommended, if available.

ABSTRACT

Heart transplantation has emerged as the most effective treatment available for patients with end-stage heart disease. Transplantation is limited by donor numbers so that only a small percentage of patients who might benefit are able to undergo the procedure. The severe shortage of donor organs has resulted in an increased utilisation of higher risk donors with an associated risk of primary graft dysfunction or failure, which poses significant challenges during the initial intensive care unit management of these patients. Nonetheless, the large majority of heart transplant recipients make an excellent recovery following transplant surgery and return to a quality of life that is close to that of normal people of the same age. Almost two-thirds of heart transplant recipients live for more than 10 years and one-third live for more than 20 years after transplantation. Improvements in donor management and organ preservation should increase the number of cardiothoracic organs available for transplantation while ongoing refinements to post-transplant management are likely to result in further improvements in the long-term survival of these patients.

KEYWORDS

Heart transplantation
ex-vivo heart perfusion
ventricular assist device

Table 104a.1 Standard versus higher risk criteria for donor hearts

DONOR PARAMETER	STANDARD CRITERIA	HIGHER RISK CRITERIA (MARGINAL)
Age	<50 years	>50 years
Donor cardiac history	Nil	Pre-existing disease
Donor co-morbidities	Absent	Hepatitis B, C
Echocardiography*	Normal	Global dysfunction (LVEF <50%) Major regional wall motion abnormality Left ventricular hypertrophy (LV wall >13 mm)
Coronary angiography*	Normal or non-occlusive disease	Occlusive coronary artery disease
Haemodynamic status	Stable	Unstable with high CVP (and/or PAoP) and low BP
Inotropic support	Low	High (>0.2 ug/kg/min of noradrenaline or equivalent)
Ischaemic time	<6 h	>6 h

*Severe abnormalities will generally result in non-use of the organ.

BP, Blood pressure; *CVP*, central venous pressure; *LV*, left ventricle; *LVEF*, left ventricular ejection fraction; *PAop*, pulmonary artery occlusion pressure.

DONOR MANAGEMENT

Management of the multiorgan donor has been discussed in detail elsewhere.

However, hormonal resuscitation is of specific relevance to cardiac transplantation. Vasopressin has been administered to the brain-dead donor often as part of a multihormonal cocktail usually with high-dose steroids and thyroid hormone, and its use results in the sparing of catecholamines, such as noradrenaline, which improves the suitability of the donor heart.[11] Use of other hormonal therapies, particularly thyroid hormone administration is controversial. In a recent systematic review, Macdonald and co-authors identified 16 case series and 7 prospective randomised controlled trials (RCTs) of thyroid hormone administration to brain-dead potential organ donors.[12] Whereas all case series reported a beneficial effect of thyroid hormone administration on a range of outcomes including donor haemodynamic stability and donor heart utilisation, none of the RCTs reported any benefit from thyroid hormone administration. Despite this controversy, thyroid hormone administration in conjunction with other hormonal therapies has been recommended as part of an aggressive management protocol for the potential cardiothoracic donor and has been incorporated into the UNOS Critical Pathway for the Organ Donor.[13]

DONOR HEART PRESERVATION

The most common method of donor heart preservation involves cardioplegia with a cold hyperkalaemic crystalloid solution then cold static storage in a preservation solution in an ice chest during transport between donor and recipient hospitals. There are multiple preservation solutions in use reflecting a lack of consensus regarding the optimal composition of these solutions.[14] All provide good preservation for up to 3 hours but beyond this there is a steady increase in the rate of PGF and mortality. This has led to a renewed interest in the use of ex vivo machine perfusion (MP) to transport hearts between donor and recipient hospitals. These provide oxygen to the donor heart and restore aerobic metabolism, thereby minimising the ischaemic insult to the donor heart. A prospective randomised trial of normothermic MP versus cold static storage of donor hearts from standard criteria donors demonstrated equivalent outcomes[15]; however, uncontrolled case series suggest that MP may yield better post-transplant outcomes when used for the preservation of higher risk donors.[16]

SELECTION OF PATIENTS FOR HEART TRANSPLANTATION

Eligibility criteria for heart transplantation have been extensively reviewed elsewhere and recently revised.[17–19] Heart transplantation is restricted to patients with end-stage heart disease who have exhausted all alternative therapies. Most patients have long-standing heart failure due either to ischaemic heart disease or some form of cardiomyopathy.[1,2] A substantial proportion of these patients require long-term mechanical circulatory support with ventricular assist devices (VADs) (so-called bridge to transplant) and currently between 30% and 50% of wait-listed patients are on such support.[1,2] There has been a dramatic evolution in the design – from large pulsatile pumps to small continuous flow devices – which have proven to be far more durable.[20,21] Two-year survival rates for persons supported on continuous flow devices are now better than 80%.[21,22] Patients on long-term

VAD support are managed as outpatients and undergo cardiac rehabilitation to optimise their physical condition prior to transplant surgery. VAD support has also been used in patients who are otherwise marginal candidates for heart transplantation due to factors such as renal impairment and pulmonary hypertension (so called 'bridge to decision'). Long-term support has been associated with reversal of these co-morbidities in several case series.[23,24]

Historically, heart transplantation has been restricted to younger patients; however, as highlighted in a recent publication of the ISHLT registry, older patients are undergoing heart transplantation.[25] Both advanced age and end-stage heart failure may be associated with physical frailty, which has been shown to be an independent predictor of mortality and is associated with increased morbidity with heart transplantation.[26] Routine frailty screening is now recommended for all patients referred for heart transplantation.[19]

Severe, irreversible pulmonary hypertension with a pulmonary vascular resistance (PVR) greater than 6–8 Wood units, which is unresponsive to pulmonary vasodilators remains one of the few contraindications. This is related to the excessive afterload placed on the donor heart and the possibility of acute right ventricular failure in the recipient. The degree of responsiveness of the pulmonary vasculature is key in patient selection. Some centres consider severe pulmonary hypertension to be a relative contraindication only and consider patients after medical therapy with pulmonary vasodilators and right ventricular inotropes in an outpatient setting and/or subject them to combined heart-lung transplantation.[27]

A small proportion of patients require consideration for transplantation present acutely in cardiogenic shock following acute myocardial infarction, cardiac surgery (post-cardiotomy) or fulminant myocarditis. Short-term survival of these patients is usually dependent on acute mechanical circulatory support, for example, with veno-arterial extracorporeal membrane oxygenation (VA-ECMO). Following the stabilisation of vital organ function and the establishment that the heart will not recover, these patients will usually be transitioned to a VAD for long-term support (so-called 'bridge to bridge').[28] Alternatively, they may be listed for urgent heart transplantation.[29]

HEART TRANSPLANT SURGERY

Heart transplantation can be performed either as an orthotopic or heterotopic procedure. The vast majority are performed orthotopically by excising the native heart and implanting the donor heart in its place. The original surgical technique described by Shumway and Lower is still widely performed. This technique involves anastomosis of the left and right donor atria to the back walls of the corresponding recipient atria containing the central connections of the vena cava and pulmonary veins. An alternative surgical technique involves bicaval anastomosis. The right atrial bicaval anastomosis can be performed alone or in conjunction with anastomosis at the level of the pulmonary veins rather than at the level of the left atrium. The proposed advantages of this technique include better preservation of atrial anatomy and function with a reduced risk of atrial thrombosis, atrial arrhythmias and atrio-ventricular (AV) valve regurgitation during long-term follow-up. Surgical series comparing these two approaches, however, suggest that long-term clinical outcomes are similar.[30]

Heterotopic heart transplantation refers to a rarely performed technique in which the native heart is retained and the donor heart is implanted 'in parallel'. The operation is achieved by anastomosing the left and right atria 'back to back' and then connecting the donor pulmonary artery and aorta to the recipient pulmonary artery and aorta with end-to-side anastomoses. The most common indication is for recipients with fixed pulmonary hypertension. In this setting, an allograft, which is used to operating against normal pulmonary pressures, would fail once transplanted into an environment of pulmonary hypertension.

Once the atrial, pulmonary artery and aortic connections are completed, vents are placed in the left ventricle (LV) and the aorta, the heart is de-aired and the cross clamp released. Temporary pacing wires are placed onto the heart and the heart is allowed a period of reperfusion while on cardiopulmonary bypass (CPB). The duration of the unloaded reperfusion varies and is related to the ischaemic time. A heart that has endured an ischaemic time (from cross clamp in the donor to reperfusion in the recipient) of 4 hours may be given up to 1 hour of reperfusion before commencing separation from CPB and allowing the heart to work. Separation from CPB and the completion of the procedure needs to proceed carefully as the transplanted heart, in particular the right ventricle (RV), is prone to acute failure.

POST-TRANSPLANT MANAGEMENT

IMMEDIATE POST-TRANSPLANT CARE AND MONITORING

In the stable uncomplicated case after transfer to the intensive care unit (ICU), the patient is extubated usually after 6–8 hours. Routine monitoring includes electrocardiogram (ECG), arterial line, pulmonary artery catheter, central venous line and urinary catheter. In some centres, separate left atrial and central venous pressure (CVP) lines have been used instead of the pulmonary artery catheter; however, the latter has the advantage of providing a calculated measure of the PVR. Pericardial, mediastinal and one or more pleural drains will be in place.

PHYSIOLOGY OF THE TRANSPLANTED HEART

The rhythm of the transplanted heart in the immediate post-transplant period is highly variable. While there may be early establishment of sinus rhythm, usually the heart is profoundly bradycardic during the first few days. Typically the sinus rate increases steadily over the first 1 to 2 weeks post-transplant and eventually stabilises at a resting rate between 90 and 100 per minute. Surgery performed with bi-atrial anastomosis may result in the appearance of dual P waves on the ECG arising from the donor and recipient atria. This is eliminated in the case of bicaval anastomosis.

As the heart is denervated, the effect of drugs is altered (Table 104a.2). Those that act by augmenting or inhibiting vagal efferent activity (e.g. digoxin, atropine) will have no effect on the transplanted heart. The transplanted heart is often 'stunned' by the IRI that occurs in the first 24 hours after transplantation. During this period the heart often demonstrates diastolic dysfunction with a restrictive filling pattern, which may persist for days. Persistent diastolic dysfunction beyond the first week post-transplant suggests the development of acute rejection.

CARDIAC RHYTHM AND PACING

AV sequential pacing with temporary pacing wires is routine in the immediate post-transplant period. Filling pressures of 10–15 mm Hg may be required to ensure adequate diastolic filling, but due to the impairment of the Frank–Starling mechanism (increased stroke volume with raised preload) from IRI, AV sequential pacing at rates up to 110 per minute may be required to maintain a normal cardiac output and stable arterial pressure. During the first week, the sinus rhythm of the transplanted heart usually increases steadily and pacing is weaned and suspended when a stable sinus rhythm above 60 per minute is established. Administration of amiodarone to the recipient prior to transplantation may delay sinus node recovery. Between 5% and 10% of transplanted hearts remain profoundly bradycardic and require implantation of a permanent pacemaker, usually after 3 weeks, which is allowed for the recovery of sinus rhythm. Oral beta agonists have been used to accelerate sinus node recovery, but it is unclear whether they are effective.

Atrial fibrillation is less common than after other forms of cardiac surgery possibly due to better preservation of atrial myocardium. Atrial flutter occurring beyond the first week post-transplant is suggestive of acute rejection and should prompt endomyocardial biopsy. If pacing wires are still present they can be used to attempt atrial overdrive pacing (AOD). Alternatively AOD pacing can be performed at the completion of the biopsy procedure. Ventricular tachyarrhythmias are very uncommon and are usually observed in the setting of severe PGF.

VASOACTIVE AGENTS

The goal in the immediate postoperative phase is to achieve an appropriate cardiac output and perfusion pressure to preserve organ function. Due to the autonomic denervation, the transplanted heart usually requires some level of chronotropic and inotropic support with catecholamines both for the right and left ventricles. At the same time, however, it is important to consider the vulnerability of the graft from IRI, and the requirement of escalating doses of catecholamines, which inevitably increase myocardial oxygen requirement, may signify the need for mechanical support in the form of intra-aortic balloon counter pulsation or VA-ECMO.

Table 104a.2 Effect of drugs on denervated heart

DRUG	EFFECT ON THE HEART	MECHANISM
Digoxin	Increased contractility; Minimal effect on AV node	Direct myocardial effect; denervation
Atropine	None	Denervation
Adrenaline	Increased contractility; increased chronotropy	Denervation hypersensitivity
Noradrenaline	Increased contractility; increased chronotropy	Denervation hypersensitivity
Isoprenaline	Normal increase in contractility; normal increase in chronotropy	No neuronal uptake
Hydralazine	No reflex tachycardia	Denervation
Beta-blockers	Increased antagonist effect	Denervation
Verapamil	Blocks AV node	Direct effect
Nifedipine	No reflex tachycardia	Denervation

AV, Atrio-ventricular.

With permission from Deng M. Cardiac transplantation. *Heart*. 2002;87:177-184.

Isoprenaline has been used traditionally in the immediate post-transplant phase based on its chronotropic, inotropic and pulmonary vasodilator properties. In the absence of large trials, it is unclear whether these properties make it any more effective than alternative inotropic agents such as dobutamine, milrinone and adrenaline. Adrenaline or noradrenaline is often co-administered if the patient is hypotensive from post CPB vasoplegia. Thyroid hormone administration to the heart transplant recipient has been advocated by some authors but as with its use in the donor, its administration to the recipient is controversial. A recent pilot RCT of levosimendan-based versus standard inotropic therapy in the early postoperative period demonstrated a lower incidence of peri-operative acute kidney injury (AKI) – albeit with a higher vasopressor requirement and longer ICU stays.[31] Usually, inotropic and vasopressor support can be weaned within the first 48–72 hours as the donor heart recovers.

Pulmonary hypertension in the postoperative phase can be damaging due to this increased afterload presented to an untrained RV. While an element of this might be 'fixed' from long-standing heart disease, most centres use inhaled nitric oxide or prostacyclin in the immediate postoperative phase to ameliorate this. Small studies in the post-transplantation phase have shown the ability of these agents to selectively dilate pulmonary vessels and thereby reduce pulmonary artery pressures and CVP, as well as increase cardiac output and mixed venous oxygen saturation.[32]

Prior to heart transplant, the recipient's arterial circulation in many cases has adapted to chronic hypotension with systolic blood pressures in the range of 80–90 mm Hg. Replacement of an end-stage failing heart with a healthy donor heart often leads to a rapid increase in blood pressure in the recipient as the donor heart regains normal function over the first few days post-transplant. This may be further exacerbated by the introduction of calcineurin inhibitors (CNIs), which can cause renal and systemic vasoconstriction. Systolic blood pressures in excess of 140 mm Hg in the first weeks after heart transplantation may result in hypertensive encephalopathy, which may manifest as headache, drowsiness and seizures. Therefore, strict control of blood pressure, initially with intravenous vasodilators, such as glyceryl trinitrate then with oral agents, may be required during this early postoperative phase.

RESPIRATORY MANAGEMENT

As mentioned, in uncomplicated cases extubation is generally achieved in the first few hours. An appreciation of cardiopulmonary interactions is especially relevant in these patients. Minimising PVR by ventilating at appropriate lung volumes (close to functional residual capacity), optimising oxygenation and minimising acidosis are important considerations. Similarly the effects of increase in systemic preload and afterload with extubation should be anticipated in patients with unstable graft function.

FLUID THERAPY AND RENAL MONITORING

Judicious attention to volume status is a key component of the early ICU management. This is due to the vulnerable state of the RV and its sensitivity to large volume boluses, which could result in a spiral of progressive RV dilatation and dysfunction. Similarly, blood and product therapy should be rationalised owing to their potential adverse effect on PVR. Patients who have had a prior left ventricular assist device are more likely to suffer bleeding due to extensive dissection and anticoagulant therapy, and use of viscoelastic tests (such as thromboelastography) to guide haemostatic therapy may be of benefit.

The incidence of AKI in heart transplant recipients varies with definitions used, but approximately 6%–10% require continuous renal replacement therapy (CRRT) in the postoperative phase. Although the majority of these patients do not require long-term renal replacement therapy (RRT), they have a higher mortality rate. Risk factors for AKI in a study of 307 consecutive recipients in Europe were previous cardiac operation, blood transfusion, troponin release and length of ischemic time.[33] Patients who are fluid overloaded may benefit from early CRRT to overcome the adverse consequences of myocardial and other organ oedema. Additionally, consideration of reduction of CNI dose or alternative immunosuppression may be required.

IMMUNOSUPPRESSION

Maintenance immunosuppression initially involves the administration of three drugs in combination – high-dose corticosteroids, an anti-metabolite (mycophenolate mofetil or azathioprine) and a CNI (cyclosporine or tacrolimus). Some transplant units also use *induction* therapy, either a T cell cytolytic agent (e.g. antithymocyte globulin) or an antibody that specifically blocks the activated IL2 receptor (e.g. basiliximab).[1,2] The T cell cytolytic agents not only are more potent immunosuppressive agents, but also are associated with more side effects related to the acute destruction of large numbers of T cells in the circulation (the so-called 'cytokine release syndrome'). Their use is associated with an increased risk of viral and fungal infections as well as later development of post-transplant lymphoproliferative disease (PTLD). The IL2R inhibitors have a much better side effect profile and their use is not associated with any increased risk of infection or PTLD.

INFECTION PROPHYLAXIS

With currently used immunosuppressive drug protocols, the risk of infection is relatively low. Prophylactic antibiotic therapy is routine. A cephalosporin administered intravenously over the first 24 hours is

routine; however, the choice of antibiotic may vary if the recipient is known to be colonised with multi-resistant organisms. Pneumocystis prophylaxis in the form of oral co-trimoxazole is commenced in the first week post-transplantation and continued indefinitely. Nystatin oral solution to prevent oropharyngeal candidiasis is also administered for the first 2 weeks post-transplant. Prophylaxis against other fungi particularly aspergillus varies and depends on local resistance patterns. Inhaled amphotericin for the first week followed by oral itraconazole for 3 months is one approach. In the event of a cytomegalovirus (CMV) mismatch (CMV-positive donor with CMV-negative recipient) oral valganciclovir is administered for the first 3–6 months. Some centres also administer valganciclovir to CMV-positive recipients.

Other routine drugs administered in the immediate post-transplant period including a typical post-transplant drug treatment protocol are listed in Table 104a.3.

Table 104a.3 Peri-operative heart transplant drug treatment protocols currently utilised in the heart transplant unit at St Vincent's Hospital, Sydney

AREA	
Pre-operative on ward	Mycophenolate mofetil 1.5 g p.o.
In anaesthetic bay	Basiliximab 20 mg IV: if creatinine >120 µmol/L on night of transplant, or previously recorded creatinine >120 µmol/L, or LVAD, BiVAD or TAH (Give second dose of 20 mg IV on day 4) Vitamin K 10 mg IV: if on warfarin Methylprednisolone 500 mg IV Ganciclovir 5 mg/kg IV: if CMV mismatch (D+/R–). Cefazolin 500 mg
In theatre off bypass	Methylprednisolone 500 mg IV Cefazolin 500 mg IV
ICU or ward	IMMUNOSUPPRESSION
	DAY 1
	Tacrolimus 0.5 mg p.o. or via nasogastric tube: if Cr <140 µmol/L: give test dose or, if unable to commence oral therapy, commence infusion at 0.015 mg/kg/day IV given as continuous infusion over 24 h If Cr >140 µmol/L: hold tacrolimus until creatinine <140 µmol/L Methylprednisolone 125 mg IV q8h × 3 doses Myocphenolate mofetil 1 g IV/p.o. b.d.
	DAY 2 ONWARDS
	Prednisolone 1.0 mg/kg/day p.o. in two divided doses until 2 weeks post-transplant then wean by 0.1 mg/kg/day each week until complete withdrawal Mycophenolate mofetil 1 g IV/p.o. b.d. Tacrolimus capsules p.o. b.d. as charted (titrate to target trough level of 8–12 µg/L by day 7) Basiliximab 20 mg IV on day *4 – if given as induction*
	BACTERIAL PROPHYLAXIS
	Cefazolin 1 g IV q8h × 3 doses
	FUNGAL PROPHYLAXIS
	Nystatin drops 1 mL p.o. q.i.d. Sulfamethoxazole 800 mg p.o. *and* Trimethoprim 160 mg (Bactrim DS), once daily on Mondays and Fridays. Itraconazole 200 mg p.o. b.d. to be given until 12 weeks post-transplant Measure itraconazole trough level on day 14 (target >500 µg/L) Tacrolimus level must be rechecked when itraconazole ceased
	VIRAL PROPHYLAXIS
	If CMV mismatch: ganciclovir 5 mg/kg/day IV on Monday, Wednesday and Friday until IV line is removed Then continue with valganciclovir 450 mg p.o. b.d. (adjusted to renal function) to be given until 12 weeks post-transplant

Continued

Table 104a.3 Peri-operative heart transplant drug treatment protocols currently utilised in the heart transplant unit at St Vincent's Hospital, Sydney—cont'd

PAIN MANAGEMENT
Morphine 1–2.5 mg IV p.r.n. Morphine 5–10 mg IM/SC p.r.n. Paracetamol 1 g p.o./IV q.i.d.
BOWEL MANAGEMENT
Docusate with sennosides (50 mg, 8 mg) p.o. 2 b.d. Movicol p.o. 1 sachet daily
GIT PROTECTION
Ranitidine 50 mg IV t.d.s., followed by Ranitidine 150 mg p.o. b.d. on ward
LIPID MANAGEMENT
Pravastatin 40 mg p.o. nocte
BONE PROTECTION
Cholecalciferol 1000 U p.o. daily Calcium citrate 2 tablets p.o. daily

BiVAD, Biventricular assist device; *CMV*, cytomegalovirus; *LVAD*, left ventricular assist device; *TAH*, total artificial heart.

Table 104a.4 Complications of heart transplantation

COMPLICATION	APPROXIMATE INCIDENCE	COMMENTS
ACUTE		
Primary graft failure	10%–20%	Requiring mechanical support with IABP, VA-ECMO or VAD
Acute rejection	25%–30%	Requiring pulse steroids in first 12 months
Bradycardia requiring pacemaker	11%	Majority sinus node dysfunction – bi-atrial technique
Acute kidney injury	15%	RIFLE score I or F, 6%–10% require RRT, very few require long-term RRT
Infection	Variable	Affected by host factors, level of immunosuppression, time after transplant.
Tricuspid regurgitation (TR)	19%–84%	Ranging from mild to severe. About 15% have long-term TR
CHRONIC		
Chronic allograft vasculopathy	11%, 22% and 45%	Angiographically detectable at year 1, 2 and 4 years
Neoplasms	2–4-fold increased risk	Predominantly skin and PTLD

IABP, Intra-aortic balloon pump; *PTLD*, post-transplant lymphoproliferative disorder; *RIFLE*, risk, injury, failure, loss, end-stage kidney disease; *RRT*, renal replacement therapy; *TR*, tricuspid regurgitation; *VAD*, ventricular assist devices; *VA-ECMO*, veno-arterial extracorporeal membrane oxygenation.

COMPLICATIONS

PRIMARY GRAFT FAILURE

PGF is a syndrome in which the transplanted heart fails to meet the circulatory requirements of the recipient in the immediate post-transplant period as a consequence of either single or biventricular dysfunction (Table 104a.4). It is manifested as hypotension and low cardiac output in the presence of adequate filling pressures.[9,10] In most instances, it is likely to result from a multifactorial process with contributing elements from the donor, the recipient and the transplant process.[9] PGF is the most feared early complication after heart transplantation and accounts for approximately 40% of all deaths within the first month.[2] The reported incidence varies widely between studies with estimates ranging between 2.3% and 26%.[9] Most of the variability can be attributed to inconsistent definitions used by different authors. When defined as the need for high dose inotropes or mechanical assist devices in the immediate post-transplant period, most investigators

Table 104a.5 International society for heart and lung transplantation diagnostic criteria and grading of primary graft dysfunction after heart transplantation

PRESENCE OF	EVIDENCED BY
Appropriate time frame	Onset <24 h post transplantation
Ventricular systolic dysfunction – left, right or biventricular dysfunction	Echocardiographic evidence of dysfunction
Cardiogenic shock lasting more than 1 h	Low systolic blood pressure <90 mm Hg and/or Low cardiac output – <2 L/min/m^2 Despite adequate intra-cardiac filling pressures – CVP >15 mm Hg and/or PAoP >20 mm Hg
Circulatory support	Mild: Low dose inotropes Moderate: High dose inotropes (Inotrope score >10) or need for IABP Severe: Need for total circulatory support: extracorporeal membrane oxygenation (ECMO) or equivalent
Exclusion of secondary causes of primary graft failure (PGF)	For example, cardiac tamponade, hyperacute rejection

CVP, Central venous pressure; *IABP*, intra-aortic balloon pump; *PAop*, pulmonary artery occlusion pressure.

Table 104a.6 Recognised risk factors for primary graft failure after heart transplantation

DONOR FACTORS	RECIPIENT FACTORS	PROCEDURAL FACTORS
Age >30 years	Age >60 years	Ischaemic time >180 min
Cardiac dysfunction on echo	Ventilator support	Donor recipient weight mismatching
High-dose inotropic support	Intravenous inotropic support, mechanical support	Female donor to male recipient
Cause of brain death	Pulmonary hypertension	Concomitant lung retrieval
Primary graft dysfunction of other organs	Overweight, diabetes mellitus	

have reported incidence rates of 10%–20% or higher. Standardised diagnostic criteria for PGF have now been developed and are listed in Table 104a.5.[10] A number of risk factors, which are donor-related, recipient-related and procedure-related, have been identified (Table 104a.6).

The management of PGF depends on the severity and the mechanism. Right ventricular failure is commonly the main contributor. The donor heart, especially when it is young and comparably small, cannot easily adapt to the often-observed pulmonary hypertension and increased PVR of the recipient. Additionally, adaptation of the donor heart may be impaired by IRI associated with organ preservation and inflammation triggered by CPB. As a result, the RV dilates and becomes ischemic which further reduces contractility. The decrease in pulmonary blood flow and the leftward shift of the interventricular septum lead to a change of the LV shape, a lower LV preload and a reduction of systemic pressure and cardiac output, which further impairs coronary perfusion. Principles of management of RV failure are listed in Table 104a.7.[34–36]

Table 104a.7 Principles of management of right ventricular failure

- Maintaining RV coronary perfusion pressure with vasopressor drugs
- Preventing RV overload by minimising excess fluid administration while monitoring the CVP closely
- Reducing (PVR) with selective pulmonary vasodilator therapy (inhaled nitric oxide or epoprostenol)
- Augmenting RV contractility by administration of inodilator drugs and using pacing as required

CVP, Central venous pressure; *PVR*, pulmonary vascular resistance; *RV*, right ventricle.

Small reports suggest that levosimendan may be a useful, adjunctive inotropic drug in the treatment of patients with primary graft dysfunction after heart transplantation.[37] In severe cases, implantation of an acute right ventricular assist device (RVAD) may be required. Longer acting agents, such as oral sildenafil, may be required to allow weaning of nitric oxide and RVAD support in such cases.[38] In severe cases

of left- or bi-ventricular failure, the early institution of total mechanical circulatory support is essential to avoid multiorgan failure.[39,40] A number of acute mechanical support options are available, but the most widely used device is VA-ECMO, which can be deployed by either peripheral or central cannulation.[39,40] Total circulatory support may be required for 7 days or longer.

INFECTIONS

Infections encountered in heart transplant recipients during the ICU phase of management are similar to those affecting routine cardiac surgical cases. Risk factors for bacterial sepsis that are of particular importance for the heart transplant recipient include pre-transplant mechanical or ventilator support and the need for high dose peri-operative immunosuppression. Other factors associated with an increased risk of sepsis in the ICU patient, such as previous colonisation with multiresistant bacteria, large volume blood loss and transfusion, acute renal failure or placement of intravenous lines, also apply to the heart transplant recipient. Classic signs of sepsis, such as high fever, may be masked or blunted by immunosuppressive therapy, so a high index of suspicion is required. Infections usually respond to conventional antibiotic therapy but choice will depend on local sensitivities. The herpes simplex virus is common in the early post-transplant period and usually responds to oral acyclovir. Clinical infections with other viruses (e.g. herpes zoster and CMV) usually have a more delayed onset after the ICU phase of treatment. Oropharyngeal candidiasis is probably the most common fungal infection and is usually preventable with oral nystatin. Occasionally, patients may present with early candidaemia, which is an important consideration in the acutely septic patient. Other fungal infections, such as aspergillus, may also occur during the immediate postoperative period but more typically occur at a later time point.

ACUTE REJECTION

Acute rejection is an adaptive immune response mounted by the recipient against the transplanted donor organ. Classical acute rejection is predominantly a T lymphocyte-mediated inflammatory response directed against the grafted organ. As the rejection response progresses, graft injury in the form of myocyte necrosis and myocardial oedema develop. In more severe rejection, other inflammatory cells, such as eosinophils and neutrophils, are recruited into the myocardium, and myocardial haemorrhage may occur. Acute cellular rejection can occur at any time but is unusual during the first week. It may be suspected on clinical grounds but is often completely asymptomatic. Symptoms are often non-specific and include fatigue, dyspnoea and fever.

Diagnosis is based on the pathological finding of a lymphocytic inflammatory infiltrate on endomyocardial biopsy, and the grading of severity is based on the extent of the inflammatory infiltrate and the presence or absence of myocyte necrosis.[41] Most transplant programmes perform regular surveillance endomyocardial biopsies commencing at about 1 week post-transplant. Biopsies are repeated weekly for the first month post-transplant, fortnightly between months 1 and 3, monthly between months 4 and 6 then less commonly thereafter, or may be performed at any time between scheduled biopsies if there is a clinical suspicion of rejection.

The overall rate of biopsy-proven acute rejection has been declining in recent years probably as a result of more effective immunosuppressive therapy.[2] Historically, most patients experienced one or more episodes of acute rejection requiring 'pulsed' steroid therapy (e.g. intravenous methylprednisolone 0.5–1.0 g daily for three doses) during the first 3 months after transplantation; however, recent registry reports indicate that only one in three heart transplant recipients will require this during the first 12 months.[2]

Antibody-mediated rejection is also now recognised as a major cause of graft injury and loss.[42] It occurs as a result of the formation of donor-specific antibodies (DSA) in the recipient that are directed usually against donor human leukocyte antigens. These may be present pre-transplant as a result of previous transfusions, organ transplants, viral infections or pregnancies. Hyperacute rejection (HAR) occurring during the first hours or days post-transplant is usually triggered by the presence of preformed DSA in high circulating titres. Fortunately, this is now a rare event as DSAs are normally detected by prospective or virtual cross-matching between the donor and recipient.[43] HAR often presents with rapid onset of severe graft dysfunction and may be difficult to distinguish from PGF. Apart from acute circulatory support, treatment involves high-dose intravenous steroids, plasmapheresis and intravenous immunoglobulin.[44] In more severe cases, monoclonal antibody treatments have been used, including rituximab and eculizumab.[44]

TRICUSPID REGURGITATION

This is the most common valvular abnormality, occurring in 19%–84% of patients, depending on the definition of significant regurgitation. In the early stages after transplantation, most tricuspid regurgitation (TR) is functional and is usually secondary to geometric distortion of the AV annular ring, and preservation of atrial and tricuspid annulus geometry may prevent the development of TR. The ISHLT guidelines recommend that patients who are identified after surgery as having moderate to severe TR should have a repeat echocardiogram in the first 24 hours after the transplantation.[45] Most patients can be managed conservatively, mainly with diuretics, and only rarely do they require surgical

intervention. Routine endomyocardial biopsies, which are required for monitoring rejection, may contribute to the TR.

LATE COMPLICATIONS

Late complications of cardiac transplant, which are sometimes encountered in the ICU patient include:

Cardiac allograft vasculopathy (CAV) – This is among the primary causes of death after the first year. This disease, which is atherosclerotic in nature and progresses rapidly, is characterised by persistent perivascular inflammation and intimal proliferation. It is sometimes considered to be a manifestation of chronic rejection. Early diagnosis of CAV is limited due to the scarcity of clinical symptoms of ischemia in the denervated graft.[46,47]

Neoplasms are among the major causes of late mortality with a two- to fourfold increase in risk compared to the general population. This elevated risk is related to the immunosuppression regimen and includes the malignant tumours related to viral infections, such as lymphoma (as a part of the PTLD) – both linked to infection by the Epstein–Barr virus, Kaposi sarcoma (related to the human herpes-virus 8), anogenital cancers (linked to the human papilloma virus) and hepatic cancer (hepatitis B and C virus).[47]

CONCLUSIONS

Heart transplantation has emerged as the most effective treatment available for patients with end-stage heart disease. Transplantation is limited by donor numbers so that only a small percentage of patients who might benefit are able to undergo the procedure. The severe shortage of donor organs has resulted in an increased utilisation of higher risk donors with an associated risk of primary graft dysfunction or failure, which poses significant challenges during the initial ICU management of these patients. Nonetheless, the large majority of heart transplant recipients make an excellent recovery following transplant surgery and return to a quality of life that is close to that of normal people of the same age. Almost two-thirds of heart transplant recipients live for more than 10 years and one-third live for more than 20 years after transplantation. Improvements in donor management and organ preservation should increase the number of cardiothoracic organs available for transplantation, while ongoing refinements to post-transplant management are likely to result in further improvements in the long-term survival of these patients.

REFERENCES

1. Lund LH, Edwards LB, Dipchand AI, et al. The Registry of the International Society for Heart and Lung Transplantation: thirty-third adult heart transplantation report – 2016; focus theme: primary diagnostic indications for transplant. *J Heart Lung Transplant*. 2016;35(10):1158–1169.
2. Stehlik J, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-eighth adult heart transplant report – 2011. *J Heart Lung Transplant*. 2011;30(10):1078–1094.
3. Coulson TG, Pilcher DV, Graham SM, et al. Single-centre experience of donation after cardiac death. *Med J Aust*. 2012;197(3):166–169.
4. Dhital KK, Iyer A, Connellan M, et al. Adult heart transplantation with distant procurement and ex-vivo preservation of donor hearts after circulatory death: a case series. *Lancet*. 2015;385(9987):2585–2591.
5. Garcia Saez D, Bowles CT, Mohite PN, et al. Heart transplantation after donor circulatory death in patients bridged to transplant with implantable left ventricular assist devices. *J Heart Lung Transplant*. 2016;35(10):1255–1260.
6. Messer SJ, Axell RG, Colah S, et al. Functional assessment and transplantation of the donor heart after circulatory death. *J Heart Lung Transplant*. 2016;35(12):1443–1452.
7. Zaroff JG, Babcock WD, Shiboski SC, et al. Temporal changes in left ventricular systolic function in heart donors: results of serial echocardiography. *J Heart Lung Transplant*. 2003;22(4):383–388.
8. Zealand TSoAaN. Authority AOaT, ed. *Clinical Guidelines for Organ Transplantation From Deceased Donors*. Canberra, Australia: Transplantation Society of Australia and New Zealand; 2016. http://www.donatelife.gov.au/sites/default/files/TSANZ%20Clinical%20Guidelines%20for%20Organ%20Transplantation%20from%20Deceased%20Donors_Version%201.0_April%202016.pdf.
9. Iyer A, Kumarasinghe G, Hicks M, et al. Primary graft failure after heart transplantation. *J Transplant*. 2011;2011:175768.
10. Kobashigawa J, Zuckermann A, Macdonald P, et al. Report from a consensus conference on primary graft dysfunction after cardiac transplantation. *J Heart Lung Transplant*. 2014;33(4):327–340.
11. Rosendale JD, Kauffman HM, McBride MA, et al. Aggressive pharmacologic donor management results in more transplanted organs. *Transplantation*. 2003;75(4):482–487.
12. Macdonald PS, Aneman A, Bhonagiri D, et al. A systematic review and meta-analysis of clinical trials of thyroid hormone administration to brain dead potential organ donors. *Crit Care Med*. 2012;40(5):1635–1644.
13. Zaroff JG, Rosengard BR, Armstrong WF, et al. Consensus conference report: maximizing use of organs recovered from the cadaver donor: cardiac recommendations, March 28–29, 2001, Crystal City, Va. *Circulation*. 2002;106(7):836–841.
14. Demmy TL, Biddle JS, Bennett LE, et al. Organ preservation solutions in heart transplantation

– patterns of usage and related survival. *Transplantation*. 1997;63(2):262–269.
15. Ardehali A, Esmailian F, Deng M, et al. Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial. *Lancet*. 2015;385(9987):2577–2584.
16. Garcia Saez D, Zych B, Sabashnikov A, et al. Evaluation of the organ care system in heart transplantation with an adverse donor/recipient profile. *Ann Thorac Surg*. 2014;98(6):2099–2105, discussion 2105–2106.
17. Macdonald P. Heart transplantation: Who should be considered and when? *Intern Med J*. 2008;38(12):911–917.
18. Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: international society for heart and lung transplantation guidelines for the care of cardiac transplant candidates – 2006. *J Heart Lung Transplant*. 2006;25(9):1024–1042.
19. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant*. 2016; 35(1):1–23.
20. Strueber M, O'Driscoll G, Jansz P, et al. Multicenter evaluation of an intrapericardial left ventricular assist system. *J Am Coll Cardiol*. 2011;57(12): 1375–1382.
21. Schmitto JD, Zimpfer D, Fiane AE, et al. Long-term support of patients receiving a left ventricular assist device for advanced heart failure: a follow-up analysis of the Registry to Evaluate the HeartWare Left Ventricular Assist System. *Eur J Cardiothorac Surg*. 2016;50(5):834–838.
22. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med*. 2009;361(23):2241–2251.
23. Torre-Amione G, Southard RE, Loebe MM, et al. Reversal of secondary pulmonary hypertension by axial and pulsatile mechanical circulatory support. *J Heart Lung Transplant*. 2010;29(2):195–200.
24. Iwashima Y, Yanase M, Horio T, et al. Serial changes in renal function as a prognostic indicator in advanced heart failure patients with left ventricular assist system. *Ann Thorac Surg*. 2012;93(3):816–823.
25. Lund LH, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: thirtieth official adult heart transplant report – 2013; focus theme: age. *J Heart Lung Transplant*. 2013;32(10):951–964.
26. Jha SR, Hannu MK, Chang S, et al. The prevalence and prognostic significance of frailty in patients with advanced heart failure referred for heart transplantation. *Transplantation*. 2016;100(2):429–436.
27. Deng M. Cardiac transplantation. *Heart*. 2002;87:177–184.
28. Shah P, Smith S, Haft JW, et al. Clinical outcomes of advanced heart failure patients with cardiogenic shock treated with temporary circulatory support before durable LVAD implant. *ASAIO J*. 2016;62(1):20–27.
29. Jasseron C, Lebreton G, Cantrelle C, et al. Impact of heart transplantation on survival in patients on venoarterial extracorporeal membrane oxygenation at listing in France. *Transplantation*. 2016;100(9):1979–1987.
30. Huenges K, Panholzer B, Fritzsche K, et al. Over ten years of experience with a modified right atrial anastomosis in orthotopic heart transplantation: follow-up and comparison with the biatrial and bicaval technique. *Thorac Cardiovasc Surg*. 2016.
31. Knezevic I, Poglajen G, Hrovat E, et al. The effects of levosimendan on renal function early after heart transplantation: results from a pilot randomized trial. *Clin Transplant*. 2014;28(10):1105–1111.
32. Ardehali A, Hughes K, Sadeghi A, et al. Inhaled nitric oxide for pulmonary hypertension after heart transplantation. *Transplantation*. 2001;72(4):638–641.
33. De Santo LS, Romano G, Amarelli C, et al. Implications of acute kidney injury after heart transplantation: what a surgeon should know. *Eur J Cardiothorac Surg*. 2011;40(6):1355–1361, discussion 1361.
34. Khan TA, Schnickel G, Ross D, et al. A prospective, randomized, crossover pilot study of inhaled nitric oxide versus inhaled prostacyclin in heart transplant and lung transplant recipients. *J Thorac Cardiovasc Surg*. 2009;138(6):1417–1424.
35. Buckley MS, Feldman JP. Inhaled epoprostenol for the treatment of pulmonary arterial hypertension in critically ill adults. *Pharmacotherapy*. 2010;30(7):728–740.
36. Rea RS, Ansani NT, Seybert AL. Role of inhaled nitric oxide in adult heart or lung transplant recipients. *Ann Pharmacother*. 2005;39(5):913–917.
37. Weis F, Beiras-Fernandez A, Kaczmarek I, et al. Levosimendan: a new therapeutic option in the treatment of primary graft dysfunction after heart transplantation. *J Heart Lung Transplant*. 2009; 28(5):501–504.
38. Lee JE, Hillier SC, Knoderer CA. Use of sildenafil to facilitate weaning from inhaled nitric oxide in children with pulmonary hypertension following surgery for congenital heart disease. *J Intensive Care Med*. 2008;23(5):329–334.
39. Marasco SF, Vale M, Pellegrino V, et al. Extracorporeal membrane oxygenation in primary graft failure after heart transplantation. *Ann Thorac Surg*. 2010;90(5):1541–1546.
40. Listijono DR, Watson A, Pye R, et al. Usefulness of extracorporeal membrane oxygenation for early cardiac allograft dysfunction. *J Heart Lung Transplant*. 2011;30(7):783–789.
41. Stewart S, Winters GL, Fishbein MC, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. *J Heart Lung Transplant*. 2005;24(11):1710–1720.
42. Kobashigawa J, Crespo-Leiro MG, Ensminger SM, et al. Report from a consensus conference on

antibody-mediated rejection in heart transplantation. *J Heart Lung Transplant*. 2011;30(3):252–269.
43. Stehlik J, Islam N, Hurst D, et al. Utility of virtual crossmatch in sensitized patients awaiting heart transplantation. *J Heart Lung Transplant*. 2009;28(11):1129–1134.
44. Chih S, Tinckam KJ, Ross HJ. A survey of current practice for antibody-mediated rejection in heart transplantation. *Am J Transplant*. 2013;13(4): 1069–1074.
45. Wong RC, Abrahams Z, Hanna M, et al. Tricuspid regurgitation after cardiac transplantation: an old problem revisited. *J Heart Lung Transplant*. 2008; 27(3):247–252.
46. Avery RK. Cardiac-allograft vasculopathy. *N Engl J Med*. 2003;349(9):829–830.
47. Mangini S, Alves BR, Silvestre OM, et al. Heart transplantation: review. *Einstein (Sao Paulo)*. 2015; 13(2):310–318.

104b

Lung transplantation

Priya Nair, Paul C Jansz, Marshall Plit

INTRODUCTION

Lung transplantation commenced in the 1960s but, as with heart transplantation, early results were poor and the procedure was largely abandoned until the 1980s. The first successful heart–lung transplant was performed at Stanford University Medical Center in 1981. During the next decade, single and bilateral lung transplantation emerged as viable procedures for patients with end-stage lung disease. The International Society for Heart and Lung Transplantation (ISHLT) registry reports more than 55,000 lung transplants and currently, internationally, more than 4000 lung transplants are performed each year.[1] Post-transplant survival – although not as good as for other organs – has improved steadily. In the most recent ISHLT report, median post-transplant survival was 7 years with 80% survival at 1 year, 54% at 5 years and 32% at 10 years.[2] Whereas heart transplant activity has plateaued in the last decade, lung transplant activity has been increasing steadily.[2]

Historically, the vast majority of donors had undergone brain death (DBD). More recently, donation after circulatory death (DCD) has re-emerged as an important source of donor lungs and in some programmes up to one-third of lung transplants are performed from DCD donors.[3,4]

Virtually all of the improvements in survival have been during the first few months after transplantation.[5] This can be explained by advances in immunosuppressive therapy, with fewer deaths due to uncontrolled rejection or infection, and better patient selection. Nonetheless, the first few days and weeks after transplantation are still a period of high mortality risk due mainly to the complications of primary graft dysfunction (PGD) or overwhelming infection.

SELECTION OF PATIENTS FOR LUNG TRANSPLANTATION

The primary indication is the presence of advanced, non-malignant lung disease for which there is no alternative therapy. Guidelines for selection have been extensively reviewed elsewhere.[6] The major disease categories are chronic obstructive pulmonary disease (COPD)/emphysema including alpha$_1$-antitrypsin (AAT) deficiency, pulmonary fibrosis, cystic fibrosis (CF), bronchiectasis and pulmonary vascular disease.[5] Collectively, these diseases account for over 90% of cases.[6] Bilateral lung transplantation is the most commonly performed, and accounts for approximately 75% of procedures.[6] Single lung transplantation is still occasionally performed for non-AAT deficiency-associated COPD and pulmonary fibrosis, but rarely for other lung diseases. Combined heart/lung transplantation is now a relatively rare procedure.

A critical aspect of the decision making regarding suitability is the capacity of the patient to survive the stresses of surgery and postoperative recovery. For this reason, patients who are either acutely or chronically unwell are deemed unsuitable. Objective criteria for defining these characteristics are lacking and decisions have, to a large extent, been based on clinical judgement.[7] Quantitative measures of frailty may provide a more objective measure on which to base decisions; however, considerable further research is required.[7,8] The problem has been further compounded by the lack of an 'artificial lung' to bridge patients on ventilatory support and enable participation in a rehabilitation programme prior to transplant surgery. Extracorporeal membrane oxygenation (ECMO) support in ambulatory patients or the use of extracorporeal carbon dioxide removal devices may go some way towards addressing this limitation.[9,10]

In general, patients with acute respiratory failure (e.g. adult respiratory distress syndrome [ARDS], pneumonia) requiring ECMO are not considered suitable due to the uncertain recovery from the underlying illness. Proposed contraindications for transplantation in this patient group are listed in Table 104b.1.[11] Due to the lack of evidence, these are based on small case series and expert opinion.

THE POTENTIAL LUNG DONOR

The donor lung has a greater tolerability to the sequelae of brain death and subsequent insults associated with lung retrieval and transplantation than was initially

ABSTRACT

Lung transplantation has emerged as the most effective treatment available for patients with non-malignant end-stage lung disease. Transplantation is limited by donor numbers, so that only a small percentage of patients who might benefit are able to undergo the procedure. The severe shortage of donor organs has resulted in an increased utilisation of higher risk donors with an associated risk of primary graft dysfunction or failure, which poses significant challenges during the initial intensive care unit (ICU) management of these patients. Nonetheless, the large majority of lung transplant recipients make an excellent recovery following transplant surgery and return to a quality of life that is close to that of a healthy non-transplant population. Median survival following lung transplantation is 6 years with one-third of patients now living beyond 10 years. Improvements in donor management, organ preservation and the availability of donor lungs after circulatory death, in addition to brain death, should increase the number of cardiothoracic organs available for transplantation. Ongoing refinements to post-transplant management are likely to result in further improvements in the long-term survival of these patients.

KEYWORDS

Single lung transplantation
bilateral sequential lung transplantation
heart–lung transplantation
ex-vivo lung perfusion

Table 104b.1 Proposed contraindications for bridging to transplant from extracorporeal membrane oxygenation

Irreversible extra pulmonary organ failure
Septic shock
Severe arterial occlusive disease
Relative
Advanced age
Limited institutional experience
Poor pre-morbid functional status with limited rehabilitation potential
Obesity (BMI >30)
Heparin-induced thrombocytopenia
Prolonged mechanical ventilation

BMI, Body mass index.

Table 104b.2 Standard versus higher risk criteria for donor lungs

DONOR PARAMETER	STANDARD CRITERIA	HIGHER RISK CRITERIA (MARGINAL)
Age	<60 years	>60 years
Smoking history	<20 pack years	>20 pack years
Chest trauma	Absent	Present
Aspiration	Absent	Present
Chest X-ray	Clear	Abnormal
Arterial blood gases	Pa_{O_2} >300 mm Hg on Fi_{O_2} of 100%	Pa_{O_2} >300 mm Hg on Fi_{O_2} of 100%
Sputum	Nil or minimal	Purulent, documented infection
Bronchoscopy	Clear or minimal secretions	Purulent

considered. In particular, the tolerability to ischaemia reperfusion injury (IRI) is better than that of the heart. Donor lung function appears to be less affected by age and donors up to age 75 years are considered. DCD donors account for increasing proportions of solid-organ transplants.[3,4]

DONOR ELIGIBILITY CRITERIA

These vary between jurisdictions and categories for standard and higher risk donors (see Table 104b.2). While there have been concerns that the use of higher risk donors will lead to increased rates of PGD and death, for characteristics such as donor age, donor Pa_{O_2} or mode of death (DCD vs DBD) this has not been corroborated.[12,13] Moreover, the risk associated with donors with characteristics associated with higher mortality (e.g. smoking) needs to be balanced against the risk of death on the waiting list.[14]

Intensive care management of the donor is covered in a separate chapter.

DONOR LUNG PRESERVATION

The major method of preservation has been the administration of a cold pneumoplegic solution followed by static storage in a preservation solution. Perfadex, a normokalaemic colloid (dextran 40) solution, has emerged as the favoured solution for both DBD and DCD organs.

A major advance has been the use of ex-vivo lung preservation (EVLP) devices. This concept was first advanced by Steen[15,16] and later developed by Keshavjee,[17] who reported that EVLP could be used not only to prevent deterioration but also to restore function in lungs from extended criteria donors. A number of EVLP devices have been approved for clinical use[18] including a portable normothermic perfusion device.[19]

LUNG TRANSPLANT SURGERY

Bilateral lung transplantation was initially developed as an en-bloc technique with a single tracheal anastomosis; however, the high incidence of ischaemic anastomotic complications has led to this procedure largely being replaced by bilateral sequential single lung transplant (BSSLT) procedure. BSSLT is most commonly performed with the larger right lung transplanted first followed by the left. The surgical approach may be via a midline sternotomy, horizontal bilateral thoracosternotomy (clam-shell incision), or two smaller anterolateral thoracotomies (without division of the sternum).[20] The operation may be performed with or without cardiopulmonary bypass (CPB), depending on the ability of the native lung to sustain the cardiac output and ventilation during implantation of the first lung, and then the ability of the transplanted lung to sustain the cardiac output and ventilation during implantation of the second lung.[21] While CPB ensures the maintenance of adequate ventilation and vital organ perfusion, it requires anticoagulation and is associated with an increased risk of peri-operative bleeding and PGD.[21,22] CPB does, however, offer the advantage of better operating conditions, and importantly allows control of lung reperfusion conditions. In the absence of CPB, the newly transplanted right lung must take over ventilation in order for the left lung to be implanted. At this time the transplanted right lung will receive the entire cardiac output, which could be detrimental. A cuff of donor left atrial tissue containing the confluence of the pulmonary veins is anastomosed

to the recipient left atrium followed by the anastomosis of the donor to recipient pulmonary artery and finally the main bronchus. More recently, improved short- and long-term outcomes have been demonstrated with lung transplant surgery performed on veno-arterial ECMO as compared to conventional CPB.[23]

Single lung transplantation is performed via a thoracotomy with the order of anastomoses being bronchus, left atrium and pulmonary artery. Combined heart–lung transplantation is the most extensive cardiothoracic transplant and is restricted almost exclusively to patients with complex congenital heart disease with irreversible pulmonary vascular disease. The operation is performed on CPB as an en-bloc procedure with sequential anastomosis of the trachea, right atrium and aorta. Uncontrollable bleeding from adhesions formed during previous thoracic operations or from systemic to pulmonary arterial collaterals is a leading cause of operative death. Damage to major nerves (e.g. vagus, phrenic and recurrent laryngeal) is another potential complication and may contribute to postoperative morbidity.

ANAESTHETIC CONSIDERATIONS

Specific recipient pathology and cardiorespiratory status should be taken into consideration. When surgery is performed off CPB, single lung ventilation needs to be safely and effectively established.

In addition to standard monitoring lines listed below, intraoperative transoesophageal echocardiography is used to evaluate volume status, assess myocardial (particularly right ventricular) function, assess pulmonary pressures, rule out intracardiac shunts and evaluate vascular (particularly pulmonary venous) anastomosis after allograft implantation.[24]

POSTOPERATIVE MANAGEMENT IN THE INTENSIVE CARE UNIT

Optimal management requires an understanding of the unique pathophysiological challenges that apply to these patients.

Transplantation results in denervation below the level of the bronchial anastomosis (or below the tracheal anastomosis in the case of heart–lung transplantation). The main consequence is loss of the normal cough reflex and markedly impaired mucociliary clearance, so patients are at high risk of sputum retention during the early postoperative phase. Respiration both at rest and during exercise is unaffected by lung denervation. Pulmonary vascular resistance, airway resistance and reactivity also appear to be unaffected.

Routine monitoring includes electrocardiography, invasive arterial and central venous lines, pulmonary artery catheter and urinary catheter. Apical and basal pleural drains will be in place and are placed on continuous suction. Air leaks can occur in the first few days but are usually minor and self-limiting. Bronchoscopy is performed to check the bronchial anastomosis and to suction any secretions. Postoperative analgesia requires careful attention using opiate-sparing strategies where possible, such as thoracic epidural infusions, which promote better respiratory function.

RESPIRATORY MANAGEMENT

The goal is to wean and extubate the patient as soon as this can be safely achieved in the individual context. There is limited evidence on optimum postoperative ventilatory management; however, data from the ARDS literature have been extrapolated to this situation.[25,26] Important considerations that distinguish this cohort from other postoperative patients include recent thoracotomies, phrenic nerve dysfunction, pleural dysfunction, air leaks and donor-patient size mismatch. Additionally, as discussed below, increased capillary permeability from IRI contributes to the risk of acute lung injury.

An international survey showed that ventilation practices varied greatly between transplant centres in 18 countries.[27] Most did not consider donor characteristics in their strategy. In the absence of randomised controlled trials in this area to inform practice, recommendations for bilateral lung transplant recipients include using tidal volumes of 6 mL/kg recipient body weight, limiting peak pressures to less than 35 cm of water, using the minimum Fi_{O_2} to achieve Pa_{O_2} of 60–80 mm Hg and the use of positive end-expiratory pressure (PEEP), but limited to less than 12.5 cm due to the increased risk of air leaks.[11] Two studies[25,28] have demonstrated an association between high inflation pressures and poor outcomes, as well as higher tidal volumes with severity of PGD, respectively, adding weight to these recommendations.

Ventilation for the unilateral lung transplant patient for emphysema presents further challenges due to the risk of hyperinflation of the native lung, which is more compliant than the transplanted lung, which can result in mediastinal shift and haemodynamic instability. Additionally, the hyperinflated lung compresses the allograft, which results in atelectasis and impaired gas exchange. This situation has been reported in 15%–30% of unilateral procedures.[29] Therefore earlier extubation is particularly advantageous. Occasionally, single lung transplant recipients may require placement of a double-lumen endotracheal tube to allow differential ventilation of the native and transplanted lungs.

In case of postextubation respiratory failure, non-invasive ventilation or high-flow nasal prongs in cases of isolated hypoxaemic respiratory failure may be effective strategies to prevent re-intubation. In case of re-intubation, early tracheostomy may facilitate weaning.[11] Approximately 14% of lung transplant recipients require prolonged mechanical ventilation. In a single-centre study, this was associated with

decreased survival. However the patients who survived to hospital discharge had similar outcomes compared to those who did not require prolonged mechanical ventilation.[30]

HAEMODYNAMIC MANAGEMENT

Most patients will require vasopressors, which can generally be weaned in the first few hours.

Recipients with pulmonary hypertension or right ventricular failure require close monitoring and potentially require the use of inodilators, such as milrinone or dobutamine, in addition to selective inhaled pulmonary vasodilators, such as nitric oxide or prostacyclin, to reduce right ventricular afterload.

Arrhythmias are common in the postoperative period, particularly in older patients with an incidence of 34%–75%, and are predominantly supraventricular. These are treated with cardioversion when haemodynamically significant or with medical therapy as in other situations.[31]

Calcineurin inhibitors (CNIs) in combination with corticosteroids predispose these patients to arterial hypertension. This should be treated assiduously to reduce the risk of acute neurological complications.

FLUID BALANCE AND RENAL SYSTEM

A restrictive fluid strategy is recommended to minimise the risk of pulmonary oedema. Pilcher et al. demonstrated an increased duration of ventilation, intensive care unit (ICU) and hospital mortality in lung transplant recipients who had a central venous pressure (CVP) greater than 7 mm Hg after excluding the effect of poor myocardial function and high inotrope requirement.[32]

Diuretics should be considered to mobilise fluid retention seen in the postoperative phase, and a further consideration is the absence of lymph drainage from the transplanted lung. On the other hand, hypovolaemia in combination with CNIs may predispose to pre-renal kidney injury.

In case of kidney injury, early renal replacement therapy with fluid removal to minimise allograft oedema may be required. Both CNIs and diuretics increase urinary magnesium excretion and hence regular checks and supplementation are required to prevent arrhythmias and lower seizure threshold.[33]

BLOOD MANAGEMENT

As with other critically ill patients, the use of blood and blood products should be rationalised. A study by Weber et al. demonstrated that the transfusion of red cells was an independent factor for worse outcome in lung transplant recipients.[34] A recent study showed no effect on all-cause mortality with red cells, but higher adjusted 1-year mortality associated with platelet transfusion.[35] Nowadays, point-of-care testing with viscoelastic tests (thromboelastography and thromboelastometry) and a goal-directed transfusion algorithm are used in some centres to rationalise blood management. However, transfusion-related immunomodulation (TRIM) might ameliorate rejection risk, although sensitisation with foreign antibodies may increase it.

GASTROINTESTINAL SYSTEM AND NUTRITION

Vagal disruption and gastroparesis make reflux common and therefore proton pump inhibitors are administered routinely. In addition, prokinetic agents, such as domperidone, are used and reverse Trendelenburg position is maintained.

Patients who are not extubated early should have a nasogastric tube inserted and enteral nutrition with high protein content (along with pancreatic enzymes in the CF population) is desirable.[33]

A combination of stool softeners and stimulants (e.g. coloxyl with senna) and osmotic laxatives are used. Further measures such as Gastrografin (Diatrizoate Meglumine) may be required if the return of bowel function is delayed. Intravenous immunosuppressive drugs are switched to the enteral route only when gastrointestinal function has recovered and efficient absorption is anticipated.

IMMUNOSUPPRESSION

Induction therapy, with a move away from polyclonal antithymocyte preparations to IL2R antagonists or alemtuzumab[2] is increasingly used. ISHLT data suggest a small improvement in survival in patients receiving induction therapy.

Maintenance immunosuppression involves the administration of three drugs in combination: corticosteroids, an antimetabolite (mycophenolate mofetil [MMF] or azathioprine) and a CNI (cyclosporine or tacrolimus). Tacrolimus and MMF are the preferred CNI and antimetabolite, respectively.[2] Recipients with CF are administered their cyclosporine with a pancreatic enzyme supplement.

INFECTION PROPHYLAXIS

Lung transplant recipients are at high risk of infection – more so than other transplant recipients – as the transplanted lung uniquely is in direct contact with the external environment and any potential airborne pathogens. Often the donor has evidence of lower airway colonisation or infection prior to retrieval. In the recipient, there is impaired ciliary function and loss of the cough reflex resulting in retained secretions. In addition, a substantial proportion of recipients – those with CF or bronchiectasis – are invariably colonised with multiresistant bacteria in the upper respiratory tract at the time of transplantation. These organisms can rapidly spread to the lower respiratory tract.

Bacterial prophylaxis: Donor sputum or bronchoscopy samples are used to guide therapy. For recipients with chronic suppurative lung disease, antibiotic prophylaxis will depend on sensitivities determined from pre-transplant surveillance. Targeted antimicrobial therapy to known donor organisms appears effective in modulating infection after transplantation. Otherwise, a third-generation cephalosporin with broad spectrum against Gram-positive and negative organisms (e.g. cefotaxime) is administered. *Fungal prophylaxis*: Pneumocystis jiroveci prophylaxis in the form of oral co-trimoxazole is commenced in the first week post-transplantation and continued indefinitely. For patients who are allergic, dapsone or monthly-inhaled pentamidine are suitable alternatives. Nystatin oral solution to prevent oropharyngeal candidiasis is also administered for the first few weeks post-transplant. Aspergillus infections are less common but potentially catastrophic. Inhaled amphotericin has been shown to significantly reduce the incidence of aspergillus and other fungal infections and is administered routinely until hospital discharge.[36] An alternative approach to aspergillus prophylaxis is the use of oral azoles such as voriconazole.[37] *Viral prophylaxis:* cytomegalovirus (CMV) may cause life-threatening pneumonitis and has been associated with an increased risk of the development of bronchiolitis obliterans syndrome (BOS). Risk is highest in recipients of lungs from CMV-seropositive donors, particularly when the recipient is CMV negative (D+/R–). Although clinical infection is extremely uncommon in the first month post-transplant, it is essential to commence prophylaxis immediately. Intravenous ganciclovir is administered initially, followed by oral valganciclovir (dose adjusted for renal function). The 2013 American Society of Transplantation guidelines recommend 12 months of prophylaxis for D+/R– lung transplant recipients.[38] Valganciclovir is administered for 6 months in D+/R+ and D–/R+ recipients. CMV hyperimmune globulin is also administered for up to 1 month to D+/R– recipients. Recipients who are Epstein–Barr Virus (EBV) naïve who receive lungs from EBV-seropositive donors (D+/R–) are at high risk of developing post-transplant lymphoproliferative disorder (PTLD), which carries a very high mortality. If they are not already receiving oral valganciclovir, EBV D+/R– recipients are maintained on valaciclovir indefinitely.

Other drugs administered in the immediate post-transplant period include an insulin infusion as required to control hyperglycaemia, which is common following the administration of high-dose steroids, calcium and vitamin D supplements to prevent osteoporosis and subcutaneous unfractionated heparin for deep vein thrombosis (DVT) prophylaxis. A typical post-transplant drug treatment protocol is shown in Table 104b.3.

Table 104b.3 Peri-operative lung transplant drug treatment protocols currently utilised in the Heart and Lung Transplant Unit at St Vincent's Hospital, Sydney

AREA	
Pre-operative on ward	Azathioprine 2–3 mg/kg PO Or Mycophenolate mofetil 1.5 g PO Tacrolimus capsules 0.05 mg/kg if creatinine <120 µmol/L Omit if creatinine >120 µmol/L
In anaesthetic bay	Methylprednisolone 500 mg IV Ganciclovir 5 mg/kg IV: if CMV mismatch Cefotaxime 1–2 g IV; unless alternative antibiotic/antifungal advised by respiratory physician based on donor and recipient microbiology
In theatre off bypass	Methylprednisolone 500 mg IV Cefotaxime 1–2 g IV; unless alternative antibiotic/antifungal advised by respiratory physician based on donor and recipient microbiology
ICU or ward	IMMUNOSUPPRESSION
	IV tacrolimus 0.01 mg/kg/day given as continuous infusion over 24 h, increasing to 0.02 mg/kg depending on first steady state level. Initial target steady-state level = 12–15 mcg/L PO tacrolimus BD once extubated and recovery of gastrointestinal function; dose titrated according to levels (target 12–15 µg/L) and renal function IV/PO azathioprine 2 mg/kg nocte **OR** IV/PO mycophenolate mofetil 1500 mg BD as per respiratory physician IV methylprednisolone 125 mg q8h ×3 doses then PO prednisolone 1 mg/kg/day in 2 divided doses, tapering by 5 mg every second day to a single daily dose of 0.2 mg/kg (until first transbronchial biopsy).

Table 104b.3 Peri-operative lung transplant drug treatment protocols currently utilised in the Heart and Lung Transplant Unit at St Vincent's Hospital, Sydney—cont'd

AREA	
	BACTERIAL PROPHYLAXIS
	Cefotaxime 1 g IV t.d.s. for 5 days – (may vary according to cultures) CF patients: antipseudomonal beta-lactam, modified as required according to microbiology results IV azithromycin 500 mg daily for 3 days then PO 250 mg on Mondays, Wednesdays and Fridays
	FUNGAL PROPHYLAXIS
	Nystatin oral drops 1 mL PO q.i.d. Nebulised salbutamol 5 mg BD 30 minutes before Nebulised amphotericin (Fungizone) 10 mg BD until discharge from hospital Sulfamethoxazole 800 mg PO *and* trimethoprim 160 mg (Bactrim DS), one daily on Mondays and Fridays (If *sulphur allergy*, check with consultant: give dapsone 100 mg daily on Monday/Wednesday/Friday)
	VIRAL PROPHYLAXIS
	CMV MISMATCH
	Ganciclovir 5 mg/kg IV daily Monday/Wednesday/Friday until IV removed, then PO valganciclovir 450 mg BD (dose adjusted according to renal function) indefinitely CMV hyperimmune globulin IV: 2 vials days 1, 2, 3, 7, 14, 21
	CMV-POSITIVE RECIPIENT
	Ganciclovir 5 mg/kg IV daily Monday/Wednesday/Friday until IV removed, then valganciclovir 450 mg PO BD (dose adjusted according to renal function) for 12 months
	EBV-NEGATIVE PATIENTS (IF NOT ALREADY ON VALGANCICLOVIR)
	VALACICLOVIR 500 MG PO BD (DEPENDING ON RENAL FUNCTION) INDEFINITELY
	PAIN MANAGEMENT
	Epidural anaesthesia (max. 5 days), if appropriate Morphine 1–2.5 mg IV p.r.n. Morphine 5–10 mg IM/SC p.r.n. Paracetamol 1 g PO q6h Oxycodone 5 mg PO q6h p.r.n.
	BOWEL MANAGEMENT
	Docusate with sennosides (50 mg, 8 mg) PO 2 BD Movicol PO 1 sachet daily For CF patients check with consultant if diatrizoic acid (Gastrografin) 25–50 mL PO p.r.n. to be given
	GIT PROTECTION/REFLUX MANAGEMENT
	Pantoprazole 40 mg IV daily or Ranitidine 50 mg IV t.d.s., then Rabeprazole 20 mg PO daily when on the ward If reflux symptoms persist, consider addition of: Domperidone 10–20 mg PO q.i.d. Sucralfate 1 g PO q.i.d.
	BONE PROTECTION
	Cholecalciferol 1000 U PO daily Calcium citrate 2 tablets PO daily IF BMD <–1: zoledronic acid 4 mg IV every 12 months

BMD, Bone mineral density; *CF*, cystic fibrosis; *CMV*, cytomegalovirus; *EBV*, Epstein–Barr virus; *GIT*, gastrointestinal tract; *ICU*, intensive care unit; *IM*, intramuscular; *IV*, intravenous; *PO*, oral; *SC*, subcutaneous.

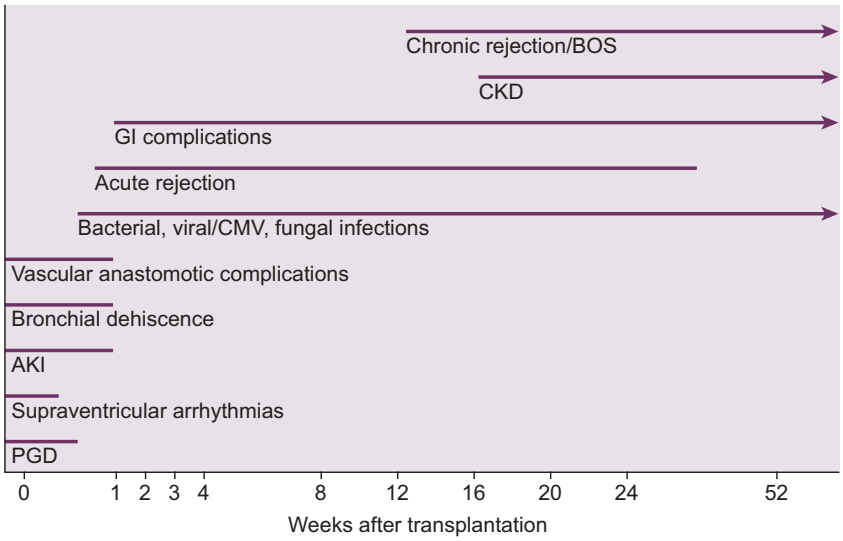


Figure 104b.1 Time course of complications following transplant. *AKI*, Acute kidney injury; *BOS*, bronchiolitis obliterans syndrome; *CKD*, chronic kidney disease; *CMV*, cytomegalovirus; *GI*, gastrointestinal; *PGD*, primary graft dysfunction.

COMPLICATIONS

In addition to immediate postoperative complications, lung transplant recipients may require ICU admission with respiratory or non-respiratory complications in the weeks or months following transplantation. Fig. 104b.1 indicates the timeline of potential complications that may require intensive care management. Recipients may be readmitted into non-transplant hospital ICUs and a basic understanding of the special complications and requirements of these patients is therefore important. However, it is strongly recommended that early communication and close cooperation between transplant centres and regional ICUs is undertaken.

PRIMARY GRAFT DYSFUNCTION

PGD is defined as a triad of worsening gas exchange, decreased lung compliance and alveolar and interstitial infiltrates, which are typically most extensive in perihilar regions, within the first 72 hours. This is multifactorial, and IRI is a major cause leading to increased capillary permeability and pulmonary oedema. The definition also requires exclusion of contributing factors, including hyperacute rejection, pulmonary venous anastomotic obstruction, cardiogenic pulmonary oedema and pneumonia.[39]

PGD is non-immune mediated, and is reported in up to 25% of recipients. The extent of the impaired oxygenation and pulmonary opacities has been used to grade severity (Table 104b.4).[40] In its most severe form, PGD3 results in fulminant ARDS. It represents the end result of multiple deleterious mechanisms provoked by donor brain death, mechanical ventilation, procurement, storage and IRI. IRI refers to sterile inflammation that occurs after substrate supply is restored following a period of ischaemia. Risk factors include prolonged graft ischemia, increasing donor age and recipient diagnosis of pulmonary hypertension (Table 104b.5).[40,41]

Table 104b.4 ISHLT grading system for primary graft dysfunction after lung transplantation

PGD GRADE	Pa_{O_2}/Fi_{O_2}	RADIOGRAPHIC INFILTRATES CONSISTENT WITH PULMONARY OEDEMA
0	>300	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

PGD, Primary graft dysfunction.

Severe PGD is the major cause of early mortality, reported at up to 50%. It is also associated with increased morbidity related to the need for prolonged ventilation and ICU/hospital stay and delayed recovery of lung function. For recipients who survive an episode of severe PGD, long-term outcomes are adversely affected.

Treatment is supportive and aimed at maintaining adequate gas exchange until the syndrome resolves, using the principles of ARDS management. Inhaled nitric oxide has been shown to improve gas exchange and lower pulmonary vascular resistance acutely, but it has not been found to affect overall survival. In the more severe cases, ECMO support may be required to maintain gas exchange until the condition resolves,

Table 104b.5 Recognised risk factors for primary graft dysfunction after lung transplantation

DONOR FACTORS	RECIPIENT FACTORS	PROCEDURAL FACTORS
Age >60 years	Age >60 years	Single lung transplantation
Smoking >20 pack years	Ventilator support	Cardiopulmonary bypass
Pneumonia on CXR or purulent secretions on bronchoscopy	Pulmonary fibrosis	
Primary graft dysfunction of other organs	Pulmonary hypertension	
	Obesity	

CXR, Chest X-ray.

and a case can be made for early initiation in severe cases to avoid the burden of ventilator-induced lung injury (VILI).

Currey et al. demonstrated that implementation of an evidence-based algorithm for respiratory and haemodynamic management in the postoperative period was feasible and safe, and was associated with a reduction in severity of PGD.[28]

INFECTIONS

The infectious agents of most concern during the immediate post-transplant period are multiresistant bacterial pathogens, particularly in those undergoing transplantation for chronic suppurative lung disease. The risk of pneumonia, the most common infectious complication, is increased by the need for prolonged ventilation (in the case of PGD) and airway complications (discussed below). Angioinvasive aspergillosis infection – although rare – may result in rapidly progressive necrotising pneumonia, bronchial anastomotic dehiscence or even pulmonary arterial or venous anastomotic dehiscence, leading to exsanguinating haemoptysis. Another mould infection that can result in significant morbidity and mortality is scedosporium, particularly in the CF population in whom this organism can frequently be a pre-transplant coloniser, which is relatively difficult to treat. An aggressive diagnostic approach – including bronchial washings or computed tomography (CT)-guided fine needle aspiration of focal pneumonic lesions to look for respiratory viruses and CMV, bacteria, fungi and pneumocystis jiroveci pneumonia (PJP) – is essential to facilitate early diagnosis and the initiation of appropriate treatment.

ACUTE REJECTION

The incidence of acute rejection after lung transplantation has been declining. The ISHLT Registry reports that 28% of patients undergo treatment for acute rejection during the first 12 months after transplantation.[2] Hyperacute rejection is a form of humoral rejection that occurs in the first 24 hours following transplantation in recipients who have pre-formed anti-human leucocyte anitgen (HLA) antibodies. With improved sensitivity of testing, it is rarely seen, but it needs to be distinguished from IRI.

Symptoms and signs of acute rejection are non-specific and include dyspnoea, cough, sputum production, fever, declining FEV_1 (forced expiratory volume at 1 s) on spirometry and the appearance of alveolar infiltrates. The major differential diagnosis is lower respiratory tract infection. If unrecognised and untreated it can lead to rapid onset of severe graft dysfunction and a clinical picture of ARDS. It is important to remember that rejection and infection can occur simultaneously. Trans-bronchial biopsy and bronchial washing are required for pathological confirmation. The severity of acute lung rejection is graded histologically.[42] Treatment for biopsy-proven acute rejection in the first instance involves pulsed steroid therapy.

Respiratory failure occurring during the first 72 hours after transplantation is usually due to PGD. However, respiratory failure occurring at any time after this suggests another cause – usually either infection or rejection. Acute cellular rejection is very uncommon in the first week post-transplant but acute antibody-mediated rejection (AMR) may occur if there are preformed donor-specific antibodies. Treatment of acute AMR is intensive and involves a combination of plasmapheresis, administration of high-dose intravenous immunoglobulin (IVIG) and rituximab.

AMR can also occur later and is usually associated with acquired anti-HLA and less commonly non–anti-HLA antibodies. The relationship between the level of antibodies and loss of lung function does not have a high positive predictive value. Unlike AMR in other solid-organ transplant recipients, there are no standardised diagnostic criteria. Key diagnostic criteria include the presence of antibodies directed towards donor HLA and characteristic lung histology with or without evidence of complement 4d within the graft. Exclusion of other causes of allograft dysfunction increases confidence in the diagnosis.[43]

AIRWAY COMPLICATIONS

Peri-anastomotic bronchial ischaemia is relatively common, as re-anastomosis of the bronchial arteries is

not performed. The establishment of bronchial blood flow to the transplanted lung occurs over the first month post-transplant via ingrowth of collaterals from the recipient, but until then the transplanted lung is reliant on low-pressure retrograde collateral bronchial flow of (deoxygenated) blood from the pulmonary artery.[44,45] Major airway complications were reported in 1.4% of lung transplant recipients in a contemporary United Network for Organ Sharing (UNOS) Registry analysis.[44,46] Although rare they are associated with significant morbidity and mortality.[46] Ischaemia of the anastomosis predisposes to a number of airway complications including bronchial stenosis at or beyond the anastomosis, bronchomalacia, endobronchial infections and bronchial anastomotic dehiscence.[46] The latter is often associated with persistent large air leaks and development of fatal mediastinitis. Repeated bronchoscopic assessment of the anastomosis is undertaken during the first 4 to 6 weeks until healing is complete. A variety of bronchoscopic interventional procedures have been developed to treat airway complications, including balloon angioplasty and stenting.[45,46]

CHRONIC REJECTION OR BRONCHIOLITIS OBLITERANS SYNDROME

Chronic rejection is referred to as BOS. Patients may require admission into the ICU for complicating infection and ventilatory support. The diagnosis is based on a sustained decrease of greater than 20% in FEV_1 or the pathological presence of obliterating bronchiolitis. The incidence is highest after the first year; however, the risk increases to 60%–80% 5–10 years after transplantation, although meticulous targeting of cyclosporin levels has demonstrated reduced rates.[47] It is the major complication that adversely affects long-term survival, and may be progressive, may plateau or may progress gradually. Treatment for established BOS has not proven to be effective; consequently, in the event of deterioration, prolonged mechanical ventilation or ECMO is not recommended unless imminent re-transplantation is being considered in special circumstances. The severity of lymphocytic bronchiolitis on transbronchial biopsies is associated with increased risk of BOS and death independent of acute rejection.[48] The ISHLT recommendations are conditional, due to low-quality evidence, and include switching from cyclosporine to tacrolimus, a trial of azithromycin, consideration of antireflux surgery for patients with confirmed gastro-oesophageal reflux and re-transplantation for end-stage refractory BOS.[49]

OTHER PULMONARY COMPLICATIONS

1. Vascular anastomotic complications: kinking or thrombosis of the pulmonary venous anastomoses is occasionally seen in the immediate postoperative period. Focal opacities on the X-ray should prompt suspicion of this complication. Early diagnosis can be made with transoesophageal echocardiography or contrast CT. Surgical correction or anticoagulation, where suitable, is important to prevent pulmonary venous infarction and potentially systemic embolisation. Pulmonary arterial anastomotic complications are rare and may result in pulmonary hypertension and right ventricular dysfunction.[50]
2. Donor-recipient size mismatch: this may result in (a) overdistension in undersized lungs if the recipient's body weight is used to calculate tidal volumes; or (b) atelectasis and altered mechanics in oversized lungs.[51]
3. Phrenic nerve palsy: this is a relatively uncommon complication, occurring in 6%–9% of patients and is more frequent in heart–lung transplantation. It results in longer hospital stays and duration of ventilation.[26]

Fig. 104b.2 depicts the differential diagnosis of respiratory failure specific to the early post-transplant phase. Down the track, in addition to the potential causes in any other patient, rejection (both cellular and antibody mediated) and infection (particularly CMV, aspergillus, PJP) should be considered.

EXTRAPULMONARY COMPLICATIONS

1. Renal: renal dysfunction is common, with an incidence of 25% at 1 year and 37% at 5 years after transplant. This is usually due to CNI toxicity caused by reversible afferent and efferent arteriolar vasoconstriction in the acute phase, and interstitial fibrosis, chronic arteriolopathy and tubular atrophy in the chronic phase.[52] Management centres on lowering the levels of CNI, which must be balanced against the risk of rejection. Associated comorbidities that can worsen renal failure, such as hypertension, diabetes and hyperlipidaemia, should be aggressively treated. Other factors should be considered in the setting of acute kidney injury (AKI). Haemolytic uremic syndrome, due to thrombotic microangiopathy secondary to CNI use, has been described.[53] The diagnosis is made when there is progressive anaemia, new-onset thrombocytopenia, and inexplicable AKI in conjunction with haemolysis. It occurs most commonly within the first 3 months post-transplantation. Reduction of the dosage or switching to an alternative CNI is usually effective.
2. Gastrointestinal: patients with CF are at particular risk of distal intestinal obstruction syndrome in the postoperative period, with an incidence of 10% reported by Morton et al.[54] A history of meconium ileus and previous laparotomy were found to be risk factors. These patients require aggressive management with timely laparotomy with enterostomy when non-operative therapy is unsuccessful.
3. Neurological: neurological complications are common; the early ones include steroid-related delirium,

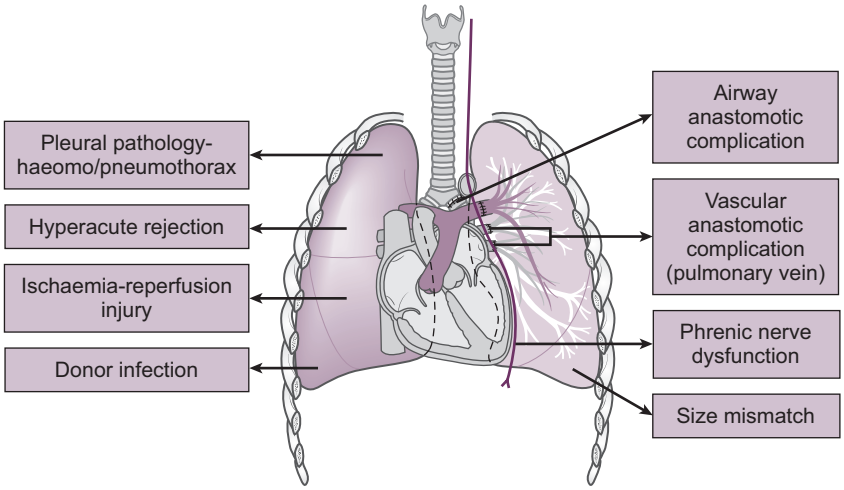


Figure 104b.2 Specific differential diagnoses for respiratory failure in the early post-transplant phase.

encephalopathy, seizures and strokes. A study of 100 patients reported a 26% incidence in the form of severe headaches, seizures, strokes and confusion. The majority were due to CNI toxicity or infections.[55] In a recent study, encephalopathy was often considered multifactorial in nature, primarily due to postoperative hypoxemia in 8 out of 29 cases, and sepsis in 3 cases.[56] The mechanism of CNI toxicity is unknown, and not necessarily related to elevated levels. CNI-associated posterior reversible encephalopathy syndrome (PRES) is characterised by headache, confusion, seizures, decreased level of consciousness, visual abnormalities and focal deficits, and usually occurs in the first month after transplantation.[57] It is always accompanied by hypertension. MRI typically shows reversible cortical and subcortical white matter changes in the posterior cerebral hemispheres.[58] The differential diagnoses include progressive multifocal leukoencephalopathy, viral encephalitis, cerebral lymphoma, cortical venous thrombosis and watershed infarcts following CPB. CNI-associated PRES generally has a favourable prognosis with early diagnosis and treatment, including alternating or discontinuing CNIs and blood pressure control. It should be considered in patients exhibiting neurological symptoms after transplantation.

