SECTION 17 Critical care medicine Section editor S

17.1 The seriously ill or deteriorating patient 38

17.1 The seriously ill or deteriorating patient 3829 Carole Foot and Liz Hickson

ESSENTIALS The first step in the clinical approach to a patient who is very ill is the recognition of this fact. While experienced clinicians will intuitively recognize a seriously ill or deteriorating patient, a large body of data has demonstrated that warning signs are often missed or not acted upon, resulting in preventable harm to patients. This has led to the development and adoption of ‘track and trigger’ systems. Track and trigger systems aim to ensure that hospitalized patients undergo regular review and objective observation, with abnormal observation or staff concerns being triggers to escalate care. Escalated care may be urgent review by the treating team, or the calling of a ‘rapid response team’ to attend to a more critically ill patient. While calling criteria and team composition varies from country to country, the principle of rapidly taking skilled care to critically ill patients re- mains the unifying underlying principle. A critically ill patient needs a rapid structured clinical assessment (relevant history and examination) with simultaneous treatment of life-threatening problems. A structured approach to the ABCs (airway, breathing, circulation) by an individual, or by a trained team with each individual having a defined role, modelled on the approach first developed to assess and treat multiply injured patients, offers patients the best outcome. Recognizing the critically ill patient The ability of an experienced clinician to stand and observe a pa- tient at the bedside and determine if they are very ill, the so-called ‘end of bed test’, remains an important clinical skill (see Fig. 17.1.1). However, such intuitive determinations are not sensitive enough to form the basis for a safe system of recognizing critically ill and deteriorating patients. The apparent tacit ability of skilled individ- uals to identify patients who are very ill has been dissected. Specific features which can reliably indicate concern have been codified into broadly relevant systematic approaches to patient assessment. The outcomes of such efforts are modern systems that seek to ensure that hospitalized patients are continuously screened for signs of deterioration. When concerns are identified, patients are assessed and managed using logical and thorough approaches by healthcare providers specifically trained for the task. The spe- cific nature of how such systems operate is highly variable inter- nationally. Despite this, the shared

focus is the use of a systematic approach that attempts to differentiate patients who are ‘well, ill, very ill, or nearly dead’, the goals of ‘track and trigger systems’ (see Fig. 17.1.2 for an example). Responding to the needs of a very ill patient is time-critical, and consequently history taking, physical examination, and ordering of investigations should be performed simultaneously, usually with more than one team member attending to each of these elements. For example, a patient may have a peripheral venous cannula in- serted and have blood tests collected while being questioned re- garding key symptoms as they receive a nebulized bronchodilator. Useful mnemonic acronyms can facilitate efficient focused history taking, some of which may be rapidly obtained from the patient’s records and prescription charts for fluids and medications (see Box 17.1.1). 17.1 The seriously ill or deteriorating patient Carole Foot and Liz Hickson Fig. 17.1.1 This patient has several worrying features suggesting he may be critically unwell. Note that his eyes are closed, suggesting a possible reduced level of consciousness. He is propped up on pillows suggesting that he may be experiencing difficulty breathing supine. His neck muscles are prominent possibly due to accessory muscle use and/or cachexia. He seems unable to hold on his own mask, which may be related to weakness, somnolence, and/or confusion. The nurse appears worried. Photograph courtesy of Matt Tinker Photography.

Section 17 Critical care medicine 3830 Fig. 17.1.2 In a track and trigger system, nursing staff review their patients regularly and in the absence of an immediate need to trigger an emergency response, they measure patients’ vital signs. These are recorded on a chart with designated ranges; observations outside the acceptable range trigger intervention or escalation. The standard observation chart shown is from New South Wales, Australia, and the system is called ‘between the flags’. This is in keeping with a Surf Life Saving programme to prevent drowning where swimmers are maintained in safe waters designated by coloured yellow and red flags. On the observation chart pictured, ill patients are designated as those entering a ‘yellow zone’ and very ill as those in a ‘red zone’.

17.1 The seriously ill or deteriorating patient 3831 Similarly, a structured approach to physical examination is es- sential to ensure that key signs are identified in order of priority. These signs, in conjunction with relevant history and simple bedside investigations (e.g. finger prick blood glucose sampling, arterial blood gas, electrocardiogram (ECG), dipstick urine ana- lysis), may be linked to immediate, life-saving therapeutic inter- ventions (see Table 17.1.1). The most commonly encountered triggers for escalation of care will vary between centres and with case mix. In some contexts ser- ious nurse concern, and more recently serious unresolved concern of a patient or their loved one have been recognized as important stimuli to help clinicians recognize critically ill patients, with some supporting evidence, particularly in the paediatric population. Useful observations such as subtle changes in behaviour, cognition, or the nature of pain may be missed with screening systems that are based exclusively on physiological data. Valuable information heralding or helping define the specific diagnosis and/or severity of serious illness may also be obtained from routine blood tests. Classical data sets or constellations of abnormalities when found together may be diagnostic or highly suggestive of pathology not obvious from clinical assessment alone (see Table 17.1.2 for some examples). Causes of acute clinical deterioration In the era of track and trigger systems, the differential diagnosis for commonly encountered causes of acute deterioration can be con- sidered in terms of the principal acute physiologic derangement that prompts escalation of care. In Boxes 17.1.2–17.1.11, important causes of abnormal systolic blood pressure and heart rate, oxygen desaturation, and altered respiratory rate, abnormal urine output,

and altered level of consciousness are summarized. General principles of management The mainstay of management of critically ill patients is meticulous supportive care that aims to correct life-threatening physiologic de- rangements and optimize organ system function while preventing complications. Well Vital signs within specified normal parameters & no other concerns Ill 1 or more vital signs outside specified range but not to a marked degree e.g. RR 5–10/min, SpO2 <90–95%, SBP 90–100 or 180–200 mm Hg, HR 40–50 or 120–140/min, temp >38.5 or <35.5ºC, no response to voice on AVPU score Very ill 1 or more vital signs outside specified range to a marked degree e.g. RR<5 or

> 30/min, SpO2 <90%, SBP<90 or >200 mm Hg, HR <40 or 140/min, temp 38.5 or <35.5ºC, uncontrolled severe pain Nearly dead Cardiopulmonary arrest or an acute crisis detected (e.g. threatened airway, severe respiratory distress, sudden loss of consciousness) Continue current management plan Simple interventions (e.g. apply oxygen) and/or review by treating team (e.g. within 30 minutes) Simple interventions (e.g. apply oxygen) and rapid review by treating team plus a critical care clinician (e.g. within 15 minutes) Initiate Basic and Advanced Life Support algorithms. Immediate response by treating team and critical care clinicians Regular nursing review Mandatory minimum frequency of vital sign monitoring with escalation triggered by detected abnormalities commensurate with their severity Fig. 17.1.2 Continued Box 17.1.1 SAMPLE history mnemonic Symptoms Allergies Medications Pertinent medical history Last oral intake Events preceding the deterioration

Section 17 Critical care medicine 3832 The simultaneous clarification of specific diagnoses and insti- tution of appropriate targeted therapies is the other pillar of care. Specific knowledge for managing diverse issues that cross specialties (e.g. from intoxications to neurologic emergencies to traumatic in- juries) may also be required. Increasingly patients also require sim- ultaneous management of chronic medical comorbidities. Respiratory support Hypoxia is a major threat to life. It may be classified based on the mechanism leading to the tissues receiving an insufficient oxygen supply for essential metabolic processes (see Box 17.1.10). Oxygen therapy is the mainstay when managing all types of hypoxia, however, specific treatment of the underlying cause is also essential. For example, blood transfusion may be required for severe acute anaemia, restoration of circulation for ischaemic hypoxia, or methylene blue for histotoxic anaemia due to severe methaemoglobinaemia. The most common type of hypoxia is hypoxaemic. Causes of this are shown in Box 17.1.11 and further classified as type 1 or 2 respira- tory failure based on the accompanying carbon dioxide (CO_2) level. The emphasis on oxygen therapy during initial resuscitation is to defend against tissue hypoxia that will injure cells rapidly. The negative effects of hypercarbia, including reduced consciousness, peripheral vasodilation, and pulmonary vasoconstriction, are secondary considerations. There are a few caveats to consider. The most recognized is in a subset of patients with chronic obstructive pulmonary disease (COPD) who have chronic hypercarbia and are dependent on hypoxic respiratory drive. In these individuals uncontrolled oxygen therapy may cause or exacerbate hypercarbia due to loss of central hypoxic respiratory centre drive and/or worsening V/Q mismatch from overcoming hypoxic vasoconstric- tion. Caution is also warranted in a tiny subset of patients who are primed for oxygen-exacerbated

pneumocyte toxicity (e.g. bleomycin chemotherapy or paraquat toxicity). Prolonged high FiO2 is also associated with lung toxicity, atelectasis from nitrogen washout with loss of the nitrogen ‘splinting effect’ in the alveoli. A recent systematic review and meta-analysis of 25 randomized controlled trials of conservative versus liberal oxygen therapy in over 16 000 acutely ill adults with a variety of conditions showed that mortality was higher with liberal oxygen (relative risk of death in hospital, 1.21; at 30 days 1.14; at longest follow up 1.10), hence targeting an SpO2 range above 94–96% would seem to be unwise. In patients where there are concerns regarding excess oxygen, aiming for a Pa02 greater than 60 mm Hg or Sp02 of 88–92% is appropriate. The rationale is that this is the area of the sigmoid shaped Hb-Oxygen dis- sociation curve close to the shoulder of the curve. Small increases in Sp02 above this point will result in disproportionately large increases in Pa02, which may be avoided by aiming for this range of oxygen saturation. Table 17.1.1 An ABCDEFG approach Element Important things to determine about the patient Possible interventions A—airway Is there audible stridor or wheeze? Can the patient talk? (If patient can then the airway must be patent) • Sit up and lean the alert patient forward in the ‘sniffing position’ • If obtunded open the airway with chin lift and jaw thrust and consider suctioning the oropharynx and sweeping with a gloved finger for a foreign body • Nebulise adrenaline for stridor • Nebulise salbutamol for bronchospasm B—breathing Is there central cyanosis? What is the work of breathing? Is there accessory muscle use? Is chest wall movement symmetrical? • Commence oxygen therapy • Consider needle thoracocentesis to decompress a tension pneumothorax • Intravenous frusemide for acute cardiogenic pulmonary oedema C—circulation Are the peripheries cold and vasoconstricted, or warm and vasodilated? Is capillary refill time prolonged? Is the patient diaphoretic? Is there skin mottling or tissue oedema? Is there any evidence of external or occult bleeding? Feel for pulse abnormalities—is it irregular, bounding, or thready? • Establish venous access • Commence an intravenous fluid bolus for hypovolaemia • Obtain an ECG to characterize a suspected dysrhythmia and look for signs of ischaemia • Rapid assessment by cardiac echo (RACE) to assess ventricular size and function, and exclude pericardial effusion D—disability What is the level of consciousness and has this changed? Do an AVPU score (are they Alert, responding only to Voice or to Pain or are they Unresponsive?) Is there any suspicion of seizure activity? • Place the patient on his/her side in the recovery position until definitive airway protection is obtained with tracheal intubation • Administer intravenous benzodiazepine (e.g. diazepam) to terminate a tonic- clonic seizure E—exposure Are there wounds including pressure areas, rashes, intravenous access devices, AV fistulas, surgical drains? Is there suspicion of a limb DVT? Is there central hypothermia or hyperthermia? • Commence cooling or warming strategies • Ensure intravenous cannulae are patent and attach a bag of fluid F—fluids What fluids have been administered? What has the urine output and fluid balance been? Does the patient look obviously fluid overloaded and oedematous or dehydrated with reduced skin turgor? • Flush the indwelling urinary catheter to exclude blockage in an oligo-anuric patient G—glucose Measure blood glucose concentration—is it high or low? • Administer 50 ml of 50% glucose intravenously if patient hypoglycaemic and obtunded AV, atrioventricular; ECG, electrocardiogram. This is based on material from the NSW Health DETECT programme. DETECT is an acronym for key principles relevant to caring for hospital patients. It stands for Detecting deterioration, making a skilled Evaluation, instituting appropriate Treatment, Escalating concerns to ensure timely medical interventions and the importance of excellent, structured Communication in Teams.

 There are several methods for delivering oxygen noninvasively. Key points related to these are summarized in Table 17.1.3. When oxygen is

required for anything other than a short period, the issue of humidification becomes increasingly important. This is the process of making inhaled gases warmed and moist in order to maintain normal cilia function and mucus composition. There is usually progressive heating and humidification of gas as it travels down the airways until the isothermic boundary is reached just below the carina where gases are 100% saturated at 37°C. A lack of humidification results in increased mucus viscosity, reduced mucociliary clearance, cytological injury to the tracheobronchial epithelium with acute inflammation, microatelectasis secondary to obstruction, and mucus plugging with airway obstruction. Table 17.1.2 Some laboratory data sets Diabetic ketoacidosis • Increased anion gap (ketoacids, lactate) and normal anion gap (HCO3 wasting) metabolic acidosis • Variable serum potassium (but total body depletion) • Increased urea and creatinine • Elevated glucose with increased osmolality and hyponatraemia (correct for glucose; serum Na decreases 1 mmol/litre for every 3 mmol/litre increase in glucose concentration) Hypoadrenalism • Hypo-osmolar hyponatraemia • Hyperkalaemia • Hypoglycaemia • Mildly increased urea • Mild metabolic acidosis • Hypercalcaemia • Eosinophilia Syndrome of inappropriate ADH secretion (SIADH) • Hypo-osmolar hyponatraemia • Increased urinary Na (>20 mmol/litre) with hypertonic urine relative to serum in the setting of normal renal, thyroid, pituitary and cardiac function in the absence of stimulating drugs or physiologic stimuli for ADH secretion Tumour lysis syndrome • Hyperkalaemia (real or pseudohyperkalaemia from potassium release from tumour cells in vitro) • Increased urea and creatinine (with increased urea:creatinine ratio) • Hyperuricaemia • Metabolic acidosis Rhabdomyolysis • Hyperkalaemia • Hyperphosphataemia • Hypocalcaemia • Increased urea and creatinine (with reduced urea:creatinine ratio) • Increased serum CK, AST, LDH • Myoglobinuria • Metabolic acidosis Acute pancreatitis • Hypocalcaemia • Hypophosphataemia • Hyperglycaemia • Increased urea and variable creatinine • Increased serum amylase and lipase Thrombotic thrombocytopaenic purpura (TTP) The classic pentad of fever, thrombocytopaenia, microangiopathic haemolytic anaemia, renal and neurologic dysfunction manifests as: • Low platelets • Reduced Hb with polychromasia, schistocytes, and spherocytes • Increased reticulocytes • Reduced haptoglobin • Increased lactate dehydrogenase • Unconjugated hyperbilirubinaemia with urinary urobilinogen • Variable neutrophilia • Increased urea and creatinine ADH, antidiuretic hormone; AST, aspartate aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; TTP, thrombotic thrombocytopaenic purpura. Box 17.1.2 Causes of hypotension Consider the categories of shock; note shock is frequently multifactorial • Hypovolaemic (e.g. blood loss, dehydration) • Distributive (e.g. sepsis, drugs, anaphylaxis, hypoadrenalism, acute high spinal cord injury) • Cardiogenic (e.g. dysrhythmia, pump failure) • Obstructive (e.g. massive pulmonary embolism, pericardial tam- ponade, tension pneumothorax) Box 17.1.3 Causes of hypertension Acute hypertension • Anxiety/fear • Pain • Urinary retention • Cushing’s response to increased intracranial pressure • Tracheal intubation • Drug effect (e.g. vasoconstrictors, amphetamines) Chronic hypertension—primary (essential) or secondary Hypertensive crises—urgency or emergency

Section 17 Critical care medicine 3834 Additional strategies to improve oxygenation and/or for CO2 management (ventilation) include noninvasive ventilation with nose or face masks (e.g. continuous/bilevel positive airway pressure—CPAP or BIPAP), tracheal intubation, and ventilation and when this fails, consideration of extracorporeal membrane oxygenation (ECMO). Principal indications for tracheal intub- ation are summarized in Table 17.1.4. Only those practitioners with the necessary knowledge and skill should perform tracheal intubation and manage such patients. In contrast, bag-valve mask ventilation is an important life-saving technique and part of the

essential skill set for providers of basic and advanced life support. Haemodynamic optimization Important aspects of haemodynamic support include administra- tion of fluids, electrolytes, blood and blood products, and the use of vasoactive drugs. These therapies necessitate intravenous access. A central venous catheter allowing simultaneous central venous pressure monitoring and vasoactive drug administration and an ar- terial line for blood pressure monitoring are commonly used. The strategy for venous access should reflect the needs of the patient with considerations such as site (peripheral versus central vein), size (catheter diameter and length), and stability of the pa- tient. For example, patients with life-threatening bleeding require rapid administration of warmed fluids and blood products with flow best achieved through short, wide bore peripheral or central venous cannulae. An intraosseous needle (e.g. EZ-IOTM) inserted into the upper humerus or tibia may be life-saving when a periph- eral cannula cannot be inserted and essential drugs and fluids for re- suscitation are required. A central line is a priority when stabilizing a patient with complex shock requiring inotropes and vasopressors. Although some advocate the use of algorithms, at the outset it is not possible to judge precisely how much fluid will be needed to resuscitate a patient. The only way to determine this is by frequent clinical examination as fluid is given. In the patient who is very un- well and clearly volume depleted, standard practice is to give 500 ml of blood, plasma expander, or 0.9% saline (as appropriate and as available) as fast as the access will allow (applying pressure to the bag by manual or mechanical compression if the patient is in extremis). Box 17.1.4 Causes of bradycardia Cardiac • sick sinus syndrome, junctional rhythm, AV block Noncardiac • Drugs (e.g. β-adrenergic or calcium channel blockers, digoxin, clonidine, narcotics) • Vagal stimulation (e.g. pain, vomiting, coughing) • Athletes/young fit patients • Hypothermia • Neurologic (e.g. increased intracranial pressure, spinal cord injury) • Severe hypoxia • Severe hyperkalaemia • Reflex response to severe hypertension Box 17.1.5 Causes of tachycardia • Narrow complex—sinus tachycardia, atrial fibrillation, atrial flutter, AV nodal re-entrant, accessory pathway, atrial tachycardia, junctional tachycardia • Broad complex—narrow complex tachycardia with conduction system defect or accessory pathway, ventricular tachycardia, pacemaker- mediated tachycardia • Precipitating factors — Increased sympathetic nervous system activity (e.g. fever, pain, anx- iety, drugs with β-adrenergic activity, hyperthyroidism) — Physiologic reflex response (e.g. hypovolaemia, vasodilatation) — Myocardial ischaemia — Acute pulmonary embolism — Sepsis Box 17.1.6 Causes of arterial desaturation/hypoxia • Brain (e.g. coma, decreased respiratory drive) • Spinal cord (e.g. trauma, myelitis) • Peripheral nervous system (e.g. Guillain-Barre syndrome) • Airways — Large airways (e.g. tumour, angioedema) — Small airways (e.g. asthma, COPD) — Lungs — Alveolar (e.g. fluid, infection, haemorrhage, tumour) — Interstitium (e.g. fibrosis) • Pleural space (e.g. effusion, pneumothorax) • Chest wall (e.g. flail chest, circumferential burn) • Diaphragm (e.g. phrenic nerve palsy) • Abdominal (e.g. abdominal distension and/or pain) Box 17.1.7 Causes of oliguria • Prerenal (e.g. hypovolaemia, shock, vascular occlusion) • Renal (e.g. acute tubular necrosis, contrast nephropathy, glomerulo- nephritis, acute interstitial nephritis) • Postrenal (e.g. bladder outlet obstruction, blocked indwelling catheter) Box 17.1.8 Causes of polyuria • Physiologic (e.g. mobilization after excess fluid loading, cold diuresis, diuretics, induced hypertension) • Pathologic (e.g. diabetes mellitus or insipidus, post relief of urinary obstruction, recovery phase of acute kidney injury) Box 17.1.9 Causes of altered level of consciousness Think ‘AEIOU TIPS’ A—alcohol, acidosis E—epilepsy, endocrine emergency, electrolytes I—infection O—overdose, oxygen/carbon dioxide problem U—uraemia and other organ failures T—trauma to brain I—insulin and glucose disorders P—psychosis and other psychiatric problems S—stroke and intracranial bleeding

17.1 The seriously ill or deteriorating patient 3835 A second 500 ml infusion is commenced while checking peripheral perfusion, pulse rate, blood pressure, and the jugular venous pres- sure. Rapid infusion is continued until there is clear evidence that the situation is beginning to improve, as manifest by warming of the peripheries, slowing of the pulse rate, and rise in blood pressure. The role of additional haemodynamic monitoring devices fo- cusing on cardiac output measurement (e.g. pulmonary artery catheters and pulse contour analysis devices) and the use of echo- cardiography, remain the subject of much debate and clinician pref- erence (see Chapter 17.6). Less common interventions for management of specific haemo- dynamic crises include pacing (transcutaneous as a bridge to transvenous), insertion of an intra-aortic balloon pump, extra- corporeal membrane oxygenation (venoarterial ECMO) and ven- tricular assist devices. The use and accepted indications for ECMO have increased considerably in recent years, including the use of eCPR, denoting the emergent use of ECMO to support patients in cardiac arrest. In some specialist centres an ECMO circuit is kept constantly primed in the emergency department for this purpose. Inherent to the principles of circulatory management is the physiologic relationships between commonly measured parameters (see Box 17.1.12). Systemic blood pressure (BP) is the most commonly used end point when employing treatments to restore tissue blood flow in shocked patients. For general organ perfusion, this is the mean ar- terial pressure (MAP). Restoring BP may involve interventions that improve cardiac output and/or optimize peripheral resistance. Tight control of systolic BP may be important in specific circum- stances (e.g. lowering BP to reduce bleeding risk in patients with brain haemorrhage or aortic dissection, increasing BP in patient with vasospasm after a subarachnoid haemorrhage to improve cere- bral perfusion). Coronary perfusion is dependent on adequate diastolic BP and preventing very low diastolic pressure may be a consideration in select patients (e.g. known or suspected coronary artery disease). The prescription of vasoactive medications is core to optimizing the blood pressure. See Table 17.1.5 for an overview of the com- monly used drugs. Box 17.1.10 Types of hypoxia • Hypoxic—reduced arterial partial pressure of oxygen • Anaemic hypoxia— reduced haemoglobin to carry oxygen • Stagnant hypoxia—lack of blood flow of oxygen • Histotoxic hypoxia—cells cannot extract oxygen Box 17.1.11 Causes of hypoxaemic hypoxia • Hypoventilation (e .g. opiates) • Shunts (e.g. patent foramen ovale with right to left shunt) • V/Q mismatch (e .g. acute pulmonary embolism) • Diffusing defects (e .g. lung fibrosis) • Reduced FiO2 (e .g. high altitude) Classification of respiratory failure • Type 1 = low PaO2 (<60 mm Hg); normal PaCO2 • Type 2 = low PaO2 (<60 mm Hg); increased PaCO2 (>50 mm Hg) Table 17.1.3 Oxygen delivery devices Device Important points Nasal prongs – Comfortable/less claustrophobic/allows patient to eat – Best if low FiO2 needed—max FiO2 40%; less if mouth breathing – No humidification except for normal mechanisms— risk of mucosal drying and injury at high flow rates (>4 litre/min) Hudson mask – Variable FiO2 depending on minute ventilation – Maximum estimated FiO2 is 50% because of air entrainment – Flow rates <5 litre/min may cause CO2 rebreathing – No humidification Venturi mask – Delivers fixed FiO2 independent of minute ventilation – Administers specific FiO2 determined by the air entrainment adaptor on the end of the mask/set flow rate—24, 28, 35, 40, 50% (vary with the design) – No humidification Mask with reservoir bag – FiO2 high but varies with minute ventilation due to air entrainment around the mask – Reservoir bag must always be inflated – One way valve into reservoir – Flaps for expiration – No humidification Bag-valve-mask – FiO2 high and consistent if a good mask seal – Can deliver positive end expiratory pressure if there is a valve in the circuit or with non-self-inflating bags that allow manual control of resistance to breathing – Self-inflating versions can allow ventilation even if oxygen flow ceases – Requires operator skill High-flow nasal cannulae – High and set FiO2 – High flow rate reduces need for room air entrainment,

has effects similar to continuous positive airway pressure (CPAP) system—reduced work of breathing and improved compliance and CO2 clearance – Gases are humidified and warmed – Comfortable/less claustrophobic than masks Table 17.1.4 Indications for endotracheal intubation Indication Examples Obtain an airway Airway obstruction of any cause Protect an airway Coma with risk of obstruction and aspiration Oxygenation Hypoxia refractory to noninvasive oxygen therapy Ventilation Hypercarbia with reduced level of consciousness Box 17.1.12 Common physiologic parameters BP = CO × TPR CO = HR × SV SV determined by: • Preload • Afterload • Contractility MAP = [(2 × DBP) + SBP]/3 BP, blood pressure; CO, cardiac output; TPR, total peripheral resistance; HR, heart rate; SV, stroke volume; MAP, mean arterial pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Section 17 Critical care medicine 3836 See Table 17.1.6 for examples of how these principles are em- ployed in developing a strategy for managing shocked patients in contrasting circumstances. Renal considerations Acute kidney injury is another important consideration in any unstable patient. Determining and treating the cause of oliguria is important in order to prevent progressive dysfunction. When renal failure is progressive, the goals of therapy are to manage life- threatening complications. This may require medical interventions such as intravenous loop diuretics to treat volume overload and/or drugs that target hyperkalaemia (e.g. calcium gluconate/chloride for myocardial stabilization, insulin/glucose to facilitate intracellular shift of potassium ions, resonium to improve potassium removal). Common indications for renal replacement therapy (RRT) are shown in Box 7.1.13. For further discussion see Chapter 21.5. Continuous RRT is commonly performed in an acute setting, par- ticularly in haemodynamically unstable patients, via a veno-venous technique using a centrally placed large bore dialysis catheter. The underlying physiologic principles include dialysis (solute movement via diffusion) and/or haemofiltration (water and solute movement via hydrostatic pressure) across a semipermeable filter utilizing an extracorporeal circuit and machine. Diagnosis of specific conditions The initial management of patients who are desperately ill does not depend on making a precise diagnosis of the cause of their pre- dicament. However, as soon as resuscitation is underway, attention must turn towards making a diagnosis. Although the naive might think that the more severe the illness, the more obvious the cause should be, the opposite is often the case. When dead, all patients look identical, and the same is true just before they die. Patients who are in extremis, whether due to profound hypoxia or with next to no blood pressure, are not lucid historians, and it may be that the only question that they can usefully answer is: ‘Do you have any pain?’ If they indicate their chest or their abdomen, this might be a helpful clue. The pragmatic approach to making a diagnosis in the patient with cardiorespiratory collapse is to use a ‘surgical sieve’ tech- nique, looking systematically for features on examination and investigation to diagnose conditions that can kill (Table 17.1.7). Details of the management of the many specific disorders listed in Table 17.1.7 can be found in the relevant sections of this book, but one general point is extremely important: if initial investiga- tions do not give any clear diagnostic lead, then treatment must be started ‘on suspicion’, especially for disorders that cannot reli- ably be diagnosed or excluded by clinical examination or by tests that are rapidly available. In particular, pulmonary embolism and sepsis should always be considered. If the clinical context makes pulmonary embolism likely, for instance the patient has collapsed after an operation a week or so ago, then—in the ab- sence of other explanation for the problem—it is sensible to start Table 17.1.5 Vasoactive drugs Principal effect Examples Vasodilators—widening of blood vessels from wall relaxation Glyceryl trinitrate, sodium nitroprusside, dobutamine, milrinone, levosimendan Vasopressors—narrowing of blood vessels from wall contraction Noradrenaline, metaraminol

phenylephrine vasopressin Chronotrope—increases heart ratea Isoprenaline, adrenaline, dobutamine Inotrope—increases myocardial force of contraction Adrenaline, noradrenaline, dobutamine, milrinone levosimendan Lusitrope—facilitates myocardial diastolic relaxation Dobutamine, milrinone a These agents also commonly have dromotrophic effects (increase rate of atrioventricular conduction). Table 17.1.6 Examples of haemodynamic strategies to optimize the circulation Condition Heart rate (HR) Preload Afterload Contractility Massive blood loss Restore circulating volume with fluids and blood and blood products Vasopressors may temporarily restore BP while fluid resuscitation is undertaken Sepsis Treat arrhythmias such as AF Fluid load aiming for CVP 8–12 Vasopressors to overcome pathological vasodilatation Inotropes if sepsis-related myocardial depression Decompensated heart failure Treat arrhythmias; avoid bradycardia with ventricular overdistention from prolonged filling time Avoid fluid overload with left ventricular overdistention; use diuretics to correct intravascular volume overload Lower afterload with vasodilators Inotropes to improve contractility Complete heart block related to a right ventricular (RV) myocardial infarct Chronotropes and pacing Fluid load but avoid RV overdistention Reduce RV afterload with pulmonary vasodilators Avoid low diastolic pressure to ensure maximal perfusing coronary blood flow; inotropes to assist RV contractility Severe aortic stenosis with left ventricular hypertrophy Slow HR 60–80 ideal to allow time for ventricular filling Maintain sinus rhythm or use atrial pacing to maintain atrial contraction and ventricular filling Fluid load for CVP >10 Normal or increased afterload to improve diastolic coronary flow to hypertrophied ventricle Inotropes not required; drugs with lusitropic properties may improve diastolic dysfunction but caution needed to avoid vasodilatation AF, atrial fibrillation; BP, blood pressure; CVP, central venous pressure; RV, right ventricular.

17.1 The seriously ill or deteriorating patient 3837 therapeutic anticoagulation with intravenous heparin (which can be reversed if necessary) immediately, pending definitive imaging, but it would be unwise to give thrombolytic agents until the diagnosis was established. However, wider availability and systematic training of emergency room and ICU clinicians in rapid assessment by cardiac echo (RACE) has made narrowing the differential diagnosis of moribund patients possible at the bedside and may provide sufficient certainty to justify the admin- istration of thrombolytic agents. If a patient who looks unwell is hypotensive for no obvious reason, then give broad-spectrum parenteral antibiotics as soon as blood cultures have been taken. And with regard to sepsis, ask the patient where they have trav- elled recently and consider malaria, which still kills in temperate parts of the world, sometimes because ‘the doctor didn’t think of the diagnosis’. Other considerations The very ill patient is at risk of preventable serious complications such as deep vein thrombosis, stress ulceration of the gastrointestinal Box 17.1.13 Indications for renal replacement therapy (RRT) • Fluid overload unresponsive to diuretics • Severe hyperkalaemia despite medical therapies • Severe metabolic acidosis • Symptomatic uraemia • Removal of select toxins in life-threatening intoxications (e.g. lithium) Table 17.1.7 Diagnosis of specific conditions in the patient with cardiorespiratory collapse Diagnosis Key finding on examination Key initial investigation Definitive investigations Cardiovascular Myocardial infarction No specific findings likely ECG ECG, cardiac enzymes Arrhythmia Pulse rate and rhythm ECG ECG Aortic dissection Absence or reduction in one or more peripheral pulses, especially left radial. Blood pressure lower in left arm than right Chest radiograph showing widened mediastinum Imaging of aorta, usually by CT scan or transoesophageal echocardiography Cardiac tamponade Raised jugular venous pressure. Pulsus paradoxus (pulse becomes impalpable on inspiration in extreme cases) Chest radiograph may show globular heart. ECG may show low-voltage complexes or electrical alternans Echocardiography

Cardiorespiratory Pulmonary embolus Raised jugular venous pressure. Right ventricular heave. Loud P2. Right ventricular gallop rhythm. Signs of deep vein thrombosis in leg ECG may show features of acute right heart strain Echocardiogram—impaired and dilated right ventricle and underfilled left ventricle Ventilation/perfusion scan. Imaging of pulmonary vessels by CT scan or pulmonary angiography CT or digital subtraction pulmonary angiogram Pulmonary oedema Gallop rhythm. Fine inspiratory crepitations Chest radiograph ECG, echocardiography, cardiac enzymes Respiratory Tension pneumothorax Tracheal deviation. Hyperexpansion of one side of chest. Mediastinal shift. Absent breath sounds on one side of chest Chest radiograph—but should be treated by needle decompressionon basis of clinical diagnosis Chest radiograph— but should be treated by needle decompression on basis of clinical diagnosis Pneumonia May have high fever. Signs of consolidation or pleurisy Chest radiograph Chest radiograph. Blood culture. Serological tests Asthma Wheezes, but beware of silent chest Response to treatment (β-agonist), but chest radiograph excludes other respiratory diagnoses Peak flow measurements before and after β-agonist Exacerbation of chronic obstructive pulmonary disease Features of chronic obstructive pulmonary disease A clinical diagnosis, but chest radiograph excludes other respiratory diagnoses See Chapter 18.8 Abdominal Gastrointestinal haemorrhage Usually obvious, but do not forget rectal examination for blood/melaena in the patient with unexplained hypotension A clinical diagnosis Endoscopy Perforated viscus Peritonism Erect abdominal radiograph to look for free air CT scan or laparotomy, depending on clinical situation Pancreatitis Peritonism. Bruising in flanks Serum amylase and lipase Imaging of pancreas, usually by CT scan Ruptured abdominal aortic aneurysm Peritonism. Palpable aneurysm. Bruising in flanks A clinical diagnosis CT scan or laparotomy, depending on clinical situation (continued)

Section 17 Critical care medicine 3838 (GI) tract, and hospital-acquired pneumonia. Ensuring adequate nu- trition (using enteral or parenteral nutrition), glucose control, and ad- dressing issues such as pain, anxiety, and delirium are also important. Communication with the patient and/or their family and rec- ognizing when a patient is dying and managing their end-of-life needs are vital. The substantial personal costs to survivors of crit- ical illness are increasingly being recognized. Strategies to improve the quality of life in survivors of critical illness may require diverse interventions ranging from physical rehabilitation of significant deconditioning to treatment of post-traumatic stress disorder. Finally, while ongoing certification to ensure responders to the very ill have vital competency in areas such as basic and advanced life support, there is a progressive recognition that the curriculum needs to extend beyond medical knowledge and skills. Education on topics such as team crisis resource management, stress management, improving self-awareness, and interprofessional communication are becoming routine. FURTHER READING Chu DK, et al. (2018). Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet, 391, 1693–705. Clinical Excellence Commission (2013). Between the Flags Program. NSW Health, Sydney. http://www.cec.health.nsw.gov.au/patient- safety-programs/adult-patient-safety/between-the-flags Dickinson E, et al. (2008). Emergency care, 11th edition. Prentice Hall, Englewood Cliffs, NJ, p. 242. Foot C, et al. (2011). Examination intensive care medicine, 2nd edition. Churchill Livingstone, Australia, pp. 179–80. Gerdik C, et al. (2010). Successful implementation of a family and pa- tient activated rapid response team in an adult level 1 trauma center. Resuscitation, 81, 1676–81. Grunau B, et al. (2018). Extracorporeal cardiopulmonary resuscita- tion for refractory out-of-hospital cardiac arrest: the state of the evidence and framework for application. Canadian J Cardiol, 34, 146–55. Jacques T, et al. DETECT E-Learning Program. NSW Health. http://

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17.10 Palliative and end- of-life care in the ICU

17.10 Palliative and end- of-life care in the ICU

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ESSENTIALS What happens when organ support leads to prolongation of life, but with no hope of ultimate survival, or survival with unacceptable quality of life? For many—but not all—patients, families, and phys- icians, prolongation of life with little or no hope of a good quality of life is considered worse than death. The cultural milieu is central in determining the responses and needs of all parties in regard to end-of-life care. Excellent communi- cation is required to prevent potential conflicts and provide both the medical team and the patient/family with peace of mind. The deci- sion to institute palliative or end-of-life care should, if at all possible, always be reached via a negotiating process between the medical staff and the patient or their family. The best protection against con- flict comes from a good bedside manner reflecting patience with the family, honesty, and some optimism. However, conflicts do arise, and rarely these require the intervention of third parties such as ethics committees or courts. Introduction As is clear from other chapters in the critical care section of this book, incredible progress has been made in ICU-based organ sup- port over the last decades. Patients are able to survive illnesses today that would have led to certain and rapid death only a few years ago. This progress, however, has been accompanied by dilemmas of quan- tity versus quality. What happens when organ support leads to pro- longation of life, but with no hope of ultimate survival, or survival with unacceptable quality of life? For many—but not all—patients, families and physicians, prolongation of life with little or no hope of good quality of life is considered worse than death. So arises the need for palliative and end-of-life care in the ICU. In this chapter we will explore the history and terms associated with end-of-life care, variability in practice, factors influencing the decision-making pro- cess, differing practices around the world, sources of conflict, and how we can improve. Two central tenets will become clear during the course of this chapter—first that the cultural milieu is central in determining

physicians', patients' and families responses and needs in regard to end-of-life care, and second that excellent communication is re- quired to prevent potential conflicts and provide both the medical team and the patient/family with peace of mind. History From the beginnings of intensive care in the 1950s until around 1970, there was only one objective of therapy: to prolong life. It was considered medically, morally, ethically, and legally imperative to pursue treatment including cardiopulmonary resuscitation (CPR) until the moment of death. During this time, however, it became clear that medical interventions did not always lead to a meaningful recovery or to recovery at all. The concept arose that some treat- ments were deferring death rather than prolonging life. For some families this was intolerable and from 1970 on they sought the sup- port of the courts in demanding that hospitals stop life-prolonging treatment and allow their loved ones to die. In the first such case (the Quinlan case in the United States in 1976) the court determined that the hospital would not be legally liable if artificial ventilation was stopped. This was a landmark case as it was the first time that a hospital could officially perform an action that might result in death rather than prolong life without fear of legal challenge or sanction. Increased involvement of the patient and their family in decision- making led to the growth of patient autonomy and the decline of physician paternalism; the patient would decide which of the offered treatments to receive rather than the physicians. This change in balance between the patients and their physicians had the potential for problems; physicians were at risk of losing their independence in medical decision-making. The change in balance also placed phys- icians in a difficult position as they possessed the knowledge of the illness and prognosis, while the family (in the extreme) was expected or considered themselves responsible for decision-making. Possibly in an attempt to rationalize this situation, medical decision-making adopted a series of positions to justify or objectify limitation of life support. These included financial justifications based on the concept of distributive justice (limiting therapy was necessary to limit costs and prevent waste), available resource justification (the demand for ICU beds often exceeded supply justifying limitation of therapy for those who were thought to have a poor prognosis), and the growth of the futility movement. 17.10 Palliative and end-of-life care in the ICU Phillip D. Levin and Charles L. Sprung

 Futility was given several definitions, all of which centred on defining treatments that were of no benefit for the patient. If a treat- ment was defined as futile, then physicians were not obliged to provide it, thus making limitation of life-sustaining treatment an objective decision reached by the physician. Repeated studies, how- ever, showed that physicians' ability to provide an accurate quali- tative prognosis or estimate of the risk of death is far from perfect. Further, it soon became clear that 'benefit' was a subjective value judgement. Prolonging life with no quality represented futility to one, while it was a religious imperative to another. Changing the term 'futile therapy' to 'inappropriate therapy', perhaps in an attempt to dampen the negative connotation and portray objectivity, made no real difference to the cultural dilemmas associated with limiting therapy. The situation today is that the decision to institute palliative or end-of-life care is almost always reached via a negotiating process between the medical staff and the patient or their family. Paternalism does still exist, with some physicians making and instituting end-of- life decisions without patient/family involvement, or even against their will. Very occasionally, physicians will also continue full care despite a patient/family's wish to stop. Conflicts do arise and these sometimes, although rarely, require the intervention of third parties such as ethics committees or the courts. Decision-making and outcome Five terms are commonly associated with levels of therapy in the ICU and describe a spectrum of limitation of life-

sustaining ther- apies. The spectrum ranges from ‘Full Therapy’ through do not re- suscitate (DNR) orders, withholding and/or withdrawing therapy, to active shortening of the dying process. Definitions and descriptions of these levels of care are provided in Table 17.10.1. Most of the large critical care or medical organizations (including the British Medical Association, the American Thoracic Society and the Society of Critical Care Medicine) concur that there is no ethical difference between decisions to withhold or withdraw therapy. There is, however, recognition that stopping an existing therapy may be associated with ‘greater emotional difficulty’ for the ICU physician and patient/family than not starting a life-prolonging therapy. Most societies and countries define active shortening of the dying process (euthanasia) by a physician as unacceptable or illegal, although the administration of drugs with the primary intent to relieve symptoms is accepted even if that has the secondary effect of shortening life (sometimes referred to as the ‘principle of double effect’). The effects and outcomes of limiting the treatments to be offered vary across the spectrum. A DNR order can be instituted by a patient in good health to be applied only if and when required. People may live healthy, long, and fulfilling lives with existing DNR orders in the form of living wills. Withholding decisions implemented during ICU admission are associated with significant mortality (89% after a median of 14 hours), while withdrawing decisions are associated with a 99% mortality within a median of 4 hours. Active shortening of the dying process is associated with 100% mortality. One of the central ethical tenets of medicine in the western world is patient autonomy, meaning that the patient should determine which of offered medical interventions he/she receives. This is re- flected in the process for acquiring informed consent before many medical interventions. When the patient is capable, consent for treatments or procedures should be sought in the ICU, but many pa- tients in the ICU are unable to express their preferences. Pre-existing medical directives (advance directives or living wills) are maintained by only a small minority of patients, but their presence should be ac- tively sought in discussion with the patient or their family. When the patient is not able to make decisions, and there is no advance directive, decision-making authority is usually passed to a proxy: a loved one, family member or close friend who is presumed to know the patient’s wishes or to share the patient’s outlook on life. In most Table 17.10.1 Terminology used to describe levels of treatment offered to patients and end-of-life care A) Full therapy All interventions to sustain and prolong life are to be employed. B) Withholding treatment Certain intermittent interventions should not be started or reinstituted. For example, do not start dialysis, or do not start vasoactive drugs if and when needed. As dialysis is an intermittent intervention, not restarting dialysis after a previous session would also be considered withholding. A Do Not Resuscitate (DNR) (also referred to as DNAR—Do Not Attempt Resuscitation, NFR—Not For Resuscitation or No Cardiopulmonary Resuscitation—No CPR) order can also be considered as a type of withholding as when and if required, cardiopulmonary resuscitation will not be started. Some consider DNR orders a special case of general withholding orders and classify DNR orders separately. C) Withdrawing treatment Cessation of an existing continuous therapy even if indicated to prolong life. Such an intervention might be extubation in a mechanically ventilated patient not expected to survive without further mechanical ventilation. Withdrawing therapy differs from withholding in that it involves cessation of a continuous life-supporting intervention while withholding relates to not instituting or restarting an intermittent therapy. D) Active shortening of the dying process (also termed active euthanasia by some) These interventions are performed to actively hasten death and might include administration of high doses of potassium chloride, opiates, or sedatives. These measures must be distinguished from palliative (comfort) measures (such as the administration of morphine to prevent dyspnoea) which have the primary purpose of preventing suffering, but might also be associated with inevitable side

effects such as depression of ventilation. The purpose of administering morphine during the dying process is usually to relieve suffering. Morphine is not given specifically to cause apnoea, although this is an accepted side effect. Therefore morphine administration is considered a comfort measure and not an intervention to actively shorten the dying process. If morphine is given in very large doses (greater than needed to relieve pain or suffering) only to produce apnoea, it would be considered an intervention to shorten the dying process. Clearly there is potential overlap between palliative therapy and active shortening of the dying process. E) Brain death (brain stem death in the United Kingdom) Removal of ventilation or cessation of vasoactive drugs after formal declaration of brain death by the appropriate criteria is considered by some to be a form of withdrawal. As brain death is an accepted definition of death by most jurisdictions, life-supporting therapy becomes an oxymoron and therefore cessation of ventilation (e.g.) is not considered by most to be a form of withdrawal.

Section 17 Critical care medicine 3916 jurisdictions the natural proxy is assumed to be the patient's parent (even if the patient is above the age of 18), partner or child, and these family members are able to make end-of-life decisions without a formal appointment. In other jurisdictions, or when there is conflict between family members, an official court order of guardianship is sometimes required. Variability in end-of-life practices From the beginning of research into end-of-life practices it became clear that there is huge variability in the decision-making process and in end-of-life practices. Across hospitals in the United States the use of withhold and withdraw orders in patients who subsequently died ranged from zero to 67% and zero to 79%, respectively. Similarly, in Europe there is great variability with a marked north/south divide. Northern European countries are significantly more liberal in their use of limitation orders than Southern European countries. In case scenarios, DNR orders were issued by 91% of Dutch physicians as compared to 8% of Italian physicians, while 71% of French phys- icians would be willing to prescribe drugs that would speed death, compared to 8% of Portuguese physicians. Many non-patient-related physician variables beyond nationality have been associated with the end-of-life decision-making process. These include physician age (younger physicians being more likely to withdraw therapies than older physicians), religiosity, religious af- filiation, specialty, level of training, and others. In other words, it ap- pears that physicians' cultural background and cognitive processes may affect end-of-life decisions as much as the patient's physio- logical condition. From the patient's perspective, the cultural (rather than ethnic) background also affects decision-making. This has been explored by examining population migration. For example, in a scenario based end-of-life questionnaire, English-speaking Japanese Americans (assumed to be highly acculturated to American life) have been compared to Japanese speaking Japanese Americans (less accul- turated to America) and to Japanese in Japan (not acculturated to America). English-speaking Japanese Americans agreed in a high proportion that the patient should be told his diagnosis, and they were more willing to withdraw care, which are values commonly found in the general American population. A progressively lower proportion of the other two groups agreed to these sentiments, with Japanese in Japan making decisions furthest away from English- speaking Japanese Americans. This study suggests a process of ac- culturation, meaning that cultural elements may be imposed on one's ethnic background. In the face of this great national, ethnic, and culture variation in end-of-life care, an attempt to identify areas of common ground and differences in attitudes to end-of-life care was recently described in the WELPICUS study. This study examined concurrence between 1366 physicians, nurses, social workers, and others from a variety of national and cultural backgrounds concerning 81 statements about end-of-life care. On

repeated questionnaire with adaptation of the end-of-life statements, consensus was reached for 77 of 81 statements (95%). Agreement could not be reached between more than 80% of the respondents for four statements. All these state- ments involved interaction with the patient's family: withholding or withdrawing therapies without the consent of the patient or family; hastening the dying process at a family member's request; and a family's refusal to accept brain death. So, in spite of variations in practice, there seems to be considerable common ground regarding the concepts of end-of-life care. This difference between theory and practice in end-of-life care has also been identified empirically. Family members often agree that the therapies being given to a patient are inappropriate or un- necessary, and even that they would not want them for themselves. However, families will not agree to stop these therapies for their loved one. This even occurs when the patient has previously clearly defined their requirements in the event of life-sustaining therapy being required. In conclusion, non-medical-related variables among both phys- icians and patients are highly influential on the end-of-life decision- making process. Given the ever increasing multicultural nature of medical practice in many countries, cultural or ethnic differences between physicians and their patients are inevitable. Communication One of the earliest investigations into communication around the end-of-life was the SUPPORT study published in 1995. This study demonstrated that on approximately 50% of occasions, ICU phys- icians were unaware of their patients' wishes regarding resuscitation. While family involvement in decision-making is almost universal in the United States, conflicts have been described by families in up to 63% of cases, many of which were not identified by physicians. In Europe physicians have been described as making end-of-life de- cisions without involving the family at all in 28% of cases, or have informed the families of the decision (rather than involved them in decision-making) on 59% of occasions. In Hong Kong and Japan family involvement is high, with decisions sometimes being made with the exclusion of the patient, even when the patient is mentally competent. The reasons for lack of good communication have not been widely explored. They may relate to difficulty in discussing end-of-life issues, physician preconceptions, cultural norms, or lack of teaching of end-of-life care in medical school and during clinical training programmes. Several tools have been published to improve communication, de- veloped mainly from the oncology field where breaking bad news is a frequent occurrence. These include SPIKES and VALUE, which share several similarities (see Box 17.10.1 and Box 17.10.2). A common element of family discussions, which we consider an error, is exaggerated attention to the risks and possibility of negative outcomes. Many physicians prefer to paint a bleak picture, as then Box 17.10.1 SPIKES Setting—patient and/or family meetings should be planned in a suitable quiet uninterrupted setting Perception—explore the patient/family's perception of the medical situ- ation before starting to impart information Invitation—establish how much the patient/family want to know Knowledge—impart information after (when appropriate) giving warning that bad news is coming; avoid excessive bluntness Empathy—show empathy for the emotional reaction Strategy—explain the future plans, for the next hours or days as appropriate

 they believe they have been honest, and that the family is prepared. If the outcome is good, then the families 'get a nice surprise'. Almost all families who have a loved one in the ICU understand that they are gravely ill and at risk of dying—why else would they be in the ICU? These families do not need to have the risks emphasized over and over: they need the truth, but they also need hope. In ex- plaining the situation the physician clearly has to be honest, but if at all possible some positive aspect should be sought, even if this is only that the patient is no longer suffering and that the team is providing

them with the best possible care and treatment. If there is a realistic chance of recovery, this should not be kept from the family. Conflict Possibly owing to cultural variation and differences in expectations, conflicts between the ICU staff (physicians and nurses) and families are not uncommon. Conflicts also occur between members of the ICU team. At least half of these conflicts relate to end-of-life care, with most arising from the family's wish for more aggressive care than the physicians are recommending. Risk factors for conflict in- clude previous discrimination in the hospital, possibly indicating a lack of trust. The best protection against conflict comes from a good bedside manner reflecting patience with the family, honesty, and some optimism. Involving the nurses, a social worker or a psych- ologist in family discussions is sometimes beneficial. These team members might be able to devote additional time to the family and explore their understanding of the information that the physicians are trying to impart. They can also raise particular areas of family concern that might require additional explanation at the next family meeting. Devoting time to communication usually leads to con- sensus and shared decision-making. Another source of conflict is mixed messages, with different prognoses being suggested by different doctors or others within the multidisciplinary team. Every effort should be made to agree a common understanding and message that should be presented by all those involved in the patient's care. Lack of good communication or conflict is associated with low family satisfaction in the ICU and once conflict occurs and trust is lost it is difficult, although not impossible, to regain that trust. In the event that an impasse is reached, third party help from outside the ICU can be sought. This might include an ethics consultation. Ethics committees vary from institution to institution but usually include nonmedical members in addition to physicians who hear both sides of the situation and attempt to mediate a decision. Unfortunately ethics committees are often seen as another arm of the hospital ad- ministration and thus as nonobjective. They are rarely convened. The judicial system remains a rare if final resort, although the time frame of court decision-making sometimes makes it irrelevant to end-of-life care. The authors' perspective Having described in depth the influence of cultural background to end-of-life decision-making, we should disclose our own envir- onment as despite our best efforts to be objective we are undoubt- edly influenced by this environment. Both authors have worked in healthcare systems in different countries with a variety of end-of-life practices. Currently we both work in an environment where with- drawal of continuous therapy is illegal, and the expectation of pa- tients and families is almost invariably to fight on until the end with quantity of life exceeding the need for quality. We are unfortunately often faced with families and colleagues who 'want everything done', even when it is very clear that 'everything' will not be enough. We are thus frequently involved in family meetings that are emotion- ally charged. Patience, sensitivity, tolerance, and training can lead to better outcomes for patients and their families. FURTHER READING Azoulay E, et al. (2009). Prevalence and factors of intensive care unit conflicts: the conflicus study. Am J Respir Crit Care Med, 180, 853–60. Cook D, Rocker G (2014). Dying with dignity in the intensive care unit. N Engl J Med, 370, 2506–14. Kaplan M (2010). SPIKES: a framework for breaking bad news to pa- tients with cancer. Clin J Oncol Nurs, 14, 514–6. Mark NM, Rayner SG, Lee NJ, Curtis JR. (2015). Global variability in withholding and withdrawal of life-sustaining treatment in the inten- sive care unit: a systematic review. Intensive Care Med, 41, 1572–85. Sprung CL, et al. (2003). End-of-life practices in European intensive care units: the Ethicus Study. JAMA, 290, 790–7. Sprung CL, et al. (2014). Seeking worldwide professional consensus on the principles of end-of-life care for the critically ill: the Consensus for Worldwide End-of-Life Practice for Patients in Intensive Care Units (WELPICUS) study. Am J Respir Crit Care Med, 190, 855–66. Truog RD, et al. (2008). 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, 36, 953–63. Box 17.10.2 VALUE Value family statements Acknowledge family emotions Listen to the patient and/or family Understand the patient as a person Elicit family questions

17.11 Diagnosis of death and organ donation 3918 P

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ESSENTIALS Death is the permanent loss of the capacity for consciousness and respiration, both of which are functions of the brain-stem. Death can be diagnosed by somatic, circulatory, or neurological criteria, which vary between countries and are influenced by prevailing attitudes towards death, legal frameworks, and available medical technologies. When organ retrieval is planned after circulatory death, there is need for a time-critical schedule for the diagnosis of death using circulatory criteria. These require the absence of consciousness and respiratory effort to be demonstrated, and emphasize the need for explicit clarity that resuscitation should not be instigated or continued, how the absence of the circulation should identified, and the minimum period of observation that is required to be as- sured that the possibility of spontaneous return of the circulation has passed. Introduction Death is usually a process rather than an instantaneous event. However, putting aside the complex and interwoven religious, cultural, socio- logical, and legal perspectives on death, there is a clear clinical require- ment to determine with confidence when an individual has died. Historically, there was a practical necessity to be able to sanc- tion the prompt disposal of a corpse before the onset of putre- faction and decay while avoiding the possibility of the premature burial of someone who was in deep coma but still alive. Clinicians now face additional problems, some of which have required a fun- damental review of the essential features of life and death. Is the irreversible loss of brain function sufficient to satisfy criteria for the determination of death even though the circulation persists for as long the patient is artificially ventilated? Can there remain clear distance between the diagnosis of death and organ donation for the purposes of transplantation, particularly with regards to donation after circulatory death following withdrawal of life sup- port such as mechanical ventilation? Diagnosis of death Overarching professional concepts While death is essentially a biological phenomenon that is the same for all humans, the diagnostic criteria for its recognition have been developed by individual countries and jurisdictions rather than by international clinical consensus. As a result, the diagnostic criteria for the diagnosis of death vary between countries and are influenced by

prevailing attitudes towards death, legal frameworks, and avail- able medical technologies. A group assembled by the World Health Organization has sought to provide an international consensus on death, defining it as ‘the permanent loss of capacity for consciousness and loss of all brain- stem functions, as a consequence of permanent cessation of cir- culation and/or catastrophic brain injury’ (the term ‘permanent’ meaning loss of function that cannot not resume spontaneously and will not be restored through intervention). Such an approach provides an overarching definition of death that is applicable to all circumstances and also avoids the suggestion that there are dif- ferent kinds of death as implied by terms such as brain death or cardiorespiratory death. There is only one kind of death; the differ- ences lie in how the state is reached and how it can be recognized (Fig. 17.11.1). The diagnosis of death by somatic criteria Somatic criteria for the diagnosis of death are primarily used by emergency medical staff to recognize circumstances in which at- tempts at resuscitation should not be made. They represent a list of conditions which are unequivocally associated with death and re- quire no further investigation or assessment (Box 17.11.1). The diagnosis of death by circulatory criteria Although clinicians across the world have for many years used cir- culatory criteria to diagnose death, very often this has been in the absence of any clear professional guidance on how the diagnosis should be made. When practised in this way, the safety of the circu- latory standard for the determination of death has depended, more or less explicitly, upon allowing sufficient time to elapse to ensure 17.11 Diagnosis of death and organ donation Paul Murphy

 that circulatory arrest is permanent and has resulted in irreversible anoxic brain damage. However, the possibility of successful trans- plantation using organs retrieved from patients whose death follows circulatory arrest, which requires organs to be retrieved as soon as possible after death, has required the schedules for the diagnosis of death by circulatory criteria to be completely reviewed. The overarching definition of death is based upon permanent loss of the capacity for consciousness and respiration, both of which are functions of the brain. A robust time-critical schedule for the diag- nosis of death using circulatory criteria requires clarity over the re- lationship between the loss of circulation and the failure of brain function as well as the factors that determine the permanence of such changes. It must also be able to accommodate the very different circumstances in how death occurs and whether continued resusci- tation is appropriate. The key dynamic relationships between loss of circulatory and brain function are shown in Fig. 17.11.2. Although brain function is lost within seconds of circulatory arrest, it is possible that some brain activity could return were cerebral perfusion to be restored within the minutes that follow asystole. It follows that the permanence of loss of brain function is dependent upon whether resuscitation is to be attempted or whether there remains a possibility for myocardial function to return spontaneously. Within the context of abandoned cardiopulmonary resuscitation, the longest period of continuously monitored asystole that has been followed by spontaneous return of the circulation (the Lazarus phenomenon) is seven minutes. In con- trast, when asystole follows withdrawal of life-sustaining treatments from intensive care (ICU), this interval is just 65 seconds. Although it is important to recognize the need to always con- firm the absence of both neurological and circulatory function, there will be many occasions on which clinicians can continue to adopt a cautious approach to the diagnosis of death—for example, when donation is not a possibility or when minimal monitoring is available. However, a more robust approach is required when organ retrieval is planned, with the key elements of such a time-critical schedule for the diagnosis of death using circulatory criteria being listed in Table 17.11.1. They emphasize the need for explicit clarity that resuscitation should not be instigated or

continued, how the absence of the circulation should identified, and the minimum period of observation that is required to be assured that the pos- sibility of spontaneous return of the circulation has passed. They also benefit from a clear requirement for the absence of consciousness and respiratory effort to be demonstrated, thereby providing a Neurological criteria Somatic criteria Circulatory criteria Permanent loss of the capacity for consciousness Permanent loss of the capacity to breathe Death Fig. 17.11.1 A unifying medical concept of death. Death is regarded as the permanent loss of the capacity for consciousness and respiration, both of which are functions of the brain-stem. The criteria best suited to diagnose death are determined by how it has occurred. Box 17.11.1 Recognition of life extinct The following conditions are unequivocally associated with death in all age groups 1 Massive cranial and cerebral destruction 2 Massive truncal injury that is incompatible with life, including trau- matic hemicorporectomy and decapitation 3 Decomposition/putrefaction 4 Incineration (charring involving >95% of body surface) 5 Post-mortem hypostasis (purple discolouration of the dependent areas of the body that is the result of gravitational pooling of deoxy- genated blood) 6 Rigor mortis In the newborn, fetal maceration is also a contraindication to resuscitation. Circulatory arrest Circulation Brain Latest recorded return of circulatory function following treatment withdrawal Latest recorded return of circulatory function following abandonned CPR Complete loss of brain function; isoelectric EEG Limit for successful restoration of normal cerebral function in laboratory animals Limit for successful restoration of any brain activity Limit for successful restoration of cardiac activity (e.g. after transplantation) hours 60 min 15 sec 11 min 65 sec 7 min Fig. 17.11.2 Dynamic relationships between loss of circulatory and brain function (not to scale). Laboratory evidence suggests that full neurological function may be restored in experimental animals after up to 11 minutes of continuous normothermic circulatory arrest. However, it is not clear how this relates to clinical circumstances, particularly those where anoxia is superimposed upon pre-existing brain injury.