4. PTLD and other malignancies.

Transplant patients are at increased risk for developing PTLDs, ranging from benign polyclonal hyperplasia to aggressive high-grade lymphoma. The disorders tend to occur within 1 year (peaking at 3–4 months). PTLDs develop in 4%–10% of lung transplant patients; as opposed to an approximate 2% in other solid organ transplant recipients.[59] Most are associated with concomitant EBV infections, which stimulate B-lymphocyte proliferation, which is unopposed because of cyclosporine-induced inhibition of T-lymphocytes. Treatment consists of decreasing or ceasing cyclosporine and administering antiviral agents (i.e. valaciclovir). Other therapies include the administration of rituximab, a CD20 monoclonal antibody and chemotherapy.[59] After immunomodulation, regression occurs in 23%–61% of patients.

There is also an increased incidence of other malignancies; particularly aggressive skin cancers in solid organ transplant recipients (three to four times increased risk), which is even higher in lung transplant recipients.

CONCLUSIONS

Lung transplantation has emerged as the most effective treatment available for end-stage lung disease. Donor numbers limit transplantation, so that only a small percentage of patients who might benefit are able to receive a transplant. This has resulted in an increased utilisation of higher risk donors with an associated risk of PGD. This poses significant challenges during the initial ICU phase. Nonetheless, the large majority make a good recovery following transplant surgery and return to a quality of life similar to that of a healthy population. Advances in donor management and organ preservation should increase the number of suitable organs, while ongoing refinements to post-transplant management will likely further improve long-term survival.

REFERENCES

1. Lund LH, Edwards LB, Dipchand AI, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Heart

Transplantation Report – 2016; Focus Theme: Primary Diagnostic Indications for Transplant. *J Heart Lung Transplant*. 2016;35(10):1158–1169.
2. Yusen RD, Edwards LB, Dipchand AI, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Lung and Heart-Lung Transplant Report – 2016; Focus Theme: Primary Diagnostic Indications for Transplant. *J Heart Lung Transplant*. 2016;35(10):1170–1184.
3. Coulson TG, Pilcher DV, Graham SM, et al. Single-centre experience of donation after cardiac death. *Med J Aust*. 2012;197(3):166–169.
4. Gries CJ, White DB, Truog RD, et al. An official American Thoracic Society/International Society for Heart and Lung Transplantation/Society of Critical Care Medicine/Association of Organ and Procurement Organizations/United Network of Organ Sharing Statement: ethical and policy considerations in organ donation after circulatory determination of death. *Am J Respir Crit Care Med*. 2013;188(1):103–109.
5. Stehlik J, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Twenty-eighth Adult Heart Transplant Report – 2011. *J Heart Lung Transplant*. 2011;30(10):1078–1094.
6. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014 – an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2015;34(1):1–15.
7. Hook JL, Lederer DJ. Selecting lung transplant candidates: where do current guidelines fall short? *Expert Rev Respir Med*. 2012;6(1):51–61.
8. Singer JP, Diamond JM, Gries CJ, et al. Frailty phenotypes, disability, and outcomes in adult candidates for lung transplantation. *Am J Respir Crit Care Med*. 2015;192(11):1325–1334.
9. Fuehner T, Kuehn C, Hadem J, et al. Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. *Am J Respir Crit Care Med*. 2012;185(7):763–768.
10. Bartosik W, Egan JJ, Wood AE. The Novalung interventional lung assist as bridge to lung transplantation for self-ventilating patients – initial experience. *Interact Cardiovasc Thorac Surg*. 2011;13(2):198–200.
11. Fuehner T, Kuehn C, Welte T, et al. ICU care before and after lung transplantation. *Chest*. 2016; 150(2):442–450.
12. Schiavon M, Falcoz PE, Santelmo N, et al. Does the use of extended criteria donors influence early and long-term results of lung transplantation? *Interact Cardiovasc Thorac Surg*. 2012;14(2):183–187.
13. Zafar F, Khan MS, Heinle JS, et al. Does donor arterial partial pressure of oxygen affect outcomes after lung transplantation? A review of more than 12,000 lung transplants. *J Thorac Cardiovasc Surg*. 2012; 143(4):919–925.
14. Bonser RS, Taylor R, Collett D, et al. Effect of donor smoking on survival after lung transplantation: a cohort study of a prospective registry. *Lancet*. 2012;380(9843):747–755.
15. Steen S, Liao Q, Wierup PN, et al. Transplantation of lungs from non-heart-beating donors after functional assessment ex vivo. *Ann Thorac Surg*. 2003;76(1):244–252, discussion 252.
16. Steen S, Sjoberg T, Pierre L, et al. Transplantation of lungs from a non-heart-beating donor. *Lancet*. 2001;357(9259):825–829.
17. Cypel M, Keshavjee S. Extracorporeal lung perfusion. *Curr Opin Organ Transplant*. 2011;16(5): 469–475.
18. Van Raemdonck D, Neyrinck A, Cypel M, et al. Ex-vivo lung perfusion. *Transpl Int*. 2015;28(6): 643–656.
19. Warnecke G, Moradiellos J, Tudorache I, et al. Normothermic perfusion of donor lungs for preservation and assessment with the Organ Care System Lung before bilateral transplantation: a pilot study of 12 patients. *Lancet*. 2012;380(9856):1851–1858.
20. Marczin N, Popov AF, Zych B, et al. Outcomes of minimally invasive lung transplantation in a single centre: the routine approach for the future or do we still need clamshell incision? *Interact Cardiovasc Thorac Surg*. 2016;22(5):537–545.
21. Mohite PN, Sabashnikov A, Patil NP, et al. The role of cardiopulmonary bypass in lung transplantation. *Clin Transplant*. 2016;30(3):202–209.
22. Diamond JM, Lee JC, Kawut SM, et al. Clinical risk factors for primary graft dysfunction after lung transplantation. *Am J Respir Crit Care Med*. 2013; 187(5):527–534.
23. Hoechter DJ, Shen YM, Kammerer T, et al. Extracorporeal circulation during lung transplantation procedures: a meta-analysis. *ASAIO J*. 2017;63(5):551–561.
24. Castillo M. Anesthetic management for lung transplantation. *Curr Opin Anaesthesiol*. 2011;24(1):32–36.
25. Thakuria L, Davey R, Romano R, et al. Mechanical ventilation after lung transplantation. *J Crit Care*. 2016;31(1):110–118.
26. Barnes L, Reed RM, Parekh KR, et al. Mechanical ventilation for the lung transplant recipient. *Curr Pulmonol Rep*. 2015;4(2):88–96.
27. Beer A, Reed RM, Bolukbas S, et al. Mechanical ventilation after lung transplantation. An international survey of practices and preferences. *Ann Am Thorac Soc*. 2014;11(4):546–553.
28. Currey J, Pilcher DV, Davies A, et al. Implementation of a management guideline aimed at minimizing the severity of primary graft dysfunction after lung transplant. *J Thorac Cardiovasc Surg*. 2010;139(1):154–161.
29. King CS, Khandhar S, Burton N, et al. Native lung complications in single-lung transplant recipients and the role of pneumonectomy. *J Heart Lung Transplant*. 2009;28(8):851–856.
30. Hadem J, Gottlieb J, Seifert D, et al. Prolonged mechanical ventilation after lung transplantation-a single-center study. *Am J Transplant*. 2016; 16(5):1579–1587.

31. Lazaro MT, Ussetti P, Merino JL. Atrial fibrillation, atrial flutter, or both after pulmonary transplantation. *Chest*. 2005;127(4):1461–1462, author reply 2.
32. Pilcher DV, Scheinkestel CD, Snell GI, et al. High central venous pressure is associated with prolonged mechanical ventilation and increased mortality after lung transplantation. *J Thorac Cardiovasc Surg*. 2005;129(4):912–918.
33. Schuurmans MM, Benden C, Inci I. Practical approach to early postoperative management of lung transplant recipients. *Swiss Med Wkly*. 2013; 143:w13773.
34. Weber D, Cottini SR, Locher P, et al. Association of intraoperative transfusion of blood products with mortality in lung transplant recipients. *Perioper Med (Lond)*. 2013;2(1):20.
35. Ong LP, Thompson E, Sachdeva A, et al. Allogeneic blood transfusion in bilateral lung transplantation: impact on early function and mortality. *Eur J Cardiothorac Surg*. 2016;49(2):668–674, discussion 674.
36. Reichenspurner H, Gamberg P, Nitschke M, et al. Significant reduction in the number of fungal infections after lung-, heart-lung, and heart transplantation using aerosolized amphotericin B prophylaxis. *Transplant Proc*. 1997;29(1–2):627–628.
37. He SY, Makhzoumi ZH, Singer JP, et al. Practice variation in Aspergillus prophylaxis and treatment among lung transplant centers: a national survey. *Transpl Infect Dis*. 2015;17(1):14–20.
38. Razonable RR, Humar A, Practice ASTIDCo. Cytomegalovirus in solid organ transplantation. *Am J Transplant*. 2013;13(suppl 4):93–106.
39. Christie JD, Carby M, Bag R, et al. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part II: definition. A consensus statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2005; 24(10):1454–1459.
40. Lee JC, Christie JD. Primary graft dysfunction. *Proc Am Thorac Soc*. 2009;6(1):39–46.
41. Boucek MM, Mashburn C, Dunn SM, et al. Pediatric heart transplantation after declaration of cardiocirculatory death. *N Engl J Med*. 2008;359(7):709–714.
42. Stewart S, Fishbein MC, Snell GI, et al. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. *J Heart Lung Transplant*. 2007;26(12):1229–1242.
43. Levine DJ, Glanville AR, Aboyoun C, et al. Antibody-mediated rejection of the lung: a consensus report of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2016;35(4):397–406.
44. Santacruz JF, Mehta AC. Airway complications and management after lung transplantation: ischemia, dehiscence, and stenosis. *Proc Am Thorac Soc*. 2009; 6(1):79–93.
45. Gottlieb J, Fuehner T, Dierich M, et al. Are metallic stents really safe? A long-term analysis in lung transplant recipients. *Eur Respir J*. 2009;34(6): 1417–1422.
46. Awori Hayanga JW, Aboagye JK, Shigemura N, et al. Airway complications after lung transplantation: contemporary survival and outcomes. *J Heart Lung Transplant*. 2016;35(10):1206–1211.
47. Glanville AR, Aboyoun CL, Morton JM, et al. Cyclosporine C2 target levels and acute cellular rejection after lung transplantation. *J Heart Lung Transplant*. 2006;25(8):928–934.
48. Glanville AR, Aboyoun CL, Havryk A, et al. Severity of lymphocytic bronchiolitis predicts long-term outcome after lung transplantation. *Am J Respir Crit Care Med*. 2008;177(9):1033–1040.
49. Meyer KC, Raghu G, Verleden GM, et al. An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome. *Eur Respir J*. 2014;44(6): 1479–1503.
50. Simpson KP, Garrity ER. Perioperative management in lung transplantation. *Clin Chest Med*. 1997;18(2):277–284.
51. Pierre AF, Keshavjee S. Lung transplantation: donor and recipient critical care aspects. *Curr Opin Crit Care*. 2005;11(4):339–344.
52. Lyu DM, Zamora MR. Medical complications of lung transplantation. *Proc Am Thorac Soc*. 2009; 6(1):101–107.
53. Hachem RR. Thrombotic microangiopathy after lung transplantation: a difficult diagnosis. *South Med J*. 2008;101(7):683–684.
54. Morton JR, Ansari N, Glanville AR, et al. Distal intestinal obstruction syndrome (DIOS) in patients with cystic fibrosis after lung transplantation. *J Gastrointest Surg*. 2009;13(8):1448–1453.
55. Goldstein LS, Haug MT 3rd, Perl J 2nd, et al. Central nervous system complications after lung transplantation. *J Heart Lung Transplant*. 1998;17(2): 185–191.
56. Mateen FJ, Dierkhising RA, Rabinstein AA, et al. Neurological complications following adult lung transplantation. *Am J Transplant*. 2010;10(4): 908–914.
57. Tsang BK, Kermeen FD, Hopkins PM, et al. Reversible posterior leukoencephalopathy syndrome: diagnosis and management in the setting of lung transplantation. *Intern Med J*. 2010;40(10): 716–720.
58. Arimura FE, Camargo PC, Costa AN, et al. Posterior reversible encephalopathy syndrome in lung transplantation: 5 case reports. *Transplant Proc*. 2014;46(6):1845–1848.
59. Kumarasinghe G, Lavee O, Parker A, et al. Post-transplant lymphoproliferative disease in heart and lung transplantation: defining risk and prognostic factors. *J Heart Lung Transplant*. 2015;34(11): 1406–1414.

This page intentionally left blank

Part Seventeen

Paediatric Intensive Care

This page intentionally left blank

105

The critically ill child

Shelley D Riphagen

The chapters on paediatric intensive care are intended to help intensivists outside specialist paediatric centres manage common paediatric emergencies. They should be read in conjunction with relevant adult chapters, as there are many areas of commonality.

CARDIORESPIRATORY ADAPTATION AT BIRTH

Dramatic physiological adaptation takes place at birth. Intracardiac pressure relationships in the foetal circulation undergo significant changes associated with clamping of the umbilical cord and subsequent disconnection of the placenta. At birth, systemic vascular resistance rises rapidly as the continuous supply of vasodilating prostaglandin and the large low-resistance vascular bed of the placenta is disconnected from the newborn circulation at cord clamping. At the same time, the newborn takes the first breath of air, resulting in a sudden and progressive fall in pulmonary vascular resistance, an increase in pulmonary blood flow and left atrial venous return with an additional increase in left-sided pressures causing physiological closure of both the foramen ovale and ductus arteriosus. Blood, which previously short-circuited the right side of the foetal heart and lungs via the foramen ovale, is forced to follow the postnatal/adult pattern of circulation.

Although there is a fall in pulmonary vascular resistance at birth, changes initiated at the time of birth are incomplete and progressive, with further reduction in pulmonary vascular resistance associated with regression in arteriolar muscularisation over days to weeks.

Reversion to foetal physiology, however, may occur during the first days to weeks of life in the case of respiratory pathology, or other causes of hypoxia and acidosis. Reversion to foetal pattern circulation means that desaturated blood short-circuits the lungs through the foramen ovale, resulting in further profound desaturation and hypoxaemia, with consequent increases in pulmonary vascular resistance and worsening acidosis. Urgent measures to reverse hypoxaemia must be instituted to prevent progression to death.

Pulmonary circulation pathophysiology is probably related to abnormalities of endogenous nitric oxide production, and the manipulation of this agent has proven useful in therapy.[1]

CAUSES OF TRANSITIONAL (POSTNATAL REVERSION TO FOETAL) CIRCULATION

A 'foetal' pattern may persist due to low lung volume states (e.g. hyaline membrane disease and perinatal asphyxia), pulmonary hypoplasia (e.g. diaphragmatic hernia and Potter syndrome), meconium aspiration syndrome, chronic placental insufficiency, perinatal hypoxia and acidosis from any cause, sepsis (e.g. group B streptococcal infection) or hyperviscosity syndrome.

Return to foetal circulation may need to be medically or surgically induced in the case of 'duct dependent' congenital cardiac defects associated with either obstructive lesions on the right or left side of the heart, and as a temporising measure in the case of transposition of the great arteries to improve mixing of oxygenated and deoxygenated blood until normal circulation is restored. This may be partly achieved by infusion of prostaglandin E_2 (a placental-derived vasodilating hormone) and/or re-opening of the foramen ovale by balloon atrial septostomy or open septectomy.

Some intracardiac or vascular shunt lesions result in high pulmonary blood flow and increasing pulmonary pressure states. If left untreated, this elevated pulmonary vascular resistance may become fixed and will make subsequent surgical repair unfeasible.

GROWTH AND DEVELOPMENT

There is progressive growth and maturational development of all organ systems throughout childhood. This necessitates knowledge of normal/expected parameters and organ function at different ages in childhood. Drug and equipment calculations are age- or weight-based, and there is less room for error. Small miscalculations, depending on the size of the child, may have significant implications. Physiologically, organs in children are still undergoing maturation. Incomplete maturation of renal and liver function, especially in neonates, needs to be considered regarding fluid management and drug dosing. Similarly, the ability to recover from injury in children is better than in adults because of ongoing organ growth and development potential in early childhood. Premature infants with significant 'chronic lung disease' may still have

ABSTRACT

Neonates, infants and young children differ from older children and adults in several ways that make them more susceptible to disease and more likely for disease to progress to critical illness without being easily recognised.

Although the principles of resuscitation and stabilisation of critically ill children is similar to adults, the main challenge in their care is recognising and identifying the critically ill child in order to initiate appropriate emergency management. The initial symptoms of critical illness in young children are often non-specific and may appear relatively benign; however, they may be the only early signs of compensation in a situation of deteriorating cardiovascular status.

The non-verbal nature of communication in young children, and the need to translate symptoms usually via a third-party caregiver, means that subtle detail can be lost in translation unless parents' concerns, often of apparently vague, non-specific symptoms, are taken seriously and examined closely.

KEYWORDS

Management of critically ill child
recognition
resuscitation
stabilisation
transfer
paediatric intensive care

the potential to recover near-normal lung function by adulthood. The brain in children undergoes significant continued maturation and development in early childhood. Ongoing neurologic maturation is evident by progressive attainment of motor milestones as myelination of motor and sensory nerves progresses in a head toe manner. Neural plasticity may allow for seemingly remarkable recovery from certain types of brain injury. Neurological development and achievement of motor milestones occurs in a head to toe manner as myelination of major motor nerves is completed.

MATURATION

The immaturity of systems and biochemical processes at birth alters the physiological response to stress and drugs. Thermoregulation, immune function, respiratory, renal, hepatic and neurological function are all immature at birth, even in the full-term infant. This immaturity is magnified in the preterm infant with associated surfactant deficiency causing respiratory distress, liver glucuronyl transferase deficiency causing jaundice, and the necessity to be nursed in a thermocontrolled environment. Human body temperature is maintained within narrow limits. The thermoneutral zone is the range of ambient temperature within which the metabolic rate and oxygen consumption is ideal for effective organ function and cellular mechanisms. Thermoregulatory mechanisms are less effective in neonates (no shivering or sweating), who are also disadvantaged by a high surface area to body weight ratio and a lack of subcutaneous insulation. The thermoneutral zone (environmental temperature of 36.5°C) is higher in premature infants and falls with increasing postnatal age. Oxidation of brown fat, found in the interscapular and peri-renal areas (non-shivering thermogenesis), is the major source of endogenous heat production when these babies are 'cold stressed'. Cold stress, per se, increases neonatal mortality and in the presence of respiratory or cardiac disease, may lead to decompensation.

SPECTRUM OF DISEASE

Congenital structural abnormalities of major systems including the heart, lung, brain and skeleton, among others, are usually evident at birth; however, some may become exposed in early childhood, often in the setting of an apparently mild intercurrent illness which 'unmasks' the problem. A good example of this is a young child with a ventricular septal defect, who develops bronchiolitis due to a common cold virus, and becomes significantly unwell requiring ventilation.

Inborn errors of metabolism, although present from birth, may become evident only during an intercurrent period of stress: something as seemingly insignificant as weaning or a mild respiratory tract infection.

The immature immune system puts children at higher risk than adults for the development of serious bacterial and viral illnesses. The inflammatory response of the newborn is attenuated. Febrile response to infection may be lacking, and both cellular (chemotaxis and phagocytosis) and humoral (complement activity and opsonisation) responses may be impaired. Cell-mediated immunity is significantly compromised in infants born without thymic function (DiGeorge syndrome); however, in the normal newborn, T-cell function is quite well developed. The B-cell system, responsible for antibody production, is immature at birth; however, to mitigate this risk, the neonate has passive immunity against some infections because of transplacental transfer of maternal antibodies. In the breast milk fed neonate, additional natural immunity is acquired as a result of immunoglobulin A in breast milk, which protects against some acquired gastrointestinal infections. Overall, the immaturity and inexperience of the immune system result in a markedly increased susceptibility to infection in the first 6 months of life. Congenital abnormalities of the immune system usually present in childhood with recurrent or overwhelming infection in this at-risk period.

The response to any illness may be physiologically immature and the mode of presentation much less well defined than in adults. For the most part, however, children are the scaled-down version of adults and, after the neonatal period, physiological principles that apply in adults generally also apply in children.

MANAGEMENT OF THE CRITICALLY ILL CHILD

Of paramount importance in the management of critically ill children are early recognition and identification of the presenting clinical emergency, and appropriate resuscitation and adequate stabilisation prior to transfer to a tertiary institution with paediatric intensive care facilities.[2]

RECOGNITION

Recognition and identification of the clinical emergency is the most challenging component of management of the critically ill child, as this element is more difficult than in adults and older children for a number of reasons. Children of various ages have different normal physiological parameters and it is important for those dealing with children to be familiar with these norms. For those unfamiliar or infrequently involved in the care of critically ill children, it is important to have a readily available information source of normal values for age. Resources are available on the Internet and as hand-held applications to provide ready access to this information.[3]

Non-verbal and younger children lack the communication skills to express their malaise in a specific

manner. Generically, as children become more unwell they will become pale, lethargic, go off their meals and eventually may start vomiting. This may be the only historical evidence of developing shock in the young child, as blood is redirected away from non-essential vascular beds including skin, muscle and gut, and the primitive 'diving reflex'[4] is employed to maintain perfusion to essential organs. Older children respond in the same ways as adults with appropriate pyrexia to an infective trigger, whereas very young children, and especially neonates, may become hypothermic. Tachycardia is one of the most important signs in the deteriorating child, and an unexplained or incompletely explained tachycardia, or one that does not respond to antipyresis and analgesia must be regarded very seriously. As a child's condition deteriorates, the child may progress from being cool peripherally with a palpable peripheral-to-central skin temperature difference, to peripheral mottling and eventually a prolonged central capillary refill time. Pulses in the deteriorating child may be noticeably different peripherally from those taken centrally, even in those with a preserved blood pressure. Disinterest in eating and then drinking, which may progress to vomiting, suggests the development of ileus and gastric stasis as perfusion to the gut is reduced. Visceral perfusion abnormality may also be noticed by the parents, as they report abdominal distension or a reduction in wet nappies or passing urine. During all this time, the deteriorating child may still have perfectly normal saturations and remain lucid, though with increasing lethargy and drowsiness. Increasing tachypnoea may not necessarily identify a respiratory focus of decompensation, but may represent the attempt to compensate for the metabolic acidosis associated with shock.[5,6]

In summary, the skill involved in recognising the deteriorating child early relies on careful history taking with the acknowledgement that the parents know what is normal for their child. Alteration from normal must not be ignored or dismissed until the child has been thoroughly and thoughtfully examined. Physiological and biochemical parameters that are not entirely normal must be critically evaluated to ensure that the early signs of decompensation are not missed. An attempt must be made to treat what is presumed wrong, with the intention that the response to treatment results in normalisation of the physiological disturbance. If this is not the case, the child should remain under vigilant and regular review, with physiological parameters documented to detect a deteriorating trend. Senior paediatric, consultant or specialist opinion should be sought to ensure that a diagnosis has not been missed.

RESUSCITATION

Identification of the presenting clinical emergency, treatment of the most likely diagnoses, awareness of the potential differential diagnosis and repeated evaluation of response to treatment are all key elements to the successful management of a critically ill or injured child. Successful treatment should return physiological parameters to within the normal range for age, where they should remain. If this does not occur, escalation of resuscitation may require more invasive organ support in the form of ventilation, infusion of inotropes and the provision of renal, hepatic and haematological support. In extreme cases, extracorporeal life support may be required.

STABILISATION AND TRANSFER

Stabilisation of a critically ill child at a referral hospital prior to transfer infers resuscitation has begun, physiological parameters are stable or returning towards normal and the appropriate level of organ support required is in place. In some situations, the organ support required (e.g. haemofiltration) may not be available during the retrieval process, and it is important to minimise delay of the transfer to a place where equipment and staffing levels are present to optimise the eventual outcome of the child.[7]

Good stabilisation implies that the child has had resuscitation procedures completed at the referral hospital and the child has appropriate airway and vascular access contingency plans to deal with destabilisation during the transfer. Ventilated children, for example, should have the appropriate-sized endotracheal tube confirmed in an ideal position (usually in the middle of the trachea, seen at C2–C3 on the chest X-ray), a gastric tube to decompress the stomach and facilitate ventilation, and the adequacy of ventilation monitored with continuous oxygen saturations and end-tidal carbon dioxide monitoring as minimum.

Children who have required volume resuscitation are on inotropes, or those who are potentially cardiovascularly unstable should have enough vascular access established to allow commencement or escalation of inotropes during transfer. Adequate cardiovascular monitoring, in the form of continuous electrocardiographic trace and regular intermittent non-invasive or continuous invasive arterial blood pressure monitoring, should be in place. Where a central line is in place in children, central venous pressure monitoring adds to the evaluation of response to treatment.

Arterial access in children is warranted in those who are cardiovascularly unstable and/or on inotropes; those who need targeted blood pressure management (e.g. for intracranial perfusion pressure); and those who require frequent blood gas or electrolyte monitoring. Peripheral arteries including radial, dorsalis pedis and posterior tibialis are preferable. Central arterial access attempts must completely avoid the brachial artery, as it is an end artery. Thrombosis may lead to limb loss. Attempt should be made to minimise blood gas monitoring by correlation of end-tidal CO_2 with arterial blood gas measurement of $PaCO_2$. Excessive

blood gas monitoring and the performance of blood tests that do not result in changes of treatment should be minimised as eventually they result in the need for red cell transfusion. The risk–benefit of this practice must be considered.[8,9]

Vascular access can be extremely challenging in critically ill children, and familiarity with intraosseous needle insertion,[10,11] and the use of the external jugular vein, may provide rapid access for the early commencement of resuscitation fluids and the institution of inotropes. Intraosseous access is technically easy and provides 'central' access to a non-collapsible venous system, into which almost all resuscitation drugs can be rapidly infused. The limb accessed must be carefully monitored.[12] The placement of central venous lines (femoral and jugular) in children is technically more difficult than in adults because of the diminutive size of the vessels, the short neck in small children and the bleeding problems that may be present in critical illness. Central venous cannulation should be attempted only by those skilled in this procedure.[13] Femoral central venous access is preferable to jugular access in children who have a coagulopathy or any suggestion of raised intracranial pressure. Central venous catheters utilising the Seldinger technique have greatly increased successful placement. Ultrasonography is useful to determine the exact location of veins and is the standard of care in many institutions.[13] Multilumen catheters are recommended when infusing multiple drugs and for parenteral nutrition. Complications including catheter-related sepsis are the same as in adults. This risk can be reduced by adherence to a care bundle of measures.[14] The need for prolonged venous access may warrant regular catheter changes, or surgical or interventional radiological implantation of a central venous device (e.g. Infusaport, Broviac, Hickman catheter or peripherally inserted central catheter).

In children undergoing resuscitation or those with the suggestion of, or potential for, raised intracranial pressure, a urinary catheter with hourly fluid balance allows a more complete assessment of the adequacy of resuscitation. Resuscitation is a process, which is often ongoing for the first 24 hours or more of care. It is not expected that the child will immediately recover during the resuscitation and stabilisation process, so the delay in transferring the child to a definitive place of care should be minimised and be specific to the requirements of each patient.[15] In some children, stabilisation may not be achievable and the time-critical nature of the problem may require transfer under very unfavourable circumstances. Good examples are children with a time-critical neurosurgical emergency,[16] neonates with obstructed total anomalous pulmonary venous drainage or occasionally transposition of the great arteries with intact ventricular septum,[17] and some surgical abdominal emergencies among others.

PAEDIATRIC INTENSIVE CARE TRANSFER

Transfer by a team skilled in the retrieval of critically ill children is associated with reduced morbidity, critical incidents and mortality.[15] There are, however, some circumstances where the disease process is time critical, and the time delay in waiting for a paediatric retrieval team imposes an unacceptable risk.[16] In these cases it is important to use the most competent and skilled team available at the time, usually an anaesthetist, paediatrician and intensive care or senior paediatric nurse. Advice and remote telephonic assistance should be available from the paediatric retrieval team or accepting paediatric intensive care unit (PICU). For those performing time-critical retrievals, it is essential that delay is minimised and only life-saving procedures are allowed to delay the transfer. In these cases it is helpful to have a discussion with the accepting team, in terms of their expectations for transfer and of what to expect about the patient's condition. A checklist for retrieval in these circumstances is helpful to ensure that all eventualities have been considered.

PAEDIATRIC INTENSIVE CARE

The development of PICU separate from adults, recognised the unique diseases, problems and requirements of critically ill children, especially very young children. Centralisation and modernisation of paediatric intensive care, along with dedicated paediatric retrieval teams, have dramatically improved outcomes in children. Critical illness or injury in children is not common, and the reduced incidence of disease means that centres that see higher volume of a specific illness become more skilled at dealing with it, and children have better outcomes.[18] Super-specialisation of paediatric intensive care is evolving (e.g. in the care of children with highly complex congenital cardiac lesions).[17,18]

The PICU does not function in isolation and the intensive care team needs support from all other paediatric sub-specialties and specialist paediatric therapists in providing the highest level of comprehensive care for this group of children. The PICU is only one part of the delivery of tertiary paediatric hospital care to children, which starts with the provision of excellent pre-hospital care; advice and support for level 1 and 2 hospitals in the resuscitation and stabilisation of critically ill children; and the subsequent safe transfer by specialised paediatric intensive care retrieval teams to the appropriate PICU.

The adult intensive care unit, with its technically skilled nursing and medical team, may be an appropriate and safe place for a critically ill child, especially if ventilated, to await retrieval, as long as the adult intensive care unit (ICU) team is appropriately supported by local paediatric consultants, and the

paediatric retrieval team or the accepting PICU continue to provide management advice on the care of the critically ill child.

MINIMUM STANDARDS

Suggested minimum standards for a PICU should be adopted. In general, a PICU should provide:

- a specialist trained in paediatric intensive care available at short notice, and available 24/7 for ongoing management advice
- a comprehensive range of paediatric sub-specialty support, available 24/7
- immediately available junior medical staff with advanced life support skills including advanced airway and vascular access competence
- nursing staff with experience in paediatric intensive care, and a nurse:patient ratio to facilitate the appropriate level of care of each patient
- allied health professionals with specific training in paediatrics, including ready access to physiotherapists, dieticians, pharmacists, speech and language therapists, occupational therapists and child psychologists, as well as ancillary support staff including clerical and portering staff
- specialised advanced life support equipment for children ranging in age from neonates to adolescents
- 24-hour laboratory, radiological and pharmacy services
- purpose-built PICU, recognising the special physical and emotional needs of critically ill children of different ages, and their families
- a programme for teaching, continuing education, research and quality assurance for all members of the PICU multidisciplinary team
- the skills and expertise to transfer critically ill children within the hospital for investigations and treatment
- an in-house paediatric intensive care retrieval team, or at least an arrangement with an external retrieval team to provide critical care transfer of children into the PICU
- support services and facilities for parents and families, whose children are critically ill in intensive care.

Neonatal intensive care units have many similar and additional requirements.

PAEDIATRIC MONITORING

Technology has allowed most aspects of adult monitoring to be applied to neonatal and paediatric practice. The ideal paediatric haemodynamic and respiratory monitoring system should be non-invasive, painless and readily interfaced with the child; constitute minimal risk to the child; provide specific, reproducible and readily understood data relevant to the child's status; and respond rapidly to changes in status. It should provide continuous visual and/or auditory display of data and have appropriate alarms. There should be facilities for recording data, and ideally it should be inexpensive and require low maintenance.

PULSE OXIMETRY

Pulse oximetry provides continuous non-invasive measurement of arteriolar saturation (Sa_{O_2}) and provides a rapid indication of hypoxaemia. Accurate information is given:

- when the oxyhaemoglobin dissociation curve is shifted to the left (e.g. foetal haemoglobin and alkalosis) or to the right (e.g. sickle-cell disease and acidosis)
- in the presence of carboxyhaemoglobin (functional saturation is accurate)
- with moderately severe desaturation (e.g. cyanotic heart disease with saturations >50%)
- with anaemia (haemoglobin concentrations above 5 g/dL)
- when skin is pigmented.

Errors occur in the presence of extreme hypoperfusion, excessive movement and rapidly changing ambient light and extreme desaturation. A range of sensors is available to monitor children of all ages.

TRANSCUTANEOUS tc_{CO_2} AND ARTERIAL P_{CO_2} MONITORING

Oxygen and carbon dioxide diffuse through well-perfused skin from the superficial capillary network and can be measured using modified polarographic and glass electrodes, respectively. The electrodes are heated to 43°C–45°C to arterialise the capillary blood and maximise capillary blood flow. Under optimal conditions, there is good correlation between arterial and transcutaneous gas tensions. Hence continuous monitoring of blood gas tensions is possible in a non-invasive manner. The Ptc O_2 (transcutaneous) to pO_2 gradient have been used as indices of the status of the microcirculation. The accuracy of these devices is mainly confined to the neonatal period.

DRUG INFUSIONS

All drugs used in the care of critically ill children, including those used for cardiovascular support, should be administered according to body weight, or occasionally body surface area. Accurate delivery is crucial. Accurate drug infusions require accurate devices, of which syringe pumps are the most useful. Potentially lethal errors in calculating drug dilutions are minimised by the use of dose/dilution/infusion rate guidelines that should be agreed upon within an

institution by pharmacy and paediatric intensive care collaboration.[19] It is safer, with fewer drug errors and communication errors, and is time saving and potentially cost saving to have infusions made up in the same way by all referring institutions within the PICU network. These should be disseminated to referral institutions by the PICU and agreed at clinical, clinical governance and management levels. Potential errors in drug dosing in PICU occur in bigger children, when their weight equals or exceeds adult weight, but paediatric drug dosing regimens based on body weight continue to be used. Above 50 kg body weight in an older child, it may be preferable to administer drugs according to adult dosing schedules with awareness of maximum dosing in adults.

PAIN RELIEF AND SEDATION IN CHILDREN

The management of pain and agitation in children has received inadequate attention and has tended to be underestimated and under-rated. Infants and children are often unable or unwilling to complain of pain, and neonates are commonly intubated without adequate anaesthesia (use of a combination of opiate, atropine and muscle relaxant). In the past, some believed that the neonate could not perceive pain.[20] It is now clear that neonates possess all the anatomical and neurochemical systems necessary for pain perception and exhibit physiological and behavioural responses to pain. Consensus regarding the best anaesthetic for the neonate during intubation is still unavailable.[21] Stress responses associated with pain and agitation may increase morbidity and mortality in critically ill patients. Analgesia can be provided by narcotic infusions, local blocks and regional techniques in children of all ages. Painful procedures in the PICU must always be accompanied by appropriate analgesia. Sedative agents can reduce agitation and minimise harmful stress responses; however, all opiates and benzodiazepines may result in a withdrawal reaction after discontinuation, and an attempt should be made to wean agents to a minimum once noxious procedures have been completed. Agents, such as oral or intravenous cloinidine,[22] are useful as opiate-sparing and benzodiazepine-avoiding adjuncts, with minimal withdrawal effects on discontinuation. Having parents at the bedside for most of the child's waking day, distraction with play therapy, reading and videos, and appropriate surroundings including reduced noise and light levels, all help to alleviate children's anxiety, and do not come at the cost of withdrawal.

OUTCOME OF PAEDIATRIC INTENSIVE CARE

Depending on admission criteria, mortality in paediatric ICUs ranges from under 5% to 15%.[23] If patients with pre-existing severe disabilities are excluded, the majority of survivors have a normal or near-normal life expectancy. Several scoring systems have been developed or modified for paediatric application to predict ICU mortality. These scoring systems allow comparison between different ICUs, internal audits, stratification of patients for research purposes and analysis of cost–benefit. The updated Paediatric RISk of Mortality (PRISM) score[24,25] and the Paediatric Index of Mortality (PIM) score[26] are applicable to a wide range of critically ill infants and children. Although PRISM performs marginally better, PIM is easier to collect and hence less prone to errors in data collection. PIM also has the advantage that it predicts mortality based on admission parameters, whereas PRISM is based on the worst variables in the first 24 hours. In many paediatric ICUs, deaths occur within the first 24 hours. PRISM is often recording the dying process rather than predicting it. Specialised scores have been developed for specific problems; for example, the Modified Injury Severity Scale and Paediatric Trauma Score for paediatric trauma, and the modified Glasgow Coma Scale for neurological insults. Numerous scoring systems have been developed for meningococcaemia, the best validated being the Glasgow Meningococcal Septicaemia Prognostic Score.[27] Compared with adult intensive care, children with equivalent Therapeutic Intervention Scoring System scores have a lower in-hospital and 1 month mortality. Although multiple organ failure increases mortality, the prognosis is considerably better than for adults.[28] There is evidence that mortality is lower in specialist paediatric ICUs[29,30] and that paediatric ICUs with a larger workload have better outcomes than those looking after fewer children. General hospitals should therefore have facilities for urgent resuscitation of children prior to early transport to a specialised PICU. Unless unavoidable, critically ill children, particularly those requiring mechanical intervention, should not be cared for in an adult ICU for longer than 24 hours. The American Academy of Pediatrics, the Society of Critical Care Medicine, the British Paediatric Association and the Australian National Health and Medical Research Council have all stated that children should receive intensive care in specialist paediatric units.

KEY REFERENCES

3. Carcillo JA, Fields AI. Clinical practice parameters for haemodynamic support of pediatric and neonatal patients in septic shock. *Crit Care Med*. 2002;30:1365–1378.
11. Orr RA, Felmet KA, Han Y, et al. Pediatric specialised transport teams are associated with improved outcomes. *Pediatrics*. 2009;124(1):40–48.
18. Arenas-Lopez S, Riphagen S, Tibby SM, et al. Use of oral clonidine for sedation in ventilated paediatric intensive care patients. *Intensive Care Med*. 2004; 30:1625–1629.

19. Wilkinson JD, Pollack MM, Ruttimann UE, et al. Outcome of pediatric patients with multiple organ system failure. *Crit Care Med*. 1986;14:271–274.
25. Pollack MM, Alexander SR, Clarke N, et al. Improved outcomes from tertiary center pediatric intensive care: a statewide comparison of tertiary and non-tertiary care facilities. *Crit Care Med*. 1991;19:150–159.


Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Kinsella JP, Neish SR, Dunbar ID, et al. Clinical responses to prolonged treatment of persistent pulmonary hypertension of the newborn with low doses of inhaled nitric oxide. *J Pediatr*. 1993;123: 103–108.
2. The International Liaison Committee on Resuscitation. The International Liaison Committee on Resuscitation (ILCOR) Consensus on Science with treatment recommendations for pediatric and neonatal patients: pediatric basic and advanced life support. *Pediatrics*. 2006;11:7955–7977.
3. Kliegman RM, Stanton BMD, Geme JS, et al. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia, PA: Elsevier; 2015.
4. Chambers D, Huang C, Matthews G. *Basic Physiology for Anaesthetists*. Cambridge: Cambridge University Press; 2015.
5. Carcillo JA, Fields AI. Clinical practice parameters for haemodynamic support of pediatric and neonatal patients in septic shock. *Crit Care Med*. 2002;30: 1365–1378.
6. Carcillo J. Pediatric septic shock and multi-organ failure. *Crit Care Clinics*. 2003;19:413–440.
7. Henning R, McNamara V. Difficulties encountered in transport of the critically ill child. *Pediatr Emerg Care*. 1991;7:133–137.
8. Chegondi M, Sasaki J, Raszynski A, et al. Hemoglobin threshold for blood transfusion in a pediatric intensive care unit. *Transfus Med Hemother*. 2016; 43(4):297–301.
9. Lacroix J, Tucci M, Du Pont-Thibodeau G. Red blood cell transfusion decision making in critically ill children. *Curr Opin Pediatr*. 2015;27(3):286–291.
10. Rosetti VA, Thompson BM, Miller J, et al. Intraosseous infusion: an alternative route of pediatric intravascular access. *Ann Emerg Med*. 1985;14: 885–888.
11. Saccheti AD, Linkenheimer R, Liberman M, et al. Intraosseous drug administration: successful resuscitation from asystole. *Pediatr Emerg Care*. 1989; 5:97–98.
12. Moscati R, Moore GP. Compartment syndrome with resultant amputation following intraosseous infusion. *Am J Emerg Med*. 1990;8:470–471.
13. Grebenik CR, Boyce A, Sinclair ME, et al. NICE guidelines for central venous catheterisation in children. Is the evidence sufficient? *Br J Anaesth*. 2004; 92(6):827–830.
14. Bernholtz SM, Pronovost PJ, Lipsett PA, et al. Eliminating catheter-related bloodstream infection in the intensive care unit. *Crit Care Med*. 2004;32: 2014–2020.
15. Orr RA, Felmet KA, Han Y, et al. Pediatric specialised transport teams are associated with improved outcomes. *Pediatrics*. 2009;124(1):40–48.
16. Soundappan SV, Holland AJ, Fahy F, et al. Transfer of pediatric trauma patients to a tertiary pediatric trauma centre: appropriateness and timeliness. *J Trauma*. 2007;62(5):1229–1233.
17. Gotlieb D, Scwartz ML, Bischoff K, et al. Predictors of outcome of arterial switch operation for complex D-transposition. *Ann Thorac Surg*. 2008;85: 1698–1703.
18. Kansy A, Ebels T, Screiber C, et al. Higher programmatic volume in paediatric heart surgery is associated with better early outcomes. *Cardiol Young*. 2015;25(8):1572–1578.
19. Shann F. Continuous drug infusions in children: a table for simplifying calculations. *Crit Care Med*. 1983;11:462–463.
20. Anand KJS, Hickey PR. Pain and its effects in the human neonate and fetus. *N Engl J Med*. 1987;317: 1321–1329.
21. Allen KA. Premedication for neonatal intubation: which medications are recommended and why? *Adv Neonatal Care*. 2012;12(2):107–111.
22. Arenas-Lopez S, Riphagen S, Tibby SM, et al. Use of oral clonidine for sedation in ventilated paediatric intensive care patients. *Intensive Care Med*. 2004;30:1625–1629.
23. Wilkinson JD, Pollack MM, Ruttimann UE, et al. Outcome of pediatric patients with multiple organ system failure. *Crit Care Med*. 1986;14:271–274.
24. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. *Crit Care Med*. 1988; 16:1110–1116.
25. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated pediatric risk of mortality score. *Crit Care Med*. 1996;24:743–752.
26. Shann F, Pearson G, Slater A, et al. Paediatric index of mortality (PIM): a mortality prediction model for children in intensive care. *Intensive Care Med*. 1997;23:201–207.
27. Thompson APJ, Sills JA, Hart A. Validation of the Glasgow meningococcal septicaemia prognostic score: a 10-year retrospective survey. *Crit Care Med*. 1991;19:26–30.
28. Yeh TS, Pollack MM, Holbrook PR, et al. Assessment of pediatric intensive care – application of the Therapeutic Intervention Scoring System. *Crit Care Med*. 1982;10:497–500.
29. Pollack MM, Alexander SR, Clarke N, et al. Improved outcomes from tertiary center pediatric intensive care: a statewide comparison of tertiary and non-tertiary care facilities. *Crit Care Med*. 1991;19:150–159.
30. Pearson G, Shann F, Barry P, et al. Should paediatric intensive care be centralized? Trent versus Victoria. *Lancet*. 1997;349:1214–1217.

106

Upper airway obstruction in children

Paul James, Sara Hanna

Upper airway obstruction is a particular clinical challenge in the paediatric population. The physics of air flow, the relative narrowness of the paediatric airway combined with the high rate of oxygen consumption in the child can produce rapid and unexpected deterioration in the clinical condition of a child. Moreover, severe airway obstruction occurs infrequently in non-specialist centres, and will require immediate intervention by the team present to secure a safe airway and maintain oxygenation. Successful management relies on an understanding of the paediatric airway, knowledge of the symptoms and signs that suggest unusual diagnoses or life-threatening obstruction, a realisation of what can and cannot be diagnosed without endoscopy and meticulous attention to basic anaesthetic principles.

ANATOMICAL AND DEVELOPMENTAL CONSIDERATIONS

The upper airway technically extends from the nares to the junction of the larynx with the trachea. It includes the nose, the paranasal sinuses, the pharynx and the larynx. It changes in size, shape and position from the neonatal period through infancy and childhood to resemble the adult airway by the age of 8 years.[1]

Children have a proportionally larger head and occiput relative to body size. The large head forces the neck into flexion when supine, which is a potential cause of airway obstruction.

NOSE

The nose is made up of nasal bones, nasal part of the frontal bones and frontal processes of the maxillae. The septum divides the cavity into two with the exterior opening at the nares and the opening into the nasopharynx at the choanae.

If the membrane that separates the palatal processes during development does not rupture the neonate will have choanal atresia and will present with airway obstruction.

Infants are obligate nasal breathers, and secretions, oedema and blood easily block the small nasal apertures. Similarly, cellulitis, oedema or abscess formation in the paranasal sinuses will lead to airway obstruction.

PHARYNX

The pharynx forms the common upper pathway of the respiratory and alimentary tracts. It is divided into three regions: the nasopharynx, oropharynx and laryngopharynx, which open into the nasal cavity, mouth and larynx, respectively.

The pharyngeal isthmus separates the nasopharynx and oropharynx. It closes off during swallowing.

The adenoids lie on the roof and posterior wall of the nasopharynx. These atrophy with age, but enlargement in early childhood may obstruct breathing. They may also be dislodged during instrumentation of the nose.

The oropharynx extends from the soft palate to the tip of the epiglottis. It is attached anteriorly to the base of the tongue via the glossoepiglottic folds, between which lies the valleculae.

At the entrance to the oropharynx is a collection of lymphoid tissue known as Waldeyer ring. This consists of the lingual tonsil at the base of the tongue and bilateral palatine tonsils as well as the adenoids and tubal tonsils. Inflammation, infection or invasion of this tissue may obstruct breathing. The shape and dimension of the oropharynx affect airway function, particularly during sleep.

The relatively large tongue decreases the size of the oral cavity and more easily obstructs the airway. Decreased muscle tone also contributes to passive obstruction of the airway by the tongue.

The laryngopharynx extends from the tip of the epiglottis to the lower border of the cricoid cartilage. The larynx bulges back into the centre of the laryngopharynx leaving a recess on either side, known as the piriform fossa. This is a common site for impaction of swallowed foreign bodies.

LARYNX

The larynx is situated between the pharynx and trachea, extending from the base of the tongue to the cricoid cartilage.

ABSTRACT

A systematic approach to upper airway obstruction in children is described. Severe life-threatening conditions are rare but prompt sensible management is key to a good outcome. The variable causes are outlined with reference to airway anatomy and pathology. Red flags in the history and examination that should alert the practitioner to the more serious or complex problems are highlighted along with a highly practical guide to managing these problems both in and outside a specialist centre.

KEY WORDS

Upper airway obstruction
symptoms
signs
red flags
causes
emergency
management

The larynx consists of the thyroid cartilage, the cricoid cartilage, the paired arytenoids and the epiglottis, together with the small corniculate and cuneiform cartilages.

The laryngotracheal tube forms from the ventral wall of the foregut. The primitive glottis is formed at 10 weeks gestation when the true vocal cords split. Failure of this process results in a congenital laryngeal web or atresia of the larynx. Incomplete division of the embryonic foregut results in a tracheo-oesophageal fistula.

The cricoid cartilage is shaped like a signet ring with the widest portion lying posterior. This is the only complete cartilage ring in the respiratory tract and is the narrowest portion of the larynx. Any oedema, infection or inflammation at this level results in airway compromise. Acquired subglottic stenosis as a result of prolonged or repeated tracheal intubation also occurs at this level. The larynx lies more anteriorly and higher, being at the level of the fourth cervical vertebra at birth, the fifth cervical vertebra at 6 years and the sixth cervical vertebra in the adult.

The epiglottis is a leaf-shaped structure attached to the posterior border of the thyroid cartilage by the thyroepiglottic ligament. The infant epiglottis is narrower, softer and more horizontally positioned than in the adult.

The more superior location of the larynx in children may create difficulty in visualising the laryngeal structures because of the acute angulation between the base of the tongue and the laryngeal opening.

The vocal cords are innervated by the recurrent laryngeal nerve, which, if damaged, results in paralysis of the corresponding vocal cord, causing it to lie motionless in the midline and at a lower level than the opposite side. Bilateral paralysis results in complete loss of voice and the two vocal cords may then flap together causing a valve-like obstruction during inspiration.

The highly compliant and poorly developed cartilage leads to increased susceptibility to dynamic airway collapse in the presence of obstruction. Loss of muscle tone in the pharynx leads to airway obstruction at the level of the soft palate and epiglottis. Laryngomalacia is a congenital abnormality of the larynx and results from the laryngeal structure being more pliable and less rigid than in the adult.[2]

PATHOPHYSIOLOGY

Resistance to laminar air flow increases in inverse proportion to the fourth power of the radius (Poiseuille's law) resulting in a marked increase in resistance to air flow with airway narrowing. The perpendicular cartilaginous ribs, which reduce the effect of the 'bucket handle' movement of the rib cage, and the immature intercostal muscles result in a mechanical 'disadvantage', and children are more reliant on the diaphragm for inspiration. Signs of increased respiratory effort to overcome airway obstruction include head bobbing (use of neck muscles), subcostal and sternal recession, tracheal tug and forced expiration (abdominal muscle contraction in expiration). Chronic airway obstruction may lead to chest wall deformity.

A higher metabolic rate and oxygen consumption, together with a smaller functional residual capacity and fewer fatigue-resistant fibres in the diaphragm, means there is little respiratory reserve and children with airway compromise can deteriorate very quickly.

However, children with chronic obstruction may manage surprisingly well with 'tolerable' airway noises and increased levels of respiratory work. Acute changes in airway calibre in these children may cause precipitous deterioration with accompanying hypoxia.

CLINICAL PRESENTATION

Stridor is a harsh, vibratory sound produced by turbulent air flow and is the cardinal feature of upper airway obstruction. Symptoms and signs vary with the level of obstruction, the aetiology and the age of the child.

When faced with a child with possible airway obstruction the clinician must decide whether investigation and intervention are necessary and, if so, in what time scale. Very few diagnoses are truly clinical as it is only on direct endoscopy that the true cause of the problem can be confirmed. However, a careful history and examination are key to the decision-making process. Features that suggest obstruction needing urgent evaluation include episodes of colour change (pallor, cyanosis), apnoea, biphasic stridor, stridor when asleep and stridor from birth.

Extrathoracic obstruction is more pronounced during inspiration as the negative intraluminal pressure causes further airway narrowing. Obstruction is characterised by stridor and the prolongation of inspiration. Intrathoracic airway diameter increases on inspiration and signs and symptoms occur mainly on expiration. There is prolonged expiration, wheeze and air trapping as seen in asthma, which is a common misdiagnosis.

Biphasic stridor is characteristic of mid-tracheal lesions or impending complete obstruction at any level (Fig. 106.1).

AETIOLOGY

The aetiology may be classified in a number of ways including according to the site of obstruction (i.e. nose, pharynx or larynx), whether it is congenital or acquired, or whether it is due to infection, malignancy, trauma, etc.

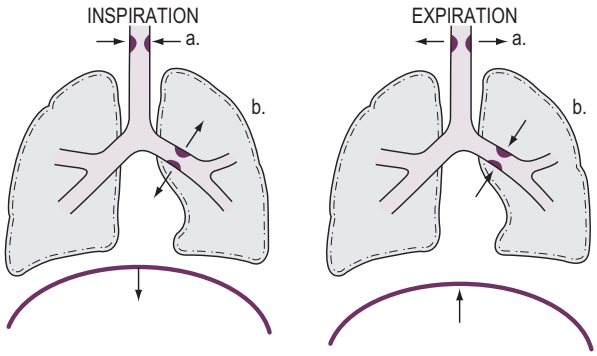


Figure 106.1 Dynamics of (a) extrathoracic, and (b) intrathoracic airways obstruction.

Box 106.1 Common causes of upper airway obstruction in neonates/infants

Nose
- Choanal atresia

Oral cavity
- Encroachment of tongue on airway
- Macroglossia: Beckwith–Wiedeman, hypothyroidism
- Micrognathia: Pierre–Robin syndrome
- Haemangioma or venous/lymphatic malformation of tongue

Laryngeal abnormalities
- Laryngeal atresia
- Laryngomalacia
- Vocal cord paralysis
- Laryngeal cleft

Subglottic abnormalities
- Subglottic stenosis – congenital or acquired
- Subglottic haemangioma

Extrinsic lesions
- Mediastinal masses
- Cystic hygroma
- Foregut malformations
- Vascular abnormalities including rings and slings

Boxes 106.1 and 106.2 list the more common causes according to the age of the child.

INFECTIONS OF THE UPPER AIRWAY

Viral and bacterial infections causing upper airway obstruction present in a very similar way and are often concurrent. A logical and useful approach to diagnosis is to identify the site of infection and consider the nature of the condition.[3]

PHARYNGEAL INFECTIONS

In the pharynx the site of infection is the peritonsillar bed in 49% of cases, the retropharyngeal space in 22% of cases and the parapharyngeal spaces resulting in abscess formation in 2%.[4]

Box 106.2 Common causes of upper airway obstruction in children

Oral cavity

Encroachment of tongue on airway
- Macroglossia: Beckwith–Wiedeman, hypothyroidism
- Micrognathia: Pierre–Robin syndrome
- Haemangioma or venous/lymphatic malformation of tongue

Other oral mass lesions
- Ectopic–lingual thyroid/thyroglossal duct cyst/dermoid cyst/ranula

Nasopharynx/oropharynx/retropharyngeal space
- Adenoid/tonsillar inflammation and abscess
- Lymphatic malformation
- Supraglottitis
- Foreign bodies
- Trauma/burns
- Neoplasms

Larynx/cervical trachea

Supraglottic
- Laryngomalacia
- Epiglottitis

Glottic abnormalities
- Vocal cord paralysis
- Laryngeal cleft
- Recurrent respiratory papillomatosis

Subglottic abnormalities
- Croup
- Subglottic stenosis
- Congenital
- Acquired (prolonged or traumatic intubation)
- Subglottic haemangioma

Bacterial tonsillitis and peritonsillar abscess (quinsy)

Tonsillitis is caused by the aerobes *Streptococcus pyogenes, Streptococcus pnemoniae* and *Staphylococcus aureus* and the anaerobes *Fusobacterium* spp., *Prevotella* spp., *Porphyromonas* spp. and *Actinomyces* spp. Aerobes predominate in the acute primary infection, whereas anaerobes are associated with abscess formation or extension across tissues. Treatment is with third-generation cephalosporins or co-amoxiclav as there is a high incidence of penicillin resistance.[5] Metronidazole or carbapenems should be added if there is extension or abscess formation. Clindamycin or linezolid should be added to reduce bacterial exotoxin release if toxic shock is suspected.

Surgical removal in the acute setting is controversial as there is potentially an increased risk of bleeding, but if there is pus then drainage is indicated to prevent spontaneous rupture.[6]

Infectious mononucleosis (glandular fever)

Infectious mononucleosis is caused by the Epstein–Barr virus, which is a virus transmitted in saliva. Airway

obstruction can occur and, despite steroids, 40%–88% of patients with airway obstruction require tonsillectomy.[7] The use of steroids does reduce the duration of fever, pharyngitis and abnormal haematological findings.[8]

Retro- and parapharyngeal abscess

Retropharyngeal abscesses are more common in boys (ratio 2:1) and occur at a median age of 3 years. The incidence appears to be rising.[9] The principal symptoms are fever, sore throat, trismus, torticollis, neck swelling and pain. Airway obstruction is rare.[10]

Staphylococci and streptococci are the usual causal agents, but growth is often polymicrobial and treatment is with broad-spectrum antibiotics. Surgical drainage is indicated if there are symptoms persisting for 2 days or more, prior administration of antibiotics, and fluid on computed tomography scan with a cross-sectional area of greater than 2 cm^2. Complications include mediastinitis and Lemierre syndrome.

Lemierre syndrome

Described in 1936, Lemierre syndrome occurs when a pharyngeal/tonsillar infection is complicated by thrombophlebitis and septic emboli. The organism is usually *Fusobacterium necrophorum*. Local effects classically include thrombosis in the ipsilateral internal jugular vein and more distant spread with suppuration most commonly affecting the lungs, but also causing septic arthritis, osteomyelitis, meningitis, and liver, renal and skin abscesses.[11]

Ludwig angina

Ludwig angina is a diffuse infection of the submandibular and sublingual spaces. Severe pain, fever, malaise and dysphagia occur with swelling that can be large enough to cause airway compromise. Antibiotic choice is as for tonsillar abscess, and surgical drainage is indicated if there is pus formation.[12]

LARYNX/TRACHEAL INFECTIONS

Croup

Croup (laryngotracheobronchitis) is common and usually caused by the virus parainfluenza, influenza type A or B, respiratory syncytial virus or rhinovirus. It is the commonest cause of acquired acute stridor in children and is a clinical diagnosis. There is a sudden onset of a seal-like barking cough usually accompanied by stridor, hoarse voice and respiratory distress. Symptoms are usually worse at night. It commonly affects children aged 6 months to 3 years with a peak incidence at 2 years. Only 2% of cases are admitted to hospital each year, of which only 0.5%–1.5% will require intubation.[13]

A Cochrane review investigated the use and effectiveness of steroids in the treatment of children with croup and recommended all children should receive either dexamethasone 0.15 mg/kg or prednisolone 1–2 mg/kg orally.[14]

Nebulised epinephrine (adrenaline) 1/1000, 0.5 mL/kg to a maximum of 5 mL may be used to reduce airway swelling acutely in severe croup. This is a short-term measure and may allow time for the steroids to work or for experienced personnel to be called to the child. It may be repeated if necessary after 30–60 minutes, but further doses should be used with caution as repeated need suggests an extremely narrow airway.

If intubation is indicated, visualisation of the larynx should not be a problem; however, a smaller tracheal tube than normal for the age is usually required because of subglottic oedema. Once the obstruction is bypassed, most children can be managed on a Swedish nose with minimal sedation and arm splinting. Extubation may be attempted after 72 hours (or earlier if a large leak develops). Around 10% will require re-intubation.

Epiglottitis

Very few clinicians have seen epiglottitis since the introduction of *Haemophilus influenzae* type B vaccination in 1992. In children, it is still almost always due to infection with *H. influenzae* type b (Hib), although it can be caused by beta-haemolytic streptococci, staphylococci or pneumococci. In a recent retrospective study, 10% of children presenting with epiglottitis were found to have Hib infection, despite having being vaccinated.[15]

It occurs usually in children aged 2–6 years, with a peak incidence at 3 years.

Epiglottitis is painful. There is an abrupt onset of high fever, sore throat, dysphagia, soft stridor and drooling. The child may prefer to sit leaning forwards with mouth open.

The key to management is to secure the airway under inhalation anaesthesia with an ear, nose and throat (ENT) surgeon standing by if a tracheostomy becomes necessary. Visualisation of the laryngeal inlet may be difficult. A bacterial swab of the epiglottis should be taken once the airway is secure. Antibiotic treatment with an extended-spectrum cephalosporin (e.g. ceftriaxone) is indicated. Recovery usually occurs about 48 hours after the institution of antibiotic therapy and confirmed by visualisation of a normal epiglottis on laryngoscopy.

Bacterial tracheitis

Bacterial tracheitis is uncommon. The condition may occur at any age. The usual pathogens are *S. aureus, H. influenzae,* streptococci, and *Neisseria* species.[16]

The signs and symptoms of bacterial tracheitis are frequently intermediate between those of viral croup and epiglottitis. Coughing produces copious tracheal secretions and retrosternal pain. The voice may be hoarse and stridor prominent. The larynx, trachea and bronchi can become acutely obstructed with purulent

debris and inflammation with adherent pseudomembranes overlying friable tracheal mucosa.

Most patients with bacterial tracheitis will require tracheal intubation.

At laryngoscopy, the epiglottis and supraglottic structures will appear normal, although slough and pus may be visible beyond the vocal cords. Significant pneumonia and systemic symptoms of bacterial septicaemia are not unusual. Ceftriaxone is a reasonable first-line antibiotic therapy. The average duration of tracheal intubation is 6–7 days and antibiotic therapy and hospitalisation may be required for up to 14 days.

Diphtheria

Diphtheria is caused by *Cornyebacterium diphtheriae* and *Cornyebacterium ulcerans*. It begins with a croup-like illness, cough and sore throat, but often progressing to death through sepsis, suffocation by the 'pseudomembranes' of serocellular exudate and direct effects of the powerful exotoxin, which has an affinity for neural endings (paralysis), cardiac muscle (heart block and myocardial failure) and the adrenal glands (hypotension with endocrine failure). Unless there is a high index of suspicion, it is a diagnosis easily missed. Treatment includes the administration of specific antitoxin and appropriate antibiotics.

Respiratory papillomatosis

Respiratory papillomatosis is characterised by recurrent proliferations of squamous papillomata within the airway, anywhere from lips to lungs. The viral pathogen is most commonly human papilloma virus types 6 and 11. The recurrent nature of this condition often necessitates multiple surgical procedures. The current management philosophy is toward a more conservative approach, aimed at ameliorating airway symptoms while limiting subsequent scarring of the larynx. Surgical debulking is the treatment of choice and several modalities have been used, including cold steel dissection, microdebridement, suction diathermy, cryotherapy, CO_2 or other laser ablation and radiofrequency cold ablation.

Any of these may be followed by systemic administration or direct injection of antiviral agents (e.g. cidofovir) into the resection sites, with the aim of reducing the frequency of reoperative surgery for recurrent papillomas.[17]

TRAUMA

INHALATIONAL BURNS

Inhalational injury should be suspected with burns occurring in a closed space, and when facial burns, singed nasal hairs and oropharyngeal carbonaceous material are present. Respiratory complications are the major cause of mortality in children who are burnt. Direct airway burns or inhalation of products of combustion may lead to rapidly progressive oedema. The situation may be compounded by small airway and lung injury and by the need to provide adequate analgesia. Early intubation is strongly recommended prior to an emergency situation developing. Tracheal tube fixation is critical and may be problematic with extensive facial burns; it may require suturing of the tube to the nasal septum or securing the tube to the teeth.

FOREIGN BODY ASPIRATION

Foreign body aspiration is one of the leading causes of death in children. It is most common in those under 3 years, but can occur at any age.[18] Most deaths occur at the time of aspiration due to complete upper airway obstruction. Of those children who reach hospital, the mortality is low.[19] The most common aspirated object is 'food', usually nuts. Peanuts account for one-third of all foreign body aspirations.

Often the inhalation event is not witnessed, and the history may be less clear than expected. Presentation varies from severe acute upper airway obstruction through to a well, pink child with a persistent cough.

More than 90% of foreign bodies lodge below the upper airway in a main bronchus, slightly more commonly on the right side in children.[20]

As the majority of inhaled material is organic in origin, a plain radiograph may fail to demonstrate an abnormality – especially in the first 24 hours, although X-rays in inspiration and expiration may show evidence of gas trapping.[18]

Management is as per the 'choking child' basic life support algorithm. Children with effective cough should be closely observed and encouraged to cough by themselves. If the cough is not effective and the child is conscious, the rescuer may intervene with five back blows followed by five chest thrusts (or abdominal thrusts in older children).

If the child is not conscious, the child should have airway, breathing and circulation assessed and managed as per the basic life support guidelines, with assisted ventilation and chest compressions.

Most children who reach hospital with an inhaled foreign body, or the possibility of such, should have a rigid bronchoscopy under general anaesthesia.[21]

Most anaesthetists will use an inhalational induction with sevoflurane in order to maintain spontaneous ventilation.

N_2O is avoided, particularly if there is radiological evidence of gas trapping. The cords and upper trachea are sprayed under direct laryngoscopy with 4 mg/kg lidocaine. Maintenance of ventilation and oxygenation during rigid bronchoscopy in children is controversial. The options are a spontaneously breathing technique (reduces the chance of distal movement or dislodgement of the foreign body) or muscle relaxation and the use of positive-pressure ventilation (reduces atelectasis and desaturation episodes). It is difficult to demonstrate the superiority of one technique over another.[19]

SUBGLOTTIC STENOSIS

Subglottic stenosis may be congenital or acquired (usually due to post-intubation laryngeal injury).

The main feature is chronic, inspiratory stridor often made worse by intercurrent viral respiratory tract infection. When a child presents acutely, the management is as for croup. However, ENT referral is necessary for diagnosis and management. The surgeon will grade the severity of the stenosis according to the size of endotracheal tube that can pass relative to that expected for age. This assessment and clinical condition will inform the decision to intervene.[22]

Treatment options available include inhaled or oral steroids to reduce inflammation and balloon dilatation of the narrowed airway with minimal mucosal trauma. Symptoms are resolved or improved in up to 70% of cases. If this fails, a laryngotracheal reconstruction (LTR) whereby a cartilage graft, from either the costal cartilages or the thyroid cartilage, is inserted into a vertical laryngotracheal fissure in order to expand the stenotic segment. Some stenoses will also require a posterior graft inserted into a posterior cricoid chondrotomy. In a double-stage LTR, a tracheostomy is inserted to safeguard the airway postoperatively and the grafted area is stented for approximately 6 weeks. A further procedure is then performed to remove the stent and assess the airway. A tracheostomy is not used in a single-stage LTR and the child is left intubated with an age-appropriate endotracheal tube for 5–7 days postoperatively, both stenting and safeguarding the airway. All patients receive antireflux medication postoperatively to negate the negative impact of gastric contents on mucosal healing.

CONGENITAL

PIERRE ROBIN SEQUENCE

The Pierre Robin sequence is a congenital anomaly presenting with micrognathia, glossoptosis and a cleft palate. Although there is a spectrum of airway obstruction most children can be managed by conservative measures or with a nasopharyngeal airway for a few months. The natural history shows that, with normal growth, airway compromise resolves without immediate surgical intervention as previously advocated. However, a few children do require tracheostomy.[23]

CYSTIC HYGROMA

Conspicuous at birth, cystic hygroma or lymphangioma is a relatively rare cause of upper airway obstruction in infancy. The tumours consist of masses of dilated lymphatic channels. They usually occur in the neck but may involve tissues of the tongue and larynx, and occasionally extend into the mediastinum. Airway obstruction may be due to infection or haemorrhage into the lesion. Surgical excision has been the mainstay of treatment, although complete removal is difficult and recurrence is common. Although some authors have reported watchful waiting of cystic hygroma, it should be considered only in patients who are asymptomatic. The medical treatment consists of the administration of sclerosing agents.

LARYNGOMALACIA

Laryngomalacia is the commonest cause of congenital stridor and usually presents within the first 2 weeks of life. Clinicians should not give this diagnosis without full airway assessment to any baby with life-threatening symptoms or stridor that is obvious at birth. Airway obstruction results from the collapse of supraglottic structures on inspiration, and expiratory symptoms are not a feature. Stridor often gets worse initially for 6–9 months before gradually improving, with most children being free of symptoms by 18–24 months.[24]

It is a dynamic condition and the supraglottic collapse is most obvious during the 'waking phase' of anaesthesia if a formal airway assessment is done.

The majority of children will not require surgical intervention, but the remaining 5%–10% require some form of surgical treatment. Surgical options include division of the aryepiglottic folds to 'open' the constricted supraglottis, resection of the redundant mucosa and suspension of the prolapsing epiglottis to uncover the laryngeal introitus. A degree of gastrooesophageal reflux disease is often associated with laryngomalacia, and all children should therefore receive antireflux medication. This possibly reflects changes in airway and intrathoracic pressures in response to the airway obstruction, as opposed to being a causal factor. A neurological form of the condition exists and may be seen in children with neurological or neuromuscular conditions, such as cerebral palsy. In such cases, surgical intervention should be approached with caution and it may be most appropriate to manage severe airway collapse with a tracheostomy.[25]

OTHER

INFANTILE HAEMANGIOMA

Infantile haemangiomas are the most common tumours of infancy, affecting approximately 1 in 10 children.[26] These are highly proliferative vascular tumours that may grow very quickly, causing obstruction when the airway is involved; if these are left untreated there is a 50% mortality rate. Most airway haemangiomas will co-exist with cutaneous lesions (but not vice versa).[27] The PHACES syndrome comprises airway haemangiomas with associated deep or diffuse cutaneous, segmental haemangiomas as well as posterior fossa malformations, arterial anomalies, cardiac/aortic defects, eye anomalies and a sternal defect.[28]

Medical and surgical interventions have included steroids, chemotherapeutic agents (vincristine, interferon-α), laser treatment, surgical excision,

tracheostomy or a combination of these, but the spectacular effect of propranolol on cutaneous haemangiomas of infancy was described for the first time in 2008[29] and confirmed by a meta-analysis as being the best treatment available for infantile haemangiomas.[30] The mean dose of propranolol was 2 mg/kg/day (range 0.5–3 mg/kg/day). The mean treatment duration was 6 months (range 1.5–10 months). Clinical improvement was seen in a range of 24 hours to 3 weeks (mean 3.8 days). Complications related to propranolol usage were found in one child (2.94%) who developed bronchoconstriction during the first week of treatment.

Because of the possible side effects of propranolol, current infantile haemangioma treatment centres recommend that a full cardiovascular and respiratory review be performed prior to initiation of therapy.

VOCAL CORD PALSY

Vocal cord palsy may be idiopathic, a result of a neurological abnormality, or traumatic (birth or iatrogenic).[31] It may be uni- or bilateral.

Unilateral palsy presents with stridor and dysphonia, which often resolves with time as the contralateral vocal cord compensates.

Bilateral vocal cord palsy is potentially life threatening, and a tracheostomy may be necessary in approximately half of the cases. Magnetic resonance imaging of the brain is mandatory in order to exclude an Arnold–Chiari malformation with hydrocephalus.[32] Spontaneous recovery rates of up to 70% are reported.[31]

ANAESTHESIA FOR RELIEF OF UPPER AIRWAY OBSTRUCTION

The principle behind safe induction of anaesthesia in the obstructed airway is the maintenance of spontaneous ventilation. Muscle relaxants should be avoided before the airway is secure in order to avoid the potentially disastrous 'can't intubate, can't ventilate' scenario.

A gaseous induction using 100% oxygen with either sevoflurane or halothane is the technique of choice. The aim is to attain a plane of anaesthesia that is deep enough to allow laryngoscopy, but this is a slow process. If the airway becomes obstructed following loss of consciousness, it can be improved by applying continuous positive airway pressure, changing the patient's position (lateral or semi-prone position), using simple airway manoeuvres or simple airway adjuncts, such as a nasal airway.

Sufficient depth of anaesthesia for laryngoscopy may not be achieved because of the obstructed airway. A laryngeal mask airway may help. If it is impossible to secure the airway then direct access to the trachea via a cricothyroidotomy or tracheostomy should be gained.

Important points are:

- A prepared induction should be undertaken with efficient suction apparatus, a range of tracheal tubes, suitable stylets, bougies, trained staff, full monitoring, etc.
- Induction in the adopted position, for example, sitting in epiglottitis, is advocated. The child is laid flat after induction and prior to intubation.
- Care must be taken not to distend the stomach as this will compound difficult ventilation.
- Orotracheal intubation is quickest and safest, and should be performed initially. After adequate tracheal suction, the tube can be changed to a nasotracheal one. Muscle relaxants may be used at this point if the operator is confident of the ability to intubate and/or ventilate.[33]

CARE OF THE SECURED AIRWAY

Successful management of upper airway obstruction in children requires optimal care of the nasotracheal tube. Such children must always be nursed in a paediatric intensive care unit with adequate nursing ratios. The nasotracheal tube must be positioned at the level of the clavicular heads (T_2) on chest X-ray. A meticulous technique of fixation must be employed to prevent accidental extubation. Adequate humidification is important to prevent obstruction of narrow tubes by secretions.

Repeated suctioning of secretions is required. Instillation of saline (0.5–1.0 mL) prior to suction may be necessary to encourage the removal of secretions. Light sedation is used to improve tolerance of the tracheal tube and to reduce the risk of self-extubation. Arm restraints may also be advisable, particularly in very young children.

In the event of clinical deterioration after intubation, a simple mnemonic may aid successful management; DOPES represents *d*isplacement of the tube, *o*bstruction of the tube, *p*neumothorax, *e*quipment failure and *s*tomach distension.

A true 'can't intubate, can't ventilate' scenario is rare in children. More often the situation has arisen due to 'operator error', for example, suboptimal positioning of the child, inadequate anaesthesia, a distended stomach, a blocked endotracheal tube or understandable panic. However, the only objective in this situation is to maintain oxygenation and if none of the basic manoeuvres resolves the situation the options are to perform a needle cricothyrotomy or a formal tracheostomy.

TRACHEOSTOMY

Tracheostomy remains a life-saving procedure and must be undertaken if tracheal intubation is impossible. It is best performed under general anaesthesia

with the neck extended. The airway can be maintained by facemask or laryngeal mask airway. Tracheostomies have been formed under local anaesthesia.

Care of a newly created tracheostomy is similar to that of an endotracheal tube, with the additional problem of some discomfort and the likelihood of fresh blood in the airway. Stay sutures in the tracheal wall lateral to the incision aid recannulation if accidental dislodgement occurs prior to formation of a well-defined tract.

The first tracheostomy tube change is undertaken once a tract has been established, usually between 5 and 7 days.

NEEDLE CRICOTHYROIDOTOMY

Cricothyroidotomy is the creation of an opening in the space between the anterior inferior border of the thyroid cartilage and the anterior superior border of the cricoid cartilage, to gain access to the airway below the glottis. It is difficult and risky in a small child. There are purpose-made paediatric kits available and these should be immediately available in every paediatric anaesthetic room.

Newer cannulae have both a 15 mm and a Luer-lock connector. It is not possible to ventilate a patient with a self-inflating bag via a needle cricothyrotomy and the cannula should be connected via the Luer-lock connection to an oxygen flowmeter via a Y-connector. The oxygen flow rate is initially set at the child's age in years. Ventilation occurs by occluding the open end of the Y-connector with a thumb for 1 second. If this does not cause the chest to rise, the flow should be increased by increments of 1 L/min.

Expiration must occur via the upper airway, even in situations of partial upper airway obstruction. If upper airway obstruction is complete, the gas flow must be reduced to 1–2 L/min. This will provide some oxygenation but little ventilation. Insufflation will buy a little time in which to secure a surgical airway. Complications include bleeding, pneumothorax, pneumomediastinum, subcutaneous emphysema, tracheo-oesophageal fistula, infection, haematoma and catheter dislodgement.

The recent national audit of major complications of airway management in the United Kingdom showed that the 'can't intubate, can't ventilate' scenario is rare in paediatric practice. Cricothyroidotomy and jet ventilation is difficult and risky, with the only reported attempt being unsuccessful. Tracheostomy by an ENT surgeon has been used successfully more often.[34]

KEY REFERENCES

2. Adewale L. Anatomy and assessment of the pediatric airway. *Pediatr Anesth*. 2009;19(S1):3–10.
5. Brook I. Current management of upper respiratory tract and head and neck infections. *Eur Arch Otorhinolaryngol*. 2009;266:315–323.
14. Russell KF, Liang Y, O'Gorman K, et al. Glucocorticoids for croup. *Cochrane Database Syst Rev*. 2011;(1):CD001955. Online. Available: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001955.pub3/full.
17. Bruce I, Rothera M. Upper airway obstruction in children. *Pediatr Anesth*. 2009;19(S1):90–101.
19. Farrell PT. Rigid bronchoscopy for foreign body removal: anaesthesia and ventilation. *Paediatr Anaesth*. 2004;14:84–89.
25. Bruce I, Rothera M. Upper airway obstruction in children. *Pediatr Anesth*. 2009;19(S1):90–101.
30. Stamatios P, Gemma P, Ioannis A, et al. A meta-analysis on the effectiveness of propranolol for the treatment of infantile airway haemangiomas. *Int J Pediatr Otorhinolaryngol*. 2011;75:455–460.
34. Cook TM, Woodall N, Frerk C. Fourth National Audit Project. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 1: anaesthesia. *Br J Anaesth*. 2011;106:617–631.


Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Brown OE. Structure and function of the upper airway. In: Westmore RF, Muntz HR, McGill TJI, eds. *Pediatric Otolaryngology, Principles and Practice Pathways*. New York: Thieme Medical Publishers; 2000:679–688.
2. Adewale L. Anatomy and assessment of the pediatric airway. *Pediatr Anesth*. 2009;19(S1):3–10.
3. Jenkins I, Saunders M. Infections of the airway. *Pediatr Anesth*. 2009;19(S1):120–132.
4. Loftis L. Acute infectious upper airway obstructions in children. *Semin Pediatr Infect Dis*. 2006; 17:5–10.
5. Brook I. Current management of upper respiratory tract and head and neck infections. *Eur Arch Otorhinolaryngol*. 2009;266:315–323.
6. Sdralis T, Berkowitz RG. Early adenotonsillectomy for relief of acute upper airway obstruction due to acute tonsillitis in children. *Int J Pediatr Otorhinolaryngol*. 1996;35:25–29.
7. Chan SC, Dawes PJ. The management of severe infectious mononucleosis tonsillitis and upper airway obstruction. *J Laryngol Otol*. 2001;115:973–977.
8. Hanna BC, McMullan R, Hall SJ. Corticosteroids and peritonsillar abscess formation in infectious mononucleosis. *J Laryngol Otol*. 2004;118:459–461.
9. Lander L, Lu S, Shah RK. Pediatric retropharyngeal abscesses: a national perspective. *Int J Pediatr Otorhinolaryngol*. 2008;72:1837–1843.
10. Page NC, Bauer EM, Lieu JE. Clinical features and treatment of retropharyngeal abscess in children. *Otolaryngol Head Neck Surg*. 2008;138:300–306.
11. Riordan T, Wilson M. Lemierre's syndrome: more than a historical curiosa. *Postgrad Med J*. 2004;80: 328–334.
12. Busch RF, Shah D. Ludwig's angina: improved treatment. *Otolaryngol Head Neck Surg*. 1997;117: S172–S175.
13. Bew S. Acute and chronic airway obstruction. *Anaesth Intensive Care Med*. 2006;7:164–168.
14. Russell KF, Liang Y, O'Gorman K, et al. Glucocorticoids for croup. *Cochrane Database Syst Rev*. 2011;(1):CD001955. Online. Available: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001955.pub3/full.
15. McEwan J, Giridharan W, Clarke RW, et al. Pediatric acute epiglottitis: not a disappearing entity. *Int J Pediatr Otorhinolaryngol*. 2003;67: 317–321.
16. Al-Jundi S. Acute upper airway obstruction: croup, epiglottitis, bacterial tracheitis and retropharyngeal abscess. In: Levin DL, Morriss FC, eds. *Essentials of Pediatric Intensive Care*. 2nd ed. Edinburgh: Churchill Livingstone; 1997:121–129.
17. Bruce I, Rothera M. Upper airway obstruction in children. *Pediatr Anesth*. 2009;19(S1):90–101.
18. Weir PM. Foreign body aspiration. In: Stoddart PA, Lauder GR, eds. *Problems in Anaesthesia: Paediatric Anaesthesia, Ch 27*. Boca Raton, FL: Taylor & Francis; 2004:163–166.
19. Farrell PT. Rigid bronchoscopy for foreign body removal: anaesthesia and ventilation. *Paediatr Anaesth*. 2004;14:84–89.
20. Hoeve LJ, Rombout J, Pot DJ. Foreign body aspiration in children. The diagnostic value of signs, symptoms and preoperative examination. *Clin Otolaryngol*. 1993;18:55–57.
21. Swanson KL, Prakash UBS, Midthun DE, et al. Flexible bronchoscopic management of airway foreign bodies in children. *Chest*. 2003;121:1695–1700.
22. Myer CM, O'Connor DM, Cotton RT. Proposed grading system for subglottic stenosis based on endotracheal tube sizes. *Ann Otol Rhinol Laryngol*. 1994;103:319–323.
23. Abel F, Bajaj Y, Wyatt M, et al. The successful use of the nasopharyngeal airway in Pierre Robin sequence: an 11-year experience. *Arch Dis Child*. 2012;97:331–334.
24. Olney DR, Greinwald JH, Smith RJH, et al. Laryngomalacia and its treatment. *Laryngoscope*. 1999;109:1770–1775.
25. Bruce I, Rothera M. Upper airway obstruction in children. *Pediatr Anesth*. 2009;19(S1):90–101.
26. Chang L, Haggstrom A, Drolet B, et al. Growth characteristics of infantile hemangiomas: implications for management. *Pediatrics*. 2008;122:360–367.
27. Perkins JA, Oliaei S, Garrison MM, et al. Airway procedures and hemangiomas: treatment patterns and outcome in U.S. pediatric hospitals. *Int J Pediatr Otorhinolaryngol*. 2009;73:1302–1307.
28. Perkins JA, Duke W, Chen E, et al. Emerging concepts in airway infantile hemangioma assessment and management. *Otolaryngol Head Neck Surg*. 2009;141:207–212.
29. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. *N Engl J Med*. 2008;358:2649–2651.
30. Stamatios P, Gemma P, Ioannis A, et al. A meta-analysis on the effectiveness of propranolol for the treatment of infantile airway haemangiomas. *Int J Pediatr Otorhinolaryngol*. 2011;75:455–460.
31. Daya H, Hosni A, Bejar-Solar I, et al. Pediatric vocal fold paralysis. *Arch Otolaryngol Head Neck Surg*. 2000;126:21–25.
32. Setz AC, De Boer HD, Driessen JJ, et al. Anesthetic management in a child with Arnold–Chiari malformation and bilateral vocal cord paralysis. *Paediatr Anaesth*. 2005;15:1105–1107.
33. Hillman D, Platt P, Eastwood P. The upper airway during anaesthesia. *Br J Anaesth*. 2003;91(1):31–39.
34. Cook TM, Woodall N, Frerk C. Fourth National Audit Project. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 1: anaesthesia. *Br J Anaesth*. 2011;106:617–631.