 direct link between loss of circulatory function and the emergence of the essential features of death. The diagnosis of death by neurological criteria Although circulatory collapse usually precedes failure of cere- bral perfusion and loss of brain function, it has been known for many years that this pathophysiological sequence may be reversed when death is the result of acute intracranial pathology. While emergency ventilatory support may prevent the progres- sion from brain-stem ischaemia to hypoxic cardiac arrest, the patient may nevertheless still display the essential features of death, namely the permanent loss of the capacity for consciousness and respiration (Fig. 17.11.3). The emergence of this state, popularly referred to as brain death, is an inevitable consequence of the development of mechanical ventilation and related critical care services. Most countries have well defined and professionally accepted schedules for the diagnosis of death using neurological criteria. There are variations in both how the diagnosis is required to be made, and also the state they seek to confirm. Thus, while the sched- ules for some countries seek to establish a state of ‘whole brain’ death (e.g. Australia, United States, mainland Europe), other criteria are based upon the view that permanent loss of function of the brain- stem is sufficient to indicate death (e.g. United Kingdom, Canada). Regardless of these differences, there are more similarities than dif- ferences between these various protocols. Although clinicians must always take a cautious approach to the neurological determination of death, particularly when excluding reversible causes of coma and Table 17.11.1 Key elements to the time-critical diagnosis of death using circulatory criteria Decision not to attempt resuscitation The clinical circumstances may be such that the decision not to attempt or continue resuscitation is straightforward. However, caution should be exhibited in the

presence of potentially reversible systemic causes of cardiorespiratory arrest such as hypothermia, severe biochemical abnormalities, and so on. Reliable identification of circulatory arrest Aystole is the absence of mechanical cardiac function, not electrical activity. When clinicians are seeking to confirm death as expeditiously as possible, asystole is best identified by echocardiography or intra-arterial pressure monitoring rather than by continuous ECG monitoring. Digital palpation of a central pulse is unreliable in such circumstances. Minimum period of observation to confirm continuous asystole, apnoea, and unconsciousness Brain function is lost within seconds of asystole. Providing that resuscitation is not being considered, the permanence of this state is determined by the possibility of spontaneous return of the circulation having passed. If asystole follows withdrawal of life-sustaining therapies in an ICU this period may be as short as 65 seconds, although in practice protocols require a somewhat longer period of observation. This ranges from 2 minutes in some institutions in Australia and the United States, 5 minutes in Canada and the United Kingdom, and 20 minutes in Italy. Should there be any return of circulatory or respiratory function during this period of observation then the period should be halted and re-started only when asystole returns. Demonstration of the lack of capacity for consciousness and respiration It is mandatory for the period of observation to be followed by a formal neurological examination that confirms unconsciousness and loss of brain-stem function. In addition to observing continuous apnoea, the UK Code of Practice also requires the demonstration of absent papillary response to light, absent corneal reflex, and absent motor response to supraorbital pressure. Prohibition of post-mortem interventions that might restore cerebral perfusion Any intervention that might re-establish cerebral perfusion would invalidate the diagnosis of death while the brain would remain responsive to its restoration. ECG, electrocardiogram; EEG, electroencephalogram. Myocardial infarction absent pulse & heart sounds absent pulse & heart sounds fixed & dilated pupils; coma fixed & dilated pupils; coma fixed & dilated pupils; coma absent breath sounds absent breath sounds Cardiovascular collapse Brain(stem) ischaemia Brain(stem) ischaemia Brain(stem) ischaemia Respiratory arrest Respiratory arrest Respiratory arrest Cardiac arrest Cardiac arrest Death determined using circulatory criteria Death determined using neurological criteria Intracranial catastrophe Intracranial catastrophe Fig. 17.11.3 Death determined using neurological criteria. Death from a massive acute coronary syndrome is the result of circulatory collapse that leads to brain failure. In comparison, an untreated and rapidly progressive intracranial pathology causes apnoea and unconsciousness through direct compression of the brain-stem, with hypoxic cardiac arrest and circulatory collapse being secondary to this. Although interruption of the later process may halt the progression from brain-stem ischaemia to cardiac arrest, the essential features of death—permanent loss of the capacity to breathe and the capacity for consciousness—may nevertheless emerge. What results is a patient who displays the essential features of death but who has a persistent circulation while ventilatory support is maintained.

 apnoea, the clinical literature confirms the neurological standard for the determination of death to be safe. The key stages for the diag- nosis of death using neurological criteria are shown in Table 17.11.2, and the causes of brain-stem death in Table 17.11.3. Deceased organ donation Organ transplantation saves and transforms lives and, for kidney transplantation at least, represents the most cost effective treatment for end-stage organ failure. Although living donation programmes make important contributions to kidney and liver transplantation, deceased donation remains the mainstay of many transplantation programmes. The ‘standard’ model for deceased donation in many countries is donation after brain death (DBD). However, improved road safety and more effective treatments for subarachnoid

haemorrhage, is- chaemic stroke, and traumatic brain injury are reducing the pool of potential DBD donors. As a result, many countries are now turning to donation after circulatory death (DCD) to increase donor num- bers and improve access to transplantation. Details of the various types of deceased donation are given in Table 17.11.4. The healthcare services of nearly 100 countries around the world support organ transplantation, although rates of deceased dona- tion vary widely (Fig. 17.11.4). The World Health Organization has called upon all such countries to work towards self-sufficiency in organ transplantation. Key to self-sufficiency is not only public support for donation (which is reflected in a country's consent rate), but also a systematic approach to the identification and re- ferral of potential donors whenever and wherever organ retrieval is a possibility. These hospital processes need to be supported by ad- equate education and training, audit and governance, and operate within nationally agreed frameworks of practice. Such an approach has recently resulted in a 63% increase in deceased donation in the United Kingdom, with a corresponding increase in transplant- ation and reduction in transplant waiting lists (Fig. 17.11.5). It is noteworthy that this was achieved without any increase in family consent rates. Table 17.11.2 The four key stages for the diagnosis of death using neurological criteria (based upon the UK Code for the diagnosis and confirmation of death using neurological criteria)

1. Satisfying essential preconditions Patients must: • be deeply unconscious (Glasgow Coma Score 3), mechanically ventilated and exhibit no sign of brain-stem reflex activity, including respiration. • have suffered a structural brain injury that is irremediable and a recognized cause of brain-stem death. This stage is designed to identify patients who should be considered to be possibly brain-stem dead.
2. Exclusion of reversible causes of coma and apnoea This stage is designed to exclude potentially reversible causes/contributions to coma and apnoea, including: • cardiorespiratory instability • hypothermia • profound endocrine, biochemical, and metabolic disorders • sedative drugs and muscle relaxants • high cervical spinal cord injury
3. Clinical demonstration of the absence of brain-stem function a. Brain-stem reflexes b. Apnoea test a. The following reflexes are examined: • pupillary light reflex • corneal reflex • peripheral and central response to deep supraorbital pressure • vestibulo-ocular reflex • gag reflex • tracheal reflex b. apnoea test The patient is disconnected from the mechanical ventilator and observed continuously for signs of respiratory effort. The period of observation should be a minimum of 5 minutes, during which time a respiratory acidosis sufficient to stimulate respiration should be confirmed.
4. Ancillary/confirmatory tests A variety of additional investigations are used around the world to consolidate the clinical diagnosis. They include assessments of cerebral function such as EEG and evoked potentials and measurements of cerebral perfusion and blood flow such as transcranial Doppler, radio-isotope perfusion scanning, and cerebral angiography. Although mandatory in some countries, they are only used in the United Kingdom when the clinical diagnosis is in doubt. Additional notes: The UK Code requires the tests to be performed by two experienced doctors, one of whom must be a Consultant. The tests can only be performed when the clinicians are satisfied that the various conditions in stages 1 and 2 have been met. Although two sets of tests must be completed, the time of death is that of completion of the first set of tests. Table 17.11.3 Common causes of brain-stem death in the United Kingdom, 2014–2015: note that trauma as a cause of brain-stem death has more than halved in the last two decades Cause of

death Incidence (%) Spontaneous intracranial haemorrhage 54.0 Hypoxic ischaemic encephalopathy 24.7 Ischaemic cerebrovascular accident 6.1 Trauma 6.2 Meningitis 2.4 Brain tumour 1.5 Other 5.1

Section 17 Critical care medicine 3922 Spain Croatia Malta Belgium Portugal USA France Austria Estonia Slovenia Italy Norway UK Czech Rep. Ireland Uruguay Belarus Finland Latvia Australia Lithuania Sweden Canada Hungary Poland Netherlands Luxembourg switzerland Argentina Brazil Iceland Slovak Rep. Germany Denmark Israel Iran South Korea New Zealand Cyprus Colombia Romania Chile Panama Hong Kong Greece Turkey Costa Rica Ecuador Paraguay Venezuela Mexico Kuwait Peru Bulgaria Russia Saudi Arabia Trinidad & Tob. Lebanon Dom. Rep. Japan Malaysia 0 5 10 15 20 Donors per million population, 2013 25 30 35 40 Fig. 17.11.4 Worldwide rates of deceased donation, 2013 (expressed as donors per million population).

17.11 Diagnosis of death and organ donation 3923 Table 17.11.4 Models of deceased donation Type Description Notes Donation after brain death (DBD) Organ retrieval from patients whose death is confirmed using neurological criteria. Donation is considered after death has been confirmed. • Established form of donation in many countries. • Supports the retrieval of kidneys, liver, small bowel, pancreas, heart and lung, as well as composite allografts such as facial tissue and limbs. • Physiological optimization of the heart beating donor after the diagnosis of death may increase both the number and quality of organs that are retrieved. • Minimal warm ischaemic injury to transplantable organs because the circulation is maintained during organ retrieval until the point of cold perfusion. • Pool of potential DBD donors is decreasing in many countries. Donation after circulatory death (DCD)—controlled Organ retreival from patients whose death follows planned withdrawal of ‘futile’ life- sustaining treatments in an ICU. Donation considered after the decision to withdraw life-sustaining treatments but before death is confirmed using circulatory criteria. • Extends the option of donation to another group of dying patients but has important implications for their end-of-life care. • Organ retrieval must begin within minutes of the onset of irreversible asystole. • Retrieval teams may be ‘stood down’ if the patient does not die within a predetermined time after treatment withdrawal (typically 1–4 hours). • Although it is possible to successfully transplant both abdominal and cardiothoracic organs from controlled DCD donors, worries over warm ischaemic injury limit the number of organs that are retrieved. • Long-term outcomes for DCD kidney grafts match those from DBD donors, although there is a higher incidence of delayed graft function. Outcomes for DCD liver grafts are inferior, but nevertheless superior to remaining on a transplant waiting list. • Controlled DCD is well established in Australia, Belgium, Canada, the Netherlands, United States, and the United Kingdom. There may be professional, ethical, and legal obstacles to introducing this type of donation in other countries. Donation after circulatory death—uncontrolled Organ retrieval from patients whose death follows an unexpected circulatory arrest. Donation is considered after death has been confirmed using circulatory criteria. • Donation from Emergency Medicine Departments rather than an ICU. • Cardiopulmonary resuscitation is used to maintain perfusion of the transplantable organs until they are perfused with cooled preservation solution of oxygenated blood using aortic and caval cannuale introduced via the femoral vessels. • Supports kidney and liver transplantation. • Established in parts of mainland Europe and United States. Number 2396 2003–04 2004–05 2005–06 2006–07 2007–08 2008–09 2009–10 2010–11 2011–12 2012–13 2013–14 770 751 764 793 809 899 959 1010 1088 1212 1320 2241 2196 2385 2381 2552 2645 2695 2912 3112 3514 8000 7000 6000 5000 4000 3000 2000 1000 0 5673 6142 6698 7219 7655 7877 7800 7636 7288

7026 7997 Donors Transplants Transplant list Fig. 17.11.5 Deceased donors, organ transplants, and transplant waiting list in the United Kingdom, 2003–2014. It is noteworthy that the increase in donor numbers from 2007 to 2008 onwards were achieved without any increase in the family consent rates for donation and were the result of improved rates of donor identification and referral and expansion of DCD transplant programmes.

Section 17 Critical care medicine 3924 FURTHER READING Academy of Medical Royal Colleges (2008). A code of practice for the diagnosis and confirmation of death. Academy of Medical Royal Colleges, London. Pallis C, Harley DH (1996). ABC of brainstem death. BMJ Publishing Group, London. The President’s Council on Bioethics (2008). Controversies in the Determination of Death: A White Paper by the President’s Council on Bioethics. Washington D.C. https://bioethicsarchive.georgetown. edu/pcbe/reports/death/ Thompson JP, Murphy PG, Bodenham AR (ed) (2012). Diagnosis of death and organ donation. Br J Anaesth, 108, i1–i2.

17.12 Persistent problems and recovery after criti

17.12 Persistent problems and recovery after critical illness 3925 Mark E. Mikkelsen and Theodore J. Iwashyna

ESSENTIALS Post-intensive care syndrome is defined as new or worsening impair- ment in cognition, mental health, or physical function that persists after a critical illness. The complexities of post-intensive care syn- drome come from the interactions of the patient's premorbid mental health and physical function, the acute physiologic derangements and acute organ injury of the critical illness, and the side effects of procedures, treatments, and potential complications incurred during the critical illness. Problems are better described as challenging syndromes rather than specific actionable diagnoses, with the four major functional problems for patients being weakness, cognitive impairment, psychological problems, and new or worsened organ dysfunction. The sequelae of critical illness often extend beyond pa- tients and impact the families of critically ill patients. The clinical approach to post-intensive care syndrome includes preventive strategies during the critical illness and a standardized ap- proach to patients recovering from critical illness. Clinicians should be encouraged to engage the family in care and decision-making to mitigate the risk of psychological distress for the patient and family. The intensive care unit diary is an established means to reduce psy- chological distress in survivors and family members. Repeated and ongoing physical therapy may serve to both prevent deconditioning and to develop compensatory strategies for weakness that may have developed. Post-intensive care syndrome (PICS) Most patients cared for in intensive care units (ICUs) survive that hospitalization. As a result an increasing number of patients are surviving critical illness but suffering a

constellation of problems previously unrecognized or uncommon in general medical care. While many survivors will flourish after a critical illness, many ex- perience neuropsychological and physical function impairments that impact their long-term health, ability to return to work, and quality of life. The residual health effects of critical illness have been termed post-intensive care syndrome (PICS). Definition and conceptual overview Post-intensive care syndrome is defined as new or worsening im- pairment in cognition, mental health, or physical function that persists after a critical illness. Memory and executive function are the cognitive domains most likely to be impaired; anxiety, depres- sion, and post-traumatic stress disorder are common psychiatric symptoms. ICU-acquired weakness, also common after critical illness, can be due to myopathy, neuropathy, or a combination of the two, termed critical-illness neuromyopathy. At the same time, it is also common for patients surviving critical illness to have exacerbations of previously well-controlled chronic illnesses, or new conditions that were either not present or not previously diagnosed. The complexities of post-intensive care syndrome come from the interactions of the following (Fig. 17.12.1): • The patient's premorbid mental health and physical function • The acute physiologic derangements and acute organ injury of the critical illness • The side effects of procedures, treatments, and potential complica- tions incurred during the critical illness These lead to four major functional problems: weakness, cognitive impairment, psychological problems, and new or worsened organ dysfunction. These functional problems can lead to disability, in- ability to return to social roles or prior employment, high recurring healthcare needs, and substantial burdens on caregivers, culmin- ating in an increased risk of death that may persist for years after the apparent resolution of critical illness. Epidemiology and specific manifestations The risk factors associated with these impairments are multiple, complex, and (at present) incompletely understood. Factors thought to contribute include critical illness-associated inflammation and ischaemia, hypotension, hypoxaemia, and hypoglycaemia, and con- sequences of the acute illness and treatments received (e.g. immobil- ization and delirium due, in part, to the use of sedative medications and mechanical ventilation) (Fig. 17.12.1). 17.12 Persistent problems and recovery after critical illness Mark E. Mikkelsen and Theodore J. Iwashyna

 While some acute intensive care unit experiences are associated with an increased prevalence of subsequent problems, causal rela- tionships have not been proven. For example, the presence of de- lirium, a common development in the ICU, does not predict poor long-term outcomes with sufficient accuracy for prognostication in individual patients although there is a strong association at the population level. Equally true, the absence of specific problems in the ICU or immediately afterwards does not exclude the possibility of a patient experiencing post-ICU sequelae. The frequency of reported cognitive, mental health, and func- tional impairments vary by study population and by the timing of assessments in relation to intensive care unit and hospital discharge (Table 17.12.1). At three months, 40% of survivors of shock or re- spiratory failure have cognitive impairment consistent with that present in patients three months after moderate traumatic brain injury, 37% experience symptoms of mild depression or worse, and 32% have disabilities that limit basic activities of daily living. Symptoms of anxiety and post-traumatic stress disorder after critical illness are similarly common. While the definition of post-intensive care syndrome focuses on neuropsychological and physical function, the effects of a crit- ical illness extend beyond these domains. Sexual dysfunction, nu- tritional deficiencies, loss of muscle mass, joint contractures, and scarring all occur after critical illness. Collectively, these changes contribute to the lower quality of life observed in survivors of crit- ical illness. Impairments in these domains frequently coexist, and im- pairment in one domain can exacerbate impairment in

another Fig. 17.12.1 Interactions in the critically ill patient leading to adverse long-term outcomes. Pathways to functional impairments and disability are hypothesized but not yet fully described. Inspired by Creditor, M. C. (1993). ‘Hazards of hospitalization of the elderly.’ Ann Intern Med, 118(3): 219–223. Table 17.12.1 The relationship between morbidity after critical illness and timing of assessments ICU discharge Hospital discharge 3 months post-discharge 12 months post-discharge Cognitive Impairment 84% 46–64% 40% 34% Anxiety 24% Depression 37% 28–33% Post-traumatic stress disorder 22% Functional impairment (activities of daily living) 32% 27% Contracture, functionally significant 34% 23% Sexual dysfunction 44%

17.12 Persistent problems and recovery 3927 (e.g. cognitive impairment may undermine coping strategies and exacerbate pre-existing or new psychiatric disorders) or re- sult in new impairment (e.g. post-discharge depression predicts incident physical impairment). PICS-Family Unfortunately, the sequelae of critical illness often extend beyond pa- tients and impact the families of critically ill patients. Termed ‘PICS- Family’ (PICS-F), family members of both surviving and deceased critically ill patients frequently experience psychological distress, including anxiety, depression, complicated grief, and post-traumatic stress disorder, in addition to sleep disorders and panic attacks. As a result, family members may experience a reduced quality of life and reduced ability to care for and support the recovering patients. Risk factors associated with psychological distress include suffering the loss of a loved one, playing an active role as a surrogate decision- maker, ineffective communication from medical and nursing staff during the acute episode, and avoidant coping strategies during the acute events and afterwards. These effects can endure for months or years. Recovery after critical illness Post-intensive care syndrome is a useful construct to conceptualize the impairments that survivors of critical illness may experience, yet it is incomplete as a guide to caring for individual patients. In par- ticular, the concept of PICS may emphasize new problems caused by the critical illness. Yet, whether impairment is attributable to critical illness or not is less important than the degree and duration of impairment experienced by the patient. Further, patients often do not experience post-intensive care syndrome as a fixed burden. Instead, it is a dynamic process of physiologic repair, ongoing med- ical needs, personal rehabilitation efforts, and psychological, social, and pragmatic adaptation to these changes. Current evidence sug- gests that this process is most dynamic during the first 3–6 months after critical illness, although problems may persist for years. This is especially true if intercurrent illnesses stall recovery or precipitate further decline. In the 90 days following critical illness, survivors are com- monly re-admitted to hospital. As many as one in four of these re- admissions require intensive care unit admission. Patients who have survived sepsis appear to be a particularly vulnerable population at high-risk for re-admission to hospital. Two observations have been made about these hospital re-admissions. First, while many hos- pital re-admissions are for new or recrudescent infections, a large number (either a substantial minority or clear majority, depending on the study) are for problems that do not appear immediately re- lated to the cause of the patient’s initial intensive care unit stay. Second, many hospital re-admissions are for problems which, if an- ticipated, may be averted by appropriate primary care in the early post-hospitalization period; examples include congestive heart failure, acute renal failure, and aspiration pneumonitis. Clinical approach The clinical approach to post-intensive care syndrome includes pre- ventive strategies during the critical illness and a standardized ap- proach to patients recovering from critical illness. Whether encountering a patient after critical illness in an acute care hospital, a post-acute care facility, or in the outpatient setting, a standardized approach should be used to examine the patient’s experiences and assess functional impairments. At present, there are few proven therapies for specific post-ICU syndromes.

Instead, practitioners should focus on recognizing conditions that exist and applying good clinical practice developed outside of the post-ICU setting. There are some strategies that can be recommended as pre- ventive strategies, and others that use a targeted diagnostic approach to patients with potential post-intensive care syndrome complaints. Preventive strategies Strategies to prevent the development of post-intensive care syndrome should begin in the intensive care unit. Evidence-based strategies to decrease the duration of mechanical ventilation and ICU length of stay, duration of delirium, and increase functional independence are incorporated in the 'ABCDE' Bundle. The ABCDE bundle includes strategies to coordinate sedation and ventilator practices to achieve earlier liberation from mechanical ventilation, delirium assessment and management, and early ambulation to promote physical recovery. The ICU Diary, a detailed account of events that occur in the ICU which are documented by both staff and family, is a strategy begun in the ICU and reviewed with the patient and family as an outpatient. It is an established means to reduce psychological distress in sur- vivors and family members who may have limited or confused recall of events during the ICU stay. In conjunction with the review of the ICU Diary as an outpatient, clinicians should take the time to educate patients and caregivers about post-intensive care syndrome as they assess the patient and caregivers for symptoms consistent with this syndrome. To mitigate the risk of psychological distress for the patient and family, clinicians should engage the family in care and decision- making in the ICU and thereafter. Early and effective communica- tion, within the first 48–72 hours of the ICU stay, is recommended, in partnership with open visitation policies and the use of patient- and family-centred ward rounds. Priorities following discharge include assessment for post-intensive care syndrome, coupled with education to provide patients and care- givers with relevant information. There is currently active research on several possible strategies to facilitate recovery and prevent post- intensive care syndrome. Repeated and ongoing physical therapy has strong face validity and plausibility, and may serve to both prevent deconditioning and—as in the pulmonary rehabilitation model used in COPD—to develop compensatory strategies for weakness that may have developed. Several groups are exploring whether psychological or cognitive rehabilitation strategies are beneficial, but the effective- ness of these strategies has not yet been proven. Early and intensive primary care access and close monitoring might be of benefit to accel- erate recovery and prevent recurrent illness. Finally, there is growing interest in (but little evaluation of) the role of peer support groups for patients and families in improving recovery. In some cases, this preventive care will be delivered in post-ICU follow-up clinics. Post-ICU follow-up clinics are an established prac- tice in the United Kingdom and an emerging option within the United States, especially after stroke, trauma, or neonatal care. Yet, there is currently no consensus on their effectiveness or optimal structure.

Section 17 Critical care medicine 3928 Medication reconciliation after the ICU While there is nothing specific to medication reconciliation after in- tensive care unit treatment, it is clear that many medications are in- appropriately stopped and started there. Population-based research in Ontario suggested that HMG-CoA reductase inhibitors (statins), antiplatelet agents, anticoagulants, and thyroxine were frequently discontinued inappropriately after hospital admissions that included an ICU stay. Conversely, medications that may be reasonable for short-term treatment in the intensive care unit may be inappropri- ately continued after discharge; attention to the potential effects of medications on cognitive health is warranted. Offenders in one or both of these categories may include antipsychotics (used to prevent or treat delirium in the ICU), short-acting antihypertensives (used during transient hypertensive urgencies), proton pump inhibitors (used for stress ulcer prophylaxis), opioids and benzodiazepines (used for procedural pain, sedation, or

unclear indications in the ICU). Clinicians should be aware that, due to insomnia and psychi- atric symptoms, psychiatric medications are prescribed in up to 20% of patients in the year after a critical illness; the appropriateness of this is unclear. Colourful stories are often told of patients who resume taking one full set of medications they were prescribed before the in- tensive care unit, and an entire second set of medications with which they were discharged: many duplicative, some unnecessary, others contraindicated. Diagnostic approach A comprehensive clinical evaluation after ICU treatment should re- view the details of the recent critical illness and intervening events, including locations of care post-discharge, in addition to conducting a physical examination. Based on the unique challenges faced by survivors of critical illness and the prevalence of neuropsychological and physical impairments, additional elements of the history and physical examination should be included as an initial screening strategy (see Table 17.12.2). A structured approach that ties together a health narrative precritical illness to the present state post-critical illness can be used to identify new and unmasked health needs Clinical investigations Neuropsychological assessment Because informal assessments of neuropsychological problems are known to have low sensitivity, survivors of critical illness should be screened for cognitive impairment and mental health disorders, including depression, anxiety, and post-traumatic stress disorder. Several simple, validated screening tests are avail- able for use (Table 17.12.3). Formal neuropsychological assess- ment by a trained neuropsychologist may be useful to further characterize the type and severity of impairment in those who screen positive or are experiencing symptoms. The effectiveness of neurocognitive rehabilitation has not been fully studied after critical illness. However, given its utility in other disease states (e.g. traumatic brain injury), early referral to an interested prac- titioner is reasonable. Those identified to have significant psy- chiatric symptoms should be considered for referral to a mental health expert, in addition to consideration of prescribing psychi- atric medications. Functional assessment Assessment of activities of daily living should be performed to assess for functional disability, which may guide referral to phys- ical or occupational therapists to develop compensatory strat- egies or assistive devices. In addition, the ‘Timed Get Up and Go’ test in which the patient is asked to stand up from a seated position, walk 3 metres, and return back to the seated position is a simple test to assess for functional status problems patients may not self-report. Lung function In survivors who experienced acute respiratory failure, and acute respiratory distress syndrome (ARDS) in particular, lung function Table 17.12.2 A targeted approach to the history and physical examination after critical illness, accounting for health pre- and post-critical illness Critical illness history Physical examination Acute event Complications, including detailed review of acute infections during the hospitalization Focused assessment for: Mobility Joint contractures Body composition Post-procedural scars Medication reconciliation, including antibiotics, psychiatric prescriptions, and sleeping aid prescriptions Post-illness review of symptoms, including constitutional (fatigue, weight change, pain), cognition (memory, ability to think clearly), anxiety, depression, post-traumatic stress disorder, insomnia, sensory changes (hearing, taste, vision), cardiopulmonary (dyspnoea, cough), musculoskeletal changes (loss of strength, mobility) Dependent on screening, post-illness functional assessment, including neuropsychological assessment, physical function, lung function, sexual function, nutritional, and sleep hygiene assessment Recovery history post-discharge, including locations of care and present support structure Table 17.12.3 Suggested strategies for assessments post-critical illness Domain assessment Instrument Cognitive function Modified Mini-Mental State Montreal Cognitive Assessment Mental health Hospital Anxiety and Depression Scale Post-traumatic stress syndrome 10-questions inventory (PTSS-10) Functional assessment Activities of daily living Instrumental activities of daily living Timed Get Up and Go

Testa Lung function Pulmonary function tests, in those with symptoms or clinical history suggestive of lung dysfunction Ancillary tests (imaging, laboratory testing) Neither routine imaging or laboratory testing are recommended in general; assessments for those recovering from an infection are recommended to ensure resolution and for secondary prevention a In this test, patients are asked to stand up from a seated position, walk 3 metres, and return back to the seated position. A normal time to accomplish the task is 10 seconds or less in healthy elders and longer times are associated with increased fall risk.

17.12 Persistent problems and recovery 3929 may be impaired after critical illness, although it is normalized sur- prisingly often. Symptom-directed testing is appropriate. Imaging Routine imaging after critical illness is not recommended. Rather, ancillary testing, including more advanced imaging such as com- puted tomography or magnetic resonance imaging, should be re- served for those with clinical symptoms and signs and based on established, routine health screening recommendations. Ancillary tests There is no formal recommendation to obtain specific labora- tory testing after critical illness. Rather, laboratory testing should be obtained based on routine health maintenance and screening recommendations. In general, clinicians should be aware that an- aemia is common after critical illness and testing should be reserved to examine resolution of acute organ dysfunction or as needed for safety monitoring. Early treatment to avoid re-admission to hospital As noted above, re-admission to hospital for infection as well as other ambulatory-care sensitive conditions is common in the 90- days after discharge, and it may be beneficial to ensure rapid access and lower treatment thresholds for such conditions. Compensation and rehabilitation strategies for identified problems Clinicians should prioritize timely referral to ancillary services based on the patient’s symptoms and testing. While the benefits of strategies to improve outcome of post-intensive care syndrome have not been proven, experts in cognitive and functional impairments can provide strategies to compensate for these impairments. While no post-intensive care syndrome-specific therapies yet exist, pru- dent generalization from experience with other conditions may pro- vide symptomatic relief and improved function. Further, in terms of health trajectory, vigilance is required to ensure that acute condi- tions resolve and new symptoms and conditions are identified and managed in a timely and effective manner. Given the complexity of care after critical illness, communica- tion among care providers is of the utmost importance to help the patient navigate their post-critical illness course. While the most effective strategy remains unclear, identifying an accessible point- person to oversee the coordination of care required after critical illness should be a priority. The number of services and related clin- icians that may needed in the care of patients after critical illness can be substantial (see Table 17.12.4). As a result, communication and coordination from hospital discharge to the outpatient setting is essential. As many survivors of critical illness will be disabled, there are plausible benefits to engaging the patient’s support net- work (family and friends) in the process. At the centre of these communications lies the patient, and while the focus shifts towards rehabilitation and recovery in many, palliative and hospice care may be reasonable considerations for others based on their symp- toms and care preferences. Conclusion The success of critical care medicine in preventing death has led to substantial new challenges for clinicians throughout the healthcare system. Patient who might once have died in the intensive care unit or subsequently in hospital are surviving, often (but not always) with enduring problems—and problems better described as chal- lenging syndromes rather than specific actionable diagnoses. New approaches to diagnosis, classification, treatment, and symptom management are emerging, offering more hope for affected patients. FURTHER READING Davidson JE, Jones C, Bienvenu J (2012). Family response to critical

illness: postintensive care syndrome-family. Crit Care Med, 40, 618–24. Garrouste-Orgeas M, et al. (2012). Impact of an intensive care unit diary on psychological distress in patients and relatives. Crit Care Med, 40, 2033–40. Hua M, et al. (2015). Early and late unplanned hospital readmissions for survivors of critical illness. Crit Care Med, 43, 430–8. Iwashyna TJ, et al. (2010). Long-term cognitive impairment and func- tional disability among survivors of severe sepsis. JAMA, 304, 1787–94. Mehlhorn J, et al. (2014). Rehabilitation interventions for postintensive care syndrome: a systematic review. Crit Care Med, 42, 1263–71. Needham DM, et al. (2012). Improving long-term outcomes after dis- charge from intensive care unit: report from a stakeholders' confer- ence. Crit Care Med, 40, 502–9. Pandharipande P, et al. (2010). Liberation and animation for ventilated ICU patients: the ABCDE bundle for the back-end of critical care. Crit Care, 14, 157. Pandharipande PP, et al. (2013). Long-term cognitive impairment after critical illness. N Engl J Med, 369, 1306–16. Prescott HC, Angus DC (2018). Enhancing recovery from sepsis: a re- view. JAMA, 319, 62–75. Prescott HC, Langa KM, Iwashyna TJ (2015). Readmission diagnoses after hospitalization for severe sepsis and other acute medical condi- tions. JAMA, 313, 1055–7. Table 17.12.4 Potential services and expertise required in the care of the recovering critically ill patient Acute care Post-acute care Outpatient Physical and occupational therapy Acute rehabilitation Physical and occupational therapy Nutrition consultation Home with home
health services Nutrition consultation Respiratory therapy Skilled care facility Mental health services, including grief counselling for family members Case manager to facilitate post-acute care needs Long-term acute care hospital Neuropsychology consultation Palliative care for symptom management Hospice care Palliative care for symptom management and/or hospice care Surgery consultations Support groups

17.2 Cardiac arrest 3839

Gavin D. Perkins, Jasmeet

17.2 Cardiac arrest 3839

Gavin D. Perkins, Jasmeet Soar, Jerry P. Nolan, and David A. Gabbott

ESSENTIALS Cardiovascular disease is the most common cause of sudden cardiac arrest, which causes over 60% of adult coronary heart disease deaths. Most cardiac arrests are preventable. Survival depends on early recognition and

prompt initiation of chest compressions and ventilations (cardiopulmonary resuscita- tion), and early defibrillation if appropriate. High-quality cardiopulmonary resuscitation is defined by com- pressions to a depth of 5–6 cm, at a rate of 100–120 per minute, full release of pressure between compressions and minimal interrup- tions to chest compression. The compression to ventilation ratio is 30:2 if the airway is not protected. Give continuous chest compressions with no pause for

ventilations once the trachea is intubated or an appropriate supraglottic airway has been inserted. Treat shockable cardiac arrest rhythms (ventricular fibrillation/ pulseless ventricular tachycardia) with attempted defibrillation. In ventricular fibrillation refractory to defibrillation attempts, iden- tify and treat reversible causes. Treat nonshockable rhythms (asys- tole and pulseless electrical activity) by identifying and treating the underlying cause. Drugs have a limited role in treating cardiac

arrest. If initial resuscitation is successful the quality of post-resuscitation care determines the patient’s final outcome. In patients who are co- matose after cardiac arrest, outcome may be improved by inter- ventions such as primary percutaneous coronary intervention in patients with ST elevation in the post-arrest 12-lead electrocar- diogram, targeted temperature management, and multimodal prognostication. Use emergency care treatment plans to record in advance, re-commendations for emergency

treatments, including CPR. Introduction Survival from cardiac arrest depends on a sequence of interventions— the Chain of Survival (Fig. 17.2.1)—all four links in the chain must be strong: • early recognition and call for help • early cardiopulmonary resuscitation (CPR) • early defibrillation • post-resuscitation care Historical perspective Current cardiopulmonary resuscitation techniques were first de- scribed relatively recently: the first report of external defibrillation was in

1956, mouth-to-mouth ventilation in 1958, and chest com- pressions in 1960. Epidemiology Sudden cardiac arrest causes over 60% of adult coronary heart dis- ease deaths. In the United Kingdom the annual incidence of ambu- lance service treated out-of-hospital cardiac arrests for all rhythms is 52 per 100 000. The presenting cardiac arrest rhythm is shockable (ventricular fibrillation or pulseless ventricular tachycardia [VF/ pVT]) in about a quarter of patients, 25–30% of whom survive to hospital discharge. The remainder

of cases are nonshockable—asystole in about 50% and pulseless electrical activity (PEA) in about 25% of cases—and have much poorer survival (less than 5%). The incidence of in-hospital cardiac arrest is difficult to assess be- cause it is influenced by factors such as the criteria for hospital ad- mission and implementation of do-not-attempt-cardiopulmonary resuscitation (DNACPR) decisions. UK National Cardiac Arrest 17.2 Cardiac arrest Gavin D. Perkins, Jasmeet Soar, Jerry P. Nolan, and David A.

Gabbott E a r l y r e c o g n i t i o n a n d c a l l f o r h e l p

t o p r e v e n t c a r d i a c a r r e s t E a r l y C P R

t o b u y t i m e E a r l y d e f i b r i l l a t i o n

t o r e s t a r t t h e h e a r t P o s t-r e s u s c i t a t i o n c a r e

t o r e s t o r e q u a li t y o f l i f e Fig. 17.2.1 Chain of survival.

Section 17 Critical care medicine 3840 Audit data from 2011 to 2013 for arrests attended by the hospital resuscitation team showed an overall incidence of adult in-hospital cardiac arrest of 160 per 100 000 hospital admissions. The presenting rhythm was VF/pVT in 16.9% and nonshockable in 72.3% of cases. Survival to hospital discharge associated with these rhythms was 49.0% and 10.5%, respectively, but varied substantially between hospitals. Prevention Out-of-hospital, most sudden cardiac death (SCD) victims have cor- onary artery disease, and have a history of heart disease and warning symptoms, most commonly chest pain, in the hour before cardiac arrest. Calling an ambulance early after the onset of symptoms can improve survival. Other causes of sudden cardiac death are com- moner in adults younger than 35 years and children, and include cardiomyopathies, valve disease, inherited ion channel disorders, and congenital heart disease. Symptoms and signs include syncope (in the supine position, or without prodrome, or during exercise), chest pain, palpitation, and heart murmur. Those at risk of sudden cardiac death, or are family members of victims of sudden cardiac death, should be assessed in a specialist clinic. In-hospital cardiac arrests are usually not sudden or unpredict- able: in up to 80% there is deterioration in clinical signs during the preceding few hours. Hypoxaemia and hypotension are often unnoticed, or are detected but not treated appropriately. The car- diac arrest rhythm is

usually pulseless electrical activity or asys- tole and prognosis is poor. Prevention of in-hospital cardiac arrest requires staff education, monitoring of patients, recognition of patient deterioration, a system to call for help, and an effective response. Use of early warning scores, such as the National Early Warning Score (NEWS) in the United Kingdom, based on vital signs can help identify those at risk of deterioration, cardiac ar- rest, or unplanned intensive care unit admission. Earlier recogni- tion also enables proactive decision-making about emergency care treatment plans, including whether CPR should be attempted in the event of cardiac arrest. Cardiopulmonary resuscitation The division between basic life support and advanced life support is arbitrary: the resuscitation process is a continuum. The keys steps are: • cardiorespiratory arrest is recognized immediately; • help is summoned; • CPR is started immediately and, if indicated, defibrillation at- tempted as soon as possible (within 3 minutes of collapse). The sequence of actions and outcome depends on: • Location—out-of-hospital/in-hospital? Witnessed/unwitnessed? Monitored/unmonitored? • Skills of the responders—in public places (e.g. airports, railway stations) access to automated external defibrillators (AEDs) en- ables a bystander to deliver the first shock before an ambulance arrives. Defibrillation within 3–5 minutes of collapse can produce survival rates of 50–70% for shockable rhythms. • Number of responders—single responders must ensure that help is coming. If others are nearby, several actions can be undertaken simultaneously. • Equipment available—AEDs are available in some public places. Hospital staff should have immediate access to resuscitation equipment and drugs. General practitioners and dental practi- tioners should have an automated external defibrillator on their premises. • Response system to cardiac arrest and medical emergencies— outside hospital, call for an ambulance. In hospital, the resus- citation team can be a traditional cardiac arrest team (called when cardiac arrest is recognized). Alternatively, hospitals can have strategies to recognize patients at risk of cardiac arrest and summon a team (e.g. medical emergency team, rapid response team, or critical care outreach team) before cardiac arrest occurs. Risks to the rescuer There are very few reports of harm to rescuers from doing CPR. The personal safety of rescuers is the first priority during any re- suscitation attempt. Check that the patient’s surroundings are safe. Put on gloves as soon as possible, and use other personal protective equipment (PPE) (e.g. eye protection, face masks, aprons, gowns) when the patient has a serious infection such as tuberculosis. Follow local infection control measures to minimize risks. Barrier devices decrease transmission of bacteria during mouth-to-mouth rescue breathing in controlled laboratory set- tings, but their effectiveness in actual CPR is unknown. Be careful with sharps, and use safe techniques for moving victims during resuscitation. Starting CPR CPR should be started as shown in Box 17.2.1. Cardiopulmonary resuscitation—mechanism of action Chest compressions create blood flow by increasing intrathoracic pressure and compressing the heart directly. However, perfusion of the brain and myocardium is at best 25% of normal. High-quality CPR leads to better outcomes and is defined by compressing the chest 5–6 cm at a rate of 100–120 compressions a minute and en- suring full release of pressure between compressions. Minimize interruptions in chest compressions to avoid harmful drops in coronary perfusion and systemic blood flow (Fig. 17.2.2). Avoid hyperventilation, which increases intrathoracic pressure and thus reduces coronary perfusion pressure. Ventilate the lungs at 10 breaths a minute. Mechanical chest compression devices can deliver consistent, high-quality CPR, but require a highly trained team to avoid harmful interruptions to CPR during device deployment. Restrict their use to situations where high-quality manual CPR is impos- sible and a trained team is available (e.g. transfer in a moving am- bulance, during cardiac catheterization, as a bridge to starting extracorporeal CPR). Advanced life support The advanced life support (ALS) algorithm enables a standardized approach to cardiac arrest management (Fig. 17.2.3). Once CPR

17.2 Cardiac arrest 3841 has started, assess the patient’s rhythm as soon as possible. Heart rhythms associated with cardiac arrest comprise: • Shockable rhythms—VF/pVT. Ventricular fibrillation is identi- fied by a characteristic pattern of random, disorganized electrical activity on the electrocardiogram (ECG). Pulseless ventricular tachycardia is a broad complex tachycardia with no palpable pulse (or other signs of life). • Nonshockable rhythms—asystole and pulseless electrical activity. Pulseless electrical activity is cardiac electrical activity in the absence of any palpable pulses (or other signs of life). Asystole is the absence of electrical activity (other than electrical activity of <0.2 mV which could represent atrial complexes) for at least 6 seconds. Treatment of shockable rhythms (VF/pVT) Shockable rhythms should be treated as shown in Box 17.2.2. Defibrillation The definitive treatment for VF/pVT is defibrillation. Maintain high- quality CPR while the defibrillator is retrieved, pads applied, and the defibrillator is charged. Defibrillation success can be optimized by delivering high-quality chest compressions with minimal interrup- tions, particularly immediately before and after shock delivery. When used for initial monitoring of a rhythm and shock delivery, both pads and paddles enable quicker delivery of the first shock compared with separate initial attachment of standard ECG elec- trodes. The use of self-adhesive defibrillation pads makes it easier to minimize interruption to chest compressions and are preferred over paddles. Place defibrillation pads or paddles in the standard sternal (to the right of the sternum below the clavicle) and apical (mid- axillary line level with the ECG V6 lead) positions. Alternative posi- tions if the standard position is not possible (or does not terminate VF/pVT) are bi-axillary, or apical-posterior (one electrode over the left precordium and the other posteriorly, and inferior to the left scapula). Transthoracic impedance is minimized by ensuring good contact between pads and skin (shaving excessive chest hair if necessary), orientating the apical pad in a cranio-caudal direction, avoiding placement of the pad on breast tissue, and in a ventilated patient delivering a shock at the end of expiration and avoiding PEEP (posi- tive end-expiratory pressure). The energy levels and configurations of waveforms vary among defibrillators, hence follow the manufacturers’ guidance for energy levels for first and subsequent shocks. If the appropriate energy levels are unknown, for adults use the highest available shock energy for all shocks. Minimize interruptions to CPR during attempted defibrillation by adopting the shock sequence described in Box 17.2.2. Resume chest compressions immediately after a shock. Even if the defib- rillation attempt is successful in restoring a perfusing rhythm, it is rare for a pulse to be palpable immediately after defibrillation. Box 17.2.1 Starting CPR (for healthcare professionals in hospital) Check the patient for a response • If you see a patient collapse or apparently unconscious: — assess responsiveness (shake their shoulders) and seek a verbal response. If the patient does not respond • Alert other members of staff. • With the patient supine, open airway using head tilt and chin lift. • Assess for signs of life such as normal breathing, coughing, movement, and if trained and experienced, palpate for a central pulse. Take no more than 10 seconds to decide if signs of life are present. • Agonal breathing (occasional gasps, slow, laboured, or noisy breathing) is common immediately after cardiac arrest—do not mistake this for a sign of life. In addition, immediately after cardiac arrest the sudden ces- sation of cerebral blood flow can cause an initial short seizure-like epi- sode that can be confused with epilepsy. If the patient has no signs of life, no pulse, or if there is any doubt, start CPR immediately • Get a colleague to call the resuscitation team and collect the resuscita- tion equipment and a defibrillator. • If alone, leave the patient to get help and equipment. • Give 30 chest compressions: • The hand position for chest compression is the middle of the lower half of the sternum • Depth 5–6 cm • Rate 100–120 compressions min–1 • Allow the chest to recoil completely after each compression • After 30 compressions give two ventilations (compression-ventilation ratio = 30:2). • Once chest compressions have started, all

interruptions in compression must be kept to a minimum, of short duration, and tasks for the interrup- tion planned before stopping compressions. • Take the same amount of time for compression and relaxation. • Use whatever equipment is available immediately for airway and ven- tilation. Use a pocket mask (which can be supplemented with an oral airway), a supraglottic airway (e.g. laryngeal mask airway or i-gel) and self-inflating bag, or bag-mask. Attempt tracheal intubation only if trained and competent to do so with minimal interruption (less than 5 seconds) to chest compressions. Use waveform capnography routinely for confirming that a tracheal tube is in the patient's airway and subse- quent monitoring during CPR. Waveform capnography can also be used to monitor the quality of CPR, as an indicator of a return of spontaneous circulation and to help with determining prognosis during CPR. • Use an inspiratory time of one second and enough volume to produce a normal chest rise. Add supplemental oxygen as soon as possible. • Avoid rapid or forceful breaths to prevent gastric distension and prevent raised intrathoracic pressure. • Once the patient's trachea has been intubated, continue chest compres- sions uninterrupted at a rate of 100–120 min–1, and ventilate the lungs at approximately 10 breaths min–1. • If airway and ventilation equipment are unavailable, give mouth-to- mouth ventilation. If there are clinical reasons to avoid mouth-to-mouth contact, do chest compressions until help or airway equipment arrives. • When the defibrillator arrives, apply the electrodes (self-adhesive defib- rillator pads) to the patient and analyse the rhythm. Do not pause chest compressions to apply defibrillator pads. See advanced life support for further steps. • Providing CPR is tiring—change the person undertaking compressions every 2 min. 5 If the patient is not breathing and has a pulse (respiratory arrest) • Ventilate the patient's lungs (as just described) and check for a circulation every 10 breaths (about every minute). • If there are any doubts about the presence of a pulse, start chest compressions.

Section 17 Critical care medicine 3842 The duration of asystole before return of spontaneous circulation (ROSC) can be longer than two minutes in as many as 25% of suc- cessful shocks, and delay in trying to palpate a pulse will further compromise the myocardium if a perfusing rhythm has not been restored. If a perfusing rhythm has been restored, giving chest com- pressions does not increase the chance of ventricular fibrillation recurring. Defibrillator safety The operator must ensure that everyone is clear of the patient be- fore delivering a shock. Ensure there is no oxygen flowing across the chest. Remove oxygen masks to greater than 1 metre away, but leave any tracheal tube or supraglottic airway device connected to its breathing circuit, bag device, or mechanical ventilator during at- tempted defibrillation. Percutaneous coronary intervention during CPR Percutaneous coronary intervention (PCI) may be indicated if the patient remains in persistent VF/pVT following a suspected acute coronary syndrome. A mechanical chest compression device can be used during transfer to the catheter lab and through the procedure. Nonshockable rhythms (pulseless electrical activity
and asystole) Identify and treat reversible causes during CPR (see Box 17.2.3). Airway and ventilation Airway management and ventilation options during CPR can vary according to patient factors, the phase of the resuscitation (during CPR, after return of spontaneous circulation), and the rescuers' skill. Basic airway options include no airway and no ventilation (compression-only CPR by untrained individuals), compression- only CPR with the airway held open (with or without supplementary oxygen), mouth-to-mouth breaths, mouth-to-mask, and bag-mask ventilation with simple airway adjuncts. Advanced options include supraglottic airways and tracheal intubation (inserted with the aid of direct laryngoscopy or videolaryngoscopy, or via a supraglottic airway). Most patients are treated with more than one airway man- agement option during CPR, and a

stepwise approach is recom- mended. Tracheal intubation provides the most reliable airway during CPR, but should be attempted only by trained rescuers. If intubation is attempted, confirm tube position using clinical as- sessment and waveform capnography. In the absence of rescuers skilled in tracheal intubation, insertion of a supraglottic airway (e.g. laryngeal mask airway (LMA), i-gel, laryngeal tube) is safer than unskilled rescuers attempting tracheal intubation. Compared with bag-mask ventilation, early ventilation with a supraglottic airway reduces the incidence of gastric distension and subsequent regurgitation, and enables more effective ventilation of the lungs of an unconscious patient. If an alternative airway has been in- serted, attempt continuous chest compressions without stopping for ventilations. If excessive gas leakage results in inadequate ventilation of the patient's lungs, interrupt the chest compressions to enable ventilation. During CPR Ensure high-quality CPR is maintained throughout a resuscitation attempt. Rotate the CPR provider at least every two minutes when Fig. 17.2.2 Effect of chest compressions on coronary perfusion pressure. Coronary perfusion pressure (CPP) is determined by the difference between aortic diastolic pressure and right atrial pressure. The lower border of the dark band (marked by the orange ellipse) depicts the aortic diastolic pressure and thus CPP. This increases progressively as chest compressions are continued but decreases to base levels each time compressions are stopped. Note also that CPP continues to increase and does not plateau after 15 compressions. Uninterrupted chest compressions will generate a higher CPP. From Kern KB, et al. (1998). Efficacy of chest compression-only BLS CPR in the presence of an occluded airway. Resuscitation, 39, 179–88, with permission from Elsevier.

17.2 Cardiac arrest 3843 possible. The quality of CPR can be monitored by CPR feedback and prompt devices, supplemented by regular review of downloads and post-event debriefing. Waveform capnography may be helpful as a monitor of CPR quality (compression depth and ventilation rate). A rapid rise in the end-tidal CO2 value may indicate return of spontaneous circulation. A low end-tidal CO2 (<1.3 kPa) after at least 20 minutes of advanced life support can indicate a poor prognosis, although this should not be the sole factor taken into account when deciding to terminate a CPR attempt. Check the rhythm every two minutes and check the pulse if the rhythm is compatible with a perfusing rhythm. Reversible causes Identify and treat reversible causes during CPR for all cardiac arrests. These are divided into two groups of four based upon their initial letter—either H or T. Key treatments are summarized in brackets. • Hypoxia (secure airway, administer oxygen) • Hypovolaemia (intravenous fluids/blood, treat cause) • Hyperkalaemia, hypokalaemia, hypocalcaemia, acidaemia and other metabolic disorders (treat specific abnormality) • Hypothermia (rewarming) • Tension pneumothorax (thoracostomy or needle thoracocentesis) Fig. 17.2.3 The advanced life support algorithm. Reproduced with permission of the Resuscitation Council (UK).

Section 17 Critical care medicine 3844 • Tamponade (resuscitative thoracotomy) • Toxic substances (consult poison advice centre, consider antidote) • Thromboembolism—pulmonary embolism/coronary throm- bosis (thrombolysis or embolectomy/percutaneous coronary intervention) Peri-arrest ultrasound by a trained rescuer with minimal interrup- tion in CPR can be used to identify and treat some reversible causes of cardiac arrest. Drugs The available evidence suggests drugs have a limited role in the management of cardiac arrest. Adrenaline 1 mg every 3–5 minutes is retained in current guidelines on the basis that it improves the short-term outcomes of return of spontaneous circulation and admission to hospital, but it remains uncertain whether there is benefit or harm in terms of survival to discharge or neurologic outcome. There is no

evidence that giving any antiarrhythmic drug rou- tinely during cardiac arrest increases survival to hospital discharge. In comparison with placebo, the use of amiodarone (300 mg IV) in shock-refractory ventricular fibrillation (three failed defibrillation attempts) in the prehospital setting improves the short-term out- come of survival to hospital admission. The routine use of thrombolytic drugs in cardiac arrest is not recommended. Where the index of suspicion is high that car- diac arrest has been caused by a pulmonary embolus, thrombo- lytic therapy and prolonged CPR (up to 60–90 minutes) may be considered. Drug delivery Peak drug concentrations are higher and circulation times are shorter when drugs are injected into a central vein compared with a peripheral vein. Insertion of a central venous catheter requires interruption of CPR and is associated with several po- tential complications. Peripheral venous cannulation is quicker, easier, and safer. Flush drugs injected peripherally with at least 20 ml of fluid and elevate the extremity for 10 to 20 seconds to facilitate drug delivery to the central circulation. If intravenous access is difficult or impossible, the intraosseous route is a rea- sonable alternative. Extracorporeal CPR (e-CPR) Smaller portable pump devices and refinements to circuits, anticoagulation and vascular access have made the emergency use of extracorporeal circulatory support feasible for both in-hospital and out-of-hospital cardiac arrest. Extracorporeal CPR is a rescue therapy that can facilitate specific interventions (e.g. Box 17.2.2 Treatment of shockable rhythms (VF/pVT) 1 Start CPR, and once pads applied, stop chest compressions to confirm VF/pVT from the ECG. This pause in chest compressions should be brief and no longer than five seconds. 2 Resume chest compressions immediately; warn all rescuers other than the individual performing the chest compressions to ‘stand clear’ and remove any oxygen delivery device as appropriate. 3 The designated person selects the appropriate energy on the defib- rillator and presses the charge button. Choose an energy setting of at least 150 J for the first shock, the same or a higher energy for subse- quent shocks, or follow the manufacturer’s guidance for the particular defibrillator. If unsure of the correct energy level for a defibrillator, in adults choose the highest available energy. 4 Ensure that the rescuer giving the compressions is the only person touching the patient. 5 Once the defibrillator is charged and the safety check is complete, tell the rescuer doing the chest compressions to ‘stand clear’; when clear, give the shock. 6 After shock delivery immediately restart chest compressions. Do not pause to reassess the rhythm or feel for a pulse. The total pause in chest compressions should be brief and no longer than 5 seconds. 7 Continue CPR for 2 min; the team leader prepares the team for the next pause in CPR. 8 Pause briefly to check the monitor. • If VF/pVT, repeat steps 2–8 and deliver a second shock. • If VF/pVT persists after a second shock, repeat steps 2–6 and deliver a third shock, then 9 Resume chest compressions immediately. Give adrenaline 1 mg IV and amiodarone 300 mg IV while performing a further 2 min CPR. Withhold adrenaline if there are signs of return of spontaneous circulation (ROSC) during CPR. 10 Repeat this 2 min CPR—rhythm/pulse check—defibrillation sequence if VF/pVT persists. 11 Give further adrenaline 1 mg IV after alternate 2 min periods of CPR (i.e. approximately every 3–5 min). 12 If organized electrical activity compatible with a cardiac output is seen during a rhythm check, seek evidence of ROSC (check for signs of life, a central pulse, and end-tidal CO2 if available). a If there is ROSC, start post-resuscitation care. b If there are no signs of ROSC, continue CPR, and switch to the non- shockable algorithm. 13 If asystole is seen, continue CPR, and switch to the nonshockable algorithm. Box 17.2.3 Treatment for pulseless electrical activity (PEA) and asystole 1 Start CPR 30:2. 2 Give adrenaline 1 mg IV as soon as intravascular access is achieved. 3 Continue CPR 30:2 until the airway is secured—then continue chest compressions without pausing during ventilation. 4 Recheck the rhythm after 2 min: a If organized electrical activity is seen, check for a pulse and/or signs of life: i If pulse and/or signs of life are present, start post-resuscitation care. ii If

no pulse and/or signs of life are present (PEA): 1 Continue CPR 2 Recheck the rhythm after 2 min and proceed accordingly 3 Give further adrenaline 1 mg IV every 3–5 min (alternate 2 min loops of CPR). b If VF/pVT at rhythm check, change to the shockable side of algorithm. c If asystole or an agonal rhythm seen at rhythm check: 1 Continue CPR 2 Recheck the rhythm after 2 min and proceed accordingly 3 Give further adrenaline 1 mg IV every 3–5 min (alternate 2 min loops of CPR).

17.2 Cardiac arrest 3845 percutaneous coronary intervention, surgical treatment of mas- sive pulmonary embolus, rewarming after severe hypothermia) where standard advanced life support interventions have failed to achieve a sustained return of spontaneous circulation. Routine use outside of these settings requires further research to opti- mize case selection criteria and determine clinical and cost effectiveness. Post-resuscitation care The quality of post-resuscitation care significantly influences the patient's ultimate outcome. ABCDE approach The ABCDE (airway, breathing, circulation, disability, exposure) system approach should be applied after resuscitation: Airway and breathing Consider tracheal intubation, sedation, and lung protective venti- lation in patients with obtunded cerebral function after return of spontaneous circulation. Maintain the oxygen saturation of arterial blood between 94–98%, avoiding hypoxaemia and hyperoxaemia, both of which may exacerbate brain injury and impair cardiac function. After cardiac arrest, hypocapnia induced by hyperventi- lation causes cerebral ischaemia. There are few data to support the targeting of a specific $PaCO_2$ after resuscitation from cardiac arrest, but it is reasonable to adjust ventilation to achieve normocapnia. Decompress the stomach by placing a nasogastric tube. Obtain a chest x-ray to check tracheal tube, NG tube and central line pos- ition, and to identify any complications of CPR (fractured ribs, pneumothorax). Circulation Haemodynamic instability is common after cardiac arrest and manifests as hypotension, low cardiac output, vasodilation, and arrhythmias. This is partly caused by reperfusion injury and is usu- ally transient, often reversing within 24–48 hours. Fluids and vaso- active drugs (noradrenaline and/or dobutamine), with or without an intra-aortic balloon pump, may be required to maintain perfu- sion of the vital organs. Echocardiography and monitoring cardiac output, urine output, and lactate clearance can be used to guide therapy. Bradycardia may occur as a consequence of targeted tem- perature management; this should be treated only if it adversely affects haemodynamics. Coronary reperfusion Acute coronary syndrome is a common cause of cardiac arrest (up to 70% of out-of-hospital cardiac arrests). Record a 12-lead electrocardiogram as soon as possible. Observational studies in- dicate that patients with acute ST-segment elevation or new left bundle branch block benefit from urgent coronary angiography and (when indicated) percutaneous coronary intervention, ir- respective of conscious level. The evidence is less certain for pa- tients without ST elevation but with a history consistent with a cardiac event. Such patients should be discussed with an inter- ventional cardiologist and considered for emergency cardiac catheterization. Other clinical issues Sedation and brain imaging Sedate the patient with short acting drugs. Consider a neuromus- cular blocking drug in the event of patient-ventilator asynchrony or uncontrolled shivering. Continuous electroencephalography (EEG) is recommended if an infusion of a neuromuscular blocker is used because this may mask seizure activity. Consider a computed tomography (CT) scan of the brain or chest if history of presentation suggests a possible cerebral or respiratory cause of the cardiac arrest. Cerebral perfusion Immediately after return of spontaneous circulation there is a period of cerebral hyperaemia, but after 15–30 minutes of reperfusion global cerebral blood flow decreases and there is generalized hypoperfusion. In about one-third of post cardiac arrest patients normal cerebral autoregulation is lost, leaving cerebral

perfusion dependent on mean arterial pressure. Under these circumstances, hypotension will compromise cerebral blood flow severely and can worsen any neurological injury. After return of spontaneous cir- culation, aim to maintain mean arterial pressure at the patient's usual level. Control of seizures Seizures and/or myoclonus occur in 5–15% of patients who achieve return of spontaneous circulation, and in approximately 40% of those who remain comatose. Seizures increase cerebral metabolism by up to fourfold and may worsen brain injury. The available data do not support prophylactic treatment with anticonvulsants. If seizures occur, treat with benzodiazepines, sodium valproate, levetiracetam, phenytoin, or propofol. Treat myoclonus with sodium valproate, levetiracetam, clonazepam, or propofol; phenytoin is rarely effective. Clinical or EEG evidence of seizures, myoclonus, and status epilep- ticus are associated with a poor outcome, particularly if these occur in the first 24–48 hours. Nevertheless, survival with good outcome despite early seizures does occur, hence the presence of seizures should not alone determine a decision to withdraw life-sustaining treatment. Glucose control Hyperglycaemia during post-resuscitation care phase is associ- ated with poor neurological outcome. Maintain blood glucose at ≤10 mmol L–1, but avoid hypoglycaemia. Temperature control and management Hyperthermia is common in the first 48 hours after cardiac arrest. The risk of a poor neurological outcome increases for each degree of body temperature over 37°C. Although there are no random- ized trials comparing treatment of hyperthermia with no treat- ment, there is consensus that hyperthermia occurring in the first 72 hours after cardiac arrest should be treated with antipyretics or active cooling. Mild hypothermia suppresses many of the chemical reactions associated with reperfusion injury. These reactions include free radical production, excitatory amino acid release, and calcium shifts, which can in turn lead to mitochondrial damage and apop- tosis (programmed cell death).