107

Acute respiratory distress in children

Tavey Dorofaeff

ACUTE RESPIRATORY FAILURE IN CHILDREN[1]

Acute respiratory failure in children, as in adults, is a failure of gas exchange – inadequate oxygenation and carbon dioxide clearance. Respiratory distress refers to both the sensation of breathlessness and the signs of increasing effort to breathe as a consequence of deteriorating gas exchange. The signs and symptoms in children are listed in Box 107.1.

EPIDEMIOLOGY[2,3]

Data extracted from the Australian and New Zealand Intensive Care Society (ANZPIC) database show that bronchiolitis, pneumonia, asthma, seizures and diabetic ketoacidosis were the top five admission diagnoses of all non-elective child admissions to intensive care in 2015. Of all admissions, just under 50% (48.9%) required some form of respiratory support. Respiratory admissions with any pathology numbered 33%, with 58% of these requiring respiratory support. Of this group, 17% were invasively ventilated, 28% received non-invasive ventilation and 60% received high-flow nasal cannula (HFNC) oxygen. The mean length of stay for respiratory admissions was 3.89 days. This is slightly longer than the combined average duration of stay of 3.63 days. The mortality rate overall was 3.4%. Those patients with a primary respiratory diagnosis had a mortality rate of 1.2% (ANZPIC, unpublished data, 2014/2015). These figures mirror data held elsewhere; however, there is a significant change in the usage of high-flow nasal oxygen, which will be discussed later in the chapter.

VENTILATORY REQUIREMENTS AND MECHANICS OF CHILDREN[4,5]

Neonates and small infants have a higher resting metabolic requirement for oxygen, which is estimated to be 7 mL/kg/min compared to 4 mL/kg/min for a school-age child or an adult.

Neonates and small infants have many differences compared with adolescents and adults, which give them a distinct disadvantage, particularly when illnesses affect the lung and reduce the compliance of the lungs or increase the airways resistance.

Specific differences in neonates and infants:

- Diaphragmatic breathers
- Compliant rib cage
- Reduced ability to generate negative pleural pressures
- Primary mechanism to increase minute ventilation is by tachypnoea
- Limited ability to increase tidal volume
- Lung volume close to functional residual capacity (FRC) at end expiration
- Tendency for airways to collapse at end expiration.

As children grow, these issues that affect neonates, infants and toddlers become less of a disadvantage as the child develops an upright and bipedal body habitus.

The airways of all children are disproportionately smaller than an adult's. Any obstruction of the lumen of the airways with increased mucous production or bronchoconstriction also increases airways resistance to the fourth power of the radius (Hagen–Poiseuille equation: $\Delta P = 8\mu LQ/\pi r^4$ where ΔP is the pressure reduction, L is length, Q is volumetric flow rate and r is radius). Hence, anatomically small airways are a distinct disadvantage. This is particularly the case in neonates and infants, but applies across the age (and size) range.

SIGNS AND SYMPTOMS OF ACUTE RESPIRATORY FAILURE

Signs and symptoms of respiratory failure in children that indicate the need for an increasing level of respiratory support are not subtle and are usually apparent from a brief focused clinical exam of the respiratory system. They relate to the developmental changes that influence the ways in which children compensate for, or decompensate from, respiratory failure. Due to pulmonary mechanics, neonates and small infants tend to become tachypnoeic.

Premature babies, term babies and very young infants can manifest apnoeas that may relate to severe tachypnoea or may be unrelated to the work

ABSTRACT

Respiratory distress is common in unwell children. A primary diagnosis of a respiratory illness is a leading indication for an admission to a paediatric intensive care unit (PICU). Bronchiolitis, asthma and pneumonia are the diseases that lead to the highest rates of children's admissions to the PICU. For the newborn, respiratory distress syndrome, transient tachypnoea of the newborn and neonatal pneumonia are leading admission indications to neonatal intensive care. In this chapter, we will concentrate on those disorders that a general intensivist is most likely to encounter in children.

KEYWORDS

Neonate
infant
child
paediatric
respiratory failure
pARDs
bronchiolitis
pneumonia

Box 107.1 Causes of respiratory failure in children

Common causes of respiratory failure in the neonate
Congenital
Respiratory distress syndrome of prematurity
Congenital heart disease
Laryngo/tracheo/bronchomalacia
Vascular rings and slings
Diaphragmatic hernia
Pulmonary hypoplasia
Gastroschisis and omphalocele
Neuromuscular and skeletal disorders
Acquired
Transient tachypnoea of the newborn
Meconium aspiration syndrome
Neonatal pneumonia
Pulmonary haemorrhage
Diaphragmatic palsy

Common causes of respiratory failure beyond the neonatal period
Bronchiolitis
Pneumonia
Asthma
Croup
Tumours
Trauma
Acute-on-chronic respiratory failure with chronic neuromuscular conditions
Acute respiratory failure with acute neuromuscular conditions
Acute respiratory distress syndrome
Respiratory failure related to immunocompromised host

of breathing, which is a significant symptom none the less. An intricate interplay of brainstem control and respiratory mechanics and airway control lead to this phenomenon that is not entirely understood. Bradycardia is almost routinely associated as a secondary consequence of the hypoxia that develops.

There are a number of other signs of respiratory distress that the reader will be very familiar with.

- Tachypnoea
- Distress/irritability/air hunger
- Grunting
- Hypoxia/cyanosis
- Bradypnoea – pre-arrest sign that requires urgent attention
- Bradycardia – pre-arrest sign that needs immediate attention.

(See Table 107.1.)

Basic physiological parameters are mostly recorded in well, non-hospitalised children. Children who are hospitalised will often exhibit compensated parameters, which, for their illness, are expected. These parameters need to be matched with clinical observation and experience.

Table 107.1 Normal heart and respiratory rates relative to age for hospitalised children

AGE GROUP	RESPIRATORY RATE MEAN (5TH–95TH PERCENTILE)	HEART RATE MEAN (5TH–95TH PERCENTILE)
0–3 months	41 (27–62)	140 (113–171)
3–6 months	38 (25–58)	135 (108–167)
6–9 months	35 (23–54)	131 (104–163)
9–12 months	33 (22–51)	128 (101–160)
12–18 months	31 (21–48)	124 (97–157)
18–24 months	29 (20–45)	120 (92–154)
2–3 years	27 (18–42)	115 (87–150)
3–4 years	25 (18–40)	111 (82–146)
4–6 years	24 (17–37)	106 (77–142)
6–8 years	23 (16–35)	100 (71–137)
8–12 years	21 (15–31)	94 (66–129)
12–15 years	19 (13–28)	87 (61–121)
15–18 years	18 (13–25)	82 (57–115)

Adapted from Bonafide CP, Brady PW, Keren R, et al. Development of heart and respiratory rate percentile curves for hospitalized children. *Pediatrics*. 2013;131(4):e1150–e1157.

PHYSICAL EXAMINATION

Respiratory examination findings are more challenging to elucidate in an active child who may be uncooperative or acutely distressed. In addition, the rate of breathing is much faster. A physical exam requires a skilled physician with a well-tuned knowledge. With practice, skills in observation, auscultation and percussion can be developed. As a rule, a truncated 'adult' type of exam that is limited to inspection and auscultation will give the examiner the best information while limiting distress to the child.

As children become more upright and mobile, they develop more of an adult body habitus, so the signs and symptoms are similar to adult respiratory failure. By the time a child is a teenager, the signs and symptoms parallel those in adult respiratory medicine.

PREMATURITY AND NEONATAL CHRONIC LUNG DISEASE[6–8]

The lungs develop throughout the foetal period until late childhood. Lung development is divided into five stages: embryonic, pseudoglandular, canalicular, saccular and alveolar. The embryonic and pseudoglandular phases have very little gas exchange ability. At 28 weeks of gestation, the middle of the canalicular stage, a significant amount of the ventilation can occur within

the respiratory bronchioles; 28–32 weeks corresponds to the saccular stage. At around 32 weeks, gestation intrinsic surfactant production begins. In preparation for premature birth this may be stimulated by the administration of corticosteroids to the mother. This is conventional therapy for any mother with threatened delivery prior to 32 weeks. Additional factors, such as foetal stress and infection, will also augment alveolar development.

Total alveolar surface area is increasing from 32 weeks and continues into childhood. This is the result of increasing maturity of alveoli, replication and increasing numbers.

Underdevelopment of the lungs of the premature infant is only one of the many issues that affect infants born prematurely. As a result, they require complex neonatal intensive care and care that will continue into childhood.

There is some complexity in the description of prematurity, gestation and birthweight. It is briefly described as follows:

- a term newborn is delivered from 37 weeks after the mother's last menstrual period; prematurity occurs when a newborn is less than 37 weeks of completed gestation
- extremely low birth weight is less than 1000 g
- very low birth weight less than 1500 g
- low birth weight is less than 2500 g
- small for gestational age is less than 5th percentile of weight for gestational age.

Chronic neonatal lung disease (CNLD) is defined as either:

- oxygen requirement at 28 days post-delivery (irrespective of premature gestation), or
- oxygen requirement at 36 weeks of gestational age.

All premature infants will have some degree of abnormal lung development. Bronchopulmonary dysplasia and hyaline membrane disease are pathological findings on biopsy or autopsy of premature infants who have respiratory failure. They are often used synonymously to describe CNLD and respiratory distress syndrome. The pathological features of CNLD include alveolar septal fibrosis with alternating collapse and hyperinflation of acini. Smooth muscle hypertrophy/hyperplasia may also be present. Chest X-ray (CXR) may reveal generalised hyperinflation, multiple cystic areas and opacities. A novel type of CNLD exists (Wilson Mikity syndrome) where babies may not have an initial oxygen requirement but go on to develop an oxygen requirement towards term or beyond.

Complications of prematurity are a common co-morbidity in children admitted to a paediatric intensive care unit (PICU) with severe respiratory failure; this is frequently in the context of an acute viral chest infection. CNLD, airway reactivity and pulmonary hypertension exacerbate any symptoms the infant may have otherwise suffered, increasing the need for invasive and non-invasive respiratory support.

Apnoea is a feature of prematurity and is a common symptom of illness in premature infants from birth until about 3 months of corrected age. Important differential diagnoses include sepsis (bacterial and viral), intraventricular haemorrhage and pain. Respiratory stimulants, such as caffeine, can be used to treat apnoea, though this is not always effective. Quite often the infant may need non-invasive support, such as HFNC oxygen, continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP), or ultimately invasive ventilation to manage the underlying condition and the apnoea.

Central hypoventilation due to a *PHOX2B* mutation is increasingly recognised as a congenital form of depressed ventilatory drive beyond the neonatal period. It manifests as hypoventilation during sleep. These children usually need non-invasive or invasive support. If undiagnosed, these children can present as sudden infant deaths.

Maternal tobacco use during pregnancy is a significant cause of prematurity, and it impairs lung development. Environmental tobacco smoke exposure exacerbates chronic lung disease, asthma and recurrent bronchiolitis in older infants.

LARYNGOMALACIA/TRACHEOMALACIA/BRONCHOMALACIA[9,10]

This results from cartilaginous weakness of the larynx, trachea, main bronchi or any combination of these. There may be malacia at single or multiple levels. Laryngomalacia is usually primary in nature. Tracheomalacia and bronchomalacia can be primary or secondary, and are caused by intrinsic anatomical abnormalities of the airways or secondary to external factors causing distortion or compression of the airways. Abnormalities of size or path of mediastinal blood vessels (primarily the aorta, pulmonary artery and right subclavian artery) and chest masses are the most common.

The result is a 'floppy' airway that tends to collapse during inspiration and/or expiration. Depending on whether these vessels are intra- or extrathoracic, stridor (extrathoracic) and/or wheeze (intrathoracic) will be present. Respiratory embarrassment may range from mild to severe, and includes cardiorespiratory arrest from acute airways obstruction – so-called 'malacic' spells.

What might be a mild illness for a normal infant becomes one that may require ventilation for a child with malacia. Ventilator weaning is often troublesome in these infants. Severe long-segment malacia can be an indication for long-term non-invasive home ventilation or tracheostomy and invasive ventilation. Over the first 18–24 months of life there is growth of the cartilage and improvement in the airway rigidity.

Tracheopexy (suspending the trachea on the sternum) and tracheal stenting are possible alternative interventions. Where malacia is a secondary effect of another abnormality, surgery to correct this defect may be warranted (e.g. vascular slings or rings, pulmonary atresia with poststenotic dilatation of the pulmonary artery); however, malacia often persists post-surgical correction. Management can be complicated and prolonged. Supportive therapies in lieu of growth and maturity of the large airways are the most common approach.

CONGENITAL HEART DISEASE[11]

Many congenital cardiac lesions present with respiratory features. Careful examination will help to elucidate the presence or absence of congenital heart disease. Features to look for include:

- Cyanosis
- Tachypnoea
- Tachycardia
- Hepatomegaly
- Murmurs, heaves and thrills in the precordium
- Absent femoral pulses
- Plethora or oligemia on chest radiography
- No improvement in cyanosis with supplemental oxygen
- Acidosis/lactataemia.

Although antenatal ultrasound scanning detects a significant number of lesions, early discharge or home birth means that symptoms can develop or go unappreciated until acute decompensation occurs.

Congenital heart lesions producing acute respiratory failure are likely to fall into one of the groups listed below:

- *Left heart obstruction (e.g. critical aortic stenosis, interrupted aortic arch and coarctation of the aorta):* this leads to pulmonary oedema, reduced pulmonary compliance and respiratory failure.
- *Large left-to-right shunts (e.g. ventricular septal defect and patent ductus arteriosus):* excessive pulmonary blood flow can cause pulmonary oedema, airway compression and obstruction. Minor intercurrent infection results in decompensation.
- *Cyanotic lesions:*
  - there is an obstruction to pulmonary blood flow (e.g. tetralogy of Fallot and critical pulmonary stenosis)
  - the pulmonary and systemic circuits are in parallel (e.g. transposition of the great arteries)
  - there is complete mixing of systemic and pulmonary blood (e.g. single ventricle and truncus arteriosus)
  - pulmonary venous abnormalities such as total anomalous pulmonary return.

Early institution of intravenous prostaglandins in company with other supportive measures, such as intubation, ventilation, judicious fluid therapy and inotropes, will be lifesaving in these infants. There are no contraindications to the commencement of prostaglandins in a collapsed infant where a paediatric cardiologist is not available to make an immediate assessment. An exception is for total anomalous pulmonary venous drainage where prostaglandin use most likely will be ineffectual, but it can worsen the cyanosis. This diagnosis requires expert assessment that is not immediately available to many collapsed infants at their initial presentation.

COMPLICATIONS OF CARDIAC SURGERY

DIAPHRAGMATIC PALSY

Palsy of the diaphragm is almost exclusively a complication of cardiothoracic surgery. These infants are difficult to wean from ventilation. If there is paradoxical upward movement of the affected diaphragm during inspiration, surgery to plicate the diaphragm is required. This stabilises the affected hemidiaphragm so the normal hemidiaphragm can still create a negative pleural pressure for inspiration. The palsy will often improve with time.

RECURRENT LARYNGEAL NERVE PALSY

Palsy of the recurrent laryngeal nerve results from an inadvertent injury sustained from surgery within the central structures of the chest. The most clinically significant manifestation is paresis of the ipsilateral vocal cord. Normal vocal cord function is necessary to maintain airway patency. Unilateral paresis is tolerable, but bilateral paralysis is poorly tolerated, sometimes resulting in recurrent extubation failure. Occasionally, a tracheostomy is needed to maintain a patent airway; fortunately, this is an uncommon situation.

VASCULAR RINGS AND SLINGS[12,13]

Vascular rings and slings may be considered complete or incomplete and result from aberrant vessels and the ductus arteriosus (or ligamentum arteriosus, if the duct is closed) leading to a constricting lesion of the trachea or bronchi. The most common type of sling is the pulmonary artery sling: an anomalous left pulmonary artery and the ductus encircling the trachea posteriorly. Vascular rings most commonly result from a right-sided aortic arch or a double aortic arch. There are a number of combinations: double aortic arch and derivatives causing complete ring, right-sided aortic arch and anomalous right subclavian artery, right-sided aortic arch, mirror image vessel branching and left ductus arteriosus, and an anomalous innominate artery.

Airway obstruction requires surgical correction. Tracheobronchomalacia often remains once the obstruction is relieved if the lesions have led to a secondary

malformation of the airway; this can lead to significant morbidity.

CONGENITAL DIAPHRAGMATIC HERNIA[14,15]

There are two types.

BOCHDALEK HERNIA

A Bochdalek hernia involves a deficiency in the postero-lateral part of the diaphragm. Most occur on the left side. A variable amount of the abdominal viscera herniates through into the chest. The presentation is dependent upon whether a hernia is diagnosed antenatally or not and whether pulmonary hypoplasia and pulmonary hypertension are present. Antenatal diagnosis may allow for the use of foetal intrauterine therapy; however, this is still experimental. The spectrum of clinical course ranges from profound, non-survivable hypoxia and pulmonary hypertension in the newborn to mild tachypnoea in infancy or an incidental finding diagnosed when a child comes to medical attention. Therapy involves respiratory support as appropriate and surgical closure of the defect. Children with severe respiratory failure may need extensive medical stabilisation with high-frequency oscillatory ventilation (HFOV), nitric oxide therapy and extracorporeal life support (ECLS). About 10% of children with congenital diaphragmatic hernia (CDH) have a chromosomal abnormality.

MORGAGNI HERNIA

A Morgagni hernia is in the anterior diaphragm. Typically, only the bowel will herniate through the defect. It is extremely uncommon for this hernia to cause respiratory discomfort. It is often an incidental finding or is associated with mild respiratory disease. Clinically significant hernias are repaired electively.

PULMONARY HYPOPLASIA

This is usually secondary to a space-occupying lesion within the chest, which limits room for lung development and results in abnormal pulmonary vasculature and pulmonary hypertension. CDH, cystic adenomatous malformation, congenital neuroblastoma and great vessel abnormalities are common causes. Pulmonary hypoplasia can be idiopathic. Depending on the residual lung function it can have a spectrum of clinical significance from an incidental finding to the requirement for long-term respiratory support.

OMPHALOCELE AND GASTROSCHISIS[16]

An omphalocele results from failed development of the abdominal wall musculature. The abdominal organs are contained within a protruding thin-walled peritoneal sac. There is a high incidence of associated abnormalities (50%–70%) and chromosomal defects (30%). Gastroschisis is herniation of the small bowel (usually) through an ischaemic defect in the abdominal wall. Approximately 15% of these children have associated defects or chromosomal abnormalities. Neither abnormality causes respiratory failure; however, surgical reduction may lead to increased intra-abdominal pressure, which limits excursion of the diaphragm and ventilation of the lungs. This is more likely with an omphalocele as more abdominal viscera are exteriorised.

NEUROMUSCULAR AND SKELETAL DISORDERS[17]

Any disorder that affects the ability of the muscles to 'drive' the ventilatory pump, or that causes a chest wall deformity, can compromise the effectiveness of ventilation. In the neonatal period these present with hypoventilation, desaturation and apnoea. Ventilator dependence as a neonate with these disorders indicates that the child is unlikely to survive without intensive support and, most likely, mechanical ventilation. Parents should be counselled appropriately. Spinal muscular atrophy (SMA) type 1 is the most common example of this. Less severe neuromuscular disorders may survive the neonatal period but go on to develop respiratory failure later (e.g. Duchene muscular dystrophy, SMA types 2 and 3). The amount of support offered needs to take into consideration ethical treatment, rational expenditure of resources and the wishes of the family and child (if appropriate).

ACQUIRED NEONATAL DISEASES[4]

TRANSIENT TACHYPNOEA OF THE NEW BORN

Transient tachypnoea of the newborn (TTN) is transient delayed clearance of foetal lung fluid. In the transition from intrauterine life the infant has to aerate the majority of its alveoli within a few minutes; a truly amazing feat. Not surprisingly, some infants may be slow to progress through this process. It is often an issue in infants that have little exposure to catecholamines due to a rapid operative delivery. Although these infants may require oxygen or CPAP, it is seldom that they need invasive ventilation.

MECONIUM ASPIRATION SYNDROME[18]

Meconium is the term used it describe faecal material of an infant prior to and in the first days of life. Passage of meconium is normal after birth. Passage of meconium prior to or during birth is an indicator of foetal stress. If inhaled or aspirated by the infant during delivery it induces a chemical pneumonitis and obstructive lung disease. If there is meconium present

and if the neonate is apnoeic, it is recommended that he/she be suctioned below the vocal cords before bag mask ventilation. Either intubation and suction via the endotracheal tube (ETT) or the use of a specialised meconium aspirator is recommended.

Once an infant develops meconium aspiration syndrome (MAS) the infant will need some degree of respiratory support. Non-invasive respiratory support and invasive ventilation are standard treatment options. Antibiotics are commonly administered as there is concern that sepsis might be an additional cause of foetal distress. Natural lung surfactant is deactivated by meconium. Surfactant therapy has not been shown to improve overall survival, but it may reduce hypoxia, though it can be poorly tolerated. There are conflicting recommendations regarding its use.

ECLS is indicated for severe MAS. Of all disease entities treated with ECLS (including all neonatal, paediatric and adult causes) MAS has the greatest survival. The Extracorporeal Life Support Organization (ELSO) database figures show that survival from severe respiratory failure due to MAS is upward of 90% with some units boasting near-100% survival.

NEONATAL PNEUMONIA[19]

Neonates are at constant risk of pneumonia. Due to the relative immaturity of their immune system, they are especially at risk from encapsulated bacteria and Gram-negative bacteria, such as *Escherichia coli*, *Klebsiella* and *Serratia*. Group B *Streptococcus* is carried as a vaginal commensal by up to 50% of women so is a common neonatal pathogen. This organism also causes sepsis and meningitis in infants and newborns. Early infections less than 14 days are likely to have come from the mother at birth, prior to delivery (chorioamnionitis, prolonged rupture of membranes) or by transplacental infection (*Listeria monocytogenies*).

Viruses, such as cytomegalovirus, varicella and other herpes viruses, tend to cause a generalised viraemia rather than isolated pneumonia. Fungal and protozoan infections are virtually unheard of in causing neonatal pneumonia and tend to cause a systemic infection.

PULMONARY HAEMORRHAGE[11]

Prematurity, surfactant deficiency and persistent foetal circulation with pulmonary hypertension all predispose an infant to the risk of pulmonary haemorrhage. Vitamin K deficiency can also present with pulmonary haemorrhage. However, gastrointestinal bleeding and intracerebral bleeding are far more common. Children with abnormal pulmonary vascularity of the bronchial arteries can also present with catastrophic pulmonary haemorrhage; however, this tends to present later in life. Disseminated intravascular coagulation can result in pulmonary haemorrhage in the setting of severe sepsis.

COMMON ACQUIRED DISEASES BEYOND THE NEONATAL PERIOD

BRONCHIOLITIS[20–25]

Bronchiolitis is the most common cause of respiratory failure beyond the neonatal period in children. Bronchiolitis is caused by infection and inflammation in the bronchioles resulting in obstructive lung disease leading to hypoxia, tachypnoea and air trapping. Chest radiographs show hyperinflation (and collapse) of lung segments and often right upper lobe collapse and/or consolidation. Respiratory syncytial virus (RSV) and human metapneumovirus (hMPV) are the most common viral pathogens. Additionally, bronchiolitis can be caused by human bocavirus, adenovirus, parainfluenzae, influenza virus and rhinovirus; all are implicated in the hospitalisation of children. Data from the Australasian ANZPIC registry show that bronchiolitis is the primary emergent diagnosis leading to PICU admission.

Treatment is primarily supportive, with the majority of infants supported by non-invasive respiratory support (largely HFNC oxygen). Only a few infants require invasive ventilation. These tend to be the very young infants in whom apnoea is a feature of the disease, and infants with underlying medical conditions, such as chronic lung disease, cardiovascular disease and neuromuscular disease.

Up to 20% of infants who require invasive ventilation for bronchiolitis have a concurrent bacterial infection, so antibiotics are often started empirically until haematology and inflammatory markers become reassuring and cultures are negative. A number of infants with bronchiolitis who need respiratory support must be transferred from their regional hospital to the nearest PICU. Although transfer with non-invasive support can be done safely for short road transfers, aeromedical transfer often necessitates intubation to secure the airway for the limitations of the aeromedical environment. Children transferred to a tertiary centre are more likely to be ventilated than those admitted from the onset of their illness.

Steroids, epinephrine (adrenaline), bronchodilators and hypertonic saline have been investigated for the treatment of bronchiolitis. None has consistently shown significant benefit in hospitalised children. Specific antiviral therapy is not indicated in the immunocompetent. Recombinant RSV antibody provides passive prophylaxis against RSV and is indicated in infants with chronic lung disease or congenital heart disease.

PNEUMONIA[26–30]

ANZPIC data show that about 13% of respiratory admissions were for pneumonia. About half of these patients required invasive ventilation. Community-acquired pneumonia is caused predominantly by

viruses followed in frequency by staphylococcal and streptococcal bacteria. Atypical infections such as *Mycoplasma pneumoniae* and *Chlamydia* also feature. Respiratory support is escalated as required to support the work of breathing and provide acceptable gas exchange. High-flow oxygen therapy is increasing in frequency and is the next most common therapy after supplemental low-flow oxygen.

If ventilation is required, current recommendations in paediatric acute respiratory distress syndrome (pARDs) (of which pneumonia is a secondary cause) should be followed. Tidal volume should be limited to less than 8 mL/kg with sufficient positive end-expiratory pressure (PEEP) to maintain lung distention. Permissive hypoxia and hypercarbia should be employed.

Treatment with empirical antimicrobials based on local sensitivity patterns should commence as soon as possible. Antibiotics should be changed to narrow-spectrum agents once organism sensitivities are known. The exception to this rule is in the treatment of cystic fibrosis where broad-spectrum cover may be needed to mitigate against the development of antimicrobial resistance. Bronchoscopy for samples is often not possible owing to the small calibre of the ETT. Blind bronchoalveolar lavage is almost routine for intubated patients. Endotracheal suction samples are also used; however, poor sensitivity and specificity limit their value.

ASTHMA[31–36]

Asthma is frequently diagnosed in childhood but not all wheezy exacerbations are asthma. They may be manifestations of an acute viral illness that presents with a constellation of symptoms including wheezing and tachypnoea, but they do not respond to bronchodilators. As an intensive care physician it is important to make an assessment of these patients regarding the underlying aetiology. The management of a wheezy lower respiratory infection is purely supportive but may often require some mechanical respiratory support.

Acute severe asthma requires specific treatments for the inflammation and bronchoconstriction that are the pathophysiological basis of asthma. For all but the most severe asthma, metered dose inhalers and spacers have been shown to have superior drug deposition. If there is significant hypoxia, oxygen-driven nebulisers are necessary. Nebulisers of salbutamol and ipratropium bromide should be given as a matter of urgency. Salbutamol nebulisers may need to be given continuously. Once the oxygen and nebulised bronchodilators have commenced then steroids are the next most important part of the asthma management. Gastric stasis is common in acute severe asthma, so oral steroids should not be relied upon. Anti-inflammatory doses of intravenous steroid should be given urgently to all patients who do not significantly improve with the initial burst of bronchodilators. Frequently, patients are also mildly dehydrated due to poor oral intake and increased insensible losses so a small fluid bolus can be helpful along with the commencement of intravenous maintenance fluids.

Intravenous salbutamol is sometimes necessary, but it can lead to side effects of tachycardia, tremor, lactic acidosis and a resultant compensatory increase in respiratory drive. An intravenous bolus of magnesium sulphate and/or aminophylline will often improve bronchoconstriction in severe refractory asthma, but it can have adverse effects. These last three medications are contentious and have protagonists and antagonists. However, the side effects of medical therapy are less than the risks of invasive ventilation.

Non-invasive ventilation (NIV) with continuous positive airways pressure (CPAP) or bi-level airways pressure (BiPAP) is increasingly used in asthma. Asthma was thought to be a contraindication, but NIV is now considered to have a place in acute severe asthma. It should not replace invasive ventilation if this is deemed to be necessary. Invasive ventilation should be approached with caution and with preparations made for managing cardiac arrest and pneumothorax should these occur. The approach taken for the ventilation of severe paediatric asthma is the same as for an adult patient. The reader is referred to Chapter 35 for the salient issues regarding ventilation of patients with asthma. Volume ventilation is preferred as this will adapt to the changing compliance of the lungs as the bronchi relax. High pressures may be needed. The alveoli are protected from these forces by the airway obstruction. The combination of steroid therapy and muscle relaxants puts the child at risk for critical illness neuropathy/myopathy. Fortunately, most children do not require more than 48 hours of ventilation. General anaesthesia and ECLS have been used on rare occasions.

Acute asphyxial asthma can present as a community cardiorespiratory arrest in children. The profound bronchoconstriction may have resolved by the time the child presents in the emergency department. These children have usually suffered a severe hypoxic-ischaemic brain injury. It is exceptionally rare for a child who presents with severe asthma to have a respiratory arrest once therapy has begun, but aggressive up-front treatment is mandatory.

Asthma is the second most common reason for admission emergently to a PICU for respiratory disease. Significant respiratory support is seldom required; however, this is a reflection of regional admission criteria.

CROUP[37–39]

Croup or laryngotracheobronchitis is infection and inflammation of the upper and lower airways. Children are more prone to croup owing to the smaller

airway radius. Further narrowing leads to a marked increase in resistance and turbulent flow. In the past, intubation was frequently required; however, the use of steroids and epinephrine (adrenaline) nebulisers now means very few children require intubation. If required, intubation for severe croup is best undertaken in the operating theatre with a gaseous induction and preservation of spontaneous breathing. If there is no significant lower airway or lung parenchymal inflammation, these children can be often supported with a nasal ETT and be awake and sometimes ambulant. Parainfluenza virus is the commonest cause of this condition. Important differentials to consider with severe stridor are foreign body, bacterial tracheitis and epiglottitis. Epiglottitis has become very uncommon with effective *Haemophilus influenzae* B vaccination.

TUMOURS

Neuroblastoma and lymphomas are the most common tumours that develop in children and cause respiratory compromise. Lymphomas tend to arise centrally from mediastinal nodes. A rapidly growing mediastinal T-cell lymphoma is a true oncological emergency. Mediastinal compression results in life-threatening respiratory and cardiovascular compromise. Maintenance of spontaneous breathing and positioning the patient in a forward sitting position are simple measures that may improve ventilation. Children will often find their preferred position. Intravenous steroids may need to be commenced before diagnosis if the respiratory compromise is severe. Intubation of these patients is risky and best done in the operating theatre with a gas induction and ear, nose and throat surgeons on standby.

ACUTE NEUROMUSCULAR DISEASE

For the most part, the acute neuromuscular conditions that children succumb to are similar to those for adults. The reader is referred to the relevant chapters. Guillain–Barré, tetanus, botulism, acute demyelinating encephalomyelitis and acute spinal injury are supported with ventilation while expectantly awaiting the return of neurological function. In Australia, tick bite paralysis can cause severe paralysis in children. The toxin binds covalently with the acetylcholine receptor complex. The cholinergic block lasts long after the source of the toxin is removed. Quite often, children require prolonged courses of supportive ventilation and intensive care. This is in contrast to the North American tick where paralysis resolves relatively quickly.

CHRONIC NEUROMUSCULAR CONDITIONS

Chronic neuromuscular disorders that are not diagnosed at birth are often diagnosed in infancy and early childhood. These children often require intermittent respiratory support with intercurrent illnesses. Many of these diseases are life-limiting and eventually children with severe neuromuscular or progressive conditions will suffer severe respiratory infections that need ventilation for prolonged periods. Cerebral palsy, Duchenne muscular dystrophy and spinomuscular atrophy are examples. Intubation can be difficult owing to scoliosis, limited jaw opening or facial dysmorphism. Ventilation is often troublesome due to chest wall deformity and underlying chronic lung disease. Weaning from ventilation is slow and laborious and may involve a protracted stay in the PICU on invasive ventilation and NIV. Some children cannot be weaned from invasive ventilator support after a severe infection so there is a risk that these children will die a very medicalised death. End-of-life care and limitation of interventions are important issues to discuss with parents and caregivers.

TRAUMA

The reader is referred to the chapters on head, chest and paediatric trauma. Pulmonary contusions and rib fractures are less common in small children. Head injury is common. As children grow, their bones ossify and they become involved in more risky activities so pulmonary contusions and rib fractures become more common. Infants tend to cope better with rib fractures, but older children have more significant issues with pain and lung expansion, as experienced by adult patients.

The management of severe chest trauma in children is no different to that in adults: maintain distension of as much of the lung as possible, and ensuring adequate ventilation. High frequency ventilation or ECLS can be used for pulmonary contusions. ECLS was previously contraindicated, but there are case reports in the literature of its use.

Bronchoscopy can be useful for pulmonary hygiene and the removal of blood casts from the bronchial tree. Lung isolation and independent ventilation are difficult in children and are seldom necessary.

ACUTE RESPIRATORY DISTRESS SYNDROME[40–50]

pARDS may occur in children of all ages from a variety of direct and indirect lung insults, as it does in adults. In children, common causes of pARDS include shock, pneumonia, sepsis, near-drowning and cardiac disease (congenital).

pARDS was redefined after the publication in June 2015 of the Proceedings of the Pediatric Acute Lung Injury Consensus Conference. This defined the criteria for the diagnosis of pARDs primarily for the purposes of research. Its use is mainly for the comparison and analysis of modalities of therapy for acute respiratory distress. Additionally, they have defined 'at risk' criteria. Tables 107.2 and 107.3 list these criteria.

Table 107.2 Paediatric acute respiratory distress syndrome criteria: adapted from consensus statements

Age	Excludes perinatal lung disease
Timing	Within 7 days of known insult
Oedema	Not explained by cardiac disease or fluid overload
Chest imaging	New infiltrates
Oxygenation	**Non-invasive ventilation** (No stratification) CPAP >5 cmH_2O. P/F ratio <300. SF ratio <264 **Invasive ventilation** Mild: OI <4 or >8, OSI <5 or >7.5 Moderate: OI <8 or >16, OSI <7.5 or >12.3 Severe: OI >16, OSI >12.3 $OI = (Fi_{O_2} \times \text{mean airway pressure} \times 100)/Pa_{O_2}$ $OSI = ((Fi_{O_2} \times \text{mean airway pressure} \times 100)/O_2 \text{ sat})$ (Used when Pa_{O_2} not available. Wean O_2 to give sat of 97% and use values required to achieve this value) SF ratio = O_2Sat/Fi_{O_2} PF ratio = Pa_{O_2}/Fi_{O_2}
Special populations	Cyanotic heart disease – cannot be explained by congenital heart disease Chronic lung disease – cannot be explained by chronic lung disease Left ventricular dysfunction – cannot be explained by left ventricular dysfunction

CPAP, Continuous positive airway pressure.

With permission from Khemani RG, Smith LS, Zimmerman JJ, Erickson S, Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: definition, incidence, and epidemiology: proceedings from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. 2015;16(5 Suppl 1):S23–S40.

Table 107.3 Paediatric acute respiratory distress syndrome risk criteria: adapted from consensus statements

Age	Excludes perinatal lung disease
Timing	Within 7 days of known insult
Oedema	Not explained by cardiac disease or fluid overload
Chest imaging	New infiltrates
Oxygenation	**Oxygen therapy** (oxygen/high-flow nasal cannula oxygen) Needing oxygen supplementation to maintain O_2 sats 88%–97% Minimum oxygen flows to achieve criteria <1 year 2 L/min, 1- to 5-year 4 L/min, 5- to 10-year 6 L/min, >10 years 8 L/min (oxygen flow = $Fi_{O_2} \times$ total flow rate) **CPAP/BiPAP** Fi_{O_2} >40% to maintain sats 88% – 97% **Invasive ventilation** Fi_{O_2} >40% maintain Sa_{O_2} >88. But OI <4 or OSI <5 $OI = (Fi_{O_2} \times \text{mean airway pressure} \times 100)/Pa_{O_2}$ $OSI = ((Fi_{O_2} \times \text{mean airway pressure} \times 100)/O_2 \text{ sat})$ (Used when Pa_{O_2} not available. Wean O_2 to give sat of 97% and use values required to achieve this value)

BiPAP, Bi-level positive airway pressure; *CPAP*, continuous positive airway pressure.

With permission from Khemani RG, Smith LS, Zimmerman JJ, Erickson S, Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: definition, incidence, and epidemiology: proceedings from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med.* 2015;16(5 Suppl 1):S23–S40.

Treatment modalities for pARDS are very similar to those for adults with the open-lung/low-tidal-volume strategy, and acceptance of permissive hypoxia and hypercarbia. HFOV is commonly employed. ECLS is considered if there is a reversible or treatable cause. The reader is referred to Chapter 33 on acute respiratory distress syndrome.

FOREIGN BODIES

Laryngeal, tracheal and bronchial foreign bodies are commonplace in children. Commonly, if not swallowed, they become lodged in the retropharynx. If they traverse the cords then they are likely to lodge at the level of the cricoid membrane (the narrowest part of the paediatric airway).

The shape of the foreign body is of crucial importance as to its final resting place. Sharp and slender foreign bodies (such as needles) and particulate food material (i.e. pieces of nuts) travel further down the bronchial tree.

Nut fragments and food particles are an important cause of morbidity. In particular, peanuts release arachidonic acid, which causes local inflammation. The resultant inflammation causes stenosis of the airway and pneumonia beyond the level of the obstruction.

Button batteries from small electrical devices tend to be swallowed and lodge in the oesophagus of the stomach. These are less of an issue in the airway.

Bronchoscopy (flexible and rigid) should be performed if there is any concern of a foreign body.

IMMUNOCOMPROMISED PATIENTS[29,51]

A PICU within a hospital with an active oncology service and, importantly, a bone marrow transplant service, will see a significant number of immunocompromised children. Quite often they present with generalised sepsis, localised pulmonary sepsis or with pulmonary complications of conditioning regimens for transplant.

Solid organ transplant patients are less immunocompromised after the initial transplant but can still present with immunosuppression-related infections.

The amount of HIV seen in a paediatrics unit mirrors that seen in the heterosexual community as the majority are from maternal transmission. Developing and third-world countries where HIV rates are extremely high in the adult population will see a lot more HIV in their critically unwell patients.

Previously undiagnosed leukaemia and lymphomas can present with respiratory failure due to:

- Sepsis
- Hyper-leukocytosis and viscosity/sludging in pulmonary vessels
- Disseminated intravascular coagulation and sequelae
- Multisystem organ failure
- Mass effects.

Genetic immunodeficiency states are rare. Severe combined immunodeficiency, combined variable immunodeficiency and chronic granulomatous disease can all present with severe respiratory failure in undiagnosed patients. T-cell defects present with opportunistic infections such as *Pneumocystis*, *Nocardia* and fungal infections. B-cell deficiencies present with severe viral or encapsulated bacterial infection. Chronic granulomatous disease presents with recurrent bacterial infections that need an efficient oxidative burst to destroy them (e.g. *Staphylococcus aureus*). Infection with an unexpected organism or severe respiratory failure in an infant that cannot be explained warrants a thorough investigation and assessment of the patient's immunocompetence.

Treatment of respiratory failure in the immunocompromised is directed towards the primary problem along with the respiratory support and antimicrobial therapy as appropriate. In some cases the immunosuppression, with steroids for example, may need to be decreased. Post-transplant lymphoproliferative disease is an example of this.

In many chemotherapy and bone marrow transplant regimens, bone marrow stimulation or autologous stem cell rescue is used to minimise the period of neutropenia and minimise the risk of sepsis in the face of aggressive chemotherapy.

INVESTIGATIONS

RADIOLOGY[6,52–55]

Although CXR is often mandatory in patients with respiratory disease to delineate the extent of lung involvement, the presence of pneumothorax or effusion or to check the position of the tracheal tube and central venous lines, routine radiology investigations can expose children to unnecessary ionising radiation. Investigations that use ionising radiation should be done only if they will answer questions important to diagnosis or management of the patient. Exposure to therapeutic radiation as a percentage of total lifetime radiation has been estimated to have risen from 15% to 50% in the United States over the last 30 years: CXRs are a significant contributor to this radiation. Children are most at risk. A chest computed tomography (CT) scan has a 1:1000 chance of inducing malignancy.

Standard CT and high-resolution spiral CT with thin cuts can provide better diagnostic detail than a plain CXR; however, their use should be justified in light of the increasing lifelong radiation exposure and the risk of transporting a critically ill patient to the scanner.

Although magnetic resonance imaging is not a good modality for lung parenchyma, it does not use ionising radiation and is safe with cumulative dosing.

Ultrasound is becoming routine in emergency departments and intensive care units (ICUs). Focused chest ultrasound can assist in the diagnosis of pneumonia, pleural effusions and pneumothorax with only a small amount of training required. Ultrasound should be used routinely for the placement of central venous lines, and it can assist with the insertion of chest drains, and the placement of intra-arterial lines and peripheral intravenous lines (where veins are not visible on the skin surface).

MICROBIOLOGY[5,22,26–28]

Appropriate microbiological samples have a crucial role in diagnosis and therapy. It is important to sample blood and respiratory secretions before administering antimicrobial therapy if possible.

Nasopharyngeal aspirate, nasal brushings or blood tests can, by the use of DNA/RNA polymerase chain reaction, detect significant viral and atypical (i.e. mycoplasma or Chlamydia) infections of the respiratory system. In children admitted to the PICU, RSV and hMPV infections are by far the most common.

Bronchoscopy is used in the PICU but to a lesser extent than in the adult ICU. It is used to inspect the airways, clear secretions and obtain samples. The need to use very small bronchoscopes for infants, plus limited experience and reduced availability of equipment limit the utility of this modality in the PICU. When required, it is undertaken by respiratory physicians or intensivists with keen interest in the procedure.

THERAPY FOR CHILDREN WITH SEVERE RESPIRATORY FAILURE

SUPPORTIVE CARE/FAMILY-CENTRED CARE

Even in the most critically ill children, parents are encouraged to be involved in the care of the child as much as is practical. The calming influence of a parent or grandparent cannot be understated and is a valuable adjunct to sedation regimens in the PICU and the neonatal intensive care unit (NICU). By inviting parents to participate in the care of their critically ill child, a partnership is forged that promotes trust and compliance with necessary medical interventions. If the child does not survive, the benefit for the parents in the subsequent grieving process should not be underestimated. Siblings may also benefit. However, this has to be matched with the needs of the patient.

NORMOTHERMIA, FLUID BALANCE AND NUTRITION[48,56–58]

Maintenance and promotion of homeostasis are the hallmarks of good intensive care. This includes adequate nutrition, euvolemic fluid balance and normothermia (unless therapeutic hypothermia is undertaken). Small infants have a large body surface to weight ratio so maintenance of normothermia can be challenging, particularly during procedures and transportation around and between hospitals. Clinicians and nursing staff need to pay particular attention at these times. Adequate nutrition promotes recovery from critical illness, so nutritional goals should be set early and all attempts made to reach these, including the use of transpyloric feeding tubes and intravenous nutrition if required. Avoidance of overfeeding is also an important consideration. Impaired carbon dioxide clearance in severe respiratory failure makes this vital as excess calorie intake promotes increased CO_2 production.

Minimising fluid overload and increased lung water are crucial and can lead to prolonged ventilator weaning if not addressed. Diuretics are commonly used to treat generalised oedema but have side effects of electrolyte imbalance and metabolic alkalosis. If fluid overload can be avoided then this is recommended.

Adherence to 'bundles' of care is necessary. The standardisation and promotion of high-quality care is augmented by the use of 'bundles' and 'checklists'. Ventilator-associated pneumonia, central line sepsis bundles and pre-procedure checklists are examples of these.

ANTIMICROBIAL USE

Antimicrobial use should always be with consideration of the local pattern of pathogen sensitivities and promote good antimicrobial stewardship to minimise the impact of resistance patterns. Patients on antimicrobial therapy often benefit from specific input by infectious diseases specialists, and routine consultation is an important part of antimicrobial stewardship.

NON-INVASIVE RESPIRATORY SUPPORT

HIGH-FLOW NASAL CANNULA OXYGEN THERAPY[59–63]

HFNC oxygen therapy has made its way rapidly into the PICU armament of support. Its introduction has preceded the supportive research relating to its use. Nonetheless, it appears to be a very useful tool at the lower end of respiratory support. HFNC oxygen therapy consists of a simple circuit comprising a gas flow regulator, an oxygen mixer, a humidifier, a gas warmer, large-calibre tubing and a patient interface. The patient interface is most commonly a soft plastic or silicone nasal cannula. The cannula may be semi-occlusive of the nares or non-occlusive. The gas flow is matched to the peak inspiratory flow so the nasopharynx is continuously replenished with a fresh gas supply. A small but not insignificant amount of PEEP is the result. Flow would be prescribed at 2 L/kg and occasionally 3 L/kg. This therapy is cheap and

is currently undergoing randomised trials to assess its efficacy. This is despite the huge uptake clinically at the bedside. There is evidence in paediatrics to suggest that this therapy is reducing intubation rates and, indeed, PICU admissions.

NASAL AND FACE MASK NON-INVASIVE VENTILATION[64]

Non-invasive ventilation supports neonatal and paediatric patients alike. Helping premature neonates in this way is useful and beneficial, and it avoids many risks associated with long-term invasive ventilation. Even very premature infants can have a brief period of invasive ventilation and surfactant instillation, and then for the majority of the time they are supported on bubble CPAP for the weeks and months they are in the NICU. Neonatologists as a rule use a nasal prong patient interface. This is due to its simplicity, lack of bulk, ease of securing and effectiveness. As patients grow, the use of masks becomes easier and the NIV devices are more able to synchronise and provide BiPAP efficiently. Soft, malleable facial structure, the general uncooperativeness of patients and difficulties with an adequate seal make patient interfaces difficult to match with individual patients. Newer plastics, the manufacturing of devices and improved cushioning help to decrease these problems. Older children, like adults, are most suited to mask ventilation support; however, with persistence and a range of masks, younger children can be supported with NIV.

Triggering and delivery of support can be limited in some devices. With newer machines and triggering modes, such as NAVA (neurally adjusted ventilatory assistance), this will change. NAVA relies on a special nasogastric tube that has electrodes that detect the electrical signal passing down the vagus nerve. The strength of this impulse is proportionate to the amount of ventilator support required by the patient. NAVA can be used in non-invasively ventilated and invasively ventilated spontaneously breathing patients.

The single most valuable resource, other than equipment, is experienced personnel who are able to persevere, use alternative interfaces and understand the equipment. In the acute setting it is very common to require sedation to augment patient compliance with the NIV. This should be used only where suitable staff members are present and emergency equipment is available for intubation.

INVASIVE VENTILATION

CUFFED VERSUS UNCUFFED ENDOTRACHEAL TUBE/NASAL VERSUS ORAL[65,66]

The debate regarding cuffed versus uncuffed ETT is not likely to be resolved. Both types are reasonable to use and each type has its advantages and disadvantages. For short-term use, security and reliable ventilation, most paediatric anaesthetists would prefer a cuffed ETT. In PICU, when ventilation is expected to be difficult or when changing the ETT is likely to cause significant deterioration, cuffed ETTs are preferred. For longer-term PICU management the issue is less clear. Cuffed ETTs need to be the appropriate size and care needs to be taken to monitor the inflation pressure and the positioning of the cuff. With either cuffed or uncuffed ETT, a leak of inspired gas around the ETT (cuff deflated if present) is a desirable finding when considering extubation and the risk of post-extubation stridor. The presence of a leak does not guarantee the patient will not suffer this complication. Usually, it is local policy that directs the use of cuffed or uncuffed ETTs.

Nasal verses oral positioning for long-term ETTs is another contentious issue. Either route is used up to the age of around 8 years when maxillary and ethmoid sinuses become aerated. Oral intubation is used first when intubating a critically unwell child due to lack of reserve and the need to expedite positive-pressure ventilation. If the intubation is uncomplicated and the patient tolerates the procedure then the ETT may be changed to a nasal ETT. However, this is dependent on local PICU policy and preference rather than clear evidence. Arguably, a nasal ETT is more comfortable for the patient and easier to secure but can cause pressure areas. The risk of changing the ETT should override any decision to match the culture of the PICU with respect to the positioning of the ETT.

CONVENTIONAL VENTILATION[5,67,68]

The debate as to volume- or pressure-regulated ventilation is ongoing, although it appears that volume control may be more lung protective. Pressure control ventilation has historically been used in children owing to early ventilators not being able to guarantee delivery of the small tidal volumes that babies and infants require. With newer, more sophisticated ventilators the volume control can be adjusted up to the nearest millilitre. Accurate volume measurement also requires the use of cuffed ETT in a majority of cases.

Triggered modes are used in patients who are spontaneously breathing. The aim is to have the patient lightly sedated, exercising the respiratory muscles and synchronising well with the ventilator. Appropriate triggering, inspiratory time and cycling to expiration are all important to synchrony.

PEEP of at least 5 cmH_2O (0.66 kPa) is routinely used in all paediatric and neonatal patients, albeit empirically. Children expire to near their FRC so that any loss of muscle tone will lead to greater likelihood of pulmonary atelectasis – hence a small amount of distending pressure is desirable. As in adults, PEEP is increased and recruitment manoeuvres are used to promote open lung ventilation. PEEP is unlikely to be increased beyond 15 cmH_2O (2 kPa). Adult strategies advocate higher PEEP but neonatal and paediatric preference is usually to change to HFOV if adequate gas exchange cannot be maintained.

HIGH-FREQUENCY OSCILLATOR VENTILATION[5,69–73]

HFOV has been instrumental in the care of infants with severe respiratory failure from any number of causes. In essence it is a set pressure – the mean airway pressure (MAP), with the oscillation of 6–12 Hz around this. Oscillations are sinusoidal with negative and positive deflections. MAP, frequency and amplitude of the ventilator waveform influence oxygen and carbon dioxide clearance in discrete but not entirely independent ways. MAP and inspired oxygen are the primary determinants of oxygenation. Frequency and amplitude are the primary determinants of carbon dioxide clearance. Alveolar ventilation is said to occur by convective and diffusional mechanisms. These include bulk gas movement, laminar and turbulent flow, Pendeluft ventilation (between alveoli), collateral ventilation by alveolar channels and Taylor dispersion.

Children ventilated with HFOV are often heavily sedated and have neuromuscular-blocking agents administered. However, depending on pathology and stability, they may be allowed to breath on top of the oscillations of the ventilator. These spontaneous breaths are not supported, so the clinician must ensure that the bias flow through the circuit is sufficient to maintain the MAP and allow for this tidal ventilation by the patient. For neonates and small infants this tidal volume is negligible compared with the bias flow. For older children this can be challenging and unachievable. Secretion clearance and humidification of gases can be challenging. High bias flow results in inadequate humidification while 'rain-out' (excessive fluid) within circuits is frequently an issue. Weaning can be achieved while on HFOV, but most units convert to conventional ventilation for weaning, especially in older children who need larger tidal volumes.

VENTILATOR STRATEGIES[15,74,75]

The general strategy in the ventilation of any neonatal or paediatric patient is the maintenance of lung distension and gas exchange, whilst minimising trauma to the lung due to overdistention, underdistention, atelectasis and oxygen toxicity. Muscle relaxants are used liberally in the initial stages of severe respiratory disease, as recommended by the Consensus Conference on Acute Lung Injury. Spontaneous breathing and early extubation are encouraged as the clinical situation allows.

Ventilation is hazardous and exposes patients to numerous risks and potential healthcare-associated injury. It is important to liberate the patient from dependence on mechanical support of any type as expeditiously as possible. Physicians, nurses and allied health staff must be proactive and creative to achieve this.

EXTRACORPOREAL LIFE SUPPORT[74,76–78]

Historically, adult ICUs had abandoned ECLS in the face of poorly constructed studies, while NICUs and PICUs fostered and nurtured its development. Dramatic improvements in ECLS were promoted by improvements in cardiopulmonary bypass technology, developments in congenital heart surgery and the need to support neonates with severe respiratory failure such as meconium aspiration. Neonates across the spectrum of the ELSO registry have the greatest survival rates.

ECLS for neonates, infants and small children is typically achieved by surgical cannulation in the neck with the right common carotid and right internal jugular vein being accessed. Femoral vessels may also be used in older children, but they are unable to provide adequate flows in babies and infants. Veno-arterial ECLS is common, but veno-venous ECLS via a double-lumen catheter or two-vein cannulation is becoming more common for pure respiratory support.

REFERENCES

1. Yende S, Watson RS. Understanding genetics of acute lung injury and acute respiratory distress syndrome in children: steps in the right direction. *Pediatr Crit Care Med*. 2008;9(6):650–651.
2. Duncan AW. The burden of paediatric intensive care: an Australian and New Zealand perspective. *Paediatr Respir Rev*. 2005;6(3):166–173.
3. ANZPIC. *Australia and New Zealand Intensive Care Society core data set*. 2015.
4. Ghuman AK, Newth CJL, Khemani RG. Respiratory support in children. *Paediatr Child Health*. 2011; 21(4):163–169.
5. Rimensberger PC. *Pediatric and Neonatal Mechanical Ventilation*. New York: Springer; 2015.
6. Agrons GA, Courtney SE, Stocker JT, et al. Lung disease in premature neonates: radiologic-pathologic correlation. *Radiographics*. 2005;25:1047–1073.
7. Kwinta P, Pietrzyk JJ. Preterm birth and respiratory disease in later life. *Expert Rev Respir Med*. 2010; 4(5):593–604.
8. Gallacher DJ, Hart K, Kotecha S. Common respiratory conditions of the newborn. *Breathe*. 2016;12(1): 30–42.
9. Masters IB, Chang AB. Tracheobronchomalacia in children. *Expert Rev Respir Med*. 2009;3(4):425–439.
10. Fraga JC, Jennings RW, Kim PC. Pediatric tracheomalacia. *Semin Pediatr Surg*. 2016;25(3):156–164.
11. Healy F, Hanna BD, Zinman R. Pulmonary complications of congenital heart disease. *Paediatr Respir Rev*. 2012;13(1):10–15.
12. Backer CL, Mong MC, Popescu AR, et al. Vascular rings. *Semin Pediatr Surg*. 2016;25(3):165–175.
13. Corno AF. Slings and rings. In: *Congenital Heart Defects*. Heidelberg: Steinkopff; 2004:195–212.
14. Mattei P. Congenital diaphragmatic hernia. In: Mattei P, ed. *Fundamentals of Pediatric Surgery*. New York: Springer; 2011:535–541.

15. Robinson PD, Fitzgerald DA. Congenital diaphragmatic hernia. *Paediatr Respir Rev*. 2007;8(4):323–334.
16. Shaaban AF. Gastroschisis. In: Mattei P, ed. *Fundamentals of Pediatric Surgery*. New York: Springer; 2011: 515–522.
17. Mercuri E, Sewry C, Brown SC, et al. Congenital muscular dystrophies. *Semin Pediatr Neurol*. 2002; 9(2):120–131.
18. Singh BS, Clark RH, Powers RJ, et al. Meconium aspiration syndrome remains a significant problem in the NICU: outcomes and treatment patterns in term neonates admitted for intensive care during a ten-year period. *J Perinatol*. 2009;29(7):497–503.
19. Nissen MD. Congenital and neonatal pneumonia. *Paediatr Respir Rev*. 2007;8(3):195–203.
20. Petruzella FD, Gorelick MH. Current therapies in bronchiolitis. *Pediatr Emerg Care*. 2010;26(4):302–307, quiz 308–311.
21. McKiernan C, Chua LC, Visintainer PF, et al. High flow nasal cannulae therapy in infants with bronchiolitis. *J Pediatr*. 2010;156(4):634–638.
22. Calvo C, Pozo F, García-García ML, et al. Detection of new respiratory viruses in hospitalized infants with bronchiolitis: a three-year prospective study. *Acta Paediatr*. 2010;99(6):883–887.
23. Wagner T. Bronchiolitis. *Pediatr Rev*. 2009;30(10): 386–395, quiz 395.
24. Grimwood K, Cohet C, Rich FJ, et al. Risk factors for respiratory syncytial virus bronchiolitis hospital admission in New Zealand. *Epidemiol Infect*. 2008;136(10):1333–1341.
25. Bordley WC, Viswanathan M, King VJ, et al. Diagnosis and testing in bronchiolitis: a systematic review. *Arch Pediatr Adolesc Med*. 2004;158: 119–126.
26. Hon KL, Leung ASY, Cheung KL, et al. Typical or atypical pneumonia and severe acute respiratory symptoms in PICU. *Clin Respir J*. 2015;9(3):366–371.
27. Rogers AD, Deal C, Argent AC, et al. Ventilator associated pneumonia in major paediatric burns. *Burns*. 2014;40(6):1141–1148.
28. Muszynski JA, Knatz NL, Sargel CL, et al. Timing of correct parenteral antibiotic initiation and outcomes from severe bacterial community-acquired pneumonia in children. *Pediatr Infect Dis J*. 2011;30(4): 295–301.
29. Morrow BM, Argent AC. Ventilator-associated pneumonia in a paediatric intensive care unit in a developing country with high HIV prevalence. *J Paediatr Child Health*. 2009;45:104–111.
30. Chang I, Schibler A. Ventilator associated pneumonia in children. *Paediatr Respir Rev*. 2016;20:10–16.
31. Korang KS, Feinberg J, Wetterslev J, et al. Noninvasive positive pressure ventilation for acute asthma in children. *Cochrane Database Syst Rev*. 2016; (9):CD012067.
32. Silva Pde S, Barreto SS. Noninvasive ventilation in status asthmaticus in children: levels of evidence. *Rev Bras Ter Intensiva*. 2015;27(4):390–396.
33. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43(2):343–373.
34. Helms PJ. Recent advances in pediatric asthma treatment. *Expert Rev Respir Med*. 2009;3(2):165–175.
35. Volovitz B. Management of acute asthma exacerbations in children. *Expert Rev Respir Med*. 2008;2(5): 607–616.
36. Calogero C, Sly PD. Optimal management of preschool asthma. *Expert Rev Respir Med*. 2007;1(3): 355–364.
37. Petrocheilou A, Tanou K, Kalampouka E, et al. Viral croup: diagnosis and a treatment algorithm. *Pediatr Pulmonol*. 2014;49(5):421–429.
38. Fernandes RM, Oleszczuk M, Woods CR, et al. The Cochrane Library and safety of systemic corticosteroids for acute respiratory conditions in children: an overview of reviews. *Evid Based Child Health*. 2014;9(3):733–747.
39. Pfleger A, Eber E. Management of acute severe upper airway obstruction in children. *Paediatr Respir Rev*. 2013;14(2):70–77.
40. Yoshida T, Boylan JF, Kavanagh BP. What do we treat when we treat ARDS? *Intensive Care Med*. 2016;42(2):284–286.
41. Djamel M, Julien T, Florence E, et al. Jean-louis B. Acute respiratory distress syndrome (ARDS) in neutropenic patients. In: Azoulay E, ed. *Pulmonary Involvement in Patients with Hematological Malignancies*. Berlin: Springer; 2011:477–487.
42. Blank R, Napolitano LM. Epidemiology of ARDS and ALI. *Crit Care Clin*. 2011;27(3):439–458.
43. Ali S, Ferguson ND. High-frequency oscillatory ventilation in ALI/ARDS. *Crit Care Clin*. 2011; 27(3):487–499.
44. Calfee CS, Matthay MA. Nonventilatory treatments for acute lung injury and ARDS. *Chest*. 2007;131(3):913–920.
45. Bindl L, Buderus S, Dahlem P, et al. Gender-based differences in children with sepsis and ARDS: the ESPNIC ARDS Database Group. *Intensive Care Med*. 2003;29(10):1770–1773.
46. Yehya N, Thomas NJ, Meyer NJ, et al. Circulating markers of endothelial and alveolar epithelial dysfunction are associated with mortality in pediatric acute respiratory distress syndrome. *Intensive Care Med*. 2016;42(7):1137–1145.
47. Wilsterman MEF, De Jager P, Blokpoel R, et al. Short-term effects of neuromuscular blockade on global and regional lung mechanics, oxygenation and ventilation in pediatric acute hypoxemic respiratory failure. *Ann Intensive Care*. 2016;6103(6): 1–11.
48. McGuire J, Basu R, Smith LS, et al. Pediatric acute respiratory distress syndrome: fluid management in the PICU. *Front Pediatr*. 2016;4(421):3389–3421.
49. Yehya N, Servaes S, Thomas NJ, et al. Corticosteroid exposure in pediatric acute respiratory distress syndrome. *Intens Care Med*. 2015;41(9):1658–1666.
50. Khemani RG, Smith LS, Zimmerman JJ, et al. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress

syndrome: definition, incidence, and epidemiology: proceedings from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. 2015; 16(5 suppl 1):S23–S40.
51. Sakhalkar V, Munker R. Congenital and acquired immunodeficiencies. In: *Modern Hematology*. Humana Press; 2007:295–313.
52. Frush DP. Radiation, thoracic imaging, and children: radiation safety. *Radiol Clin North Am*. 2011; 49(5):1053–1069.
53. Dorfman AL, Fazel R, Einstein AJ, et al. Use of medical imaging procedures with ionizing radiation in children: a population-based study. *Arch Pediatr Adolesc Med*. 2011;165(5):458–464.
54. Frush DP, Applegate KE. *Evidence-Based Imaging in Pediatrics*. New York, NY: Springer New York; 2010.
55. Bajoghli M, Bajoghli F, Tayari N, et al. Children, CT scan and radiation. *Int J Prev Med*. 2010;1(4):220–222.
56. Wilson B, Typpo K. Nutrition: a primary therapy in pediatric acute respiratory distress syndrome. *Front Pediatr*. 2016;4:108.
57. Flori HR, Church G, Liu KD, et al. Positive fluid balance is associated with higher mortality and prolonged mechanical ventilation in pediatric patients with acute lung injury. *Crit Care Res Pract*. 2011;2011:854142. doi:10.1155/2011/854142.
58. Silversides JA, Major E, Ferguson AJ, et al. Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. *Intensive Care Med*. 2017;43(2): 155–170.
59. Wilkinson D, Andersen C, O'Donnell CP, et al. High flow nasal cannula for respiratory support in preterm infants. *Cochrane Database Syst Rev*. 2016;(2): CD006405.
60. Schibler A, Franklin D. Respiratory support for children in the emergency department. *J Paediatr Child Health*. 2016;52(2):192–196.
61. Mikalsen IB, Davis P, Øymar K. High flow nasal cannula in children: a literature review. *Scand J Trauma Resusc Emerg Med*. 2016;24:93.
62. Hutchings FA, Hilliard TN, Davis PJ. Heated humidified high-flow nasal cannula therapy in children. *Arch Dis Child*. 2015;100(6):571–575.
63. Schibler A, Pham TMT, Dunster KR, et al. Reduced intubation rates for infants after introduction of high-flow nasal prong oxygen delivery. *Intensive Care Med*. 2011;37(5):847–852.
64. Morley SL. Non-invasive ventilation in paediatric critical care. *Paediatr Respir Rev*. 2016;20:24–31.
65. Rimensberger PC, Cheifetz IM. Ventilatory support in children with pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. 2015;16(5 suppl 1):S51–S60.
66. Tobias JD, Schwartz L, Rice J, et al. Cuffed endotracheal tubes in infants and children: should we routinely measure the cuff pressure? *Int J Pediat Otorhinolaryngol*. 2012;76(1):61–63.
67. Maung AA, Kaplan LJ. Mechanical ventilation after injury. *J Intensive Care Med*. 2012;29(3):128–137.
68. Duyndam A, Ista E, Houmes RJ, et al. Invasive ventilation modes in children: a systematic review and meta-analysis. *Crit Care*. 2011;15(1):R24.
69. Sud S, Sud M, Friedrich JO, et al. High-frequency oscillatory ventilation versus conventional ventilation for acute respiratory distress syndrome. *Cochrane Database Syst Rev*. 2016;(4):CD004085-CD.
70. Guo Y-X, Li Y-T, Cai L-M. High-frequency oscillatory ventilation is an effective treatment for severe pediatric acute respiratory distress syndrome with refractory hypoxemia. *Ther Clin Risk Manag*. 2016;12:1563–1571.
71. Ali S, Ferguson ND. High-frequency oscillatory ventilation in ALI/ARDS. *Crit Care Clin*. 2011;27(3): 487–499.
72. Rotta AT. Mechanical ventilation strategies in children. *Pediatr Health*. 2008;2(3):301–314.
73. Arnold JH, Anas NG, Luckett P, et al. High-frequency oscillatory ventilation in pediatric respiratory failure: a multicenter experience. *Crit Care Med*. 2000;28(12):3913–3919.
74. Turner D, Cheifetz IM. Pediatric acute respiratory failure: areas of debate in the pediatric critical care setting. *Expert Rev Respir Med*. 2011;5(1):65–73.
75. Rotta AT. Mechanical ventilation strategies in children. *Pediatr Health*. 2008;2(3 SRC–GoogleScholar): 301–314.
76. Dalton HJ, Macrae DJ, Pediatric Acute Lung Injury Consensus Conference Group. Extracorporeal support in children with pediatric acute respiratory distress syndrome. *Pediatr Crit Care Med*. 2015;16: S111–S117.
77. Reed-Thurston D, Shenberger J, Qiu F, et al. Neonatal extracorporeal life support: will the newest technology reduce morbidity? *Artif Organs*. 2011; 35(11):989–996.
78. Vats A, Pettignano R, Culler S, et al. Cost of extracorporeal life support in pediatric patients with acute respiratory failure. *Crit Care Med*. 1998;26(9): 1587–1592.

108

Paediatric fluid and electrolyte therapy

Sophie Skellett

Fluid and electrolyte therapy is an important aspect of the care of critically ill children. In some regards, children and infants differ from adults, but many of the controversies regarding fluid therapy are similar.

Fluid therapy may be required to correct or maintain fluid and electrolyte balance for normal physiological function in acutely unwell children for a number of reasons. It is important to distinguish these reasons as the treatments differ, and one or more of these conditions may co-exist:

- **Fluid resuscitation**: to rapidly expand effective circulating volume in the intravascular space in order to restore blood flow to the vital organs.
- **Maintenance fluids**: if children and infants are unable to tolerate enteral feeds or fluids to meet their fluid needs.
- **Fluid replacement**: to compensate for ongoing losses such as gastrointestinal losses from vomiting, diarrhoea.

CHILDREN AND INFANTS ARE DIFFERENT

They require proportionally greater volumes of water for their weight than adults to maintain their fluid equilibrium and are more susceptible to fluid depletion and fluid losses. The reasons include:

- High total body water (TBW) content: TBW in preterm neonates can be as high as 80%; infants 70%; children 65%; adults 60%. As the child grows the intracellular space increases and the extracellular space reduces.
- Higher surface area to body mass index: higher transepidermal losses, particularly in neonates, and more susceptible to changes in temperature.
- Higher metabolic and respiratory rates: increased use for growth (dramatic in the first year particularly) and increased water loss from lungs.
- Immature renal function: low glomerular filtration rate (GFR) at birth (25% of adult values) gradually increasing over the first year and immature renal concentrating function in neonates and infants, which can result in water loss in urine even in the face of dehydration.
- Dependency on caregivers for fluids and food, particularly relevant for neonates and infants. To compound this, dehydration in this group is not always easy to identify.[1]

The susceptibility of children and infants to greater fluid and electrolyte disturbances means that great care and attention must be paid to intravenous (IV) fluid therapies as the morbidity and mortality following inadequate or improper management can be significant. Children and infants, unlike adults, are prescribed IV fluids based on their body weight. Additionally, children and infants are at greater risk of developing cerebral oedema and neurological complications as a result of hyponatraemia compared to adults.[2]

FLUIDS IN RESUSCITATION

The controversies regarding fluid resuscitation in paediatrics currently include the size of the fluid bolus used for resuscitation and the composition of the fluid bolus given.

BOLUS SIZE

For approximately the past 3 decades accepted practice for the management of circulatory failure and shock has been prompt, and early resuscitation with IV fluid boluses each of 20 mL/kg repeated until circulatory status was stable and vital organ perfusion restored. Although this was largely based on observational studies,[3] the practice – widely promoted by national resuscitation training courses (European Paediatric Advanced Life Support [EPALS], Pediatric Advanced Life Support [PALS], Advanced Paediatric Life Support [APLS]) – has occurred alongside a huge reduction in paediatric mortality from sepsis in the developed world. In 2010 a large randomised controlled trial (RCT) of fluid bolus therapy 20–40 mL/kg of either 0.9% saline or 5% albumin solution versus maintenance fluids only in East African children with severe febrile illness was published, which showed that bolus therapy was associated with a

ABSTRACT

There have been many recent controversies regarding the use of intravenous fluids in both children and adults. The correct bolus size for fluid resuscitation for children in the developed world remains unknown but what is recognised is that far more care has to be taken in our approach, with careful assessment of our patients after every fluid treatment. Isotonic fluids are the fluids of choice for resuscitation, and there is increasing interest in the potential benefits of balanced solutions. In critically ill children the morbidity that fluid overload confers is increasingly recognised, leading clinicians to adopt more conservative fluid strategies particularly once haemodynamic stability has been achieved. Children and infants are particularly susceptible to fluid and electrolyte disorders, hence the assessment of weight and fluid balance becomes an imperative on the intensive care unit along with the use of isotonic fluids as maintenance therapy – at least initially. An individualised approach to fluid therapy in each patient is advocated.

KEYWORDS

Fluid resuscitation
isotonic fluids
maintenance fluids
fluid overload
SIADH
hyperchloraemic acidosis
balanced solutions
crystalloids
dehydration
parenteral nutrition

significantly higher mortality.[4] This study was set in a resource-poor setting with no intensive care back-up and notably fewer than 3% of patients met the World Health Organization (WHO) criteria for the diagnosis of shock, hence it is probable that some patients treated with fluids did not require them.[5] This trial therefore does not offer conclusive evidence that fluid bolus therapy is unsafe. Nevertheless it has caused those who look after critically ill children to pause and re-think about fluid resuscitation in children and infants.

It is important therefore that after giving an IV fluid bolus there is careful re-assessment of the child's clinical status so that further boluses are only given if necessary. This assessment should include the capillary refill time (CRT) (central and peripheral), blood pressure, peripheral and central pulse volume, heart rate, liver edge, presence or absence of basal lung crepitations (the latter two may indicate fluid overload [FO]), urine output and the level of consciousness of the child. If further fluid boluses are indicated they ***should not*** be withheld but careful re-assessment should follow each one. Current recommendations for IV fluid bolus size vary from 10 mL/kg (WHO recommendation) to 20 mL/kg (PALS, EPALS, APLS) dependent on clinical scenario. In the case of sepsis, early use of inotropes or vasopressors should be considered; that is, after two IV fluid boluses of 20 mL/kg have been given, as this represents more than half the circulating volume of the child.

TARGETED FLUID BOLUS THERAPY

Following the publication of the Rivers paper[6] in 2001, the adoption of early goal-directed therapy (EGDT) in the treatment of septic shock in children became common (although not universally accepted) in the developing world. Standard management of septic patients via EGDT involves achieving a number of target parameters aimed at improving oxygen delivery to the tissues during resuscitation; this includes fluid bolus therapy to a targeted central venous pressure (CVP) value. However, subsequent trials in adults have not replicated the early success of EGDT. The ProMISE,[7] ARISE[8] and ProCESS[9] trials were all large randomised studies comparing outcomes for EGDT versus usual care for septic shock in the United Kingdom, Australia and New Zealand, and the United States, respectively. These trials recruited over 4000 patients at 140 sites. Patients were randomised to an EGDT protocol and compared to usual treatment, which included prompt IV antibiotics and adequate fluid resuscitation. All three trials found that the EGDT group received increased use of IV fluid, pressors and inotropes, and that the mortality outcome between the groups was not different. One trial found EGDT patients had significantly worse organ-failure scores, more days receiving haemodynamic support and longer stays in the intensive care unit (ICU). All three trials concluded that EGDT conferred no morbidity or mortality advantage in the care of patients with septic shock. It seems likely that CVP-directed IV fluid bolus administration is not a useful practice and more conservative fluid strategies may be indicated; further studies in paediatrics may be useful. Why are the results so different? In the past 15 years mortality from septic shock has reduced markedly in adults and children and there have been changes in many aspects of ICU practice; combined, these may have made any minor benefits derived from EGDT, at the time of the first trial, less significant.

FLUID OVERLOAD

The physiological rationale for fluid therapy is worth highlighting. Its value is only in increasing stroke volume and hence the cardiac output. If an increase in cardiac output is not achieved by volume expansion, the potential harm from fluid therapy outweighs the benefits. The ability of the clinician to estimate fluid responsiveness or indeed cardiac output[10] remains poor; hence frequent reassessment is indicated.

The morbidity and mortality resulting from fluid administration during resuscitation and intensive care admission are largely related to FO, though the fluid composition may also influence this. Is it just that sicker children need more fluid resuscitation? One study in over 600 children looked at oxygenation, length of ventilation and outcome in relation to the percentage of FO at 48 hours while controlling for severity of illness.[11] It found that the percentage of FO at 48 hours correlated to length of ventilation and oxygenation index but not mortality; similar results were seen in another smaller paediatric study.[12] Other studies in both adults and paediatrics have suggested a deleterious effect on renal function and mortality associated with FO though the evidence for this is not yet conclusive.[13–16] It would appear that positive fluid balance after restoration of effective circulating volume may negatively affect organ function in children on ICU and should be avoided and treated promptly. Critically ill children are particularly susceptible to FO when given large volumes of IV fluid because of the high incidence of inappropriate antidiuretic hormone (ADH) secretion, which is discussed below.

There are certain clinical situations where a smaller fluid bolus size should be considered.

DIABETIC KETOACIDOSIS

The mortality from diabetic ketoacidosis (DKA) is usually due to cerebral oedema and hence large fluid shifts should be avoided. It is uncommon for a child with DKA to present with shock; they will be dehydrated but these fluid losses can be more slowly replaced. However if the child presents with severe DKA (defined as pH <7.1) with shock they may cautiously be given one 10 mL/kg fluid bolus to restore effective

circulating volume and very carefully re-assessed. Some studies suggest that rapid, large volume fluid administration in DKA is associated with a greater risk of cerebral oedema.[17]

CARDIAC FAILURE

Assessing volume status in infants and children presenting with heart failure is difficult. Lesions leading to volume overload and congestive heart failure (e.g. ventricular septal defect presenting at 6 weeks of age) benefit from diuresis. However, a history of poor feeding, weight loss and excess energy expenditure may result in a volume deplete state, in which case the clinician may trial fluid resuscitation. In this setting it can be difficult to determine if fluid may improve the infant's condition or cause worsening heart failure. If the clinician decides to try IV fluid therapy, this should be restricted to 5–10 mL/kg bolus of isotonic fluid with careful re-assessment to determine if the condition is improved or made worse by fluid therapy.

TRAUMA

Recent studies in mostly adult trauma patients indicate that excessive fluid and blood administration causes excessive morbidity and mortality in the least severely injured patients.[18] The WHO recommendation for cautious fluid and blood therapy with bolus sizes of 10 mL/kg with careful re-assessment after each bolus appears sensible and may prevent early clot destabilsation. When giving blood, bedside haematocrit evaluations may help guide further therapy. It is worth noting that the majority of traumatic injuries sustained by children are head injuries causing traumatic brain injury (TBI). TBI outcome can be positively influenced by maintaining good blood pressure and oxygenation. Fluid bolus therapy and inotropes can be used to help maintain good blood pressure, but FO may adversely affect cerebral oedema.

BOLUS COMPOSITION

It is widely accepted that fluid boluses should be composed of isotonic fluids and the most commonly used is 0.9% saline (Na^+ 153 mmol/L, Cl^- 153 mmol/L). Hypotonic fluid boluses are known to cause hyponatraemia resulting in dangerous fluid shifts, which potentially cause cerebral oedema and seizures as water moves intracellularly. Additionally, isotonic fluids expand the intravascular compartment more effectively than hypotonic fluids.[19]

GLUCOSE-CONTAINING FLUIDS

Glucose-containing fluids are quickly metabolised to water; hence, the glucose content should not be taken into consideration when calculating tonicity of an IV fluid to be given as they are effectively hypotonic in vivo. Glucose-containing fluids should never be used unless they are required to correct hypoglycaemia as hyperglycaemia is associated with poor outcome in critically ill children, particularly those with central nervous system (CNS) disease and trauma. Hypoglycaemia is also associated with poor outcome in the acutely unwell child so must be vigorously looked for and corrected if found. If a child or infant has a blood glucose <3 mmol/L then 2 mL/kg 10% dextrose should be given as a bolus and the blood glucose rechecked within 5 minutes; if the hypoglycaemia recurs, repeat the bolus and ensure maintenance fluids with glucose are started to maintain normoglycaemia. There is no evidence that tight control of glycaemia (maintaining blood glucose 4–7 mmol) in critically ill children is of any benefit; indeed, it may lead to increased numbers of children suffering hypoglycaemia from the higher doses of insulin administered.[20]

COLLOID AND CRYSTALLOID DEBATE

Saline at 0.9% is isotonic, cheap and infection free, hence its wide spread use. Colloids are definitively indicated for fluid therapy in some circumstances, such as blood to replace blood loss in haemorrhage, but their routine use for volume expansion is declining as studies fail to show superiority over crystalloids, and in some situations they even indicate that they may cause harm.[21] A large Australian study, the SAFE study, compared human albumin solution (HAS) 4.5% with 0.9% saline in adults for fluid resuscitation and found no difference in mortality between the two groups at 1 month.[22] Subgroup analysis indicated a trend to improved survival in the sepsis group with the use of 4.5% HAS and a trend for decreased survival with its use in resuscitation in trauma patients, but statistical significance was not reached. Once commonly used in paediatric practice, the use of 4.5% HAS is now declining; it is worth noting that it is expensive, carries an infection risk and because albumin is in suspension in 0.9% saline it carries the same risk of causing hyperchloraemic acidosis. Additionally, it is becoming clear that colloid solutions do not offer the advantages over crystalloid solutions with respect to hemodynamic effects once previously thought.[23] Synthetic colloids, though infection free, are expensive so are not commonly used in children, particularly the large synthetic molecules that interfere with coagulation and renal function.

HYPERCHLORAEMIC ACIDOSIS

Normal saline (0.9% saline) bolus therapy is associated with the development of hyperchloraemic acidosis as comparatively it contains a much higher concentration of chloride (Cl^-) ions than is present in the plasma, and it has a pH of 5.5 – hence it is not 'normal'. It also has a slightly higher concentration of sodium (Na^+) ions than in the plasma, but this is a much smaller

difference. Normal plasma concentration of sodium ions is 140 mmol/L, normal plasma concentration of chloride ions is 100 mmol/L. After several large fluid boluses have been given a metabolic acidosis ensues from chloride excess. Calculating the anion gap (AG) shows a normal result in the face of an acidosis:

$$AG = (Na + K) - (Cl + HCO_3) \text{ range } 8–12 \text{ mmol/L}$$
(where HCO_3^- = bicarbonate)

For many years this acidosis was not thought to be significant, but some studies have suggested that this may not be the case and that either the acidosis and/or the chloride load may have deleterious effects on coagulation and kidney function; hyperchloraemia has been shown to induce renal vasoconstriction and reduce GFR.[24] This suggests that perhaps a more 'physiological' solution should be considered for fluid bolus therapy. These 'physiological solutions' – also called 'balanced solutions' – contain lower concentrations of chloride and a buffer is provided so that the solutions are electroneutral. Buffers used in some of these solutions include acetate, lactate, gluconate and maleate. One large retrospective study in adults compared the use of balanced solutions and unbalanced solutions (0.9% saline) for resuscitation in over 30,000 patients and found decreased incidence of acute kidney injury and a suggestion of improved survival in the much smaller group receiving balanced fluid resuscitation.[25] Additionally a recent prospective RCT involving almost 16,000 adult ICU patients, the SMART trial (isotonic solutions and major adverse renal events trial), found the use of balanced crystalloids for intravenous fluid administration resulted in a lower rate of the composite outcome of death from any cause, new renal-replacement therapy, or persistent renal dysfunction than the use of 0.9% saline.[26] In contrast the SPLIT trial (saline versus Plasma-Lyte for ICU fluid therapy) found no significant differences in the incidence of acute kidney injury, length of ventilation or outcome between patients receiving 0.9% saline and those receiving the balanced solutions.[27] Studies looking at the outcome between balanced and unbalanced solutions in children have yet to demonstrate a convincing argument, but this is an interesting area for further development. Some examples of balanced solutions are shown in Table 108.1.

KEY POINTS

1. Patients with capillary leak may need large amounts of fluid resuscitation.
2. Each fluid bolus must be followed by careful assessment; inadequate resuscitation results in poor organ perfusion whilst excess fluid administration is associated with organ dysfunction and poor outcomes.
3. Fluid bolus size in sepsis in the clinical setting including intensive care should be 20 mL/kg of isotonic crystalloids.
4. Certain clinical settings may require smaller fluid bolus sizes (e.g. cardiac failure, trauma).
5. Glucose-containing fluids should not be used for resuscitation.
6. Hypotonic fluids should not be used for resuscitation.
7. The use of balanced isotonic crystalloids rather than 0.9% saline in resuscitation will reduce the incidence of hyperchloraemic acidosis, which may be advantageous.
8. Hypoglycaemia is very dangerous in infants and hyperglycaemia is less dangerous than in adults.