Section 17 Critical care medicine 3846 Randomized trials from 2002 reported improved neurological outcomes in patients treated with therapeutic hypothermia (32– 34°C) for 12–24 hours after out-of-hospital cardiac arrest. The more recent Targeted Temperature Management (TTM) trial re- ported similar outcomes with temperature targets of 33°C versus 36°C in comatose out-of-hospital cardiac arrest survivors. Current guidelines recommend maintaining a constant target temperature value between 32–36°C for 24 hours in all cardiac arrest survivors who remain unresponsive after return of spontaneous circulation, irrespective of cardiac arrest location and initial cardiac arrest rhythm. Therapeutic hypothermia reduces overall metabolic rate; glucose should be closely monitored during rewarming as it may precipitate hypoglycaemia in patients being treated with insulin. Use targeted temperature management cautiously in patients with severe systemic infection and pre-existing coagulopathy; in such patients consider using a target of 36oC instead of a lower temperature. Prognosis Survival For out-of-hospital cardiac arrest, among those in whom resus- citation is attempted, 25–30% initially achieve return of spon- taneous circulation but only about 8% survive to go home from hospital. For in-hospital cardiac arrest, the rate of return of spontaneous circulation is 45%, with 18.5% surviving to hospital discharge. Some patients with out-of-hospital cardiac arrest have recovered consciousness by admission to hospital, while many have obtunded conscious levels requiring admission to intensive care. Of 8664 patients admitted to intensive care units in the United Kingdom after in- or out-of hospital cardiac arrest in 2014, 47% survived to leave intensive care and 37% survived to hospital discharge. Most (>90%) of patients who survive to discharge have a cerebral per- formance category of 1 or 2, indicating a moderate to good neuro- logical outcome. Prediction of outcome Unless return of spontaneous circulation is achieved rapidly after the onset of cardiac arrest, most patients who achieve return of spontaneous circulation will have an obtunded conscious level. There are no tests to predict

reliably which of those patients may benefit from intensive care. The decision about whether to admit to intensive care is informed by a careful assessment of the patient's prearrest functional status, comorbidities, and the cause of the car- diac arrest. Of those admitted to intensive care after cardiac arrest in the United Kingdom, 35–40% survive to hospital discharge. Two-thirds of those dying after admission to intensive care following out-of- hospital cardiac arrest die from neurological injury, compared to a quarter of those dying after admission following in-hospital cardiac arrest. International guidelines recommend a multimodal approach to prognostication in the comatose post-cardiac arrest patient, which includes clinical, radiological and electrophysio- logical tests and measure of biomarkers (Fig. 17.2.4). Assessment is made only after sufficient time has passed to enable clearance of sedatives and neurological recovery (usually at least 72 hours from cardiac arrest). Clinical tests There are no neurological signs that can predict outcome in the first few hours after return of spontaneous circulation. By three days after the onset of coma relating to cardiac arrest, 50% of patients with no chance of ultimate recovery have died. Brain stem reflexes may recover up to 72 hours after cardiac arrest. The bilateral absence of the pupillary reflex to light and/or corneal reflex 72 hours after return of spontaneous circulation predicts poor outcome with a low false positive rate, yet sensitivity is low (about 19%), that is, these signs are only present in one in five patients with a poor outcome. An absent or extensor motor response to pain at 72 hour is more sensitive (75%) but has a high false positive rate (27%). An extended period of assessment is required in cases of residual sedation or muscle relaxants. Status myoclonus suggests significant cerebral insult but is not universally associated with adverse outcome. Some variants of myo- clonus (e.g. Lance Adams syndrome, a chronic action myoclonus beginning within days or weeks after CPR) can be associated with a good outcome and it is important to involve experienced clinicians in making the diagnosis. Clinical tests are relatively easy to perform, yet lack sufficient precision to be relied upon in isolation, hence the presence of ad- verse clinical signs should prompt multimodal imaging and electro- physiological assessments. Imaging The evidence supporting the use of diagnostic imaging is less certain than with other test modalities. Sulcal effacement and loss of grey/ white matter differentiation on CT scan of the brain suggests cere- bral hypoxic-ischaemic injury. Magnetic resonance imaging (MRI) is more sensitive than CT for detecting cerebral hypoxic-ischaemic injury. Cerebral/CT or MRI angiography may also play a role as an- cillary tests for brain stem death. Electrophysiological tests The bilateral absence of the N20 component median nerve somato- sensory evoked potentials in normothermic patients, comatose for at least 72 h after cardiac arrest, predict poor outcome with high reliability (false positive rate 0–2%). Electro-encephalographic (EEG) patterns associated with poor outcomes are absence of EEG reactivity, status epilepticus, and burst suppression. Biomarkers Neuron-specific enolase and S-100B proteins are markers of neuro- logical injury. High and sustained (or increasing) values are associ- ated with poor outcome.

17.2 Cardiac arrest 3847 Management of cardiac arrest survivors Rehabilitation Cognitive impairment, emotional and memory problems, and fa- tigue are common after cardiac arrest and adversely effect recovery and quality of life. Early evidence suggests post-discharge assess- ment and rehabilitation improves outcomes. Cardiac electrophysiological assessment Consider the possible requirement for an implantable cardioverter defibrillator (ICD) in any patient who has been resuscitated from cardiac arrest in a shockable rhythm outside the context of proven acute ST-segment elevation myocardial infarction. All such patients should be referred before discharge from hospital for assessment by a cardiologist with expertise in heart rhythm disorders Other considerations Organ donation Depending on national laws and codes of practice, organ dona- tion

can be considered after brain stem death is confirmed (dona- tion after neurological determination of death) or after withdrawal of life-sustaining treatment (controlled donation after circulatory Fig. 17.2.4 Prognostication for comatose survivors of cardiac arrest. Reproduced with permission of the Resuscitation Council (UK).

Section 17 Critical care medicine 3848 death) in those who achieved initial return of spontaneous circula- tion after cardiac arrest but remained comatose. In some countries, when advanced life support fails to achieve return of spontaneous circulation, organ donation may be considered (uncontrolled dona- tion after circulatory death). Audit The Utstein template provides a standardized approach to auditing demographic, process, and outcomes from cardiac arrest. Structured quality improvement initiatives linked to local performance data such as the Resuscitation Academy concept (http://www. resuscitationacademy.eu) have great potential to improve quality and outcomes. Data from regional, national, and international registries allow evaluation of the safety and effectiveness of interventions diffi- cult to test in a randomized controlled trial. Decisions relating to cardiopulmonary resuscitation It is essential to identify patients for whom cardiopulmonary arrest represents an anticipated terminal event and in whom CPR is in- appropriate. All healthcare settings (hospital and community) should ensure that there are clear and explicit resuscitation plans for those at risk of cardiac arrest. Generally accepted reasons for withholding CPR are (i) when it is deemed that it will be ineffective (i.e. will not restart the heart and breathing for a sustained period; (ii) CPR will not provide overall benefit (informed by discussion with the pa- tient or their family or other nominated surrogate decision makers); (iii) the patient has refused CPR. Emergency care treatment plans allow resuscitation decisions to be considered as part of an overall treatment plan. Observational data suggest that this approach is associated with more patient- centred decision-making, better communication, and less risk that a decision to withhold resuscitation will mean an overall reduction in the quality and quantity of care. Likely developments over the next 5–10 years The International Liaison Committee on Resuscitation (ILCOR) coordinates evidence-based reviews of resuscitation science. Technology advances will enable a more continuous review of emerging science to feed into clinical guidelines in future years. A greater emphasis on training the community to recognize cardiac arrest and how to initiate CPR and use an automated ex- ternal defibrillator will be key to saving more lives. National and international initiatives to introduce CPR and automated external defibrillator training in schools, optimizing dispatcher recognition of cardiac arrest, and provision of telephone CPR instruction are likely to have significant impact. The registration of automated ex- ternal defibrillators in the community and intelligent systems (using app-based technology) to support their deployment may increase the proportion of patients receiving early defibrillation before the emergency services arrive. Few advanced life support interventions are based on robust evi- dence. Large multicentre trials are in progress and will provide de- finitive information on the optimal advanced airway technique, and whether drugs are safe and effective as treatments for cardiac ar- rest. Research will also define if percutaneous coronary intervention during cardiac arrest improves survival. Global (e.g. blood pressure/flow, lactate clearance) and regional measurements (e.g. end-tidal CO_2, cerebral oximetry, coronary perfusion pressure, ventricular fibrillation waveform analysis) are likely to play a growing role in tailoring specific interventions to the patient’s physiological status. The increased portability of technology that can provide extracor- poreal resuscitation means that it is now feasible to initiate e-CPR at the scene of a cardiac arrest. Further research is required to deter- mine for which patients it is clinically and cost effective to deploy this technology. FURTHER READING Fritz Z, Slowther AM, Perkins GD (2017).

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ESSENTIALS The term anaphylaxis describes both IgE immune-mediated re- actions, plus non-IgE immune-mediated, and nonallergic, non- immunologically triggered events. Comorbidities such as asthma or infection, exercise, alcohol, or stress and concurrent medications such as β-blockers and aspirin increase the risk, a concept known as ‘summation anaphylaxis’. Aetiology and pathogenesis—activated mast cells and basophils re- lease preformed, granule-associated mediators and newly formed lipid mediators, and generate cytokines and chemokines. These cause vasodilatation, increased capillary permeability, and smooth muscle contraction, as well as attracting new cells to the area. Positive feedback enhancing mechanisms amplify the reaction in a ‘mast cell—leucocyte cytokine cascade’, although conversely reactions can be self-limiting. Parenteral penicillins, hymenopteran stings, and food are the most common causes of IgE immune-mediated fatal- ities, with radiocontrast media, aspirin, and other nonsteroidal anti- inflammatory drugs most commonly responsible for non-IgE and nonallergic fatalities. Diagnosis—anaphylaxis is a clinical diagnosis and is highly likely when any one of the following three criteria is fulfilled: (1) acute onset (minutes to hours) of an illness with involvement of the skin, mucosal tissues, or both, together with (a) respiratory compromise, or (b) hypotension/syncope/collapse; (2) two or more of the fol- lowing that occur rapidly after exposure to a likely allergen for that patient: (a) involvement of the skin, mucosal tissues, or both, (b) re- spiratory compromise,
(c) hypotension/syncope/collapse, or (d) per- sistent abdominal symptoms; (3) reduced blood pressure after exposure (minutes to hours) to a known allergen for that patient. Clinical features—80–95% of patients with anaphylaxis have cu- taneous manifestations, which assist prompt early diagnosis. These cutaneous or mucosal features alone do not constitute anaphylaxis, which requires multisystem involvement. Deaths occur by hypoxia from upper airway obstruction or severe bronchospasm or by pro- found shock from vasodilatation and extravascular fluid shift. Management—if anaphylaxis is suspected, any potential causative agent (e.g. intravenous drug/infusion) should be stopped immedi- ately. First-line treatment is with (1) adrenaline—0.01 mg/kg to a max- imum of 0.5 mg (0.5 ml of 1:1000 adrenaline) given intramuscularly into the lateral thigh which acts to reverse all the features of anaphyl- axis, as well as inhibiting further mediator release; (2) oxygen—high flow or to maintain adequate oxygen saturations; (3) intravenous fluid—crystalloids (0.9% saline) at 10 to 20 ml/kg are essential in shock. Other issues

relating to immediate management—(1) If skilled as- sistance is available, intravenous adrenaline should be given for se- vere hypotension or critical bronchospasm. If intravenous access is not immediately available, intramuscular adrenaline should be given while intravenous access is obtained. Intravenous adrenaline should be given as a dilute solution (1 mg in 100 ml 0.9% saline, i.e. 10 µg/ ml), slowly (0.5–1.5 ml/min), and titrated against clinical response. Nebulized adrenaline (5 mg, i.e. 5 ml of undiluted 1:1000 adrenaline) can be given while parenteral adrenaline is being prepared, particu- larly for upper airway oedema and bronchospasm. (2) The roles of H1 and H2 antihistamines, steroids, salbutamol, and glucagon are unclear: they should only be considered once cardiovascular sta- bility has been achieved with first-line agents. (3) Patients must be observed for at least 4–6 h after full recovery before discharge from immediate medical care, when a clear plan for further management is essential. Further management—(1) Referral to an immunologist is needed for all those who have had significant, recurrent, unavoidable, or unknown reactions. (2) Patient education is important for successful long-term care. (3) An adrenaline autoinjector should be given to patients with anaphylaxis after known allergen exposure outside of a medical setting, patients with food allergy (particularly to nuts or peanuts), and those in whom the reaction was severe and/or the cause unknown, including idiopathic anaphylaxis. Whoever takes responsibility for prescribing must explain and demonstrate exactly how to use the device provided, educating both the patient and an- other caregiver, particularly in children with anaphylaxis. Introduction The term anaphylaxis, literally meaning ‘against protection’, was introduced by Richet and Portier in 1902 (Fig. 17.3.1). It repre- sents the most catastrophic of the immediate-type, generalized hypersensitivity reactions, and remains the quintessential medical 17.3 Anaphylaxis Anthony F.T. Brown

Section 17 Critical care medicine 3850 emergency. Anaphylaxis following exposure to a trigger can range from mild to severe, gradual in onset to fulminant, and may involve multiple organ systems or cause isolated shock or wheeze. It pre- sents unheralded in otherwise healthy people, and mandates prompt clinical diagnosis based on pattern recognition and probability in the absence of any immediate confirmatory test. All clinicians and other healthcare workers must be familiar with the condition: urgent treatment can prevent death from hypoxia or hypotension. Definition There is no absolute agreement on the classification, diagnosis, or severity grading of anaphylaxis, although published guidelines mostly differ on emphasis rather than content. After convening international consensus meetings in 2004 and 2005, the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) in the United States of America recommended a brief, broad definition as ‘Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death’, with the agreed full definition aimed at capturing more than 95% of clinical cases within three diagnostic criteria (see Box 17.3.1). Criterion 1 should identify at least 80% of anaphylaxis cases, even if the allergic status of the patient and potential cause of the reac- tion may be unknown, as most anaphylactic reactions include skin symptoms. Criterion 2 is anaphylaxis in the absence of cutaneous features such as in children with food allergy, or insect sting allergy, but requires a known allergic history and possible exposure: gastro- intestinal symptoms are included. Criterion 3 captures the rare pa- tient with an acute hypotensive episode after exposure to a known allergen. This inclusive definition for anaphylaxis underlies the up- dated guidelines (Practice Parameters) developed by the American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI), as well as the World Allergy Association (WAO) and European Academy of Allergy and Clinical Immunology (EAACI) guidelines. These consensus criteria should be used by researchers, until refined by future

prospective data. Most recently in 2014, the EAACI Taskforce on Anaphylaxis pro- posed the succinct definition that ‘Anaphylaxis is a severe, potentially life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with life-threatening airway, breathing, or cir- culatory problems and is usually, although not always, associated with skin and mucosal changes’. Severity grading There is no prospectively validated grading system linking the clinical features of anaphylaxis with its severity, urgency, treat- ment, or outcome. One system based on retrospective multi- variate analysis of over 1000 clinically diagnosed generalized hypersensitivity reactions defined three grades (Table 17.3.1). Mild cases were generalized allergic reactions confined to the skin and subcutaneous tissues, but moderate and severe grades with multisystem involvement correlated with the need for adrenaline and represent true anaphylaxis according to the NIAID/FAAN criteria. This grading system should again be used as a starting point by researchers for descriptive purposes, until future pro- spective data refine the criteria. Important clinical categories of anaphylaxis include anaphylaxis related to medications, biologicals, and vaccines, as well as insect Fig. 17.3.1 The discovery of anaphylaxis in 1901. Stamps showing Charles Richet, Paul Portier, and Prince Albert of Monaco. Box 17.3.1 Definition of anaphylaxis: clinical criteria for diagnosis Anaphylaxis is highly likely when any one of the following three criteria is fulfilled: 1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus, or flushing, swollen lips–tongue–uvula), and at least one of the following: • Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxaemia) • 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 (minutes to several hours) after exposure to a likely allergen for that patient: • Involvement of the skin–mucosal tissue (e.g. generalized hives, itch-flush, swollen lips–tongue–uvula) • Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxaemia) • Reduced BP or associated symptoms (e.g. hypotonia (collapse), syn- cope, incontinence) • Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting) 3 Reduced BP after exposure (minutes to several hours) to known allergen for that patient: • Infants and children: low systolic BP (age-specific) or more than 30% decrease in systolic BPa • Adults: systolic BP of less than 90 mm Hg or more than 30% decrease from that person’s baseline BP, blood pressure; PEF, peak expiratory flow. a Low systolic blood pressure for children is defined as less than 70 mm Hg from one month to one year; less than 70 mm Hg + (2 × age) from 1 to 10 years; and less than 90 mm Hg from 11 to 17 years. Reproduced from Journal of Allergy and Clinical Immunology, 117, Hugh A. Sampson 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, 391–397, 2006 with permission from Elsevier.

 stings, food, anaesthesia, latex exposure, exercise, and idiopathic anaphylaxis (see Table 17.3.2). Aetiology IgE-dependent activation of mast cells and basophils is the key trigger for most cases of antigen-induced, immune-mediated allergic anaphylaxis. An identical clinical syndrome due to non-IgE-mediated, and nonimmunologic mechanisms leads to release of the exact same inflammatory mediators. Non-IgE- mediated and nonimmunologic anaphylaxis (terms preferred by the WAO and EAACI to ‘anaphylactoid’, whose use is dis-couraged) may occur on first exposure to an agent and do not require a period of sensitization. However, immune-mediated anaphylaxis may also occur on first exposure from prior aller- genic cross-sensitization, as for instance with the neuromus- cular blocking drugs (see later). Drug-

induced anaphylaxis Penicillin is the most common cause of drug-induced anaphylaxis, with around 1:500 patient courses having an apparent allergic reac- tion, mostly urticaria alone. True allergic cross-reactivity to ceph- alosporins occurs in around 1–2% of cases and is largely with the first-generation cephalosporins. Aspirin and nonsteroidal anti- inflammatory drugs (NSAIDs) are the next most common cause of drug-induced anaphylaxis. Reactions appear to be medication- specific, as there is no clinical cross-reactivity with structurally un- related NSAIDs. Reactions to chemotherapy drugs including cis-/carboplatinum and doxorubicin are becoming increasingly common as their use increases, as well as reactions to monoclonal antibodies such as omalizumab, cetuximab, and rituximab. In the case of cetuximab this may relate to IgE directed against galactose-α-1,3-galactose (α-gal), an oligosaccharide also responsible for red meat allergy following tick-bite. Skin or serum tests for IgE-mediated reactions are unreliable for most drugs or biological agents, with the exception of penicillins. Short-term desensitization may be possible, supervised by an al- lergy/immunology specialist. Insect sting anaphylaxis Reactions to stings from bees, wasps, and ants of the order Hymenoptera are second only to drug-induced anaphylaxis in adults and occur in up to 3% of the population (<1% of children). Reactions are often rapid and may be fatal within 30 min, mandating the early use of adrenaline, including by self-administration. Insect stings are the most common cause of severe anaphylaxis in patients with indolent systemic mastocytosis. Nonanaphylactic toxic, large local, or late serum sickness-like reactions also occur following a sting (see Chapter 10.4.2). Food-induced anaphylaxis This cause of anaphylaxis is most common in the young, particu- larly following the ingestion of peanuts, tree nuts such as walnuts and pecans, fish, shellfish, milk, eggs, wheat, and soy—the eight most common ingredients that trigger 90% of food allergies, known as ‘The Big-8’, and included among food products that require mandatory labelling. Cross-reactivity with other foods is unpredictable, or re- actions may occur to additives such as carmine, metabisulphite, and tartrazine. Mislabelling and contamination during manufacturing or at home can lead to inadvertent exposure, and associated factors, such as exercise after food, must be recognized (see later). Although fatalities are rare and usually associated with pre- existing asthma, biphasic reactions are seen as symptoms sub- side then recur several hours later. Patient and carer education is Table 17.3.1 Severity grading system for generalized hypersensitivity reactions Grade Defined by

1. Milda (skin and subcutaneous tissues only) Generalized erythema, urticaria, periorbital oedema, or angioedema
2. Moderateb (features suggesting respiratory, cardiovascular, or gastrointestinal involvement) Dyspnoea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain
3. Severeb (hypoxia, hypotension, or neurological compromise) Cyanosis or SpO2 ≤92% at any stage, hypotension (systolic blood pressure <90 mm Hg in adults), confusion, collapse, loss of consciousness, or incontinence a Mild reactions can be further subclassified into those with and without angioedema. b Grades 2 and 3 constitute true anaphylaxis. Reproduced from Journal of Allergy and Clinical Immunology, 114, Simon G. A. Brown, Clinical features and severity grading of anaphylaxis, 371–376. 2004, with permission from Elsevier. Table 17.3.2 Causes of anaphylaxis IgE-dependent, immunologic mechanisms Drugs, chemicals, and biological agents: Penicillins, cephalosporins, sulphonamides, muscle relaxants, vaccines, insulin, thiamine, protamine, γ-globulin, cis-/carboplatinum and doxorubicin, monoclonal antibodies omalizumab/cetuximab/rituximab, antivenoms, formaldehyde, ethylene oxide, chlorhexidine, semen Foods: Peanuts, tree

nuts, shellfish, finfish, milk, eggs, wheat, soy, fruits, vegetables, sesame Hymenopteran sting venom, insect saliva, other venoms: Bees, wasps, ants, hornets, ticks, triatomid bugs, snakes, scorpions, jellyfish Natural rubber latex Environmental: Pollen, horse dander, hydatid cyst rupture Non-IgE-dependent, and nonimmunologic mechanisms Medications and biological agents: Opiates, aspirin, and NSAIDs, ACEI, vancomycin, radiocontrast media, N-acetylcysteine, fluorescein Food additives: Metabisulphite, tartrazine Physical factors: Exercise, cold, heat, sunlight Idiopathic No apparent trigger ACEI, angiotensin-converting enzyme inhibitors; NSAIDs, nonsteroidal, anti-inflammatory drugs. Note: Cross-reactivity occurs, and both IgE-dependent and nonimmunologic reactions may happen with the same agent. Several mechanisms may coexist such as exercise-induced following food. Non-IgE-dependent, and nonimmunologic mechanisms include complement activation, coagulation system activation, kinin production or potentiation, and direct mediator release.

Section 17 Critical care medicine 3852 paramount including carrying an adrenaline autoinjector at all times, with schools in particular prepared to respond with adren- aline in an emergency. Radiocontrast media anaphylaxis Nonimmunologic reactions requiring treatment occur in around 1% of patients receiving iodinated radiocontrast media, with se- vere reactions in less than 0.01%. Patients at greatest risk are those with asthma, cardiovascular disease particularly if on a β-blocker, a previous reaction, and those given ionic high-osmolality contrast. Seafood allergy is not relevant, and subsequent use of gadolinium- based contrast with MRI is safe. Pretreatment with prednisone 50 mg, for instance at 13 h, 7 h, and 1 h before, with or without anti- histamine reduces the frequency of symptoms, but does not prevent a life-threatening reaction. Perioperative anaphylaxis The incidence of perioperative anaphylaxis, both IgE-related and nonimmunologic, ranges from 1:4000 to 1:25 000 cases, with around 4% of reported reactions being fatal. Neuromuscular blocking drugs (muscle relaxants), antibiotics, latex, and induction agents cause most cases of anaphylaxis, but opioids, NSAIDs, colloids, blood products, radiocontrast dye, isosulphan, or methylene blue, methyl methacrylate, chlorhexidine, and protamine may be responsible. Muscle relaxants cause 60% of all reactions, with suxamethonium and rocuronium most commonly responsible. Reactions to suxa- methonium and other relaxants occur in the absence of prior use: this suggests cross-reactivity and renders large-scale preopera- tive testing untenable. Latex-induced anaphylaxis The highest risk group for natural rubber latex allergy includes healthcare workers, children with spina bifida and genitourinary ab- normalities, and occupational exposure. Atopy and cross-reacting fruit allergy are also associated with an increased risk. Reactions follow direct contact, parenteral contamination, or aerosol trans- mission. Patients at known risk must be treated in a latex-free en- vironment with glass syringes and non-latex-containing gloves, stethoscopes, breathing systems, blood pressure cuffs, intravenous tubing, and administration ports. Exercise-induced anaphylaxis Anaphylaxis can occur with a variety of physical activities. Up to 50% of cases are associated with the prior ingestion of a food—food dependent—in the preceding hours, or can follow aspirin/NSAID use, and high pollen level triggers. Prophylactic medication is in- consistently effective and unreliable, unlike with exercise-induced asthma, although reactive episodes themselves are occasional and unpredictable. Idiopathic anaphylaxis This is defined as anaphylaxis in which no discernible causative allergen or inciting physical factor can be identified: most cases occur in adults of whom 50% are atopic, but it is seen in children. Diagnosis is by exclusion including C1 esterase inhibitor deficiency, mastocytosis, and IgE to serum galactose-α-1,3-galactose (α-gal) following red meat ingestion. Steroid and an H1 antihistamine

prophylaxis is essential. Cofactors ‘summation anaphylaxis’ Various cofactors, comorbidities, and concurrent medications in- crease the risk of anaphylaxis, giving rise to the concept of ‘sum- mation anaphylaxis’. These include asthma, severe atopy, exercise, intercurrent infection, cardiac disease, premenstrual status, psycho- logical stress, alcohol, and drugs such as β-blockers, angiotensin- converting enzyme inhibitors, NSAIDs, and, to a lesser extent, angiotensin II blockers. Cofactors are reported in up to 30% of ana- phylactic episodes, and may explain an individual’s unpredictable response to recurrent antigen exposure (see Table 17.3.3). Pathophysiology Mast cells and basophils release inflammatory mediators following binding of multivalent allergen that cross-links surface, high-affinity IgE Fc receptors (FcεRI), or from cell membrane perturbation. This is coupled with mobilization of calcium in the endoplasmic re- ticulum and leads to the release of preformed, granule-associated mediators by exocytosis, or the de novo synthesis of eicosanoid lipid mediators based on arachidonic acid metabolism, and the activation of genes for various cytokines and chemokines. Mast cell and basophil inflammatory mediators The preformed mediators released by mast cells and basophils include histamine, proteases such as tryptase, chymase, and carboxypeptidase A, and proteoglycans such as heparin and chon- droitin sulphate E. Newly synthesized lipid mediators include pros- taglandin D2 and thromboxane A2 via the cyclo- oxygenase pathway, and the leukotrienes LTC4, LTD4, and LTE4 via the 5-lipoxygenase pathway. The cytokines released include TNFα, various interleu- kins such as IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, and IL-16, and granulocyte-macrophage colony-stimulating factor (GM-CSF). The chemokines include platelet activating factor, neutrophil chemo- tactic factor (IL-8), and eosinophil chemotactic factor, plus macro- phage inflammatory protein-1α. Mediator actions Mediators act to induce systemic vasodilatation, coronary artery vasospasm, increased capillary permeability and glandular secretion, smooth muscle spasm—particularly bronchoconstriction—and to Table 17.3.3 Cofactors and risk factors in anaphylaxis Medical conditions Asthma Severe atopy Infection Cardiac disease Mastocytosis Patient dependent Exercise Psychological stress Premenstrual status Drugs / ingestions Alcohol Beta-blockers (β-blockers) ACEI NSAID ARB ACEI, angiotensin-converting enzyme inhibitor; NSAID, nonsteroidal anti-inflammatory drug; ARB, angiotensin II receptor blocker.

 attract new cells such as eosinophils, leucocytes, and platelets to the area. Positive feedback enhancing mechanisms amplify and per- petuate reactions to recruit further effector cells to release increasing amounts of mediators in a ‘mast cell–leucocyte cytokine cascade’ effect. In addition, it appears that severe and/or fatal reactions also re- late not only to the amount of mediators released, but also to the speed of their degradation, for instance in the case of reduced platelet activating factor (PAF) catabolism from lower levels of PAF acetylhydrolase. By contrast, other anaphylactic reactions self-limit, with spontaneous recovery related to endogenous compensatory mechanisms including increased secretion of adrenaline, angio- tensin II, and endothelin 1. Epidemiology The true incidence of anaphylaxis is unknown. Data—which are unreliable with lack of a standard definition—are almost exclu- sively in the form of diverse, retrospective case collections from the emergency department, anaesthetic department, or the allergist/ immunologist’s office. Under-reporting is common due to missed diagnoses, or following spontaneous recovery, prehospital treat- ment, or fatality. However, all the data from western countries show the incidence of anaphylaxis admissions is increasing; for instance, in England and Wales it went up sevenfold between 1992 and 2012. Emergency department anaphylaxis Between 1:439 and 1:1100 presentations of adults to the emergency department are with anaphylaxis, representing up to one adult pres- entation per 3400 population per year. Anaphylaxis is the cause of about 1:1000 of paediatric emergency department presenta-

tions, although generalized allergic reactions in children (without multisystem involvement) are almost 10 times more common than this. A causative agent is found in over 75% of cases of anaphylaxis pre- senting to the emergency department, recognized from a prior re- action or by close temporal association with the onset of symptoms. The most frequent in childhood are food-induced or drug-related, whereas in adults drug-related and hymenopteran stings predom- inate. Respiratory features appear more common in paediatric ana- phylaxis and cardiovascular features in adults. Fatal anaphylaxis Fatalities are rare: less than one per million population per year, with the overall rate remaining stable despite an increase in anaphylaxis admissions, as well as in drug-induced anaphylactic deaths. When they do happen, fatal reactions are rapid, with a median time to car- diorespiratory arrest of just 5 min after parenteral medication (iatro- genic), 15 min for venom, and 30 min following foods. Deaths follow hypoxia in upper airway swelling with asphyxia, bronchospasm, and mucus plugging, and/or shock related to vasodilatation, extra- vascular fluid shift, and direct myocardial depression. Tachycardia is usual in shock, but bradycardia related to a neurocardiogenic, vagally mediated mechanism (Bezold–Jarisch reflex) has occasion- ally been observed. The most common causes include drugs, foods, and insect stings; patients may have had no prior or only a minor previous reaction to the agent. Risk factors for a severe and potentially fatal episode include asthma, cardiovascular disease, peanut or tree nut allergy, and a lack of early treatment. One study found adrenaline was given in only 14% cases prior to cardiopulmonary arrest, and not at all in 38% of fatalities. Clinical features Anaphylaxis characteristically affects fit people and is rarely seen or described in critically ill or shocked patients, other than asth- matics. The speed of onset relates to the mechanism of exposure and the severity of the reaction. Parenteral antigen exposure may cause life-threatening anaphylaxis within minutes, whereas symp- toms can be delayed for some hours following oral or topical exposure. Between 80 and 95% of patients with anaphylaxis have cuta- neous features, which assist prompt early diagnosis. However, alerting cutaneous features may be absent because of prehospital treatment or their spontaneous resolution, be subtle clinically and missed, or the onset of other life-threatening complications such as laryngeal oedema or shock may precede them. Cutaneous or mucosal changes alone do not constitute anaphylaxis, the hall- mark of anaphylaxis being the precipitate onset of respiratory, cardiovascular, gastrointestinal, and/or neurological dysfunction (see Table 17.3.4). Cutaneous and general reactions A premonitory aura, tingling or warm sensation, anxiety, and feeling of impending doom precede generalized erythema, urti- caria with pruritus, and angioedema of the neck, face, lips, and tongue (Fig. 17.3.2). Rhinorrhoea, conjunctival injection, and tearing are seen. Respiratory manifestations Throat tightness and cough precede mild to critical respiratory dis- tress due to oropharyngeal or laryngeal oedema with dyspnoea, hoarseness, stridor, and even aphonia; or related to bronchospasm Table 17.3.4 Clinical features of anaphylaxis Cutaneous Tingling or warmth, erythema (flushing), urticaria, pruritus (itch), angioedema Rhinorrhoea, conjunctival injection, lacrimation Respiratory Throat tightness, cough, dyspnoea, hoarseness, stridor, aphonia Tachypnoea, wheeze, Spo2 ≤92%a, cyanosisa Cardiovascular and neurological Tachycardia (rarely bradycardia), hypotensiona, chest pain, arrhythmias, cardiac arresta Light-headedness, sweating, incontinencea, syncopea, confusiona, comaa Gastrointestinal Odynophagia (difficult or painful swallowing), abdominal cramps, nausea, vomiting, diarrhoea Nonspecific Premonitory aura, anxiety, feeling of impending doom Pelvic cramps Sao2, oxygen saturation (on pulse oximetry). a Indicates severe reaction (see Table 17.3.1).

 with tachypnoea and wheeze. Hypoxia with oxygen saturation less than 92% on pulse oximetry and central cyanosis indicate severe anaphylaxis and

the need for immediate treatment (see severity grading in Table 17.3.1). Cardiovascular and neurological manifestations Light-headedness, sweating, syncope, incontinence, or coma may precede or accompany cardiovascular collapse with tachycardia, hypotension, and cardiac arrhythmias. These can appear benign supraventricular rhythms, particularly in children, but with an impalpable pulse. Chest pain may occur due to coronary artery vasospasm from cardiac mast cell release of histamine, leukotrienes and platelet activating factor even in the absence of coronary artery disease, or exacerbate this when it is present or subclinical in the older patient. Cardiovascular involvement during anaphylaxis plays a key nega- tive role in prognosis, irrespective of the additional, well-known side effects of adrenaline on the heart. Gastrointestinal manifestations Difficult or painful swallowing, nausea, vomiting, diarrhoea with soiling, and abdominal cramps may be associated with a severe reaction, but are usually overshadowed by more immediately life- threatening features. Differential diagnosis The protean manifestations of anaphylaxis have a potentially vast differential diagnosis, although the rapidity of onset, accompanying cutaneous features, and relationship to a likely or known potential trigger suggest the diagnosis in most cases, but the following may need to be considered. Wheeze and difficulty breathing—bronchial asthma, cardiogenic pulmonary oedema, foreign body inhalation, irritant chemical ex- posure, and tension pneumothorax are distinguished by the history, comorbidity, and associated presenting features. Light-headedness and syncope—an anxiety or vasovagal reaction need to be considered when there is a history of fearing an actual reaction, or in the context of a painful procedure such as an in- jection or local anaesthetic infiltration. Bradycardia, sweating and pallor without urticaria, erythema, or itch, associated with a brief prodrome and rapid response to the recumbent position favour the diagnosis of a vasovagal reaction. Facial swelling or angioedema—bacterial or viral infections usu- ally cause fever and/or pain, and traumatic or anticoagulant-related bleeding causes recognizable bruising. Angioedema in the absence of urticaria or pruritus can be bradykinin-related due to angiotensin- converting enzyme inhibitor (ACEI), or caused by actual or func- tional C1 esterase inhibitor deficiency. This may be hereditary (HAE), an autosomal dominant condition associated with prom- inent abdominal symptoms and recurrent attacks related to minor stress, or acquired (lymphoproliferative and some connective tissue disorders). Measurement of serum C4 is a rapid and inexpensive screening test, followed by the more specific C1 esterase inhibitor assays to confirm the diagnosis if the C4 is low. Management of a serious attack of HAE is with 20 units/kg C1 esterase inhibitor con- centrate intravenously, or with icatibant 30 mg subcutaneously, a bradykinin 2 receptor (BR-2) antagonist. Flushing—scombroid poisoning following ingestion of spoiled fish, carcinoid syndrome, alcohol-induced and systemic mastocytosis all produce flushing and require differentiation by a careful history and investigation. Other forms of shock—hypovolaemic, septic, cardiogenic, and other forms of shock should all be apparent from the history and examination. These are commonly associated with tachypnoea, but not with the other cutaneous and respiratory features of anaphylaxis. Clinical investigations The diagnosis of anaphylaxis is clinical: no immediate laboratory or radiological test confirms the process, and these must never delay immediate management. Disease progress may be monitored by pulse oximetry, haem- atocrit level (may rise with fluid extravasation), and arterial or venous blood gases (looking for respiratory or metabolic acidosis). Measurement of electrolytes and renal function, blood glucose, chest radiography, and electrocardiogram (ECG) are indicated if there is a slow response to treatment, or when there is doubt about the diagnosis. Mast cell tryptase, histamine, and platelet activating factor Despite initial promise, mast cell tryptase (MCT) in blood taken from 1 to 6 h after a suspected episode cannot be totally relied upon to diagnose anaphylaxis. It is not elevated consistently above the ref-

erence range of 1–11.4 ng/ml, particularly following food allergy or in children, and conversely it may be elevated post-mortem in nonanaphylactic deaths including trauma. However, measuring serial levels, or specific allelic subtypes such as mature β tryptase im- prove diagnostic value. When possible, three MCT samples should be taken: one immediately following resuscitation; the next 1–2 h after symptom onset (but no later than 6 h); the last at 24 h or during convalescence to establish the patient's baseline tryptase level. Fig. 17.3.2 Massive facial and body oedema with cardiovascular collapse in rapid sequence induction-related anaphylaxis, within 2 min of intravenous drug bolus. Picture reproduced with permission.

17.3 Anaphylaxis 3855 Serum histamine levels are impractical to measure as they are unstable and evanescent, only remaining elevated for 30 to 60 min maximum. Urinary histamine metabolites remain raised for sev- eral hours, but their interpretation requires further standardization. Platelet activating factor, chymase, and mast cell carboxypeptidase A3 levels may offer alternative marker profiles in the future. IgE skin testing, in vitro testing, and challenge testing Skin or blood tests for specific IgE antibodies must be done by those trained in their performance and interpretation, ideally about four weeks after the acute episode. Skin prick testing is the more sensi- tive: standardized extracts should be used with correct technique, supervised by an experienced physician in case of the occasional se- vere reaction. In vitro testing for allergen-specific IgE is less sensitive and depends on clinical correlation and the availability of specific assays. Over 600 different allergens are available for testing with the ImmunoCAP® system, or clinicians may use a radioallergosorbent (RAST) test (see Chapter 5.3). Challenge testing may be particularly useful in the diagnosis of nonimmunologic anaphylaxis, or to verify the clinical rele- vance of positive skin or IgE tests. False positive and false nega- tive reactions do occur, but are much less likely than with skin prick or in vitro testing; supervision by an experienced physician is essential. Immediate treatment A patient with anaphylaxis may present directly to his or her family doctor, or the emergency department, or the reaction may happen in hospital on a ward, in the operating theatre, the radiology depart- ment, and even in the outpatient department. Make certain that an ambulance is called at an early stage for all out-of-hospital anaphyl- actic reactions. Stop any potential causative agent such as an intravenous drug or infusion immediately. Manage the patient in a monitored resuscita- tion area, or bring equipment including at least a pulse oximeter, a noninvasive blood pressure device, and an ECG monitor to them. Obtain a brief history of possible allergen exposure and perform a rapid assessment of the extent and severity of the reaction. Look particularly for signs of upper airway swelling, bronchospasm, or circulatory shock. The first priority is to achieve cardiorespiratory stability by giving adrenaline, oxygen, and fluids with the patient supine. Antihistamines and steroids play no role until this has been achieved, and even then their value is debatable (see Box 17.3.2). Adrenaline Adrenaline is the drug of choice for acute anaphylaxis, whether allergic IgE-mediated or nonallergic. This should be given in all but the most trivial cases, certainly if there is progressive airway swelling, bronchospasm, or hypotension. It has beneficial α-, β1- and β2-adrenergic effects that counteract the profound vasodila- tation, mucosal oedema, and bronchospasm. Equally important is that adrenaline, via β2-adrenergic receptors, triggers a rise in intra- cellular cAMP and thereby inhibits further mast cell and basophil mediator release, thus attenuating the severity of the reaction when given early. Intramuscular adrenaline Intramuscular adrenaline is recommended when anaphylaxis is treated early, is progressing slowly, in the unmonitored patient, or if venous access is difficult or delayed. The dose is 0.01 mg/kg up to a maximum of 0.5 mg (1:1000 aqueous adrenaline up to a maximum of 0.5 ml), repeated every 5–15 min as necessary. This should be given into the upper outer thigh and may be injected

through clothing in an emergency, including when self-administered prehospital using an EpiPen® or other autoinjector. Intramuscular adrenaline is su- perior to subcutaneous, and the vastus lateralis muscle in the thigh is preferred to the arm deltoid muscle. Safe and practical intramuscular adrenaline doses in children are 0.3 mg (0.3 ml of 1:1000 aqueous adrenaline) for children aged 6– 12 years and 0.15 mg (0.15 ml of 1:1000 aqueous adrenaline) for chil- dren aged less than six years (Working Group Resuscitation Council UK, 2008). Intravenous adrenaline Intravenous adrenaline is only ever needed if there is rapidly progressive vascular collapse with shock, imminent airway ob- struction, or critical bronchospasm. It should only be given by practitioners experienced in its use, with continuous ECG moni- toring. It must be given with extreme care, suitably diluted, slowly, and titrated to response to avoid potentially lethal complications such as cardiac arrhythmias, myocardial ischaemia, and cerebro- vascular accident. The initial intravenous dose is 0.75–1.5 µg/kg (i.e. 50–100 µg) given slowly over up to 5 minutes depending on the rapidity and severity of the patient's decline, with the dose repeated according to response. Although 1:10 000 adrenaline containing 100 µg/ml is readily available (e.g. as a Minijet preparation), it is difficult to give slowly enough (10 µg/min) for intravenous use. An infusion of adrenaline containing 1 mg in 100 ml 0.9% saline (10 µg/ml) can be delivered at 30–90 ml/h (5–15 µg/min) and titrated to response, con- tinuing for up to 60 min after the resolution of all symptoms and signs of anaphylaxis, then weaning over the next 30 min and stop- ping while watching closely for any recurrence. Box 17.3.2 Initial treatment of anaphylaxis • Stop delivery of any potential causative agent • Call for help • Give adrenaline 0.01 mg/kg intramuscularly into lateral thigh, to max- imum 0.5 mg (0.5 ml of 1:1000 adrenaline) — May be repeated every 5–15 minutes — Alternatively, use the patient's EpiPen® or other autoinjector if readily available—may be given through clothing • Lay supine (or elevate legs) for shock • Give high flow oxygen • Insert large-bore intravenous cannula (14 G or 16 G) and give crystal- loid fluid bolus of 10–20 ml/kg Failure to respond or rapid deterioration • Start adrenaline infusion 1 ml (1 mg) of 1:1000 adrenaline in 100 ml normal saline at 30–90 ml/h (5–15 µg/min) titrated to response — Institute continuous ECG monitoring — Give adrenaline faster in cardiopulmonary collapse/arrest. • Consider assisted ventilation and endotracheal intubation by a skilled doctor, which may be extremely difficult

 Nebulized adrenaline (5 mg, which is 5 ml of undiluted 1:1000 adrenaline) can be given while parenteral adrenaline is being pre- pared as just described, particularly for upper airway oedema and bronchospasm. Oxygen and airway patency Give oxygen by face mask to all patients, aiming for an oxygen sat- uration above 93%. Place the patient supine, preferably with the legs elevated to optimize venous return in shock. Elevate the head and torso if respiratory distress is prominent or worsened. Call urgently for skilled airway assistance if there are signs of impending airway obstruction such as worsening stridor or hoarseness, or rapidly pro- gressive respiratory failure with tachypnoea and wheeze. Cyanosis and exhaustion indicate imminent respiratory arrest, but sedative or muscle relaxant drugs should never be given un- less the physician is trained in the management of the difficult airway. Endotracheal intubation and mechanical ventilation are extremely challenging. Create a surgical airway via the crico- thyroid membrane as a last resort, but before hypoxic cardiac ar- rest occurs. Fluid replacement A large-bore intravenous cannula should be inserted as soon as possible in patients showing signs of shock to give an initial fluid bolus of 10–20 ml/kg 0.9% saline, with up to 50 ml/kg needed in total to counter the massive intravascular fluid shifts and peripheral vaso- dilatation that occur in minutes with anaphylactic shock. There are no outcome data favouring colloids over crystalloids. Second-

line treatment Once oxygen, adrenaline, and fluids have been given to optimize the cardiorespiratory status and tissue oxygenation, the following drugs may be administered in a support role. Recommendations differ, and in the absence of any evidence base their use is largely extrapo- lated from success in other diseases. Their preparation or use must never delay the prompt administration of adrenaline. H1 and H2 antihistamines There is only weak evidence to support the use of antihista- mines, which should be reserved for the symptomatic relief of skin symptoms such as urticaria, mild angioedema, and prur- itus, although the Resuscitation Council (UK) recommends chlorphenamine 10 mg intramuscularly or (given slowly) intravenously to counter histamine-mediated vasodilation and bronchoconstriction. They must never be relied upon as sole therapy in significant anaphylaxis. Side effects of sedation, con- fusion, and vasodilatation can be troublesome, particularly when given parenterally. The combination of an H2 antihistamine with an H1 antihistamine is better at attenuating the cutaneous manifestations of a generalized allergic reaction than an H1 antagonist alone. However, there are no data in severe anaphylaxis and their combined use remains contro- versial. Choose a nonsedating H1-antihistamine on discharge (e.g. cetirizine 10 mg or loratadine 10 mg), both once daily, if the patient intends to continue working or driving a vehicle (see discharge oral medication). Corticosteroids As with the antihistamines, there are no placebo-controlled trials to confirm the effectiveness of steroids in anaphylaxis, despite their many theoretical benefits on mediator release and tissue responsive- ness. Most clinicians give prednisone 1 mg/kg (up to 50 mg) orally or hydrocortisone 1.5–3 mg/kg intravenously, particularly in pa- tients with airway involvement and bronchospasm, based on their important role in asthma. It is also thought that steroids prevent a biphasic reaction with recrudescence of symptoms following re- covery, but again supporting data are unconvincing, although they are essential in the management of recurrent idiopathic anaphylaxis. Salbutamol, glucagon, and atropine Nebulized salbutamol can be given in addition to adrenaline for re- sistant bronchospasm, which has the advantage of familiarity. Patients taking β-blockers are prone to very severe or treatment- refractory anaphylaxis. Glucagon should be given if adrenaline has been ineffective, 1–5 mg intravenously, followed by an infusion at 5–15 μg/min titrated to response. This raises cAMP by a nonadren- ergic mechanism, but may cause nausea and vomiting. Some patients with anaphylactic shock develop bradycardia re- sistant to adrenaline, possibly mediated by a neurocardiogenic vagal reflex. Atropine 0.6 mg intravenously up to 0.02 mg/kg has been suc- cessful in this situation. Vasopressors Vasopressors such as noradrenaline, metaraminol, phenylephrine, and vasopressin have anecdotally been reported as treatments for hypotension resistant to initial adrenaline and fluid therapy. As with intravenous adrenaline, these agents should only be given by those experienced in their use. Methylene blue Methylene blue, a competitive inhibitor of guanylate cyclase, at a dose of 1.5–2.0 mg/kg may counter resistant, nitric oxide-medi- ated vasodilatation particularly related to platelet activating factor. However, in turn it has occasionally caused anaphylaxis itself. Observation Most anaphylactic reactions are uniphasic and respond rapidly and completely to treatment. However, some patients develop pro- tracted reactions with an incomplete response to adrenaline, or deteriorate on attempted weaning from adrenaline. Such patients with unstable vital signs should be monitored and admitted to an intensive care facility. Biphasic anaphylaxis Patients who relapse after apparent complete resolution of all their initial symptoms and signs are described as having biphasic ana- phylaxis, which is reported in less than 1 to 20% of cases. It is un- known if this is predisposed to or caused by more severe presenting features, delayed or inadequate doses of adrenaline, or the failure to give steroids. However, the risk of a biphasic response means that patients with systemic anaphylactic reactions, including all those who have received adrenaline, must be observed for at

least 4–6 h after apparent full recovery. Those with a more prolonged reaction,

17.3 Anaphylaxis 3857 oral allergen exposure, reactive airways disease, or cardiac disease should be kept under close watch a little longer (8–10 h) because deaths from anaphylaxis occur in this group. Observation is safely performed in the emergency department, if a suitable holding area exists: ECG monitoring is not essential. Ongoing management All patients should be given a letter to take home detailing the nature and circumstances of the anaphylactic reaction, the treatment given, and the suspected causative agent(s). Before discharge, the need for take-home medication, an adrenaline autoinjector, and an allergy/ immunology referral must be considered (see Table 17.3.5). Oral medication Although there are no good data to support or refute their use, it is common practice to prescribe a two- or three-day discharge supply of combined H1 and H2 antihistamines plus oral steroids to pre- vent early relapse. Consider cetirizine 10 mg or loratadine 10 mg once daily, ranitidine 150 mg every 12 h, and prednisolone 50 mg once daily in adults with predominant cutaneous features such as urticaria following a generalized allergic reaction, or in those with bronchospasm. Adrenaline autoinjector The quandary of who to prescribe an adrenaline autoinjector to, and what to write in an action plan, is well described. As a guide, an adrenaline autoinjector should be given to a patient with ana- phylaxis after known allergen exposure outside of a medical setting, patients with food allergy (particularly to nuts or peanuts), and those in whom the reaction was severe and/or the cause unknown, including idiopathic anaphylaxis. Various autoinjectors are available in the United Kingdom and Europe including EpiPen®, Jext®, Emerade®, and Anapen® (latter under review in the United Kingdom). These autoinjector pens typically contain a single dose of 0.3 mg (300 µg) of adrenaline for adults, and 0.15 mg (150 µg) for children, with some manufacturers also producing a 0.5 mg (500 µg) adult device. They are approved for self-administered intramuscular use, although they are not interchangeable as their delivery technique differs, and inadequate needle length has caused concern particularly in the obese. The Auvi-Q® currently only available in the United States, was devel- oped as a ‘smart’, credit-card sized device with visual and audio prompts plus a retractable needle. Attitudes vary as to whether the emergency physician or general practitioner should initiate adrenaline autoinjector use, rather than waiting for specialist allergy/immunology review. However, who- ever takes responsibility must explain and demonstrate exactly how to use the device, and educate both the patient and another care- giver, particularly for children. Both need to be able to recognize the symptoms and signs of anaphylaxis and be prepared to actually use the autoinjector, particularly if distant from a healthcare facility. Recipients must be reminded that self-injectable adrenaline has a relatively short shelf life of between 18–24 months, and be shown how to look after it. Also as up to 30% patients will require more than one dose of adrenaline, this raises the need for two autoinjectors to be provided at a time. Allergy/immunology referral Disappointingly, few patients who suffer an episode of anaphyl- axis are referred for specialist allergy/immunology follow-up. Referral should be mandatory for anyone prescribed an adrenaline autoinjector device, and for patients following a wasp or bee sting suitable for immunotherapy, suspected food-induced, drug- in- duced, or exercise-induced anaphylaxis, and those with severe reac- tions without an obvious trigger. To assist the allergist/immunologist it is useful to ask the patient to write a brief diary of events in the 6–12 h preceding the reaction, particularly when the cause was un- clear. This should include all foods ingested, drugs taken (including nonproprietary), cosmetics used, and activities performed outside as well as indoors. Later recall of events will be flawed unless docu- mented contemporaneously. Prevention Education A written anaphylaxis action plan suitable for the patient, carer, or school (in children) is essential, particularly for anyone given an adrenaline

autoinjector. Patients must understand the nature and cause of the reaction, how to recognize anaphylaxis, and the importance of carrying an adrenaline autoinjector at all times. Individualized antigen elimination measures such as hymenopteran avoidance must be explained, with information on hidden or un- expected sources of antigen such as salicylate in over-the-counter preparations, trace food elements such as nuts, and possible cross- reactions to unrelated substances. Also, make certain patients are on optimal therapy for any coexistent asthma or severe atopy, and appropriate cardiovascular medication (see next). It is sensible to recommend that the patient wears an alert bracelet such as the MedicAlert® following a severe reaction that may recur with sufficient severity to prevent them from giving a history, par- ticularly highlighting drug or vaccine allergy to avoid inadvertent iatrogenic exposure. Table 17.3.5 Discharge checklist following anaphylaxis Adrenaline autoinjectora EpiPen®, Jext®, Emerade® Anapen® Auvi-Q® Oral medication 2–3 day supply Allergy/immunology referral Include comprehensive description of acute event Education+ Anaphylaxis Action Plan Allergen avoidance Optimize other management Coexistent asthma/atopy Appropriate cardiovascular therapy (avoid β-blocker / ACEI) Patient alert Discharge summary Printed allergy warning MedicAlert® bracelet a Available in 0.15 mg, 0.3 mg, or 0.5 mg (some) intramuscular dose; +, provide information in writing; ACEI, angiotensin-converting enzyme inhibitor.

 A variety of web-based resource material is now available, including from the British Society for Allergy and Clinical Immunology (http://www. bsaci.org), the Anaphylaxis Campaign (http://www.anaphylaxis.org. uk), the European Academy of Anaphylaxis and Clinical Immunology (http://www.eaaci.org), the American Academy of Allergy, Asthma & Immunology (http://www.aaaai.org), and the American College of Allergy, Asthma & Immunology (http://www.acaai.org). Pretreatment There is no convincing justification for pretreatment. In particular, the practice of giving prophylactic corticosteroids and/or antihis- tamines to reduce the risk of a severe iodinated contrast media reaction during radiological procedures is neither reliable, nor sup- ported by the literature, and should be abandoned. Skin testing and short-term desensitization Skin testing should be considered in certain clinical circumstances, such as when penicillin is considered essential but there is a history of possible penicillin allergy. If positive, it can be followed by short- term desensitization over several hours, with increasing doses at 15 min intervals under strict medical control in a monitored area. There are well-tried desensitization regimes for other β-lactams and sulphonamides, and some that are empirically derived for a var- iety of other antimicrobials, chemotherapeutic drugs including the platins, and the monoclonal antibodies. Long-term desensitization (immunotherapy) Venom immunotherapy (VIT) hyposensitization is reserved for Hymenoptera venom in wasp and bee allergy because these reac- tions may become life-threatening and yet are preventable in over 90% of cases. Patients with asthma or on a β-blocker or angiotensin- converting-enzyme (ACE) inhibitor require careful risk–benefit evaluation. Therapy needs to be continued at increasing intervals for at least three to five years. Drug and allergen avoidance Wherever possible give drugs orally or, if intravenously, administer slowly. Avoid drugs known to predispose to reactions in allergic pa- tients, particularly aspirin, NSAIDs, and ACE inhibitors, as well as β-blockers. Patients at risk of recurrent anaphylaxis with hyperten- sion or ischaemic heart disease should ideally not take β-blockers. This may need discussion with the patient’s other specialists to be certain that the overall risk–benefit favours medication change if the patient is already taking a β-blocker, and care should be taken not to substitute an ACE inhibitor. Patients should be advised to reduce the chance of allergen ex- posure risk by destroying nearby wasp nests and removing al- lergenic foods from the house, also to avoid

insect sting with appropriate clothing and certain foods by always checking the manufacturer's label. Areas of uncertainty and future developments Progress in anaphylaxis research is hampered by the lack of a univer- sally accepted definition, or an agreed grading system for severity. Prospective data collection, preferably in multiple sites, is essential to improve the evidence base and allow validation of assessment, treatment, and follow-up protocols. Particular areas that need elucidating include which symptoms or signs most reliably pre- dict the risk of severe anaphylaxis; which laboratory test(s) could be employed to confirm and ideally quantify the severity of an ana- phylactic reaction; what predicts a biphasic reaction; the true role of steroids and antihistamines; and finally whether novel treatments such as anti-IgE therapy in peanut allergy, oral or sublingual im- munotherapy for other food allergy, or even sublingual adrenaline for self-medication will prove effective and acceptable. FURTHER READING Guidelines and practice parameters Campbell R, et al. (2014). Emergency department diagnosis and treat- ment of anaphylaxis: a practice parameter. Ann Allergy Asthma Immunol, 113, 599–608. Lieberman P, et al. (2015). Anaphylaxis - a practice parameter update 2015. Ann Allergy Asthma Immunol, 115, 341–84. Muraro A, et al. (2014). Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy, 69, 1026–45. Sampson HA, et al. (2005). Symposium on the definition and man- agement of anaphylaxis: summary report. J Allergy Clin Immunol, 115, 584–91. Sampson HA, et al. (2006). 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, 117, 391–7. Scolaro R, et al. (2017). Australian and New Zealand anaesthetic al- lergy group perioperative anaphylaxis investigation guidelines. Anaesth Intensive Care, 45, 543–55. Simons FER, et al. (2011). International Consensus on (ICON) ana- phylaxis. World Allergy Organisation J, 7, 9. Simons FER, et al. (2011). World Allergy Organization guidelines for the assessment and management of anaphylaxis. J Allergy Clin Immunol, 127, 593.e1–e22. Simons FER, et al. (2015). World Allergy Organization anaphyl- axis guidelines: 2015 update of the evidence base. World Allergy Organization J, 8, 32. Truhlar A, et al. (2015). European Resuscitation Council Guidelines for Resuscitation 2015 Section 4. Cardiac arrest in special circum- stances. Resuscitation, 95, 148–201. Working Group of the Resuscitation Council (UK) (2008). Emergency treatment of anaphylactic reactions—guidelines for healthcare pro- viders. Resuscitation, 77, 157–69. Reviews and overviews Brown SG (2004). Clinical features and severity grading of anaphyl- axis. J Allergy Clin Immunol, 114, 371–6. Brown SG (2006). Anaphylaxis: clinical concepts and research prior- ities. Emerg Med Australas, 18, 155–69. Brown SG, Mullins RJ, Gold MS (2006). Anaphylaxis: diagnosis and management. Med J Aust, 185, 283–89. Dhami S, et al. (2014). Management of anaphylaxis: a systematic re- view. Allergy, 69, 168–75. Sicherer S, Sampson H (2018). Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention and manage- ment. J Allergy Clin Immunol, 141, 41–58. Simons FER, Sheikh A (2013). Anaphylaxis: the acute episode and be- yond. BMJ, 346, f602.

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17.4 Assessing and preparing patients with medical

17.4 Assessing and preparing patients with medical conditions for major surgery 3860 Tom Abbott and Rupert Pearse

ESSENTIALS The assessment of patients before surgery is complex. However, since surgery is offered to increasing numbers of patients with mul- tiple comorbidities, the demand for comprehensive preoperative assessment is expected to increase. Perioperative medicine provides a patient-centred approach from preoperative assessment through to hospital discharge and beyond. Preoperative assessment serves to identify comorbidity that may require optimization before surgery, plan perioperative care, identify a need for a nonstandard anaesthetic technique, assess functional reserve, brief patients on the perioperative care pathway, and provide patients with an opportunity to have questions answered. Patients with active cardiac or respiratory conditions are among
those most likely to benefit from preoperative optimization. Smoking cessation reduces the incidence of postoperative pul- monary complications. During surgery, goal-directed haemo- dynamic therapy is used to optimize cardiovascular performance. It is unclear what practical steps can be taken to prevent illness in the immediate postoperative period, over and above increased vigilance. There are a variety of tools for preoperative assessment and rec- ognized approaches to managing patients with existing chronic disease during the perioperative period, but the absence

of robust evidence to favour any particular clinical approach is striking. Introduction Surgical treatments are now offered to more and more patients. This due to growing global population, increased healthcare cap- acity, and because improvements in surgical and anaesthetic care mean that patients considered too high-risk only a few years ago are now routinely offered surgery. The result is a shifting demo- graphic of the surgical population toward older patients with multiple comorbidities. Modern perioperative care therefore re- quires a robust and considered approach to each stage of a patient's journey and a multidisciplinary approach best termed periopera- tive medicine. Here, we review current approaches for assessing and preparing patients for surgery. Perioperative morbidity and mortality:
A global perspective An estimated 300 million surgical procedures are performed world- wide each year, which is greater than the worldwide prevalence of malaria (c.200 million cases). However, little is known about the global incidence of postoperative death and disability. Accepted es- timates of perioperative mortality in developed countries range be- tween 0.5 to 2.0% of surgical procedures, although one estimate was as high as 4% for noncardiac surgery. In contrast, data from small studies suggest the postoperative mortality rate may be as high as 5–10% in resource-poor countries. The most common causes of death within two days of surgery are cardiovascular in origin, fol- lowed by sepsis and multiorgan failure. Death is more common fol- lowing emergency compared to elective surgery. However, different population demographics and public health profiles make accurate comparisons between developing and developed countries complex. Nonfatal complications following surgical procedures are common. These range from wound pain and immobility to more serious conditions, including pneumonia, surgical site infection, myocardial infarction, acute kidney injury, and stroke. The presence of any postoperative complication is associated with reduced long- term survival. In developed countries, estimates of the proportion of patients with complications or adverse events following surgery vary between 3 to 20% of procedures (Table 17.4.1) with the incidence affected by patient factors, the nature of the surgical procedure, and the quality of the care the patient receives. The 'high-risk' surgical patient Epidemiological studies have described a high-risk group of patients that account for 80% of postoperative deaths, but represent only 15% of patients having major surgery. The characteristics of this high-risk group are not well defined, but the typical patient is older, with sig- nificant comorbid disease, and often undergoes emergency surgery. The risk of postoperative complications is influenced by multiple factors, which can be divided into two broad categories: procedure- related factors and patient-related factors. Procedure-related factors include surgical technique (e.g. open or laparoscopic), duration, 17.4 Assessing and preparing patients with medical conditions for major surgery Tom Abbott and Rupert Pearse

 and type of surgery, intraoperative complications (e.g. blood loss), procedure-specific postoperative complications (e.g. anastomotic leak after bowel resection), and—much less frequently—surgical or anaesthetic error. The influence of these factors is compounded by abnormal physiology during emergency procedures, resulting in worse outcomes. However, most postoperative complications are likely to occur, not as a direct result of the surgical procedure, but as a secondary consequence of indirect factors such as immobility, tissue inflammation, or hospital-acquired infection. Patient-related factors refer to an individual's state of general physical health or functional capacity. This is usually considered in the context of the ability to withstand the physiological stress as- sociated with surgery, such as elevated cardiac output or minute ventilation, fluid shifts between body compartments, the effects of mechanical ventilation, or inflammation associated with tissue in- jury. The resultant increase in cellular

respiration increases the total body oxygen requirement. Inadequate functional capacity in one or more organ systems can manifest as an inability to adequately in- crease oxygen transport to the body tissues during surgery, which is thought to be causally associated with postoperative complications and death. Functional capacity is influenced by age, cardiorespira- tory fitness, and comorbidities, but cannot be reduced to a list of chronic diseases or measurement of any one variable. Inter-relation of functional reserve, comorbidity, and procedural factors is com- plex (Fig. 17.4.1). There is considerable overlap between functional reserve and comorbidity because physical illness affects cardio- respiratory fitness. For example, patients with congestive cardiac failure, or those receiving cytotoxic chemotherapy, often experience a reduction in exercise performance. Equally comorbid disease can directly influence a surgical procedure, mandating a specific surgical or anaesthetic technique. Preoperative assessment and risk stratification Ideally, the anaesthetic assessment will be performed days or weeks in advance of surgery to allow time for planning of perioperative care. However, in many healthcare systems, assessment on the morning of surgery is the routine. This often leaves clinical staff with the diffi- cult decision to either proceed with surgery or postpone surgery at the last minute to address the management of chronic disease. The preoperative assessment clinic, led by nurses and doctors, provides an opportunity to evaluate the patient in the days or weeks before a planned surgical procedure and formulate a definitive plan for peri- operative care. Preoperative assessment serves several purposes: • To identify comorbidity that may require optimization before surgery • To plan perioperative care • To identify a need for a nonstandard anaesthetic technique • To assess functional reserve • To brief patients on the perioperative care pathway and provide an opportunity to have questions answered A typical appointment involves a medical history and physical examination including: resting observations, height, and weight; blood tests such as routine haematology, biochemistry, and coagu- lation tests; urine analysis and electrocardiography. Further inves- tigations, for example, chest X-ray, spirometry, echocardiography, or exercise testing, or referral to a specialist, are performed on a case-by-case basis. Some centres use standard criteria to trigger a review by an anaesthetist or referral to other specialists such as a cardiologist. It seems intuitive that patients attending a preoperative assessment clinic are less likely to have their procedure postponed on the day of surgery. However, growing evidence suggests that at- tending a preoperative assessment clinic could also result in lower postoperative mortality, reduced hospital and high-dependency unit (HDU) length of stay, and fewer unplanned critical care unit admissions. Unfortunately, the provision of preoperative assessment clinics is not universal and 20% of patients undergoing high-risk surgery in the United Kingdom do not attend a preoperative assess- ment clinic. The global availability and use of preoperative assess- ment clinics is unknown. Opinion leaders suggest that all patients undergoing major surgery should be reviewed by an experienced anaesthetist in a preoperative Table 17.4.1 Approximate incidence of common postoperative complications following elective noncardiac surgery Complication Incidence (%) All complications 15% Infectious complications Sepsis 5% Superficial surgical site 3% Pneumonia 2% Urinary tract 2% Deep surgical site 1% Body cavity <1% Cardiovascular complications Myocardial injury 8% Myocardial infarction 3% Arrhythmia 3% Heart failure 2% Pulmonary embolism <1% Stroke <1% Cardiac arrest <1% Other complications Postoperative bleeding 3% Acute kidney injury 2% Acute respiratory distress syndrome <1% Gastrointestinal bleed <1% Procedure-related factors Functional reserve Co-morbidity Fig. 17.4.1 The three principle components of perioperative risk.