MAINTENANCE FLUIDS

Children and infants who are unable to tolerate enteral feeds and fluids may require IV fluid maintenance. The aim is to provide fluid and electrolytes in order to maintain the extracellular volume and hence tissue perfusion with a normal electrolyte balance; it is calculated based on 'expected' daily fluid and electrolyte losses. There is controversy within current paediatric practice regarding both the most effective means of calculating routine maintenance requirements for infants and children, particularly whether weight or body surface area is the more appropriate, and what the composition of maintenance fluids should be.

Commonly used formulae for calculating IV fluid requirements in hospitalised children and infants are those developed by Holliday and Segar in 1957, but there remains no consensus for their use, even 60 years later.[28] It is clear that there are problems with applying these 'standard' calculated volumes to the entire hospitalised paediatric population, particularly to critically ill children who often have conditions that impair normal water and electrolyte handling.

Table 108.1 Electrolyte composition plasma and crystalloids

	Na^+ mmol/L	Cl^- mmol/L	K^+ mmol/L	BUFFER mmol/L	OSMOLALITY mOsm/kg
Plasma	140	100	5	HCO_3^-[25]	280
0.9% saline	154	154	0	0	286
Hartmann's/Ringer's lactate	131	111	5	Lactate[29]	274
Plasmalyte	140	98	5	Acetate[27] Gluconate[24]	271

The Holliday and Segar formulae for calculating paediatric maintenance fluids were based on expected energy expenditure. The caloric expenditure for the average active child was calculated based on body weight and for every 100 calories burned there was approximately 100 mL water lost. This resulted in the maintenance fluid requirements for every 24 hours calculated as below, giving the so-called 4-2-1 rule for calculating maintenance:

4 mL/kg/h for first 10 kg body weight of the child or infant, plus
2 mL/kg/h for every kilogram between 11 and 20 kg body weight, plus
1 mL/kg/h for every kilogram above 20 kg body weight

Daily electrolyte requirements were also calculated based on dietary intake as follows:

Na^+ – 3 mmol per 100 calories
K^+ – 2 mmol per 100 calories
Cl^- – 2 mmol per 100 calories

As a result, fluids subsequently chosen for 'standard' maintenance for children and infants were often 0.45% saline with dextrose or more hypotonic fluids (0.18% saline/4% dextrose) at volumes far higher than needed for inactive hospitalised children and infants. This practice still continues in a few centres, resulting in an increased risk for the development of hyponatraemia and FO. This risk is greatly increased when there is inappropriate ADH release, which is relatively common – particularly in acutely unwell children. In the 1950s when the formulae were developed, this was not a recognised entity. A more recent meta-analysis studying hospitalised children demonstrated that the use of isotonic IV maintenance fluids with Na^+ concentrations similar to that of plasma reduce the risk of hyponatraemia when compared with hypotonic intravenous fluids.[29]

ANTIDIURETIC HORMONE

Sodium and water regulation is usually controlled by a combination of interactions of arginine vasopressin (also known as antidiuretic hormone or ADH), the renin–angiotensin–aldosterone axis and natriuretic peptides. Normally when plasma osmolality increases, ADH is released from the posterior pituitary in response to the activation of osmoreceptors in the hypothalamus and baroreceptors in the carotid sinus, aortic arch and left atrium. ADH acts on the kidney at the collecting ducts making them more permeable to water (by insertion of aquaporin channels) and by increasing medullary tonicity resulting in the conservation of water.[30] When patients are unable to drink in response to thirst then ADH will be the main determinant of plasma osmolality. If disease states or drugs affect the release or action of ADH then sodium/water homeostasis will be disturbed. In critically ill children and infants there are a number of triggers that can cause ADH to be released without the usual trigger of an increase in plasma osmolality or volume depletion; this is called the syndrome of inappropriate ADH (SIADH). The triggers include:

- **CNS disease**: meningitis, encephalitis, head injury, space occupying lesions
- **Pulmonary disease**: ventilation, pneumonia, asthma, hypoxaemia, hypercapnia
- **Drugs**: opiates, barbiturates, valproate, ciprofloxacin
- **Surgery**: postoperative states
- Pain, nausea, vomiting, hypoglycaemia, inflammation, cancer.

The result is retention of excess free water making the patient susceptible to the development of both hyponatraemia and FO. The diagnosis of SIADH can be made by the patient fulfilling the following criteria:

- Plasma osmolality less than 275 mOsm/kg with serum sodium less than 135 mmol/L and an inappropriately high urine osmolality.

This will usually occur in the clinical setting of a positive fluid balance. Consequently, adjustments need to be made to the volume and sometimes the sodium concentration of maintenance fluids.

Volume adjustments to 'standard' maintenance for children and infants in intensive care should be made not only in the setting of SIADH but for a variety of other reasons including: reduced metabolic rate when sedated and muscle relaxants are used, reduced water losses if ventilated with humidified inspired gas and maintenance of body temperature.[31–36] Table 108.2 outlines the adjustments that should be made in each setting and Tables 108.3 and 108.4 give a guide to maintenance fluid volumes in the active, sick and sick plus intubated ventilated patient.

Worked example: 15 kg child with a head injury

Standard maintenance = 4 mL/kg/h for first 10 kg weight + 2 mL/kg/h for each kg between 10 and 20 kg weight
= (4 × 10) + (5 × 2) = 50 mL/h maintenance fluid[28]
Adjust for SIADH by × 0.7[32]
Adjust for muscle relaxant decrease in metabolic rate × 0.7[28]
Adjust for ventilation with humidified gas × 0.75[31]
Adjust for maintenance of body temperature 36° – 12%
Total fluids for maintenance becomes = (50 × 0.7 × 0.7 × 0.75) – 12%
= 16 mL/h

This wide variety in IV maintenance fluid needs of different critically ill patients requires that each child and infant has a tailored approach to their IV fluid prescriptions daily, and emphasises the vital importance of close monitoring of the fluid balance of children and infants in the ICU with daily weights when possible.

Table 108.2 Modifications to the fluid intakes for active children shown in table 108.3

	ADJUSTMENT
DECREASE	
Humidified inspired air[31]	×0.75
Basal state (e.g. paralysed)[28]	×0.7
High ADH (IPPV, brain injury)[32]	×0.7
Hypothermia	12% per ˚C
High room humidity	×0.7
Renal failure	×0.3 (+urine output)
INCREASE	
Full activity + oral feeds[28]	×1.5
Fever	+ 12% per ˚C
Room temperature >31˚C	+ 30% per ˚C
Hyperventilation[33]	×1.2
Neonate – preterm (1–1.5 kg)[34]	×1.2
– Radiant heater[35]	×1.5
– Phototherapy[36]	×1.25

ADH, Antidiuretic hormone; *IPPV,* intermittent positive-pressure ventilation.

Table 108.3 Approximate intravenous fluid requirements for children (mL/kg/day)

ACTIVE CHILD IN HOSPITAL	
<10 kg	100 mL/kg/day
10–20 kg	1000 mL + (50 mL/kg/day for each kg over 10 kg)
>20 kg	1500 mL + (20 mL/kg/day for each kg over 20 kg)
SICK, BUT NOT INTUBATED	
<10 kg	50 mL/kg/day
10–20 kg	500 mL + (30 mL/kg/day for each kg over 10 kg)
>20 kg	800 mL + (20 mL/kg/day for each kg over 20 kg)
INTUBATED, WITH HUMIDIFIED INSPIRED GASES	
<10 kg	35 mL/kg/day
10–20 kg	350 mL + (20 mL/kg/day for each kg over 10 kg)
>20 kg	550 mL + (12.5 mL/kg/day for each kg over 20 kg)

Table 108.4 Approximate intravenous fluid requirements for children (mL/h)

	WEIGHT IN kg											
	3	5	7	10	15	20	25	30	40	50	60	70
Active	12	20	30	40	50	60	65	70	80	90	95	100
Sick	6	10	14	20	25	30	35	40	45	55	60	70
Intubated	4	7	10	14	17	21	25	28	32	40	45	50

COMPOSITION OF MAINTENANCE FLUIDS

To prevent the development of hyponatraemia from maintenance fluids there have been many recent studies performed in hospitalised children, in both the ward and intensive care setting, which have shown that using isotonic maintenance fluids, such as 0.9% saline, in place of hypotonic solutions, reduces the risk of developing hyponatraemia.[29,37–39] Most of these studies also concluded that using isotonic maintenance was associated with few side effects and did not predispose to hypernatraemia. Hypernatraemia does not occur as a result of the use of 0.9% saline in patients unless there is a renal concentrating defect or a large extra renal free water losses because the kidney is capable of excreting hypertonic urine.[30] As yet there is little evidence to suggest that the use of balanced solutions for maintenance therapy confers any advantage in children but this is an area of increasing interest. Dextrose can be added to maintenance fluids for children and infants to give sufficient glucose to prevent hypoglycaemia and limit tissue catabolism (in the short term).

In general, it is recommended that children and infants have isotonic IV fluid maintenance at least as initial therapy, but note specific conditions may require more targeted therapy (see below). Children and infants should then have at least daily plasma electrolyte measurements, fluid balance measurements and weight measurements (where possible) in order to tailor their ongoing IV fluid needs for both maintenance therapy and correction of any fluid deficits.

Most importantly, it should be recognised that children and infants should be fed enterally whenever possible and as soon as possible, obviating the need for IV maintenance fluid therapy as this provides both gut protection and nutrition.

KEY POINTS

1. Use isotonic crystalloid fluids for maintenance initially, then tailor fluid according to electrolyte and fluid needs.
2. Use restricted fluid volumes of ‘standard’ maintenance for critically ill children and infants.
3. Fluid balance, weight and urine output measurements should be carefully monitored and action taken when ongoing fluid accumulation is present

outside the setting of haemodynamic instability requiring fluid resuscitation.

4. Measure daily plasma electrolyte levels and watch out for hyponatraemia and the development of SIADH.
5. Enteral feeds are far superior to IV fluid maintenance and should be used whenever possible.

REPLACEMENT FLUIDS

Children may also need IV fluids to account for losses of red blood cells, plasma, water or electrolytes beyond the usual losses in urine, stool and sweat. In these situations the aim is to replace any depleted fluids and restore electrolyte imbalances.

Children who present with dehydration and shock should be treated with fluid bolus therapy to restore effective circulating volume and then any further fluid deficits should be corrected. The speed of fluid deficit replacement is determined by the child's clinical condition; in most cases of gastroenteritis this may be achieved in 24 hours (and preferably by the enteral route) but for children with DKA, hypernatraemia and or CNS pathology deficit fluids should be replaced more slowly over 48 hours. Do not forget to check the blood glucose of any child presenting with dehydration, particularly in the setting of altered mentation. Weight loss is the best method of assessing the degree of dehydration[1]; however, recent weights are often not available for comparison.[39] Clinical assessment of dehydration is less reliable[1]; however, some of the more useful clinical signs are:

- decreased peripheral perfusion, as demonstrated by prolonged CRT
- deep breathing
- decreased skin turgor.

Because of the difficulty in determining the degree of dehydration, a number of other methods of assessing this have been developed. These include a number of clinical scores, such as the clinical dehydration scale and Gorelick scores[41,42]; bedside ultrasound measurement of the ratio of aortic diameter to inferior vena cava diameter (IVC)[43] or degree of inspiratory IVC collapse[44]; urinary ketone measurement[45]; and capillary digital videography.[46] A recent meta-analysis[47] looked at the usefulness of the various techniques and concluded that clinical dehydration scores were more accurate than unstructured clinical examination, though still not optimally accurate. However, current evidence does not support the use of ultrasound or urinalysis to determine the severity of dehydration in children; there was insufficient evidence to assess the usefulness of capillary digital videography.

IV fluid therapy is usually given to treat cases of severe dehydration, whilst for mild to moderate dehydration oral/enteral rehydration is preferred where possible. Dehydration can be classified as either mild to moderate (5%–10%) or severe (>10%).

MILD TO MODERATE

Thirst, normal to mildly prolonged CRT, normal to slight increase in respiratory rate, mild decreased tissue turgor.

SEVERE

Prolonged CRT, signs of shock, decreased skin turgor, altered mental status, tachypnoea and hyperpnoea, tachycardia and/or bradycardia.

The child's water deficit can be calculated following an estimation of the degree of dehydration expressed as percentage of body weight. The deficit is usually replaced over 48 hours, but this should be adjusted according to the child's clinical condition and plasma electrolyte measurements as rehydration proceeds.

Worked example: 10 kg child with 10% dehydration from diarrhoea

$$\text{Deficit} = 10\ \text{kg} \times 0.1 \times 1000\ \text{mL} = 1000\ \text{mL}$$

The child received one 20 mL/kg bolus of 0.9% saline (200 mL) to restore effective circulating volume leaving 800 mL deficit to be replaced over 48 hours = 16.5 mL/h

Maintenance requirement = 4 mL/kg/h for first 10 kg weight = 40 mL/h

Then the child should be given: 40 + 16.5 mL/h = 56.5 mL/h for 48 hours.

The more common causes of increased loss of fluid from the intravascular space in children and infants are outlined in Table 108.5.

The replacement of ongoing fluid losses in the ICU depends on accurate measurements of all the losses (e.g. stoma, gastric, wound and chest drain losses, urine output) and fluid balance measurements together with serum electrolyte, blood gas and lactate analysis. Ongoing losses are best measured and replaced either hourly, or over each subsequent 4-hour period depending on the clinical setting.

The type of fluid chosen will be dependent on the type of fluid loss. Table 108.6 indicates typical electrolyte losses in different bodily fluids.

A few conditions requiring special consideration with regard to fluid management in children and infants are outlined below:

1. In a child with oliguria following a severe ischaemic or hypoxic insult (such as birth asphyxia, drowning or cardiac arrest), it may be helpful to measure the urine sodium concentration to determine fluid therapy.[48] In oliguria due to acute tubular necrosis, where the restriction of fluid intake may be necessary, the urine sodium is usually more than 40 mmol/L. In oliguria due to hypovolaemia, the urine sodium is usually less than 20 mmol/L. Urinary sodium

Table 108.5 Causes of fluid loss from the intravascular space in children and infants (dehydration and or volume depletion)

Excess loss of fluids and electrolytes	Vomiting and diarrhoea	**GI**: gastroenteritis, malabsorption, intussusception, inflammatory bowel disease, short gut syndromes, volvulus, obstruction, pyloric stenosis, hepatitis, hepatic failure, appendicitis, peritonitis, drug toxicity **CNS**: infections and raised intracranial pressure **Renal**: infections, renal failure **Endocrine**: DKA, congenital adrenal hypoplasia, Addisonian crisis, thyrotoxicosis
	Renal losses	Renal tubular acidosis, polyuric renal failure, DI, diuretics, concentrating defects
	Endocrine losses	DKA, central DI, cerebral salt wasting
	Other	Haemorrhage, surgical and chest drain losses
Accumulation of fluid in the interstitial space (3rd spacing)	Heart failure, sepsis, peritonitis, pancreatitis, protein losing enteropathy, nephrotic syndrome, ascites	
Increased insensible losses or poor intake	Burns, prematurity, fever, increased sweating, hyperventilation, stomatitis, coma, dysphagia	

CNS, Central nervous system; *DI*, diabetes insipidus; *DKA*, diabetic ketoacidosis; *GI*, gastrointestinal.

Table 108.6 Typical electrolyte losses in different bodily fluids

FLUID	Na^+ mmol/L	K^+ mmol/L	Cl^- mmol/L	BICARBONATE mmol/L
Gastric	70	5–15	120	0
Ileostomy	130	15–20	120	25–30
Diarrhoea	50	25	40	50

measurement is an unreliable guide to volume status if diuretics have been administered.

2. Conditions requiring increased free water to compensate for losses[30] are prematurity, burns, fever, diarrhoea.
3. Conditions requiring increased free water to compensate for renal concentrating defects[30] are nephrogenic diabetes insipidus (DI), sickle cell disease, renal dysplasia. In such circumstances, the administration of hypotonic fluids may be indicated.
4. Conditions requiring increased salt and water to compensate for solute diuresis[30] are polyuric phase of renal acute tubular necrosis, DKA, cerebral salt wasting.
5. Condition requiring salt and water restriction in the setting of polyuria[30] is renal failure.
6. Conditions requiring fluid restriction for oedematous states[30] are heart failure, nephrotic syndrome (isotonic fluids but small volumes).

SODIUM

Sodium is the principal determinant of effective plasma osmolality as it is the main extracellular ion and cannot move freely into cells. Changes in serum sodium should be interpreted in conjunction with the child's hydration status as they are usually due to changes in body water rather than total body sodium.

In the first 1 or 2 days of life, small preterm babies often have poor urine output and high transcutaneous fluid losses. They are therefore prone to hypernatraemia and hyperkalaemia, and such infants should usually be given 10% dextrose without sodium or potassium. From 2 days of age, 2–4 mmol/kg/day of sodium and potassium will usually be sufficient, but much higher intakes of sodium are needed in some preterm neonates owing to their impaired renal conservation of sodium.

CAUSES OF HYPONATRAEMIA

- Associated with euvolaemia/hypervolaemia: increased body water due to excessive water intake or retention, especially in the presence of high levels of ADH; glucocorticoid deficiency; heart failure; renal failure; nephrotic syndrome; SIADH
- Associated with hypovolaemia: low body sodium due to diuretic therapy, cerebral salt wasting, excessive loss in sweat, diarrhoea or vomiting; poor renal conservation of sodium, or a low sodium intake (e.g. breast milk).

Hyponatraemia (defined as serum sodium (Na+) < 135 mmol/L) can cause hyponatraemic encephalopathy with serious neurological morbidity and even mortality. Children and infants, and those with hypoxaemia or CNS disease, are particularly at risk of hyponatraemic encephalopathy as there is reduced tolerance to brain oedema. Symptoms are usually apparent at serum sodium levels of 125 mmol/L or less and may result in seizures.

Hyponatraemia due to sodium deficit should usually be corrected slowly, raising the serum sodium by a maximum of 0.5 mmol/L/h[49] to prevent large fluid shifts and the development of central pontine myelinolysis (CPM). The risk of CPM is thought to be related to the chronicity of the hyponatraemia. However, if the child is seizing, urgent treatment to elevate the serum sodium may be required using 3% saline 4 mL/kg to raise the serum sodium by 3 mmol/L.[50] This can be repeated if the child is still seizing, targeting a level of 125 mmol/L. Hyponatraemia due to water excess rather than sodium deficiency should be treated with a restriction of water intake and diuretics in the non-urgent setting.

CAUSES OF HYPERNATRAEMIA

- Associated with hypovolaemia: diuretics (loop); post obstructive diuresis; acute and chronic renal disease; sweating, fistula, burns, diarrhoea, vomiting; DI (central, nephrogenic); osmotic diuresis (caused by glycosuria); inadequate fluid intake; high insensible losses
- Associated with euvolaemia/hypervolaemia: increased body sodium from the administration of large amounts of sodium (e.g. sodium bicarbonate, hypertonic saline, total parenteral nutrition [PN]) or salt poisoning.

Hypernatraemia (defined as serum sodium >145 mmol/L) also affects the CNS and can cause seizures, haemorrhage, coma and death. Fluid moves out of the brain causing structural changes with neuronal cell shrinkage; severe hypernatraemia is defined as serum Na+ greater than 170 mmol/L.

Shock should be treated with IV fluid bolus therapy and the water deficit should then be corrected very slowly using 0.9% saline so that the serum sodium falls no faster than 0.5 mmol/L/h, to prevent cerebral oedema.[51] If salt ingestion causes severe acute hypernatraemia without dehydration, peritoneal dialysis or haemofiltration may be indicated.

POTASSIUM

Potassium[52] is predominantly an intracellular ion, so total body potassium is poorly represented by the serum concentration. The concentration of potassium in the serum depends on pH as well as the total body potassium (which is usually about 50 mmol/kg). A child may have hypokalaemia without a deficit of total body potassium in the presence of alkalosis and, conversely, there may be a large total body deficit of potassium without hypokalaemia in the presence of acidosis.

All patients with volume depletion will have a potassium deficit, though it is not usually clinically significant; however, if it is not corrected along with the volume replacement then significant hypokalaemia may develop.[30] Commonly, potassium is not added to replacement fluid until an adequate urine output is obtained. Potassium can be infused into a peripheral vein usually at concentrations up to 20 mmol/L. Higher concentrations must only be given centrally at a rate of no more than 0.3 mmol/kg/h, and this should be accompanied by cardiac monitoring. Hypokalaemia on the paediatric intensive care unit (PICU) is common due to the use of loop diuretics; to minimise this, a potassium-sparing diuretic should be given alongside.

CALCIUM, MAGNESIUM AND PHOSPHATE

Hypocalcaemia in children occurs in:

- Sick neonates in the first 2 days of life and in infants of diabetic mothers
- Exchange transfusion with citrated blood (a temporary effect) and alkalosis
- Magnesium deficiency, loop diuretics, renal insufficiency
- Infants fed cow's milk (which has a high phosphate content), vitamin D deficiency, and hypoparathyroidism.

Hypocalcaemia and hypomagnesaemia cause jitters, tetany, cardiac arrhythmias, laryngospasm and convulsions. The doses of calcium and magnesium are given in Table 108.4. The normal IV maintenance requirements in infants are 1 mmol/kg/day of calcium and 0.3 mmol/kg/day of magnesium.

OEDEMA

Oedema is common in children in ICUs. It may be due to:

- FO (often in combination with SIADH)
- Capillary leak (due to the effects of hypoxia, ischaemia, acidosis or sepsis)
- Hypoalbuminaemia
- Heart failure
- Renal failure.

Multiple causes can co-exist, and it can be difficult to decide which is the most important. Children with oedema and high levels of ADH will have a serum osmolality less than 270 mosm/kg (with hyponatraemia) and a urine osmolality greater than 100 mosm/kg; the appropriate treatment is fluid restriction. On the other hand, in children with oedema due to capillary leak, fluid restriction and attempts to remove water (diuretics, dialysis) are unlikely to reduce the oedema, and often cause hypovolaemia; in fact, large amounts of fluid (e.g. blood and normal saline) may be needed to preserve the intravascular volume in these children – the oedema will resolve only when the capillary damage resolves.

PARENTERAL NUTRITION

Although IV maintenance fluids may contain glucose, they offer a very poor source of long-term nutrition, particularly when small children are concerned. A solution of 5% dextrose with sodium and potassium chloride provides maintenance amounts of water, sodium, potassium and chloride, but few calories and no protein, trace elements or vitamins.

For example, 100 mL/kg/day of 5% dextrose provides 17 kcal/kg/day (70 kJ/kg/day), which is less than 20% of the requirement of a normal infant (let alone a child with increased calorie requirements).

It has been estimated that, although an adult has the energy reserve to survive for about a year on 3 L of 10% dextrose a day, a small preterm infant will survive only 11 days on 75 mL/kg/day of 10% dextrose.[53] Therefore if IV maintenance fluids are used for more than a few days, a pronounced macronutrient deficit may develop, which predisposes the child to an increased infection rate, muscle weakness (which may prolong mechanical ventilation) and subsequently delay recovery. Therefore attempts to establish enteral feeding as early as possible should be attempted. Depending on the case mix in the intensive care (intensive care with a high general surgical population may be different) most children are able to absorb adequate amounts of food from the gut. Studies have indicated that enteral delivery of 66% of the nutrient target has been associated with improved outcomes in children receiving mechanical ventilation.[54] If this cannot be achieved and in the setting of poor gut function, PN should be considered. Specialist advice should be sought as delivery PN in children and infants is not without a number of risks including infection and PN-associated liver disease (Table 108.7).

Table 108.7 Potential complications associated with parenteral nutrition

Hyperglycaemia
Hypoglycaemia
Sepsis
Extravasation of solutions with necrosis of tissue
Thrombocytopenia
Hypoproteinaemia
Electrolyte imbalance
Acidosis
Anaemia
Hyperlipaemia
Uraemia
Cholestatic jaundice

The timing of administration of PN in critically ill children has recently been the subject of investigation in the PEPaNIC trial.[55] This large paediatric RCT randomised critically ill children in the PICU to early or late (7 days) PN. Mortality was similar in the two groups, but the use of late PN resulted in clinically superior outcomes: fewer infections, shorter length of ventilation, shorter hospital stay, lower plasma levels of γ-glutamyltransferase and alkaline phosphatase (suggestive of less cholestasis in children in the late-parenteral-nutrition group). This mirrors results in adult studies.[56] The explanation of these results is most likely multifactorial, but it should be noted that the actual caloric needs of the critically ill child are difficult to accurately estimate,[57] and the early PN group may have been overfed and/or this may reflect the risks associated with parenteral feeding and the central catheter needed to deliver it.

The usual requirements for amino acids, dextrose and fat in PN in children are shown in Table 108.8. The amino acid solution can be mixed with dextrose in the pharmacy department to make a 'nutrient solution'. For short-term nutrition, the solution need not provide fluoride, iron or vitamins A, D and E, but a paediatric multivitamin preparation should be given to children on long-term PN. Fat can be given as a 20%

Table 108.8 Parenteral nutrition

STANDARD NUTRIENT SOLUTION	
Amino acids	1–2 g/kg/day
Dextrose	10–20 g/kg/day
Lipid	1–3 g/kg/day
Sodium	4 mmol/kg/day
Potassium	3 mmol/kg/day
Calcium	7.5 mmol/L
Phosphate	7.5 mmol/L
Magnesium	4 mmol/L
Manganese	0.2 µmol/kg/day
Zinc	3 µmol/kg/day
Copper	0.5 µmol/kg/day
Iodide	0.04 µmol/kg/day
Chromium	0.005 µmol/kg/day
Hydroxycobalamin	20 µg/L
Vitamin K	2 mg/L
Folic acid	1 mg/L
Multivitamin preparation	

Notes: 1 mL/kg/day of fluid is needed for each kcal/kg/day; 1 kcal = 4.2 kJ; total kcal/kg/day = g/kg/day of (amino acids × 4) + (dextrose × 4) + (fat × 10).

emulsion, either through a separate IV line or alternating with the nutrient solution. Nutrient solutions for paediatric use contain high concentrations of calcium, magnesium and phosphorus, and they should not be mixed with the fat emulsion, even in a Y-connection placed just before the cannula. The types of lipid used for PN formulations may impact on the development of PN-associated liver disease, which accounts for substantial morbidity and mortality, particularly in infants with intestinal failure. Newer lipid preparations (e.g. SMOF, this is a mixture of 4 different lipid sources; soybean oil, olive oil, medium chain triglycerides and fish oil – hence the name) and medium chain triglycerides rather than the standard soya-based lipid (e.g. intralipid) have been shown to reduce liver disease associated with PN in some infants on long-term PN, and it has become standard use in many centres.[58]

For a child on PN, it is important that abnormal fluid losses (see Table 108.5) be replaced with an appropriate solution (in addition to the nutrient solution), and that PN always be introduced and withdrawn slowly. A dislodged IV cannula should be replaced immediately in a child on PN, to prevent rebound hypoglycaemia. If nutrient solution is not available at any time, it should be replaced with an infusion of a similar amount of dextrose. Frequent, careful monitoring is essential initially, and particularly in preterm babies, but can be less frequent once a child is stabilised on PN.

Acknowledgements

I would like to acknowledge Professor Frank Shann, Professor of Children's Critical Care Medicine, Royal Children' Hospital, Melbourne, Australia, as the previous author and I have used much of his invaluable material; and Dr Tom Brick, Consultant Paediatric and Neonatal Intensive Care, Great Ormond Street Hospital, London, United Kingdom, for reviewing my work and keeping me on track.

REFERENCES

1. Steiner MJ, DeWalt DA, Byerley JS. Is this child dehydrated? *JAMA*. 2004;291(22):2746.
2. Choong K. Hypotonic versus isotonic saline in hospitalised children: a systematic review. *Arch Dis Child*. 2006;91(10):828–835.
3. Carcillo JA, Davis AL, Zaritsky A. Role of early fluid resuscitation in pediatric septic shock. *JAMA*. 1991;266:1242–1245.
4. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med*. 2011;364:2483–2495.
5. Duke T. What the African fluid-bolus trial means. *Lancet*. 2011;378(9804):1685–1687.
6. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345:1368–1377.
7. Mouncey PR, Osborn TM, Sarah Power G, et al. Trial of early, goal-directed resuscitation for septic shock (The ProMISe Trial). *N Engl J Med*. 2015;372:1301–1311.
8. The ARISE Investigators and the ANZICS Clinical Trials Group. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med*. 2014;371:1496–1506.
9. The ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014;370:1683–1693.
10. Tibby SM, Hatherill M, Marsh MJ, et al. Clinical validation of cardiac output measurements using femoral artery thermodilution with direct Fick in ventilated children and infants. *Intensive Care Med*. 1997;23(9):987–991.
11. Sinitsky L, Walls D, Nadel S, et al. Fluid overload at 48 hours is associated with respiratory morbidity but not mortality in a general PICU: retrospective cohort study. *Pediatr Crit Care Med*. 2015;16:205–209.
12. Arikan AA, Zappitelli M, Goldstein SL, et al. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. *Pediatr Crit Care Med*. 2012;13:253–258.
13. Brotfain E, Koyfman L, Toledano R, et al. Positive fluid balance as a major predictor of clinical outcome of patients with sepsis/septic shock after ICU discharge. *Am J Emerg Med*. 2016;34(11):2122–2126.
14. Bhaskar P, Dhar AV, Thompson M, et al. Early fluid accumulation in children with shock and ICU mortality: a matched case–control study. *Intensive Care Med*. 2015;4:1445.
15. Selewski DT, Goldstein SL. The role of fluid overload in the prediction of outcome in acute kidney injury. *Pediatr Nephrol*. 2016;doi:10.1007/s00467-016-3539-6.
16. Li Y, Wang J, Bai Z, et al. Early fluid overload is associated with acute kidney injury and PICU mortality in critically ill children. *Eur J Pediatr*. 2016;175(1):39–48.
17. Edge JA, Jakes RW, Roy Y, et al. The UK case-control study of cerebral oedema complicating diabetic ketoacidosis in children. *Diabetologia*. 2006;49:2002–2009.
18. Haut ER, Kalish BT, Cotton BA, et al. Prehospital intravenous fluid administration is associated with higher mortality in trauma patients: a National Trauma Data Bank analysis. *Ann Surg*. 2011;253(2):371–377.
19. Moritz ML, Ayus JC. Maintenance intravenous fluids in acutely ill patients. *N Engl J Med*. 2015;373:1350–1360.
20. Macrae D, Grieve R, Allen E, et al. A randomized trial of hyperglycemic control in pediatric intensive care. *N Engl J Med*. 2014;370:107–118.
21. Roberts E. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ*. 1998;317(7153):235.
22. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350(22):2247–2256.

23. Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med*. 2013;369:1243–1251.
24. Wilcox CS. Regulation of renal blood flow by plasma chloride. *J Clin Invest*. 1983;71(3):726–735.
25. Emrath E, Travers C, McCracken C, et al. Resuscitation with balanced fluids is associated with improved survival in pediatric severe sepsis. *Crit Care Med*. 2015;43(12 suppl 1):263–264.
26. Semler MW, Self WH, Wanderer JP, the SMART investigators. Balanced crystalloids versus saline in critically III adults. *N Engl J Med*. 2018;378:829–839.
27. Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. *JAMA*. 2015;314(16):1701–1710.
28. Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics*. 1957;19:823–832.
29. McNab S, Ware RS, Neville KA, et al. Isotonic versus hypotonic solutions for maintenance intravenous fluid administration in children. *Cochrane Database Syst Rev*. 2014;(12):CD009457.
30. Moritz ML, Ayus JC. Maintenance intravenous fluids in acutely ill patients. *N Engl J Med*. 2015;373: 1350–1360.
31. Soulski R, Polin RA, Baumgart S. Respiratory water loss and heat balance in intubated infants receiving humidified air. *J Pediatr*. 1983;103(2):307–310.
32. Bouzarth WF, Shenkin HA. Is 'cerebral hyponatraemia' iatrogenic? *Lancet*. 1982;1(8280):1061–1062.
33. Schmidt A, Bundgaard A. Water loss from the respiratory tract during hyperventilation in normal subjects and in asthmatics. *Eur J Respir Dis Suppl*. 1986;143:78–80.
34. Rutter N, Hull D. Water loss from the skin of term and preterm babies. *Arch Dis Child*. 1979;54(11):858.
35. Marks KH, Gunther RC, Rossi JA, et al. Oxygen consumption and insensible water loss in premature infants and under radiant heaters. *Pediatrics*. 1980;66(2):228–232.
36. Maayan-Metzger A, Yosipovitch G, Hadad E, et al. Transepidermal water loss and skin hydration in preterm infants infants during phototherapy. *Am J Perinatol*. 2001;18(7):393–396.
37. Ramanathan S, Kumar P, Mishra K, et al. Isotonic versus hypotonic parenteral maintenance fluids in very severe pneumonia. *Indian J Pediatr*. 2016;83:27.
38. Foster BA, Tom D, Hill V. Hypotonic versus isotonic fluids in hospitalized children: a systematic review and meta-analysis. *J Pediatr*. 2014;165:163–169.
39. Choong K, Arora S, Cheng J, et al. Hypotonic versus isotonic maintenance fluids after surgery for children: a randomized controlled trial. *Pediatrics*. 2011;128:857–866.
40. Chen L, Hsiao A, Langhan M, et al. Use of bedside ultrasound to assess degree of dehydration in children with gastroenteritis. *Acad Emerg Med*. 2010;17(10):1042–1047.
41. Friedman JN, Goldman RD, Srivasta R, et al. Development of a clinical dehydration scale for use in children between 1 and 36 months of age. *J Pediatr*. 2004;145(2):201–207.
42. Gorelick MH, Shaw KN, Murphy KO. Validity and reliability of clinical signs in the diagnosis of dehydration in children. *Pediatrics*. 1997;99(5):E6.
43. Ng L, Khine H, Taragin BH, et al. Does bedside sonographic measurement of the inferior vena cava diameter correlate with central venous pressure in the assessment of intravascular volume in children? *Pediatr Emerg Care*. 2013;29(3):337–341.
44. Jauregui J, Nelson D, Choo E, et al. The BUDDY (Bedside Ultrasound to Detect Dehydration in Youth) study. *Crit Ultrasound J*. 2014;6(1):15.
45. Steiner MJ, Nager AL, Wang VJ. Urine specific gravity and other urine indices: inaccurate tests for dehydration. *Pediatr Emerg Care*. 2007;23(5):298–303.
46. Shavit I, Brant R, Nijssen-Jordan C, et al. A novel imaging technique to measure capillary-refill time: improving diagnostic accuracy for dehydration in young children with gastroenteritis. *Pediatrics*. 2006;118(6):2402–2408.
47. Freedman S, Vandermeer B, Milne A, et al. Diagnosing clinically significant dehydration in children with acute gastroenteritis using noninvasive methods: a meta-analysis. *J Pediatr*. 2015; 166:908–916.
48. Harrington JT, Cohen JJ. Measurement of urinary electrolytes – indications and limitations. *N Engl J Med*. 1975;293(24):1241–1243.
49. Moritz ML, Ayus JC. Management of hyponatraemia in various clinical situations. *Curr Treat Options Neurol*. 2014;16(9):310.
50. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med*. 2013;126(10 suppl 1):S1–S42.
51. Adrogue HJ, Madias NE. Hypernatremia. *N Engl J Med*. 2000;342(20):1493–1499.
52. Gennari FJ. Hypokalaemia. *N Engl J Med*. 1998; 339(7):451–458.
53. Heird WC, Driscoll JM Jr, Schullinger JN, et al. Intravenous alimentation in pediatric patients. *J Pediatr*. 1972;80(3):351–372.
54. Mehta NM, Bechard LJ, Cahill N, et al. Nutritional practices and their relationship to clinical outcomes in critically ill children – an international multicenter cohort study. *Crit Care Med*. 2012;40: 2204–2211.
55. Fivez T, Kerklaan D, Mesotten D, et al. Early versus late parenteral nutrition in critically ill children. *N Engl J Med*. 2016;374:1111–1122.
56. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med*. 2011;365:506–517.
57. Hunter DC, Jaksic T, Lewis D, et al. Resting energy expenditure in the critically ill: estimations versus measurement. *Br J Surg*. 1988;75:875–878.
58. Attard M, Patel N, Simpson J. Change from intralipid to SMOF lipid is associated with improved liver function in infants with PN associated liver disease. *Arch Dis Child*. 2012;97:A54–A55.

109

Sedation and analgesia in children

Andy Petros

ASSESSMENT OF DEPTH OF SEDATION AND PAIN

There is no one perfect scoring system to assess the adequacy of sedation or pain relief in children. The wide age spectrum from preterm neonates to 16-year-old teenagers requires age-appropriate tools. Consequently, there are a number of validated tools to match the various age groups. These tools fall into two main categories: (1) those that assess and score a number of behaviours considered typical of distress and (2) those that simply judge the level of consciousness. One example of the latter is the University of Michigan Sedation Scale (UMSS) which assess level of consciousness on a scale of 0–4 with 4 being unconscious.[1] Another frequently used scale is the State Behavioral Scale (SBS) specifically designed for and tested in young intubated and mechanically ventilated patients.[2] Perhaps the most commonly used tool for assessing distress in children is the COMFORT scale subsequently modified to the COMFORT behavior scale (COMFORT-B).[3] Both have been validated for pain and sedation in ventilated and spontaneously breathing 1–3-year-olds. Neither score can be used in patients receiving muscle relaxants. It is important to achieve optimal levels of sedation, as over-sedation can lead to tolerance, dependency and withdrawal symptoms.

The Richmond Agitation-Sedation Scale (RASS) is a single tool that is easy to use and includes both agitation and sedation. It correlated highly against the visual analogue scale and the UMSS, and allowed the accurate assessment of awareness in both ventilated and spontaneously breathing patients, and it may improve our ability to titrate sedatives and assess for delirium in paediatrics.[4]

Assessing postoperative pain in pre-verbal children can be difficult, and the Face, Legs, Activity, Cry and Consolability (FLACC) scale[5] and the Multidimensional Assessment of Pain Scale (MAPS)[6] are both useful tools. In preterm and term neonates the Neonatal Pain, Agitation and Sedation Scale (N-PASS),[7] the Premature Infant Pain Profile (PIPP)[8] and CRIES (Cry, Requires oxygen, Increased vital signs, Expression, Sleeplessness) scales have all been used and are objective measures of pain in this group.[9]

The bispectral index (BIS) is a numerical scale derived from the encephalogram, which purports to correlate with the level of consciousness. It is most commonly used in adult anaesthesia but is also used in children, and a range of 40–60 is considered an adequate level of sedation. The use of BIS in children has its limitations. It can be useful in children receiving muscle relaxants in whom it is not possible to assess behavioural indicators.

Vet et al. identified 25 randomised controlled trials reporting optimal sedation levels, scoring systems and agents used on the paediatric intensive care unit (PICU).[10] The most frequently used paediatric sedation scores were COMFORT, COMFORT–B, Ramsay (an adult score) and SBS. Six studies (23%) reported the use of BIS.

ACHIEVING ADEQUATE SEDATION

Pain, discomfort, anxiety, loss of the sleep–wake cycle, withdrawal symptoms and delirium are the challenges in paediatric intensive care. A European systematic review concluded that optimal sedation was achieved only 58% of the time, and there was a tendency to over-sedate in 32% of their observations.[10]

Numerous attempts have been made at producing protocols and sedation guidelines for children. However, because of the relative paucity of evidence for the various agents available, there are no universally adopted guidelines. The Pediatric Cardiac Intensive Care Society 2014 consensus statement on the use of sedation, analgesia and muscle relaxant attempted to establish some guidelines. It concluded that the management of the cardiac patient requires an individualised sedative and analgesic strategy that maintains hemodynamic stability.[11] In a mixed PICU environment protocolised sedation did not produce any significant advantages over physician-led management.[12] In practice, the common default position on the PICU are nurse-led adjustments according to their subjective assessment of the child.

Rather than using continuous infusions of sedatives and leaving adjustments to any one individual, there is evidence that interruption of infusions

ABSTRACT

One of the main objectives for any intensivist, adult or paediatric, must be to ensure their patient is pain free with minimum distress while in intensive care. Children are arguably more in need of good sedation than adults as they are often too young to reason with and can become distressed by being separated from their parents. There is an art in providing good sedation and analgesia whether the child is receiving muscle relaxants or when they are improving and weaning from ventilation. The use of continuous infusions can lead to excess amounts of either sedative or analgesic being given, resulting in problems with withdrawal and delirium, thereby complicating the patient's stay and subsequent recovery. The appropriate choice of agents together with the use of validated scoring systems to assess pain and discomfort and reliance upon a good evidence base should inform our management of children on the ICU.

KEYWORDS

Sedation
analgesia
paediatric intensive care
monitoring
evidence base

significantly reduces the length of mechanical ventilation, the duration of ICU stay and the total dose of midazolam administered,[13] and may be a technique worth pursuing.

Strategies to promote a normal sleep–wake cycle include maintaining a quiet environment and natural light during the day and no artificial light during the night, to help promote the normal day/night pattern. Eye masks, earplugs and other noise reduction strategies can potentially decrease the need for chemical sedation.

AGENTS FOR SEDATION

Sedative agents do not provide analgesia. Hence a combination of analgesics and sedatives is the standard approach to ensure the child is comfortable and accepts mechanical ventilation. The most commonly used sedatives on PICU are benzodiazepines, followed by ketamine, and barbiturates; enteral agents are also used and include chloral hydrate and alamemazine.

BENZODIAZEPINES

Benzodiazepines are the agents of first choice to reduce anxiety in children. Their main sites of actions are in the limbic and reticular activating system on gamma-aminobutyric acid ($GABA_A$) receptors. These transmembrane proteins have five subunits surrounding a selective chloride ion pore with binding sites for both GABA and benzodiazepines. GABA opens these chloride channels, resulting in neuronal hyperpolarisation and decreased excitability. Benzodiazepines increase the affinity of GABA for the receptors and enhance GABA-mediated inhibitory transmission.

Benzodiazepines have a large volume of distribution due to their lipid solubility and are metabolised in the liver, being oxidised to active metabolites or converted to glucuronides, and are excreted in urine. The production of active metabolites and enterohepatic recirculation prolongs their duration of action.

MIDAZOLAM

Midazolam is probably the most commonly used benzodiazepine on the PICU and is the drug of choice in combination with morphine to provide sedation and analgesia on the PICU.[14] A single dose has an onset of action within 1–5 minutes and can last 30–120 minutes. It is metabolised in the liver to the equally potent 1-hydroxymidazolam. The standard intravenous (IV) sedative dose is 0.1–0.2 mg/kg; the oral dose is 0.5 mg/kg and is used for premedication. As an infusion (1–4 µg/kg/min) it is commonly used in combination with an opioid such as morphine (10–40 µg/kg/h). In higher doses it can cause respiratory depression and particular care has to be taken in children with compromised cardiac function where it can induce significant hypotension. Midazolam is not commonly used in neonatal intensive care because of concerns over neurodevelopment and neurological damage.[15] It is increasingly being recognised that midazolam is a major cause of withdrawal and delirium post-ICU. The use of midazolam as a continuous infusion may soon become obsolete on the PICU.

CLONIDINE

Clonidine is a α_2-adrenoreceptor agonist with a half-life of 9–12 hours. It can be administered either orally or intravenously. If given orally it is metabolised by the liver and excreted by the kidney with approximately 50% unchanged in urine. Clonidine has an important role in managing opioid withdrawal by ameliorating the symptoms of withdrawal.

DEXMEDETOMIDINE

Dexmedetomidine is a selective α_2-agonist with a similar pharmacology to clonidine, although it is about eight times more potent. The use of dexmedetomidine is increasing on the PICU and has become a viable alternative to midazolam, and may well replace it as the sedative agent of first choice. A number of studies in children have investigated the safety and efficacy of dexmedetomidine. A continuous infusion of 0.7 µg/kg/h without a loading dose was well tolerated with minimal effects on heart rate and blood pressure.[16] In a single centre retrospective report of 144 children with a median age of 34 months, dexmedetomidine 0.05–2.0 µg/kg/h was well tolerated, although withdrawal symptoms were reported as a problem.[17] It is used increasingly on the PICU because of its short half-life of 2 hours and relative lack of respiratory depression; it allows fewer opioids to be used and shortens the duration of mechanical ventilation. Bradycardia and hypotension are seen with both clonidine and dexmedetomidine during continuous infusion. Dexmedetomidine has been used in term and preterm neonates for up to 24 hours without serious side effects.[18]

KETAMINE

Ketamine is a non-competitive antagonist of the excitatory neurotransmitter *N*-methyl-D-aspartate (NMDA) receptor sites in the central nervous system (CNS). Its onset of action is about 2 minutes to achieve maximal effect when given intravenously and can be longer when given intramuscularly. It has a duration of action of 10–20 minutes after an IV dose of 1–2 mg/kg. Ketamine produces a dissociative anaesthetic state where the patient appears to be awake with eyes open but is anaesthetised and pain free.

Systemic effects include increased cerebral blood flow and intracranial pressure. Cardiovascular effects include an increase in cardiac output, pulmonary vascular resistance and systolic and diastolic pressures. It is metabolised in the liver and its metabolites are less potent.

Ketamine is very useful in paediatric practice for venous access or repeated minor surgical procedures. It also has a role in severe asthma as the agent of choice for intubation and continued sedation as opposed to morphine, which can release histamine. A continuous infusion of 10–40 μg/kg/min can be used. Ketamine increases secretions of saliva and can cause unpleasant hallucinations.

PROPOFOL

Because of its short half-life and rapid wake-up time, propofol is the mainstay of sedation in adult intensive care. However, in paediatric intensive care it has a limited role. There are well-documented reports of serious adverse events and deaths while using continuous infusions of propofol in children. Propofol infusion syndrome (PRIS) was reported by Bray[19] and includes hyperkalaemia, metabolic acidosis, hyperlipidaemia, myocardial dysfunction, brady-arrythmias, rhabdomyolysis and death. Doses of greater than 4 mg/kg/h for greater than 48 hours are significant risk factors. Immature hepatic metabolism of the lipid carrier, and consequent accumulation and infiltration into the cardiac conduction system is speculated as the cause of the arrhythmias.[20] In 2001 the Committee on Safety of Medicines and the Medicines Control Agency in the United Kingdom both advised against the use of propofol in children younger than 16 years of age as a continuous infusion on the PICU.

Propofol bolus given at 1.5–2.5 mg/kg for intubation produces a rapid loss of consciousness. On rapid induction it can cause respiratory depression and apnoea, and a reduction in systemic blood pressure by reducing systemic vascular resistance.

CHLORAL HYDRATE

Chloral hydrate is an orally active agent with sedative–hypnotic properties and is able to produce sedation without significant respiratory depression. It is a prodrug being metabolised to tri-chloroethanol, which is then excreted in urine. It is a useful enteral agent to supplement IV sedation or it can be effective on its own at 30–50 mg/kg. Its absorption can be variable depending on the activity of the gut. Chloral can be used in neonates but with caution as its metabolites have a longer half-life in this group and it accumulates in renal impairment. It can also cause withdrawal symptoms when used for greater than 7 days if stopped abruptly.

PHENOTHIAZINES

Phenothiazines have potent central anticholinergic sedative effects. Antagonism of central acetylcholine synapses and central histamine H_1-receptors may be responsible for their sedative activity. The use of promethazine has declined, whilst alimemazine increases and is usually given orally. Alimemazine is an H_1-histamine antagonist, which is more powerful than promethazine. Given at 1–2 mg/kg it provides good sedation within 30–40 minutes lasting for 4–6 hours. It should be used with caution in neonates, if at all.

THIOPENTAL

Thiopental has a number of uses on the PICU, including the induction of anaesthesia for elective intubation at 2–4 mg/kg, as an infusion (1–5 mg/kg/h) to reduce raised intracranial pressure and in refractory status epilepticus. When used for the latter two conditions, continuous electroencephalogram (EEG) monitoring to ensure burst suppression should accompany it. A retrospective review of eight UK PICUs revealed that thiopentone was the most commonly used anticonvulsant to treat refractory convulsive status epilepticus on admission to the PICU.[21]

ISOFLURANE

Isoflurane is not a suitable or practical agent to use on the PICU. Occasional case reports continue to surface using tailored devices, such as the Anesthetic Conserving Device (AnaConDav), a modified heat and moisture exchanger, suggesting it may provide an alternative in difficult cases needing prolonged sedation.[22] However, the use of isoflurane is rare.

EVIDENCE BASE FOR SEDATION

Applying the principles of Level of Evidence (Level) and Grade of Recommendation (Grade) there is very little high-quality evidence to guide the use of sedation in children on the PICU.[23] Reviewing the current literature reveals only one systematic review[24] that advocates the use of continuous sedation in children (Level 1a, Grade B). As to which sedative agents to use, there have been no validated randomised controlled trials (RCTs) to help; only anecdotal evidence is available (Level 5).

There is reasonably good recent evidence (Level 1b, Grade B) supporting the use of clonidine,[25] or dexmedetomidine[26] as continuous IV agents to achieve sedation. The use of dexmedetomidine in neonates has been shown to be safe and effective for up to 24 hours.[18]

Daily interruption of sedation until the child becomes fully awake[13] or reaches a specific COMFORT score[27] has been shown to significantly reduce the length of mechanical ventilation, the duration of ICU stay and the total dose of midazolam in two recent studies in children (Level 1b Grade B).

Sedation in neonates can be difficult as the developing brain is very vulnerable. A systematic review of three papers in the Cochrane database reports that there is insufficient evidence to support the use of midazolam in neonates and that there may be an increased associated risk of adverse neurological effects (Level 1A, Grade A). When IV sedation is needed in neonates, morphine is the single agent of choice and is safer than midazolam (Level 1A, Grade B).[28]

AGENTS FOR ANALGESIA

MORPHINE

Morphine is the mainstay of analgesia on the PICU and as part of a sedative regimen for children. Its main action is via μ-receptors in the CNS. In neonates it is the only agent used and provides sufficient analgesia and sedation. Morphine has a number of unwanted actions, including respiratory depression even with therapeutic analgesic doses, and the release of histamine from mast cells resulting in bronchospasm. The active metabolite, morphine-6-glucuronide further prolongs its activity. The bolus dose is 0.1–0.2 mg/kg and the infusion rate is 10–40 μg/kg/h.

Nurse or patient-controlled analgesia devices are very useful following surgery. They deliver a continuous background infusion of a fixed dose of opioid and allow the patient or nurse to administer an extra dose at fixed time intervals if more analgesia is required.

FENTANYL AND ALFENTANIL

Fentanyl is 100 times more potent than morphine; it is cardiovascularly stable over a wide range of doses and is a frequent substitute for morphine. An induction dose of 1–2 μg/kg IV is sufficient for intubation, and infusions of 1–6 μg/kg/h produce effective sedation in children and neonates on mechanical ventilation. Fentanyl causes dose-dependent respiratory depression and at very high doses it can produce chest wall rigidity. A bolus is often helpful prior to painful procedures in neonates with pulmonary hypertension.

Alfentanil is a synthetic opioid structurally related to fentanyl. It has a more rapid onset and a shorter duration of action, but approximately 10%–20% of its potency. It is rarely used on the PICU.

REMIFENTANIL

Remifentanil is an ultrashort-acting potent synthetic opioid 10 times more potent than fentanyl and 1000 time more potent than morphine; it is ideal for stimulating procedures such as physiotherapy or chest drain removal. It is ideal for neurosedation because of its short half-life. It can be stopped briefly to enable a window of consciousness allowing neurological assessment.

Following initial redistribution, remifentanil is metabolised rapidly via non-specific esterases. Having a context-sensitive half-time of 3–5 minutes, its duration of action is not influenced by the total time of infusion. Rates of infusion of 3–80 μg/kg/h produces satisfactory analgesia and sedation in ventilated children aged 1 month to 12 years and for those over 12 years of age 3–120 μg/kg/h.

The use of remifentanil in children and neonates in intensive care is increasing.[29] In an RCT of neonates and infants, the authors concluded that remifentanil could be the ideal opioid for analgesia and sedation of mechanically ventilated infants.[30]

PARACETAMOL AND NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

The IV dose for infants weighing less than 10 kg is 7.5 mg/kg every 6 hours; in children it is 15 mg/kg and the total daily IV dose should be limited to 60 mg/kg. The oral dose is 20–30 mg/kg for one dose, then 15–20 mg/kg/day up to 60 mg/kg/day. Higher doses are required when used rectally, 30–40 mg/kg initially then 15–20 mg/kg 6 hourly to a maximum of 60 mg/kg/day. It is metabolised in the liver and renally excreted.

Non-steroidal anti-inflammatory drugs (NSAIDs) are less commonly used on the PICU. Most NSAIDs work by inhibiting cyclo-oxygenases, which increase prostaglandin levels, which in turn sensitises peripheral nerve endings to agents such as histamine and bradykinins. Concerns around compromising renal function and increasing bleeding tendency have reduced the use of NSAIDs on the PICU.

EVIDENCE BASE FOR ANALGESIA

There is evidence for using continuous IV opioid infusions (Level 2b, Grade B). Continuous morphine therapy appeared to be effective in controlling neonatal postoperative pain, as judged by nursing observations.[31]

The combination of opioid and non-opioid analgesia is supported by work from Wong[32] who undertook a systematic review of 31 RCTs and concluded that multiple doses of NSAIDs on a background of continuous opioid infusion gave significant benefit (Level 2b, Grade A).

Patient-controlled analgesia (PCA) has not been rigorously evaluated in terms of advantage over any other form of intermittent analgesia. However, a meta-analysis of 49 studies revealed children using PCA had lower visual analogue scale pain intensity scores than children who did not receive PCA (Level 1b, Grade B).[33]

A recent Cochrane review of eight trials and 614 infants concluded that paracetamol may reduce the total need for morphine following major surgery, and when combined with morphine it is useful in severe pain.[34]

SUCROSE IN NEONATES

There is good evidence for the beneficial effect of 0.5 mL sucrose (24%) in reducing heel-prick pain and 2 mL is useful reducing venipuncture and intramuscular injections. The effectiveness of sucrose for reducing pain/stress from other interventions, such as arterial puncture, subcutaneous injection, insertion of nasogastric or orogastric tubes, bladder catheterisation, eye examinations and echocardiography examinations, were inconclusive.[35]

WITHDRAWAL SYNDROMES

Iatrogenic withdrawal syndrome is a well-recognised problem in children receiving benzodiazepines and opioids for periods greater than 5 days. Recent work

suggests that monitoring for withdrawal should start as early as 3 days and that rates of infusion of midazolam greater than 0.35 mg/kg/h or 6 μg/kg/min will put children at high risk of withdrawal.[36] Infusion of fentanyl for greater than 5 days or a total dose greater than 1.5 mg/kg is associated with greater than 50% incidence of withdrawal.[37] The Sophia Observation withdrawal Symptoms scale is a useful tool when weaning from sedation/analgesia,[38] as is the Withdrawal Assessment Tool-1 (WAT-1).[39]

MANAGEMENT OF DELIRIUM

Delirium is an increasingly recognised problem following PICU admission and can result in significant cognitive impairment on leaving intensive care. Delusional memories were reported in almost one-third of children following their PICU admission and were associated both with the duration of opiates/benzodiazepines and with the increased risk of developing post-traumatic stress.[40] A significant minority of school-aged children admitted to the PICU are at risk of reduced mental and physical well-being in the short term.[41]

Two validated bedside tools help to incorporate delirium monitoring into the critical care setting. The Preschool Confusion Assessment Method for the ICU (psCAM-ICU) identifies delirium in critically ill infants and children less than 5 years of age. The Pediatric Confusion Assessment Method for the Intensive Care Unit (pCAM-ICU) assesses delirium in children 5 years of age and older.[42] The ps/pCAM-ICU were adapted from the adult Confusion Assessment Method for the ICU (CAM-ICU).[43] In practice the RASS is a used to measure the sedation level prior to using tools such as the Cornell Assessment of Pediatric Delirium (CAP-D) or pCAM-ICU to assess delirium.[44]

REGIONAL TECHNIQUES

Although a number of regional blocks are described, the most commonly encountered regional block used for postoperative pain is the lumbar epidural. The procedure is usually performed in theatres and is not commonly instituted on the PICU. However, it is important that the advantages and complications of this technique are known, as it may remain in situ for days while on the PICU. A complication rate of 1.5/1000 has been reported, with dural puncture and intravascular injection seen most commonly at the time of insertion. Other complications include epidural infection and excessive motor blockade and high-level blockade, which is particularly important in smaller children.

HOLISTIC APPROACH

The use of physical restrains with arms tied to cot sides and elbows splinted to prevent self-extubation have been superseded by chemical restraints. Rapid developments in the adult ICU world are leading the way and guiding us to attempt to make the child's stay on the PICU as normal as possible. Measures such as eye masks, earplugs and other noise reduction strategies[45] and single rooms improve quality of sleep and reduce the prevalence of delirium in the adult ICU setting[46] and should be considered on the PICU. These initiatives will be more challenging in the paediatric population but should not be impossible.

SUMMARY

The purpose of sedation and analgesia in children while on the PICU is to reduce pain, anxiety and distress. We are moving away from an era when chemical restraint is the standard of care. We need to adapt to novel measures that allow our children to be comfortable and pain free, yet interactive while being ventilated and, most importantly of all, not suffer from iatrogenic complications caused during and following their stay on the PICU. Symptoms of withdrawal and delirium are our major challenges following discharge. The child's need for the PICU should not be further complicated by problems caused by the sedation and analgesia we administer.

Guidelines for the route of administration, bolus and infusion doses of commonly used sedative and analgesic agents in children. (Modified from the British National Formulary for Children)

DRUG	ROUTE	DOSAGE
Diazepam	IV	Bolus: 0.2–0.4 mg/kg Infusion: NOT recommended
Midazolam	IV	Bolus: 0.1–0.2 mg/kg Infusion: 1–4 μg/kg/min
Lorazepam	IV	Bolus: 0.1 mg/kg
Chloral hydrate	Oral	30–50 mg/kg 6–8 hourly
Alimemazine	Oral	1–2 mg/kg 6 hourly
Ketamine	IV	Bolus: 1–2 mg/kg Infusion: 10–40 μg/kg/min
Clonidine	Oral IV	4 μg/kg Infusion: 0.1–2 μg/kg/h
Dexmedetomidine	IV	Infusion: 0.7–1.4 μg/kg/h
Thiopentone		Bolus: 2–4 mg/kg Infusion: 1–5 mg/kg/h
Paracetamol	Oral	20–30 mg/kg stat then 15–20 mg/kg to a max of 60 mg/kg/day
	IV	Bolus: 7.5 mg/kg <10 kg 15 mg/kg >10 kg
	Rectal	30–40 mg/kg stat then 15–20 mg/kg to a max of 60 mg/kg/day

DRUG	ROUTE	DOSAGE
Morphine	IV	Bolus: 0.1–0.2 mg/kg Infusion: 10–40 µg/kg/h
Fentanyl	IV	Bolus: 1–2 µg/kg Infusion: 1–6 µg/kg/h for children 0–1.5 µg/kg/h for neonate
Remifentanil	IV	Infusion: 3–80 µg/kg/h 1 month–12 years 3–120 µg/kg/h 12–18 years

IV, Intravenous.

REFERENCES

1. Malviya S, Voepel-Lewis T, Tait AR, et al. Depth of sedation in children undergoing computed tomography: validity and reliability of the University of Michigan Sedation Scale (UMSS). *Br J Anaesth*. 2002; 88(2):241–245.
2. Curley MA, Harris SK, Fraser KA, et al. State Behavioral Scale: a sedation assessment instrument for infants and young children supported on mechanical ventilation. *Pediatr Crit Care Med*. 2006;7(2):107–114.
3. Ista E, van Dijk M, Tibboel D, et al. Assessment of sedation levels in pediatric intensive care patients can be improved by using the COMFORT "behavior" scale. *Pediatr Crit Care Med*. 2005;6(1):58–63.
4. Kerson AG, DeMaria R, Mauer E, et al. Validity of the Richmond Agitation-Sedation Scale (RASS) in critically ill children. *J Intensive Care*. 2016;4:65.
5. Crellin DJ, Harrison D, Santamaria N, et al. Systematic review of the Face, Legs, Activity, Cry and Consolability scale for assessing pain in infants and children: is it reliable, valid, and feasible for use? *Pain*. 2015;156(11):2132–2151.
6. Ramelet AS, Rees N, McDonald S, et al. Development and preliminary psychometric testing of the Multidimensional Assessment of Pain Scale: MAPS. *Paediatr Anaesth*. 2007;17:333–340.
7. Hummel P, Puchalski M, Creech SD, et al. Clinical reliability and validity of the N-PASS: neonatal pain, agitation and sedation scale with prolonged pain. *J Perinatol*. 2008;28(1):55–60.
8. Gibbins S, Stevens BJ, Yamada J, et al. Validation of the Premature Infant Pain Profile-Revised (PIPP-R). *Early Hum Dev*. 2014;90(4):189–193.
9. Krechel SW, Bildner J. CRIES: a new neonatal postoperative pain measurement score. Initial testing of validity and reliability. *Paediatr Anaesth*. 1995; 5(1):53–61.
10. Vet NJ, Ista E, de Wildt SN, et al. Optimal sedation in pediatric intensive care patients: a systematic review. *Intensive Care Med*. 2013;39(9):1524–1534.
11. Lucas SS, Nasr VG, Ng AJ, et al. Pediatric Cardiac Intensive Care Society 2014 consensus statement: pharmacotherapies in cardiac critical care: sedation, analgesia and muscle relaxant. *Pediatr Crit Care Med*. 2016;17(3 suppl 1):S3–S15.
12. Curley MA, Wypij D, Watson RS, et al. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: a randomized clinical trial. *JAMA*. 2015;313(4):379–389.
13. Gupta K, Gupta VK, Jayashree M, et al. Randomized controlled trial of interrupted versus continuous sedative infusions in ventilated children. *Pediatr Crit Care Med*. 2012;13(2):131–135.
14. Garcia Guerra G, Joffe AR, Cave D, et al. Survey of sedation and analgesia practice among Canadian pediatric critical care physicians. *Pediatr Crit Care Med*. 2016;17(9):823–830.
15. Ng E, Taddio A, Ohisson A. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. *Cochrane Database Syst Rev*. 2003;(1):CD002052.
16. Cummings BM, Cowl AS, Yager PH, et al. Cardiovascular effects of continuous dexmedetomidine infusion without a loading dose in the pediatric intensive care unit. *J Intensive Care Med*. 2015;30(8):512–517.
17. Carney L, Kendrick J, Carr R. Safety and effectiveness of dexmedetomidine in the Pediatric Intensive Care Unit (SAD-PICU). *Can J Hosp*. 2013;66(1):21–27.
18. Chrysostomou C, Schulman SR, Herrera Castellanos M, et al. A phase II/III, multicenter, safety, efficacy, and pharmacokinetic study of dexmedetomidine in preterm and term neonates. *J Pediatr*. 2014;164(2):276–282.
19. Bray RJ. Propofol infusion syndrome in children. *Paediatr Anaesth*. 1998;8(6):491–499.
20. Ahlen K, Buckley CJ, Goodale DB, et al. The 'propofol infusion syndrome': the facts, their interpretation and implications for care. *Eur J Anaesthesiol*. 2006;23:990–998.
21. Tully I, Draper ES, Lamming CR, et al. Admissions to paediatric intensive care units (PICU) with refractory convulsive status epilepticus (RCSE): a two-year multi-centre study. *Seizure*. 2015;29:153–161.
22. Sackey PV, Martling CR, Radell PJ. Three cases of PICU sedation with isoflurane delivered by the 'AnaConDa. *Paediatr Anaesth*. 2005;15(10):879–885.
23. DAS-Taskforce 2015, Baron R, Binder A, et al. Evidence and consensus based guideline for the management of delirium, analgesia, and sedation in intensive care medicine. Revision 2015 (DAS-Guideline 2015) – short version. *Ger Med Sci*. 2015;13:Doc19.
24. Hartman ME, McCrory DC, Schulman SR. Efficacy of sedation regimens to facilitate mechanical ventilation in the pediatric intensive care unit: a systematic review. *Pediatr Crit Care Med*. 2009;10(2):246–255.
25. Hünseler C, Balling G, Röhlig C, et al. Continuous infusion of clonidine in ventilated newborns and infants: a randomized controlled trial. *Pediatr Crit Care Med*. 2014;15(6):511–522.
26. Whalen LD, Di Gennaro JL, Irby GA, et al. Long-term dexmedetomidine use and safety

profile among critically ill children and neonates. *Pediatr Crit Care Med*. 2014;15(8):706–714.
27. Vet NJ, de Wildt SN, Verlaat CWM, et al. A randomized controlled trial of daily sedation interruption in critically ill children. *Intensive Care Med*. 2016;42:233–244.
28. Ng E, Taddio A, Ohlsson A. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. *Cochrane Database Syst Rev*. 2012;(6):CD002052.
29. Kamata M, Tobias JD. Remifentanil: applications in neonates. *J Anesth*. 2016;30(3):449–460.
30. Welzing L, Oberthuer A, Junghaenel S, et al. Remifentanil/midazolam versus fentanyl/midazolam for analgesia and sedation of mechanically ventilated neonates and young infants: a randomized controlled trial. *Intensive Care Med*. 2012;38(6):1017–1024.
31. Farrington EA, McGuinness GA, Johnson GF, et al. Continuous intravenous morphine infusion in postoperative newborn infants. *Am J Perinatol*. 1993;10(1):84–87.
32. Wong I, St John-Green C, Walker SM. Opioid-sparing effects of perioperative paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) in children. *Paediatr Anaesth*. 2013;23(6):475–495.
33. McNicol ED, Ferguson MC, Hudcova J. Patient controlled opioid analgesia versus non-patient controlled opioid analgesia for postoperative pain. *Cochrane Database Syst Rev*. 2015;(6):CD003348.
34. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for prevention or treatment of pain in newborns. *Cochrane Database Syst Rev*. 2016;(10):CD011219.
35. Stevens B, Yamada J, Ohlsson A, et al. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev*. 2016;(7):CD001069, doi:10.1002/14651858.CD001069.pub5.
36. da Silva PS, Reis ME, Fonseca TS, et al. Opioid and benzodiazepine withdrawal syndrome in PICU patients: which risk factors matter? *J Addict Med*. 2016;10(2):110–116.
37. Katz R, Kelly WH, Hsi A. Prospective study on the occurrence of withdrawal in critically ill children who receive fentanyl by continuous infusion. *Crit Care Med*. 1994;22:763–767.
38. Ista E, de Hoog M, Tibboel D, et al. Psychometric evaluation of the Sophia Observation withdrawal symptoms scale in critically ill children. *Pediatr Crit Care Med*. 2013;14(8):761–769.
39. Franck LS, Scoppettuolo LA, Wypij D, et al. Validity and generalizability of the Withdrawal Assessment Tool-1 (WAT-1) for monitoring iatrogenic withdrawal syndrome in pediatric patients. *Pain*. 2012;153(1):142–148.
40. Colville G, Kerry S, Pierce C. Children's factual and delusional memories of intensive care. *Am J Respir Crit Care Med*. 2008;177(9):976–982.
41. Als LC, Picouto MD, Hau SM, et al. Mental and physical well-being following admission to pediatric intensive care. *Pediatr Crit Care Med*. 2015;16(5):e141–e149.
42. Smith HA, Boyd J, Fuchs DC, et al. Diagnosing delirium in critically ill children: validity and reliability of the Pediatric Confusion Assessment Method for the Intensive Care Unit. *Crit Care Med*. 2011;39:150–157.
43. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med*. 1990;113(12):941–948.
44. Daoud A, Duff JP, Joffe AR, et al. Diagnostic accuracy of delirium diagnosis in pediatric intensive care: a systematic review. *Crit Care*. 2014;18(5):489–498.
45. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41(1):263–306.
46. Caruso P, Guardian L, Tiengo T, et al. ICU architectural design affects the delirium prevalence: A comparison between single-bed and multibed rooms. *Crit Care Med*. 2014;42:2204–2210.

110

Shock and cardiac disease in children

Johnny Millar

SHOCK

Shock is the clinical state resulting from insufficient oxygen delivery to meet oxygen demand, and is described in detail in Chapter 15. Shock in children is most commonly due to hypovolaemia or sepsis and remains an important cause of global infant and child mortality. The cellular effects of tissue hypoxia in shock are the same in children and adults, but there are important developmental changes in anatomy, physiology and immunity during childhood, which influence the incidence, presentation and natural history of shock.

DEVELOPMENTAL DIFFERENCES

BODY FLUID COMPARTMENTS[1]

Although the extracellular fluid volume in children is greater than in adults when indexed to body weight, the small absolute volumes involved are critical when blood or fluid loss causes shock; 100 mL blood loss is inconsequential for an adult, but represents one-third of the blood volume for a neonate (Table 110.1).[1]

CARDIAC[2–4]

There are many differences between the newborn and the mature heart that have important effects on function, particularly under stress. The newborn heart has a relatively small left ventricular muscle mass that must cope with the newly imposed demands of the systemic circulation. In response to increased afterload, the neonatal myocardium increases in mass by both hypertrophy and hyperplasia, with the capacity for the latter of these mechanisms being lost after the first 6 months of life. Neonatal cardiac myocytes appear small and blunted with a higher proportion of non-contractile elements than mature myocytes. The fewer myofibrils are poorly aligned and there are sparser, disorganised-looking mitochondria. Less efficient handling of calcium by the myocyte membrane and sarcoplasmic reticulum make the neonatal myocyte more dependent on extracellular fluid calcium concentration, which may contribute to limited cardiac reserve.

The physiological consequence is a stiffer, less compliant ventricle that is less able to generate contractile force. Physiological changes at birth (see later) increase both volume and pressure load to the left ventricle. The ability of the ventricle to increase output in response to further volume or pressure loading is limited. The neonatal heart functions at a high state of beta-adrenergic stimulation and therefore has a restricted capacity to increase contractility and rate. Following birth there is a steady increase in stroke volume index and cardiac index over the first 3 years of life.

VASCULAR[5]

Antenatal pulmonary blood flow is low (<10% of combined ventricular output) through a relatively muscularised high-resistance circulation. Blood ejected by the right ventricle is mostly diverted through the ductus arteriosus to the systemic circulation. Pulmonary vascular resistance (PVR) falls abruptly at birth with a concomitant increase in pulmonary blood flow. The PVR then falls more slowly, reaching adult levels over the next 6 weeks as a result of pulmonary vascular remodelling. The increase in pulmonary blood flow immediately following birth results in increased preload to the left ventricle. With clamping of the umbilical cord, the low resistance placental circulation is removed and the systemic vascular resistance rises acutely, causing an increase in systemic arterial pressure. Following the transition from foetal to neonatal circulation, the systemic vascular resistance index remains relatively constant throughout early childhood.[6]

MICROCIRCULATION

There are animal and human data to support the notion of maturation of the microcirculation.[7,8] The infant and young child's microcirculation is leakier at baseline and functions at a higher turnover of fluid and protein than the adult. This state of higher turnover may predispose the child to greater capillary leak in response to inflammatory and traumatic stimuli resulting in hypovolaemic shock.

IMMUNITY AND THE INFLAMMATORY RESPONSE[9,10]

The newborn has had little prior exposure to pathogens and has limited capacity to respond to infection,

ABSTRACT

Distinctive maturational changes in body composition, cardiovascular function, immunity and the inflammatory response throughout childhood influence the susceptibility to and consequences of shock in children. Children with unrecognised and untreated shock will decompensate rapidly. Septic shock remains an important cause of paediatric mortality, even in the developed world. Children with septic shock are more likely to present with cold shock and myocardial dysfunction than vasodilated, warm shock, necessitating a different treatment approach.

Heart failure in children can be due to primary or secondary myocardial dysfunction or the consequences of congenital heart disease. Congenital heart disease is increasingly prevalent and it is important for all critical care practitioners to develop an approach to diagnosis and initial treatment of common presentations and complications.

KEYWORDS

Paediatric
intensive care
shock
sepsis
congenital heart disease
cardiac disease

Table 110.1 Body fluid compartments during childhood (mL/kg)

AGE	TOTAL BODY WATER	EXTRACELLULAR FLUID	INTRACELLULAR FLUID	BLOOD
Pre-term newborn	800	550	300	95
Birth	750	450	300	85
1 year	700	350	350	80
5 years	650	250	400	75
Adult	600	200	400	70

Friis-Hansen B. Body water compartments in children: changes during growth and related changes in body composition. *Pediatrics*. 1961;28(2): 169–181.

so is at increased risk of invasive infection. This risk persists beyond the newborn period as the immune system remains immature through infancy and early childhood, with deficits in both innate and adaptive immunity. In addition to immature barriers to infection, infants have lower levels of circulating complement components and defective natural killer cell function. A mature pattern of cytokine and chemokine production is not attained until later in childhood. B cells are geared towards producing immunoglobulin (Ig)M rather than IgG or IgA, and there are multiple distinct deficiencies in T-cell function. The inflammatory response to sepsis also appears to undergo complex developmental changes, the implications of which are hard to define. Aspects of the pro- and anti-inflammatory response are qualitatively and quantitatively different in children compared to adults, including a relative exaggeration of the anti-inflammatory response.

Like adults, children are placed at risk of infection by therapeutic immunosuppression, but there are also a large number of congenital diseases that are characterised by generalised or specific defects in immune function.

RECOGNITION OF SHOCK

Recognition of early shock is very important as children compensate well initially, but their capacity to do so is rapidly exhausted and decompensation can then be sudden; during the early stages of compensated shock in infants, signs may be limited to tachycardia and tachypnoea (Table 110.2). Hypotension is a late finding and demands urgent attention.

INITIAL ASSESSMENT AND INVESTIGATION

HISTORY

- Fever, feeding, urine output, diarrhoea, vomiting
- Rapid breathing, sweating, tiring while feeding
- Irritability, lethargy
- Trauma

Table 110.2 Ninety-five percent ranges for heart rate, blood pressure and respiratory rate in childhood[11–13]

AGE	HEART RATE (BEATS PER MINUTE)	MEAN BLOOD PRESSURE (mm Hg)	RESPIRATORY RATE (BREATHS PER MINUTE)
Birth	95–145	40–60	29–65
6 months	110–175	50–90	22–58
1 year	105–170	50–100	22–50
4 years	80–140	50–100	20–26
7 years	70–120	60–90	17–24
14 years	60–100	65–95	12–20

- Potential for trauma in infants
- Potential for ingestion
- Vaccination history.

EXAMINATION

- Temperature
- Conscious level
- Peripheral perfusion, capillary refill
- Rash
- Skin turgor
- Mucous membranes
- Pulses
- Heart rate, rhythm
- Blood pressure
- Respiratory rate.

INITIAL INVESTIGATIONS

- Chest X-ray
- Arterial blood gas, lactate
- Full blood count and film examination
- Blood glucose
- Plasma electrolytes, urea, creatinine, liver function tests.

If there is evidence of sepsis or if there is no obvious cause for shock, take cultures and start antibiotic therapy (Table 110.3).

Table 110.3 Suggested initial antibiotic treatment of septic shock in children

FIRST FEW DAYS OF LIFE	
Benzylpenicillin	60 mg/kg 12-hourly
Gentamicin	5 mg/kg 36-hourly
BEYOND FIRST FEW DAYS OF LIFE	
Flucloxacillin	50 mg/kg 6-hourly
Cefotaxime	50 mg/kg 6-hourly
Gentamicin	6 mg/kg 24-hourly
IF HOSPITAL ACQUIRED, REPLACE FLUCLOXACILLIN WITH	
Vancomycin	25 mg/kg load then 15–20 mg/kg 8-hourly

- Blood cultures – peripheral blood and from any lines already in place
- Urine cultures (suprapubic aspirate or in–out urinary catheter in young infants)
- Throat swab
- Urine, stool and nasopharyngeal aspirate for virology
- Do not do a lumbar puncture in a shocked child. Commence antibiotics following other cultures. Cerebrospinal fluid for bacterial and viral culture and polymerase chain reaction can be obtained later.

TYPES OF SHOCK

The traditional classification of shock (Chapter 15) is valid in children, but a combination of these is likely to be present in any given clinical situation. In particular, it is best to think of septic shock as a clinical entity that incorporates features of several shock types.

HYPOVOLAEMIC SHOCK

This is a common presentation in childhood, which is particularly secondary to water and electrolyte losses with diarrhoea and vomiting.

The initial compensatory response to hypovolaemia is an increase in catecholamine secretion, leading to poor peripheral perfusion, tachycardia and a normal blood pressure with diminished pulse pressure. Lethargy and tachypnoea secondary to increasing metabolic acidosis are variably present. Up to 15%–20% of the circulating blood volume may be lost before hypotension occurs. With further volume loss, end-organ perfusion and oxygen delivery are compromised leading to worsening acidosis, coma, oligo/anuria and ultimately myocardial dysfunction.

The cause of hypovolaemia is usually evident from the history and examination, but hidden blood loss must be considered, particularly in infants where unreported head or abdominal trauma may have occurred with few external signs.

TREATMENT

Ensure adequate airway protection and breathing and administer oxygen. After establishment of intravenous (or intraosseous) access, early and aggressive intravenous fluid resuscitation is vital to restore the circulating blood volume. Give fluid (10–20 mL/kg 0.9% NaCl) rapidly with frequent clinical reassessment to verify signs of reversal of shock. Give blood if shock is due to ongoing blood loss.

CARDIOGENIC SHOCK

See section on Cardiac Disease.

DISTRIBUTIVE SHOCK

CAUSES

These include anaphylaxis, spinal cord injury or administration of vasodilators. Septic shock in children may have a distributive component, but this is not as common a finding as in adults (see below).

PRESENTATION

In distributive shock, tissue perfusion is inadequate despite an initially normal circulating blood volume and normal (or high) cardiac output. Abnormal vasomotor tone with profound vasodilatation leads to a reflex tachycardia (in spinal cord injury absence of sympathetic activity may result in bradycardia). Examination reveals warm peripheries, tachycardia and hypotension with a wide pulse pressure. The cause of distributive shock is likely to be clear from clinical examination.

TREATMENT

Attend to airway and breathing, obtain intravenous access and give rapid fluid boluses (20 mL/kg 0.9% NaCl). If there is inadequate reversal of shock then vasopressors may be necessary to restore blood pressure (or counteract the effects of vasodilator drugs).

Anaphylaxis must be treated specifically and urgently. Table 110.4 shows paediatric epinephrine (adrenaline) doses.

OBSTRUCTIVE SHOCK

CAUSES

These include pericardial tamponade, tension pneumothorax, pulmonary embolus and mediastinal mass.

PRESENTATION

In obstructive shock, extracardiac restriction of cardiac output prevents adequate oxygen delivery. There may be obstruction to the pulmonary or systemic outflow

Table 110.4 Paediatric cardiac drug doses

DRUG	DOSE
Adenosine	0.1 mg/kg (max 3 mg); increase by 0.1 mg/kg/dose to 0.3 mg/kg (max 12 mg)
Alprostadil (PGE_1)	10–50 ng/kg/min
Amiodarone	25 µg/kg/min for 4 h, then 5–15 µg/kg/min
Atropine	0.02 mg/kg (max 0.6 mg)
Bicarbonate (10% $NaHCO_3$)	1–2 mL/kg
Digoxin	15 µg/kg, then 5 µg/kg after 4 h, then 3–5 µg/kg 12-hourly
Dobutamine	2–10 µg/kg/min
Epinephrine	
Bolus	10 µg/kg (0.1 mL/kg 1:10,000)
Infusion	0.05–0.5 µg/kg/min
Anaphylaxis	10 µg/kg (0.01 mL/kg 1:1000) by deep intramuscular injection
Esmolol	500 µg/kg over 1 min, then 25–250 µg/kg/min
Isoproterenol	0.05–0.5 µg/kg/min
Levosimendan	12.5 µg/kg over 10 min, then 0.2 µg/kg/min for 24 h
Metaraminol	
Bolus	0.01 mg/kg
Infusion	0.05–0.5 µg/kg/min
Metoprolol	0.1 mg/kg over 5 min (max 5 mg)
Midazolam	
Bolus	0.1 mg/kg
Infusion	1–4 µg/kg/min
Milrinone	0.25–0.75 µg/kg/min
Morphine	
Bolus	0.1 mg/kg
Infusion	10–60 µg/kg/h
Nitric oxide (inhaled)	10–20 parts per million
Norepinephrine	0.05–0.5 µg/kg/min
Sodium nitroprusside	0.5–3 µg/kg/min
Vasopressin	0.0005–0.002 U/kg/min

PGE_1, Prostaglandin E_1.

Walsh EP. Clinical approach to diagnosis and acute management of tachycardias in children. In: Walsh EP, Saul PJ, Triedman JK, eds. *Cardiac Arrhythmias in Children and Young Adults with Congenital Heart Disease*. Philadelphia, PA: Lippincott, Williams & Wilkins; 2001:95–113.

tract or circulation, or compression by pericardial tamponade or tension pneumothorax.

TREATMENT

Treatment is aimed at ensuring adequate circulating volume and identifying and remedying the cause of the obstruction. Tamponade and tension pneumothorax require urgent drainage.

SEPTIC SHOCK[14–17]

In Australia and New Zealand, septic shock accounts for 2.1% of paediatric admissions to the intensive care unit (ICU) and has a mortality of 17%. The clinical presentation of septic shock in young children is different to adults, who reliably present with peripheral vasodilation, hypotension and a relatively high cardiac output ('warm shock'). The picture in children is usually dominated by myocardial suppression and peripheral vasoconstriction ('cold shock'). Hypovolaemia occurs rapidly due to capillary leak secondary to the sepsis-induced inflammatory response. Septic shock in children may be difficult to distinguish from cardiogenic shock or hypovolaemic shock. Neonatal sepsis often presents with features of persistent pulmonary hypertension, with right heart failure and a degree of cyanosis depending on patency of the ductus arteriosus and foramen ovale.

TREATMENT[16,17]

Despite the concerns raised by the findings of the Mortality after Fluid Bolus in African Children with Severe Infection (FEAST) trial,[18] current guidelines for the treatment of septic shock in the developed world continue to emphasise the importance of prompt and aggressive fluid resuscitation, along with the early institution of inotropic therapy. Both of the consensus guidelines cited here are currently undergoing revision.

Airway

Administer supplemental oxygen to all children with shock. Intubate patients who are unable to protect their airway or have impending respiratory failure.

Circulation and access

If peripheral access is difficult and the child is obtunded or severely shocked, consider intraosseous access early. Give fluid boluses (10 mL/kg) to restore circulating blood volume. Children with septic shock often require large amounts of fluid resuscitation – occasionally more than 100 mL/kg. In patients who do not have reversal of signs following 60 mL/kg of fluid, gain central venous access. This allows measurement of central venous pressure, administration of inotropes or vasoconstrictors and measurement of central venous saturation (see below). Insert an arterial line for frequent sampling and invasive monitoring of blood pressure.

Echocardiography is an important means of guiding inotrope and vasopressor management, allowing

assessment of cardiac filling, contractility and PVR. Invasive measurement of cardiac output is rarely performed in children; pulmonary artery catheter insertion is technically difficult and although several non-invasive methods are available to estimate cardiac output in children none are widely used.

Inotrope/vasodilator/vasoconstrictor therapy (see Table 110.4 for drug doses)

Do not delay starting vasoactive drugs if there is difficulty gaining central venous access. Dilute infusions of inotropes and vasoconstrictors may be administered through a peripheral line, with care taken to avoid and check for extravasation.

Decreased contractility on echo or clinical suspicion

Dobutamine is a useful first-line inotrope in children and is relatively safe to administer through a peripheral intravenous line. Although dopamine is still widely used, it inhibits anterior pituitary release of thyrotropin, growth hormone and prolactin[19] and may be relatively ineffective in young infants. Epinephrine should be started as a second-line drug if cardiac function remains inadequate despite dobutamine.

Hypotension and warm peripheries

A vasoconstrictor may be used alone if myocardial function is adequate or is added to an inotrope if contractility is poor. Norepinephrine is the drug of choice, but an inadequate response to it may be due to the down-regulation of catecholamine receptor numbers or function. Apparent norepinephrine resistance warrants a trial of vasopressin; however, a randomised controlled trial in paediatric shock failed to demonstrate any outcome benefit with vasopressin treatment (and showed a trend towards increased mortality).[20]

Hypotension and cool peripheries

Treat decreased contractility as above. As discussed earlier, peripheral vasoconstriction is a compensatory mechanism to maintain adequate perfusion pressure. Do not add a vasodilator to an already hypotensive patient. A vasoconstrictor may be needed in addition to an inotrope if hypotension persists.

Normotension and cool peripheries

If blood pressure is normal or high, addition of a vasodilator may reduce afterload and improve cardiac output. Sodium nitroprusside (SNP) has a short half-life and can be discontinued rapidly if the blood pressure falls. In addition to being a powerful vasodilator, milrinone has inotropic effects, but should be used with care because of its relatively long half-life.

Pulmonary hypertension

If there is evidence of pulmonary hypertension during shock start an inotrope (dobutamine or epinephrine) to support the right ventricle. Intubate (if not already done), ventilate using a high Fi_{O_2} to a normal $PaCO_2$ and correct acidosis. Inhaled nitric oxide should be added to reduce PVR.

Antibiotics

Early and appropriate antibiotic therapy is associated with improved survival and morbidity.[21] Administer antibiotics to patients in whom the cause of shock is not immediately apparent. After appropriate cultures, selection of antimicrobials is guided by the clinical picture, including any available results from prior cultures. In the absence of specific information, a suggested first-line treatment schedule is shown in Table 110.3, but consideration must be given to local antibiotic stewardship and prescription practices, and resistant organism prevalence. A search for the source or site of infection should be undertaken and it may be necessary to drain collections or remove infected tissue.

Blood transfusion

Transfusion of packed red cells to replace blood loss is essential. In a patient with ongoing evidence of inadequate oxygen delivery current guidelines recommend transfusion to maintain a haemoglobin of >10 g/L, particularly in septic shock.[16,17]

Corticosteroids

Give hydrocortisone to shocked patients who are at risk of absolute adrenal insufficiency (recent or ongoing treatment with corticosteroids, known hypothalamic/pituitary/adrenal disease or purpura fulminans). There is no good evidence to support the routine administration of corticosteroids in paediatric septic shock. Current adult guidelines suggest the use of hydrocortisone in fluid and inotrope resistant septic shock.[17] However, there are limited and conflicting data in children, and corticosteroid use remains controversial.[22,23]

Intravenous immunoglobulin

Intravenous pooled immunoglobulin (IVIG) has been used in both children and adults with septic shock, but there is no high quality evidence for an effect on mortality.[24] IVIG has the potential to neutralise superantigens in toxic shock syndrome and its use is often suggested or recommended in this setting, but again clear evidence regarding clinical efficacy is lacking.[25] Anticytokine and antiendotoxin monoclonal immunoglobulin therapies remain experimental.

Extracorporeal membrane oxygenation

Current guidelines recommend extracorporeal membrane oxygenation (ECMO) for refractory septic shock or for respiratory failure in acute respiratory distress syndrome associated with sepsis.[16,17] There is emerging

evidence that central veno-arterial ECMO cannulation via sternotomy is superior to peripheral or neck cannulation in refractory paediatric septic shock, allowing insertion of larger cannulae and consequently higher ECMO flows.[26]

Insulin

Hyperglycaemia is common in shock and may be exacerbated by epinephrine and corticosteroid treatment. Treat sustained hyperglycaemia with insulin infusion, but critically ill children are relatively sensitive to insulin[27] and have limited metabolic reserve, increasing the risk of hypoglycaemia. Tight glycaemic control in critically ill children does not confer any mortality or morbidity benefit and increases the incidence of severe hypoglycaemia.[28]

GOALS OF TREATMENT

The goals of treatment are to reverse the shock state and ensure ongoing adequate tissue oxygen delivery. Frequent clinical reassessment is aided by laboratory investigations including:

- *heart rate:* normal for age (see Table 110.2)
- *blood pressure:* normal for age (see Table 110.2)
- *central venous pressure:* 10–12 mm Hg (1.33–1.96 kPa)
- *central capillary refill:* <3 seconds
- *mental state:* normal
- *urine output:* >0.5 mL/kg/h
- *serum lactate:* <2.0 mmol/L
- *central venous saturation:* >70%.

Plasma lactate concentrations are indicative of inadequate tissue oxygenation and therefore a useful marker of shock. Hyperlactaemia can also be due to dead gut, liver dysfunction or epinephrine infusion.[29]

Measurement of central venous saturation (Scv_{O_2}) can be used to assess adequacy of oxygen delivery in the absence of a pulmonary artery catheter.[30] A sample taken from the superior vena cava (SVC) or SVC/RA (right atrium) junction is best; sampling from within the RA may be polluted by poorly saturated blood from the coronary sinus or by interatrial shunting. Although goal-directed treatment of septic shock in children with a target Scv_{O_2} >70% was associated with improved survival in one single-centre study,[31] the clear lack of demonstrable benefit from early goal-directed therapy in adult septic shock[32,33] demands a more cautious approach to rigorous pursuit of such targets. In children with structural heart disease and intracardiac mixing, an $Sa_{O_2} - Scv_{O_2}$ difference of ≤30% is roughly equivalent to an Scv_{O_2} >70% in a conventional circulation.

CARDIAC DISEASE

Appropriate drug doses for this section are given in Table 110.4.

Box 110.1 Causes of cardiogenic shock

- Primary cardiac disease
  - Congenital heart disease
  - Post cardiac surgery
  - Cardiac trauma
  - Myocarditis
  - Cardiomyopathy
  - Arrhythmias and conduction defects
  - Endocarditis
- Local disease with cardiac effects
  - Constrictive pericarditis
  - Pericardial tamponade
  - Compression of heart by tumour, tension pneumothorax
- Systemic disease with cardiac effects
  - Sepsis
  - Hypoxic ischaemic injury
  - Autoimmune disease
  - Kawasaki disease
  - Drug ingestion

CARDIOGENIC SHOCK

Cardiogenic shock can be difficult to distinguish from septic shock. Causes of cardiogenic shock are listed in Box 110.1.

Patients present with tachycardia, low pulse volume and poor peripheral perfusion as vasoconstriction maintains blood pressure in the initial stages. Tachypnoea, obtundation and decreased urine output are present early. Examination may reveal a gallop rhythm, hepatomegaly, sweating and peripheral oedema. The presence or absence of a cardiac murmur is unlikely to be helpful in acute diagnosis. Ongoing shock leads to progressive hypoperfusion of end organs.

INVESTIGATION

Initial investigations include chest X-ray, electrocardiogram (ECG) and echocardiogram, with further tests prompted by individual findings. Take blood cultures and start antibiotics if there is no known cause for cardiogenic shock.

TREATMENT

Treat as described for septic shock in the preceding section (see Table 110.4).

Consider ECMO early if the patient is deteriorating or unresponsive to therapy.

CARDIAC FAILURE[34,35]

Children with heart failure are a diverse group of patients with a heterogeneous group of diseases leading to worsening heart function. Cardiac failure can be due to primary or secondary myocardial

Table 110.5 Causes of heart failure in children

CAUSE	EXAMPLES
BIRTH–2 WEEKS	
Sepsis	Neonatal sepsis, group B *Streptococcus*
Hypoxic ischaemic injury	Birth asphyxia
SVT	Congenital/neonatal
Congenital heart block	Isolated or with structural heart disease
Arteriovenous malformations	Vein of Galen malformation
Duct-dependent systemic circulation	Aortic coarctation or stenosis, HLHS
Persistent pulmonary hypertension of newborn	Secondary to sepsis, hypoxic ischaemic injury, etc.
Anaemia	Twin-to-twin transfusion, Rhesus incompatibility
Cardiomyopathy	Infant of diabetic mother, congenital
Neonatal myocarditis	Enterovirus
Cardiac tumour	Rhabdomyoma
2 WEEKS–6 MONTHS	
Large volume left to right shunt lesions	VSD, AVSD, truncus arteriosus, AP window
Cardiomyopathy, myocarditis	
Coronary lesion	ALCAPA
Metabolic	Hypothyroidism
LATER CHILDHOOD	
Unrepaired congenital heart disease	
Left ventricular failure	Left to right shunt lesions Aortic or mitral valve disease
Right ventricular failure	Pulmonary or tricuspid valve disease Pulmonary hypertension
Systemic right ventricular failure	Congenitally corrected transposition
Operated congenital heart disease	
Left ventricular failure	Residual aortic or mitral valve disease Subaortic stenosis
Right ventricular failure	Pulmonary valve disease (repaired TOF) Pulmonary hypertension
Systemic right ventricular failure	Post Senning or Mustard
Single ventricular failure	Post aortopulmonary shunt, Glenn or Fontan
Arrhythmia	Post Fontan, Senning, Mustard
Cardiomyopathy, myocarditis	
Acquired cardiac disease	Rheumatic heart disease, endocarditis, Marfan syndrome, cor pulmonale
Transplant rejection	

ALCAPA, Anomalous origin of left coronary artery from pulmonary artery; *AP*, aorto-pulmonary; *AVSD*, atrioventricular septal defect; *HLHS*, hypoplastic left heart syndrome; *SVT*, supraventricular tachycardia; *TOF*, tetralogy of Fallot; *VSD*, ventricular septal defect.

disease, or the effects of congenital heart disease or its treatment (Table 110.5).

INVESTIGATIONS

- Chest X-ray
- ECG
- Echocardiogram
- Further imaging with computed tomography, magnetic resonance imaging and cardiac catheter may be warranted
- Blood gas
- Electrolytes, renal and liver function
- Coagulation
- B-type natriuretic peptide, troponin I

- Viral cultures – urine, stool and nasopharyngeal aspirate
- Serum amino acids
- Urine amino and organic acids
- Serum carnitine.

TREATMENT

Treat any identified underlying cause for heart failure (sepsis, correctable congenital heart disease, arrhythmias, anaemia). Further treatment is in the following sections on cardiomyopathy, congenital heart disease and disorders of cardiac rhythm.

CARDIOMYOPATHY[36]

Primary cardiomyopathy is rare in childhood (1.13–1.24 per 100,000 children per year) with the highest incidence in the first year of life. With increasingly sophisticated diagnostic approaches, the cause of cardiomyopathy can be identified in most cases.[37] Dilated and hypertrophic cardiomyopathies account for the majority (~80%) of cases, and there is considerable phenotypic overlap between the different types of cardiomyopathy. The 5-year mortality or transplant rate for children with dilated cardiomyopathy is 46%, with younger children and those who are sickest at presentation being at highest risk.

The clinical presentation is usually one of congestive cardiac failure. Infants present with poor feeding and failure to thrive, along with tachycardia, tachypnoea and sweating. There may be a hyperdynamic precordium and a gallop rhythm. In older children a careful history will often elicit decreased physical activity in comparison to their peers for many months. The clinical presentation becomes more like that seen in adults, with hepatomegaly, ascites, oedema and poor peripheral perfusion.

TREATMENT (SEE Table 110.4 FOR DRUG DOSES)[38]

Compared to adult heart failure, there are relatively few data on which to base treatment of heart failure in children. However, recent consensus guidelines have been published, providing guidance on management whilst acknowledging the weak evidence base. Mainstays of chronic treatment are diuretic therapy and angiotensin converting enzyme (ACE) inhibitors, or beta blockers. The sicker child in the ICU with acute or acute on chronic heart failure will require further measures.

Oxygen

Treat decompensated heart failure with facemask oxygen.

Ventilation

Intubation and positive-pressure ventilation improve gas exchange and reduce the work of breathing. Although positive pressure probably has no direct effect on left ventricular contractility, it improves output by reducing left ventricular afterload.[39] High pressures may impair cardiac output by reducing preload and increasing afterload to the right ventricle.

Afterload reduction

Vasodilator therapy is useful as long as an adequate blood pressure can be maintained. SNP is a potent pure vasodilator. Milrinone has the additional advantage of some inotropic and lusitropic effects.

Inotropes

Dobutamine or milrinone (if vasodilatation is tolerated) can be used as first-line agents. Despite limited data in children, levosimendan is being used increasingly in paediatric heart failure. It appears capable of increasing cardiac output at minimal metabolic cost and is a potent vasodilator.

Blood transfusion

Correct anaemia. Transfuse packed red blood cells to maintain Hb >10 g/dL.

Cardiac resynchronisation therapy[40]

Cardiac resynchronisation therapy (CRT) has been shown to be very effective in the treatment of subpopulations of adults with heart failure. Patient selection and systematic assessment is made difficult in children by the heterogeneous nature of heart failure in this age group and the relatively low prevalence of the underlying diseases. In addition, there are important technical considerations related to size. Nonetheless, CRT has been successfully applied in paediatric heart failure, with a relatively low rate of non-responders, and work continues to identify appropriate selection criteria.

Mechanical support[41–43]

Veno-arterial ECMO (see Chapter 41) or centrifugal ventricular assist device (VAD) can provide excellent short-term mechanical support, but are unsuitable for the longer periods necessary for bridging to transplantation. There are very few durable VADs available for such support of the smaller child. The Excor Paediatric VAD ('Berlin Heart') is the most widely used of these, with a range of ventricular chambers down to 10 mL. Successful support to transplantation or recovery can be achieved in 70%–90% of cases, but there is a high risk of infective, bleeding and thrombotic complications. Larger (>30 kg) children can be supported with smaller continuous flow implantable devices designed for adults, which may carry less risk of complications. Development of miniaturised versions of these devices for children is ongoing, but as yet none is ready for clinical use.

AN APPROACH TO CONGENITAL HEART DISEASE

An in-depth discussion of congenital heart disease and its management is beyond the scope of this chapter.

What follows is an overview of situations in which the intensivist or emergency physician may encounter congenital heart disease, based loosely on age and mode of presentation.

NEWBORN WITH CYANOSIS[43,44]

Most cyanosed newborns have respiratory disease and this needs to be treated appropriately. Cyanosis in the absence of respiratory distress is likely to be due to congenital heart disease. Cyanotic heart disease is likely if the Pa_{O_2} does not rise to 150 mm Hg (≈20 kPa) after the baby has been breathing 100% oxygen for 10 minutes. The presence or absence of a murmur is not particularly helpful; many children with cyanotic heart disease do not have a murmur and murmurs can be heard in many newborn infants. There may be diagnostic clues on examination and chest X-ray, but all such infants need an urgent echocardiogram for definitive diagnosis.

SEVERE CYANOSIS (Sa_{O_2} <70%) (SEE Table 110.4 FOR DRUG DOSES)

Table 110.6 shows the features of congenital heart lesions presenting with severe cyanosis at birth. These infants must be treated urgently.

1. Intubate and ventilate to reduce oxygen consumption and treat any respiratory disease. Use a high Fi_{O_2} and avoid high pressures that might increase PVR.
2. Start alprostadil (prostaglandin E_1, Prostin) to keep the ductus arteriosus open. There is a risk of exacerbating pulmonary oedema in obstructed total anomalous pulmonary venous drainage, but unless this diagnosis has been made with certainty the ductus should be kept open.
3. Correct metabolic acidosis.
4. Use an inotrope if there is evidence of heart failure (see above).
5. Inhaled nitric oxide may be helpful in persistent pulmonary hypertension of the newborn and severe Ebstein anomaly.
6. Refer for advice and urgent transport to a specialist paediatric cardiac centre. Persistent severe cyanosis may require ECMO support prior to definitive treatment.

LESS SEVERE CYANOSIS (<90%)

Less profound cyanosis is seen in neonates with transposition of the great arteries (TGA) and adequate mixing, milder forms of pulmonary stenosis (including tetralogy of Fallot) and Ebstein anomaly. There is a degree of cyanosis associated with all defects where there is mixing of pulmonary and systemic venous blood (e.g. unobstructed anomalous pulmonary venous drainage, single ventricle lesions). These infants are less sick and desaturation may be relatively difficult to detect without pulse oximetry. All such children require careful assessment and prompt referral to a paediatric cardiac centre.

Table 110.6 Differential diagnosis of severe cyanosis in the newborn

LESION	PATHOPHYSIOLOGY	CHEST X-RAY	MANAGEMENT
Transposition of great arteries	Pulmonary and systemic circulations in parallel, without mixing	Normal cardiac size Narrow pedicle ('egg on side' appearance) Normal/increased pulmonary vascularity	Alprostadil Balloon atrial septostomy
Pulmonary atresia/critical pulmonary stenosis	No forward flow from right ventricle Intracardiac right to left shunting Pulmonary blood flow via ductus arteriosus	Normal cardiac size Absent pulmonary artery silhouette Reduced pulmonary vascularity	Alprostadil Will need surgery or catheter procedure
Neonatal Ebstein anomaly	Severe tricuspid regurgitation Intracardiac right to left shunting +/– pulmonary valve disease	Massive atrial enlargement Lung fields difficult to see	Alprostadil Inhaled nitric oxide May need surgical procedure
Obstructed TAPVD	Severe pulmonary venous obstruction Pulmonary oedema	Normal cardiac size Diffuse pulmonary interstitial oedema	Cardiac surgical emergency
Persistent pulmonary hypertension of the newborn	High PVR Right heart failure Right to left shunting through ductus arteriosus	Normal cardiac size and silhouette Reduced pulmonary vascularity	Alprostadil Inhaled nitric oxide Inotropes Look for and treat underlying cause

PVR, Pulmonary vascular resistance; *TAPVD*, total anomalous pulmonary venous drainage.

NEWBORN WITH CARDIAC FAILURE

In lesions that cause obstruction to the left side of the heart (aortic stenosis, coarctation, hypoplastic left heart syndrome) systemic blood flow is provided by the right ventricle through the ductus arteriosus. Patients may not present until the ductus arteriosus begins to close when systemic blood flow diminishes and the left ventricle fails in the face of greatly increased afterload. There is a rapidly deteriorating clinical picture of pallor, cold peripheries and barely palpable pulses. Tachycardia and tachypnoea are universal and there is progressive hepatomegaly, cardiomegaly and pulmonary oedema. This is accompanied by profound metabolic acidosis and oliguria.

Other conditions presenting with cardiovascular collapse in the first 2 weeks of life are sepsis, inborn errors of metabolism, myocarditis/cardiomyopathy and sustained tachyarrhythmia. These can be difficult to differentiate initially and all neonates presenting in this fashion should be treated with appropriate antibiotics (see Table 110.3) until a definitive diagnosis is made.

TREATMENT (SEE Table 110.4 FOR DRUG DOSES)

1. Intubate and ventilate with resuscitation drugs to hand.
2. Sedate and ventilate to reduce oxygen consumption.
3. Start inotropes – dobutamine or epinephrine depending on severity of cardiac dysfunction.
4. Start alprostadil – a high dose (50–100 ng/kg/min) may be needed to reopen the ductus arteriosus.
5. Refer for advice and urgent transport to a paediatric cardiac centre.

INVESTIGATIONS

- Chest X-ray
- Echocardiogram
- ECG
- Arterial blood gas, electrolytes, renal and hepatic function
- Full blood count and film examination
- Coagulation
- Blood cultures
- Serum amino acids
- Urinary amino and organic acids.

CYANOSIS BEYOND THE NEWBORN PERIOD

Infants and young children with unoperated tetralogy of Fallot may present with episodic profound cyanosis associated with crying and agitation. These 'tet spells' are mostly due to dynamic obstruction of the right ventricular outflow tract with consequent right to left shunting through the ventricular septal defect (VSD). Administration of oxygen and bringing the child's knees up tight to the chest will often terminate the spell (presumably by increasing systemic vascular resistance). Volume expansion may be helpful. If there is persisting cyanosis try sedation with morphine. In very resistant spells either a beta blocker (esmolol) or a peripheral vasoconstrictor (metaraminol) can be used. Inotropes and vasodilators will worsen the cyanosis.

Children with unrepaired or undiagnosed atrial or VSDs (or residual defects following repair) may become cyanosed under conditions of increased PVR, for example during acute respiratory illness. Cyanosis due to progressive pulmonary vascular disease with unrepaired long-standing left to right shunt (Eisenmenger's complex) is increasingly rare.

Certain operations for congenital heart disease leave patients with obligatory intracardiac mixing, producing cyanosis. Pulse oximetry readings in these patients will usually be in the range of 70%–85% (parents will know their child's usual saturations). These children often have pulmonary blood flow supplied via an aorto-pulmonary shunt (e.g. modified Blalock Taussig ['BT'] shunt or central shunt).

Two operations redirect systemic venous return directly to the pulmonary artery, bypassing the heart: the Glenn, or bidirectional cavopulmonary connection (SVC to pulmonary artery) and the Fontan (inferior vena cava and SVC to pulmonary artery). Patients with a Glenn remain cyanosed, whereas patients with a Fontan have variable desaturation. In both cases pulmonary blood flow is extremely sensitive to PVR. If these patients require mechanical ventilation it is important to use low pressures and low rates if possible as positive intrathoracic pressure will impair pulmonary blood flow.

EMERGENCIES AND IMPORTANT PRESENTATIONS

Dehydration

Dehydration is particularly dangerous in cyanosed patients. These patients often have a high haematocrit and further haemoconcentration places them at risk of thrombosis. Intravenous rehydration should be aggressively pursued in dehydrated children with cyanotic heart disease.

Profound desaturation

Acute profound desaturation in a patient with shunt-dependent pulmonary blood flow suggests the possibility of shunt blockage and is a life-threatening emergency. Give volume (10 mL/kg 0.9% NaCl) and repeat if necessary. Discuss urgently with a paediatric cardiac centre and consider giving heparin (100 U/kg).

Intercurrent respiratory illness

Respiratory tract infections are common in childhood and these have important effects on children with limited or shunt-dependent pulmonary blood flow (see above). Increased work of breathing and increased PVR will worsen cyanosis. Respiratory failure must be treated on its merits, but the nature of pulmonary

blood flow and the potential for increasing PVR must be borne in mind if mechanical ventilation is necessary.

HEART FAILURE BEYOND THE NEWBORN PERIOD[45]

Congenital-heart-disease-related heart failure beyond the newborn period may be due to the consequences of an unrepaired left to right shunt lesion. High pulmonary blood flow places a volume load on the left ventricle. Left ventricular enlargement and increased end-diastolic pressures ensue and the patient presents with tachycardia, tachypnoea, sweating, poor feeding and poor growth. There is often a gallop rhythm and a systolic murmur, and peripheral vasoconstriction leads to cool peripheries. These children respond well to diuretics and ACE inhibitors, but may need inotropes and positive-pressure ventilation at presentation. Worsening cardiac failure in the first few months of life is often due to the normal fall in haematocrit at this age and will respond to blood transfusion.[46] These children will need repair of the underlying lesion, but this is rarely urgent.

An important lesion to consider in the infant with previously undiagnosed disease is anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA). These children present with poor growth and episodic inconsolable crying in the first few months of life. There is cardiomegaly and evidence of antero-lateral infarction on ECG. Echo confirms markedly diminished ventricular function, ventricular dilation and mitral regurgitation. This lesion warrants rapid surgical repair.

Heart failure is an important problem in both children and adults with treated congenital heart disease. There are multiple potential causes for systolic or diastolic dysfunction in this population, such as residual shunts, valvular dysfunction, abnormal loading conditions, dysrhythmias and the consequences of previous surgeries. Ischaemic cardiomyopathy occurs rarely, but it can be seen following repair of coronary artery abnormalities or operations involving manipulation or reimplantation of the coronaries, most notably the arterial switch operation.[47]

EMERGENCIES AND IMPORTANT PRESENTATIONS

Intercurrent respiratory illness

Respiratory tract infections will cause an exacerbation of heart failure in children with congenital heart disease. Increased work of breathing and fever are poorly tolerated and often necessitate hospitalisation. This is most commonly seen in infants with unrepaired left to right shunt lesions and viral respiratory tract infections during the winter. It may be difficult to differentiate the effects of the respiratory disease from the heart failure, but initial attention to treatment of respiratory failure must be accompanied by careful assessment of the underlying disease.

DISORDERS OF CARDIAC RHYTHM[48,49] (SEE Table 110.4 FOR DRUG DOSES)

SINUS BRADYCARDIA

Sinus bradycardia (see Table 110.2) may appear more dramatic due to the frequent occurrence of sinus arrhythmia in children. Pathological causes of bradycardia include sinus node dysfunction, hypothermia, high intracranial pressure, cervical spinal cord injury, hypothyroidism, drug effects (beta blockers, digoxin, amiodarone, clonidine) and organophosphate poisoning. Sinus bradycardia very rarely needs treatment apart from addressing any underlying cause. Atropine or isoproterenol (isoprenaline) will increase the heart rate if necessary (Table 110.4).

SINUS NODE DYSFUNCTION

Sinus node dysfunction causes bradycardia, sinus pauses and alternating bradycardia/tachycardia. It is most common following operations for congenital heart disease, particularly those involving extensive atrial surgery, and can occur many years later. Sinus node dysfunction is rare in children with structurally normal hearts and is well tolerated in this group. Emergency treatment involves treatment of bradycardia, if symptomatic, and consideration for pacemaker insertion.

COMPLETE HEART BLOCK

Complete heart block is usually congenital in children, with more than 90% being due to the transplacental passage of maternal autoantibodies in autoimmune disease. In later childhood, complete heart block is most likely to be associated with recent cardiac surgery or complex forms of congenital heart disease (congenitally corrected TGA, left atrial isomerism), but may also occur with myocarditis, cardiomyopathy, cardiac transplant rejection and some muscular dystrophies.

MANAGEMENT

Atropine will increase the ventricular rate and an infusion of isoproterenol will maintain it pending establishment of temporary or permanent cardiac pacing.

Inotropes should be used in patients with poor ventricular function due to long-standing bradycardia or underlying myocardial disease.

Transvenous temporary pacing is difficult in small children and external cardiac pacing may be necessary as a resuscitative measure.

Asymptomatic patients may still require insertion of a pacemaker, depending on cause, ventricular escape rate and myocardial function.

Table 110.7 Age-related approximate electrocardiogram intervals (and upper limits of normal)[50]

	NEWBORN	6–12 MONTHS	5–8 YEARS	12–16 YEARS
PR interval (ms)	100 (120)	110 (140)	130 (160)	135 (180)
QRS duration (ms)	65 (85)	65 (85)	80 (100)	90 (110)
QTc interval (ms)	420 (450)	410 (450)	410 (445)	410 (450)

All intervals in milliseconds. QTc = corrected QT interval = QT$\sqrt{}$(heart rate/60).

FIRST-DEGREE HEART BLOCK

A prolonged PR interval (Table 110.7 for normal intervals in different age groups) can be seen in normal children during periods of increased vagal tone. Pathological causes of first-degree block include hypothermia, electrolyte abnormalities, acute rheumatic fever and any of the causes of complete heart block described above.

SECOND-DEGREE HEART BLOCK

Isolated Mobitz type I block (Wenckebach) is usually well tolerated. Mobitz type II is more likely to be symptomatic and require a pacemaker. Either form of second-degree atrioventricular (AV) block should be investigated for an underlying cause.

TACHYARRHYTHMIAS

Sinus tachycardia (see Table 110.2) is more common than tachyarrhythmia. Underlying causes (fever, pain or agitation, drugs) should be considered and treated.

SUPRAVENTRICULAR TACHYCARDIA (See Chapter 22)

Re-entrant supraventricular tachycardia (*SVT*) is common in childhood. Most cases occur in the first few months of life in the absence of congenital heart disease. However, structural heart disease should be ruled out in all cases.

The re-entry circuit usually involves the AV node and an accessory conduction pathway. These tachycardias are abrupt in onset and have a relatively fixed rate. In neonates and infants, the accessory pathway is discrete from the AV node and may conduct in either direction (accessory-pathway-mediated SVT). In older children and adults, the alternative conduction route is often within the AV node itself, with two limbs of the node conducting at different frequencies and with different refractory periods (AV node re-entrant tachycardia).

Diagnosis

The ECG shows a narrow complex (see Table 110.7) tachycardia at greater than 200 beats per minute. P-waves are often difficult to discern, but occur with a 1:1 ratio to the QRS complexes. P-waves are usually inverted, but morphology and position will depend on the nature of the re-entry circuit.

Treatment

If shocked give:

- oxygen by mask, and sedation (midazolam)
- synchronised cardioversion (1 J/kg).

If stable:

1. *Vagal stimulation:* apply ice water to entire face for less than 30 seconds, gag, tracheal suction or held inspiration if ventilated. Give carotid sinus massage in older children. Do not apply eyeball pressure.
2. *Adenosine rapid intravenous bolus and flush:* give as centrally as possible. If unresponsive increase the dose (see Table 110.4). Adenosine is painful and causes vasodilatation.
3. *Atrial or transoesophageal overdrive pacing:* may terminate the arrhythmia.
4. *If unsuccessful or the tachycardia reverts after successful termination:* consider amiodarone or digoxin.
5. Do *not* use digoxin or verapamil if there is pre-excitation on the ECG (they both may enhance anterograde conduction in the accessory pathway).
6. Do *not* use verapamil in infants (it can cause shock and cardiac arrest).
7. *Following conversion to sinus rhythm:* check ECG for evidence of pre-excitation and look for structural disease.

Automatic SVTs are caused by an ectopic rapidly firing focus within the atrium or AV conducting tissue. These are unusual in the absence of structural heart disease and are commonly seen following cardiac surgery. Typically there is variability of the ventricular rate.

Ectopic atrial tachycardia (EAT) has an abnormal P-wave axis on the ECG with normal conduction to ventricles. Junctional ectopic tachycardia (JET) arises at the AV node or high in the bundle of His. There is complete AV dissociation on the ECG, the ventricular rate being greater than the atrial rate.

Treatment is aimed at reducing automaticity with adequate sedation and analgesia, and avoiding catecholamines and other chronotropes. Keep serum potassium, calcium and magnesium in the high normal range. Whole-body cooling is useful. Amiodarone can be used in resistant postoperative JET.

Atrial fibrillation

Atrial fibrillation is rare in children and is usually associated with cardiomyopathy or previous atrial surgery.

Box 110.2 Causes of ventricular arrhythmias in children

- Congenital heart disease (repaired tetralogy of Fallot, aortic stenosis)
- Cardiomyopathy
- Myocarditis
- Ischaemia (coronary abnormalities, Kawasaki disease)
- Transplant rejection
- Electrolyte abnormalities (hypo/hyperkalaemia, hypocalcaemia)
- Drugs (tricyclic antidepressants)
- Cardiac channelopathies (long QT syndrome, Brugada syndrome)
- Cardiac tumours
- Commotio cordis

Atrial flutter

Atrial flutter is an atrial re-entrant tachycardia. It can occur in newborns in the absence of structural heart disease but is more common in older patients with congenital heart disease, particularly those who have had surgery involving extensive atrial manipulation. Atrial flutter rates in children are faster than adults (>400 per minute in newborns). Diagnosis may be evident from the sawtooth baseline pattern of the ECG, but this may not be revealed until adenosine is given, blocking AV conduction.

Treat shocked patients as described above for SVT.

In the stable patient, atrial or transoesophageal overdrive pacing may terminate the arrhythmia.

VENTRICULAR ARRHYTHMIAS

Isolated premature ventricular contractions are common in infants and children with normal hearts. Ventricular arrhythmias are very rare in children (most cases of paediatric cardiac arrest present with severe bradycardia or asystole). Documented ventricular fibrillation or ventricular tachycardia must prompt an exhaustive search for an underlying cause (Box 110.2).

Emergency treatment of ventricular arrhythmias is described in Chapter 115.

REFERENCES

1. Friis-Hansen B. Body water compartments in children: changes during growth and related changes in body composition. *Pediatrics*. 1961;28(2):169–181.
2. Penny DJ, Mynard J. The pressure–volume relationship in heart failure. In: Chang AC, Towbin JA, eds. *Heart Failure in Children and Young Adults*. Philadelphia: Saunders Elsevier; 2006:103–113.
3. Mahajan T, Chang AC. Heart failure in the neonate. In: Chang AC, Towbin JA, eds. *Heart Failure in Children and Young Adults*. Philadelphia: Saunders Elsevier; 2006:376–387.
4. Price JF. Unique aspects of heart failure in the neonate. In: Shaddy RE, ed. *Heart Failure in Congenital Heart Disease*. London: Springer; 2011:21–42.
5. Hooper SB, Te Pas AB, Lang J. Cardiovascular transition at birth: a physiological sequence. *Pediatr Res*. 2015;77(5):608–614.
6. Cattermole GNB, Leung PYM, Mak PSKB, et al. The normal ranges of cardiovascular parameters in children measured using the ultrasonic cardiac output monitor. *Crit Care Med*. 2010;38(9):1875–1881.
7. Brace RA, Christian JL. Transcapillary starling pressures in the fetus, newborn, adult, and pregnant adult. *Am J Physiol*. 1981;240(6):H843–H847.
8. Gamble J, Bethell D, Day NP, et al. Age-related changes in microvascular permeability: a significant factor in the susceptibility of children to shock? *Clin Sci*. 2000;98(2):211–216.
9. Simon AK, Hollander GA, McMichael A. Evolution of the immune system in human from infancy to old age. *Proc Biol Sci*. 2015;282(1821):doi:10.1098/rspb.2014.3085. Available from: http://rspb.royalsocietypublishing.org/content/282/1821/20143085.
10. Wynn J, Cornell TT, Wong HR, et al. The host response to sepsis and developmental impact. *Pediatrics*. 2010;125(5):1031–1041.
11. Shann F. *Drug Doses*. 17th ed. Melbourne: Collective Pty; 2017.
12. Rusconi F, Castagneto M, Porta N, et al. Reference values for respiratory rate in the first 3 years of life. *Pediatrics*. 1994;94(3):350–355.
13. Wallis LA, Healy M, Undy MB, et al. Age related reference ranges for respiration rate and heart rate from 4 to 16 years. *Arch Dis Child*. 2005;90(11):1117–1121.
14. Aneja R, Carcillo JA. Differences between adult and pediatric septic shock. *Minerva Anestesiol*. 2011;77(10):986–992.
15. Schlapbach L, MacLaren G, Festa M, et al. Prediction of pediatric sepsis mortality within one hour of admission. *Intensive Care Med*. 2017;43(8):1085–1096. doi:10.1007/s00134-017-4701-8. Available from: http://link.springer.com/article/10.1007%2Fs00134-017-4701-8.
16. Brierley J, Carcillo JA, Choong K, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med*. 2009;37(2):666–688.
17. Dellinger R, Levy M, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41(2):580–637.
18. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med*. 2011;364:2483–2495.
19. Van den Berghe G, de Zegher F, Lauwers P. Dopamine suppresses pituitary function in infants and children. *Crit Care Med*. 1994;22(11):1747–1753.
20. Choong K, Bohn D, Fraser DD, et al. Vasopressin in pediatric vasodilatory shock. *Am J Respir Crit Care Med*. 2009;180(7):632–639.

21. Weiss SL, Fitzgerald JC, Balamuth F, et al. Delayed antimicrobial therapy increases mortality and organ dysfunction duration in pediatric sepsis. *Crit Care Med*. 2014;42(11):2409–2417.
22. Annane D, Bellisant E, Bollaert PE, et al. Corticosteroids for treating severe sepsis and septic shock. *Cochrane Database Syst Rev*. 2004;(1): CD002243.
23. Menon K, McNally D, Choong K, et al. A systematic review and meta-analysis on the effect of steroids in pediatric shock. *Pediatr Crit Care Med*. 2013;14(5):474–480.
24. Alejandria MM, Lansang MAD, Dans LF, et al. Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock. *Cochrane Database Syst Rev*. 2013;(9):CD001090, doi:10.1002/14651858.CD001090.pub2. Available from: www.cochranelibrary.com.
25. Shah SS, Hall M, Srivastava R, et al. Intravenous immunoglobulin in children with streptococcal toxic shock syndrome. *Clin Infect Dis*. 2009;49(9): 1369–1376.
26. MacLaren G, Butt W, Best D, et al. Central extracorporeal membrane oxygenation for refractory pediatric septic shock. *Pediatr Crit Care Med*. 2011;12(2):133–136.
27. Van Herpe T, Vanhonsebrouck K, Mesotten D, et al. Glycemic control in the pediatric intensive care unit of Leuven: two years of experience. *J Diabetes Sci Technol*. 2012;6(1):15–21.
28. Agus MSD, Wypij D, Hirshberg EL, et al. Tight glycemic control in critically ill children. *N Engl J Med*. 2017;376:729–741.
29. Radermacher P, Trager K. Catecholamines in the treatment of septic shock: effects beyond perfusion. *Crit Care Resusc*. 2003;5(4):270–276.
30. Reinhart K, Bloos F. Central venous oxygen saturation (Scv_{O_2}) functional hemodynamic monitoring. In: Pinsky M, Payen D, eds. *Functional Hemodynamic Monitoring*. Berlin Heidelberg: Springer; 2005:241–250.
31. de Oliveira C, de Oliveira D, Gottschald A, et al. ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcomes comparison with and without monitoring central venous oxygen saturation. *Intensive Care Med*. 2008;34(6):1065–1075.
32. Angus DC, Barnato AE, Bell D, et al. A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. *Intensive Care Med*. 2015;41(9):1459–1460.
33. The Prism Investigators. Early, goal-directed therapy for septic shock – a patient-level meta-analysis. *N Engl J Med*. 2017;376(23):2223–2234. doi:10.1056/NEJMoa1701380. Available from: http://www.nejm.org/doi/full/10.1056/NEJMoa1701380.
34. Hsu DT, Pearson GD. Heart failure in children. *Circ Heart Fail*. 2009;2(5):490–498.
35. Hsu DT, Pearson GD. Heart failure in children. *Circ Heart Fail*. 2009;2(1):63–70.
36. Wilkinson JD, Westphal JA, Bansal N, et al. Lessons learned from the pediatric cardiomyopathy registry (PCMR) study group. *Cardiol Young*. 2015;25(S2):140–153.
37. Kindel SJ, Miller EM, Gupta R, et al. Pediatric cardiomyopathy: importance of genetic and metabolic evaluation. *J Card Fail*. 2012;18(5):396–403.
38. Kirk R, Dipchand AI, Rosenthal DN, et al. The International Society for Heart and Lung Transplantation guidelines for the management of pediatric heart failure: executive summary. *J Heart Lung Transplant*. 2014;33(9):888–909.
39. Luecke T, Pelosi P. Clinical review: positive end-expiratory pressure and cardiac output. *Crit Care*. 2005;9(6):607–621.
40. Motonaga KS, Dubin AM. Cardiac resynchronization therapy for pediatric patients with heart failure and congenital heart disease: a reappraisal of results. *Circulation*. 2014;129:1879–1891.
41. Stiller B, Benk C, Schlensak C. Mechanical cardiovascular support in infants and children. *Heart*. 2011;97(7):596–602.
42. Adachi I, Burki S, Zafar F, et al. Pediatric ventricular assist devices. *J Thorac Dis*. 2015;7(12):2194–2202.
43. Silberbach M, Hannon D. Presentation of congenital heart disease in the neonate and young infant. *Pediatr Rev*. 2007;28(4):123–131.
44. Savitsky E, Alejos J, Votey S. Emergency department presentations of pediatric congenital heart disease. *J Emerg Med*. 2003;24(3):239–245.
45. Stout KK, Broberg CS, Book WM, et al. Chronic heart failure in congenital heart disease: a scientific statement from the American Heart Association. *Circulation*. 2016;133(8):770–801.
46. Lister G, Hellenbrand WE, Kleinman CS, et al. Physiologic effects of increasing hemoglobin concentration in left-to-right shunting in infants with ventricular septal defects. *N Engl J Med*. 1982; 306(9):502–506.
47. Vargo P, Mavroudis C, Stewart RD, et al. Late complications following the arterial switch operation. *World J Pediatr Congenit Heart Surg*. 2011;2(1):37–42.
48. Walsh EP. Clinical approach to diagnosis and acute management of tachycardias in children. In: Walsh EP, Saul PJ, Triedman JK, eds. *Cardiac Arrhythmias in Children and Young Adults with Congenital Heart Disease*. Philadelphia: Lippincot, Williams & Wilkins; 2001:95–113.
49. Hanash C, Crosson J. Emergency diagnosis and management of pediatric arrhythmias. *J Emerg Trauma Shock*. 2010;3(3):251–260.
50. Rijnbeek PR, Witsenburg M, Schrama E, et al. New normal limits for the paediatric electrocardiogram. *Eur Heart J*. 2001;22(8):702–711.

111

Neurological emergencies in children

Anthony J Slater

Neurological emergencies are the most common life-threatening emergencies in children. In developed societies, after the first year of life, the leading cause of death in childhood is injury, particularly traumatic brain injury. There is a range of conditions affecting the brain, spinal cord and peripheral nervous system that require prompt recognition, resuscitation and definitive management. The pathophysiology, clinical features, treatment and outcome of these acute neurological emergencies are influenced by several important differences between adults and children. These differences include response to injury, developmental maturity and capacity for growth and recovery.

PATHOPHYSIOLOGY OF BRAIN INJURIES IN CHILDREN

Brain injuries are usually caused by a primary event (e.g. trauma, ischaemia, infection or metabolic disturbance), and are frequently accompanied by secondary injuries including oedema, altered cerebrovascular autoregulation, tissue hypoxia or other cytotoxic events. Therapy administered after the event will not influence the outcome of the primary injury; however, appropriate resuscitation, treatment and the avoidance of iatrogenic complications may prevent or reduce the impact of secondary injuries.

Features of brain injury particular to the paediatric patient are described below.

DIFFUSE CEREBRAL SWELLING

Diffuse brain swelling in the absence of oedema is a frequent early finding in paediatric brain injury, and is due to generalised cerebral vasodilation. It often resolves in 1–2 days if there is no other significant brain injury. With more severe primary traumatic injury, diffuse cerebral swelling may be accompanied by areas of contusion, multifocal petechial haemorrhage and vasogenic oedema that progress over several days.

CEREBRAL BLOOD FLOW AND METABOLISM

The cerebral perfusion pressure (CPP) represents the difference between mean arterial pressure (MAP) and intracranial pressure (ICP):

$$CPP = MAP - ICP$$

If autoregulation is disturbed as part of the illness, CPP becomes the major determinant of cerebral blood flow, particularly in areas with more severe damage. The ideal CPP in childhood is not known. The normal range of MAP varies with age from 40 mm Hg (5.32 kPa) in a term neonate to 80 mm Hg (10.64 kPa) in an adolescent. The target CPP is usually adjusted with age, taking into consideration the normal blood pressure for age. For example, for an adolescent patient the therapy may be directed at maintaining a CPP of 60 mm Hg (7.98 kPa), whereas for a child aged 5 years the aim may be to maintain a CPP of 50 mm Hg (6.65 kPa). In conditions where vasogenic oedema occurs, arterial hypertension may increase vascular shift of fluid and worsen brain swelling; however, treatment aimed at lowering arterial pressure (e.g. with vasodilators) may interfere with homeostatic mechanisms and should be used cautiously.

The brain comprises 12% of body weight in infancy compared with 2%–3% in adulthood. Cerebral oxygen and glucose consumption are therefore proportionately greater in childhood and glycogen stores are readily depleted. Hypoglycaemia occurs commonly in severe illnesses such as sepsis; therefore blood glucose should be monitored regularly.

HYPOVOLAEMIA

Children have small blood volumes and commonly develop hypovolaemia from scalp bleeding or intracranial haemorrhage. For example, hypovolaemia will develop in a 5-kg infant (blood volume 400 mL) following blood loss of less than 100 mL. Hypovolaemia should be treated aggressively with fluid boluses of 20 mL/kg to ensure adequate cerebral perfusion.

ABSTRACT

The principles of providing physiological support to children with brain injuries are similar to those applied in adults; however, it is important to appreciate the physiologic differences in children.

The approach to an unconsciousness child should focus on early consideration of treatable causes of coma such as bacterial meningitis or viral encephalitis; empiric treatment should commence if lumbar puncture is contra-indicated or delayed.

Children with seizure disorders require intensive care either to gain control of status epilepticus, or to manage the depressant side effects of therapy. A structured approach to monitoring and escalating therapy is needed to minimise the risk of further neurologic injury.

Autoimmune disorders of the brain (acute demyelinating encephalomyelitis, anti-*N*-methyl-D-aspartate receptor encephalitis), spinal cord (transverse myelitis) or peripheral nerves (Guillain–Barré syndrome) may present as an emergency due to respiratory failure, depressed conscious state, or seizures. These conditions usually, but not universally, respond well to immunosuppression.

KEYWORDS

Coma
status epilepticus
meningitis
encephalitis
autoimmune
metabolic encephalopathy
spinal cord

RELATIVE GROWTH

The child's short stature and proportionately large head confer a number of risks. The toddler's head is at the level of the front of a motor vehicle and isolated head injury is therefore common following pedestrian injury in this age group. The neck muscles are relatively weak in infancy and they support a large head. This renders the brain prone to deceleration injury in motor vehicle crashes and in cases of domestic violence. Injury inflicted by shaking an infant by the shoulders snaps the head to and fro leading to compression of brain tissue and rupture of delicate bridging veins.

BONE DEVELOPMENT

The bones of the skull in the first year of life are thin with open sutures and open fontanelles. Beyond 2 years, the skull sutures close and the cranial vault thickens. In young children there tends to be less bony protection from high-impact trauma, although the nonrigid skull may expand to partially decompress expanding lesions.

UNDIAGNOSED COMA

An ordered approach to diagnosis and treatment is required for a child with a depressed conscious state of unknown origin. This approach must consider common life-threatening and rare treatable diseases (Box 111.1).

Box 111.1 Causes of coma in children

STRUCTURAL	METABOLIC
Trauma	Post-ictal state
Accidental	Infection
Inflicted	Meningitis
Hydrocephalus	Encephalitis
Haemorrhage	Autoimmune
AVM	Encephalitis
Aneurysm	Acute disseminated encephalomyelitis
Tumour	Drugs and toxins
Tumour	Hypoxia–ischaemia
Cerebral	Circulatory shock
abscess	Biochemical
	Hypoglycaemia
	Sodium and/or water disorder
	Calcium disorder
	Acid base disorder
	Hyperthermia
	Hepatic failure
	Haemolytic–uraemic syndrome
	Inborn errors of metabolism

AVM, Arteriovenous malformations.

INITIAL MANAGEMENT

Management should always begin with rapid assessment of the adequacy of airway, ventilation and circulation. If inadequacies are detected, interventions aimed at correcting them should occur immediately. Once venous access is obtained, blood should be collected for routine tests including immediate measurement of blood glucose. If hypoglycaemia is demonstrated 1 mL/kg of 25% glucose or 2.5 mL/kg of 10% glucose should be given intravenously as the neurological sequelae of unrecognised hypoglycaemia can be profound.

Concurrent with the initial assessment and resuscitation, relevant details of the present and past history should be obtained. A detailed neurological and general physical examination should be performed. It is important to accurately document the conscious state so that changes over time, particularly deterioration, can be easily recognised. The Glasgow Coma Scale (GCS) is appropriate for this purpose; the responses of children change with development and therefore the GCS requires modification for paediatric use (Table 111.1). After completing the clinical assessment, the likely diagnosis is often apparent, and appropriate investigation and treatment can commence. Multiple factors may compound to produce coma. For example, a child with severe gastroenteritis may have hyperthermia, hyponatraemic dehydration, metabolic acidosis and hypovolaemic shock.

CONTROLLED VENTILATION

Indications for ventilating a comatose child are:

- upper airway obstruction or loss of airway reflexes
- apnoea or respiratory failure
- rapidly worsening coma
- signs of progressive elevation of ICP (i.e. bradycardia, hypertension, abnormal pupillary light reflexes and localising signs).

Raised ICP should be considered in any case of rapidly progressive coma. If critical intracranial hypertension is suspected clinically, management should include moderate hyperventilation and intravenous mannitol (0.25–0.5 g/kg) or hypertonic saline given as 3 mL/kg of 3% solution (0.5 mmol/mL).[1] Once ventilation is initiated and stability achieved, adequate sedation and analgesia are required. Muscle relaxants may be necessary to facilitate ventilation and prevent straining; however, their use precludes further neurological assessment, and therefore if long-acting muscle relaxants are continued, ICP monitoring is advisable. Hyperventilation is a short-term manoeuvre and, if used during the early resuscitation phase, a gradual return to a low–normal $PaCO_2$ should be the aim. This is best achieved with end-tidal CO_2 and ICP monitoring. Particular attention should be paid

Table 111.1 Glasgow coma scale for children

GLASGOW COMA SCALE (4–15 YEARS)		CHILD'S GLASGOW COMA SCALE (<4 YEARS)	
RESPONSE	SCORE	RESPONSE	SCORE
EYE OPENING		EYE OPENING	
• Spontaneously	4	Spontaneously	4
• To verbal stimuli	3	To verbal stimuli	3
• To pain	2	To pain	2
• No response to pain	1	No response to pain	1
BEST MOTOR RESPONSE		BEST MOTOR RESPONSE	
• Obeys verbal command	6	Spontaneous or obeys verbal command	6
• Localises to pain	5	Localises to pain or withdraws to touch	5
• Withdraws from pain	4	Withdraws from pain	4
• Abnormal flexion to pain (decorticate)	3	Abnormal flexion to pain (decorticate)	3
• Abnormal extension to pain (decerebrate)	2	Abnormal extension to pain (decerebrate)	2
• No response to pain	1	No response to pain	1
BEST VERBAL RESPONSE		BEST VERBAL RESPONSE	
• Orientated and converses	5	Alert, babbles, coos, words to usual ability	5
• Disorientated and converses	4	Less than usual words, spontaneous irritable cry	4
• Inappropriate words	3	Cries only to pain	3
• Incomprehensible sounds	2	Moans to pain	2
• No response to pain	1	No response to pain	1

to restoring intravascular volume and maintaining an adequate CPP.

CRANIAL COMPUTERISED TOMOGRAPHY

A computed tomography (CT) scan is required in comatose children with localising signs, and in those in whom the diagnosis is not clear. A CT should also be performed if the conscious state is abnormal and there is a history of trauma. Even if the general condition does not warrant controlled ventilation, a CT is often best performed under general anaesthesia. Unwanted movement will cause poor-quality images, and sedation alone may place the child at risk of hypoventilation or aspiration.

LUMBAR PUNCTURE

Lumbar puncture (LP) should be performed when there is reasonable suspicion of meningitis or encephalitis. The risks and contraindications to LP are discussed under bacterial meningitis.

ADDITIONAL INVESTIGATIONS

Additional investigations include arterial blood gas analysis, serum electrolytes, glucose, urea, creatinine, liver function tests, serum ammonia, serum and cerebrospinal fluid (CSF) lactate and pyruvate, and urine analysis. Appropriate screening of blood and urine will exclude common poisons and drug intoxications.

SPECIFIC TREATMENT

The clinical signs and results of investigations generally guide treatment. If hypoglycaemia occurs, it should be corrected rapidly and care should be taken to ensure that it does not recur. Appropriate glucose-containing intravenous fluid should be commenced with regular blood glucose monitoring. Herpes simplex encephalitis can present in many ways and is not excluded by the absence of CSF pleocytosis. Acyclovir therapy should therefore be considered in any patient in whom herpes cannot be confidently excluded.

STATUS EPILEPTICUS

Convulsive status epilepticus (CSE) is usually defined as a continuous convulsion lasting 30 minutes or longer or repeated convulsions lasting 30 minutes or longer without recovery of consciousness between convulsions.[2] As 30 minutes is generally considered too long to wait before starting treatment, an alternative 'operational definition' of a seizure lasting more than 5 minutes has been proposed for adults and older children (>5 years old). Terminology has been adapted to fit clinical scenarios with practical implication. ***Impending SE*** refers to continuous seizures lasting more than 5 minutes, or intermittent clinical or electroencephalograph (EEG) seizures lasting more than 15 minutes without full recovery between seizure; ***refractory SE*** refers to clinical or EEG seizures lasting longer than 60 minutes despite treatment with at least one first-line and one second-line antiepileptic drug (AED);

super-refractory SE refers to refractory CSE that continues or recurs 24 hours or more after the onset of general anaesthesia administered to control the CSE.[3]

It is acknowledged that the biology and clinical features of CSE in young children differ from that in adults.[4] The common causes of CSE in children are:

- prolonged febrile convulsion
- epilepsy associated with the first presentation, AED withdrawal or intercurrent illness
- central nervous system (CNS) infection (e.g., meningitis or encephalitis)
- metabolic disturbance (e.g., hypoglycaemia, hyponatraemia, hypocalcaemia)
- trauma, including inflicted injury.

PATHOPHYSIOLOGY

Many physiological changes occur during prolonged seizures. There is an initial phase of compensation lasting less than 30 minutes. Following a period of transition there is a phase of decompensation commencing between 30 and 60 minutes and evolving over hours. Physiological changes during the compensated phase include tachycardia, hypertension, increased catecholamine release and increased cardiac output. Changes within the brain include increased cerebral blood flow and increased cerebral utilisation of glucose and oxygen. After 30–60 minutes the mechanisms for homeostatic compensation fail. During the decompensated phase there may be falling blood pressure and cardiac output, hypoglycaemia, hypoxia, acidosis, electrolyte disturbance and rhabdomyolysis. The cerebral physiology is characterised by failing autoregulation and reduced cerebral blood flow, and oxygen and glucose utilisation. Over hours a deficit in brain energy develops and this is associated with the development of brain damage.[5]

EXCITATORY AMINO ACIDS AND BRAIN INJURY

Mesial temporal sclerosis is the most common acquired brain lesion following CSE. There is evidence that the accumulation of a number of excitatory and inhibitory amino acids has a role in the pathophysiology of neuronal injury. In particular, glutamate accumulation and stimulation of *N*-methyl-D-aspartate receptors (NMDAR) lead to an influx of intracellular calcium, which triggers a number of cytotoxic events and ultimately cell death.[6]

MANAGEMENT

The initial management is as for other neurological emergencies, with attention to the airway and oxygenation. Most seizures in childhood cease spontaneously in a short time, but if they persist after presentation to an emergency department they should be stopped to avoid metabolic and ischaemic neuronal damage. Hypoglycaemia should be excluded or detected early.

FIRST-LINE THERAPY

Benzodiazepines remain the first-line AED for stopping seizures and should be administered for seizures that do not stop spontaneously within 5 minutes. The efficacy of benzodiazepines is reduced if administration is delayed.[7] Therefore, there is strong argument for first-line therapy to be administered pre-hospital either by the parents, care providers or paramedics.[8] Intravenous access is unlikely in the community; however, midazolam can be administered via the buccal, intranasal or intramuscular route. Buccal midazolam is more effective, easier and more socially acceptable to administer than rectal diazepam.[9–11] Once intravenous access is available lorazepam is usually considered the drug of choice because, compared with diazepam, it is at least as effective, is safer and has a longer duration of action.[12–14] If a seizure has not responded to two doses of benzodiazepine, a second-line AED should be administered. If a benzodiazepine has been administered prehospital then only one further dose should be administered in the emergency department.

SECOND-LINE THERAPY

Traditionally phenytoin has been the second-line AED of choice in most situations. It is given as 20 mg/kg IV over 20 minutes, which is followed by maintenance dosing (4–8 mg/kg/day in 2–3 doses). It causes minimal sedation or respiratory depression, but is not suitable in neonates and in patients who are already on maintenance doses. Fosphenytoin, a prodrug of phenytoin, can be administered intramuscularly and has less irritant effect when given IV.[15] Fosphenytoin is used preferentially in the United States. When phenytoin is contraindicated, phenobarbitone (20 mg/kg IV over 20 minutes) should be given. Respiratory depression and hypotension can occur with phenobarbitone, particularly when administered after benzodiazepines. Further doses can be safely administered to ventilated children who have ongoing seizures. Intravenous levetiracetam is now used in some centres as the second-line AED of choice due to the superior safety profile and the capacity to administer the drug more rapidly than phenytoin or phenobarbitone.

THIRD-LINE THERAPY

Levetiracetam, more commonly considered a third-line AED, is effective against a broad range of seizure types and can be administered enterally or IV. Case series have described the use of intravenous levetiracetam at doses of 20–60 mg/kg in children with CSE and reported the drug to be safe and effective either as a single agent or in combination with other AEDs.[16] Rapid infusion of leviteracetam of up to 60 mg/kg (maximum 3 g) infused over 6 minutes has been reported without adverse cardiorespiratory effects.[17] Valproate is commonly used for maintenance therapy in epilepsy. There are several reports of successfully using intravenous valproate to abort CSE in children.

The doses reported range from 20 to 40 mg/kg. The rate of infusion reported also varies from 5 to 30 minutes.[18] Valproate can rarely cause encephalopathy or hepatotoxicity. Therefore levetiracetam may have a safety advantage over valproate as a third-line agent for CSE. In some centres rectal paraldehyde (0.3 mL/kg, max 5 mL, mixed with an equal quantity of olive oil) is used in the management of CSE. One advantage of paraldehyde is that it can be administered rectally if intravenous access is difficult to obtain.

FOURTH-LINE THERAPY

If CSE continues for longer than 30–60 minutes despite the administration of two or at most three different AEDs, induction of intravenous anaesthesia should occur followed by intubation and ventilation and admission to intensive care. Thiopentone 2–5 mg/kg slowly IV then 1–5 mg/kg per hour by continuous infusion into a central vein can be given. Thiopentone necessitates endotracheal intubation and mechanical ventilation, and possibly inotropic drugs to counter its hypotensive effects. Continuous EEG monitoring is recommended with a target end-point of burst suppression. If breakthrough seizures occur repeating bolus doses of 1–2 mg/kg should be administered. If dosing is titrated by adjusting the infusion rate without repeat bolus dosing, unnecessary delay in achieving the therapeutic goal will occur. Blood concentrations need to be monitored during prolonged use. Thiopentone infusions are associated with significant risks of hypotension, infection (particularly ventilator associated pneumonia), and ileus. Midazolam infusion has been used as an alternative to thiopentone. After a bolus of 0.2 mg/kg (maximum 10 mg) an infusion is commenced at 0.1 mg/kg per hour. If seizures continue or recur the bolus dose is repeated and the infusion is increased up to 1 mg/kg per hour if tolerated, although even higher doses have been reported.[19–21] High doses necessitate mechanical ventilation for respiratory depression; however, lower doses are effective at controlling CSE in some cases without the need for ventilation. There are also small case series describing the use of ketamine to control refractory CSE in children with requirement for ventilation.[22]

Finally, continuous administration of inhalational anaesthetic agents can be used in ventilated intensive care unit (ICU) patients resistant to other therapeutic strategies. General anaesthesia is not without risk, but is highly effective at controlling CSE, and can provide time to adjust the dose and stabilise the levels of other AEDs.

OUTCOME

The outcome of CSE is dependent on the aetiology. Neurologically normal children in whom CSE is precipitated by fever are considered to have a good prognosis with mortality reported between 0% and 2%.[23] The incidence of neurological deficits or cognitive impairment in this group is also very low. In acute symptomatic CSE (where CSE is a symptom of an acute neurological process such as infection or trauma) mortality is 12–16% and the incidence of new neurological dysfunction is more than 20%.[23] However, in this setting it is very difficult to tease out the extent to which prolonged seizures contribute to neurological sequelae.

ELECTROGRAPHIC STATUS EPILEPTICUS

Electrographic status epilepticus (ESE) is relatively common in critically ill children. Retrospective studies of continuous EEG monitoring in symptomatic or encephalopathic children in paediatric intensive care unit have reported that 30% of monitored children were found to have electrographic seizures. Approximately one-third of cases were ESE and another third had electrical seizures with no clinical manifestations.[24] ESE but not electrical seizures (without status) is associated with worse neurodevelopmental outcomes and increased mortality.[24,25] However, it is not known if the ESE itself contributes to permanent neurologic injury, or if the presence of ESE is a maker of more severe brain disease. Risk factors for ESE have been identified, including young age, convulsive seizures or CSE prior to EEG monitoring, acute structural brain injury, and interictal eleptiform discharges. However, it is not possible to accurately predict which critically ill children will have ESE.[26] Acknowledging that resources for continuous EEG monitoring vary between centres, ICUs should develop local guidelines for selecting suitable cases for continuous EEG monitoring.

BACTERIAL MENINGITIS

PATHOPHYSIOLOGY

Bacterial meningitis (BM) usually occurs following haematogenous spread of organisms carried in the nasopharynx. In childhood the common bacteria causing BM are *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* type b (Hib). Group B *Streptococcus*, *Escherichia coli* and *Listeria monocytogenes* are the most common causative organisms of neonatal BM. Occasionally, meningitis occurs as a complication of other pathology such as base of skull fracture, chronic middle ear infection or infection of a congenital dermoid sinus.

In the early stages of the disease cerebral hyperaemia occurs. This can be followed by cerebral ischaemia, which may occur by several different mechanisms. Local vasculitis of vessels traversing the subarachnoid space can progress to arterial thrombosis and focal infarction. Other vascular abnormalities, including vasospasm and sagittal sinus thrombosis, can also occur. Cerebral oedema is relatively common in

meningitis and is caused by a combination of vasogenic, cytotoxic and hydrostatic factors. If cerebral oedema is severe, raised ICP and impaired cerebral perfusion can occur, leading to global cerebral ischaemia.

CLINICAL FEATURES

In children the typical features of BM are fever, headache, photophobia, neck stiffness and vomiting. The history may extend over several days; however, in fulminant cases the time from first symptom to coma and death may only be a few hours.[27] Neonates and young infants do not present with the typical localised symptoms and signs. Instead, they present with generalised signs of illness including lethargy, poor feeding and pallor. Generalised or focal convulsions, or apnoea may be the presenting clinical symptoms. Tuberculous meningitis usually presents with a more insidious onset of symptoms and may be associated with focal neurological signs.

Complications occur commonly in BM. During the early phase, meningitis may be associated with septic shock and disseminated intravascular coagulation. Fluid and electrolyte abnormalities are relatively common, particularly hyponatraemia and hypoglycaemia. Focal and generalised convulsions are also relatively common and may progress to status epilepticus. During the recovery phase subdural effusions or hydrocephalus may occur.

INVESTIGATIONS

LP for CSF microscopy, culture, and polymerase chain reaction (PCR) testing is required for definitive diagnosis of BM, and to guide antibiotic therapy. Although an LP can be performed safely in the majority of children with BM, it may precipitate brainstem herniation if raised ICP is present.[28] Identifying children at risk of this complication is difficult; however, it is generally recommended that empirical antibiotic therapy be commenced and LP deferred if any of the following clinical features are present: depressed conscious state, decorticate or decerebrate posturing, focal neurological signs or other signs of raised ICP. A normal CT scan does not exclude the possibility of elevated ICP.[28] Therefore, the decision to defer an LP should be based on clinical rather than radiological signs. In addition to signs of increased ICP, other indications for deferring the LP include cardiorespiratory instability, and severe coagulopathy. If LP is deferred, alternative methods of establishing a bacterial diagnosis include blood culture and PCR testing of blood.[29,30]

MANAGEMENT

RESUSCITATION

Severely ill patients require rapid resuscitation. Comatose patients require intubation and ventilation to prevent airway obstruction and hypoventilation. Hypovolaemia should be treated rapidly with boluses of fluid. Patients with septic shock will also require inotropic support.

CEREBRAL RESUSCITATION

General principles of supporting brain injury apply to BM. These include optimising cerebral oxygen delivery, controlling ICP and preventing cerebral metabolic stress. The role of ICP monitoring is controversial. There is some anecdotal evidence to support the use of ICP monitoring in a small number of selected cases. Unfortunately, there are no large studies that assess the benefit or harm of ICP monitoring and ICP-targeted therapy in BM.

ANTIBIOTIC THERAPY

Empirical broad-spectrum antibiotics should be selected based on likely pathogens and local resistance patterns. A common protocol for BM is to use ampicillin plus cefotaxime for the first 3 months of life and to use a third-generation cephalosporin (cefotaxime or ceftriaxone) after 3 months of age.[31] In regions where penicillin- and cephalosporin-resistant *Pneumococcus* occurs, vancomycin should be added to the initial empirical antibiotics until the causative organism is identified and the antibiotic sensitivities are known. When cephalosporin-resistant *Pneumococcus* are found to be the causative organism in meningitis, both a third-generation cephalosporin and vancomycin should be continued as vancomycin penetrates into CSF poorly and therefore should not be used as a single agent. The addition of rifampicin should be considered.[32]

ADJUVANT THERAPY

If dexamethasone is used as adjuvant therapy it should be used only for children over 3 months of age and ideally be given before the first dose of antibiotics and continued for 4 days (0.15 mg/kg 6 hourly).[33] There is evidence that dexamethasone reduces the incidence of neurological sequelae and sensorineural deafness; however, the beneficial effects are greatest in Hib meningitis *(Haemophilus influenzae)*.[34,35] A meta-analysis of steroid trials in BM suggest that the improved outcome with steroids is seen in high-income but not low-income countries.[36] With immunisation, changing epidemiology and the emergence of antibiotic-resistant pneumococcal strains, it is possible that the relationship between risk and benefit of dexamethasone therapy has changed. However, current recommendations support the use of dexamethasone prior to or at the time of the first doses of antibiotics for children older than 3 months of age with BM.[31,32] Oral glycerol has also been investigated as an adjuvant agent. One large randomised controlled trial and a meta-analysis demonstrated reduced neurological sequelae and reduced hearing loss with oral glycerol compared with placebo.[37,38]

FLUID THERAPY

There is consensus that hypovolaemia should be treated rapidly and aggressively; however, fluid therapy after the initial resuscitation is controversial. Hypotonic fluids should not be administered in BM owing to the risk of hyponatraemia and cerebral oedema.[39,40] Hyponatraemia is often attributed to the syndrome of inappropriate antidiuretic hormone (ADH) secretion and therefore fluid restriction is logical. However, there is evidence that ADH is *appropriately* elevated in response to hypovolaemia[41] and that hyponatraemic patients with BM tend to be more dehydrated than normonatraemic patients.[42] Compared with fluid restriction, fluid therapy aimed at providing maintenance plus correcting the fluid deficit has been reported to result in a more rapid correction of sodium and ADH[41,43] and has also been associated with reduced short-term morbidity and neurological sequelae at follow-up.[44] The trials of fluid therapy in BM have all been undertaken in low-income countries where delayed presentation is common. The effect of fluid therapy on the outcome of BM in populations where children present early and mortality is low is unknown.

OUTCOME

Bacterial meningitis is associated with significant mortality and morbidity. Overall mortality for BM in childhood is 5%–10%; however, in children requiring mechanical ventilation, a mortality rate of 30% has been reported with major neurological sequelae occurring in 33% of survivors.[45]

ENCEPHALITIS

Common causes of encephalitis include herpesviridae enteroviruses (herpes simples, varicella zoster, cytomegalovirus, Epstein–Barr), and respiratory viruses (adenovirus and influenzae). The most significant causes worldwide are the insect-transmitted arbovirus encephalitides including Australian (Ross River and Murray Valley), Japanese B and St Louis. These can cause profound coma and are associated with a significant incidence of residual neurological deficit.

Presenting symptoms of encephalitis include seizures, focal neurological deficits in the setting of an acute febrile illness, confusion and coma. Meningeal irritation may not be obvious. CSF analysis may show a pleocytosis, and in the early phase this can consist predominantly of neutrophils. Herpes simplex encephalitis is the most important diagnosis to make because it is treatable. EEG, CT and magnetic resonance imaging (MRI) are helpful in making the diagnosis. MRI is more sensitive than CT for detecting signs of encephalitis, particularly during the early stages of the illness. PCR on CSF may also aid rapid diagnosis.[46,47] Acyclovir, if used early, improves outcome and should be commenced when the diagnosis is suspected.

The enteroviruses are important causes of encephalitis in children. In addition they cause other acute neurological illnesses, including acute flaccid paralysis due to transverse myelitis and Guillain–Barré syndrome.[48] Pleconaril is a promising new antiviral agent that appears to have clinical benefit in enteroviral infections, including CNS disease.[49] Acyclovir is recommended for varicella zoster encephalitis, foscarnet and ganciclovir for cytomegalovirus and oseltamivir for encephalitis due to influenza.[50] The outcome of viral encephalitis is worse in infancy than in older age groups.

ANTI-*N*-METHYL-D-ASPARTATE RECEPTOR ENCEPHALITIS

Knowledge and understanding of immune mediated neurologic disorders is expanding rapidly. Several disorders have been described with clinical and laboratory features of encephalitis associated with the presence of auto-antibodies to either intracellular or neuronal surface antigens.[51] Of this group of disorders, anti-NMDAR encephalitis is the condition that most frequently presents in childhood and adolescence. A Californian study of encephalitis epidemiology found anti-NMDAR encephalitis to be more common than the most frequent type of viral encepahalitis (enterovirus).[52]

Approximately 60% of children present with psychiatric symptoms such as psychosis or hallucinations. Younger children may present with behavioural change, temper tantrums or hyperactivity. Altered behaviour can progress to unresponsiveness fluctuating with periods of agitation. Other presenting symptoms can be movement disorders (including dystonia, dyskinesia, chorea, choreoathetosis, ataxia, catatonic posturing or myoclonus), seizures or status epilepticus. Autonomic instability (hypertension, tachycardia or hyperthermia) or central hypoventilation necessitating mechanical ventilation may occur during the acute phase of the illness.[51,53]

INVESTIGATION

Once suspected, the diagnosis is confirmed by detection of serum and CSF NMDAR antibodies. CSF analysis may reveal mild pleocytosis, elevated protein and oligoclonal bands; however, CSF may be normal initially. MRI may be normal or demonstrate nonspecific T2 or fluid-attenuated inversion recovery (FLAIR) signal hyperintensity in the frontal or parietal cortex, hippocampus, basal ganglia cerebellum or brainstem.[54] Anti-NMDAR encephalitis can be a para-neoplastic condition associated with ovarian, testicular or mediastinal teratomas, Hodgkin lymphoma and neuroblastoma. Therefore screening for tumours

should be undertaken with abdominal, pelvic and testicular ultrasound followed by abdominal and thoracic MRI.

MANAGEMENT

There is evidence that early treatment improves outcome. If present, tumour removal speeds recovery. First-line immunotherapy consists of high-dose methylprednisolone, intravenous immunoglobulin (IVIG) or plasmapheresis and should be administered regardless of whether or not a tumour is identified and removed. Patients who do not respond or who relapse should be considered for second-line therapy with more aggressive and sustained immunosuppression using rituximab or cyclophosphamide.[51,54]

Therapeutic decisions are challenging as clinical recovery is slow and there is little evidence to support different treatment strategies. Supportive medical therapy is often required; sedation may be needed for agitation, and psychiatry consultation should be sought for the management of behavioural disturbance or psychosis.

OUTCOME

Recovery from anti-NMDAR encephalitis is slow over weeks to months. Prolonged hospitalisation and rehabilitation is usually required.[54] Complete recovery is reported in about 50% of children and adolescents with the condition, with another 30% considered to have a good outcome at 2 years.[55] Cognitive sequelae include impaired memory and executive functions. Relapse occurs in 10–15% of patients.

NONTRAUMATIC INTRACRANIAL HAEMORRHAGE

Nontraumatic intracranial haemorrhage (ICH) is uncommon in children. Arteriovenous malformations (AVM) are a more common cause of haemorrhage in children than aneurysms (Box 111.2).[56] The presenting features are similar to those seen in adults, and include sudden severe headache, altered conscious state and seizures. Diagnosis can usually be made by CT scan. Raised ICP, if present, is managed in the usual manner. A mass lesion or acute obstructive hydrocephalus requires neurosurgical assessment. Following a diagnosis of ICH, further investigations may be required to clarify the underlying cause. These include coagulation profile and platelet count. Angiographic images can be obtained with CT, MRI, or digital subtraction. In some cases, definitive cerebral angiography may be required to define the underlying vascular malformation or tumour. Definitive surgery or endovascular treatment of an AVM can be planned once the underlying lesion has been defined. A period of close observation is required as children may be at greater risk of rebleeding from an AVM than adults. The efficacy of therapies (e.g. calcium channel blockers) used to prevent vasospasm in adults has not been studied in children with aneurysmal haemorrhage. Sequelae of ICH include hemiparesis, aphasia, seizures and hydrocephalus.

Box 111.2 Aetiology of spontaneous intracranial haemorrhage in children

- Vascular malformations
  - Arteriovenous malformation
  - Capillary telangiectasia
  - Cavernous malformation
  - Venous malformation
- Aneurysm
  - 'Berry'
  - Mycotic
  - Post-traumatic
- Coagulopathy
  - Thrombocytopenia
  - Haemophilia
  - Anticoagulant therapy
- Tumours
  - Gliomas
- Hypertension

HYPOXIC–ISCHAEMIC ENCEPHALOPATHY

The most common causes of hypoxic–ischaemic encephalopathy outside the neonatal period are:

- near-miss sudden infant death syndrome
- immersion
- accidents, including drug ingestion and strangulation
- inflicted injury.

PATHOLOGY

The brain depends on an uninterrupted supply of oxygen and glucose to produce, via aerobic glycolysis, sufficient high-energy adenosine triphosphate (ATP) to maintain neuronal membrane and synthetic function. Under anoxic conditions anaerobic glycolysis occurs, which produces lactic acid but less ATP (by 18 times). As there are virtually no stores of ATP, rapid neuronal failure ensues. If ischaemia accompanies hypoxia, there is associated failure of both substrate delivery and metabolic waste removal, which amplifies the cellular insult. Ischaemia produces coma in less than 10 seconds and cerebral damage in as little as 2 minutes.

Following restoration of cerebral blood flow there is a period of relative hyperaemia followed by relative hypoperfusion. Cytotoxic cerebral oedema may subsequently develop, but significant elevation of ICP is unusual unless ischaemia and damage are profound.

MANAGEMENT

The principles of therapy are similar to those for other brain injuries. It is mandatory to provide rapid cardiopulmonary resuscitation and prevent secondary insults. In cases of out-of-hospital cardiac arrest, full resuscitation must be attempted while the history is sought. Post-resuscitation care is important for optimising outcome. Comatose patients with hyper- or hypotonia and a GCS score <8 are probably best managed by mechanical ventilation and sedation for at least 1–2 days, although benefits are not proven. Ventilation should be targeted at normocapnoea, and hyperventilation avoided owing to the risk of further cerebral ischaemia.[57] Haemodynamic disturbance may develop because of primary cardiac dysfunction or hypovolaemia secondary to fluid loss from capillary leak syndrome. Circulating volume should be restored, and inotropic agents considered, to improve the state of the circulation. The dose and choice of vasoactive agent should be individualised based on haemodynamic monitoring.

Following cardiac arrest children are usually hypothermic. Fever commonly develops during the subsequent hours and is associated with worse outcome.[58] There are trials in adults following cardiac arrest[59,60] and trials in newborns following birth asphyxia[61,62] demonstrating improved neurological outcome if hypothermia is used for between 12 and 72 hours. A more recent adult trial demonstrated that fever prevention with 'therapeutic normothermia' was as effective as 'therapeutic hypothermia'.[63] Two recent trials of therapeutic hypothermia following out-of-hospital and in-hospital cardiac arrest in children did not show any difference in survival with good functional outcome between the intervention and the control groups.[64,65] Therefore therapeutic hypothermia cannot be recommended following cardiac arrest in children; however, temperature should be actively managed to prevent fever. Hyperglycaemia has been associated with a worse prognosis and, although it may simply be a marker of injury severity, active treatment has been advocated. The role of ICP measurement is limited as intracranial hypertension usually occurs only in the setting of severe injury and poor outcome.[66]

PROGNOSIS

The major determinants of recovery are ischaemic time, cerebral metabolic rate and quality of resuscitation. There are no simple clinical rules to reliably predict outcome when a child presents following cardiac arrest. Factors that should be considered include the duration of cardiopulmonary resuscitation (CPR), the cause of arrest, pre-existing medical conditions, the location of the arrest, whether the arrest was witnessed and, the duration of arrest before resuscitation commenced.[67] In general, survival from out-of-hospital cardiac arrest is unlikely if asystole is present on arrival at hospital.[68] In immersion injuries in young children, full recovery may be possible despite prolonged ischaemia if sufficient rapid cerebral cooling has occurred. In these cases the onset of ischaemia may be delayed by bradycardia with preferential cerebral flow (the 'diving reflex'). Prolonged CPR may be justified in selected cases when profound hypothermia was induced rapidly. Coma persisting for more than 24 hours is a predictor of poor prognosis and minimal long-term improvement is likely in this group.[69] Residual neurological deficits present at the end of the first week are less likely to improve following ischaemic injury than following traumatic brain injury.

A number of ancillary tests have been investigated as predictors of neurological outcome. Somatosensory evoked potentials (SEPs) performed at the bedside are the most useful aid to prediction. One report of 109 children with severe brain injury concluded that, with appropriate patient selection, the positive predictive value for poor outcome of bilaterally absent SEPs is 100% (95% confidence interval 92%–100%).[70]

GUILLAIN–BARRÉ SYNDROME

CLINICAL FEATURES

Guillain–Barré syndrome (GBS) is characterised by acute areflexic paralysis with raised CSF protein and normal CSF cell counts. It is the most common cause of acute motor paralysis in children. There is strong evidence to support an autoimmune cause with many patients having raised anti-ganglioside antibodies. Many cases are preceded by symptoms of upper respiratory tract infection or diarrhoea. Infectious agents associated with subsequent development of GBS include *Campylobacter jejuni*, cytomegalovirus, Epstein–Barr virus, varicella zoster virus and *Mycoplasma pneumoniae*. An emerging association between GBS and acute arbovirus infection, including Zika virus, is being closely monitored globally.[71,72] The syndrome includes a number of peripheral nerve disorders that have been classified based on the distribution of weakness, antibody profiles and nerve conduction studies.[73]

Although most patients develop typical ascending, symmetrical areflexic weakness, GBS may present insidiously with apparent lethargy or loss of motor milestones in the young child. There also may be rapid progression and admission criteria to the ICU, which include respiratory failure, bulbar palsy, severe autonomic disturbance or rapidly progressive weakness. Sensory loss is usually minimal and transient. Pain in the back and legs, possibly neurogenic in origin, is common and may be the presenting feature.[74] This pain may be severe and is often difficult to control. Papilloedema and encephalopathy occasionally occur.[75] The complications of deep-venous thrombosis and thromboembolism are not common problems in young children but they may occur in adolescents.