Section 17 Critical care medicine 3862 assessment clinic. This provides an opportunity to evaluate the risk of postoperative morbidity or mortality. Risk estimates can be used to identify patients who are likely to require enhanced perioperative care, to determine whether a patient requires critical care immedi- ately following surgery, and to provide patients with important de- tail during the informed consent process. The optimal approach to estimating the risk of perioperative morbidity or mortality remains uncertain. Potential methods include risk stratification scores or in- dices, objective assessment of functional capacity through exercise, and plasma biomarkers. Similar approaches are used in audit and re- search to adjust for individual patient risk factors and facilitate com- parisons between different patients or institutions. However, the most commonly used risk-adjustment models use a combination of preoperative and intraoperative factors, which limit their use for risk prediction before surgery. Risk stratification tools Clinical prediction rules are ubiquitous to medical practice and comprise main five types: scoring systems, prediction models, nomograms, decision trees, and neural networks. The underlying principle is to identify factors associated with a particular outcome and to calculate the probability of that outcome occurring given the presence of one or more predictors. Scoring systems tend to feature a concise group of predictors, weighted according to their association with the outcome measure. The total score indicates a risk category, but does not provide an absolute measure of risk. More complex risk prediction models feature a larger number of variables and often provide a numerical estimate of risk. However, due to the amount of information required, the latter can be cumbersome to use.
A variety of surgical scoring systems and risk prediction models are available for general and specific surgical populations and out- come measures. However, most of these have only been validated in single-centre studies or in specific patient groups. Four preoperative risk stratification tools have been validated in multiple centres: the American Society of Anesthesiologists' Physical Status Score (ASA- PS), the Surgical Risk Score, the Surgical Risk Scale, and the Charlson Comorbidity Index. ASA-PS is a simple and commonly used risk assessment tool, whereby a patient is placed into one of five groups according the presence and severity of comorbid disease. However, it has been criticized due to reportedly low inter-rater reliability. The Surgical Risk Scale is favoured because it is concise, easy to use, and comprises only preoperative variables. It is a composite score de- rived from the ASA-PS, urgency of surgery and the grade of surgery according to the British United Provident Association (BUPA) clas- sification (Table 17.4.2). However, it has only a moderate predictive accuracy. While it is simple is to use and could be easily integrated into clinical practice, it has been criticized for including ASA-PS, which requires a subjective assessment by the clinician. The Charlson Comorbidity Index, which is more objective, has a poor predictive accuracy. The Revised Cardiac Risk Index is one of the best models for predicting postoperative cardiac complications. It consists of six components: high-risk type of surgery, history of ischaemic heart disease, history of congestive cardiac failure, history of cerebrovas- cular disease, preoperative insulin usage, and preoperative serum creatinine levels of more than 2.0 mg/dl (>177 µmol/litre). Other risk stratification models used for risk-adjustment have a higher predictive accuracy, for example, the P-POSSUM. However, these models use intraoperative and postoperative variables, so they do not have a preoperative application. Despite their utility, preopera- tive risk stratification tools are not widely used. Assessing functional capacity For many years, anaesthetists and surgeons have subjectively as- sessed their patients' functional capacity to provide an indication of cardiorespiratory reserve. There are also more objective methods to evaluate functional capacity. Metabolic equivalents (METs) provide a semi-quantitative measure of exercise tolerance. One MET repre- sents resting oxygen consumption of c.3.5 ml/kg/min when sitting. Nomograms and tables provide a list of day-to-day activities with corresponding average

METS, which allow the clinician to estimate functional capacity. A more reliable method is to use a patient ques- tionnaire, for example, the Duke Activity Status Index (DASI), which is a set of 12 standardized questions relating to a range of activity levels. The total score correlates with maximal oxygen consump- tion measured during exercise testing in surgical and nonsurgical cohorts. However, the ability of the index to predict postoperative mortality or morbidity is still being evaluated. Perhaps the most robust method for assessing functional cap- acity is cardiopulmonary exercise testing (CPET). Most commonly a cycle ergometer operating an incremental ramp protocol is used, whereby the workload increases along a fixed gradient according to predicted exercise tolerance. The aim is for the patient to reach peak exertion within 8–12 minutes. Noninvasive haemodynamic and gas exchange measurements are recorded continuously, which allows multiple parameters, with variable predictive accuracies, to be de- rived. The two most widely used cardiopulmonary exercise testing- derived variables are peak oxygen consumption (VO2peak) and Table 17.4.2 Surgical Risk Scale, incorporating American Society of Anesthesiologists' Physical Status Score (ASA-PS) Category Description/Example surgery Score Urgency of surgery Elective Routine booked nonurgent case 1 Scheduled Booked admission 2 Urgent Case requiring treatment within 24–48 hours of admission 3 Emergency Case requiring immediate treatment 4 Grade of surgery Minor Removal of sebaceous cyst, skin lesion, oesophagogastric duodenoscopy 1 Intermediate Unilateral varicose vein, unilateral hernia repair, colonoscopy 2 Major Appendicectomy, open cholecystectomy 3 Major plus Gastrectomy, colectomy 4 Complex major Carotid endartarectomy, AAA repair, limb salvage, anterior resection, oesophagectomy 5 ASA-PS I No systemic disease 1 II Mild systemic disease 2 III Systemic disease affecting activity 3 IV Serious disease but not moribund 4 V Moribund, unlikely to survive 5 AAA, abdominal aortic aneurysm.

17.4 Assessing and preparing patients 3863 oxygen consumption at the anaerobic threshold (VO2AT), the point where the metabolism switches from predominantly aerobic res- piration to predominantly anaerobic respiration (Fig. 17.4.2). Most evidence supporting preoperative cardiopulmonary exercise testing comes from single-centre studies of restricted cohorts of surgical patients. In only a handful of the studies were clinicians blinded to the result of the cardiopulmonary exercise testing, adding fur- ther potential for bias. Growing evidence suggests that VO2peak may be the best cardiopulmonary exercise testing-derived predictor of surgical outcome. However, VO2AT is probably the most commonly used. Cardiopulmonary exercise testing is becoming increasingly popular as an objective method of preoperative assessment in some countries. In the United Kingdom, approximately half of hospitals have access to it. Biochemical markers of risk Biochemical markers are a core feature of modern medical practice. Familiar examples include creatinine as a marker of renal function and cardiac troponin as a marker of cardiac injury. In the context of surgery, biochemical markers are used before, during, and after pro- cedures to identify and categorize disease, track clinical progress and response to treatment, and to aid prognostication. However, there is growing interest in their use to predict short- and long-term surgical outcomes. Current evidence is mainly restricted to morbidity and mortality associated with perioperative cardiac and renal disease and features a limited number of candidate molecules. Brain natriuretic peptide (BNP) is most commonly used to aid diagnosis and prognosis in patients with heart failure, but it is be- coming increasingly clear that increased preoperative BNP is as- sociated with postoperative mortality and nonfatal myocardial infarction. When combined with the Revised Cardiac Risk Index, preoperative BNP improves the accuracy of risk prediction com- pared with the risk index alone. Other candidate biochemical markers are cardiac troponin

and cystatin-c. Troponin is elevated before 10% of cardiac surgical procedures and may be associated with postoperative cardiac complications, although this has not been widely studied in patients undergoing noncardiac surgery. Preoperative cystatin-c may be associated with kidney injury after surgery, but needs further investigation. One in ten patients experience myocardial injury after non- cardiac surgery, defined by a transient increase in serum troponin concentration. This is associated with mortality, the risk of which increases with the magnitude of troponin release. Most cases of postoperative myocardial injury are asymptomatic and there is increasing awareness that traditional tests of myocardial ischaemia and infarction do not identify the bulk of these. Postoperative brain natriuretic peptide and C-reactive protein are both associated with mortality and adverse cardiac events. Gas exchange AT 0:00 2:00 4:00 6:00 8:00 10:00 12:00 Time (min) 14:00 16:00 Increasing workload VO2 and VCO2 18:00 20:00 22:00 Slope (ml/min / W) = 10.0 Fig. 17.4.2 Gas exchange during a cardiopulmonary exercise test. Blue line—VO2, red line—VCO2. The anaerobic threshold (AT) is indicated.

Section 17 Critical care medicine 3864 Perioperative medicine: managing the high-risk surgical patient The supposition that most postoperative complications arise either during surgery or in the immediate postoperative period seems intuitive. Anaesthesia, mechanical ventilation, and surgical ma- nipulation are physiologically abnormal, hence it is not surprising that postoperative complications occur. Patients undergoing high-risk procedures or those with existing medical conditions are obvious candidates for perioperative interventions aimed at improving outcomes after surgery. The goal of perioperative medi- cine is to facilitate surgery and minimize associated morbidity and mortality—this has considerations before, during, and after sur- gery (Fig. 17.4.3). Before surgery Patients with active cardiac or respiratory conditions are among those most likely to benefit from preoperative optimization (Fig. 17.4.4). Suspected cardiac failure or valvular disease can be investigated with echocardiography. Hypertension is often treated if the systolic or diastolic pressures are greater than 180 mm Hg or 110 mm Hg, respectively. New guidelines suggest that patients referred for elective surgery should have a blood pressure of less than 160/100 mm Hg recorded in primary care. Gradual reduc- tion in blood pressure before surgery is preferable to rapid control using intravenous agents. Some patients with unstable coronary artery disease may require procedural intervention before sur- gery. However, prophylactic preoperative revascularization may not reduce postoperative cardiac events but will delay surgery. Pharmacotherapy to reduce postoperative cardiac events is also controversial. Until recently, perioperative blockers were recom- mended for patients with cardiovascular risk factors. However, while β-blockade reduces rates of postoperative myocardial infarc- tion, it increases the risk of stroke, hypotension, and death. These agents are now only recommended for patients at intermediate or high-risk of myocardial ischaemia and when prescribed should be started far enough in advance of planned surgery to allow safety and tolerability to be assessed prior to surgery. Other negatively chronotropic agents like ivabradine may represent an alternative, but this has yet to be investigated. Patients undergoing vascular surgery may benefit from risk factor modification with statins. Similarly, patients taking aspirin often continue to do so, when the risk of cardiovascular complications if aspirin is withheld out- weighs the risk of bleeding if aspirin is continued. In this respect, patients with coronary artery stents require special consideration. Patients with existing respiratory disease are at increased risk of postoperative pulmonary complications and may benefit from en- hanced perioperative care. This is particularly important for patients with chronic obstructive pulmonary disease (COPD), poorly con- trolled chronic respiratory conditions, or obesity-related disease such as obstructive sleep apnoea. The mainstay

of preoperative manage- ment is optimization of existing treatments and considering a lower threshold for postponing surgery in the event of an exacerbation. In addition, several preoperative respiratory interventions are gaining widespread support. Smoking cessation reduces the incidence of postoperative pulmonary complications, although the optimum duration of abstinence before surgery is unclear. Respiratory physio- therapy in the immediate postoperative period is widely adopted as prophylaxis against respiratory complications, and physio- therapy before surgery may provide added benefit. Similarly, there is growing evidence that increasing preoperative fitness through ex- ercise training can improve surgical outcomes, but more research is needed to better to define the optimum target population and exer- cise regimen. During surgery It is widely accepted that tissue oxygenation may become im- paired during surgery due to the effects of tissue injury, inflam- mation, and the sympathetic response to surgical stimulation. Many clinicians use intraoperative goal-directed haemodynamic Before surgery During surgery After surgery Home Risk assessment Procedure-related factors Functional capacity Co-morbidity Biomarkers Optimization Optimising existing treatments Starting new treatment where appropriate Consider goal-directed therapy Surveillance Consider screening for asymptomatic disease Reduce long-term harm Routine follow-up Identify perioperative complications Fig. 17.4.3 Flow diagram of the perioperative care pathway.

 therapy to optimize cardiovascular performance, thus improving cellular respiration and tissue oxygenation with the aim of improving perioperative outcome. The most common method of achieving this is with intravenous fluid therapy and inotropic agents guided by cardiac output monitoring. Meta-data sug- gest that goal-directed therapy might be associated with lower rates of postoperative complication, but further evidence from multicentre trials is needed. After surgery The genesis and mechanism of most postoperative complications are poorly understood. Major surgery triggers a systemic inflam- matory response similar to that which follows sepsis or major trauma, although it is usually less severe. New evidence suggests that surgery can suppress the immune response for several days, indicating a period of potentially increased vulnerability to noso- comial infection. Furthermore, most postoperative myocardial in- jury, detected by raised cardiac troponins, occurs in the first 24 hours after surgery. However, it is unclear what practical steps can be taken to prevent illness in the immediate postoperative period, over and above increased vigilance. In the case of myocardial in- jury, routine troponin sampling is a potential surveillance option, but little is known about the aetiology of postoperative myocardial injury and myocardial infarction, and there are no proven treat- ment strategies. Further research is needed to define the clinical approach to prevention and treatment of postoperative cardiac complications. It is also possible that extending intraoperative treatment strat- egies, for example, goal-directed therapy and high intensity nursing, into the early postoperative period may improve patients' outcomes. This already occurs in some centres operating postanaesthesia care units for patients that are not transferred to the critical care unit immediately after surgery. Given the clear association between postoperative morbidity and subsequent mortality, enhanced sur- veillance of patients for postoperative complications after hospital discharge may be prudent. However, there is no defined protocol or pathway for postoperative surveillance over and above existing sur- gical outpatient follow-up. FURTHER READING Abbott, et al. (2017). Frequency of surgical treatment and related hos- pital procedures in the UK: a national ecological study using hos- pital episode statistics. Br J Anaesth, 119, 249–57. Fleisher LA, et al. (2014). 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing General haemodynamic measures 1. 5% dextrose at 1

ml/kg/hr 2. Transfuse blood to maintain haemoglobin >8 g/dl 3. Clinician retains discretion to adjust therapy if concerned about risks of hypovolaemia or fluid overload 4. Mean arterial pressure 60–100 mmHg; SpO2 ≥ 94%; core temperature 37°C; heart rate <100 bpm Administering fluid to a stroke volume end point 1. 250 ml colloid boluses to achieve a maximal value of stroke volume [Note: Start dopexamine after first fluid challenge –see below] 2. Fluid challenges should not be continued in patients who are not fluid responsive in terms of a stroke volume increase 3. Fluid responsiveness is defined as a stroke volume increase ≥10% 4. If stroke volume decreases further fluid challenge(s) are indicated 5. Persistent stroke volume responsiveness suggests continued fluid loss Dopexamine

1. Start dopexamine infusion at fixed rate of 0.5 µg/kg/min after first colloid fluid challenge
2. Halve dose if heart rate rises to the greater of: (a) >120% of baseline value, or (b) >100 bpm for more than 30 minutes.
3. Stop dopexamine if tachycardia persists Example intraoperative optimization algorithm (OPTIMISE Trial) Fig. 17.4.4 Intraoperative goal-directed therapy algorithm from the OPTIMISE Trial.

Section 17 Critical care medicine 3866 noncardiac surgery: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. Circulation, 130, e278–333. International Surgical Outcomes Study Group (2016). Global pa- tient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries. Br J Anaesth, 117, 601–9. Khuri SF, et al. (2005). Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg, 242, 326–41; discussion 41–3. Moonesinghe SR, et al. (2013). Risk stratification tools for predicting morbidity and mortality in adult patients undergoing major sur- gery: qualitative systematic review. Anesthesiology, 119, 959–81. National Institute for Health and Care Excellence (NICE) (2003). Preoperative Tests: The Use of Routine Preoperative Tests for Elective Surgery. Clinical guideline [CG3]. http://guidance.nice. org.uk/cg3 The Royal College of Anaesthetists (2015). Perioperative Medicine: The Pathway to Better Surgical Care. http://www.rcoa.ac.uk/perioperati vemedicine

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ESSENTIALS Acute respiratory failure Acute respiratory failure is defined clinically by hypoxaemia (Pao2 <8 kPa, normal range 10–13.3 kPa) with (type 2) or without (type 1) hypercapnia (Paco2 >6.5 kPa). It is one of the most common prob- lems afflicting critically ill patients and is a common indication for transfer to an intensive care unit. Clinical context—critical illness may be manifest solely as respira- tory insufficiency, especially in patients with covert infection. Acute respiratory failure frequently coexists with other organ system failures in the critically ill, and delayed recognition of the condition adversely affects outcome. Clinical features—the signs of critical illness tend to be similar what- ever the precipitating cause and are manifest in failure of the respira- tory, cardiovascular, and neurological systems. The airway, breathing, circulation, disability, and exposure approach to clinical assessment is advocated. Respiratory rate should normally be 12–20 breaths per minute: a higher or increasing rate is a ‘hard’ sign of critical illness. Full and repeated physical examination may be required to assess the cause and severity of acute respiratory failure and its associated complications, but in severe cases should not delay the instigation of life-saving support and treatment. Investigation—pulse oximetry allows the continuous noninvasive monitoring of arterial oxygen saturation and is useful in all clinical settings. Arterial blood gas analysis confirms the type and severity of acute respiratory failure, and may reveal nonpulmonary organ dysfunction. A full range of imaging modalities, including computed tomography and echocardiography, may be required for diagnosis. Management—the main steps in treating acute

respiratory failure are: (1) Establishing and securing the airway often necessitating (i) endotracheal intubation—the decision to intubate is based on several factors including: (a) inability to maintain the airway, (b) deteriorating physiological parameters despite adequate therapy and often noninvasive respiratory support, (c) reversibility of the underlying condition; (ii) tracheostomy—this may be indicated early in the course of acute respiratory failure in patients likely to require prolonged ventilatory support. (2) Increasing Fio2 to treat hypoxaemia—oxygen can be admin- istered by a variety of methods depending on the required oxygen concentration. (3) Instituting mechanical ventilation (invasive or noninvasive) as necessary to treat hypoxaemia and hypercapnia—noninvasive positive pressure ventilation involves the delivery of mechanically generated breaths via an interface with the upper airway; usually a tight-fitting nasal or full face mask. In patients receiving mechanical ventilation, the optimum mode depends in part upon the nature of the underlying illness, particularly the presence or absence of pul- monary parenchymal or airway pathology, the phase of the illness (acute or chronic), and the aims of support at the time it is applied. (4) Identifying and managing the precipitating condition. (5) Discontinuing and withdrawing support in stages (‘weaning’) as the underlying condition improves, or if recovery is no longer deemed possible. Acute respiratory distress syndrome Acute respiratory distress syndrome results from acute neutrophilic inflammation causing dysfunction of the gas exchange surface of the lung, the alveolar-capillary membrane. Precipitating factors, which may be single or combined, can either primarily affect the lung dir- ectly (e.g. pneumonia, aspiration of gastric contents, chest trauma) or act through the circulation, often causing acute respiratory distress syndrome as part of a multiple organ dysfunction syndrome (e.g. se- vere sepsis and shock). Histological phases have been observed, but these usually overlap and can all coexist simultaneously. The initial phase is characterized by high-permeability pulmonary oedema in which the airspace is filled with proteinaceous neutrophilic exudate. During the subse- quent fibroproliferative response, inflammation resolves, and repair and regeneration processes predominate. Diagnosis—this requires: (1) An appropriate clinical setting, with one or more recognized risk factors. (2) New, bilateral, diffuse, patchy, or homogenous pulmonary in- filtrates consistent with pulmonary oedema on chest radiography. (3) No clinical evidence of heart failure, fluid overload, or chronic lung disease. 17.5 Acute respiratory failure Susannah Leaver, Jeremy Cordingley, Simon Finney, and Mark Griffiths

 (4) Pao2:Fio2 ratio of less than 40 kPa (<300 mm Hg) for mild cases, less than 26.6 kPa (<200 mm Hg) for moderate cases, and less than 13.3 kPa (100 mm Hg) for severe cases in the presence of a positive airway pressure of at least 5 cmH2O. Investigations—these are aimed at estimating the severity of lung injury and elucidating the precipitating cause. Computed tomog- raphy, if practical, may be useful in guiding therapy and detecting complications. Management and prognosis—aside from other standard supportive measures, low tidal volume (‘protective’) ventilation, and for patients with severe ARDS managed in experienced centres, managing in prone position for 16 hours each day, has been shown to improve outcome. Overall mortality of patients with acute respiratory distress syndrome is in the range 25–40%, but higher in some subgroups (e.g. sepsis) than others (e.g. trauma). Survivors of acute respiratory distress syndrome may have persistent nonpulmonary functional disability and require long-term follow-up and support. Acute respiratory failure Definition and epidemiology Respiratory failure is defined by reduced arterial oxygen tension (Pao2), with or without elevated levels of carbon dioxide (Paco2), and is one of the most common indications for intensive care unit (ICU) admission. Traditionally, it has been classified according to rapidity of onset (acute and

chronic), and into hypoxaemic and hypoxaemic/hypercapnic subtypes. Chronic respiratory failure is discussed in Chapter 18.15. Type 1 (hypoxic or acute hypoxaemic) is defined by hypoxaemia (Pao2 <8 kPa, normal range 10–13.3 kPa) with a normal or low Paco2 (normal range 4.8–6.1 kPa). It is attributable to a loss of functioning gas exchange surface and impaired hypoxic pulmonary vasoconstric- tion in which alveoli are perfused but not ventilated; extrapulmonary shunt may also occur (e.g. in patients with cyanotic heart disease). The less common type 2 (ventilatory or hypercapnic) respira- tory failure is characterized by hypercarbia (Paco2 >6.5 kPa) associated with hypoxaemia (Pao2 <8 kPa). While more severe forms of the same conditions that cause type 1 failure are often responsible, type 2 failure can also be caused by conditions that increase ana- tomical or physiological dead space or reduce minute ventilation by impairing respiratory drive or respiratory pump function. Common causes of acute respiratory failure are shown in Table 17.5.1. In practice, patients may progress from type 1 to type 2 re- spiratory failure as the precipitating condition evolves. Moreover, either type of respiratory failure may complicate a wide variety of pathologies. The incidence, prevalence, and attributable mor- tality is therefore difficult to determine, particularly as acute respiratory failure often coexists with other organ system fail- ures in the critically ill. Nevertheless, recent studies suggest an incidence in the order of 77.6–88.6 cases per 100 000 population per year, with an associated mortality rate of approximately 40%.

Table 17.5.1 Causes of acute respiratory failure

Type of cause	Type 1 acute respiratory failure	Type 2 acute respiratory failure
Acute conditions	Pneumonia Acute asthma Pulmonary oedema Acute lung injury/acute respiratory distress syndrome Pneumothorax Lobar collapse Pulmonary contusion (blunt chest trauma) Aspiration Pleural effusion	Acute severe asthma Depression of respiratory drive (e.g. drug overdose with narcotic drugs) Upper airway obstruction (e.g. foreign body)
Chronic lung diseases	Chronic obstructive pulmonary disease Pulmonary fibrosis Interstitial lung disease Lymphangitis carcinomatosis Pneumoconiosis Bronchiectasis Granulomatous lung diseases	Chronic obstructive pulmonary disease
Pulmonary vascular diseases	Pulmonary embolism Right-left shunts Pulmonary arterial hypertension Fat embolism	
Neuromuscular diseases	Intensive care unit acquired weakness Myasthenia gravis Polyneuropathy Poliomyelitis Acute neuropathies (e.g. Guillain-Barré) Primary muscle disorders (e.g. muscular dystrophy)	Primary alveolar hypoventilation Obesity hypoventilation syndrome Brainstem and cervical cord injury Skeletal disorders Chest wall deformities (e.g. kyphoscoliosis, ankylosing spondylitis) Flail chest injury
Other	Exhaustion from any cause of type 1 respiratory failure	

 While mortality rates for acute respiratory failure alone are prob- ably lower than this, death rates increase with each additional organ failure. Clinical approach History and examination Acute respiratory failure can be caused by extrapulmonary as well as pulmonary conditions. Clinical evaluation must therefore not be re- stricted to the respiratory system. Early identification of patients re- quiring organ support is essential, as delayed intervention adversely affects outcome. Clinical assessment aims to identify the cause of respiratory failure, as well as to categorize its severity. Critically ill patients require a flexible approach to clinical assessment. A full history may not be available from the patient. Intervention or resuscitation and crucial investigations (chest radiograph and arterial blood gases) may be re- quired immediately. The airway, breathing, circulation, disability, and exposure (ABCDE) approach incorporated into the Resuscitation Council (UK) Guidelines is advocated. Finally, other issues that have to be considered immediately include transfer to areas of the hospital where more intensive

monitoring is available (usually the intensive case unit), and calling for help from more experienced colleagues. The signs of critical illness tend to be similar whatever the precipitating cause and are manifest in failure of the respiratory, cardiovascular, renal, and neurological systems. Abnormal physio- logical signs are frequently encountered in patients cared for in gen- eral wards, but their charting and recognition are often inadequate. Medical early warning scoring systems, rapid response teams (see Chapter 17.1), and critical care outreach teams have been developed to address this deficiency. Alternatively, critical illness may be manifest solely as respira- tory insufficiency. In these circumstances, the history should help to elicit the cause of the clinical deterioration. Thus, central chest pain and breathlessness in a patient with known cardiac disease is suggestive of pulmonary oedema; a history of underlying chronic respiratory insufficiency such as chronic obstructive pulmonary dis- ease (COPD) or asthma, with worsening breathlessness and wheeze, suggests an acute exacerbation of these conditions; and respiratory distress in patients with sepsis, trauma, multiple blood transfusions, or pancreatitis may be caused by incipient acute respiratory distress syndrome (ARDS). Respiratory symptoms may also be a nonspecific indication of increased respiratory demand from a nonpulmonary source, for example, metabolic acidosis associated with diabetic ketoacidosis, poisoning, or acute renal failure. Clinical examination should quantify the signs of respiratory dis- tress (Table 17.5.2). The respiratory rate should normally be 12–20 breaths per minute, and a higher or increasing rate is a ‘hard’ sign of critical illness and a warning that the patient may deteriorate sud- denly. The depth of each breath should be assessed, and whether chest expansion is bilateral and symmetrical. Reduced expansion and breath sounds with tracheal shift to the contralateral side are indicative of tension pneumothorax, and the presence of bronchial breathing of pneumonia. An inability to lie flat with pink frothy sputum and bilateral crackles is suggestive of cardiogenic pul- monary oedema. However, clinical examination may be unhelpful and clinical signs absent in conditions such as pulmonary thrombo- embolism or early acute respiratory distress syndrome. Clinical investigations Arterial blood gas analysis Arterial blood gas (ABG) analysis confirms the type and severity of acute respiratory failure, but always remember that for interpretation of PaO2 it is crucial to record the inspired oxygen concentration at the time of sampling and the mode of respiratory support (see Box 17.5.1). ABGs often need to be repeated and the associated pain may warrant insertion of an indwelling arterial catheter. Oximetry, an invaluable aid to monitoring (see next), may be used to minimize the number of ar- terial punctures required by determining the concentration of inspired oxygen that corresponds to the desired oxygen saturation. Note the oxygen content of blood is primarily determined by the haemoglobin concentration and oxygen saturation rather than SpO2. Blood gas analysers provide additional information concerning electrolyte, lactate, and haemoglobin levels. These and other standard haematological and biochemical indices can provide diag- nostic information (Table 17.5.3). Table 17.5.2 Signs of respiratory distress and hypercapnia General clinical signs of respiratory distress Indicators of hypercapnia Respiratory rate >25/min or <8/min Bounding pulse Tachycardia/ bradycardia/ arrhythmia Warm peripheries Inability to speak in full sentences Carbon dioxide retention flap (asterixis) Cyanosis Somnolence/lethargy/confusion Sweating Decreased consciousness Obstructed airway/stridor Headache Use of accessory muscles of respiration Intercostal recession Pulsus paradoxus Restlessness/agitation Asynchronous respiration Inability to lie flat Paradoxical respiration Box 17.5.1 Interpretation of arterial blood gases in acute respiratory failure Steps in interpreting arterial blood gas results: 1 Confirm presence of respiratory failure: is Pao2 less than 8 kPa on room air? 2 What is the Paco2? Does the patient have type 1 or type 2 respiratory failure? 3 Is the A-a Po2 gradient high (normal range depends on age, usually <3.5 kPa (26 mm Hg))? 4 A normal/low A-a gradient suggests that hypoxaemia is due to hypoventilation? 5

A high A-a gradient suggests that hypoxaemia is secondary to ventilation:perfusion (V/Q) mismatch 6 If hypoxia does not correct with oxygen, respiratory failure is due to V/Q mismatch (alveolar perfusion without ventilation). A-a gradient (PAo2–Pao2), alveolar–arterial gradient; PAo2, alveolar partial pressure of oxygen, obtained from the alveolar gas equation (see Chapter 18.3.1); Paco2, partial pressure of carbon dioxide in arterial blood; Pao2, partial pressure of oxygen in arterial blood, obtained from arterial blood gases; V/Q, ventilation/perfusion.