INVESTIGATIONS

An LP should be done ideally before treatment with IVIG is commenced. CSF typically shows a WCC <10 $\times 10^6$, while CSF protein is usually raised but may be normal during the first week of illness. Nerve conduction studies may be normal if performed early. Neurophysiological criteria have been used to classify GBS subtypes according to either demyelinating or axonal neuropathies, and whether or not both sensory and motor nerves are involved.[76] Antiganglioside antibodies are raised in some but not all patients.[77]

If there is uncertainty about the clinical diagnosis then brain and spinal cord imaging, as well as screening for infection, should be considered. Contrast-enhanced spinal MRI demonstrates contrast enhancement of spinal nerve roots and the cauda equina in most patients with GBS.[78,79]

MANAGEMENT

Adequate respiratory care is the basis of minimising morbidity and mortality in GBS. Up to one-third of patients require ventilatory support and, ideally, mechanical ventilation should be undertaken electively. Early indications are increased work of breathing, fatigue, poor cough and progressive bulbar palsy. Hypercarbia is a late sign and should be avoided. In children who are old enough to cooperate, forced vital capacity (FVC) should be monitored during the progressive phase of the illness. Mechanical ventilation should be considered if FVC falls below 15–20 mL/kg. Careful frequent clinical assessment is necessary. Once mechanically ventilated, many patients require some degree of hyperventilation to prevent 'air hunger'. Although nasotracheal intubation is satisfactory initially, a tracheostomy should be performed if recovery is delayed. This will improve comfort and allow speech via the ventilator generating an air leak around the tracheostomy tube. Successful weaning is unlikely unless vital capacity exceeds 12 mL/kg and maximum negative inspiratory force is at least 20 cm H_2O (2 kPa).

Autonomic dysfunction is an important cause of morbidity and mortality in children with GBS. Airway manipulation or induction of anaesthesia, particularly in the presence of hypoxia, may provoke serious cardiac arrhythmias. Fluctuating blood pressure, urinary retention and gut dysfunction also occur.

Plasma exchange (PE) and IVIG are effective therapies. The indications for either are rapid progression, respiratory insufficiency or weakness to the point of being unable to walk unassisted. The strongest evidence for these therapies is from adult trials.[80–82] Large trials adequately powered to separately test the efficacy of PE and IVIG in children have not been performed; however, a number of small retrospective studies have described local experiences with these immune therapies in children with mixed results.[83–87] As IVIG has significant potential technical advantages over PE, IVIG is generally the first-line therapy in children. Indications for IVIG are based on the degree of functional impairment and time from onset of symptoms. The indications are not influenced by the clinical or neurophysiological subtype, or the results of antibody screening. There is no evidence to support sequential treatment using both PE and IVIG.[88,89]

Pain is a common feature of GBS and may have a neuropathic basis. Paracetamol or nonsteroidal anti-inflammatory drugs are useful, while drugs to treat neuropathic pain, including gabapentin, carbamazepine and amitriptyline, may also be beneficial.

The problems of long-term ventilation in a conscious patient, compounded by emotional immaturity, speech failure, fear of procedures and family disruption, make the management of a child with GBS and their family particularly challenging. A sensitive team approach is essential.

PROGNOSIS

The prognosis in acute GBS may be better for children than for adults. Full recovery is likely if the time from maximal deficit to onset of recovery is less than 18 days. However, complete recovery, despite a longer plateau phase, has been reported. Good recovery can occur in patients who have required ventilation and the need for ventilation may not be a poor prognostic factor in children.[83] Those presenting with a subacute course are at risk of relapse and permanent motor deficits.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Acute disseminated encephalomyelitis (ADEM) is defined as an episode of inflammatory CNS demyelination with polyfocal neurological deficits accompanied by encephalopathy (behavioural change or altered consciousness). The condition is one of several demyelinating conditions that occur in childhood including transverse myelitis, optic neuritis and multiple sclerosis. The clinical features of ADEM include encephalopathy (which is required to make the diagnosis), ataxia, hemiparesis, cranial nerve palsies, hypotonic, seizures and polyfocal neurological deficits.[90] The encephalopathy varies in severity from subtle signs of irritability and headache to life-threatening coma and decerebrate rigidity. Respiratory failure can occur from brainstem involvement or a severely impaired conscious state. Case series have reported a requirement for mechanical ventilation in 11–16% of patients.[91,92]

ADEM is preceded by a triggering event in 70% of cases, most commonly a nonspecific upper respiratory tract infection or occasionally a recent vaccination. Common agents associated with the prodromal phase include Epstein–Barr virus, cytomegalovirus, herpes simplex virus and *Mycoplasma*; however, in the

majority of cases a specific agent cannot be identified. Although the precise immunopathogenesis of ADEM is unknown, there is a consensus that ADEM is mediated by an autoimmune reaction with antibody formation to myelin.

INVESTIGATION

LP should be performed to exclude infectious encephalomyelitis. There may be a modest elevation of the CSF white cell and red cell counts. CSF oligoclonal bands and raised CSF immunoglobulin levels occur more commonly in multiple sclerosis than in ADEM.[90] MRI with T2 and FLAIR show bilateral asymmetrical hyperintense demyelinating lesions. The lesions predominantly involve the deep white matter, juxtacortical white matter and deep grey nuclei. Lesions can also occur in the brainstem, cerebellum and spinal cord. The size of lesions varies from punctate to large tumefactive (puffy/swollen) mass-like lesions.[93] Some patients with ADEM have normal MRI findings on initial presentation, but develop features typical of ADEM if the study is repeated several weeks later. In some patients the MRI changes first appear at a time when clinical improvement is occurring.[94]

A large number of infective, inflammatory metabolic and rheumatologic conditions can mimic the MRI appearances of ADEM. Therefore it is important to have a systematic approach to investigations for potential differential diagnoses. Red flags that suggest an alternative diagnosis include age of onset less than 1 year; developmental delay; gradual progression; multisystem involvement; or a family history of consanguinity or severe neurologic symptoms. MRI features that suggest an alternative diagnosis include a single supratentorial white matter lesion, symmetrical white matter involvement or lesions restricted to the brainstem or basal ganglia.[95]

MANAGEMENT

Although there are no randomised therapeutic trials in ADEM, high-dose corticosteroids are considered the treatment of choice. Intravenous methylprednisolone 30 mg/kg/day (maximum 1 g/day) for 3–5 days followed by oral prednisolone tapered over 4–6 weeks often results in rapid clinical improvement. Other treatment options include IVIG (2 g/kg intravenously for 2–3 days) and plasmapheresis.[96]

OUTCOME

Most children with ADEM recover completely, although a small percentage of children have significant neurological and neuropsychological sequelae. The most common neurocognitive abnormality identified at long-term follow-up is impaired attention.[97] Rarely is ADEM fatal. Approximately 20% of children initially diagnosed with ADEM experience a recurrence of neurological symptoms and subsequently receive the diagnosis of multiple sclerosis.[98]

METABOLIC ENCEPHALOPATHY

Approximately 0.1% of babies have an inborn error of metabolism. Acute encephalopathy is one of the many ways neurometabolic diseases present in childhood.[99] In general, acute presentations occur in the neonatal period and early infancy. Symptoms are often vague and include lethargy, poor feeding and vomiting. Some in-born errors do not present until later in childhood or even in adulthood. Although older children may present with a chronic encephalopathy, they may also present with an acute metabolic emergency, which is usually precipitated by an inter-current illness or catabolic stress.

APPROACH TO DIAGNOSIS

A careful history and examination may elicit clues to a possible metabolic problem. Family history and history of drug exposure are extremely important. Valproate, in particular, has been associated with liver dysfunction and encephalopathy. The following readily available investigations are useful to allow broad categorisation and to direct further detailed investigations: blood gas analysis; blood glucose; serum ammonia; serum lactate; plasma amino acids; blood and urine ketones; and urine metabolic screen for amino, orotic and organic acids. While lactic acidosis and hypoglycaemia can occur in a number of disease states including sepsis, persisting abnormalities require further investigation. Lactic acidosis can be further assessed with measurement of lactate/pyruvate ratio. Fig. 111.1 provides an algorithm proposed by Ellaway and colleagues to direct the investigation of metabolic disease presenting in the newborn period based on the metabolic abnormalities detected from baseline investigations.[100] This is best done in collaboration with a metabolic disease specialist or a clinical biochemist.

MANAGEMENT

Initial management includes elimination of toxic metabolites and administration of calories to switch off catabolism. Metabolic derangements, such as acidosis and hypoglycaemia, should be corrected. The role of ICP monitoring for acute intracranial hypertension is controversial; however, patients with suspected raised ICP, and unconscious patients, should receive standard modalities of support including intubation and mechanical ventilation. Hyperammonaemia should be managed by stopping enteral feeds to limit protein intake. Agents, such as arginine and sodium benzoate, can be administered to increase ammonia metabolism. Providing calories intravenously in the form of glucose

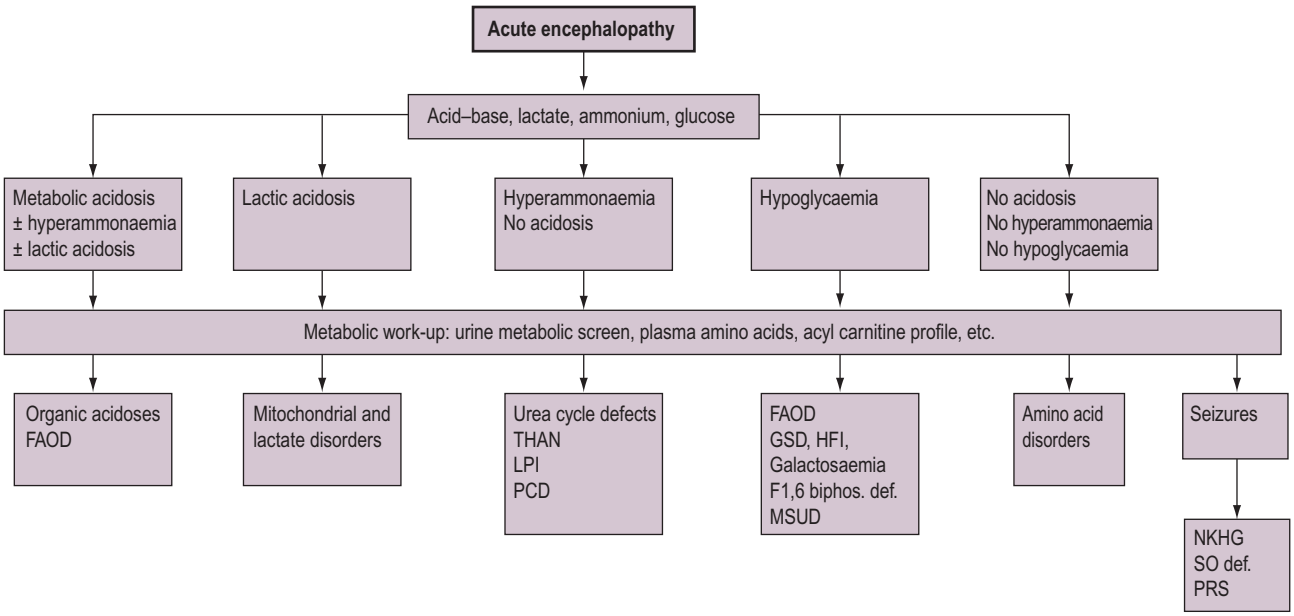


Figure 111.1 Flow diagram to guide investigation of inborn errors of metabolism presenting in the newborn period. *FAOD*, Fatty acid oxidation disorder; *F1,6 biphos. def.*, fructose 1,6 biphosphatase deficiency; *GSD*, glycogen storage disorder; *HFI*, hereditary fructose intolerance; *LPI*, lysinuric protein intolerance; *MSUD*, maple syrup urine disease; *NKHG*, nonketotic hyperglycinaemia; *PCD*, pyruvate carboxylase deficiency; *PRS*, pyridoxine-responsive seizures; *SO def.*, sulphite oxidase deficiency; *THAN*, transient hyperammonaemia of the newborn.

and fat limits the extent of catabolism and thereby helps to curtail the metabolic crisis. Haemodiafiltration is effective at controlling hyperammonaemia (urea cycle defects), leucine toxicity (maple syrup urine disease) and propionic acid (propionic acidaemia).[101,102]

SPINAL INJURY

INCIDENCE

Paediatric spinal trauma is relatively rare, comprising <5% of all spinal injuries. Approximately 5% of children with severe head trauma will have a cervical spine injury. However, a high proportion of children who die following motor vehicle trauma, particularly those who suffer immediate cardiorespiratory arrest, or who die before arrival at hospital, have disruption of the spinal cord above C3, particularly at the cervicomedullary junction.[103] The most common causes of paediatric spinal trauma are motor vehicle crashes, as either a pedestrian or passenger, falls, and diving injuries. Sports-related injuries are uncommon.

PATHOPHYSIOLOGY

The patterns of spinal injury in children differ from those seen in adults in many ways. Spinal cord injury without radiographic abnormality (SCIWORA) occurs almost exclusively in children (20%–60% of spinal cord injuries). It is associated with a high incidence of complete neurological deficit. Spinal injury in the first decade of life occurs most commonly in the first two cervical segments, with atlanto-axial rotatory subluxation, bony or ligamentous injuries, or SCIWORA and severe cord injury. Although not as common as upper cervical injuries, lower cervical injuries (below C4) do occur in young children,[104] while injury may occur at more than one level. Atlanto-axial rotatory subluxation may occur after minor trauma or without an identifiable precipitating event, and is rarely associated with neurological deficit. However, ligamentous injury is more likely to be associated with permanent neurological deficit than high cervical fractures. As the bony spine matures, the pattern of injury becomes more adult-like, with lower cervical and thoracic injuries seen in the second decade.[105]

CLINICAL FEATURES

The immediate effects of spinal cord damage are similar at any age. Frequently, an associated head injury can render clinical assessment extremely difficult; confirmation of cord injury is sometimes delayed. Clues to the diagnosis in the unconscious patient include:

- flaccidity, immobility and areflexia below the level of the lesion
- hypoventilation with paradoxical chest movement; this occurs in the absence of airway obstruction

where the intercostal muscles are paralysed and the phrenic nerves are intact
- apnoea with rhythmic flaring of the alae nasi (Duncan's sign), which is seen when the lesion is above C3
- hypotension with inappropriate bradycardia and cutaneous vasodilatation below the level of injury, due to absent spinal sympathetic outflow
- priapism.

There may be visible or palpable evidence of trauma to the spine and surrounding soft tissues, including retropharyngeal or retrolaryngeal haematomas. Spinal shock is common with temporary complete loss of function. As this resolves after 3–5 days, reflexes progressively return, usually starting with bulbocavernosus and anal reflexes. Incomplete lesions, including the Brown–Sequard cord hemisection, and anterior and central cord syndromes may become apparent at this stage.

INVESTIGATIONS

Resuscitation, including emergency intubation, should not be delayed to perform X-rays. However, the entire spinal column should be X-rayed subsequently, to demonstrate the presence of subluxation, fractures or dislocations. MRI is useful both in the acute setting and in assessment at later stages and is now accepted as the standard for identifying haemorrhage, contusion or compression of the cord. CT produces better definition of bony injuries, and may also show cord involvement by haematomas, bone fragments and foreign bodies. SCIWORA was defined in an era before MRI was routinely available. In the majority of children with SCIWORA, MRI also will be normal; however, if intramedullary lesions are demonstrated with MRI, permanent neurological deficits are more likely.[106,107] Somatosensory-evoked potentials may be useful to evaluate the integrity of the spinal cord, particularly in the comatose patient.

MANAGEMENT

Achieving control of airway, ventilation and circulation is always the first priority. If tracheal intubation is indicated, and if stability of the neck is unknown, skilled assistance is necessary to immobilise the head and neck and to prevent flexion or extension. Because of the sympathectomised state in high cord injuries, a relatively low blood pressure can be expected even after hypovolaemia is corrected. Significant hypotension becomes more likely the higher the lesion and the younger the patient. Haemodynamic support with a vasoconstrictor, such as norepinephrine (noradrenaline), is useful if hypotension is problematic following restoration of intravascular volume. As up to 20% of patients will have multiple trauma, many will require major surgical procedures, during which the spinal cord must remain protected. If muscle relaxants are required 2–3 days following the injury, suxamethonium is contraindicated owing to the risk of fatal hyperkalaemia.

Adult trials of high dose steroids in acute spinal injury have been controversial[108,109]; however, there are no studies specific to children. Steroid administration is not recommended in acute spinal injury.[110]

As with brain injuries, preventing secondary injury is vital. Adequate perfusion of the cord should be ensured, as autoregulation of blood flow is lost after trauma. The vast majority of paediatric cervical spine injuries can be effectively treated nonoperatively. The most effective means of immobilisation appears to be achieved with halo devices or thermoplastic Minerva jackets. Consideration of primary operative therapy is recommended for isolated ligamentous injuries of the cervical spine and unstable or irreducible fractures or dislocations with associated deformity, including atlanto-occipital dislocation.[110,111]

The incidence of venous thromboembolism after spinal injury in adolescents approaches that in adults; therefore patients in this age group should receive standard prophylaxis. Venous thromboembolism is rare in prepubertal children (approximately 1%), and the risk–benefit ratio of routine prophylaxis in this age group is unknown.[112] There should be early consultation with a specialised spinal injuries unit. Optimal rehabilitation requires a team of orthopaedic and neurosurgeons, rehabilitation specialists, nurses, physiotherapists, occupational therapists, psychiatrists, social workers and schoolteachers.

PROGNOSIS

The prognosis of all spinal injuries in children may be better than in adults. In one series of 113 children with spinal column injuries, 55 (48%) had no neurological deficit and 38 (34%) had an incomplete deficit; of these, 23 (20%) made a complete recovery and 11 (10%) improved. The remaining 20 (18%) children had a complete cord injury; of these, 4 improved and 3 died.[103]

KEY REFERENCES

3. Wilkes R, Tasker RC. Pediatric intensive care treatment of uncontrolled status epilepticus: systematic literature search of midazolam and anesthetic therapies. *Crit Care Clin*. 2013;29(2):239–257.
23. Raspall-Chaure M, Chin RFM, Neville BG, et al. Outcome of paediatric convulsive status epilepticus: a systematic review. *Lancet Neurol*. 2006;5(9): 769–779.
24. Abend N, Arndt D, Carpenter J, et al. Electrographic seizures in pediatric ICU patients: Cohort study of risk factors and mortality. *Neurology*. 2013; 81(4):383–391.

31. Visintin C, Mugglestone MA, Fields EJ, et al. Management of bacterial meningitis and meningococcal septicaemia in children and young people: summary of NICE guidance. *BMJ*. 2010;340: c3209.
36. Brouwer M, Mcintyre P, Prasad K, et al. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev*. 2015;(9):CD004405.
55. Zekeridou A, Karantoni E, Viaccoz A, et al. Treatment and outcome of children and adolescents with *N*-methyl-d-aspartate receptor encephalitis. *J Neurol*. 2015;262(8):1859–1866.
64. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. *N Engl J Med*. 2015;372(20): 1898–1908.
65. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after in-hospital cardiac arrest in children. *N Engl J Med*. 2017;376: 318–329.
96. Benson LA, Olson H, Gorman MP. Evaluation and treatment of autoimmune neurologic disorders in the pediatric intensive care unit. *Semin Pediatr Neurol*. 2014;21(4):284–290.
100. Ellaway C, Wilcken B, Christodoulou J. Clinical approach to inborn errors of metabolism presenting in the newborn period. *J Paediatr Child Heal*. 2002; 38(5):511–517.
107. Liao C-C, Lui T-N, Chen L-R, et al. Spinal cord injury without radiological abnormality in preschool-aged children: correlation of magnetic resonance imaging findings with neurological outcomes. *J Neurosurg*. 2005;103(1 suppl):17–23.


Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Suarez J, Qureshi A, Bhardwaj A, et al. Treatment of refractory intracranial hypertension with 23.4% saline. *Crit Care Med*. 1998;26(6):1118–1122.
2. Hanhan U, Fiallos M, Orlowski J. Status epilepticus. *Pediatr Clin North Am*. 2001;48(3):683–694.
3. Wilkes R, Tasker RC. Pediatric intensive care treatment of uncontrolled status epilepticus: systematic literature search of midazolam and anesthetic therapies. *Crit Care Clin*. 2013;29(2):239–257.
4. Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. *Epilepsia*. 1999;40(1):120–122.
5. Lothman E. The biochemical basis and pathophysiology of status epilepticus. *Neurology*. 1990;40(5 suppl 2):13–23.
6. Scott RC, Surtees RAH, Neville BGR. Status epilepticus: pathophysiology, epidemiology, and outcomes. *Arch Dis Child*. 1998;79(1):73–77.
7. Lewena S, Young S. When benzodiazepines fail: How effective is second line therapy for status epilepticus in children? *Emerg Med Australas*. 2006;18(1):45–50.
8. Dieckmann RA. Is the time overdue for an international reporting standard for convulsive paediatric status epilepticus? *Emerg Med Australas*. 2006; 18(1):1–3.
9. Chamberlain JM, Altieri MA, Futterman C, et al. A prospective, randomized study comparing intramuscular midazolam with intravenous diazepam for the treatment of seizures in children. *Pediatr Emerg Care*. 1997;13(2):92–94.
10. Mahmoudian T, Mohammadi Zadeh M. Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children. *Epilepsy Behav*. 2004;5(2):253–255.
11. McIntyre J, Norris E, Appleton R, et al. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. *Lancet*. 2005;366:205–210.
12. Chiulli D, Terndrup T, Kanter R. The influence of diazepam or lorazepam on the frequency of endotracheal intubation in childhood status epilepticus. *J Emerg Med*. 1991;9(1–2):13–17.
13. Appleton R, Sweeney A, Choonara I, et al. Lorazepam versus diazepam in the acute treatment of epileptic seizures and status epilepticus. *Dev Med Child Neurol*. 1995;37(8):682–688.
14. Appleton R, Macleod S, Martland T. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. *Cochrane Database Syst Rev*. 2010;(10):CD001905.
15. Wheless J. Pediatric use of intravenous and intramuscular phenytoin: lessons learned. *J Child Neurol*. 1998;13(S1):11–14.
16. Ng Y, Hastriter E, Cardenas J, et al. Intravenous levetiracetam in children with seizures: a prospective safety study. *J Child Neurol*. 2010;25(5):551–555.
17. Wheless JW, Clarke D, Hovinga CA, et al. Rapid infusion of a loading dose of intravenous levetiracetam with minimal dilution: a safety study. *J Child Neurol*. 2009;24(8):946–951.
18. Abend NS, Huh JW, Helfaer MA, et al. Anticonvulsant medications in the pediatric emergency room and intensive care unit. *Pediatr Emerg Care*. 2008;24(10):705–718.
19. Abend NS, Gutierrez-Colina AM, Dlugos DJ. Medical treatment of pediatric status epilepticus. *Semin Pediatr Neurol*. 2010;17(3):169–175.
20. Rivera R, Segnini M, Baltodano A, et al. Midazolam in the treatment of status epilepticus in children. *Crit Care Med*. 1993;21(7):991–994.
21. Koul RL, Aithala GR, Chacko A, et al. Continuous midazolam infusion as treatment of status epilepticus. *Arch Dis Child*. 1997;76(5):445–448.
22. Ilvento L, Rosati A, Marini C, et al. Ketamine in refractory convulsive status epilepticus in children avoids endotracheal intubation. *Epilepsy Behav*. 2015;49:343–346.
23. Raspall-Chaure M, Chin RFM, Neville BG, et al. Outcome of paediatric convulsive status epilepticus: a systematic review. *Lancet Neurol*. 2006;5(9): 769–779.
24. Abend N, Arndt D, Carpenter J, et al. Electrographic seizures in pediatric ICU patients: Cohort study of risk factors and mortality. *Neurology*. 2013; 81(4):383–391.
25. Wagenman KL, Blake TP, Sanchez SM, et al. Electrographic status epilepticus and long-term outcome in critically ill children. *Neurology*. 2014; 82(5):396–404.
26. Abend NS. Electrographic status epilepticus in children with critical illness: Epidemiology and outcome. *Epilepsy Behav*. 2015;49:223–227.
27. Radetsky M. Fulminant bacterial meningitis. *Pediatr Infect Dis J*. 2014;33(2):204–207.
28. Rennick G, Shann F, de Campo J. Cerebral herniation during bacterial meningitis in children. *BMJ*. 1993;306(6883):953–955.
29. Seward RJ, Towner KJ. Evaluation of a PCR-immunoassay technique for detection of Neisseria meningitidis in cerebrospinal fluid and peripheral blood. *J Med Microbiol*. 2000;49:451–456.
30. Newcombe J, Cartwright K, Palmer WH, et al. PCR of peripheral blood for diagnosis of meningococcal disease. *J Clin Microbiol*. 1996;34(7):1637–1640.
31. Visintin C, Mugglestone MA, Fields EJ, et al. Management of bacterial meningitis and meningococcal septicaemia in children and young people: summary of NICE guidance. *BMJ*. 2010;340: c3209.
32. Chavez-Bueno S, McCracken GHJ. Bacterial meningitis in children. *Pediatr Clin North Am*. 2005;52(3): 795–810, vii.
33. Odio CM, Faingezicht I, Paris M, et al. The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis. *N Engl J Med*. 1991;324(22):1525–1531.
34. McCracken GH, Lebel MH. Dexamethasone therapy for bacterial meningitis in infants and children. *Am J Dis Child*. 1989;143(3):287–289.

35. Schaad UB, Lips U, Gnehm H, et al. Wedgwood j. Dexamethasone therapy for bacterial meningitis in children. *Lancet*. 1993;342(8869):457–461.
36. Brouwer M, Mcintyre P, Prasad K, et al. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev*. 2015;(9):CD004405.
37. Peltola H, Roine I, Fernandez J, et al. Adjuvant glycerol and / or dexamethasone to improve the outcomes of childhood bacterial meningitis: a prospective, randomized, double-blind, placebo controlled trial. *Clin Infect Dis*. 2007;45:1277–1286.
38. Wall ECB, Ajdukiewicz KMB, Heyderman RS, et al. Osmotic therapies added to antibiotics for acute bacterial meningitis. *Cochrane Database Syst Rev*. 2013;(3):CD008806.
39. Duke T, Molyneux EM. Intravenous fluids for seriously ill children: Time to reconsider. *Lancet*. 2003;362(9392):1320–1323.
40. Duke T, Mokela D, Frank D, et al. Management of meningitis in children with oral fluid restriction or intravenous fluid at maintenance volumes: a randomised trial. *Ann Trop Paediatr*. 2002;22(2): 145–157.
41. Powell KR, Sugarman LI, Eskenazi AE, et al. Normalization of plasma arginine vasopressin concentrations when children with meningitis are given maintenance plus replacement fluid therapy. *J Pediatr*. 1990;117(4):515–522.
42. Bianchetti MG, Thyssen HR, Laux-End R, et al. Evidence for fluid volume depletion in hyponatraemic patients with bacterial meningitis. *Acta Paediatr*. 1996;85(10):1163–1166.
43. Singhi SC, Singhi PD, Srinivas B, et al. Fluid restriction does not improve the outcome of acute meningitis. *Pediatr Infect Dis J*. 1995;14(6):495–503.
44. Maconochie I, Bhaumik S. Fluid therapy for acute bacterial meningitis. *Cochrane Database Syst Rev*. 2016;(11):CD004786.
45. Madagame E, Havens P, Bresnahan J, et al. Survival and functional outcome of children requiring mechanical ventilation during therapy for acute bacterial meningitis. *Crit Care Med*. 1995;23(7): 1279–1283.
46. Aurelius E, Johansson B, Sköldenberg B, et al. Rapid diagnosis of herpes simplex encephalitis by nested polymerase chain reaction assay of cerebrospinal fluid. *Lancet*. 1991;337(8735):189–192.
47. Troendle-Atkins J, Demmler GJ, Buffone GJ. Rapid diagnosis of herpes simplex virus encephalitis by using the polymerase chain reaction. *J Pediatr*. 1993; 123(3):376–380.
48. McMinn P, Stratov I, Nagarajan L, et al. Neurological manifestations of enterovirus 71 infection in children during an outbreak of hand, foot, and mouth disease in Western Australia. *Clin Infect Dis*. 2001;32(2):236–242.
49. Rotbart HA, Webster AD. Treatment of potentially life-threatening enterovirus Infections with pleconaril. *Clin Infect Dis*. 2001;32(2):228–235.
50. Kramer AH. Viral encephalitis in the ICU. *Crit Care Clin*. 2013;29:621–649.
51. Ramanathan S, Mohammad SS, Brilot F, et al. Autoimmune encephalitis: Recent updates and emerging challenges. *J Clin Neurosci*. 2014;21(5): 722–730.
52. Gable MS, Sheriff H, Dalmau J, et al. The frequency of autoimmune *N*-methyl-d-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the california encephalitis project. *Clin Infect Dis*. 2012;54(7):899–904.
53. Ryan N. Anti-N-methyl-d-aspartate receptor-mediated encephalitis: recent advances in diagnosis and treatment in children. *Curr Probl Pediatr Adolesc Health Care*. 2016;46(2):58–61.
54. Jones KC, Benseler SM. Moharir M. Anti-NMDA receptor encephalitis. *Neuroimaging Clin N Am*. 2013; 23:309–320.
55. Zekeridou A, Karantoni E, Viaccoz A, et al. Treatment and outcome of children and adolescents with *N*-methyl-d-aspartate receptor encephalitis. *J Neurol*. 2015;262(8):1859–1866.
56. Al-Jarallah A, Al-Rifai M, Riela A, et al. Nontraumatic brain hemorrhage in children: etiology and presentation. *J Child Neurol*. 2000;15(5): 284–289.
57. De Caen AR, Maconochie IK, Aickin R, et al. Part 6: Pediatric basic life support and pediatric advanced life support: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation*. 2015;132: S177–S203.
58. Zeiner A, Holzer M, Sterz F, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. *Arch Intern Med*. 2001; 161(16):2007–2012.
59. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346(8):557–563.
60. The Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346(8):549–556.
61. Shankaran S, Laptook A, Ehrenkranz R, et al. Whole-body hypothermia for neonates with hypoxic–ischemic encephalopathy. *NEJM*. 2005;353:1574–1584.
62. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: Multicentre randomised trial. *Lancet*. 2005;365(9460): 663–670.
63. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33oC versus 36oC after cardiac arrest. *N Engl J Med*. 2013;369(23): 2197–2206.
64. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. *N Engl J Med*. 2015;372(20): 1898–1908.

65. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after in-hospital cardiac arrest in children. *N Engl J Med*. 2017;376:318–329.
66. Sarnaik A, Preston G, Lieh-Lai M, et al. Intracranial pressure and cerebral perfusion pressure in near-drowning. *Crit Care Med*. 1985;13:224–227.
67. Maconochie IK, Bingham R, Eich C, et al. European Resuscitation Council Guidelines for Resuscitation 2015. Section 6. Paediatric life support. *Resuscitation*. 2015;95:223–248.
68. Schindler MB, Bohn D, Cox PN, et al. Outcome of out-of-hospital cardiac or respiratory arrest in children. *N Engl J Med*. 1996;335(20):1473–1479.
69. Kriel RL, Krach LE, Luxenberg MG, et al. Outcome of severe anoxic/ischemic brain injury in children. *Pediatr Neurol*. 1994;10(3):207–212.
70. Beca J, Cox PN, Taylor MJ, et al. Somatosensory evoked potentials for prediction of outcome in acute severe brain injury. *J Pediatr*. 1995;126(1): 44–49.
71. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barre syndrome. *Lancet*. 2016;388:717–727.
72. Parra B, Lizarazo J, Jiménez-Arango JA, et al. Guillain-Barré syndrome associated with Zika virus infection in Colombia. *N Engl J Med*. 2016; 375(16):1513–1523.
73. Yuki N, Hartung H-P. Guillain-Barre syndrome. *N Engl J Med*. 2012;366(24):2294–2304.
74. Manners PJ, Murray KJ. Guillain-Barre syndrome presenting with severe musculoskeletal pain. *Acta Paediatr*. 1992;81(12):1049–1051.
75. Cole GF, Matthew DJ. Prognosis in severe Guillain-Barré syndrome. *Arch Dis Child*. 1987;62(3):288–291.
76. Hadden RDM, Cornblath DR, Hughes RAC, et al. Electrophysiological classification of guillain-barré syndrome: Clinical associations and outcome. *Ann Neurol*. 1998;44:780–788.
77. Pritchard J. What's new in Guillain-Barre syndrome? *Postgrad Med J*. 2008;84(996):532–538.
78. Coskun A, Kumandas S, Pac A, et al. Childhood Guillain-Barre syndrome. MR imaging in diagnosis and follow-up. *Acta Radiol*. 2003;44(2):230–235.
79. Yikilmaz A, Doganay S, Gumus H, et al. Magnetic resonance imaging of childhood Guillain-Barre syndrome. *Childs Nerv Syst*. 2010;26(8):1103–1108.
80. van der Meché FGA, Schmitz PIM. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. *N Engl J Med*. 1992;326(17):1123–1129.
81. Hughes R, Swan A, van Doorn P. Intravenous immunoglobulin for Guillain-Barré syndrome. *Cochrane Database Syst Rev*. 2014;(9):CD002063.
82. Raphaël J, Chevret S, Hughes R, et al. Plasma exchange for Guillain-Barré syndrome. *Cochrane Database Syst Rev*. 2012;(7):CD001798.
83. Jansen P, Perkin R, Ashwal S. Guillain-Barre syndrome in childhood: natural course and efficacy of plasmapheresis. *Pediatr Neurol*. 1993;9(1):16–20.
84. Lamont PJ, Johnston HM, Berdoukas VA. Plasmapheresis in children with Guillain-Barre syndrome. *Neurology*. 1991;41(12):1928–1931.
85. Shahar E, Leiderman M. Outcome of severe Guillain-Barre syndrome in children: comparison between untreated cases versus gamma-globulin therapy. *Clin Neuropharmacol*. 2003;26(2):84–87.
86. Ortiz-Corredor F, Peña-Preciado M. Use of immunoglobulin in severe childhood Guillain-Barré syndrome. *Acta Neurol Scand*. 2007;115(4):289–293.
87. Vajsar J, Sloane A, Wood E, et al. Plasmapheresis vs intravenous immunoglobulin treatment in childhood Guillain-Barre syndrome. *Arch Pediatr Adolesc Med*. 1994;148(11):1210–1212.
88. Hughes R, Wijdicks E, Barohn R, et al. Practice parameter: immunotherapy for Guillain-Barre syndrome: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2003;61(6):736–740.
89. Oczko-Walker M, Manousakis G, Wang S, et al. Plasma exchange after initial intravenous immunoglobulin treatment in Guillain-Barre syndrome: critical reassessment of effectiveness and cost-efficiency. *J Clin Neuromuscul Dis*. 2010;12(2):55–61.
90. Dale RC, Brilot F, Banwell B. Pediatric central nervous system inflammatory demyelination: acute disseminated encephalomyelitis, clinically isolated syndromes, neuromyelitis optica, and multiple sclerosis. *Curr Opin Neurol*. 2009;22(3):233–240.
91. Pavone P, Pettoello-Mantovano M, Le Pira A, et al. Acute disseminated encephalomyelitis: A long-term prospective study and meta-analysis. *Neuropediatrics*. 2010;41(6):246–255.
92. Absoud M, Parslow RC, Wassmer E, et al. Severe acute disseminated encephalomyelitis: a paediatric intensive care population-based study. *Mult Scler*. 2011;17(10):1258–1261.
93. Singh S, Alexander M. Acute disseminated encephalomyelitis: MR imaging features. *AJR Am J Roentgenol*. 1999;173:1101–1107.
94. Marin SE, Callen DJA. The magnetic resonance imaging appearance of monophasic acute disseminated encephalomyelitis. An update post application of the 2007 consensus criteria. *Neuroimaging Clin N Am*. 2013;23(2):245–266.
95. Rostasy K, Bajer-Kornek B, Venkateswaran S, et al. Differential diagnosis and evaluation in pediatric inflammatory demyelinating disorders. *Neurology*. 2016;87(9 suppl 2):S28–S37.
96. Benson LA, Olson H, Gorman MP. Evaluation and treatment of autoimmune neurologic disorders in the pediatric intensive care unit. *Semin Pediatr Neurol*. 2014;21(4):284–290.
97. Suppiej A, Cainelli E, Casara G, et al. Long-term neurocognitive outcome and quality of life in pediatric acute disseminated encephalomyelitis. *Pediatr Neurol*. 2014;50(4):363–367.
98. Ketelslegers IA, Neuteboom RF, Boon M, et al. A comparison of MRI criteria for diagnosing pediatric ADEM and MS. *Neurology*. 2010;74(18): 1412–1415.
99. Chaves-Carballo E. Detection of inherited neurometabolic disorders. A practical clinical approach. *Pediatr Clin North Am*. 1992;39(4):801–820.

100. Ellaway C, Wilcken B, Christodoulou J. Clinical approach to inborn errors of metabolism presenting in the newborn period. *J Paediatr Child Heal*. 2002; 38(5):511–517.
101. Schaefer F, Straube E, Oh J, et al. Dialysis in neonates with inborn errors of metabolism. *Nephrol Dial Transplant*. 1999;14:910–918.
102. Fletcher JM. Metabolic emergencies and the emergency physician. *J Paediatr Child Heal*. 2016;52(2): 227–230.
103. Hadley MN, Zabramski JM, Browner CM. Pediatric spinal trauma: Review of 122 cases of spinal cord and vertebral column injuries. *J Neurosurg*. 1988;68:18–24.
104. Givens TG, Polley KA, Smith GF, et al. Pediatric cervical spine injury: a three-year experience. *J Trauma*. 1996;41(2):310–314.
105. McCall T, Fassett D, Brockmeyer D. Cervical spine trauma in children: a review. *Neurosurg Focus*. 2006;20(2):E5.
106. Dare AO, Dias MS, Li V. Magnetic resonance imaging correlation in pediatric spinal cord injury without radiographic abnormality. *J Neurosurg*. 2002;97(1 suppl):33–39.
107. Liao C-C, Lui T-N, Chen L-R, et al. Spinal cord injury without radiological abnormality in preschool-aged children: correlation of magnetic resonance imaging findings with neurological outcomes. *J Neurosurg*. 2005;103(1 suppl):17–23.
108. Bracken MB, Shepard MJ, Holford TR, et al. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. *JAMA*. 1997;277(20):1597–1604.
109. Sayer FT, Kronvall E, Nilsson OG. Methylprednisolone treatment in acute spinal cord injury: the myth challenged through a structured analysis of published literature. *Spine J*. 2006;6(3):335–343.
110. Rozzelle CJ, Aarabi B, Dhall SS, et al. Management of pediatric cervical spine and spinal cord injuries. *Neurosurgery*. 2013;72(S2):205–226.
111. Theodore N, Aarabi B, Dhall SS, et al. The diagnosis and management of traumatic atlantooccipital dislocation injuries. *Neurosurgery*. 2013; 72(S2):114–126.
112. Jones T, Ugalde V, Franks P, et al. Venous thromboembolism after spinal cord injury: Incidence, time course, and associated risk factors in 16,240 adults and children. *Arch Phys Med Rehabil*. 2005;86(12):2240–2247.

112

Paediatric trauma

Kevin McCaffery

In developed countries, trauma continues to be the leading cause of death in children over 1 year of age.[1] When the additional vast burden of morbidity is added, it is clear that this spectrum of pathologies deserve urgent, ongoing and proactive attention.

Paediatric trauma is *complex* – an easily overlooked concept, particularly for those who mostly care for traumatised adults, yet this understanding is crucial to the provision of an effective paediatric trauma service.

This chapter is written principally from the viewpoint of the intensive care specialist faced with a seriously injured child. As intensive care involvement frequently begins with a request to assist with pre-hospital care or retrieval, key management priorities for this phase are included in the wider intensive care discussion.

OPPORTUNITIES FOR INTERVENTION

Death following trauma has long been considered to have a trimodal distribution (immediate, early <4 hours and delayed). Later publications challenge this pattern of distribution, though the concept remains philosophically useful. A number of phases can be defined in the journey of a severely traumatised patient, requiring different types of intervention (Fig. 112.1). A mature 'trauma system' or 'trauma team' would be expected to be aware of and active in all phases of trauma management from pre-injury prevention to rehabilitation following definitive care.

TRAUMA

This phase is commonly unexpected and sudden, with little opportunity to mitigate harm. All useful interventions at the point of injury are derived from those emplaced during the pre-trauma phase. *The most important interventions in the management of trauma are those that prevent injury occurring in the first place.*

PRE-TRAUMA

In a number of areas, legislation and public safety campaigns have led to decreased morbidity and mortality. Notable successes lie in the areas of motor vehicle legislation (e.g. seatbelt laws, drink–driving legislation), bicycle legislation (cycle helmets and education), water safety (pool fencing, water safety and swimming lessons) and burn reduction (smoke detectors, limitation of hot water temperature).

By any measure, politicians and legislators rank amongst the most effective members of the expanded 'trauma team', though it should be noted that they can be susceptible to influence by pressure groups, as exemplified by the turbulent (and ongoing) evolution of swimming-pool fencing regulations in Australia.[2]

PRE-HOSPITAL CARE

Two models for pre-hospital care predominate in the Western world.[3] In the United States, the prevailing concept is that of 'scoop and run' by paramedical staff to designated 'trauma centres'. The principal driver of this process was the decreased battlefield mortality seen between World War II (4.5%) and the Vietnam War (1.9%). A number of innovations contributed to this decrease, but increasing rapidity of casualty evacuation to well-equipped surgical hospitals was a key feature.

Conversely, the model adopted by several European and Scandinavian countries involves the use of paramedic-crewed ambulances supported by a well-developed network of physician-manned ambulances – essentially mobile intensive care units.

On current evidence, neither system is demonstrably superior to the other, for it is likely that differences in such variables as geography and distance, prevalence of penetrating versus blunt trauma, and cost and resource implications will favour different models in different areas.

Furthermore, in comparison with adults, seriously traumatised children are more likely to require secondary transfer to a paediatric trauma centre after initial stabilisation is undertaken, owing to concentration of paediatric expertise in a smaller number of centres.

THE DEVELOPMENT OF 'TRAUMA TEAMS, CENTRES AND SERVICES'

The concept of multidisciplinary teams and institutions with specific interest and expertise in trauma

ABSTRACT

Trauma is the leading cause of childhood death above 1 year of age in developed countries, and differs in a number of important respects from adult trauma. Anatomical, physiological and developmental differences between ages result in differing injury patterns and often management. Assessment is increasingly challenging with decreasing age. Furthermore, concentration of paediatric trauma services into fewer institutions may lead to both increased likelihood of secondary transfers and increased time to definitive care. As with adult trauma, development of trauma teams and systems active in all phases of trauma from pre-injury through to rehabilitation may assist in the development of integrated trauma response systems for paediatric trauma and advocacy for public health measures aimed at trauma prevention.

KEYWORDS

Paediatric
trauma
injury
head injury
abdominal injury
spinal injury
thoracic injury
non-accidental injury
burns

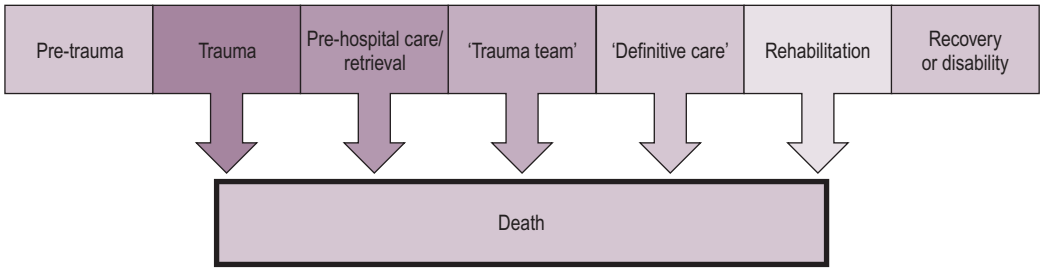


Figure 112.1 Phases of severe paediatric trauma.

management began to develop in the 1950s and 1960s. Currently, most developed countries have accreditation processes for trauma services and designate different centres by 'level' based on their capabilities.

In addition to doctors and nurses from acute specialties, such as the emergency department, surgical subspecialties, anaesthesiology and critical care, the wider multidisciplinary team frequently includes trauma coordinators, research staff and rehabilitation specialists such as physiotherapists, psychologists and social workers. Similarly, the remit of trauma teams, centres and services has expanded beyond simple care of the traumatised patient to include data collection and analysis, development of injury-prevention strategies, education and coordination of regional trauma services.

There is growing evidence that the development of trauma teams, centres and services improves outcomes for injured adults[4] and children.[5] However, opinion is more divided on whether or not outcomes for seriously traumatised children are improved when managed in designated paediatric trauma centres compared with adult trauma centres.[6,7]

SPECIFIC PAEDIATRIC TRAUMA PRESENTATIONS

Differing mechanisms of injury may be associated with specific patterns of injury in both children and adults, though anatomical and physiological differences between age groups will alter the pattern seen. Children requiring intensive care admission will have serious injury to one or more of the following systems.

TRAUMATIC BRAIN INJURY

Brain injury, resulting either directly from trauma or indirectly from hypoxic–ischaemic insult, accounts for the majority of deaths and long-term severe morbidity in paediatric trauma. Once the insult has occurred, management is entirely focused on the prevention of secondary insults and further damage. Conventionally this involves control of intracranial hypertension, defence of cerebral perfusion pressure (CPP) and minimisation of injurious factors such as seizures, hypo- or hyperglycaemia and fever. An overview of this topic is provided below, but those wishing a comprehensive review of the current evidence base behind current management of paediatric traumatic brain injury (TBI) are directed to guideline documents published by the Brain Trauma Foundation.[8]

PAEDIATRIC TRAUMATIC BRAIN INJURY: ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

Adult brain volume is reached around 6 years of age, whereas skull growth continues until around 16 years of age. Children thus have less room for brain swelling within the rigid skull. This is compounded by differences between children and adults in adaptive mechanisms to defend against raised intracranial pressure (ICP), including smaller relative cerebrospinal fluid (CSF) volumes, higher intracellular concentrations of sodium and impaired ability of neurons to extrude sodium. In addition to the propensity of smaller children to raised ICP, CPP may be further compromised by the similarities in autoregulation of cerebral blood flow between small and larger children, affording smaller patients less safety margin.[9]

NEUROLOGICAL ASSESSMENT AND MONITORING OF CHILDREN

Priorities of the assessment process are as follows:

- to benchmark neurological function over time
- to identify lesions and problems requiring treatment
- to identify prognostic markers.

Neurological assessment in childhood presents challenges in compliance with examination. An appreciation of child development and the use of age-appropriate tools (e.g. a modified Glasgow Coma Score) greatly facilitate this assessment. Assessment is best done as a process involving frequent clinical assessments over time, supplemented where indicated by targeted investigations such as computed tomography (CT) or magnetic resonance imaging (MRI).

Invasive monitoring of ICP and arterial blood pressure allows identification of deleterious ICP and permits calculation of CPP.

ICP monitoring should be zero calibrated at the tragus of the ear with the patient inclined 30 degrees. The target ICP threshold requiring management has not been defined in paediatrics, but current evidence would support an upper value of 20 mm Hg (2.66 kPa). Lower values of 15–20 mm Hg (2–2.66 kPa) may be more appropriate for small infants.

CPP is defined as *mean arterial pressure (MAP) – mean ICP*. Mean arterial pressure should be zero calibrated at the level of the right atrium with the patient inclined 30 degrees. It should be noted that the difference in zero level between ICP and MAP will not give a true CPP as stated, and that the error will increase with increasing patient length. It does, however, allow for standardisation of measurement within routine clinical practice. As with ICP, target CPP thresholds requiring management have not been defined for children, but current evidence *in TBI* supports a CPP target of ≥40 mm Hg (5.32 kPa) for 0–5-year-olds, and ≥50 mm Hg (6.65 kPa) for 6–17-year-olds.[10]

MANAGEMENT PRIORITIES IN THE CHILD WITH HEAD INJURY

Management of paediatric neurotrauma is entirely focused on minimising secondary injury to neurons. Principles include the following:

Management of intracranial pressure

This involves manipulation of intracranial contents as described in the Monroe–Kellie hypothesis. Thus, the intracranial volume lying within the incompressible skull is composed of brain tissue, blood and CSF, and any increase in the volume of one of the components must be compensated for by a reduction in volume of the others. Interventions may therefore manipulate the following volumes:

- **Blood compartment:** decreasing intracranial blood volume may be tackled in three ways:
  - *Extravasated blood:* significant collections require surgical evacuation.
  - *Venous compartment:* venous drainage may be optimised by avoidance of venous obstruction (spinal collar, internal jugular lines, excessive positive end-expiratory pressure [PEEP]) and patient positioning (30 degrees head up, head midline). One small paediatric study demonstrated that increased head-up bed angle decreased ICP but not CPP.[11] Judicious sedation and muscle relaxation decrease the incidence of coughing, shivering and asynchrony with mechanical ventilation.
  - *Arterial compartment:* manipulation of this compartment requires brain tissue with preserved autoregulation to P_{CO_2}, pH, viscosity and metabolic demand. Thus, mild hyperventilation will vasoconstrict these areas, thereby decreasing the volume of the arterial bed. Prolonged or extreme hypocarbia should be avoided due to the potential for ischaemia, particularly to vulnerable penumbral areas of the injured brain. Hypercarbia must also be avoided as it will increase ICP. Volume-controlled ventilation may permit more stable blood gases.

    Osmotic agents such as 3% (hypertonic) saline or mannitol exert a rheological effect by dehydrating red blood cells. The resultant decrease in blood viscosity permits a degree of cerebral vasoconstriction while still meeting metabolic demands. The use of hypertonic saline in preference to mannitol appears better supported in the literature to date.

    Decreasing neuronal metabolic demand can lower ICP. Seizures should be controlled and hyperthermia avoided. Second-tier therapies, such as barbiturates and therapeutic hypothermia (32°C–33°C), have been demonstrated to decrease refractory raised ICP. However, both have potential serious side effects and limited evidence to support routine use. Recent randomised controlled trials (RCTs) of therapeutic hypothermia versus normothermia in children have failed to demonstrate differences in functional outcome, and either no difference in mortality[12,13] or a trend towards increased morbidity and mortality in the cooled group.[14]
- **CSF volume:** external ventricular drainage of the lateral ventricles allows decrease in CSF volumes in addition to ICP monitoring. However, this may not be practical if the ventricles have already been effaced.
- **Brain volume:** osmotherapy with hypertonic saline or mannitol may decrease intracranial volume by dehydrating neurons in areas with an intact blood–brain barrier.

A fourth mechanism for decreasing ICP is to undertake a decompressive craniectomy. Although recent RCT data in adults demonstrated decreased ICPs in patients receiving this intervention, the operated group also experienced worse outcomes.[15] In paediatrics, although a number of small studies have demonstrated the utility of decompressive craniectomy in reducing raised ICP, evidence of effect on outcomes is lacking.[4,16]

Centres with limited experience in managing paediatric neurotrauma may benefit from structured guidelines, an example of which is the Scottish Intercollegiate Guideline Network (SIGN) guideline 110: Early management of patients with a head injury.[17]

A number of prognostic markers in head injury have been identified. These include the Glasgow Coma Scale, Injury Severity Score and initial hypotension.[18] Of note, the motor score component of the Glasgow Coma Scale may be as predictive as using the entire score.[19]

THORACIC TRAUMA

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

The immature rib cage is largely cartilage, and ossifies through childhood. Compliant ribs allow transmission of greater impact energy to underlying viscera, allowing severe contusion without necessarily fracturing. Furthermore, the compliant infant chest and relatively transverse ribs impair the tolerance of upper airway obstruction.

Increased basal metabolic rate and reduced functional residual capacity result in a more rapid onset of hypoxaemia in younger children, and this may be compounded in infancy by physiologically low haemoglobin.

ASSESSMENT AND MANAGEMENT OF THORACIC TRAUMA

Immediate assessment of a child with thoracic trauma is focused on identifying life-threatening injuries, which include:

- large airway disruption
- tension pneumothorax
- open pneumothorax
- massive haemothorax
- flail segment
- cardiac tamponade.

Management is guided by the specific findings from the primary survey, but severe thoracic trauma is likely to require intubation and ventilation, with pleural or pericardial drainage as indicated. Rare, but severe, injuries that may be difficult to detect during resuscitation and therefore require a high index of suspicion include major vascular injuries, thoracic spinal injuries and traumatic diaphragmatic hernia.

A chest X-ray is a component of routine trauma assessment and may be supplemented as indicated by ultrasound assessment and CT. Angiography of the great vessels may be undertaken formally or as part of the CT scan. Serial arterial gases guide requirements for ventilatory support.

ABDOMINAL TRAUMA

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

The orientation of the compliant ribs in small children affords less protection to the disproportionately large liver and spleen when compared with older children or adults, while the shallow pelvis leaves the bladder at similar risk.

Small children are difficult to examine. They are also prone to aerophagia with distension of the stomach increasing emesis risk, and in some cases leading to diaphragmatic splinting.

Paediatric abdominal trauma is largely blunt in nature, and solid organ injury occurs far more commonly than hollow visceral injury. Certain mechanisms of injury should lead to the suspicion of characteristic injuries. These include 'handlebar into epigastrium' associated with pancreatic or duodenal injury, lap-belt injuries in motor vehicle accidents leading to small bowel rupture, diaphragmatic injury or Chance fracture (flexion) of the lumbar spine. Given the difficulties in diagnosis, a high index of suspicion for abdominal injuries in trauma in children is essential.

When suspicion of abdominal injury exists, repeated clinical examination over time is supplemented by plain abdominal x-rays, ultrasonography or CT scanning as indicated. In haemodynamically stable blunt paediatric trauma, focused abdominal sonography for trauma (FAST) currently lacks the sensitivity and positive predictive power for use as a definitive screening tool, but may be a useful adjunct to better target CT assessment.[20] CT scanning of the abdomen is considered the gold standard.

In most paediatric trauma involving the abdomen, management is expectant. Laparotomy is generally reserved for the following situations:

- penetrating injury
- hollow viscus perforation (bladder rupture/pneumoperitoneum)
- haemodynamic instability despite adequate fluid resuscitation (≥40 mL/kg)
- peritonism (later sign)
- diaphragmatic rupture.

Even high grades of splenic or hepatic laceration may be managed conservatively, provided assessment is frequent and the patient is managed in a facility with the ability to intervene surgically at short notice.

SPINAL INJURY

Spinal injury in children is rare, often difficult to diagnose and potentially devastating if missed. Challenges include the anatomical and physiological differences between adults and children, which both change the types of injury commonly seen and make radiological interpretation difficult and clinical examination challenging. Furthermore, as spinal injuries are rare, the benefits of managing injured children in a paediatric facility must be balanced against the expertise available in adult spinal injury centres.

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

There are differences in the immature spine and the proportionally more massive head change patterns of paediatric injury compared with adults. High lesions from the occipitoaxial junction to C3 are more common than the more typical C4–C5 lesions seen in older patients. In addition, the elasticity of paediatric

ligaments may lead to the phenomenon of spinal cord injury without radiological abnormality (SCIWORA), present in 17%–43% of paediatric cord injuries.[21,22]

Mechanisms of injury change at different stages of development, with an increasing incidence of sports injuries in older children.[21]

Pre-verbal children present challenges in assessment and even older children may regress and become uncompliant with clinical examination. Additionally, progressive ossification of the spine during childhood renders radiological interpretation problematic.

Spinal cord injury in children, particularly when very young, leads to an increased incidence of scoliosis, tracheostomy (due to the increased incidence of high lesions) and progressive pulmonary insufficiency.

ASSESSMENT AND MANAGEMENT

The possibility of spinal cord injury should be considered in all significant trauma, and particularly following motor vehicle accidents, rapid deceleration injuries or in the presence of multisystem trauma, head injuries, other injuries above the clavicle or abnormal neurological signs.

The first priority is spinal immobilisation, which should occur in the pre-hospital phase.

Clinical assessment is supplemented by plain radiography in the initial assessment. In severely traumatised patients, early neck clearance by clinical examination is not possible, and even plain radiography in three views – which has 94% sensitivity – may fail to detect SCIWORA. CT and MRI contribute additional information, but still will not detect all lesions even when motor signs are present.[23]

Spinal precautions must be maintained until either the neck is deemed to be uninjured, stable on clinical and radiological grounds or until fixation has occurred.

Use of steroids or hypothermia in paediatric spinal injury is not supported by evidence at this time and is not regarded as mainstream therapy.

Early feeding, gastric protection with proton pump inhibitors, bowel care, care of skin and pressure points and prevention of contractures are important interventions if not precluded by other injuries. Similarly, early access to rehabilitation services may improve functional outcomes.

BURNS

Burns are a common cause of accidental death in childhood.[24] Younger children predominantly suffers scalds, whereas older children are more likely to present with flame burns. Burns are often included within the extended scope of trauma as many mechanisms leading to burns are also associated with traumatic injury (motor vehicle accidents, explosions, etc.). Additionally, when confronted by the prospect of burning, patients will frequently risk or incur traumatic injuries during attempted escape.

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

The increased surface area/weight ratio of children compared with adults leads to a number of problems. Fluid loss from the burn may rapidly lead to dehydration, and any surface cooling undertaken increases the risk of iatrogenic hypothermia. Furthermore, alteration in body proportions from birth to adulthood mandates the use of specific methods for estimating paediatric burn surface area such as the modified Lund and Browder chart. Estimated burn surface area may be made using the area of the child's palm with outstretched fingers with each such area corresponding to 1% of body surface area (areas of erythema should *not* be included in estimation of burn surface area).

Mechanisms of injury and patterns of burn are different to adults. Small, curious children below the level of kitchen work surfaces are commonly scalded on the face, head and upper body when pulling pans and kettles down, an injury exacerbated by a disproportionately large head. Similarly, severe hand injuries may follow attempts to grasp hot objects or, in older children, fireworks.

The small paediatric airway is particularly vulnerable to upper airway obstruction following smoke inhalation.

Finally, paediatric burn injury may result in profound and progressive disability. Thick burn scarring may distort normal somatic growth, and psychological scarring may severely compromise social development.

INITIAL MANAGEMENT

First aid for burns involves cooling for no longer than 20 minutes, using tepid (not cold) water. As burns and trauma frequently co-exist, a trauma primary survey (**a**irway + cervical spine control, **b**reathing, **c**irculation, **d**isability) should be rapidly carried out. The findings of particular relevance are listed in Box 112.1.

Once cooled, burns should be covered with sterile, non-occlusive dressings. Creams or ointments should not be applied unless advised by the local burns surgeon. Adequate hydration is required to optimise perfusion of injured areas. Fluid regimens such as the Parkland, Brooke or Galveston formulae (or modifications thereof – see Box 112.2: modified Parkland formula) are routinely initiated.

Pain relief with opioids and consideration of need for escharotomy where burns are circumferential should occur early, and be repeated frequently as required.

DEFINITIVE CARE

Major burns are best managed by burns centres. Burned patients in the intensive care unit are commonly ventilated for inhalational injury or to facilitate pain management. These patients require meticulous attention to fluid and electrolyte balance, nutrition, analgesia and wound care. Frequent trips to the operating room

Box 112.1 Primary survey findings in burns

Airway: is there actual or impending airway compromise?
- History of burn in enclosed space
- Facial burns/swelling
- Stridor or respiratory distress
- Carbonaceous sputum

Breathing: is there respiratory compromise?
- Respiratory distress
- Cyanosis
- Thoracic or upper abdominal burns
- Circumferential thoracic burns

Circulation: is there evidence of hypotension or hypovolaemia?
- Calculate burn surface area, ascertain time of injury to facilitate fluid management
- Shock from associated injuries?

Disability (neurology): is there impairment of conscious level?
- Carboxyhaemoglobin level?
- Other toxins from smoke (e.g. cyanide)?
- Associated head injury?

Box 112.2 Modified parkland formula

Patients require resuscitation fluids + maintenance fluids.

Resuscitation fluids: 3–4 mL Hartmann's solution × weight (kg) × %total body surface area burned.

Half of this volume is given in the first 8 h from time of injury, with the remainder given over the subsequent 16 h.

Maintenance fluids (commonly Hartmann's + 5% dextrose): 100 mL/kg/day for the first 10 kg, 50 mL/kg/day for the next 10 kg then 20 mL/kg/day for every kg thereafter.
- This formula is used in burns exceeding 15% of total body surface area.
- Fluid boluses given during resuscitation may be subtracted *unless* pre-existing dehydration or associated injuries exist.
- The aim is for *adequate* urine output: 1–2 mL/kg/h < 30 kg; 0.5–1 mL/kg/h > 30 kg

for dressing changes, wound debridement or skin grafting are expected. Routine antibiotics are not indicated, but patients require close monitoring for signs of evolving sepsis. Wound swabs and debrided tissue for culture assist in surveillance for sepsis.

NON-ACCIDENTAL INJURY

A significant proportion of children presenting with trauma will have been injured deliberately or through neglect, often by a parent or care giver. Although confrontational, this is an important diagnosis to consider as it has profound implications for the future safety of both the affected child and the family at large. In many countries there is an obligation on health care practitioners to report concerns to child protective services.

Although presentations are highly variable and may be covert, there are a number of risk factors that may increase the likelihood of an injury being factitious, as follows.

INJURY CHARACTERISTICS
- Delayed presentation of injury
- Injury inconsistent with history provided
- Injury inconsistent with child's developmental stage
- Injury with suspicious pattern as follows:

Bruising
- Specific patterns (e.g. belt buckle, handprints, loop marks from flex)
- Multiple bruises of differing ages

Fractures
- Fractures of different ages
- Specific patterns (e.g. spiral humeral fracture)

Burns
- Specific patterns (e.g. immersion [glove/stocking/thighs, sometimes sparing buttocks and backs of knees], cigarette or cooker-top)
- Burns of different ages

Others
- Retinal haemorrhages
- Bite marks
- Bleeding from, or trauma to, anus, genitalia or oral frenula.

In addition to features of the injury, there are numerous patient and social factors increasing the risk of factitious injury, which include amongst others:

- *patient factors:* young age, congenital anomalies, physical or intellectual disability, adoption, etc.
- *social factors:* young or single parents, unstable family situations, substance abuse and parents who were themselves abused. Environmental stresses include divorce or financial/legal/professional difficulties.

SUMMARY

Paediatric trauma differs in important respects from trauma in adults, and is associated with a vast burden of morbidity and mortality. The development of dedicated paediatric trauma teams or services appears to be associated with improved outcomes, and represents a powerful mechanism for developing and disseminating regionally appropriate protocols, undertaking research and engaging legislators.

KEY REFERENCES

1. *Deaths, final data for 2009*. National Vital Statistics Reports 2012. Centers for Disease Control and Prevention. Online. Available: http://www.cdc.gov/nchs/data_access/Vitalstatsonline.htm.
3. Nathens AB, Brunet FP, Maier RV. Development of trauma systems and effect on outcomes after injury. *Lancet*. 2004;363:1794–1801.
5. Rupp RA, Megargel R, Reed III J, et al. Traumatic pediatric mortality based on Injury Severity Score (ISS): a retrospective study from the Delaware Trauma System 1998–2007. *Ann Emerg Med*. 2011; 58(4s):S241.
8. Kochanek PM, Carney N, Adelson PD, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents – second edition. *Pediatr Crit Care Med*. 2012;13(suppl 1):S1–S82.
14. Hutchison JS, Ward RE, Lacroix J, et al. Hypothermia therapy after traumatic brain injury in children. *N Engl J Med*. 2008;358:2447–2456.
15. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med*. 2011;364(16):1493–1502.

Access the complete references list online at http://www.expertconsult.com.

REFERENCES

1. *Deaths, final data for 2009*. National Vital Statistics Reports 2012. Centers for Disease Control and Prevention. Online. Available: http://www.cdc.gov/nchs/data_access/Vitalstatsonline.htm.
2. Scott I. *Prevention of drowning in home pools: lessons from Australia*. Online. Available: http://www.royallifesaving.com.au.
3. Nathens AB, Brunet FP, Maier RV. Development of trauma systems and effect on outcomes after injury. *Lancet*. 2004;363:1794–1801.
4. MacKenzie EJ, Rivara FP, Jurkovich GJ, et al. A national evaluation of the effect of trauma-center care on mortality. *N Engl J Med*. 2006;354:366–378.
5. Rupp RA, Megargel R, Reed J III, et al. Traumatic pediatric mortality based on Injury Severity Score (ISS): a retrospective study from the Delaware Trauma System 1998–2007. *Ann Emerg Med*. 2011;58(4s):S241.
6. Amini R, Lavoie A, Moore L, et al. Pediatric trauma mortality by type of designated hospital in a mature, inclusive trauma system. *J Emerg Trauma Shock*. 2011;4(1):12–19.
7. Osler TM, Vane DW, Tepas JJ, et al. Do pediatric trauma centres have better survival rates than adult trauma centers? An examination of the National Pediatric Trauma Registry. *J Trauma*. 2001;50(1):96–101.
8. Kochanek PM, Carney N, Adelson PD, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents – second edition. *Pediatr Crit Care Med*. 2012;13(suppl 1):S1–S82.
9. Vavilala MS, Lee LA, Lam AM. The lower limit of cerebral autoregulation in children during sevoflurane anesthesia. *J Neurosurg Anesthesiol*. 2003;15:307–312.
10. Allen BB, Chiu Y, Gerber LM, et al. Age-specific cerebral perfusion pressure thresholds and survival in children and adolescents with severe traumatic brain injury. *Pediatr Crit Care Med*. 2014;15(1):62–70.
11. Agbeko RS, Pearson S, Peters MJ, et al. Intracranial pressure and cerebral perfusion pressure responses to head elevation changes in pediatric traumatic brain injury. *Pediatr Crit Care Med*. 2012;13(1):e39–e47.
12. Adelson PD, Ragheb J, Kanev P, et al. Phase II clinical trial of moderate hypothermia after severe traumatic brain injury in children. *Neurosurgery*. 2005;56:740–754.
13. Adelson PD, Wisniewski SR, Beca J, et al. Comparison of hypothermia and normothermia after severe traumatic brain injury in children (Cool Kids): a phase 3, randomized controlled trial. *Lancet Neurol*. 2013;12:546–553.
14. Hutchison JS, Ward RE, Lacroix J, et al. Hypothermia therapy after traumatic brain injury in children. *N Engl J Med*. 2008;358:2447–2456.
15. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med*. 2011;364(16):1493–1502.
16. Taylor A, Butt W, Rosenfeld J, et al. A randomized trial of very early decompressive craniectomy in children with traumatic brain injury and sustained intracranial hypertension. *Childs Nerv Syst*. 2001;17:154–162.
17. Scottish Intercollegiate Guideline Network (SIGN). *Guideline 110: Early management of patients with a head injury*. Online. Available: www.sign.ac.uk/sign-110-early-management-of-patients-with-a-head-injury.html.
18. Ducrocq SC, Meyer PG, Orliaquet GA, et al. Epidemiology and early predictive factors of mortality and outcome in children with traumatic severe brain injury: experience of a French pediatric trauma center. *Pediatr Crit Care Med*. 2006;7(5):461–467.
19. Fortune PM, Shann F. The motor response to stimulation predicts outcome as well as the full Glasgow Coma Scale in children with severe head injury. *Pediatr Crit Care Med*. 2010;11(3):339–342.
20. Ben-Ishay O, Daoud M, Peled Z, et al. Focused abdominal sonography in the clinical evaluation of children with blunt abdominal trauma. *World J Emerg Surg*. 2015;10:27.
21. Brown RL, Brunn MA, Garcia VF. Cervical spine injuries in children: a review of 103 patients treated consecutively at a level 1 pediatric trauma centre. *J Pediatr Surg*. 2001;36:1107–1114.
22. Patel JC, Tepas JJ 3rd, Mollitt DL, et al. Pediatric cervical spine injuries: defining the disease. *J Pediatr Surg*. 2001;36:373–376.
23. Dare AO, Dias MS, Li V. Magnetic resonance imaging correlation in pediatric spinal cord injury without radiographic abnormality. *J Neurosurg*. 2002;97:33–39.
24. *10 Leading causes of Injury Deaths by Age Group Highlighting Unintentional Injury Deaths, United States – 2009*. Online. Available: http://www.cdc.gov/Injury/wisqars/pdf/Leading_causes_injury_deaths_age_Group_highlighting_Unintentional_Injury%20Deaths_US_2009-a.pdf.

113

Treatment limitation and organ procurement

James Tibballs

INTRODUCTION

Limitation of treatment either by withholding or by withdrawing life-sustaining medical treatment is common in intensive care units (ICUs). Such practice results in the majority of deaths; approximately 70% of deaths occur after either withdrawing or limiting life-sustaining treatment while failed cardiopulmonary resuscitation (CPR) accounts for 14%–19% and brain death for 13%–16%.[1–4]

Usually, decisions regarding the limitation of therapy are based on ethical considerations and are derived by discussion and mutual agreement between parents and clinicians. However, disputes sometimes arise. When such disputes are settled in court, the judgements constitute common law.

All common law cases have been decided in the child's 'best interests'– a nebulous term. Although each case has its own circumstances, a composite view reveals three legal and hence ethical criteria for 'best interests'. These are based on the present and future '*quality of life*', the '*futility*' of present treatment and a comparison of '*burdens versus benefits*' of present and future treatment and its discontinuance. These principles should guide discussions when any form of limitation of treatment is being considered. This chapter briefly discusses the derivation of these principles in legal cases (which serve as the ethical basis for withholding and withdrawing life-sustaining medical treatment), selected clinical ethical guidelines for the limitation of treatment, and of organ procurement.

BACKGROUND LEGALITIES

Although no Australian legislation exists, judgements in common-law cases on withholding or withdrawing life-sustaining treatment establish the legal basis for the limitation of medical treatment. Common-law cases often involve disputes between parents and doctors, usually because parents want treatment that doctors do not consider to be in the best interests of the child, but sometimes because parents want treatment that doctors do not support.

Palliative care cannot lawfully be withheld or withdrawn. Such care includes the provision of reasonable medical procedures for the relief of pain, suffering and discomfort, and the reasonable provision of food and water. However, artificial provision of food and hydration, such as by nasogastric tube, gastrostomy or intravenous administration, is medical not palliative care and may be legally withdrawn.

When parents and doctors agree to withhold or withdraw treatment, their decisions are usually made on ethical grounds. However, disagreements between parents and hospital staff, between hospital staff or between parents, sometimes arise because of differences in ethical opinions. This is unsurprising since one's ethical position is derived from diverse social, cultural, religious, moral and familial influences.

The common ethical and legal mantra for withholding and withdrawing treatment is the so-called 'best interests' of the child. This term, somewhat nebulous, is enshrined in, but not clarified by, section 68F of the Family Law Act 1975 (Cth), in which courts are directed to determine a child's 'best interests'.

Although the 'best interests' considered by courts in each case are specific to the circumstances of the child, when all cases are considered together three recognisable circumstances permit lawful withholding or withdrawing treatment. Several 'withholding' cases have come before Australian courts but, as only one case of withdrawing treatment from children (Baby D, see later) has been considered, it is necessary to consider a few cases from other jurisdictions with similar systems of law.

Other legal requirements in this setting are presumed. These include:

- sanctity of life but which is not absolute
- limitations of treatment are omissions not acts
- withholding and withdrawing treatment are legally equivalent
- any deliberate attempt to shorten life or cause death is a criminal act
- euthanasia either active or passive is unlawful
- competent persons, who may include teenagers, have the right of self-determination

ABSTRACT

Limitation and withdrawal of treatment is the most common mode of death in paediatric intensive care units. The basis for the withdrawal or withholding of life-sustaining treatment is when treatment is futile (prolonging death rather than saving life) or disproportionately burdensome compared with benefits or resulting in extremely poor quality of life. These ethical principles, the so-called 'best interests' of the child, are derived from case law. With the agreement of parents, organ procurement may be undertaken from a suitable organ donor when death is diagnosed as irreversible cessation of *all* function of the brain or *irreversible cessation* of the circulation. Brain death should be diagnosed by a test that shows the absence of all brain blood circulation, not by performance of an apnoeic-oxygenation test. Organ procurement after circulatory death is increasing the total availability of organs for transplantation; however, it is exacerbating a shortfall in the availability of donated hearts.

KEYWORDS

Children
withdrawal life-support
brain death
circulatory death
organ procurement

- parents, as legal guardians, make decisions on behalf of their child, but they cannot demand a particular treatment, nor demand that a particular treatment be withdrawn or withheld, nor withhold consent for treatment if not in the child's 'best interests'
- a doctor cannot be ordered to provide treatment not in the child's 'best interests'
- sedation or analgesia may be administered with the purpose of relieving pain, suffering and distress, but which may also unintentionally shorten life
- death following lawful limitation of treatment is due to the underlying disease
- parents and doctors may together decide to withhold or withdraw treatment in a child's 'best interests', but neither should do so alone and both parents should participate in discussions and agree
- a court is the final arbiter of disputes.

Although ethical standards and clinical guidelines are not legally enforceable, adherence to these may be scrutinised by courts in the context of meeting an appropriate standard of care. It is evident that ethical and legal principles are interdependent. It would be difficult, but not impossible, to imagine that legal judgements would not be ethical and vice versa. Each espouses almost identical positions. Nevertheless, an occasional judgement may astound physicians, as for example the case of 'In the matter of Baby K',[5] in which a judge ruled that mechanical ventilation could not be discontinued for an anencephalic infant.

QUALITY OF LIFE

That the future quality of life could be considered a factor in a decision to withhold treatment was foreshadowed in Australia by the Victorian case of Baby M (see below). Although the concept had already been accepted in Britain, it had been originally rejected in the Australian case of Re F; F v F.

RE F; F V F

This case,[6] concerning an infant with spina bifida, was brought hurriedly before the court in a father's affidavit, which (disputed by the mother) claimed that his infant was being denied sustenance and sedated for the apparent purpose of permitting or causing death. The judge stated that his concern was to deal only with the immediate and specific problem – that is, the administration of sustenance, which was ordered. However, he also said:

> *'… whatever may be the justification through some form of ethical assessment, for the adoption of a deliberate course of conduct designed to terminate the life of a child, the law in this community is clear and simple. It gives no warrant whatever for any such decision to be made. … Difficult problems … may be … involved in the preservation or continuation of life, but no parent, no doctor, no court, has any power to determine that the life of any child, however disabled that child may be, will be deliberately taken from it. … It does not permit decisions to be made concerning the quality of life, nor does it enable any assessment to be made as to the value of any human being'.*

BABY M

Although the Baby M case[7] was heard in the Victorian State Coroner's Court, whose findings did not, at that time, constitute law, nevertheless it suggested that a line of reasoning would be important in future cases before Australian courts. It concerned an infant born with a severe spina bifida with a large lumbar myelomeningocele, hydrocephalus, Arnold–Chiari malformation of the brainstem, vocal cord paresis and severe deformities of the lower limbs. She was relatively unresponsive, had little spontaneous movement and had difficulty swallowing, sucking and breathing. If she survived, she would be unable to walk, be doubly incontinent, have no sexual function, probably require an artificial airway and would certainly require multiple operations on her spine and lower limbs. Her quality of future life was estimated extremely poor. Accordingly, the medical staff of the hospital and parents decided that no active treatment, including surgery to close the myelomeningocele, be undertaken. Feeding was restricted to that on demand and she was given paracetamol and phenobarbital. Subsequently, she developed respiratory difficulty, was treated with an infusion of morphine and died 12 days after birth. However, a member of the 'Right-to-Life' association complained to police about the infant's treatment. An autopsy was performed. The deputy coroner ruled that the infant had died of natural causes secondary to bronchopneumonia and hypoxia secondary to vocal cord paralysis obstructing the upper airway obstruction in the presence of toxic amounts of phenobarbital and morphine.

The case focused on the validity of withholding medical treatment in circumstances based on a *quality of life*. The deputy coroner, while noting that generally quality of life factors are not valid reasons to withhold treatment, the very serious disabilities of Baby M placed her in a group who would not be selected for surgery. Medical staff involved in the case was exonerated by the deputy coroner who stated that their decisions were legally, ethically and morally sound.

BABY D

This Victorian State case concerned Baby D,[8] who had been born at 27 weeks' gestation and required intubation and mechanical ventilation for apnoea of prematurity while a twin developed normally. Several extubation attempts were unsuccessful over several months due to the development of tracheal stenosis. At one re-intubation, hypoxaemia caused cardiac arrest requiring external cardiac compression. A subsequent magnetic resonance imaging scan revealed major

hypoxic brain damage that was expected to result in severe cerebral palsy and blindness. However, she was conscious, had intact brainstem function and intact cardiorespiratory function except for life dependence on intubation. Her parents applied to the court to allow extubation (withdrawal of therapy) without re-intubation if airway obstruction re-occurred. The court sanctioned this withdrawal of therapy on the basis that continuation of life-maintaining treatment would result in a very poor quality of life, which was not in her best interests. The principle of 'double effect' of appropriate use of sedative agents to allay suffering but inevitably shortening life was also affirmed.

RE J

In this British case,[9] a 4-month-old infant was the subject of a medical recommendation to withhold mechanical ventilation. It was this case that introduced assessment of 'quality of life' as a touchstone.

The infant, asphyxiated and born prematurely at 27 weeks' gestation and weighing 1.1 kg, had required mechanical ventilation for 1 month initially and then recurrently over the course of the next 3 months. On one occasion he was resuscitated from pulselessness. At 3 months of age ultrasound studies revealed gross irreparable hypoxic brain damage. He was blind and neonatologists predicted that he would have spastic quadriplegia, deafness and be unlikely to develop even limited intellectual abilities. The judge ordered the hospital, in the infant's 'best interests', not to re-ventilate him.

On appeal it was argued that, as in Re C [1989] 2 All ER 782, court-sanctioned withholding of treatment applied to an infant who was dying or in whom death could only be postponed, whereas Baby J was in no immediate danger. It was argued that a court is justified in withholding consent to such treatment only if it is certain that the quality of the child's subsequent life would be 'intolerable' to the child, 'bound to be full of pain and suffering' and 'demonstrably … so awful that in effect the child must be condemned to die' as per Judges Dunn and Templeman in Re B [1990] 3 All ER 927.

The court baulked at the terms 'condemned to die' and 'the child must live'. Although 'Thou shalt not kill' is an absolute commandment in this context, it is permissible to add 'but need'st not strive officiously to keep alive'. A court can never sanction steps to terminate life and as Judge Taylor stated, 'The court was concerned only with the circumstances in which steps should not be taken to prolong life'. Thus, 'What doctors and the court have to decide is whether, in the best interests of the child patient, a particular decision as to medical treatment should be taken which as a side effect will render death more or less likely'. There is a 'balancing exercise' to be performed in assessing the course to be adopted in the best interests of the child. Accordingly:

> *'account has to be taken of the pain and suffering and quality of life which the child will experience if life is prolonged. … also … of pain and suffering involved in the proposed treatment itself. … I do not think that we are bound to, or should, treat (Judge) Templeman's use of the words 'demonstrably so awful' or Judge Dunn's use of the word 'intolerable' as providing a quasi-statutory yardstick. … there will be cases in which it is not in the interests of the child to subject it to treatment which will cause increased suffering and produce no commensurate benefit'.*

The issue before Lord Donaldson was whether it would be in the 'best interests' of the child to restart mechanical ventilation and subject him to all the associated processes of intensive care if at some future time he could not continue breathing unaided. In dismissing the appeal, his judgement strongly speaks to the issue of quality of life, and introduces an unacknowledged concept of futility as a basis for withholding treatment in appropriate circumstances.

Judge Taylor, concurring, also introduced a concept observed in American judgements: that of 'a substituted judgement':

> *'the correct approach is … to judge the quality of life the child would have to endure if given that treatment and decide whether in all circumstances such a life would be so afflicted as to be intolerable to that child. I say 'that child' because the test should not be whether the life would be tolerable to the decider. The test must be whether the child in question, if capable of exercising sound judgement, would consider the life intolerable'.*

The interpretation of quality of life may be variable, depending on the patient's circumstances, as illustrated by examples given by Judge Taylor in Re J. In a case of disability following an accident, as opposed to one of disability from birth, a perception by the child of what has been lost, rather than never known, may be relevant to judging the quality of life.

RE WYATT

This is another English case[10] in which the parents of a severely disabled infant and doctors could not agree on treatment should the infant's condition deteriorate. It defined the role of a court order in subsequent medical management and re-examined the meaning of 'best interests'.

At the age of 1 year after birth at 26 weeks' gestation, this infant with microcephaly and profound brain damage was blind, deaf, incapable of voluntary movement or response, and had severe spastic quadriplegia. In addition she had irreparable chronic lung damage necessitating permanent oxygen administration and had kidney dysfunction that would require dialysis. Following a dispute between the infant's parents and doctors, a court order was made that doctors could

withhold mechanical ventilation otherwise necessary to prolong life, on the grounds that to do otherwise was not in the infant's best interests. Unexpectedly, mechanical ventilation was not needed. When the infant attained the age of 18 months, the parents applied to court to have the previous declaration discharged on the grounds that she was now not terminally ill. However, Judge Hedley declined to discharge the declaration after considering that her condition was unchanged. In doing so, he remarked on the utility of 'intolerability' as the test of best interests:

> *'it is in my view essential that the concept of "intolerable to that child" should not be seen as a gloss on, much less a supplementary test to, best interests. It is a valuable guide in the search for best interests in this kind of case'.*

The declaration was reviewed when the child was 2 years of age when again the concept of 'best interests' of the child was scrutinised. The court again de-emphasised 'intolerability' as the touchstone of 'best interests' and reaffirmed its meaning as enunciated in *Re A*, that ' "best interests" encompasses medical, emotional and all other welfare issues' and that 'The court must conduct a balancing exercise in which all the relevant factors are weighed'. Notwithstanding, since any case will be highly specific: 'any criteria which seek to circumscribe the best interests tests are … to be avoided'. On this occasion, as on the previous ones, the court declined to discharge the initial declaration but added that the declaration was permissive, not mandatory, and was subject to discussion between parents and doctors before implementation. It was not the court's role to oversee the treatment plan for a gravely ill child, which was for the doctors in consultation with the child's parents.

FUTILITY

Futility is difficult to define and may be quite different according to the perspectives of parent and physician – as illustrated in the matter of Baby K[5] when doctors, opposed by the mother, sought to discontinue mechanical ventilation for an anencephalic infant solely on the basis of futility. Nevertheless, the concept has been drawn upon in an Australian case involving an adult but no children, and it has appeared in American and British cases involving adults and children.

AIREDALE NHS TRUST V BLAND

Withdrawal of treatment from persons in persistent vegetative status (PVS) came to legal notice in Britain in 1993 with Airedale NHS Trust v Bland.[11] The physicians of Anthony Bland, a young man in PVS after being asphyxiated in a crowd stampede, proposed cessation of artificial feeding and withholding of antibiotic therapy in case of infection. These actions would culminate in his death by starvation and, although unpleasant for hospital staff, would not cause discomfort or stress to the patient. His 'best interests' lay in being able to lawfully discontinue all life-sustaining treatment and medical support.

Lord Hoffmann considered that it is not just the interests of the patient that are being considered and reminded us of the American substituted judgement when he opined:

> *'in the extraordinary case of Anthony Bland, we think it more likely that he would choose to put an end to the humiliation of his being and the distress of his family. Finally, Anthony Bland is a person to whom respect is owed and we think that it would show greater respect to allow him to die and be mourned by his family than to keep him grotesquely alive'.*

Moreover, 'the decision does not involve … a decision that he may die because the court thinks that "his life is not worth living". There is no question being worth living or not worth living because the stark reality is that Anthony Bland is not living a life at all'.

Lord Mustill delivered comprehensive and clear statements related to the benefits to be gained by different parties. It was in the best interests of the community that Anthony Bland be allowed die:

> *'it is the best interests of the community at large that Anthony Bland's life should now end. …. Nothing will be gained by going on and much will be lost. The stress of the family will get steadily worse. The strain on the devotion of a medical staff charged with the care of a patient whose condition will never improve, who may live for years and who does not even recognise that he is being cared for, will continue to mount. The large resources of skill, labour and money now being devoted to Anthony Bland might in the opinion of many be more fruitfully employed in improving the condition of other patients, who if treated may have useful, healthy and enjoyable lives for many years to come.'*

In addition, according to Lord Mustill, it would be in best interests of his family that he die, and therefore in his own best interest to die:

> *'He suffers no pain and feels no mental anguish … and (he experiences) the progressive erosion of the family's happy recollections by month after month of distressing and hopeless care'. 'By ending his life the doctors will not relieve him of a burden become intolerable, for others carry the burden and he has none … he has no interests of any kind'.*

The invasiveness of treatment, the indignity and its futility should be in the best interests of the family not to experience:

> *'… account should be taken of the invasiveness of the treatment and the indignity to which, as the present case shows, a person has to be subjected if his life is prolonged by artificial means, which must cause*

considerable distress to the family – a distress which reflects not only their own feelings but their perception of the situation of their relative who is being kept alive. But in the end it is the futility of the treatment which justifies its termination'.

MESSIHA V SOUTH EAST HEALTH

This Australian case involved a 75-year-old man in a deep coma with absent cortical activity several days after sustaining an hypoxic–ischaemic injury during asystolic cardiac arrest secondary to heart and lung disease.[12] Physicians proposed withdrawing mechanical ventilation, which would culminate in his death earlier than if treatment was continued. This was opposed by family members. A judge ruled that withdrawal of treatment was permitted on the grounds of futility:

'Apart from extending the patient's life for some relatively brief period, the current treatment is futile … burdensome and … intrusive. The withdrawal of treatment may put his life in jeopardy but only to the extent of bringing forward what I believe to be the inevitable in the short term. I am not satisfied that the withdrawal of his present treatment is not in the patient's best interests and welfare'.

RE L

Dame Elizabeth Butler-Sloss stressed that 'best interests' was the appropriate test and also clarified the role of futility and 'intolerability' in paediatric cases. The issue concerned a 9-month-old infant with trisomy 18 who had multiple heart defects, chronic respiratory failure, gastroesophageal reflux, severe developmental delay, epilepsy and hypotonia, and who had already suffered cardiac and respiratory arrests.[13] In supporting the judgement of Judge Hedley in Wyatt, she remarked:

'There is a strong presumption in favour of preserving life, but not where treatment would be futile, and there is no obligation on the medical profession to give treatment which would be futile. I agree with (Judge) Hedley that the court should be focusing on best interests rather than the concept of intolerability, although the latter may be encompassed within the former'.

RE L.H.R.

Futility as noted above is sometimes difficult to define but it was done clearly in this American case in which the parents of a 4-month-old infant wanted unwilling doctors and a hospital to withdraw treatment.[14] The infant had suffered a 'medical catastrophe' 15 days after birth and had since been in a persistent vegetative state. A State Supreme Court, acknowledging that the infant never had an opportunity to develop and express ideas and was terminally and hopelessly ill with no reasonable possibility of ever attaining cognitive function, pronounced 'Under these circumstances, we find that the *life-support system was prolonging her death rather than her life*' (emphasis added). The author of this chapter continues to find this concept of 'futility' very acceptable to relatives of a child for whom it is proposed to limit treatment.

BURDENS VERSUS BENEFITS

Sometimes determination of the 'best interests' is a matter of weighing burdens versus benefits.

This was described clearly by the judgement in *In the matter of AB*[15] in which an American court ruled that, upon a request from a mother, that treatment could be withdrawn from her 3½-year-old child who had sustained hypoxic brain damage secondary to a cardiac arrhythmia. The decision hinged on the 'best interest' standard, which 'requires a weighing of the benefits and burdens of treatment options including non-treatment as objectively as possible. Factors that should be considered when making decisions about life-sustaining or life-saving treatments for a seriously ill newborn include: (1) the chance the therapy will succeed, (2) the risks involved with treatment and non-treatment, (3) the degree to which the therapy if successful will extend life, (4) the pain and discomfort associated with the therapy, and (5) the anticipated quality of life with and without treatment'.

Benefit versus burden was also the issue in the British case of *An NHS Trust v B*[16] – a case in which doctors wanted to withdraw mechanical ventilation, against the wishes of parents, from an 18-month-old child who had spinal muscular atrophy (SMA) type I. The child's illness had progressed to the point where the only spontaneous movement possible was that of eyebrows. The case is notable for three reasons. First, the court drew up an extensive list of burdens and benefits specific to the child that serve as a good illustration of factors needing consideration in an individual case. Second, although the burdens appeared to heavily outweigh the benefits and hence favour discontinuation of treatment, Judge Holman ruled in favour of continuing mechanical ventilation via endotracheal intubation. Third, as the judge also ruled against the need for a tracheostomy, this created a difference between withdrawing treatment (cessation of mechanical ventilation) and withholding treatment (tracheostomy).

This astounding decision attracted considerable media attention in Britain. The decision is not in agreement with a previous case of a 16-month-old ventilated child with SMA type I, *Re C*,[17] in which the judicial decision was to allow the withholding of mechanical ventilation against parental wishes in the event of a future respiratory arrest once the present mechanical ventilation had been successively weaned. The decision was also not in agreement with a subsequent case – *Re K*,[18] in which the court ruled that it was appropriate to cease parenteral nutrition and allow to die a

5½-month-old infant with congenital myotonic dystrophy who had required mechanical ventilation for intermittent episodes of septicaemia associated with central venous access. The judge distinguished the circumstances from those in *An NHS Trust v B* on the basis of age and development.

MOHAMMED'S CASE

The Australian case of *TS & DS v Sydney Children's Hospital Network* ('Mohammed's case')[19] was adjudicated on the basis of a preponderance of burden over benefit in determining a child's best interests. Parents demanded invasive mechanical ventilation for their 9-month-old infant with a severe neurodevelopmental disorder due to pyruvate dehydrogenase deficiency. After a prolonged period of hypoxaemia, their infant was unresponsive, had seizures, blindness, deafness and cardiac failure requiring continuous positive airway pressure. Doctors advised against invasive ventilation on the basis that the infant's condition was incurable. The court ruled that such ventilation would cause pain and discomfort, would provide only temporary benefit and would not alleviate his underlying condition. Rather, his best interests were to receive pain relief and palliative care. Notably, the judge rejected evidence related to the medical assessment of Mohammed's quality of life. Subsequently, Mohammed was given non-invasive ventilation, and was discharged from hospital but succumbed to his condition after some months.

CLINICAL GUIDELINES ON WITHHOLDING AND WITHDRAWING TREATMENT

The withholding and withdrawal of life-sustaining treatment are the subjects of numerous guidelines. Most relevant and useful are those of the Royal College of Paediatrics and Child Health (RCPCH) and those of the American Academy of Pediatrics.

ROYAL COLLEGE OF PAEDIATRICS AND CHILD HEALTH GUIDELINES

The RCPCH guidelines,[20] revised in 2014, are an excellent overview of the issues and a considerable improvement on the previous edition of 2004.

The new guidelines, based on relevant case and statute law (for Britain), take into account the developments in palliative care and acknowledge the wishes and preferences of young people who are able to make decisions for themselves. Limitation of treatment is based on the 'quantity or quality of life' and sets out circumstances under which withholding or withdrawing life-sustaining treatment *might* be ethically permissible and describes situations in which individual children should be spared inappropriate invasive procedures. It purposefully avoids stating the circumstances under which treatment *must* be limited and the conditions of children for whom appropriate procedures *should* be denied.

Treatment limitation is defined as withholding treatment that has not been commenced or withdrawing treatment that has already started, or to impose limits on that treatment (e.g. by agreeing on a maximum level of respiratory or cardiovascular support that will be provided).

The guideline defines life-sustaining treatments as those that have the potential to prolong life. They may include experimental therapies that are not validated by research, as well as more conventional treatments such as CPR, mechanical ventilation, intravenous inotropes, antibiotics, renal dialysis and clinically assisted nutrition and hydration.

The basis for limitation of life-sustaining treatment in these guidelines is the concept of 'best interests' as defined in statute law, case law and in published professional guidance. Determination of clinical best interests involves balancing benefits and burdens of treatments and outcomes, whilst considering the ascertainable wishes, beliefs, values and preferences of the child and their family, the cultural and religious views of the latter, the views of those providing care for the child and what choice is least restrictive of future options.

The guidelines consider limitation of treatment under the following situations:

I. **When life is limited in quantity**. If treatment is unable or unlikely to prolong life significantly it may not be in the child's best interests to provide it. These situations comprise:
   - **A. Brainstem death**, as determined by agreed professional criteria appropriately applied. In this circumstance intensive technological support is no longer necessary and should be withdrawn unless organ donation is being considered.

Curiously, this condition is not only inconsistent with the overall stated aim of these guidelines, as indeed it was in the 2004 version, which is to describe conditions under which life-sustaining treatment *may* be withdrawn, but is also not applicable in Australia. This situation is superfluous – its inclusion is hardly necessary since life has already ceased. In Britain, 'brain stem death' is legal death (permitting organ procurement), whereas in Australia it is a legal requirement to show that death of all brain function has ceased. (Any short-term reasonable requirements of parents should be respected, e.g. continuation of treatment until the imminent arrival on scene of close family members.)

   - **B. Imminent death**, where physiological deterioration is occurring irrespective of treatment and its continuation can no longer restore life or health. It is no longer appropriate to continue treatment because it is futile and

burdensome to do so, and little or no benefit is likely to be derived from CPR. The aim should be to provide emotional and psychological support to the child and family, and to provide them with privacy and dignity for that last period of the child's life (palliative care).

C. **Inevitable death**, where death is not immediately imminent within minutes or hours but will occur within days or weeks and where the possible prolongation of life by life-sustaining treatment confers no overall benefit. In this situation a shift in focus from life prolongation to palliation is appropriate.

II. **When life is limited in quality**. This includes situations where treatment may be able to prolong life significantly but will not alleviate the burdens associated with illness or treatment itself. These situations are more difficult to define than quantity of life because of potential or actual differences in views of the health care team, children and families as to what constitutes quality of life and the values that should be applied to define it. Poignant illustrative cases are Mohammed's case (*vide supra*) in Australia and the recent case of Charlie Gard in Britain. In the latter, the child was afflicted with the rare fatal disease mitochondrial DNA depletion syndrome that causes progressive brain damage and muscle failure.

In some children, continuing treatment may prolong life significantly, yet it may be in their best interests to consider limiting it if there is no overall benefit in prolonging life because of the adverse impact entailed. In entering discussions about treatment limitation it is important to acknowledge the importance of the value that the child and his/her parents place upon their life and their view of its quality for that child, regardless of disability. These discussions may arise in the context of any or a combination of the following three conditions:

A. **Burdens of treatments**, where the treatments themselves produce sufficient pain and suffering which may be physical, psychological and emotional so as to outweigh any potential or actual benefits. Examples are invasive ventilation in severe irreversible neuromuscular disease, extracorporeal membrane oxygenation, renal dialysis and sometimes intensive chemotherapy – treatments which may be only deliverable at the expense of compromising the child's consciousness by deep sedation such that potential benefit is significantly reduced.

Where the reason for withholding or withdrawing life-sustaining treatment is on the basis of the burdens of treatment or the inevitability of demise, it may be appropriate to limit some treatments but not others. For example, it may be appropriate to withhold invasive ventilation in a child with a severe neuromuscular disorder, but to provide other less burdensome treatments, including non-invasive respiratory support, nutritional support, antibiotics or blood transfusions. In other situations, where the probability of recovery is very low, it may be appropriate to withhold CPR, but to provide other forms of life-sustaining treatment.

B. **Burdens of the child's underlying condition**; here the severity and impact of the child's underlying condition is in itself sufficient to produce such pain and distress as to overcome any potential or actual benefits in sustaining life. Some children have such severe degrees of illness associated with pain, discomfort and distress that life is judged by them (or on their behalf if they are unable to express their wishes and views) to be intolerable. All appropriate measures to treat and relieve the child's pain and distress should be taken. If, despite these measures, it is genuinely believed that there is no overall benefit in continued life, further life-sustaining treatment should not be provided, for example, in advanced treatment-resistant malignancy, or severe epidermolysis bullosa.

C. **Lack of ability to benefit**; the severity of the child's condition is such that it is difficult or impossible for them to derive benefit from continued life. Examples include children in PVS, a minimally conscious state, or those with such severe cognitive impairment that they lack demonstrable or recorded awareness of themselves or their surroundings and have no meaningful interaction with them, as determined by rigorous and prolonged observations. Even in the absence of demonstrable pain or suffering, continuation of life-sustaining treatment may not be in their best interests because it cannot provide overall benefit. Individuals and families may differ in their perception of benefit to the child and some may view even severely limited awareness in a child as sufficient grounds to continue life-sustaining treatment. It is important, here as elsewhere, that due account of parental views, wishes and preferences is taken, and that due regard is given to the acute clinical situation in the context of the child's overall situation.

Although it is possible to distinguish these different groups of decisions to limit life-sustaining treatments that are based on quality-of-life considerations, in practice combinations may be present. For example, a child or infant in the ICU may have sustained such significant brain injury that future life may provide little benefit, while both intensive treatment and future life are likely to cause the child substantial pain and distress.

III. Informed, competent, supported refusal of treatment

Adults who have the capacity to make their own decisions have the right to refuse treatments (including those intended to sustain life), even if health care professionals regard such treatments as being in the adults' best interests.

Similarly, in some circumstances the child or young person, who often has extensive experience of illness, clearly and repeatedly refuses treatment that professionals may regard as being in their best interests. In practice these refusals are likely to occur in situations where the young person's life is limited in quantity or quality or both, and where limitation of treatment may have already been considered as a possible option. Examples might include a child who requires cardiac transplantation for cardiomyopathy induced by therapy for leukaemia, or lung transplantation for complications of cystic fibrosis.

These circumstances should trigger a careful and detailed assessment of the child/young person's understanding of their illness, their capacity to make such far-reaching decisions and their understanding of the impact of their decision on their family. Also there should be a thorough exploration of parental/family views on treatment options, including the provision of supportive care and the determination of whether a consensus exists or can be reached.

If the child/young person does understand the nature and consequences of their decision, is assessed as having capacity to make the decision and is supported by their parents, the provision of further life-sustaining treatment may no longer be ethically justifiable even if it has the potential to provide some limited clinical benefit.

Other Issues. These guidelines discuss other important aspects of treatment limitation, which include but are not limited to:

i. **Initiation of CPR** is inappropriate if (a) unlikely to be successful in restarting the heart or breathing because of the child's underlying condition, or there is a limitation of treatment agreement or other end-of-life care plan that excludes its use; (b) even if successful it is likely to produce more burdens than benefits.

ii. **Clinically assisted nutrition and hydration** is legally a medical treatment in Britain (and in Australia) and in some circumstances is life-sustaining, and like other such treatments may or may not promote the best interests of the child. For example, in a child with a swallowing disorder due to a slowly progressive neurodegenerative disease, it would be appropriate, but rarely so for a child with rapidly progressive, disseminated malignant disease. It may be ethically appropriate to limit this treatment for a child in a persistent vegetative state or in a minimally conscious state. However, in Britain at present, an application to a court is required to limit such treatment for these conditions.

iii. **Muscle relaxants**, drugs that cause only neuromuscular blockade, should not be used to treat or prevent terminal gasping. This sensible advice is in contrast to the advice in the 2004 edition of the guidelines. Not only do such drugs mask distress without treating it, their use can be interpreted as an intention to hasten death, which is tantamount to euthanasia. Although terminal gasping is distressing to parents (and to staff) its significance – a response to hypoxaemia – should be explained, and appropriate palliative care given to prevent distress and suffering. (Although this may seem like 'splitting hairs' the perceived perception of the intention of treatment is important.)

iv. **Provision of palliative care.** This should begin whenever it is apparent that a child's illness may result in premature death, whether it is provided by a specialist service or the clinical team already caring for the child. It should address the child's physical needs, for example, pain and symptom relief, and address the emotional, social and spiritual needs of both the child and their family. All these aspects of palliative care can be provided wherever a child and family are cared for – whether in hospital, at home or in a children's hospice. The introduction of palliative care should not be left until a decision is made to limit life-sustaining treatment. Such care may include transferring a child out of hospital for ventilation withdrawal in a preferred place of care/place of death.

v. **Organ donation** should be considered in any child dying in the intensive care environment. Discussions about organ donation must be separated from discussions about withholding or withdrawing life-sustaining treatment. Only after a decision has been made to withhold or withdraw life-sustaining treatment is it appropriate to raise with the family the possibility of organ donation after death.

vi. **Legal input**. The health care team and parents usually come to agreement over a course of action. If agreement cannot be reached, legal advice should be sought from specialist health care lawyers. Institutions should also facilitate access to independent legal representation for the parents.

vii. **Responsibilities of the health care team**. Health care teams have individual and collective obligations to act in the child's best interests and have a responsibility to fully inform parents allowing them to reach their own independent un-coerced opinion. Doctor–parent partnered decisions should be made on the basis of confirmed clinical evidence. It is important to be clear to all involved (including the child when competent and where appropriate) as to which

treatments are appropriate and which are not; and which will be provided, and which will not. The range of chosen interventions should be recorded and updated according to circumstance and discussion with parents. All members of the treating health care team should have opportunity to be part of the decision-making process and their views accorded due weight according to knowledge, understanding and experience. Openness between disciplines and grades will enhance mutual understanding of individual roles and responsibilities, and will heighten the sense of shared moral responsibility. However, unanimity is not required. Final responsibility for decisions rests with the senior doctor in charge.

viii. **Transition to adult services**. Some children with life-limiting illnesses live beyond their 16th or 18th birthdays. Arrangements for transition should accord with best practice.

ix. **Bereavement**. Professional duties and responsibilities do not cease when a child dies. The quality of care at the end of life and after the child's death can have a major impact on the family's grieving. Each institution should have readily available specific policies that provide guidance for staff in addressing the needs of bereaved families and which describe the procedures that need to be followed when a child dies. It should include details about asking for postmortems, the needs of different religions, beliefs and cultures, and the provision of mementos for the family. There should be practical guidance on the steps that families will need to take for registering the death and making funeral arrangements. An offer of follow-up should be made to all parents of a child who has died. Follow-up contact between 1 and 2 months after the death gives the opportunity to discuss the results of a postmortem or other investigations that may shed more light on the precise cause of death. Such contact also allows professionals to answer families' medical questions and to explore their feelings.

AMERICAN ACADEMY OF PEDIATRICS GUIDELINES[21]

Issued initially in 1994, and reaffirmed in 2008, they utilise the term 'forgo' to refer to both stopping (withdrawing) treatment already begun and not starting (withholding) a treatment. Decisions turn on the 'best interests' standard. This involves balancing the benefits and burdens of treatment. Benefits may include prolongation of life (unless prolonged unconsciousness is not considered a benefit), improved quality of life after treatment (including reduction of pain or disability), and increased physical pleasure, emotional enjoyment and intellectual satisfaction. The burdens of treatment include intractable pain, irremediable disability or helplessness, emotional suffering, invasive or inhumane interventions designed to sustain life or other activities that detract from the patient's quality of life.

'Quality of life' refers to that perceived by the patient, not how others perceive it. Accordingly, a 'substituted judgement standard' should apply in which parents or surrogates must make inferences about the preferences of previously competent children. However, in states of prolonged unconsciousness, this standard cannot be easily applied.

Curiously, despite exhortation to regard quality of life only from the patient's perspective, 'Physicians and families should also consider whether continued treatment conforms with respect for the meaning of human life and accords with the interests of others, such as family members and other loved ones'.

CONCLUSIONS

In considering whether to withhold or withdraw life-sustaining treatment from a child, the appropriate test is that of 'best interests', which – although a nebulous term – essentially means a determination of the quality of life, futility and a comparison of benefits and burdens.

These three concepts are not independent as 'quality of life' with continuation of treatment may be derived by a 'comparison of benefits and burdens' flowing from treatment. 'Best interests' should also incorporate, but not exclusively, a notion of tolerability of continued treatment. The concept of futility was prominent in early cases and remains important but it is less easily defined unless it is related to prolongation of the dying process. These legal concepts may be helpful in the clinical situation when litigation is unlikely, but when parties nevertheless dispute courses of action each of which is considered correct under different ethical positions. It may be surprising to physicians that these principles are well described in law. Indeed, rather than consider withdrawal or withholding treatment under ethical principles, it is perhaps more helpful to first ask 'Is it lawful?' and then ask 'Is it ethical?' Whatever ethical position is adopted when contemplating withholding or withdrawing treatment from children, notwithstanding disputes, these principles should be observed because, in the end, the legal position is decisive.

ORGAN PROCUREMENT

This section concerns paediatric cadaveric organ procurement in Australian jurisdictions. It is an addendum to the Chapter 102, which also encompasses adult organ procurement. It focuses on legal requirements and notable differences in paediatric practices of organ procurement.

Contrary to organ procurement from adults, which may proceed with either the pre-morbid consent of the patient ('opt-in' consent) or the consent of 'next-of-kin' if the patient had not 'opted-in' to organ donation, organ procurement from a deceased child may only proceed with the consent of a parent.

As with adults, the gap between the need for organ donation for transplantation and organ procurement continues to widen. Every opportunity should be taken to maximise organ procurement in the paediatric ICU. Whenever a child is anticipated to die and would be a potential suitable donor of organs, discussions should be undertaken with their parents who should be given an opportunity to consent to organ donation from their child. Practice along these lines is equivalent to a 'soft opt-out' system of organ donation, recently adopted in Wales under their *Human Transplantation Act* (Wales) s4(2)(3), in which every (adult) person is presumed to have given pre-morbid consent, wrong that it is,[22] unless they had pre-morbidly registered a refusal. Unlike 'hard opt-out' systems, however, relatives have the right to declare unregistered refusal but they cannot stop organ procurement if refusal had not been expressed at all.

In Australian jurisdictions, according to various 'Human Tissue Acts',[23] cadaveric organ procurement may proceed when there is 'irreversible cessation of all function of the brain' (brain death) or there is 'irreversible cessation of circulation' (circulatory death). The demonstration of brain death allows procurement of any tissues and organs, including the heart.

BRAIN DEATH

The law does not define what constitutes brain death, except that it should be the lack of each and every brain function; nor does the law specify how brain death should be proven. Medical practices are quite varied and sometimes unreliable in making this diagnosis.[24,25] Provided that no confounding and remediable factors are present (see Chapter 102), the key clinical test is that of apnoeic-oxygenation. Simply put, if an oxygenated patient fails to begin spontaneous respiration in the presence of hypercapnia ($PaCO_2$ >60 mm Hg), brain death is present. However, this is an unreliable test for brain death and may contribute to or cause brain damage; it is a self-fulfilling test and recommended against by this and another author.[25,26] As is well known, hypercarbia causes an increase in intracranial pressure and will damage any live brain tissue.

It is far more preferable to diagnose brain death by showing that blood flow to the whole brain has ceased by the performance of a scan using a radionuclide, such as with technetium 99m-hexamethylpropyleneamineoxime or technetium 99m-ethylcysteinate dimer, which are brain-lipid soluble. The complete absence of radionuclide uptake, consistent with no brain blood flow, not only satisfies the legal requirement that *all* function of the brain has ceased irreversibly, but is also a convincing test for clinical staff and parents that death has indeed occurred. There are no confounding factors for this test and it may be used in any age group, including neonates. Organ procurement may then proceed in a non-time-critical manner. If some brain blood flow is demonstrated by this test, the diagnosis of brain death cannot be made but it does not stipulate that organ procurement cannot proceed under the basis of circulatory death when life-sustaining treatment is withdrawn. The timing of a scan is important – it should only be undertaken when brain death is suspected from clinical circumstances and observations, such as absent brainstem reflexes, excluding any performance of an apnoeic-oxygenation test. If some blood flow is initially evidenced by a scan, later re-performance of an isotopic scan may be confounded by residual radioactivity unless a suitable interval is allowed between scans.

CIRCULATORY DEATH

Organ procurement may proceed when the circulation of the potential donor has ceased, invariably after withdrawal of life-supporting treatment. Organ procurement is undertaken provided the circulation ceases within 90 minutes after withdrawal of treatment. Beyond this period, organs are not suitable for transplantation and planned procurement is abandoned. Surgery may be commenced between 2 and 5 minutes after the circulation ceases. The latter time is preferred and fits well with the observations that circulation may spontaneously recommence up to approximately 90 seconds after death is diagnosed, and may persist for up to approximately 3 minutes.[27]

Logistically, organ procurement after circulatory death is more difficult than after brain death because withdrawal of life-sustaining treatment can only be undertaken when the surgical transplant team is ready to operate in the unguaranteed expectation that death will occur. If it does occur, surgery then must be performed urgently in a time-critical manner to ensure the viability of organs.

This mode of organ procurement is increasing because 'brain death' arises infrequently and because parents and doctors often agree on treatment withdrawal before the condition of the child progresses to brain death. Although the availability of other organs is increasing with this practice, it does not yield a heart suitable for transplantation for the obvious reason that the heart of the donor has already failed. Nonetheless, it is possible to resuscitate a procured heart using ex-vivo techniques and later transplant it. However, this practice carries a risk of exposing the transplant team to criminal prosecution because it is difficult to argue that the circulation of the donor had ceased irreversibly, as required by law, before surgical

procurement of the heart.[28] A protocol for procurement after paediatric circulatory death is available online from a paediatric hospital: <http://www.rch.org.au/picu/Donation_after_cardiac_death_protocol/>

KEY REFERENCES

8. *Re: Baby D (NO.2)*. 2011. FamCA 176.
9. *Re J* 1990. 3 All ER 930.
10. *Re Wyatt (a child) (medical treatment: continuation of order)* 2005. EWCA Civ 1181.
11. *Airedale NHS Trust v Bland* 1993. 1 All ER 821.
12. *Messiha v South East Health* 2004. NSWSC 1061.
19. *TS & DS v Sydney Children's Hospital Network ('Mohammed's case')* 2012.
20. Larcher V, Craig F, Bhogal K, et al; Royal College of Paediatrics and Child Health. Making decisions to limit treatment in life-limiting and life-threatening conditions in children: a framework for practice. *Arch Dis Child*. 2015;100(suppl 2):s1–s26.
22. Bhatia N, Tibballs J. The development of property rights over cadaveric tissues and organs: legal obstructions to the procurement of organs in an "opt-out" system of organ donation in Australia and New Zealand. *NZ Univ Law Rev*. 2017;27:946–974.
24. Tibballs J. A critique of the apneic oxygenation test for the diagnosis of 'brain death'. *Pediatr Crit Care Med*. 2010;11:475–478.
28. Tibballs J, Bhatia N. Transplantation of the heart after circulatory death of the donor: time for a change in law? *Med J Aust*. 2015;203:268–270.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Meert KL, Keele L, Morrison W, et al. End-of-life practices among tertiary care PICUs in the United States. *Pediatr Crit Care Med*. 2015;16:e231–e238.
2. Burns JP, Sellers DE, Meyer EC, et al. Epidemiology of death in the PICU at five U.S. teaching hospitals. *Crit Care Med*. 2014;42:2101–2108.
3. Vernaz S, Casanova L, Blanc F, et al. To maintain or to withdraw life support? Variation on the methods of ending life in a pediatric intensive care unit over a period of 6 years [French]. *Ann Fr Anésth Réanim*. 2012;33:400–404.
4. Oberender F, Tibballs J. Withdrawal of life-support in pediatric intensive care – a study of time intervals between discussion, decision and death. *BMC Pediatr*. 2011;11:39–44.
5. *In the matter of baby 'K'* 1993. 832 F. Suppl 1022.
6. *Re F; F v F – BC8601367 – 2* July 1986. (Victoria – Unreported Judgements).
7. *Baby M, Record of investigation into death, Case No 3149/89*, 29 October 1991.
8. *Re: Baby D (NO.2)*. 2011. FamCA 176.
9. *Re J* 1990. 3 All ER 930.
10. *Re Wyatt (a child) (medical treatment: continuation of order)* 2005. EWCA Civ 1181.
11. *Airedale NHS Trust v Bland* 1993. 1 All ER 821.
12. *Messiha v South East Health* 2004. NSWSC 1061.
13. *Re L (Medical treatment: benefit)* 2005. 1 FLR 491.
14. *Re L.H.R*. 1984. 321 S.E.2d 716.
15. *In the matter of AB* 2003. 768 N.Y.S.2d 256 at 35.
16. *An NHS Trust v B* 2006. EWHC 507 (Fam).
17. *Re C (a minor)(medical treatment)* 1998. 1 FLR 384.
18. *Re K (a child)(withdrawal of treatment)* 2006. EWHC 1007 (Fam).
19. *TS & DS v Sydney Children's Hospital Network ('Mohammed's case')* 2012. NSWSC 1609.
20. Larcher V, Craig F, Bhogal K, et al; Royal College of Paediatrics and Child Health. Making decisions to limit treatment in life-limiting and life-threatening conditions in children: a framework for practice. *Arch Dis Child*. 2015;100(suppl 2):s1–s26.
21. American Academy of Pediatrics. Guidelines on foregoing life-sustaining medical treatment. *Pediatrics*. 1994;93:532–536.
22. Bhatia N, Tibballs J. The development of property rights over cadaveric tissues and organs: legal obstructions to the procurement of organs in an "opt-out" system of organ donation in Australia and New Zealand. *NZ Univ Law Rev*. 2017;27:946–974.
23. *Human Tissue Act 1982* (Vic) s 41; *Human Tissue Act 1983* (NSW) s 33; *Human Tissue Act 1985* (Tas) s 27A; *Human Tissue and Transplant Act 1982* (WA) s 24(2); *Transplantation and Anatomy Act 1979* (Qld) s 45(1); *Transplantation and Anatomy Act 1983* (SA) s 24(2) and *Death (Definition) Act 1983* (SA) s 2. The legislative *Acts* by Territory are: *Transplantation and Anatomy Act 1978* (ACT) s 45; *Transplantation and Anatomy Act 2014* (NT) s 23.
24. Tibballs J. A critique of the apneic oxygenation test for the diagnosis of 'brain death'. *Pediatr Crit Care Med*. 2010;11:475–478.
25. Tibballs J. The non-compliance of clinical guidelines for organ donation with Australian statute law. *J Law Med*. 2008;16:335–355.
26. Tibballs J, Joffe AR. The diagnosis of brain death: apneic-oxygenation as a self-fulfilling diagnostic test. In: Leisman G, Merrick J, eds. *Considering Consciousness Clinically*. New York: Nova Science Publishers; 2016:47–56.
27. Dhanani S, Hornsby L, Ward R, et al. Vital signs after cardiac arrest following withdrawal of life-sustaining therapy: a multicenter prospective observational study. *Crit Care Med*. 2014;42:2358–2369.
28. Tibballs J, Bhatia N. Transplantation of the heart after circulatory death of the donor: time for a change in law? *Med J Aust*. 2015;203:268–270.

114

Paediatric poisoning and envenomation

James Tibballs

EPIDEMIOLOGY

Poisoning in childhood is common. In the year 2012–2013, almost 6500 children (0–17 years) in Australia were hospitalised after poisoning.[1] The majority were adolescents (15–17 years) at a rate of almost 600/100,000 population but significant numbers were also recorded among infants (<12 months), early childhood (1–4 years) and late childhood (10–14 years). A minority were life-threatening but no deaths occurred, and hospitalisation was required on average for 2 days. Poisoning often occurs in the home when a single prescribed or over-the-counter medication or a household product is ingested. Whatever treatment is applied to remove a poison, care should be taken to ensure that it does not cause additional illness.

Poisoning among young children is called 'accidental' – erroneously because it is usually the result of inadequate supervision or unsafe storage of poisons. Occasionally, poisoning in childhood is either truly accidental as in ingestion of a decanted chemical, or is part of a syndrome of child abuse, or is iatrogenic as when a parent mistakes medications at home or when medical or nursing staff make errors in drug administration in hospital.[2] Self-poisoning in late childhood (10–14 years) or adolescence is usually with the intention to manipulate their psychosocial environment or to commit suicide, or is the result of substance abuse. All such circumstances of poisoning require remedial action. Occasionally toxic gases are inhaled during fires.

PRINCIPLES OF MANAGEMENT

The four basic principles in management of any poisoning are:

- support vital functions
- confirm the diagnosis
- remove the poison from the body
- administer an antidote (Table 114.1).[3,4]

Individual poisons may require specific measures. Consult current toxicology texts[5–7] for details and consult Chapter 90. A working knowledge of important poisons is indispensable for paediatric practice. A number of poisons or classes of poison are potentially fatal to a small child if taken as a single tablet or a teaspoonful.[8] These include opiates (methadone, buprenorphine, lomotil), camphor, quinine derivatives, cyclic antidepressants, clonidine, sulfonylureas, salicylates, calcium channel blockers and colchicine. If a poison is unfamiliar, a poison information centre provides valuable information, but clinical judgement rests with the treating physician.

The support of paediatric vital functions (life-support) is detailed in Chapters 105–115 of this volume. When conventional resuscitation is failing, extracorporeal life-support may be required.

CONFIRMATION OF DIAGNOSIS

Commonly the diagnosis of poisoning in paediatric practice is self-evident from a history detailed by parents or guardians. Although a single poison is usually involved, the possibility of several or multiple poisons should be considered. Occasionally the diagnosis is unknown on presentation. Any child who presents with unexplained obtundation, fitting, hypoventilation, hypotension or has a metabolic derangement must have poisoning excluded.

Recognition of a 'toxidrome', a constellation of symptoms and signs, may make the diagnosis.[5–7] Although numerous toxidromes exist, the four prominent types and their causative drugs or agents are shown in Table 114.2.

Laboratory analysis of body fluid specimens can assist in the diagnosis and management of poisoning. For example, rapid routine analyses are widely available for glucose, potassium, calcium, pH, osmolarity, alcohols, paracetamol, phenytoin, digoxin, salicylate, theophylline, iron, lead and methaemoglobin. If particular toxins are suspected, discussion with laboratory staff will optimise the information to be gained.

REMOVAL OF THE POISON

Treatment should be determined by the poison, the severity of poisoning as judged by the observed and the expected effects of the poison, by the amount ingested,

ABSTRACT

Childhood poisoning is often minor but serious poisoning by true accident or self-harm may require intensive care management. The diagnosis is usually evident but must be suspected if convulsions, central nervous system obtundation or cardiorespiratory compromise are unexplained. Often, recovery occurs with only support of vital functions. Removal of poisons by extracorporeal or gastrointestinal decontamination or by forced diuresis must match the severity of poisoning to avoid complications. Potentially lethal poisons are a wide range of therapeutic drugs (paracetamol, opiates, benzodiazepines, antipsychotic drugs), lead, petroleum distillates, essential oils and caustics. Some poisons have antidotes, notably for paracetamol, naloxone for opiates, flumazenil for benzodiazepines, benztropine for phenothiazines, desferrioxime for iron, beta-blockade for amphetamines, calcium for calcium-channel blockade. An oesophageal impacted button battery must be removed urgently to avoid fatal erosion. Management of envenomation is similar to adults with the additions that the diagnosis may not be apparent and the toxicity more severe.

KEYWORDS

Children
poisoning
antidotes
button battery
paracetamol
envenomation
antivenom

Table 114.1 Antidotes to some poisons

POISON	ANTIDOTES	COMMENTS
Amphetamines	Esmolol IV 500 µg/kg over 1 min, then 25–200 µg/kg/min Labetalol IV 0.15–0.3 mg/kg or phentolamine IV 0.05–0.1 mg/kg every 10 min	Treatment for tachyarrhythmia Treatment for hypertension
Anticholinergic toxidrome (antimuscarinic)	Physostigmine 0.01–0.02 mg/kg IV slowly, repeatable but titrated to improve consciousness	Beware cholinergic effects including bradycardia, bronchospasm and weakness (treat with atropine)
Benzodiazepines	Flumazenil IV 3–10 µg/kg, repeat 1 min, then 3–10 µg/kg/h	Specific receptor antagonist. Beware convulsions
Beta blockers	Glucagon 50–150 µg/kg IV then 0.20–2.0 µg/kg/min infusion Isoprenaline 0.05–2 µg/kg/min IV infusion Noradrenaline 0.05–0.5 µg/kg/min infusion	Stimulates non-catecholamine cAMP (preferred antidote) Beware β_2 hypotension Antagonises toxin at receptors
Calcium channel blocker	Calcium chloride IV 10%, 0.2 mL/kg	Antagonises at receptors
Carbon monoxide	Oxygen 100%	Decreases carboxyhaemoglobin May need hyperbaric oxygen
Cyanide	Hydroxycobalamin (Vit B_{12}) 70 mg/kg IV plus sodium thiosulphate 25% IV 1.65 mL/kg (max 50 mL) at 3–5 mL/min. Sodium nitrite 3% IV (0.33 mL/kg over 4 minutes) then sodium thiosulphate as above.	Give 50 mL 50% glucose after dose 'Cyanide antidote kit'; beware anaphylaxis Nitrites form methaemoglobin-cyanide complex: beware of excess methaemoglobin – restrict to <20%. Thiosulphate forms non-toxic thiocyanate from methaemoglobin-cyanide.
Digoxin	Magnesium sulphate IV 25–50 mg/kg (0.1–0.2 mmol/kg) Digoxin Fab IV: acute – 10 vials per 25 tablets (0.25 mg each), 10 vials per 5 mg elixir; steady state: vials, serum digoxin (ng/mL) × BW(kg)/100; empirical therapy: 10–20 vials acute poisoning, 1–2 vials chronic	Antagonises digoxin at sarcolemma Binds digoxin
Ergotamine	Sodium nitroprusside infusion 0.5–5.0 µg/kg/min Heparin IV 100 units/kg, then 10–30 units/kg/h	Treats vasoconstriction; monitor BP continuously Monitor partial thromboplastin time
Lead	If symptomatic or blood level >2.9 µmol/L dimercaprol (BAL) 75 mg/m^2 IM 4-hourly 6 doses, then calcium disodium edetate (EDTA) 1500 mg/m^2 IV over 5 days. If asymptomatic and blood level 2.18–2.9 µmol/L infuse EDTA 1000 mg/m^2 per day for 5 days	Chelating agents
Heparin	Protamine 1 mg/100 units heparin	Direct neutralisation
Hydrofluoric acid	Calcium chloride 10% IV 0.2 mL/kg Calcium gluconate gel, topically	For systemic toxicity For burns
Iron	Deferrioxamine 15 mg/kg/h 12–24 h if serum iron >90 µmol/L (500 µg/dL) or >63 µmol/L (350 µg/dL) and symptomatic, give slowly	Beware anaphylaxis

Continued

Table 114.1 Antidotes to some poisons—cont'd

POISON	ANTIDOTES	COMMENTS
Isoniazid (or hydrazine exposure)	Pyridoxine (vitamin B6) 70 mg/kg (max 5 g) IV 3–5 min if seizing, 30–60 min if not, *and* Diazepam	Metabolic acidosis may be mildly exacerbated
Local anaesthetic drug cardiovascular toxicity	Intralipid 20% IV 1.5 mL/kg over 1 min, repeat ×2 intervals 5 min then infusion 0.25–0.50 mL/kg/min as needed to maintain BP	Mechanism uncertain – may bind toxin; suitable for other lipophilic drugs including sertraline, bupropion, quetiapine and possibly clomipramine, propranolol, thiopentone, verapamil
Methanol, ethylene glycol, glycol ethers	Ethanol IV loading dose 10 mL/kg 10% diluted in glucose 5%, then 0.15 mL/kg/h to maintain blood level 0.1% (100 mg/dL), *or* Fomepizole (4-methylpyrazole) 15 mg/kg over 30 min, then 10 mg/kg 12-hourly, four doses	Competes with poison for alcohol dehydrogenase Inhibits alcohol dehydrogenase (not available in Australia)
Methaemoglobinaemia	Methylene blue IV 1–2 mg/kg over several minutes	Reduces methaemoglobin to haemoglobin
Methotrexate	Leucovorin (folinic acid) IV 100–1000 mg/m^2 6-hourly until methotrexate 0.05–0.1 µmol/L, *and* Glucarpidase 50 units/kg IV	Sustains folate cycle blocked by methotrexate Cleaves methotrexate to non-cytotoxic metabolites
Opiates	Naloxone IV 0.01–0.1 mg/kg, then 0.01 mg/kg/h as needed	Direct receptor antagonist
Organophosphates and carbamates	Atropine IV 20–50 µg/kg every 15 min until secretions dry Pralidoxime IV 25 mg/kg over 15–30 min then 10–20 mg/kg/h for 18 h or more	Blocks muscarinic effects Reactivates cholinesterase; not for carbamates
Paracetamol	N-acetylcysteine if serum paracetamol (µmol/L) exceeds: 1500 at 2 h, or 1000 at 4 h, or 500 at 8 h, or 200 at 12 h, or 80 at 16 h, or 40 at 20 h: ***Intravenous*** 300 mg/kg total in age/weight volume appropriate 5% dextrose or normal saline: In 3 phases; (i) 150 mg/kg over 1 h; (ii) plus 50 mg/kg over 4 h; and (iii) plus 100 mg/kg over 16 h. OR In 2 phases; (i) 200 mg/kg over 4 h; (ii) plus 100 mg/kg over 16 h. OR ***Oral*** 1330 mg/kg total as 140 mg/kg, then 17 doses each of 70 mg/kg 4 hourly over 72 h.	Restores glutathione-inhibiting metabolites; beware anaphylaxis, minor reactions common
Phenothiazine (and other drug) dystonia	Benztropine IV or IM 0.01–0.03 mg/kg	Blocks dopamine reuptake

Table 114.1 Antidotes to some poisons—cont'd

POISON	ANTIDOTES	COMMENTS
Potassium	Calcium chloride 10% IV 0.2 mL/kg Glucose IV 0.5 g/kg plus insulin IV 0.05 units/kg	Antagonises cardiac effects (immediate) Decreases serum potassium (rapid marked effect); monitor serum glucose
	Salbutamol aerosol 0.25 mg/kg	Decreases serum potassium (rapid marked effect)
	Sodium bicarbonate IV 1 mmol/kg	Decreases serum potassium (slight effect); beware hypocalcaemia
	Resonium oral or rectal 0.5–1 g/kg	Adsorbs potassium (slow effect)
Sulfonylureas and other drugs causing hypoglycaemia	Glucose 0.5–1.0 g/kg IV then infusion Octreotide 1–2 µg/kg IV or SC 8-hourly 2–3 doses	Monitor serum glucose frequently Refractory hypoglycaemia from sulfonylureas and quinine; inhibits insulin release
Tricyclic antidepressants	Sodium bicarbonate IV 1–2 mmol/kg to maintain blood pH >7.45, aim for 7.55	Reduces cardiotoxicity
Valproic acid	L-carnitine IV if serum valproate ≥450 mg/L, no coma and ammonia and liver enzymes normal: 25 mg/kg 6-hourly (max 6 g/day); if coma with raised ammonia and hepatic enzymes 100 mg/kg load (max 6 g) over 30 min then 15 mg/kg 4-hourly over 10–30 min until improvement	Replaces depleted carnitine levels; measure valproate – if ≥1000 mg/L start haemodialysis or haemofiltration

BAL, British anti-Lewisite; *BP*, blood pressure; *BW*, body weight; *cAMP*, cyclic adenosine monophosphate; *DMSA*, dimercaptosuccinic acid; *EDTA*, ethylenediaminetetraacetic acid; *IM*, intramuscular; *IV*, intravenous; *SC*, subcutaneous.

Table 114.2 Toxidromes

TOXIDROME	SIGNS AND SYMPTOMS			DRUGS/AGENTS (EXAMPLES)
Anticholinergic	Agitation Coma Delirium Mydriasis Dry mouth Hyperthermia Tachycardia (sinus) Hypertension Skin flushed and dry Urinary retention Ileus or decreased motility			Antihistamines Atropine and related drugs and substances (incl. plants) Carbamazepine Phenothiazines Tricyclic antidepressants Benzatropine
Cholinergic	*MUSCARINIC*	*NICOTINIC*	*CENTRAL*	
	Diarrhoea Urinary incontinence Miosis Bradycardia Bronchorrhoea Vomiting Lacrimation Salivation	Weakness/paralysis Fasciculation Tachycardia Hypertension	Obtundation/coma Agitation Seizures	Organophosphates Carbamates

Continued

Table 114.2 Toxidromes—cont'd

TOXIDROME	SIGNS AND SYMPTOMS	DRUGS/AGENTS (EXAMPLES)
Sympathomimetic	Agitation Delirium/coma Seizures Mydriasis Hyperthermia Sweating Hypertension Tachycardia Hyperpnoea	Amphetamines and derivatives Cocaine Caffeine Catecholamines Ketamine Phenylcyclidine Theophylline Lysergic acid diethylamide
Opioid/opiate	Obtundation/coma Hypoventilation Hypotension Miosis	Morphine Heroin Methadone Fentanyl Oxycodone Buprenorphine Propoxyphene

by the interval between ingestion and presentation, and by the existence or otherwise of an antidote.

The range of treatment options is to: (1) do nothing apart from advice and discharge home; (2) observe for a short duration in the emergency department or ward; (3) provide intensive nursing care; or (4) treat medically. The modes of medical therapy include extracorporeal decontamination, diuresis or gastrointestinal decontamination, with the last named being the most important. The task with all poisonings is to match the treatment and its intensity to the severity of the poisoning, thereby avoiding under- and overtreatment.

EXTRACORPOREAL DECONTAMINATION

Occasionally, removal from the circulation by an extracorporeal technique is needed by charcoal haemoperfusion, haemodialysis, plasma filtration or haemofiltration. Examples of toxins removable by these techniques are barbiturates, lithium, metformin, salicylates, theophylline, toxic alcohols, carbamazepine and valproic acid.[3,9] Such techniques, combined with extracorporeal circulatory support, should be applied when conventional therapy is failing or is anticipated to fail.

ALKALINE DIURESIS

Induce diuresis of 2–5 mL/kg/h with alkalinisation of the urine by 1–2 mmol/kg sodium bicarbonate intravenously then infuse 50–75 mmol/L in intravenous fluid titrated to maintain alkaline urinary pH without exceeding serum pH of 7.55. Monitor serum pH, sodium, potassium, calcium and avoid clinical problems of fluid overload. This reduces reabsorption in distal renal tubules of drugs including phenobarbitone, salicylate, methotrexate and chlorpropamide.[3]

GASTROINTESTINAL DECONTAMINATION

Since the vast majority of poisoning in childhood is by ingestion, potential exists for removal from the gastrointestinal tract before absorption. However, the correct choice and timing of a gastrointestinal decontamination technique are crucial to uncomplicated recovery. The usual choices are activated charcoal, induced emesis, gastric lavage, whole bowel irrigation or a combination of these techniques. Occasionally endoscopic removal may be needed. The efficacy, indications, contraindications, disadvantages and complications of these techniques are discussed below. A general plan of management is presented in Fig. 114.1.

A crucial point in management is the initial recognition that the patient is in a state of either 'full-consciousness' or 'less-than-full consciousness'. Traditionally, management has been dependent on a judgement of whether the gag reflex is present or absent, but in practice this is rarely tested. Since aspiration pneumonitis is a common feature of poisoning management, particularly among (but not confined to) obtunded patients, it is prudent to regard all obtunded patients as having incompetent pharyngeal reflexes.

The decision to attempt removal of a poison should always be made with due reference to two facts:

- The vast majority of childhood poisonings recover with merely supportive care or no treatment at all.
- Aspiration pneumonitis is more serious than most poisonings.

ACTIVATED CHARCOAL

Charcoal adsorbs many drugs and is regarded as a 'universal antidote'.[3,10] Although advocated as sole treatment in most poisonings, it is overused for minor

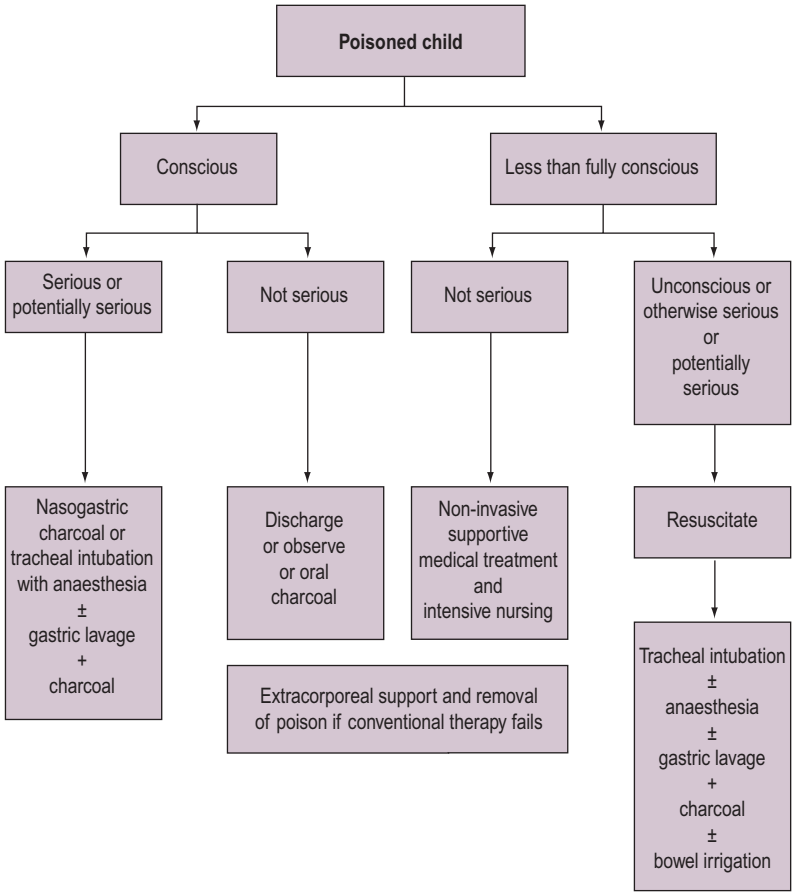


Figure 114.1 General management of the poisoned child.

poisonings, and for many poisons no data exist regarding efficacy.

Treatment of charcoal with chemicals and heat increases its surface area to approximately 950 m^2/g in so-called low-surface-area activated charcoal and to 2000 m^2/g in superactivated charcoal. The latter adsorbs paracetamol better and is more palatable.[11,12] Activated charcoal is not pleasant to drink and is associated with vomiting in 20% of poisoned children.[13] It is superior to induced emesis and gastric lavage in the treatment of symptomatic poisoned patients,[14–16] but its efficacy diminishes with time after ingestion. Activated charcoal reduces the absorption of ingested experimental drugs in volunteers by 85%–100% when administered 5 minutes after ingestion,[17–19] by 40%–75% at 30 minutes[20] and by 30%–50% at 60 minutes.[19,21] At mean times of 98 minutes[22] or more than 2 hours[23] after poisoning, it was not effective at all.

Activated charcoal alone is as effective as when combined with either emesis or with lavage,[24] but in combination with these methods has an 8.5% incidence of aspiration, compared with zero when used alone.[18]

Repeated doses of activated charcoal (multidose) enhance the elimination of some drugs by increased adsorption and by post-absorption elimination by interruption of an enterohepatic circulation and by removing the drug from the gastrointestinal mucosa ('gastrointestinal dialysis'). Although multiple reports exist in experimental and clinical practice (Box 114.1),[25] there is no convincing evidence to show that this therapy reduces mortality or morbidity. Only in life-threatening poisoning by carbamazepine, dapsone, phenobarbital, quinine or theophylline should multiple-dose activated charcoal be considered.[25]

A suitable single dose is 1–2 g/kg. A multiple-dose regimen for children is 1–2 g/kg stat followed by 0.25–0.5 g/kg 4–6-hourly. An alternative is 0.25–0.5 g/kg hourly for 12–24 hours.[26]

Contraindications

- Ileus
- A less-than-fully-conscious patient unless already intubated
- Substances not adsorbed, for example strong corrosive acids and alkalis, cyanide, metals (iron, lithium,

Box 114.1 Elimination and lack of elimination of drugs by multiple-dose activated charcoal

ELIMINATION INCREASED IN EXPERIMENTAL AND CLINICAL STUDIES	ELIMINATION INCREASED IN VOLUNTEER STUDIES	ELIMINATION NOT INCREASED IN EXPERIMENTAL OR CLINICAL STUDIES
Carbamazepine	Amitriptyline	Astemizole
Dapsone	Dextropropoxyphene	Chlorpropamide
Phenobarbital	Digitoxin	Doxepin
Quinine	Digoxin	Imipramine
Theophylline	Disopyramide	Meprobamate
	Nadolol	Methotrexate
	Phenylbutazone	Phenytoin
	Phenytoin	Sodium valproate
	Piroxicam	Tobramycin
	Sotalol	Vancomycin

Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol*. 1999;37: 731–751.

mercury, lead), alcohols, glycols, petroleum distillates (not all) and essential oils[5–7]

Complications

Aspiration of charcoal causes severe and often fatal pneumonitis, bronchiolitis obliterans and adult respiratory distress syndrome. Inadvertent intratracheal instillation of activated charcoal causes a significant increase in lung microvascular permeability and arterial blood gas derangements.[27]

Constipation is common after charcoal, but bowel obstruction is fortunately rare. The addition of a laxative (e.g. sorbitol or magnesium sulphate) is not recommended because, although transit time through the gut is decreased, efficacy of the charcoal is reduced and life-threatening fluid and electrolyte imbalance may occur.[28]

INDUCED EMESIS

For many reasons, induced emesis with ipecacuanha (ipecac) has disappeared from hospital practice and should not be performed routinely in this setting.[29] Ipecac contains alkaloids, mainly emetine and cephaeline, which induce emesis by stimulation of the chemoreceptor trigger zone of the medulla and by irritation of the gastric mucosa.

The efficacy of ipecac is limited and decreases with time from ingestion. Although it causes vomiting in a high percentage (93%–100%) of children within 25 minutes, the percentage of stomach contents ejected is small (28%) even when administered immediately after ingestion.[30] Moreover, solids are retained in the stomach or may even be propelled into the duodenum.[20] In adults, ipecac is even less useful and has to be given immediately to have quantifiable effects.[31]

It does not improve outcome and may reduce effectiveness of the alternative treatments of activated charcoal, oral antidotes and whole bowel irrigation. However, its use in the home is safe and is associated with fewer paediatric emergency department attendances,[32] and it is still recommended by authoritative paediatric health organisations in the United States.[33] Although ipecac was recommended inappropriately in 20% of cases reported to poisons information centres, it caused little morbidity.[34]

Experimentally, approximately 50%–83% of ingested experimental drug is removed if ipecac is given after 5 minutes,[17] falling to 2%–44% if given at 30 or 60 minutes.[21,35–38] In paediatric paracetamol poisoning, the 4-hour post-ingestion serum level was approximately 50% of controls if ipecac-induced vomiting occurred within 60 minutes of ingestion, but no benefit was derived if emesis occurred beyond 90 minutes after ingestion.[39] Similarly, serum levels of paracetamol were reduced approximately 50% if ipecac was administered at home, inducing emesis at a mean of 26 minutes after ingestion, compared with ipecac administered at a medical facility at a mean of 83 minutes.[40]

Critics claim that induced emesis merely creates work, delays discharge from the emergency department[41] increases complications and does not benefit the patient who presents more than 1 hour after ingestion.[42] Importantly, ipecac did not alter the clinical outcome of patients who presented awake and alert to the emergency department.[15]

Induced emesis appears superior to gastric lavage but inferior to activated charcoal. In salicylate poisoning, emesis retrieved twice as much as gastric lavage.[43] In adult volunteers ipecac-induced vomiting, occurring at an average of 19 minutes after ingestion, removed 54% of a tracer compared with 30% with gastric lavage performed at the equivalent times after ingestion.[14,44,45]

Contraindications

Specific contraindications include actual or impending loss of full consciousness or ingestion of corrosives or hydrocarbons.[29]

Complications

Potential complications include time-related lack of efficacy, protracted vomiting (17%), diarrhoea (13%) and lethargy (12%).[46] More serious, but rare, complications include gastric, oesophageal or brain haemorrhage, pneumomediastinum, aspiration pneumonitis, which may occur even in the fully conscious patient, delayed onset of vomiting, which is a threat if loss of consciousness subsequently occurs, and abuse in

bulimia, which may cause cardiotoxicity as well as the sequelae associated with repetitive vomiting.

In hospital, induced emesis has no practical role. Even when a child presents very early after significant poisoning, oral or nasogastric charcoal is preferred. Importantly, whenever induced emesis is used the child must be fully conscious on administration and is expected to be fully conscious when vomiting occurs.

GASTRIC LAVAGE

The place of this in the management of the poisoned victim is very limited.[47] It is invasive, ineffective and potentially harmful. It should be reserved for the child who presents very soon after a life-threatening ingestion such as iron or colchicine.

It involves the passage of a large-bore oro- or nasogastric tube into the stomach and the repeated instillation of fluid, usually water; however, some authorities advocate normal or half-normal saline. The oral route is preferred because there is less potential for traumatic injury, but an oropharyngeal airway may be needed to prevent tube occlusion by chomping. A smaller tube may be used if the poison is a liquid. Traditionally, the child should be placed in the left lateral position to limit stomach emptying, but the volume of intragastric contents rather than body position determines gastric emptying.[48]

Experimental studies on liquids indicate that gastric lavage retrieves 90% at 5 minutes,[49] 45% at 10 minutes[45] and 30% at 19 minutes,[44] and reduces the absorption or bioavailability by 20%–32% at 1 hour after ingestion.[35,50] When performed 5 minutes after ingestion of tablet drugs, it failed to prevent absorption, presumably because the tablets had not disintegrated.[18] In true overdose situations, gastric lavage within 4 hours of admission reduced serum paracetamol levels by 39%.[51]

Efficacy of gastric lavage, even with large-bore tubes, is poor because tablets are not removed and lavage encourages propulsion into the duodenum.[30] In symptomatic patients, gastric lavage alone compared with gastric lavage and activated charcoal increased pneumonic aspiration and did not alter the duration of intubation or the stay in the emergency department or the intensive care unit,[16] and was not beneficial unless performed within 1 hour of ingestion.[15] A randomised controlled trial of gastric lavage in acute overdose[24] suggested that it made no difference to the outcome of obtunded patients when preceding activated charcoal.

Contraindications

- Less-than-fully conscious patient (unless already intubated) because of the risk of aspiration pneumonitis – which is not negligible even during full consciousness.[16]
- After ingestion of corrosives because of the risk of perforation.
- After ingestion of hydrocarbons or petrochemicals because of the risk of pneumonitis.

Complications

- Aspiration pneumonitis
- Water intoxication
- Minor trauma to oropharynx (gastro-oesophageal perforation occurs rarely)
- Intrabronchial instillation of lavage fluid.

As expected, infants and children never cooperate fully for gastric lavage, thus increasing the risk of complications and the degree of psychological trauma.

If lavage is indicated (i.e. for life-threatening poisoning), rapid sequence induction of anaesthesia with intubation is mandatory. The largest possible lubricated tube of diameter similar to an appropriate-sized endotracheal tube should be used, and correct placement in the stomach confirmed. Small volumes (1–2 mL/kg) of warm tap water or 0.9% saline may be used to lavage until clear. However, most fluids should be retrieved to avoid complications with fluid and electrolytes, particularly hyponatraemia if water is used.

WHOLE BOWEL IRRIGATION

Irrigation of the bowel with an iso-osmolar solution of polyethylene glycol and electrolytes is effective in reducing the absorption of an experimental drug by 24%–67% at 1 hour after ingestion[53,54] and up to 73% at 4 hours after ingestion.[55] The technique has limited applications to sustained-release or enteric-coated drugs and remains a theoretical option for ingestions of iron, lead, zinc (substances not adsorbed by activated charcoal), packets of illicit drugs[56] and lithium.[57] The technique has been used most commonly for ingestion of calcium channel blockers, iron and antidepressants.[58] Whole bowel irrigation may be useful in delayed presentations when poisons have progressed beyond the stomach.

Since irrigation solutions are adsorbed by activated charcoal and cause desorption of drug, this necessitates prior administration of charcoal if a combined technique is used.[59] However, whole bowel irrigation did not add to the benefits of activated charcoal in an experimental model of sustained-release theophylline poisoning.[60]

A suitable regimen is approximately 30 mL/kg/h for 4–8 hours until rectal effluent is clear. A regimen of 25 mL/kg/h has been used safely for 5 days (total 44.3 L),[61] but a total of 3 L was as effective as 8 L in a simulated poisoning.[62]

Contraindications

Risk of aspiration during:

- less-than-full consciousness
- bowel obstruction or ileus.

PLAN OF MANAGEMENT

A general plan of management is suggested in Fig. 114.1, but each case of poisoning mandates a specific

management according to circumstances: consciousness and risk of aspiration, timing of presentation in relation to the severity of poisoning and the existence or otherwise of an effective antidote dictate if removal should be attempted, and by what means.

POISONING BY SPECIFIC SUBSTANCES

Like adults, children are poisoned regularly by therapeutic prescription or over-the-counter therapeutic drugs and substances (see Chapter 90). The poisons probably reflect their availability in the home. In surveys, the most common agents responsible for hospital admission of children are benzodiazepines, anticonvulsants, antiparkinsonism drugs, paracetamol, major tranquillisers, antidepressants and cardiovascular drugs.[62] Fatal poisonings are often by opiates, especially methadone[63] and pesticides, particularly paraquat and its derivatives,[64] which cause pulmonary fibrosis and hepatorenal failure.

The inquisitive nature of young children results in poisoning by substances not normally regarded as dangerous and not encountered in adults. A few of these are considered here briefly.

BUTTON AND DISC BATTERIES

Ingestion may cause electrolytic injury and potentially corrosive, toxic or pressure injury. There are many types of batteries that contain a variety of substances; the most important are lithium, mercury and potassium hydroxide.

Impaction in the oesophagus is the most significant situation; this can result in oesophageal perforation and tracheo-oesophageal fistula or aorto-oesophageal fistula. An impacted battery must be removed endoscopically as soon as possible. Lithium batteries are large and impact readily and they have higher voltages than other types. Electrolysis commences as soon as the battery surfaces are immersed in oesophageal fluid. The consequence is local and surrounding tissue destruction, including the trachea.[65,66] Strong alkali is produced at the cathode and strong acid is produced at the anode. Mercury batteries are more likely to fragment[66] but mercury poisoning is very uncommon.

Sufficient follow-up is necessary to detect early any oesophageal and tracheal damage and to ensure that a battery in the stomach or distal bowel is eliminated.

PETROLEUM DISTILLATES

Numerous by-products of petroleum distillation are utilised for industrial and domestic purposes. Ingestion of these hydrocarbons may cause central nervous system (CNS) toxicity (comprising obtundation and convulsion), pneumonitis, arrhythmias,[67] gastrointestinal irritation and occasional hepatorenal toxicity.

Pneumonitis is the most significant and it may occur during ingestion or subsequent vomiting. Although variable, these substances generally have low surface tension, which enables their rapid dispersement throughout contiguous mucosal surfaces including the respiratory tree. Prime examples are petrol, kerosene, lighter fluid, lamp oil and mineral spirits. Any child who ingests a distillate must be assessed for pneumonitis, and this should include clinical examination, a chest X-ray and at least a non-invasive measurement of oxygenation such as pulse oximetry. Although most children who ingest petroleum distillates do not develop pneumonitis, the onset of this complication may be within 30 minutes[68] and progress rapidly to severe lung disease. An adequate period of observation (6 hours) is necessary to exclude this complication. There is a poor correlation between the amount ingested and the severity of pulmonary toxicity.

Deliberate inhalation of volatile hydrocarbons, such as petrol or aerosolised paint, has the additional toxicity on myocardial tissue, including fatal tachydysrhythmia, which is possibly due to sensitisation to endogenous catecholamines. The deliberate inhalation of fumes, usually via a plastic bag, is known as 'chroming'.

ESSENTIAL OILS

The oils from certain plants contain mixtures of terpenes, alcohols, aldehydes, ketones and esters, which are used domestically for various purposes. The well-known oils are eucalyptus, turpentine, citronella, cloves, tea tree, peppermint, wintergreen and lavender. In general, small amounts cause depression of the conscious state, irritation of the gastrointestinal tract, liver dysfunction and pneumonitis if inhaled. Each has different toxicity. For example, as little as 5 mL of eucalyptus oil[69] or 15 mL of turpentine may cause depression of the conscious state.

Emesis should not be induced and gastric lavage performed only if airway protection is required.

LEAD

Children are more susceptible to lead poisoning after ingestion than are adults, possibly because of better absorption. Any amount of lead is neurotoxic.

Acute poisoning usually occurs after ingestion of a lead salt or metallic foreign body, or a lead-containing product, such as paint, a traditional remedy or a cosmetic. Acute poisoning by a salt may cause life-threatening cardiovascular collapse and encephalopathy.

Chronic poisoning can occur insidiously by multiple mechanisms, such as with ingestion of lead-contaminated water or by inhalation of leaded petrol

fumes, contaminated house dust or by parental work-related 'take-home' exposure. Chronic poisoning causes multiorgan dysfunction including neuromuscular dysfunction and encephalopathy. Unfortunately, interventions to reduce domestic lead exposure to date have been largely ineffective.[70]

Treatment consists of gastric decontamination in the case of recent ingestion of lead salts. The use of intravenous or oral chelating agents may be indicated.[71] In the case of ingestion of a lead foreign body, serial X-rays should be taken to ensure elimination, otherwise surgical/interventional removal is indicated. In the case of multiple embedded gunshot pellets and in all cases of chronic poisoning, serum lead levels should be measured to guide chelation therapy (see Table 114.1).

PARACETAMOL

This is the most common drug ingested by children in an accidental, iatrogenic or deliberate overdose situation. Overdose has the potential for hepatic failure and, less commonly, renal failure. Massive overdose may cause cardiovascular collapse and CNS depression. The onset of toxicity is delayed – up to several days. Consequently, the need for acute gastric decontamination is uncommon, but would be justifiable for acute large-dose presentations. The hepatic toxicity in part is caused by the metabolite of the drug (*N*-acetyl-*p*-benzoquinoneimine), which accumulates when endogenous glutathione, which facilitates conversion of *N*-acetyl-*p*-benzoquinoneimine to non-toxic substances, becomes exhausted. Adequate supply of glutathione is ensured by administration of N-acetylcysteine (NAC), a glutathione precursor that can be administered intravenously or orally (see Table 114.1).

The time of presentation after ingestion, as well as the dose, determines the management. If presentation is within 2 hours of ingestion, effective gastric removal or administration of activated charcoal may be all that is required pending a serum paracetamol level. In contrast, if presentation is several hours after ingestion, administration of the antidote according to serum paracetamol level takes precedence and, although it may be administered orally or intravenously, the intravenous route is generally preferred.[72] In one study, hepatic toxicity was slightly less in patients treated with the intravenous regimen compared with the oral regimen in patients whose treatment was initiated within 12 hours of ingestion. However, later than 18 hours hepatic toxicity was slightly less in patients treated with the oral regimen compared with the intravenous regimen, with no difference in toxicity in those treated with either regimen at presentations between 12 and 18 hours after ingestion.[73]

Near-simultaneous administration of activated charcoal and acetylcysteine may be of some benefit but it may also cause vomiting or desorption, thus decreasing the effectiveness of the oral antidote. If presentation is many hours after the poisoning, activated charcoal is not indicated, so the antidote could be administered orally if necessary according to serum paracetamol levels. Serial levels of paracetamol should be obtained, especially for slow-release preparations, but such cases are adequately managed if the protocol for NAC administration is followed.[74] Although numerous protocols exist for intravenous NAC administration, the recommended protocols are either that based on the Rumack-Matthew nomogram of a total of 300 mg/kg administered in three phases over a total of 21 hours[75] or on a protocol of the same dose in two phases over 20 hours (Table 114.1). In cases of massive overdose, for example 40 g or serum paracetamol level of 3300 µmol/L at 4 hours after ingestion, a protocol of 980 mg/kg of NAC over 48 hours has been successfully used.[76]

When the following doses are ingested, the antidote, *NAC*, should be commenced immediately[77] but then guided by time-related serum levels (see Table 114.1):

200 mg/kg or 10 g as a single dose (whichever is lower)
150 mg/kg/24 hours or 6 g (whichever is lower) for less than 48 hours
100 mg/kg/24 hours or 4 g (whichever is lower) for more than 48 hours

Unfortunately, toxic overdosing by chronic administration is not uncommon even in Australian and New Zealand institutions.[78] If serum levels of paracetamol cannot be obtained and >200 mg/kg has been ingested as a single dose, or liver dysfunction is present after chronic poisoning or any acute poisoning irrespective of the dose, the antidote should be given. Adverse reactions to NAC are common (approximately 7%–8%), but not serious, and they respond to an antihistamine[79] and its temporary cessation. High-dose NAC causes adverse reactions in almost 30% of patients.[76]

If hepatic function worsens despite antidote treatment, liver transplantation may be required.

IRON

Small quantities of elemental iron (>20 mg/kg) are toxic to children. A lethal dose may be reached by ingestion of a few iron tablets. The initial effects are gastrointestinal, which may include gastric erosion, followed sometimes by an interval before cardiovascular failure occurs at 6–24 hours and then followed by multiorgan failure (including encephalopathy), and hepatic and renal failure up to some 48 hours after ingestion. In addition to general supportive measures, specific management should include an abdominal X-ray to determine if unabsorbed tablets are present, in which case gastric lavage or whole bowel irrigation may be useful. Activated charcoal is useless. Chelation therapy with deferrioxamine (see Table 114.1) should be guided by the serum iron level and the clinical status.

CAUSTIC SUBSTANCES (DISHWASHER AND LAUNDRY DETERGENTS)

In a study of 743 children,[80] the incidence of oesophageal burns caused by ingestion of automatic machine dishwashing detergents was 59%, caustic soda 55% and drain cleaners 55%. All are strongly alkaline and are corrosive. Dishwasher detergents are presented as liquids, powders or tablet blocks and are commonly accessed in an open dishwasher.[81] Pharyngeal and oesophageal irritation, burns or corrosion may occur. There may be simultaneous ocular and dermal toxicity. Any child presenting with a history of ingestion of a caustic substance, irrespective of clinical signs, should be considered for oesophagoscopy and follow-up since the correlation between symptoms and signs and oesophageal burns is poor, and significant oesophageal damage may occur in the absence of more proximal injury.[82]

The recently available liquid laundry detergent pods and capsules are also alkaline and more toxic than traditional laundry products. Oral contact causes CNS obtundation, seizures, pulmonary oedema and aspirational lung disease while eye contact causes conjunctivitis and keratitis.[83–85]

ENVENOMATION

Children are subject to envenomation by a wide variety of terrestrial creatures including snakes, scorpions, spiders, bees, ants and wasps. Marine envenomation is mainly caused by jellyfish and stinging fish and only occasionally by venomous octopuses. The clinical manifestations and management of envenomation are expectedly similar to those observed in adults (see Chapter 90) but with several additional considerations:

1. A history of envenomation may not be forthcoming when a young child, unsupervised, is bitten by a snake, particularly of the elapid genus, whose fang marks may not be evident. The diagnosis should be suspected in a child who presents with sudden onset of neurological signs *and* coagulopathy. Similarly, a diagnosis of spider envenomation in a child should be among the causes considered for a painful skin lesion.
2. The clinical effects of envenomation may be more pronounced in a child compared with an adult for the simple reason of their smaller body mass in relation to injected venom.
3. The dose of an antivenom is not reduced.

KEY REFERENCES

3. Smith SW. Drugs and pharmaceuticals: management of intoxication and antidotes. *Mol Clin Environ Toxicol*. 2010;2:397–460.
6. Erickson TB, Ahrens WR, Aks SE, et al., eds. *Pediatric Toxicology: Diagnosis and Management of the Poisoned Child*. New York: McGraw Hill; 2005.
8. Michael JB, Sztajnkrycer MD. Deadly pediatric poisons: nine common agents that kill at low doses. *Emerg Med Clin North Am*. 2004;22:1019–1050.
10. Lapus RM. Activated charcoal for pediatric poisonings: the universal antidote? *Curr Opin Pediatr*. 2007;19:216–222.
29. Krenzelok EP, McGuigan M, Lheur P. Position statement: ipecac syrup. American Academy of Clinical Toxicology; European Associations of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol*. 1997;35:699–709.
47. Academy of Clinical Toxicology and European Association of Poisons Centres and Clinical Toxicologists. Position statement: gastric lavage. *J Toxicol Clin Toxicol*. 2004;42:933–943.
56. Tenenbein M. Position statement: whole bowel irrigation. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol*. 1997;35:753–762.
66. Litovitz T, Schmitz BF. Ingestion of cylindrical and button batteries: an analysis of 2382 cases. *Pediatrics*. 1992;89:747–757.
71. Bradberry S, Vale A. Dimercaptosuccinic acid (succimer; DMSA) in inorganic lead poisoning. *Clin Toxicol*. 2009;47:617–631.
75. Wong A, Graudins A. Simplification of the standard three-bag intravenous acetylcysteine regimen for paracetamol poisoning results in a lower incidence of adverse drug reactions. *Clin Toxicol*. 2016;54:115–119.

Access the complete references list online at http://www.expertconsult.com

REFERENCES

1. Australian Institute of Health and Welfare. *Poisoning in children and young people. Australian Government, Canberra*. 2016. http://www.aihw.gov.au/publication-detail/?id=60129555543.
2. Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in paediatric inpatients. *JAMA*. 2001;285:2114–2120.
3. Smith SW. Drugs and pharmaceuticals: management of intoxication and antidotes. *Mol Clin Environ Toxicol*. 2010;2:397–460.
4. Betten DP, Vohra RB, Cook MD, et al. Antidote use in the critically ill poisoned patient. *J Intens Care Med*. 2006;21:255–277.
5. Shannon M, Borron SW, Burns MJ, eds. *Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose*. 4th ed. Philadelphia: WB Saunders; 2007.
6. Erickson TB, Ahrens WR, Aks SE, et al., eds. *Pediatric Toxicology: Diagnosis and Management of the Poisoned Child*. New York: McGraw Hill; 2005.
7. Hoffman RS, Howland MA, Lewin NA, et al., eds. *Goldfrank's Toxicologic Emergencies*. 10th ed. New York: McGraw Hill; 2014.
8. Michael JB, Sztajnkrycer MD. Deadly pediatric poisons: nine common agents that kill at low doses. *Emerg Med Clin North Am*. 2004;22:1019–1050.
9. de Pont A-CJM. Extracorporeal treatment of intoxications. *Curr Opin Crit Care*. 2007;13:668–673.
10. Lapus RM. Activated charcoal for pediatric poisonings: the universal antidote? *Curr Opin Pediatr*. 2007;19:216–222.
11. Roberts JR, Gracely EJ, Schoffstall JM. Advantage of high-surface-area charcoal for gastrointestinal decontamination in a human acetaminophen ingestion model. *Acad Emerg Med*. 1997;4:167–174.
12. Fischer TF, Singer AJ. Comparison of the palatabilities of standard and superactivated charcoal in toxic ingestions: a randomized trial. *Acad Emerg Med*. 1999;6:895–899.
13. Osterhoudt KC, Durbin K, Alpern ER, et al. Risk factors for emesis after therapeutic use of activated charcoal in acutely poisoned children. *Pediatrics*. 2004;113:806–810.
14. Albertson TE, Derlet RW, Foulke GE, et al. Superiority of activated charcoal alone with ipecac and activated charcoal in the treatment of acute toxic ingestions. *Ann Emerg Med*. 1989;18:56–59.
15. Kulig K, Bar-Or D, Cantrill SV, et al. Management of acutely poisoned patients without gastric emptying. *Ann Emerg Med*. 1985;14:562–567.
16. Merigian KS, Woodard M, Hedges JR, et al. Prospective evaluation of gastric emptying in the self-poisoned patient. *Am J Emerg Med*. 1990;8:479–483.
17. Neuvonen PJ, Vartiainen M, Tokola O. Comparison of activated charcoal and ipecac syrup in prevention of drug absorption. *Eur J Clin Pharmacol*. 1983;24:557–562.
18. Lapatto-Reiniluoto O, Kivisto KT, Neuvonen PJ. Gastric decontamination performed 5 min after ingestion of temazepam, verapamil and moclobemide: charcoal is superior to lavage. *Br J Clin Pharmacol*. 2000;49:274–278.
19. Neuvonen PJ, Elonen E. Effect of activated charcoal on absorption and elimination of phenobarbitone, carbamazepine and phenylbutazone in man. *Eur J Clin Pharmacol*. 1980;17:51–57.
20. Saetta JP, March S, Gaunt ME, et al. Gastric emptying procedures in the self-poisoned patient: are we forcing gastric content beyond the pylorus? *J R Soc Med*. 1990;84:274–276.
21. McNamara RM, Aaron CK, Gemborys M, et al. Efficacy of charcoal cathartic versus ipecac in reducing serum acetaminophen in a simulated overdose. *Ann Emerg Med*. 1989;18:934–938.
22. Anderson BJ, Holford NHG, Armishaw JC, et al. Predicting concentrations in children presenting with acetaminophen overdose. *J Pediatr*. 1999;135:290–295.
23. Yeates PJ, Thomas SH. Effectiveness of delayed activated charcoal administration in simulated paracetamol (acetaminophen) overdose. *Br J Clin Pharmacol*. 2000;49:11–14.
24. Pond SM, Lewis-Driver DJ, Williams GM, et al. Gastric emptying in acute overdose: a prospective randomised controlled trial. *Med J Aust*. 1995;163:345–349.
25. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol*. 1999;37:731–751.
26. Ohning BL, Reed MD, Blumer JL. Continuous nasogastric administration of activated charcoal for the treatment of theophylline intoxication. *Pediatr Pharmacol*. 1986;5:241–245.
27. Arnold TC, Willis BH, Xiao F, et al. Aspiration of activated charcoal elicits an increase in lung microvascular permeability. *J Toxicol Clin Toxicol*. 1999;37:9–16.
28. Palatnick W, Tenenbein M. Activated charcoal in the treatment of drug overdose. *Drug Saf*. 1992;7:3–7.
29. Krenzelok EP, McGuigan M, Lheur P. Position statement: ipecac syrup. American Academy of Clinical Toxicology; European Associations of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol*. 1997;35:699–709.
30. Corby DG, Decker WJ, Moran MJ, et al. Clinical comparisons of pharmacologic emetics in children. *Pediatrics*. 1968;4:361–364.
31. Saincher A, Sitar DS, Tenenbein M. Efficacy of ipecac during the first hour after drug ingestion in human volunteers. *J Toxicol Clin Toxicol*. 1997;35:609–615.
32. Bond GR. Home use of syrup of ipecac is associated with a reduction in pediatric emergency department visits. *Ann Emerg Med*. 1995;25:338–343.
33. Manoguerra AS, Cobaugh DJ. Guidelines for the management of poisoning consensus panel.

Guidelines on the use of ipecac syrup in the out-of-hospital management of ingested poisons. *Clin Toxicol*. 2005;43:1–10.
34. Wrenn K, Rodewald L, Dockstader L. Potential misuse of ipecac. *Ann Emerg Med*. 1993;22:1408–1412.
35. Tenenbein M, Cohen S, Sitar DS. Efficacy of ipecac-induced emesis, orogastric lavage, and activated charcoal for acute drug overdose. *Ann Emerg Med*. 1987;16:838–841.
36. Curtis RA, Barone J, Giacona N. Efficacy of ipecac and activated charcoal/cathartic. Prevention of salicylate absorption in a simulated overdose. *Arch Intern Med*. 1984;144:48–52.
37. Danel V, Henry JA, Glucksman E. Activated charcoal, emesis, and gastric lavage in aspirin overdose. *BMJ*. 1988;296:1507.
38. Vasquez TE, Evans DG, Ashburn WL. Efficacy of syrup of ipecac-induced emesis for emptying gastric contents. *Clin Nucl Med*. 1988;13:638–639.
39. Bond GR, Requa RK, Krenzelok EP, et al. Influence of time until emesis on the efficacy of decontamination using acetaminophen as a marker in a pediatric population. *Ann Emerg Med*. 1993;22:1403–1407.
40. Amitai Y, Mitchell AA, McGuigan MA, et al. Ipecac-induced emesis and reduction of plasma concentrations of drugs following accidental overdose in children. *Pediatrics*. 1987;80:364–367.
41. Kornberg AE, Dolgin J. Pediatric ingestions: charcoal alone versus ipecac and charcoal. *Ann Emerg Med*. 1991;20:648–651.
42. Foulke GE, Albertson TE, Derlet RW. Use of ipecac increases emergency department stays and patient complication rates. *Ann Emerg Med*. 1990;17:402.
43. Boxer L, Anderson FP, Rowe MD. Comparison of ipecac-induced emesis with gastric lavage in the treatment of acute salicylate ingestion. *J Pediatr*. 1969;74:800–803.
44. Young WF Jr, Bivins HG. Evaluation of gastric emptying using radionuclides: gastric lavage versus ipecac-induced emesis. *Ann Emerg Med*. 1993;22:1423–1427.
45. Tandberg D, Diven BG, McLeod JW. Ipecac-induced emesis versus gastric lavage: a controlled study in normal adults. *Am J Emerg Med*. 1986;4:205–209.
46. Czajka PA, Russell SL. Nonemetic effects of ipecac syrup. *Pediatrics*. 1985;75:1101–1104.
47. Academy of Clinical Toxicology and European Association of Poisons Centres and Clinical Toxicologists. Position statement: gastric lavage. *J Toxicol Clin Toxicol*. 2004;42:933–943.
48. Doran S, Jones KL, Andrews JM, et al. Effects of meal volume and posture on gastric emptying of solids and appetite. *Am J Physiol*. 1998;275:R1712–R1718.
49. Auerbach PS, Osterich J, Braun O, et al. Efficacy of gastric emptying: gastric lavage versus emesis induced with ipecac. *Ann Emerg Med*. 1986;15:692–698.
50. Grierson R, Green R, Sitar DS, et al. Gastric lavage for liquid poisons. *Ann Emerg Med*. 2000;35:435–439.
51. Underhill TJ, Greene MK, Dove AF. A comparison of the efficacy of gastric lavage, ipecacuanha and activated charcoal in the emergency management of paracetamol overdose. *Arch Emerg Med*. 1990;7:148–154.
52. Whyte IM, Buckley NA. Progress in clinical toxicology: from case reports to toxicoepidemiology. *Med J Aust*. 1995;163:340–341.
53. Smith SW, Ling LJ, Halstenson CE. Whole bowel irrigation as a treatment for acute lithium overdose. *Ann Emerg Med*. 1991;29:536–539.
54. Tenenbein M, Cohen S, Sitar DS. Whole bowel irrigation as a decontamination procedure after acute drug overdose. *Arch Intern Med*. 1987;147:905–907.
55. Kirshenbaum LA, Mathews SC, Sitar DS, et al. Whole-bowel irrigation versus activated charcoal in sorbitol for the ingestion of modified-release pharmaceuticals. *Clin Pharmacol Ther*. 1989;46:264–271.
56. Tenenbein M. Position statement: whole bowel irrigation. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol*. 1997;35:753–762.
57. Scharman EJ. Methods used to decrease lithium absorption or enhance elimination. *J Toxicol Clin Toxicol*. 1997;35:601–608.
58. Lo JC, Ualdo C, Cantrell FL. A retrospective review of whole bowel irrigation in pediatric patients. *Clin Toxicol*. 2012;50:414–417.
59. Makosiej FJ, Hoffman RS, Howland MA, et al. An in vitro evaluation of cocaine hydrochloride adsorption by activated charcoal and desorption upon addition of polyethylene glycol electrolyte lavage solution. *J Toxicol Clin Toxicol*. 1993;31:381–395.
60. Burkhart KK, Wuerz RC, Donovan JW. Whole bowel irrigation as adjunctive treatment for sustained-release theophylline overdose. *Ann Emerg Med*. 1992;21:1316–1320.
61. Kaczorowski JM, Wax PM. Five days of whole-bowel irrigation in a case of pediatric iron ingestion. *Ann Emerg Med*. 1996;27:258–263.
62. Olsen KM, Gurley BJ, Davis GA, et al. Comparison of fluid volumes with whole bowel irrigation in a simulated overdose of ibuprofen. *Ann Pharmacother*. 1995;29:246–250.
63. Anderson M, Hawkins L, Eddleston M, et al. Severe and fatal pharmaceutical poisoning in young children. *Arch Dis Child*. 2016;101:653–656.
64. Duan Y, Wang Z. To explore the characteristics of fatality in children poisoned by paraquat with analysis of 146 cases. *Int J Artif Organs*. 2016;39:51–55.
65. Tibballs J, Wall R, Velandy Koottayi S, et al. Tracheo-oesophageal fistula caused by electrolysis of a button battery impacted in the oesophagus. *J Paediatr Child Health*. 2002;38:201–203.

66. Litovitz T, Schmitz BF. Ingestion of cylindrical and button batteries: an analysis of 2382 cases. *Pediatrics*. 1992;89:747–757.
67. Tormoehlen LM, Tekulve KJ, Nanagas KA. Hydrocarbon toxicity: a review. *Clin Toxicol*. 2014;52:479–489.
68. Anas N, Namasonthi V, Ginsburg CM. Criteria for hospitalizing children who have ingested products containing hydrocarbons. *JAMA*. 1981;246:840–843.
69. Tibballs J. Clinical effects and management of eucalyptus oil ingestion in infants and young children. *Med J Aust*. 1995;163:177–180.
70. Nussbaumer-Streit B, Yeoh B, Griebler U, et al. Household interventions for preventing domestic lead exposure in children. *Cochrane Database Syst Rev*. 2016;(10):CD006047.
71. Bradberry S, Vale A. Dimercaptosuccinic acid (succimer; DMSA) in inorganic lead poisoning. *Clin Toxicol*. 2009;47:617–631.
72. Buckley NA, Whyte IM, O'Connell DL, et al. Oral or intravenous N-acetylcysteine: which is the treatment of choice for acetaminophen (paracetamol) poisoning? *J Toxicol Clin Toxicol*. 1999; 37:759–767.
73. Yarema MC, Johnson DW, Berlin RJ, et al. Comparison of the 20-hour intravenous and 72-hour oral acetylcysteine protocols for the treatment of acute acetaminophen poisoning. *Ann Emerg Med*. 2009;54:606–614.
74. Graudins A. Overdose with modified-release paracetamol (Panadol Osteo) presenting to a metropolitan emergency medicine network: a case series. *Emerg Med Aust*. 2014;26:398–402.
75. Wong A, Graudins A. Simplification of the standard three-bag intravenous acetylcysteine regimen for paracetamol poisoning results in a lower incidence of adverse drug reactions. *Clin Toxicol*. 2016;54:115–119.
76. Heard K, Rumack BH, Green JL, et al. A single-arm clinical trial of a 48-hour intravenous N-acetylcysteine trial for treatment of acetaminophen poisoning. *Clin Toxicol*. 2014;52:512–518.
77. Duffall SB, Isbister GK. Predicting the requirement for N-acetylcysteine in paracetamol poisoning from reported dose. *Clin Toxicol*. 2013;51: 772–776.
78. Rajanayagam J, Bishop JR, Lewindon PJ, et al. Paracetamol-associated acute liver failure in Australia and New Zealand children: high rate of medication errors. *Arch Dis Child*. 2015;100:77–80.
79. Heubi JE, Barbacci MB, Zimmerman HJ. Therapeutic misadventures with acetaminophen: hepatotoxicity after multiple doses in children. *J Pediatr*. 1998;132:22–27.
80. Bautista Casasnovas A, Estevez Martinez E, Varela Cives R, et al. A retrospective analysis of ingestion of caustic substances by children. Ten-year statistics in Galicia. *Eur J Pediatr*. 1997;156:410–414.
81. Cornish LS, Parsons BJ, Dobbin MD. Automatic dishwasher detergent poisoning: opportunities for prevention. *Aust N Z J Public Health*. 1996;20: 278–283.
82. Krenzelok EP, Clinton JE. Caustic esophageal and gastric erosion without evidence of oral burns following detergent ingestion. *JACEP*. 1979;8:194–196.
83. Williams H, Bateman DN, Thomas SH, et al. vale JA. Exposure to liquid detergent capsules: a study undertaken by the UK National Poisons Information Service. *Clin Toxicol*. 2012;50:776–780.
84. Claudet I, Honorat R, Casasoprana A, et al. Paediatric exposures to laundry pods or capsules: more toxic than traditional laundry products [French]. *Arch Pediatr*. 2014;21:601–607.
85. Valdez AL, Casavant MJ, Spiller HA, et al. Pediatric exposure to laundry detergent pods. *Pediatrics*. 2014;134:1127–1135.

115

Paediatric cardiopulmonary resuscitation

James Tibballs

INTRODUCTION

Basic and advanced cardiopulmonary resuscitation (CPR) for newborns, infants and children are described. The essentials of resuscitation are presented in figures for the infant and child (Fig. 115.1) and for newborns (Fig. 115.2). Recommendations are based on guidelines published by resuscitation organisations,[1–3] which are derived from evaluation of the science of resuscitation by the International Liaison Committee on Resuscitation in 2015[4] and from selected studies since that date.

This chapter is intended for medical and nursing personnel in hospital and complements Chapters 21 and 105. To add ability to knowledge, it is advisable to undertake a specialised paediatric CPR course, such as the Advanced Paediatric Life Support, Paediatric Advanced Life Support or Resus4kids courses.

DEFINITIONS

Distinctions within the term 'paediatric' are based on combinations of physiology, physical size and age. Some aspects of CPR are different for the 'newborn', infant, small (younger) child and large (older) child:

- *'newborn':* the infant at birth or within several hours of birth
- *'infant':* an infant outside the 'newborn' period and up to the age of 12 months
- *'small/young child':* a child of preschool and early primary school from the age of 1–8 years
- *'large/older child':* a child of late primary school from the age of 9 up to 14 years
- children older than 14 years may be treated as adults, but they do not have the same propensity for ventricular fibrillation (VF) as do adults.

EPIDEMIOLOGY

The causes of cardiopulmonary arrest (CPA) in infants and children are many and include any cause of hypoxaemia or hypotension or both. Common causes are trauma (motor vehicle accidents, near-drowning, falls, burns, gunshot, non-accidental injury), drug overdose and poisoning, respiratory illness (asthma, upper-airway obstruction, parenchymal diseases), postoperative (especially cardiac), septicaemia and sudden infant death syndrome. As many as 10% of infants at birth require some form of resuscitation for varied conditions of which birth asphyxia is the most common.

PREVENTION

CPA occurring in hospital may be preventable. Every institution which admits children should have a system to recognise deterioration, call for assistance and to provide rapid enhancement of the level of care, hence the use of medical emergency teams, rapid response teams and paediatric early warning scores.[5]

PROGNOSIS

Survival to discharge from cardiac arrest in hospital is reported from large series as 37%–41%.[6–8] With slightly higher survival for arrest in the paediatric intensive care unit (40%–45%).[9,10] Survival is less if arrest occurs after hours.[11] Extracorporeal CPR has a survival to discharge of 40%–55% with good neurological outcomes.[12,13]

Not unexpectedly, survival from out-of-hospital cardiac arrest is less than in-hospital arrest but is not hopeless. Overall survival from all causes is 6%–11% and survival with favourable neurological outcome up to 9%.[6,14–16] Outcomes are better when bystanders have given conventional CPR (chest compressions with ventilation) compared with compression-only CPR or no CPR, and better when the required duration of CPR is short.[14,17] In non-asphyxial arrest, compression-only CPR may be better.[18] A favourable neurological outcome can be predicted by pre-hospital return of spontaneous circulation (ROSC), the presence of a shockable rhythm and a witnessed arrest.[19] Only 1% of children arriving at hospital without ROSC have a favourable neurological outcome.[16]

ABSTRACT

This chapter describes practical aspects of techniques, equipment and drugs used in basic and advanced cardiopulmonary resuscitation (CPR). A chest compression rate of 100–120 per minute to a depth of 5 cm for children and 4 cm for infants is recommended combined with ventilation via bag-mask or tracheal intubation in advanced CPR. A compression–ventilation ratio of 15:2 is recommended for advanced resuscitation by health care personnel, and a ratio of 30:2 is recommended for basic life support by a single rescuer. Interruptions to chest compressions must be minimised. A single direct current shock of 4 J/kg followed by immediate resumption of CPR is recommended for ventricular fibrillation or ventricular tachycardia. Adrenaline 10 μg/kg is recommended for asystole and non-shockable rhythm. Automated external defibrillation for out-of-hospital arrest is encouraged. Extracorporeal CPR is sanctioned in-hospital where practical. Invasive maintenance of vital functions post arrest is crucial with either therapeutic hypothermia or normothermia. Prognostication should include clinical examination and neurological investigations.

KEYWORDS

Cardiopulmonary resuscitation
children
infants
guidelines

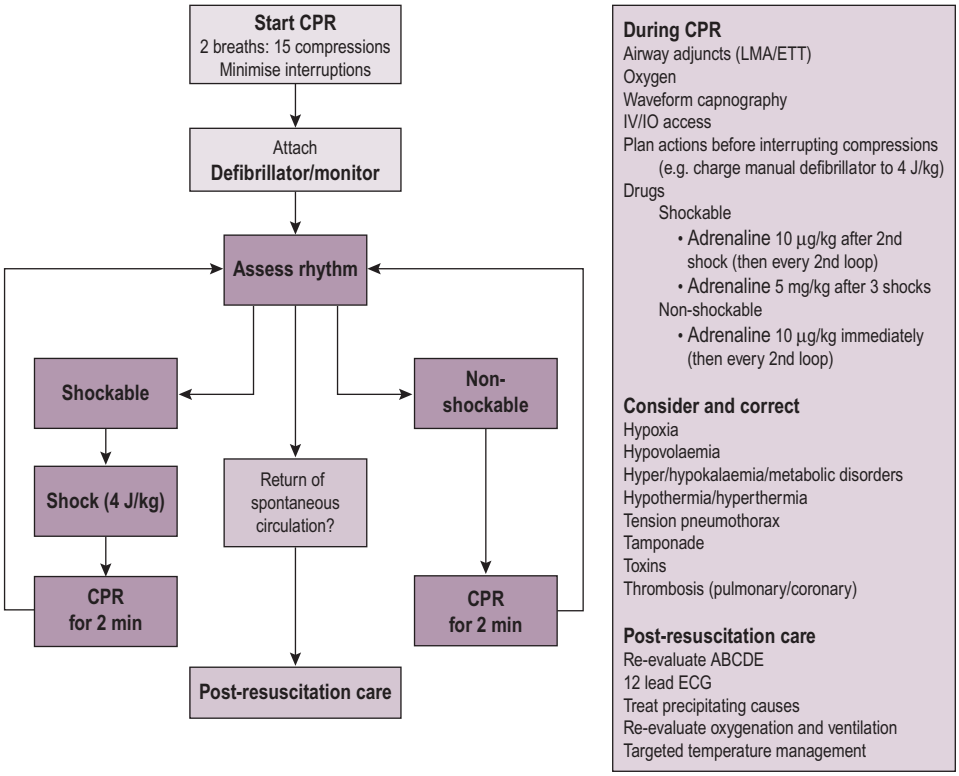


Figure 115.1 Advanced life support for infants and children. *CPR*, Cardiopulmonary resuscitation; *ECG*, electrocardiograph; *ETT*, Endotracheal tube; *IV*, intravenous; *IO*, intraosseous; *LMA*, laryngeal mask airway.

BASIC LIFE SUPPORT

ASSESSMENT OF AIRWAY AND BREATHING

If the child is not responsive to tactile and auditory stimulation, not breathing normally and not moving, the rescuer should assess the airway and breathing, which can be achieved in either the supine or lateral position. Obvious causes of airway obstruction in the pharynx should be removed. Fluids such as vomitus or blood should be aspirated with a Yankauer sucker. Solid or semi-solid objects such as food particles or foreign objects should be removed with an instrument (e.g. Magill's forceps). Since the most common cause of airway obstruction in an obtunded state is the tongue, first-aid manoeuvres to elevate it should be performed. These manoeuvres are backward head tilt, chin lift and jaw thrust. Head tilt and chin lift are often combined. If neck injury is present or suspected, neither the head tilt nor the chin lift manoeuvre should be used. Following establishment of an airway, the presence or absence of adequate breathing is assessed by inspection of movement of the chest and abdomen, and by listening and feeling for escape of exhaled air from the mouth and nose (look, listen and feel). If adequate breathing is occurring the patient should be placed on the side in a coma position.

RESCUE BREATHING (EXPIRED AIR RESUSCITATION)

If breathing is inadequate then expired air resuscitation or bag-(valve)-mask ventilation should be commenced immediately. Initially at least two breaths are recommended, but some guidelines suggest up to five. (There is no definitive evidence.) While maintaining the airway, administer slow breaths over 1–1.5 seconds to achieve adequate chest inflation. In children of all sizes, a mouth-to-mouth technique is possible by pinching the nostrils closed. In the newborn and infants, a mouth-to-mouth-and-nose technique is recommended, but if the rescuer has a small mouth then a mouth-to-nose technique is an alternative. Lack of chest rise may signify obstruction of the airway requiring repositioning of the head and neck.

ASSESSMENT OF CIRCULATION

If the child is unresponsive and not breathing, external cardiac compression (ECC) should be commenced immediately. Pulse by palpation may be performed, but the 'pulse check' has been removed from CPR guidelines for lay persons because of their inability to reliably check the pulse, which may also be an issue for health care personnel. Palpation of any major

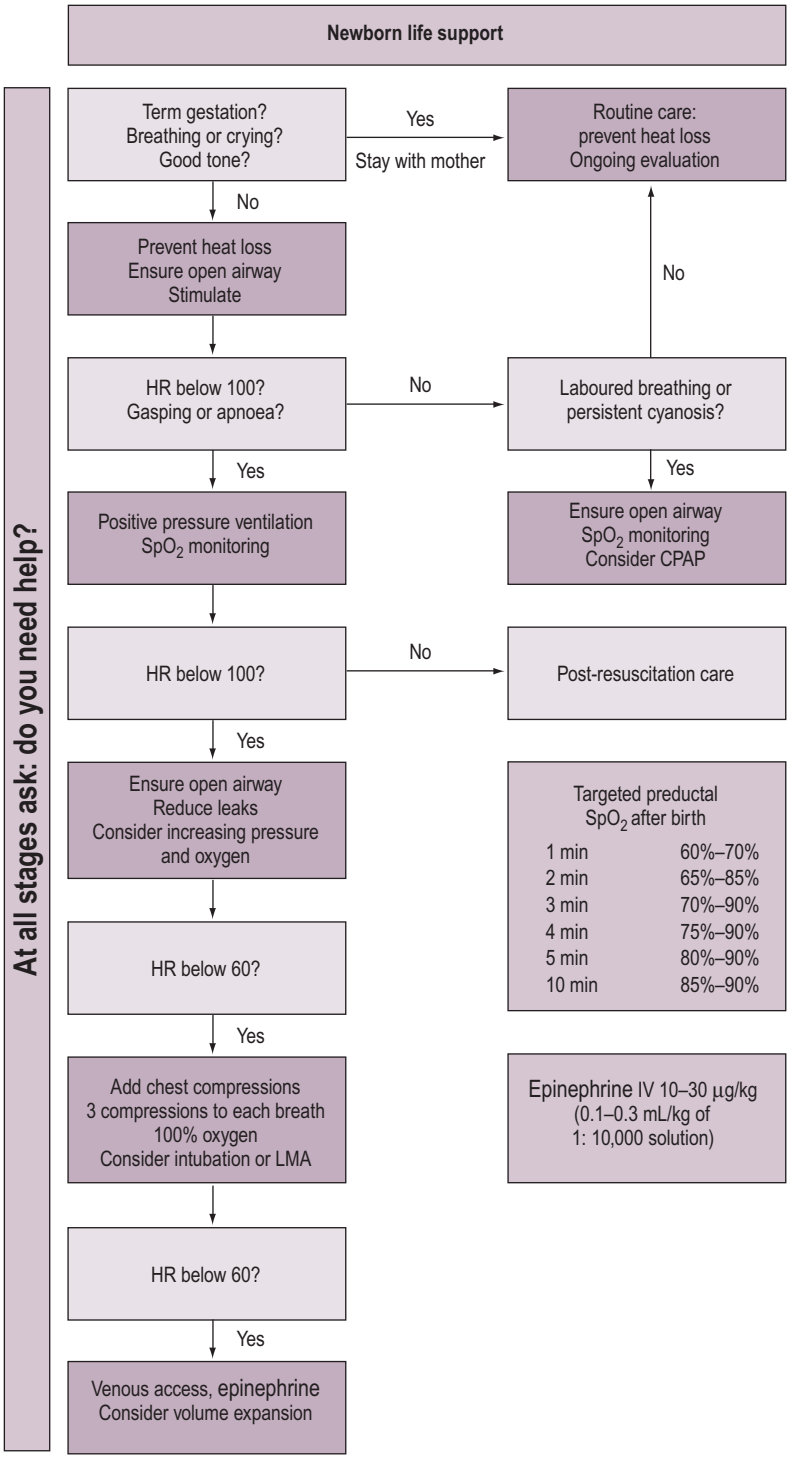


Figure 115.2 Newborn life support. *LMA*, Laryngeal mask airways. *(Reproduced with permission from the Australian Resuscitation Council, Melbourne.)*

pulse (carotid, brachial, femoral) is appropriate. If a pulse cannot be detected within 10 seconds or the rate is inadequate (<60 beats/min) then ECC should be commenced.

EXTERNAL CARDIAC COMPRESSION

Different techniques are used for infants and children of different sizes but in all patients the depth of compression is one-third the depth of their chest. This is about 5 cm for children and 4 cm for infants. For newborns and infants, two techniques are in common use. In the 'two-finger technique', the middle finger and forefinger are used. This technique is taught to laypersons and is also the preferred technique for a single health care rescuer. With the better 'two-thumb technique', the hands encircle the thorax, approaching the chest from either above or below, and the thumbs are placed either opposite, alongside or atop one another. With this technique, the rescuer must take care to avoid restriction of the patient's chest during inflation. With premature newborn and small infants, the rescuer's encircling fingers may reach and stabilise the vertebral column without limiting chest inflation. With both techniques, the sternum is compressed above the xiphoid or about one fingerbreadth below the internipple line.

Either a single hand or both hands may be used for infants and children as determined by the relationship between the size of the patient's chest and the hands of the rescuer. For young children, ECC can be performed with the heel of one hand. For older children, a bimanual technique as per adults may be used. In all ages, the 'centre of the chest' – which corresponds to the lower sternum – is compressed. Approximately 50% of each cycle should be compression. Every effort should be made to minimise 'hands-off' time (interruptions to compressions). This requires coordinated teamwork when, for example, ECC is paused to allow rhythm analysis or the application of direct current (DC) shock.

RATES OF COMPRESSION AND RATIO OF COMPRESSION TO VENTILATION

In hospitals (two or more rescuers), the ratio of compression to ventilation for infants and children should be 15:2. Resuscitation may be commenced with either ventilations or compressions. After every 15 compressions, a pause should allow delivery of two ventilations whenever expired air resuscitation or any type of mask ventilation is given. ECC can be given during the second exhalation. The aim should be to achieve about 5 cycles/min (i.e. about 75 compressions and 10 breaths/min). If circulation returns, but respiration remains inadequate, the number of ventilations should be higher, but care should be taken to avoid hypocarbia, which results in cerebral ischaemia. A sole health care rescuer may use the layperson ratio of 30:2, aiming to achieve about five cycles in 2 minutes (i.e. about 75 compressions and 5 breaths/min).

For infants and children, compressions should be delivered at a rate of 100–120 per minute (i.e. one compression every 0.6 seconds or approximately two per second). As ventilation is interposed between compressions, the actual compressions delivered will be less than 100 each minute. If the airway has been secured (e.g. by endotracheal intubation), strict coordination of compression and ventilation is not crucial; ventilation can be given against resistance imposed by chest compression. In this case about 100–120 compressions/min will be achieved, but ventilation should be limited to about 10–12 per minute and wherever possible guided by arterial blood gas analysis. This low rate is all that is needed to match low cardiac output achieved during ECC. Excessive ventilation detracts from effectiveness of ECC and causes hypocarbia.

For infants at birth the total number of recommended 'events' per minute is 120, with the aim of achieving 90 compressions and 30 inflations each minute (i.e. in a ratio of 3:1). Beyond the newborn period (i.e. when the lungs have been inflated), the compression–ventilation ratio of 15:2 should be used.

ADVANCED LIFE SUPPORT

As soon as practicable, mechanical ventilation with added oxygen should be commenced with either a bag-mask or via endotracheal intubation. Although intubation is preferred (see below), valuable time should not be wasted in numerous unsuccessful attempts. Initial effective bag-mask ventilation is sufficient and necessary prerequisite for successful paediatric CPR. Bags of appropriate sizes should be available for infants, small children and large children. A bag of ~500 mL volume should be available for infants at birth. Insertion of an oropharyngeal (Guedel) airway may be necessary to facilitate bag-mask ventilation. Access to the circulation and display of the electrocardiograph (ECG) and oximetry should also be achieved as soon as possible. Thereafter treatment should be guided by the cardiac rhythm. Underlying causes of CPA should be sought and treated.

AIRWAY MANAGEMENT

If attending personnel are skilled, the trachea should be intubated as soon as practicable. Although the role of intubation on survival is being increasingly questioned,[20] it is still regarded as advantageous and the standard intervention.[21] Tracheal intubation establishes and maintains an airway, facilitates mechanical ventilation with 100% oxygen, minimises the risk of pulmonary aspiration, enables suctioning of the trachea and provides a route for the administration of selected drugs. If difficulty is experienced at initial

intubation, oxygenation should be established with bag-mask ventilation before a re-attempt at intubation. If intubation is attempted, it should initially be via the oral route (not nasal) because oral intubation is invariably quicker than nasal, is less likely to cause trauma and haemorrhage, and enables the endotracheal tube (ETT) to be more easily exchanged if the first choice is inappropriate. On the other hand, a tube placed nasally can be better affixed to the face and so is less likely to enter a bronchus or be subject to inadvertent extubation, and is preferred for transport and long-term management. A nasogastric tube should be inserted after intubation to relieve possible gaseous distension of the stomach sustained during bag-mask ventilation.

Correct placement of the ETT in the trachea must be confirmed. In the hurried conditions of emergency intubation at CPA, it is not difficult to mistakenly intubate the oesophagus or to intubate a bronchus. There is no substitute for:

- visualising the passage of the tip of the ETT through the vocal cords at intubation
- confirmation of bilateral pulmonary air entry by auscultation in the axillae
- continuous observation of bilateral rise and fall of the chest on ventilation
- observation of the patient becoming and remaining pink.

Immediately after intubation, tracheal placement of the tube should be confirmed by capnography or colorimetric CO_2 detection. Capnography is preferred because it also affords ongoing assessment of adequacy of ECC and ventilation as well as a continuous warning of accidental extubation. Excretion of CO_2 needs effective pulmonary blood flow and ventilation of the lungs. Failure to detect CO_2 while there is either spontaneous or ECC-generated cardiac output necessitates immediate exclusion of oesophageal intubation by direct laryngoscopic inspection. If the tube is correctly located in the trachea, and CO_2 is not detected or is low, ECC should be improved and hyperventilation, if occurring, limited. Oxygenation should be confirmed with use of a pulse oximeter or measurement of arterial gas tension.

Uncuffed tube sizes (internal diameter)

- 2.5 mm tube for a premature newborn <1 kg; 3.0 mm for infants 2.0–3.0 kg; 3.0 or 3.5 mm for infants >3.0 kg and up to age 6 months; 4 mm for infants 7 months to 1 year
- for children over 1 year, the size is approximately determined by the formula: size (mm) = age (years)/4 + 4

Cuffed tube sizes (internal diameter)

- 3.0 mm for newborns ≥3 kg and ≤1 year; 3.5 mm for children 1–2 years
- for children over 2 years, the size is approximately determined by the formula: size (mm) = age (years)/4 + 3.5

Larger and smaller tubes should be available. The correct size should allow a small leak on application of moderate pressure but also ensure adequate pulmonary inflation. Cuffed tubes have the advantage of avoiding a change when deemed too small in a hazardous situation but occupy more volume in a small airway.

The tube is inserted a specific depth to avoid accidental extubation and endobronchial intubation, both of which may threaten oxygenation. Assessment of the depth of insertion at laryngoscopy is not reliable because this is performed with the neck extended, and when the laryngoscope is removed the head assumes a position of neutrality or flexion with the depth of insertion increasing automatically. Whether oral or nasal intubation, on a chest X-ray taken with the head in neutral position, the tip of the tube should be at the interclavicular line. If not, its depth should be adjusted.

Appropriate initial depths of insertion measured from the centre of the lips for an oral tube are:

- 9.5 cm for a term newborn; 11.5 cm for a 6-month-old; 12 cm for a 1 year old
- after 1 year of age the depth is given by the formula: depth (cm) = age (years)/2 + 12.

Appropriate initial depths of insertion measured at the nares for a nasal tube are:

- 11–11.5 cm for a term newborn; 13 cm for a 6-month-old; 14 cm for a 1 year old
- after 1 year of age the depth is given by the formula: depth (cm) = age (years)/2 + 15.

Laryngeal mask airways (LMA) may be used to establish and maintain an airway in the spontaneously breathing patient and for emergency relief of upper airway obstruction, but they have a limited role during CPR. Their role in provision of mechanical ventilation remains uncertain. Like bag-mask ventilation, they do not protect the airway from aspiration. Although insertion of an LMA is easier to learn than endotracheal intubation, training should not replace mastery of bag-mask ventilation. An LMA is not suitable for long-term use or during transport when endotracheal intubation is preferred. Sizes are available to suit body weight (kg) of newborns, infants and children: <5 kg size 1, 5–10 kg size 1½, 10–20 kg size 2, 20–30 kg size 2½, 30–50 kg size 3, 50–70 kg size 4, 70–100 kg size 5, and >100 kg size 6.

ELECTROCARDIOGRAPH

The ECG should be displayed with either leads or paddles. Drug therapy or immediate DC shock is determined by the existing rhythm.

ACCESS TO THE CIRCULATION

Access to the circulation via a peripheral or central vein should be attempted immediately (depending on operator skill). Any site is acceptable. Visible or palpable peripheral veins are to be found on the dorsum of the hand, wrist, forearm, cubital fossa, chest wall, foot and ankle. In infants, scalp veins are accessible and the umbilical vein can be used up to about 1 week after birth. Although the external jugulars are usually distended and easily cannulated at CPR, this may be impeded by performance of intubation or bag-mask ventilation. Cannulation of femoral, subclavian or internal jugular veins is an option, but it is difficult and hazardous in this situation. Surgical cutdown onto a long saphenous, saphenofemoral junction or basilic vein is a valuable skill sometimes required in traumatic exsanguination. Any pre-existing functioning line can be used provided it does not contain any drug or electrolyte precipitating the CPA.

INTRAOSSEOUS INJECTION

If intravenous (IV) access cannot be achieved rapidly (within 60 seconds), intraosseous (IO) access should be obtained. This route has been used for patients of all ages and provides rapid, safe and reliable access to the circulation. It serves as an adequate route for any parenteral drug and fluid administration.

A metal needle with a trocar (e.g. disposable IO needle; Cook, IL) is preferable. Although many sites have been used for bone marrow injection, the easiest to identify is the anteromedial surface of the upper or lower tibia, especially in children younger than 6 years. The site of the former is a few centimetres below the anterior tuberosity and the latter a few centimetres above the medial malleolus. The handle of the device needle is held in the palm of the hand while the fingers grip the shaft about a centimetre from the tip. It is inserted perpendicular to the bone surface and a rotary action is used to traverse the cortex. Sudden loss of resistance signifies entry to bone marrow. Correct positioning of the needle is confirmed by aspiration of bone marrow (which may be used for biochemical and haematological purposes) but that is not always possible. Bone injection guns (e.g. PerSys Medical, Houston, Texas), which propel a needle to a preset depth or drills (e.g. Arrow EZ-IO, Emergo Australia, Sydney, Australia), enable easy IO injection for infants, children and adults. The latter devices are preferred.

Volume expanders need to be given by syringe to achieve rapid restoration of circulating volume and rapid access of drugs to the central circulation. This is best achieved using a 10 mL syringe with a three-way tap in the IV tubing so that the IO needle does not become dislodged inadvertently.

Care should be exercised to avoid complications, particularly cutaneous extravasation, compartment syndrome of the leg and osteomyelitis. Contraindications include local trauma and infection.

ENDOTRACHEAL ADMINISTRATION OF DRUGS

Lipid-soluble drugs – epinephrine (adrenaline), atropine, lidocaine and naloxone – may be administered via the ETT if neither IV nor IO access is possible. Although the optimal doses of these drugs by this route are not known, work in animal models suggests doses should be 10 times the IV doses. The drugs should be diluted in normal saline up to 2 mL for infants, 5 mL for small children and 10 mL for large children. It is acceptable and simplest to squirt the drugs from the syringe (after removing the needle) directly into the ETT and disperse them throughout the respiratory tree with bagging. Neither sodium bicarbonate nor calcium salts should be administered via the tracheal route because they injure the airways.

DIRECT CURRENT SHOCK

Defibrillators should have paediatric paddles of cross-sectional area 12–20 cm^2 for use in children <10 kg body weight. For others, adult-sized paddles (50–80 cm^2) are satisfactory provided the paddles do not contact each other. Selectable energy levels should enable delivery of doses 0.5–4 J/kg. The closest level to the dose should be selected. One paddle is placed over the midaxilla opposite the xiphoid or nipple, and the other to the right of the upper sternum below the clavicle. Conductive gel (confined to the area beneath the paddles) or gel pads and firm pressure are needed to deliver optimum energy to the heart without causing skin burns. The doses for monophasic and biphasic shock are the same.

In the treatment of refractory arrhythmias, equipment failure should be excluded. An anteroposterior position of the paddles (one over the cardiac apex, one over the left scapula) may be efficacious in refractory arrhythmia. Dextrocardia may be present with congenital heart disease and the position of the paddles should be altered accordingly.

Monophasic and biphasic automated external defibrillators (AEDs) with attenuated energy doses (approximately 50 J or less) may be used for children 1–8 years of age (approximately 10–25 kg). Adult energy doses of 150–200 J may be used in children older than 8 years of age or 25 kg body weight. Although AEDs are not recommended for use in infants as they may not reliably distinguish VF from tachycardia and hence pose a risk of harmful DC shock, in the situation of a 'shockable' rhythm with poor or no cardiac output, an AED with dose attenuation may be used. If that is not available, an adult AED may be used.

Rescuers should be cognisant of the risk of inadvertent shock to themselves and colleagues during operation of defibrillators. They should ensure that they have no physical contact with the patient directly

or indirectly at the time of electrical discharge. Surgical gloves provide minimal protection against shock. Paddles should be charged only when already placed on the chest of the patient. If the need to give DC shock abates while the paddles are charged, they should be disarmed before replacing them in their cradles.

TREATMENT OF SPECIFIC ARRHYTHMIAS

The following discussion of specific arrhythmias assumes that mechanical ventilation with oxygen and ECC has been commenced. The treatment of pulseless arrhythmias is summarised in Fig. 115.3. Reversible causes of arrhythmias should be sought and treated during resuscitation. For example:

- hypoxaemia or hypotension causing bradycardia: may respond to ventilation
- hypocalcaemia and toxicity caused by calcium channel blockade: may be treated with calcium IV or IO (chloride 10% 0.2 mL/kg, gluconate 10% 0.7 mL/kg)
- hyperkalaemia: may be antagonised with a calcium salt then the serum level lowered with insulin

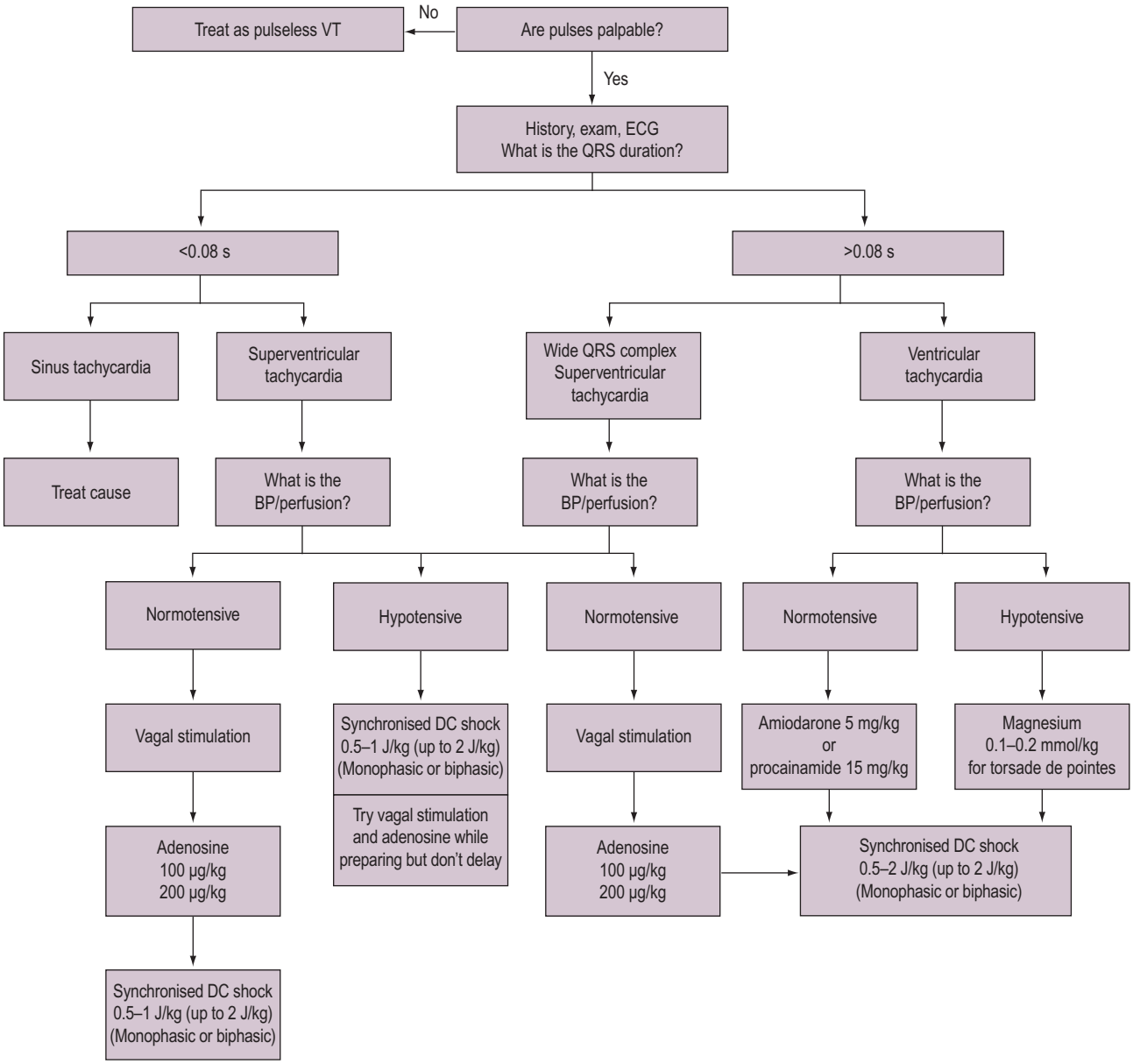


Figure 115.3 Treatment of tachyarrhythmias. *DC*, Direct current; *ECG*, electrocardiograph. *(Reproduced with permission from the Australian Resuscitation Council, Melbourne.)*

(0.05 U/kg) + dextrose (0.5 g/kg), but beware of hypoglycaemia. Additional treatments of hyperkalaemia are salbutamol, sodium bicarbonate, hyperventilation or combinations.

All drugs should be flushed into the circulation with a small bolus of isotonic fluid. To prevent their inactivation, drugs should not be mixed together in the syringe or in infusion lines.

ASYSTOLE AND BRADYCARDIA

Asystole and hypotensive bradycardia (<60 beats/min) should be treated with epinephrine 10 µg/kg IV or IO If these routes are not available, epinephrine 100 µg/kg should be administered via ETT.

Unresponsive asystole should be treated with additional similar doses of epinephrine (10 µg/kg IV, IO; 100 µg/kg ETT) every 3–5 minutes. Higher doses, up to 200 µg/kg IV or IO, may be indicated in special circumstances (e.g. beta-blocker toxicity) but should not be used routinely as they have not altered outcome and predispose to complications (post-arrest myocardial dysfunction, hypertension, tachycardia). In newborns, the initial bolus dose is 100–300 µg/kg.

Recurrent bradycardia or asystole may require an infusion of epinephrine at 0.05–3 µg/kg/min: doses <0.3 µg/kg/min are predominantly beta adrenergic; doses >0.3 µg/kg/min are predominantly alpha adrenergic. Infuse into a secure large vein. If sinus rhythm cannot be restored, sodium bicarbonate 1 mmol/kg IV or IO may be helpful, but do not allow mixing with epinephrine since catecholamines are inactivated in alkaline solution.

Sinus bradycardia, sinus arrest with slow junctional or idioventricular rhythm, and atrioventricular block are the most common preterminal arrhythmias in paediatric practice. Untreated, bradycardia progresses to asystole. Bradycardia caused by vagal stimulation should be managed with cessation of the stimulus and/or atropine 20 µg/kg IV or IO (minimum dose 100 µg) but persistent vagal-mediated bradycardia should be treated with epinephrine 10 µg/kg IV or IO

If facilities are available, bradycardia may be treated with pacing (oesophageal, transcutaneous, transvenous, epicardial) if sinus node dysfunction or heart block exists, but it is not helpful in asystole.

VENTRICULAR FIBRILLATION AND PULSELESS VENTRICULAR TACHYCARDIA

The initial dose for VF or pulseless ventricular tachycardia (VT) is a single unsynchronised DC shock of 4 J/kg followed by immediate resumption of ECC without pausing to analyse the rhythm. If VF or pulseless VT persists, subsequent single shocks of 4 J/kg are given, each followed by 2 minutes of ECC. Higher doses may be given in refractory VF.

Failure of VF to revert to sinus rhythm after the first shock should also be treated with epinephrine 10 µg/kg IV or IO or 100 µg/kg ETT every 3–5 minutes. Persistent (refractory) or recurrent VF or VT may also be treated with the antiarrhythmic drug amiodarone interspersed with single DC shocks. The dose of amiodarone is 5 mg/kg IV or IO as a bolus, which may be repeated to a maximum of 15 mg/kg. If amiodarone is not available, lidocaine in a dose of 1 mg/kg IV or IO or 2–3 mg/kg via ETT may be used, but the evidence for its efficacy is poor. An infusion of lidocaine at 20–50 µg/kg/min may be used to suppress excitability. Alternatives to epinephrine as a vasopressor, such as other catecholamines or vasopressin, have not been adequately investigated for use during CPR for children.

The witnessed (monitored) onset of VF or pulseless VT, such as in the cardiac catheter laboratory or intensive care unit setting, should be treated with successive (if needed) unsynchronised DC shocks up to a stack (salvo) of three shocks all of 4 J/kg. Rescuers should maintain the paddles on the chest and be prepared to deliver the series of the three shocks in quick succession, pausing only to verify the rhythm. Automatic external defibrillators are not suitable for this purpose because of time delays in their recognition of rhythms and charging. A precordial thump may be given before DC shock but its efficacy has not been proven.

Magnesium, 25–50 mg/kg (0.1–0.2 mmol/kg) IV or IO, is indicated for polymorphic VT (torsade de pointes).

ELECTROMECHANICAL DISSOCIATION AND PULSELESS ELECTRICAL ACTIVITY

A normal ECG complex without pulse or circulation is called electromechanical dissociation (EMD). If untreated, the ECG initially deteriorates to an abnormal but still recognisable state when it is called pulseless electrical activity (PEA). Both conditions should be treated as for asystole and their causes ascertained and treated.

PULSATILE VENTRICULAR TACHYCARDIA

Haemodynamically stable VT may be treated with an antiarrhythmic agent such as amiodarone (5 mg/kg IV over 20–60 minutes) or procainamide (15 mg/kg IV over 30–60 minutes). Since both drugs prolong the QT interval, they should not be given together. If torsade de pointes is present, magnesium (25–50 mg/kg, 0.1–0.2 mmol/kg IV or IO) may be used. If cardioversion is needed, it should be synchronised at 0.5–2 J/kg under sedation/anaesthesia. Pulsatile VT may be difficult to distinguish from wide-complex supraventricular tachycardia (SVT) when its QRS duration is >0.08 seconds.

SUPRAVENTRICULAR TACHYCARDIA

SVT is the most common spontaneous arrhythmia in childhood and infancy. It may cause life-threatening

hypotension. It is usually re-entrant with a rate of 220–300 per minutes in infants, but less in children. The QRS complex is usually narrow (<0.08 seconds) making it difficult sometimes to discern from sinus tachycardia (ST). However, whereas ST is a part of other features of illness, SVT is a singular entity, and whereas the rate in ST is variable with activity or stimulation, it is uniform in SVT. In both rhythms, a P-wave may be discernible. SVT with aberrant conduction (QRS >0.08 seconds) may resemble VT. Relative treatment of these tachycardias is summarised in Fig. 115.3.

If SVT is haemodynamically stable (adequate perfusion and blood pressure), initial treatment should be vagal stimulation. For infants and young children, application to the face of a plastic bag filled with iced water is often effective. Older children may be treated with carotid sinus massage or guided to perform a Valsalva manoeuvre (e.g. blowing through a narrow straw). If the patient is ventilated, apply vagal stimulation by tracheal or pharyngeal suction. If vagal stimulation is unsuccessful, give adenosine 100 µg/kg IV (maximum 6 mg) as a rapid bolus aided by an injection of 0.9% saline. If unsuccessful, double the dose to 200 µg/kg (maximum 12 mg) and again inject rapidly. An adenosine-induced pro-tachyarrhythmia (e.g. torsade de pointes) is rare.

An alternative drug treatment of haemodynamically stable SVT is amiodarone whose schedules are either infusions of 5 mg/kg over 1 hour followed by 5 µg/kg/min, or initially 25 µg/kg/min for 4 hours followed by 5–15 µg/kg/min. Amiodarone may cause hypotension, hypothyroidism and pulmonary toxicity. Other alternative drugs include procainamide in a dose of 15 mg/kg IV over 30–60 minutes, digoxin, a beta blocker or a calcium channel blocker. However, calcium channel blockers should not be used at all to treat SVT in infants and should be avoided or used with extreme caution in children because they may induce hypotension and cardiac depression. Haemodynamically stable SVT unresponsive to vagal stimulation and drug therapy may be treated with synchronised DC shock (cardioversion) in a dose of 0.5–1.0 J/kg.

SVT may cause severe hypotension or pulselessness, in which case synchronised DC shock (cardioversion) at 0.5–1.0 J/kg should be given immediately, progressing to 2 J/kg if necessary. While preparations are made to give DC shock, vagal stimulation and adenosine (IV or IO) may be tried provided they do not delay cardioversion.

POST-RESUSCITATION CARE

Supportive therapy should be provided until there is recovery of function of vital organs. This may require provision of oxygen therapy, mechanical ventilation, inotropic/vasopressor infusion, renal support, parenteral nutrition and other therapy for several days or longer. However, the percentage of inspired oxygen should be reduced as soon as possible after resuscitation to achieve only normal levels of Pa_{O_2}. Hyperoxaemia, like hypoxaemia, should be avoided. Recovery of infants and children is usually slow because cardiorespiratory arrest is often secondary to prolonged global ischaemia or hypoxaemia, which implies that other organs sustained damage before cardiorespiratory arrest. Particular care should be taken to ensure adequate cerebral perfusion with well-oxygenated blood. Hyperventilation is not useful for this purpose.

Therapeutic hypothermia post resuscitation (32°C–34°C) up to 3 days may improve neurological outcome, but is controversial and may predispose to infection and coagulopathy. However, an inadvertently hypothermic patient (e.g. one nearly drowned in icy water), provided the temperature is above 33°C, should not initially be actively warmed. During therapeutic hypothermia, shivering should be prevented with sedation and/or neuromuscular blockade, seizures should be actively sought and treated with anticonvulsant and the cause of the CPA should be investigated and treated appropriately (e.g. sepsis or drug overdose). Hyperthermia should be aggressively treated, in all instances.

Complications of CPR should be sought, especially if secondary deterioration occurs. A chest X-ray should be obtained to check the position of the ETT, to exclude pneumothorax, lung collapse, contusion or aspiration, and to check the cardiac silhouette – although an echocardiographic examination is preferable to specifically check contractility and to exclude a pericardial effusion. Measurements of haemoglobin, pH, gas tensions, electrolytes and glucose are important.

CESSATION OF CARDIOPULMONARY RESUSCITATION

Long-term outcome from paediatric CPR is mediocre, but better if arrest is respiratory alone or if CPA occurs in hospital. The decision to cease CPR should be based on a number of factors including the duration and quality of resuscitation, response to treatment, pre-arrest status, remediable factors, likely outcome if ultimately successful, opinions of personnel familiar with the patient and, whenever appropriate, the informed wishes of the parents. In general, unless hypothermia or drug toxicity exists, survival to normality is unlikely if there has been a failure to respond to full competent CPR after 30 minutes and several doses of epinephrine. In the newborn, discontinuation of treatment is appropriate if CPR does not establish a spontaneous circulation within 10–15 minutes. In out-of-hospital arrest, adult termination-of-resuscitation

criteria may not be suitable for paediatric arrest since sensitivity for predicting death was 48% and specificity 93%.[22] Loss of grey–white matter differentiation or sulcal effacement on head computed tomography within only several hours of arrest, is associated with unfavourable neurological outcome.[23] Family members should be kept informed, allowed to be present or asked if they want to be present during resuscitation.

POST-RESUSCITATION STAFF MANAGEMENT

Unfortunately, CPA occurring in hospital is often unexpected; for example, when a moribund patient arrives unannounced in the emergency department, a patient's condition deteriorates rapidly on the ward or when a mishap occurs under anaesthesia. These situations test the readiness, training, abilities and skills of individuals and the organisation of the institution. Performance should be audited with a view to improvement. These events have significant psychological impact on individuals, and sensitive debriefing sessions should be encouraged.

KEY REFERENCES

1. Australian and New Zealand Resuscitation Council. *Guidelines 12.1-12.7*. Online. Available: http://www.resus.org.au.
2. Maconochie IK, Bingham R, Eich C, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 6. Paediatric life support. *Resuscitation*. 2015;95:223–248.
3. de Caen AR, Berg MD, Chameides L, et al. Part 12: Pediatric advanced life support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2015;132(18 suppl 2):S526–S542.
4. Maconochie IK, de Caen AR, Aickin R, et al. Part 6: Pediatric basic life support and pediatric advanced life support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation*. 2015;95:e147–e168.


Access the complete references list online at http://www.expertconsult.com.

REFERENCES

1. Australian and New Zealand Resuscitation Council. *Guidelines 12.1-12.7*. Online. Available: http://www.resus.org.au.
2. Maconochie IK, Bingham R, Eich C, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 6. Paediatric life support. *Resuscitation*. 2015;95:223–248.
3. de Caen AR, Berg MD, Chameides L, et al. Part 12: Pediatric advanced life support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2015;132(18 suppl 2):S526–S542.
4. Maconochie IK, de Caen AR, Aickin R, et al. Part 6: Pediatric basic life support and pediatric advanced life support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation*. 2015;95:e147–e168.
5. Tibballs J. Systems to prevent in-hospital cardiac arrest. *Paediatr Child Health*. 2011;21:322–328.
6. Phillips RS, Scott B, Carter SJ, et al. Systematic review and meta-analysis of outcomes after cardiorespiratory arrest in childhood. *PLoS ONE*. 2015;10:e0130327.
7. Del Castillo J, Lopez-Herce J, Matamoros M, et al. Long-term evolution after in-hospital cardiac arrest in children: prospective multicenter multinational study. *Resuscitation*. 2015;96:126–134.
8. Lopez-Herce J, del Castillo J, Canados S, et al. In-hospital pediatric cardiac arrest in Spain. *Rev Esp Cardiol*. 2014;67:189–195.
9. Del Castillo J, Lopez-Herce J, Canadas S, et al. Cardiac arrest and resuscitation in the pediatric intensive care unit: a prospective multicenter multinational study. *Resuscitation*. 2014;85:1380–1386.
10. Berg RA, Nadkarni VM, Clark AE, et al. Incidence and outcomes of cardiopulmonary resuscitation in PICUs. *Crit Care Med*. 2016;44:798–808.
11. Bhanji F, Topjian AA, Nadkarni VM, et al. Survival rates following pediatric in-hospital cardiac arrests during nights and weekends. *JAMA Pediatr*. 2017; 171:39–45.
12. Lasa JJ, Rogers RS, Localio R, et al. Extracorporeal cardiopulmonary resuscitation (E-CPR) during pediatric in-hospital cardiopulmonary arrest is associated with improved survival to discharge: a report from the American Heart Association's Get With The Guidelines-Resuscitation (GWTG-R) Registry. *Circulation*. 2016;133(2):165–176.
13. Garcia Guerra G, Zorzela L, Robertson CM, et al. Survival and neurocognitive outcomes in pediatric extracorporeal-cardiopulmonary resuscitation. *Resuscitation*. 2015;96:208–213.
14. Fukuda T, Ohashi-Fukada N, Kobayashi H, et al. Conventional versus compression-only versus no-bystander cardiopulmonary resuscitation for pediatric out-of-hospital cardiac arrest. *Circulation*. 2016;134:2060–2070.
15. Naim MY, Burke RV, McNally BF, et al. Association of bystander cardiopulmonary resuscitation with overall and neurological favorable survival after pediatric out-of-hospital cardiac arrest in the United States. *JAMA Pediatr*. 2017;171:133–141.
16. Goto Y, Funada A, Nakatsu-Goto Y. Neurological outcomes in children dead on hospital arrival. *Crit Care*. 2015;19:410.
17. Goto Y, Funada A, Goto Y. Duration of prehospital cardiopulmonary resuscitation and favorable neurological outcomes for pediatric out-of-hospital cardiac arrest: a nationwide, population-based cohort study. *Circulation*. 2016;134:2046–2059.
18. Zhan L, Yang LJ, Huang Y, et al. Continuous chest compression versus interrupted chest compression for cardiopulmonary resuscitation of non-aspyxial out-of-hospital cardiac arrest. *Cochrane Database Syst Rev*. 2017;(3):CD010134.
19. Goto Y, Maeda T, Nakatsu-Goto Y. Decision tree model for predicting long-term outcome in children with out-of-hospital cardiac arrest: a nationwide, population-based observational study. *Crit Care (London)*. 2014;18:R133.
20. Andersen LW, Raymond TT, Berg RA, et al. American Heart Association's Get With the Guidelines–Resuscitation Investigators. Association between tracheal intubation during pediatric in-hospital cardiac arrest and survival. *JAMA*. 2016;316:1786–1797.
21. deCaen AR, Garcia Guerra G, Maconochie I. Intubation during pediatric CPR early, late, or not at all? *JAMA*. 2016;316:1772–1774.
22. Rotering VM, Trepels-Kottek S, Heimann K, et al. Adult "termination-of-resuscitation" (TOR)-criteria may not be suitable for children – a retrospective analysis. *Scand J Trauma Resusc Emerg Med*. 2016;24:144.
23. Starling RM, Shekdar K, Licht D, et al. Early head CT findings are associated with outcomes after pediatric out-of-hospital cardiac arrest. *Pediatr Crit Care Med*. 2015;16:542–548.

Appendix I

Respiratory physiology symbols and normal values

SYMBOLS

Primary	Secondary symbols for gas phase
C Concentration of gas in blood	A Alveolar
F Fractional concentration in dry gas	B Barometric
f Frequency of respiration (breaths/min)	D Dead space
P Pressure or partial pressure	E Expired
Q Volume of blood	I Inspired
$\dot{Q}$ Volume of blood per unit time	L Lung
R Respiratory exchange ratio	T Tidal
S Saturation of haemoglobin with O_2	
$\dot{V}$ Volume of gas per unit time	*Secondary symbols for blood phase*
	a arterial
	c capillary
	ć end-capillary
	i ideal
	v venous
	$\bar{v}$ mixed venous

– Above any symbol denotes a mean value.
· Above any symbol denotes a value per unit time.

NORMAL VALUES

1. Blood
   (a) *Arterial*

pH	:	7.36–7.44	(H^+ = 44–36 nmol/L)
PaO	:	85–100 mm Hg	(11.3–13.3 kPa)
$PaCO_2$	:	36–44 mm Hg	(4.8–5.9 kPa)
O_2 content	:	20–21 vols %	(8.9–9.4 nmol/L)
CO_2 content	:	48–50 vols %	(21.6–22.5 nmol/L)

   (b) *Venous*

pH	:	7.34–7.42	(H^+ = 38–46 nmol/L)
PO_2	:	37–42 mm Hg	(5–5.6 kPa)
PCO_2	:	42–50 mm Hg	(5.6–6.7 kPa)
O_2 content	:	15–16 vols %	(6.7–7.2 mmol/L)
CO_2 content	:	52–54 vols %	(23.3–24.2 mmol/L)

2. Gases
   (a) *Inspired air*

O_2	:	20.93%	
PI_{O_2}	:	149 mm Hg	(19.9 kPa)
N_2	:	79.04%	
PI_{N_2}	:	563 mm Hg	(75 kPa)
CO_2	:	0.03%	

   (b) *Expired air*

O_2	:	16%–17%	
PE_{O_2}	:	113–121 mm Hg	(15–16 kPa)
N_2	:	80%	
PE_{N_2}	:	579 mm Hg	(77 kPa)
CO_2	:	3%–4%	
PE_{CO_2}	:	21–28 mm Hg	(2.8–3.7 kPa)

3. Ventilation: perfusion
   (a) *Alveolar–arterial oxygen gradient:*
   5–20 mm Hg (0.7–2.7 kPa) breathing air
   25–65 mm Hg (3.3–8.6 kPa) breathing 100% oxygen
   (b) *Venous admixture* ($\dot{Q}_S:\dot{Q}_T$): 5% of cardiac output
   (c) *Right to left physiological shunt*: 3% of cardiac output
   (d) *Anatomical dead space*: 2 mL/kg body weight
   (e) *Dead space: tidal volume ratio* ($V_D:V_T$): 0.25–0.4 or 33 + (Age/3) per cent
4. Lung volumes
   Approximate values in adults are listed. Values are less in smaller subjects and in females.

Tidal volume	:	400 mL or 6 mL/kg
Inspiratory capacity	:	3.6 L
Inspiratory reserve volume	:	3.1 L
Expiratory reserve volume	:	1.2 L
Functional residual capacity	:	2.4 L
Residual volume	:	1.2 L
Total lung capacity	:	6.0 L
Vital capacity	:	4.8 L

   or 2.5 L/sq m body surface *or* 2.5 L/m height in males
   2.0 L/sq m body surface *or* 2.0 L/m height in females
   or 65–75 mL/kg
5. Lung mechanics
   (a) *Peak expiratory flow rate* : 450–700 L/min (males)
   : 300–500 L/min (females)
   (b) *Forced expiratory volume in 1 s* (FEV_1) : 70%–83% of vital capacity
   (c) *Compliance* (approximate values)

		Static	*Dynamic*
(i) Lung compliance (CL)			
conscious (erect)	:	200 mL/cmH_2O	180 mL/cmH_2O
paralysed anaesthetised (supine)*	:	160 mL/cmH_2O	80 mL/cmH_2O
(ii) Chest wall compliance (CCW)	:	200 mL/cmH_2O	
(iii) Total compliance (CT):			
conscious (erect)	:	150 mL/cmH_2O	100 mL/cmH_2O
paralysed anaesthetised (supine)*	:	74 mL/cmH_2O	56 mL/cmH_2O

   (d) *Airways resistance*:
   conscious : 0.6–3.2 cmH_2O/L/s
   sedated, partially paralysed and ventilated : 5–10 H_2O/L/s
   (includes resistance of endotracheal tube and catheter mount)
   (e) *Work of breathing*: 0.3–0.5 kg m/min
   or oxygen consumption of 0.5–1 mL/L ventilation

*Compliance values would be lower for the sedated, partially paralysed, ventilated patient in the intensive care unit; that is, effective dynamic compliance = 40–50 mL/cmH_2O.

6. **Cardiovascular** — pressures in kPa are given within brackets

(a)	Cardiac index	:	2.5–3.6 L/min/m^2
(b)	Stroke volume	:	42–52 mL/m^2
(c)	Ejection fraction	:	0.55–0.75
(d)	End-diastolic volume	:	75 ± 15 mL/m^2
(e)	End-systolic volume	:	25 ± 8 mL/m^2
(f)	Left ventricular stroke work index	:	30–110 g-m/m^2
(g)	Left ventricular minute work index	:	1.8–6.6 kg-m/min/m^2
(h)	Oxygen consumption index	:	110–150 mL/L
(i)	Right atrial pressure	:	1–7 mm Hg (0.13–0.93)
(j)	Right ventricular systolic pressure	:	15–25 mm Hg (2.0–3.3)
(k)	Right ventricular diastolic pressure	:	0–8 (0–1)
(l)	Pulmonary artery systolic pressure	:	15–25 mm Hg (2.0–3.3)
(m)	Pulmonary artery diastolic pressure	:	8–15 mm Hg (1–2)
(n)	Pulmonary artery mean pressure	:	10–20 mm Hg (1.3–2.7)
(o)	Pulmonary capillary wedge pressure	:	6–15 mm Hg (0.8–2.0)
(p)	Systemic vascular resistance	:	770–1500 dyne-s/cm^5
		:	77–150 kPa-s/L
(q)	Pulmonary vascular resistance	:	20–120 dyne-s/cm^5
		:	2–12 kPa-s/L

Appendix II

Physiological equations

RESPIRATORY EQUATIONS

(a) *Oxygen consumption* (250 mL/min)
Oxygen consumption = amount of oxygen in inspired gas minus amount in expired gas

i.e. $\dot{V}O_2 = (\dot{V}I \times FI_{O_2}) - (\dot{V}E \times FE_{O_2})$

(b) *Carbon dioxide production* (200 mL/min)
Volume CO_2 eliminated in expired gas = expired gas volume × CO_2 concentration in mixed expired gas

i.e. $\dot{V}CO_2 = (\dot{V} \times F\bar{E}_{CO_2})$

As expired volume is made up of alveolar and dead space gas,

$$\dot{V}CO_2 = (\dot{V}A \times FA_{CO_2})(\dot{V}D \times FI_{CO_2})$$

As FI_{CO_2} is negligible, especially if there is no rebreathing,

$$\dot{V}CO_2 = \dot{V}A \times FA_{CO_2}$$

or $$FA_{CO_2} = \frac{\dot{V}_{CO_2}}{\dot{V}A}$$

or $$PA_{CO_2}\ (\text{mm Hg}) = \frac{\dot{V}_{CO_2}\ (\text{mL/min STPD})}{\dot{V}A\ (\text{L/min BTPS})} \times 0.863$$

or $$PA_{CO_2}\ (\text{kPa}) = \frac{\dot{V}_{CO_2}\ (\text{mmol/min})}{\dot{V}A\ (\text{L/min BTPS})} \times 2.561$$

STPD: Standard temperature (0°C) and pressure (760 mm Hg or 101.35 kPa) dry gas
BTPS: Body temperature and ambient pressure, saturated with water vapour

(c) *Physiological dead space*

Bohr's equation, $$\frac{V_D}{V_T} = \frac{PA_{CO_2} - P\bar{E}_{CO_2}}{PA_{CO_2}}$$

or $$\frac{V_D}{V_T} = \frac{Pa_{CO_2} - P\bar{E}_{CO_2}}{Pa_{CO_2}}$$

(d) *Alveolar oxygenation*

$$PA_{O_2} = PI_O - \frac{Pa_{CO_2}}{R}$$

where R is the respiratory quotient (normally 0.8).

$$PA_{O_2} = PI_{O_2} - Pa_{CO_2}\left(\frac{PI_{O_2} - P\bar{E}_{O_2}}{P\bar{E}_{CO_2}}\right)$$

or $$PA_{O_2} = PI_{O_2} - PA_{CO_2}\left(\frac{FI_{O_2} + 1 - FI_{O_2}}{R}\right)$$

when $FI_{O_2} = 1.0$ (patient breathing 100% oxygen),
then $PA_{O_2} = (PB - \text{saturated water vapour pressure}) - PA_{CO_2}$
$= (PB - 47) - Pa_{CO_2}$

(e) *Venous admixture*

(f) *Fractional inspired oxygen concentration*

$$FI_{O_2} = \frac{O_2 \text{ flow in L/min} + (\text{air flow in L/min} \times 0.21)}{\text{Total } O_2 + \text{air flow in L/min}}$$

(g) *Henderson–Hasselbalch equation*

$$pH = pKA + \log\frac{(HCO_3^-)}{CO_2}$$

$$pH = 6.1 + \log\frac{(HCO_3^- \text{ in mmol/L})}{(PCO_2 \text{ in mm Hg}) \times 0.03}$$

$$[H^+]\,\text{nmol/L} = 24 \times \frac{(PCO_2 \text{ in mm Hg})}{(HCO_3^- \text{ in mmol/L})}$$

$$[H^+]\,\text{nmol/L} = 180 \times \frac{(PCO_2 \text{ in kPa})}{(HCO_3^- \text{ in mmol/L})}$$

CARDIOVASCULAR EQUATIONS

(a) *Mean blood pressure* (BP) = DBP + ⅓ (SBP–DBP)

(b) *Rate pressure product* (RPP) = $P \times$ SBP

(c) *Body surface area* (BSA) in $m^2 = (Ht)^{0.725} \times (Wt)^{0.425} \times 71.84 \times 10^{-4}$

(d) **Cardiac index* (CI) $= \frac{CO}{BSA} = mL/min/m^2$

(e) *Stroke volume* (SV) $= \frac{CO}{P} = mL/beat$

(f) **Stroke volume index* (SVI) $= \frac{SV}{BSA} = mL/beat/m^2$

(g) **Left ventricular stroke work index* (LVSWI) = (BP–PCWP) (SVI) (0.0136) = g-m/m^2/beat

(h) *Systemic vascular resistance* (SVR) $= \frac{BP - RAP}{CO}$ resistance units

(Multiply × 79.9 to convert to absolute resistance units, dynes-s cm^{-5})

(i) *Pulmonary vascular resistance* (PVR) $= \frac{PAP - PCWP}{CO}$ resistance units

(Multiply × 79.9 to convert to absolute resistance units, dynes-s cm^{-5})

(j) *Left ventricular pre-ejection period* (PEP) = QS_2–LVET ms

(k) *Other systolic time index ratios* may easily be calculated:

$$\frac{1}{PEP^2} \quad \text{and} \quad \frac{PEP}{LVET}$$

*For interpatient comparisons and reference standards, the 'index' term, output normalised to body surface, may be used when:

SBP = systolic blood pressure in mm Hg
DBP = diastolic blood pressure in mm Hg
P = heart rate in beats/min
Ht = height in cm
Wt = weight in kg
CO = cardiac output in mL/min
PCWP = pulmonary capillary wedge pressure in mm Hg
RAP = right atrial pressure in mm Hg
PAP = mean pulmonary artery pressure in mm Hg
LVET = left ventricular ejection time in ms
QS_2 = total electromechanical systole in ms.

RENAL EQUATIONS

(a) *Standard creatinine clearance* (mL/min/1.73 m^2)

$$= \frac{\text{urine creatinine (mmol/L)}}{\text{serum creatinine (mmol/L)}} \times \text{urine volume (mL/min)} \times \frac{1.73}{\text{body surface area } (m^2)}$$

(b) *Per cent filtered Na^+ excreted*

$$= \frac{\text{urine } Na^+ \text{ (mmol/L)}}{\text{serum } Na^+ \text{ (mmol/L)}} \times \frac{\text{serum creatinine (mmol/L)}}{\text{urine creatinine (mmol/L)}} \times 100$$

(c) *Free water clearance* (mL/min)

$$= \text{urine volume (mL/min)} - \frac{\text{urine osmolality (mOsm/kg)}}{\text{plasma osmolality (mOsm/kg)}} \times \text{urine volume (mL/min)}$$

(d) *Additional calculated parameters*:

(i) $\frac{\text{urine}}{\text{plasma}}$ osmolality ratio

(ii) $\frac{\text{urine}}{\text{serum}}$ creatinine ratio

(iii) $\frac{\text{blood urea nitrogen}}{\text{serum creatinine}}$ ratio

(iv) $\frac{\text{urine}}{\text{plasma}}$ urea ratio

(v) Urinary Na^+ and K^+ excretion (mmol)

(vi) $\frac{\text{urinary } Na^+}{\text{urinary } K^+}$ ratio

Appendix III

Mortality/dysfunction risk scores and models

PAEDIATRIC RISK OF MORTALITY SCORE

Mortality risk assessment.

Parameter	Age limit	Ranges		Points
Systolic blood pressure		(mm Hg)	(kPa)	
	Infants	130–160	17.3–21.3	2
		55–65	7.3–8.7	2
		>160	>21.3	6
		40–54	5.3–7.2	6
		<40	<5.3	7
	Children	150–200	20–26.7	2
		65–75	8.7–10	2
		>200	>26.7	6
		50–64	6.7–8.5	6
		<50	<6.7	7
Diastolic blood pressure		(mm Hg)	(kPa)	
	All ages	>110	>14.6	6
Heart rate (beats/min)	Infants	>160		4
		<90		4
	Children	>150		4
		<80		4
Respiratory rate (breaths/min)	Infants	61–90		1
		>90		5
		Apnoea		5
	Children	51–70		1
		>70		5
		Apnoea		5
$Pa_{O_2} : Fi_{O_2}$ ratio		(mm Hg)	(kPa)	
	All ages	200–300	26.6–39.9	2
		<200	<26.6	3
$PaCO_2$		(torr [mm Hg])	(kPa)	
	All ages	51–65	6.8–8.7	1
		>65	>8.7	5
Pupillary reactions	All ages	Unequal or dilated		4
		Fixed and dilated		10
Prothrombin time (PT)/partial thromboplastin time (PTT)	All ages	1.5 times control		2
Total bilirubin (mg/dL)	>1 month	>3.5		6
Potassium (mEq/L)	All ages	3.0–3.5		1
		6.5–7.5		1
		<3.0		5
		>7.5		5
Calcium (mg/dL)	All ages	7.0–8.0		2
		12.0–15.0		2
		<7.0		6
		>15.0		6
Glucose (mg/dL)	All ages	40–60		4
		250–400		4
		<40		8
		>400		8
Bicarbonate (mEq/L)	All ages	<16		3
		>32		3

Infants: 0–1 year of age. Paediatric risk of mortality (PRISM) score = (systolic blood pressure points) + (diastolic blood pressure points) + (heart rate points) + (respiratory rate points) + (oxygenation points) + (Glasgow Coma Score points) + (pupillary reaction points) + (coagulation points) + (bilirubin points) + (potassium points) + (calcium points) + (glucose points) + (bicarbonate points).

SEPSIS-RELATED ORGAN FAILURE ASSESSMENT SCORE

Easy to calculate, describes the sequence of complications in a critically ill patient rather than predicting outcome.

Organ system	Measure
Respiration	$Pa_{O_2} : Fi_{O_2}$ ratio
Coagulation	Platelet count
Liver	Serum bilirubin
Cardiovascular	Hypotension
Central nervous system	Glasgow Coma Score
Renal	Serum creatinine or urine output

Measure	Finding		Points
$Pa_{O_2} : Fi_{O_2}$ ratio	(mm Hg)	(kPa)	
	≥400	≥53.2	0
	300–399	39.9–53.1	1
	200–299	26.6–39.8	2
	100–199	13.3–26.5	3
	<100	<13.3	4
Platelet count	≥1500/μL		0
	1000–149,999/μL		1
	500–99,999/μL		2
	200–49,999/μL		3
	<200/μL		4
Serum bilirubin	<1.2 mg/dL		0
	1.2–1.9 mg/dL		1
	2.0–5.9 mg/dL		2
	6.0–11.9 mg/dL		3
	≥12.0 mg/dL		4
Hypotension	(mm Hg)	(kPa)	
	Mean arterial pressure ≥70	≥9.3	0
	Mean arterial pressure <70 then (no pressor agents used)	<9.3	1
	Dobutamine any dose		2
	Dopamine ≤5 μg/kg/min		2
	Dopamine >5–15 μg/kg/min		3
	Dopamine >15 μg/kg/min		4
	Epinephrine ≤0.1 μg/kg/min		3
	Epinephrine >0.1 μg/kg/min		4
	Norepinephrine ≤0.1 μg/kg/min		3
	Norepinephrine >0.1 μg/kg/min		4
Glasgow Coma Score	15		0
	13–14		1
	10–12		2
	6–9		3
	3–5		4
Serum creatinine or urine output	Serum creatinine <1.2 mg/dL		0
	Serum creatinine 1.2–1.9 mg/dL		1
	Serum creatinine 2.0–3.4 mg/dL		2
	Serum creatinine 3.5–4.9 mg/dL		3
	Urine output 200–499 mL/day		3
	Serum creatinine >5.0 mg/dL		4
	Urine output <200 mL/day		4

Pa_{O_2} is in mm Hg/kPa and Fi_{O_2} in percentages, from 0.21 to 1.00. Adrenergic agents as administered for at least 1 hour with doses in μg/kg/min. A score of 0 indicates normal and a score of 4 indicates most abnormal. Data can be collected and the score calculated daily during the course of the admission. Interpretation: minimum total score: 0; maximum total score: 24. The higher the organ score, the greater is the organ dysfunction. The higher the total score, the greater is the multiorgan dysfunction.

MORTALITY RATE BY SEPSIS-RELATED ORGAN FAILURE ASSESSMENT SCORE[1]

Organ system	0	1	2	3	4
Respiratory	20%	27%	32%	46%	64%
Cardiovascular	22%	32%	55%	55%	55%
Coagulation	35%	35%	35%	64%	64%
CNS	32%	34%	50%	53%	56%
Renal	25%	40%	46%	56%	64%

CNS, Central nervous system.

LOGISTIC ORGAN DYSFUNCTION SYSTEM

Assess patients for severity of critical organ dysfunction. To predict the probability of death for the patient.

Data collection	During the first 24 h in the ICU
Data point	If not measured then it is assumed to be normal for scoring purposes If several measurements, use the most severe value

LOD score = (neurological score) + (cardiovascular score) + (renal score) + (pulmonary score) + (haematological score) + (hepatic score).
ICU, Intensive care unit.

NEUROLOGICAL SCORE

Glasgow coma score	Points
14–15	0
9–13	1
6–8	3
<6	5

Use lowest value. If sedated, estimate the score prior to sedation.

CARDIOVASCULAR SCORE

		Systolic BP		
Heart rate (beats/min)		(mm Hg)	(kPa)	Points
30–139	*and*	90–239	11.9–31.8	0
≥140	*or*	240–269	31.9–35.8	1
		70–89	9.3–11.8	1
		≥270	≥35.9	3
		40–69	5.3–9.2	3
<30	*or*	<40	<5.3	5

The most abnormal value for heart rate or systolic blood pressure, either minimum or maximum.

RENAL SCORE

Serum urea nitrogen (mg/dL)		Creatinine (mg/dL)		Urine output (L/d)	Points
<17	*and*	<1.20	*and*	0.75–9.99	0
17–27.99	*or*	1.2–1.59			1
28–55.99	*or*	≥1.60	*or*	≥10	3
				0.5–0.74	3
≥56					5
				<0.5	5

Highest value for urea nitrogen and for creatinine; if the urine output data are for less than a 24-hour period, adjust that value to 24 hours, assuming the same rate of excretion. On haemodialysis, use the value of urine output prior to initiating haemodialysis.

PULMONARY SCORE

On ventilation or continuous positive airway pressure?		Ratio (Pa_{O_2} [mm Hg]: Fi_{O_2})	Ratio (Pa_{O_2} [kPa]: Fi_{O_2})	Points
No				0
Yes	*and*	≥150	≥20	1
Yes	*and*	<150	<20	3

Respiratory support; use the lowest ratio of Pa_{O_2} to Fi_{O_2}.

HAEMATOLOGICAL SCORE

White blood cell count (10^9/L)		Platelet count (10^9/L)	Points
2.5–4.9/μL	*and*	≥50/μl	0
		≥50/μL	1
1–2.4/μL	*or*	<50/μL	1
<1/μL			3

Note: Most abnormal values for the white cell count are either minimum or maximum; minimum platelet count if several values are available.

HEPATIC SCORE[2]

Bilirubin		Prothrombin time	Points
<2.0 mg/dL (< 34.2 μmol/L)	*and*	≤3 s above standard (≥25% of standard)	0
≥2.0 mg/dL (≥34.2 μmol/L)	*or*	>3 s above standard (<25% of standard)	1

Highest value for bilirubin available. Highest value for prothrombin time in seconds.

MPM II, MORTALITY PROBABILITY MODELS[3,4]

Excluded
- Age less than 18 years
- Burn patients
- Coronary care patients
- Cardiac surgery patients
- (The scoring is either present or not present)

Definitions
- Coma or deep stupor at time of intensive care unit (ICU) admission
  - Not due to drug overdosage
  - If patient is on paralysing muscle relaxant, is awakening from anaesthesia or is heavily sedated, use your best judgement of the level of consciousness prior to sedation
  - *Coma*: no response to any stimulation; no twitching, no movements in extremities, no response to pain or command; Glasgow Coma Score 3
  - *Deep stupor*: decorticate or decerebrate posturing; posturing is spontaneous or in response to stimulation or deep pain; posturing is not in response to commands; Glasgow Coma Score 4 or 5

Heart rate at ICU admission
- Heart rate ≥150 beats/min within 1 hour before or after ICU admission

Systolic blood pressure at ICU admission
- Systolic blood pressure ≤90 mm Hg (11.9 kPa) within 1 hour before or after ICU admission

Chronic renal compromise or insufficiency
- Elevation of serum creatinine greater than 2 mg/dL and documented as chronic in the medical record
- If there is the acute diagnosis on chronic renal failure then record only 'yes' for acute renal failure

Cirrhosis
- History of heavy alcohol use with portal hypertension and varices
- Other causes of liver disease with evidence of portal hypertension and varices
- Biopsy confirmation of cirrhosis

Metastatic malignant neoplasm
- Stage IV carcinomas with distant metastases
- Do not include involvement only of regional lymph nodes
- Include if metastases are obvious by clinical assessment or confirmed by a pathology report
- Do not include if metastases is not obvious, or if the pathology report is not available at the time of ICU admission
- Acute haematological malignancies are included
- Chronic leukaemias are not included unless there are findings attributable to the disease or the patient is under active treatment for the leukaemia. Findings include sepsis, anaemia, stroke caused by clumping of white blood cells, tumour lysis syndrome with elevated uric acid following chemotherapy, pulmonary oedema or the lymphangiectatic form of acute respiratory distress syndrome

Acute renal failure
- Acute tubular necrosis or acute diagnosis on chronic renal failure
- Prerenal azotaemia is not included

Cardiac dysrhythmia
- Cardiac arrhythmia, paroxysmal tachycardia, fibrillation with rapid ventricular response, second- or third-degree heart block
- Do not include chronic and stable arrhythmias

Cerebrovascular incident
- Cerebral embolism, occlusion, cerebrovascular accident, stroke, brainstem infarction, cerebrovascular arteriovenous malformation (acute stroke or cerebrovascular haemorrhage, not chronic arteriovenous malformation)

Gastrointestinal (GI) bleeding
- Haematemesis, melaena
- A perforated ulcer does not necessarily indicate GI bleeding; may be identified by obvious 'coffee grounds' in the nasogastric tube
- A drop of haemoglobin by itself is not sufficient evidence of acute GI bleeding

Intracranial mass effect
- Intracranial mass (abscess, tumour, haemorrhage, subdural) as identified by computed tomography (CT) scan associated with any of the following: (1) midline shift; (2) obliteration or distortion of cerebral ventricles; (3) gross haemorrhage in cerebral ventricles or subarachnoid space; (4) visible mass greater than 4 cm; or (5) any mass that enhances with contrast media
- If the mass effect is known within 1 hour of ICU admission, it can be indicated as yes
- CT scanning is not mandated and is indicated only for patients with major neurological insult

Age in years
- Patient's age at last birthday

Cardiopulmonary resuscitation (CPR) within 24 hours prior to ICU admission
- CPR includes chest compression, defibrillation or cardiac massage
- Not affected by the location where the CPR was administered

Mechanical ventilation
- Patient is using a ventilator at the time of ICU admission or immediately thereafter

Medical or unscheduled surgery admission
- Do not include elective surgical patients (surgery scheduled at least 24 hours in advance) or pre-operative Swan–Ganz catheter insertion in elective surgery patients

REFERENCES

1. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med*. 1996;22:707–710.
2. Le Gall J, Klar J, Lemeshow S, et al. The logistic organ dysfunction system. *JAMA*. 1996;276:802–810.
3. Lemeshow S, Teres D, Klar J, et al. Mortality Probability Models (MPM II) based on an international cohort of intensive care patients. *JAMA*. 1993;270:2478–2486.
4. Lemeshow S, Le Gall J-R. Modeling the severity of illness of ICU patients. *JAMA*. 1994;272:1049–1055.

This page intentionally left blank