Section 17 Critical care medicine 3870 Screening for infection A full infection screen should be dispatched immediately. This should include samples for blood, sputum, and urine culture, especially if signs of sepsis, or septic shock are present. Ideally samples should be obtained prior to administration of antimicro- bial agents, provided this does not delay treatment. Requests for typical and atypical (e.g. viral, legionella, mycoplasma) organisms should be made if clinically appropriate. In patients with pneu- monia, urine should be tested for pneumococcal and legionella antigens. Depending upon the immune status of the patient and the presence of underlying pathologies (e.g. malignancy, im- munosuppression), evidence of tuberculous and fungal infections should be sought. Chest radiograph A chest radiograph is an essential investigation in any patient with acute respiratory failure, and not infrequently reveals the cause. Chest radiography is also mandatory following re/placement of central venous catheters, endotracheal tubes, nasogastric tubes, and pleural drains, both to confirm correct positioning and to exclude complications. Ultrasonography If a pleural collection is suspected clinically or following plain chest radiography, then a diagnostic or therapeutic tap can be performed under ultrasonic guidance and the fluid sent for Gram stain, culture, cytology, pH, and leukocyte count. Removal of moderate quantities of pleural fluid may improve ventilation, perfusion (V/Q) mismatch, oxygenation, and pulmonary compliance. Computed tomography (CT) Thoracic CT, especially high resolution and contrast-enhanced, can reveal pathologies not detected by a plain chest radiograph, such as pulmonary embolus, abscess cavity, parenchymal infiltrates, or pleural effusions. Transporting critically ill patients to and from the CT scanner is not without risk, but has been shown to identify at least one new significant finding resulting in a change in man- agement in up to 30% of patients. Nonpulmonary causes of acute respiratory failure may also be revealed by CT examination of extrapulmonary sites. Electrocardiography and echocardiography An electrocardiogram (ECG) is necessary to identify arrhythmias and reveal evidence of cardiac ischaemia. Echocardiography is the investigation of choice for the bedside diagnosing of acute massive pulmonary embolism (PE). The presence of right ventricular dilata- tion and haemodynamic instability are indications for thrombolysis (Chapter 16.16.1). It is also helpful in differentiating between cardiac and high-permeability pulmonary oedema in cases of suspected ARDS. Fibreoptic bronchoscopy Fibreoptic bronchoscopy with directed bronchoalveolar lavage is useful for obtaining samples for microbiological and cytological examination. It may be indicated therapeutically for the alleviation of endobronchial obstruction, or for localizing sources of bleeding or sites of trauma. However, bronchoscopy should only be per- formed once the patient is stabilized and the airway secured, the only exception being when a bronchoscope is required to aid diffi- cult endotracheal intubation. Respiratory monitoring Arterial oxygen saturation (Sao2)/pulse oximetry A pulse oximeter allows the continuous noninvasive monitoring of arterial oxygen saturation by spectrophotometric analysis of the relative proportions of oxygenated and deoxygenated haemoglobin. This is useful in all clinical settings, during transfers, and in the ICU, reducing the need for regular ABG analysis. Oxygenation is usually regarded as acceptable if the Sao2 is above 90%. A sudden drop in arterial oxygen saturation should prompt an immediate and full re-evaluation of the patient. However, it

should be remembered that pulse oximetry is unre- liable in several circumstances, especially if there is poor periph- eral perfusion, nail polish has been applied, or if there is excessive movement or high ambient light. It does not measure arterial carbon dioxide levels and cannot be used in patients with a var- iety of (rare) conditions, including carbon monoxide poisoning and methaemoglobinaemia. Indwelling arterial catheter Insertion of an arterial line not only provides invasive blood pres- sure monitoring, but permits repeated ABG analysis. Estimation of lung function In mechanically ventilated patients the efficiency of gas exchange can be quantified by the alveolar–arterial (A-a) Po2 gradient or the Pao2/fractional inspired oxygen concentration (Fio2) ratio. Most machines used to apply ventilatory support via an endotracheal tube provide breath by breath quantification of tidal volume, respiratory rate, minute volume (the product of tidal volume and respiratory rate), airway pressure, and compliance. The latter is an index of the pressure-volume relationship of the respiratory system (elasticity) and is high when the lungs are distensible (e.g. in emphysema) and Table 17.5.3 Blood tests used in the assessment of patients with acute respiratory failure Investigation Utility Full blood count Anaemia contributes to tissue hypoxia; polycythaemia is indicative of chronic hypoxaemia. May suggest acute infection. Coagulation screen Altered in disseminated intravascular coagulation. Electrolytes, renal function, liver blood tests, C-reactive protein Guide to associated complications, underlying causes, and premorbid conditions. Phosphate and magnesium Low levels aggravate respiratory failure. Serum amylase/lipase Pancreatitis is a cause of ARDS. Thyroid function tests Hypothyroidism is a rare cause of hypoventilation. Creatine kinase and
Troponin I Biomarkers of recent myocardial infarction. A high creatine kinase with a normal troponin may indicate myositis. ARDS, acute respiratory distress syndrome.

17.5 Acute respiratory failure 3871 low when they are stiff (e.g. in ARDS). Compliance may also be de- creased by chest wall or abdominal pathology. In self-ventilating patients, serial measurements of peak expira- tory flow rate (PEFR) may be useful to assess therapeutic response to bronchodilators. Serial estimations of vital capacity are a useful indicator of deterioration in patients with neuromuscular problems involving the respiratory muscles, such as Guillain-Barré syndrome. Capnography A continuous measurement of exhaled/end tidal carbon dioxide (ETCO2) concentration mirrors Paco2 and is therefore a useful in- dicator of alveolar ventilation in patients without significant airflow limitation. A large difference between ETCO2 and Paco2 suggests an increase in alveolar dead space. Portable machines are available and should always be used to confirm endotracheal tube placement when continuous capnography is unavailable. Management The main steps in treating acute respiratory failure are: • Establishing and securing the airway • Increasing Fio2 to treat hypoxaemia • Instituting mechanical ventilation (invasive or noninvasive) as ne- cessary to treat impaired oxygenation and hypercapnia • Identifying and managing the precipitating condition • Discontinuing and withdrawing support in stages (‘weaning’) as the underlying condition improves or if it is decided that recovery will not occur. Airway management Ensuring airway patency and an adequate oxygen supply is a priority in all circumstances. Simple techniques such as head positioning (jaw thrust or head tilt) and removal of obstructions (e.g. dentures, secretions in the oropharynx) may be life-saving. However, inser- tion of a nasopharyngeal or oropharyngeal airway, which lifts the tongue off the posterior pharynx, and the application of positive pressure ventilation using a self-inflating bag valve mask apparatus may be required. Continuing respiratory support can be delivered by several de- vices, ranging from face masks to deliver oxygen to positive pressure ventilation administered noninvasively (via nasal or full face mask) or invasively (via endotracheal tube or tracheostomy). Endotracheal intubation

Endotracheal intubation is a task that should be undertaken only by those experienced in the technique. The decision to intubate is based on several factors including: • Inability to maintain and protect the airway—endotracheal intub- ation is almost always indicated in patients with a Glasgow Coma Score of 8 or less. • Exhaustion—elective intubation is considerably safer than an emergency procedure. • Deteriorating physiological parameters (specifically arterial gas tensions, acid base status, and respiratory rate more than 35 or less than 10 breaths/minute) despite the provision of adequate therapy. • Reversibility of underlying condition—intubation and mechan- ical ventilation are not therapeutic interventions and supporting respiration in this manner may be inappropriate in patients with irreversible pathology. The equipment, sedative, and neuromuscular blocking agents re- quired, and the exact techniques employed are beyond the scope of this chapter, however.
Tracheostomy Tracheostomy is a useful intervention in patients who require airway protection and toilet, or prolonged periods of assisted ventilation. A tracheostomy is better tolerated than prolonged endotracheal in- tubation, allowing sedation to be decreased. Resistance to airflow is reduced and dead space diminished, thereby aiding weaning. Tracheostomies facilitate communication, oral nutrition, removal of secretions, and prevent the nasal, laryngeal, and pharyngeal com- plications associated with prolonged translaryngeal intubation. As with endotracheal tubes, cuff pressure should be measured regularly and maintained between 24 to 30 mm H_2O. However, recent high quality trials have reported that early tracheostomy (within 72 hours of intubation) does not reduce mortality and a high proportion of patients randomly assigned to late tracheostomy recovered without undergoing the procedure. Mini-tracheostomy (3.5–4 mm diameter, uncuffed) can be used in patients with an ineffective cough or neurological impairment who require regular suctioning for sputum clearance, however, being uncuffed a mini-tracheostomy does not protect against aspir- ation and is too narrow to allow use of a wide bore suction catheter.
Oxygen therapy Oxygen is administered by a variety of methods depending on the required oxygen concentration (Table 17.5.4). Systems used for the delivery of oxygen can be broadly classified into fixed and variable performance devices. The flow rate of gas supplied, the volume of the mask itself, and the presence of holes or other entrainment systems determine into which category the device fits. Fixed performance devices These are designed to provide a constant and predictable inspired oxygen concentration, irrespective of the patient's ventilatory pat- tern. Oxygen is passed through a jet in the mask, which entrains air through ports in the side. The total flow rate of gas to the mask should Table 17.5.4 Oxygen delivery systems Method of delivery Fio_2 achieved Type of patient Nasal cannula
(1–2 litres/min) 0.24–0.30 Stable patients Venturi mask 0.24–0.50 Type 2 respiratory failure and COPD Partial rebreathing
mask 0.60–0.80 Acute type 1 respiratory failure (e.g. pneumonia, asthma, and acute pulmonary oedema) Non-rebreathing reservoir mask Up to 0.90 Severely hypoxic patients Nasal high flow Up to 1.0 Acute type 1 respiratory failure Anaesthetic face mask
or endotracheal tube Up to 1.0 Patients requiring intubation COPD, chronic obstructive pulmonary disease; Fio_2, inspired oxygen concentration.

 exceed the peak inspiratory flow rate of the patient at rest. Examples of fixed performance devices include the Venturi, Hudson, and me- dium concentration (MC) masks. Variable performance devices These provide an inspired oxygen concentration (Fio_2) which varies according to the gas flow rate and patient's ventilatory pattern. Most patients require only a modest increase in Fio_2 to overcome the com- bined effects of mild hypoventilation, diffusion hypoxia, and some degree of ventilation/perfusion mismatch. In these circumstances a

Fio2 of 0.3 is usually adequate, which is achieved by supplying a flow rate of 4 litres/min to any of the variable performance devices. However, in patients with COPD and/or type 2 respiratory failure, ventilatory drive may be stimulated by hypoxaemia. If this is relieved by the administration of oxygen in an uncontrolled fashion (e.g. ap- plying a large increase in Fio2 via a variable performance device), then arterial oxygen tension rises and respiratory drive is depressed. This leads to reduced entrainment of room air, an increase in the pro- portion of oxygen inhaled, and respiratory drive is further reduced. In rare circumstances a high Fio2 is needed. Large capacity sys- tems with an added reservoir bag are required to achieve this. Nevertheless, using these masks, an Fio2 up to 85% can be achieved using oxygen flows of 10 litres/min or greater. However, consider- able CO_2 rebreathing occurs if the oxygen supply fails or is reduced. Rebreathing can be eliminated and delivered Fio2 increased still fur- ther if unidirectional valves are added. Nasal high flow In this mode heated, humidified oxygen is delivered via nasal cannulae at high flow rates of up to 60 litre/min. The high flow gen- erates a low level of positive pressure as well as ensuring the patient receives the set FiO_2 by reducing entrained air. High flow oxygen was recently found to reduce 90-day mortality in patients with acute type 1 respiratory failure when compared to noninvasive ventilation and standard oxygen therapy. Mechanical ventilation The primary aim of mechanical ventilation is to support adequate gas exchange, while minimizing complications (Table 17.5.5). Modern mechanical ventilators contain sophisticated micropro- cessors that enable operators to control Fio2, tidal volume, airway pressures, respiratory rate, gas flow rates, and the time spent in in- spiration and expiration. The optimal mode of ventilation depends in part upon the nature of the underlying illness, particularly the presence or absence of pulmonary parenchymal or airway path- ology, the phase of the illness (acute or chronic), and the aims of support at the time it is applied (e.g. initiation of mechanical venti- lation or weaning). Noninvasive ventilation (NIV) Noninvasive positive pressure ventilation involves the delivery of mechanically generated breaths via a tight-fitting nasal or full face mask. Most modern systems deliver gas to preset inspiratory (IPAP) and expiratory (EPAP) positive airway pressures. Noninvasive ven- tilation also incorporates negative pressure ventilation, such as jacket (cuirass) ventilators, which are now rarely used in adult prac- tice. Box 17.5.2 and Table 17.5.6 show the contraindications to the use of noninvasive ventilation and its limitations. In the acute setting, the evidence base supporting the use of non-invasive ventilation is most complete in patients with acute ex- acerbations of COPD who do not require immediate endotracheal intubation. Following intensive care unit admission, one good study found that noninvasive ventilation significantly reduced the need for intubation (26% in NIV group vs. 64% in standard group) and thus the associated complications, and length of stay and inpatient mortality were both reduced. A similar study has Table 17.5.5 Complications associated with mechanical ventilation System affected Complication Comment Cardiac Reduced cardiac output Positive pressure ventilation increases intrathoracic pressure, causing a reduction in venous return and thus stroke volume and cardiac output Renal Reduced renal perfusion Salt and water retention (especially when
associated with PEEP) As a result of a reduced cardiac output Due to increased ADH secretion, reduced renal blood flow, and a reduction in antinatriuretic peptide secretion Respiratory Ventilator induced lung injury Pneumothorax Pneumomediastinum Pneumopericardium Subcutaneous emphysema Ventilator-associated pneumonia Due to ventilation with high tidal volumes resulting in overdistension of the alveoli Due to barotrauma Early recognition and prompt management of a tension pneumothorax is essential. This is nosocomial pneumonia developing more than 48 h postintubation. It is partly due to microaspiration of gastric contents or nasopharyngeal secretions and is associated with increased mortality Gastrointestinal Abdominal distension and ileus Stress

ulceration Also associated with the use of opiates The most common cause of gastrointestinal bleeding in ICU. Associated with an increased mortality when compared to patients without bleeding Neurological Critical illness myopathy and polyneuropathy Attributed to immobility, treatment with corticosteroids and paralysing agents and associated with the systemic inflammatory response syndrome Others Oxygen toxicity Ventilator failure or disconnection High inspired oxygen concentrations can cause reabsorption atelectasis and direct cellular toxicity. It is usual clinical practice to decrease the inspired oxygen concentration to <60% where possible Alarms must be in place to alert the clinicians of ventilator failure or disconnection. A bag valve mask for manual ventilation and oxygen should be available at each bed space ADH, antidiuretic hormone; ICU, intensive care unit; PEEP, positive end-expiratory pressure.

17.5 Acute respiratory failure 3873 supported the use of noninvasive ventilation on medical wards in patients with COPD with mild to moderate acidosis. Other bene- fits of noninvasive ventilation include the facilitation of ventila- tion ‘breaks’ for food and drugs, easier communication, earlier mobilization, more cooperation with physiotherapy, and cough preservation. A trial of noninvasive ventilation can therefore be advocated in patients with acute exacerbations of COPD who have a persistent re- spiratory acidosis (pH <7.35) despite controlled oxygen therapy and maximal medical treatment. Prior to its institution, however, a deci- sion should be made as to whether the patient will proceed to endo- tracheal intubation and invasive ventilation if deterioration should occur. In some patients, endotracheal intubation is not appropriate and noninvasive ventilation is employed as a ‘ceiling’ therapy. It can be delivered on general medical wards if staff have received appro- priate training, and provided that monitoring with continuous pulse oximetry and regular arterial blood gas analysis is available. The benefit to patients with more severe acidosis (pH <7.25) is less clear, and in such cases noninvasive ventilation should be administered on the intensive care ward where facilities for endotracheal intubation are readily available. The evidence base concerning the benefits of noninvasive ventilation is less strong for patients with acute respiratory failure secondary to restrictive lung disease, cystic fibrosis/bronchiec- tasis, ARDS, trauma, and postoperatively. It is probably reason- able to attempt a trial of noninvasive ventilation for hypoxaemic respiratory failure in such cases, but preferably in the ICU setting if the patient is a candidate for endotracheal intubation. If there is no significant improvement in pH, Paco2 and respiratory rate after 1 to 2 h of noninvasive ventilation, the trial is likely to fail and invasive ventilation must be considered. Noninvasive ventilation is not routinely recommended for the treatment of acute exacer- bations of asthma. Noninvasive ventilation has also been shown to be of benefit in some groups of patients to aid weaning and can be used to relieve respiratory distress in patients receiving palliative care for end-stage respiratory disease. Positive end-expiratory pressure (PEEP) By preventing airway pressure returning to atmospheric at the end of expiration, the application of PEEP minimizes alveolar col- lapse, thereby increasing functional residual capacity and compli- ance. In addition, recruitment of atelectatic alveoli is encouraged, and V/Q mismatch reduced. Lymphatic drainage may be stimu- lated, decreasing alveolar oedema and further improving oxygen- ation. Its main disadvantage is that airway pressures are raised, thereby reducing venous return and impairing cardiac output. The effect on right ventricular afterload, another major determinant of cardiac output, is complex: pulmonary vascular resistance is increased both by atelectasis (low PEEP) and extrinsic compres- sion of pulmonary microvasculature by raised airway pressures (high PEEP). Continuous positive airway pressure (CPAP) This can be delivered either via an endotracheal tube or to a con- scious patient via a noninvasive interface (e.g. face or nasal mask, and helmet). It is generated either using a

bellows/pressure device, or through a flow generator. Gas must be delivered at a sufficient flow rate to ensure that airway pressure does not fall below zero during inspiration, with a PEEP valve fitted to the system. CPAP can be used in a trial of spontaneous ventilation at the end of weaning from mechanical ventilation. In patients with cardiogenic pulmonary oedema that remain hypoxic despite med- ical therapy, CPAP reduced intubation rates, with a trend towards reduced mortality. Acute respiratory distress syndrome (ARDS) Definition This syndrome, defined by refractory hypoxaemia associated with high-permeability pulmonary oedema, complicates a wide var- iety of acute serious conditions, not all of which involve the lung directly (Fig. 17.5.1). The first widely accepted radiological and physiological criteria based definition was developed in 1994 by an American-European Consensus Conference (AECC), which cre- ated syndromes acute lung injury and ARDS, which were separated according to the oxygenation deficit. The emergence of these cri- teria facilitated the design of clinical investigations by permitting direct comparisons between patient groups with widely differing Table 17.5.6 Limitations of noninvasive ventilation Limitations Comment Mask leak and discomfort Can be minimized by correct mask fitting: numerous, different sized, full face,
and nasal masks are available Nasal bridge ulceration Protective barrier dressings can be used to reduce this Gastric dilatation and vomiting A nasogastric tube should be inserted, although this may increase leak Lack of airway protection If a patient is unable to protect their airway,
an endotracheal tube should be inserted No endotracheal suction Patients often require regular physiotherapy Exact Fio2 delivered
unknown Oxygen is entrained proximally in the circuit or directly into the mask. Pulse oximetry and ABGs are used to guide oxygen enrichment Exact tidal volume and minute volume delivered unknown Due to leak ABG, arterial blood gas; Fio2, inspired oxygen concentration. Box 17.5.2 Contraindications to noninvasive ventilation • Confusion/agitation • Life-threatening hypoxaemia • Reduced Glasgow Coma Score/inability to protect airway • Vomiting • Recent facial, upper airway, or upper gastrointestinal surgery • Fixed upper airway obstruction • Facial abnormalities (e.g. trauma or burns) • Bowel obstruction • Excessive secretions • Haemodynamic instability • Undrained pneumothorax

 underlying pathologies. However, these definitions took no account of the prognostic significance of the precipitating condition, failed to account for the effect of ventilatory strategy on hypoxaemia, and made no recommendation concerning the interpretation of chest radiographs. In 2011 a panel of experts developed the Berlin def- initions for ARDS. Three grades of ARDS were developed based on severity of hypoxaemia, which included a stipulation for the level of PEEP applied, and the term acute lung injury (ALI) was removed (Box 17.5.3). Aetiology Susceptibility to ARDS is determined in part by the nature of the underlying condition (Fig. 17.5.1), thus 40–60% of patients with se- vere sepsis and septic shock develop ARDS, regardless of the ana- tomical site of infection, but only 16% develop ARDS following trauma. The Lung Injury Prediction Score (LIPS: Table 17.5.7) was de- rived from large data sets of patients and validated prospectively with a view to using it as a basis for recruiting patients to ARDS pre- vention studies. Evaluation of the score discriminated between pa- tients who did and who did not develop ARDS. When a cutoff score of greater than 4 points is used, sensitivity of the score for ARDS is 0.69 (95% CI 0.64–0.74), specificity is 0.78 (95% CI 0.77–0.79), positive predictive value is 0.18 (0.16–0.20) and negative predictive value is 0.97 (0.97–0.98). The score demonstrates the ranking of common predisposing conditions as well as comorbidities that in- fluence susceptibility to ARDS. Finally, genetic polymorphisms and biomarkers have been demonstrated

that increase susceptibility to lung injury, but these have currently been useful in research as pointers to pathophysiological mechanisms, rather than having clinical utility. Epidemiology In Europe, the most recent epidemiological data found AECC cri- teria (pre-Berlin definitions) were met in 15.8% of patients admitted to intensive care for treatment of acute respiratory failure of all causes. Of those who developed ARDS, 65.4% of cases fulfilled the relevant criteria early in intensive care admission and the remainder did so within a median of 3 days. Of those who developed ALI (com- parable with Berlin definition of mild ARDS) within the first 24 h, 54.4% evolved to ARDS (comparable with Berlin definition of mod- erate and severe ARDS). By contrast, only 18.4% of patients with established ARDS had preceding ALI identified. Precipitating cause or risk factors for ALI Genetic factors Co-morbidities Alcoholism Diabetes Smoking Obesity Inflammation Coagulation Altered cell function Tissue injury Fibrogenesis/repair Pulmonary causes Pneumonia Aspiration of gastric contents Inhalational injury Pulmonary contusion Near drowning Hypoxia/reperfusion injury Nonpulmonary causes Sepsis Cardiopulmonary bypass Severe trauma Blood transfusion Drug overdose Accute pancreatitis Infection VALI TRALI fluid overload Fig. 17.5.1 Aetiology of the ARDS. A combination of patient factors (blue: genetic and comorbidities) and iatrogenic factors (red: including ventilator-associated lung injury—VALI) contribute to the pathological processes of ARDS. ALI, acute lung injury; TRALI, transfusion related acute lung injury. Box 17.5.3 Berlin definition of ARDS • Appropriate clinical setting with one or more recognized risk factors • New (within 1 week of known clinical insult), bilateral pulmonary infiltrates on chest radiograph not fully explained by lobar/lung collapse • Respiratory failure not solely due to heart failure or fluid overload. Objective assessment (e.g. echocardiography) required to exclude cardiac failure if no risk factor present • In patients with a PEEP/CPAP 5 cmH20: • Mild ARDS PaO2:FiO2 ratio of less than 40 kPa or less than 300 mm Hg • Moderate ARDS PaO2:FiO2 ratio of less than 26.6 kPa or less than 200 mm Hg • Severe ARDS PaO2:FiO2 ratio of less than 13.3 kPa or less than 100 mm Hg Fio2, inspired oxygen concentration; Pao2, arterial partial pressure of oxygen; PAOP, pulmonary artery occlusion pressure. Table 17.5.7 The Lung Injury Prediction Score (LIPS)
Predisposing
conditions LIPS
points Risk modifiers LIPS
points Shock 2 Alcohol abuse 1 Aspiration 2 Obesity (BMI >30) 1 Sepsis 1 Hypoalbuminaemia 1 Pneumonia 1.5 Diabetes mellitu –1 High-risk surgery Chemotherapy 1 • Orthopaedic spine 1 FiO2 >0.35 or >4 2 • Acute abdomen 2 litres/minute • Cardiac 2.5 Tachypnoea RR >30 1.5 • Aortic vascular 3.5 SpO2 <95% 1 High-risk trauma Acidosis (pH <7.35) 1.5 • Traumatic brain injury 2 • Smoke inhalation 2 • Near drowning 2 • Lung contusion 1.5 • Multiple fractures 1.5

 In North America, a prospective, population-based cohort study in 21 hospitals over 14 months, also using AECC criteria, found an incidence of 78.9 per 100 000 population. This increased with age (16 per 100 000 for patients 15–19 years; 306 per 100 000 for those aged 75–84). Overall, this study suggested there are around 190 000 cases of ARDS per year in the United States of America, with 74 500 deaths and some 3.6 million hospital days taken up by such patients. Pathogenesis ARDS is caused by intense inflammation affecting the gas exchange surface of the lung—the alveolar-capillary membrane. Increased permeability of this barrier is associated with an exudate in the airspace, the physico-chemical nature of which causes inactiva- tion of surfactant and atelectasis of lung units. Inflammation in the vascular space counteracts hypoxic pulmonary vasoconstriction, partly by causing dysregulation of the production of vasoactive mediators including prostanoids, endothelins, and nitric oxide. The refractory

hypoxaemia that characterizes ARDS is attributable to the combination of loss of lung units and hypoxic pulmonary vasoconstriction. Loss of pulmonary vasculature caused by lung destruction and intravascular coagulation causes increased dead space ventilation and carbon dioxide retention. Dysregulation of pulmonary vascular tone is associated with increased pulmonary vascular resistance which is exacerbated by the use of high airway pressure mechanical ventilation. Rarely, right heart failure may develop, usually in the presence of very severe type 2 ventilatory failure. Pathology The pathological appearances of ARDS are termed ‘diffuse alveolar damage’, although the same features are seen in distinct clinical con- ditions like acute interstitial pneumonia. Histological phases have been observed, but they usually overlap and can all coexist simul- taneously, particularly in the later stages. Three overlapping phases are recognized that correlate loosely with the clinical evolution of the disease: the exudative phase of oedema and haemorrhage, the proliferative phase of organization and repair, and the fibrotic phase. Eosinophilic hyaline membranes, composed of plasma proteins and cell debris, are characteristic features of the neutrophil predominant exudate that fills the airspace in early ARDS. The proliferative phase is characterized by organization of intra-alveolar and interstitial ex- udates with the formation of granulation tissue and regeneration of the alveolar epithelium with undifferentiated cuboidal cells. Total lung collagen is increased in ARDS patients surviving more than 14 days, and there is a progressive increase in lung collagen with the duration of the disease. This probably represents a normal healing response: in most cases this provisional matrix remodels, but in a few fibrosis becomes fixed and progressive, manifesting clinically as low lung compliance and prolonged ventilator dependence. These patients have a poor outcome. Clinical features and differential diagnosis The clinical features of ARDS will be largely determined by the underlying cause and are nonspecific to the syndrome apart from the degree of hypoxaemia being out of proportion to the pulmonary oedema compared with cardiogenic causes. Considering alterna- tive diagnoses is important because many conditions that cause respiratory failure and pulmonary infiltrates have specific treat- ments (Table 17.5.8). Clinical investigations Initial investigations should be aimed at defining the extent of lung injury and accompanying organ failures, and elucidating the precipitating causes. Subsequent investigations detect complica- tions and guide therapy. CT of the thorax is increasingly used in patients with ARDS because it has greater sensitivity for detecting pneumothoraces, pleural collections, abscess, and lung infiltrates than plain chest radiography. Typically, areas of dense opacification are apparent in dependent lung regions, with ground glass shadowing elsewhere (Fig. 17.5.2), this pattern being more often seen in indirect or blood-borne causes of ARDS like sepsis, rather than direct causes where the original lung pathology is often evident (e.g. lobar pneumonia). Fibreoptic bronchoscopy is often used to obtain microbiological samples and bronchoalveolar lavage cytology may reveal unex- pected diagnoses (Table 17.5.8). A panel of investigations has been developed for patients with the severest forms of ARDS. Close coordination with local micro- biologists and public health experts is vital because of the annual changes in prevalent causative organisms of pneumonia and the constantly developing molecular means of detecting pathogens, for example, 16S polymerase chain reaction based assays. Treatment of both the precipitating conditions and managing generic complications of critical illness and its support, most not- ably nosocomial infection, are essential in the care of patients with ARDS. A management algorithm is shown in Fig. 17.5.3. Ventilatory management The pathophysiology of ARDS encourages the use of high airway pres- sures to re-aerate (‘recruit’) collapsed lung but also results in extreme sensitivity to ventilatory-associated lung injury. Most patients with ARDS require invasive mechanical ventilation to maintain adequate gas Table 17.5.8 Conditions that mimic or cause ARDS but have a distinct pathology, clinical

course, and treatemnt Pneumonia Bacterial Miliary tuberculosis Viral Cytomegalovirus Herpes simplex Hantavirus Fungal Pneumocystis carinii Others Strongyloidiasis Cryptogenic Acute interstitial pneumonia Cryptogenic organizing pneumonia Acute eosinophilic pneumonia Malignancy Bronchoalveolar cell carcinoma Lymphangitis Acute leukaemia Lymphoma Pulmonary vascular
disease Diffuse alveolar haemorrhage Sickle lung

Section 17 Critical care medicine 3876 exchange. While some studies have indicated that a significant propor- tion of patients with mild ARDS are successfully managed outside inten- sive care with NIV, most cases require endotracheal intubation. While the application of extreme ventilatory parameters to normal lungs can cause ARDS, the use of 'normal tidal volumes (10 ml/kg predicted body weight)' causes ARDS in patients at risk and kills patients with estab- lished ARDS when compared to 6 ml/kg predicted body weight. As a result, ventilatory strategies now aim to limit the shear forces applied to the lung parenchyma and reduce the cyclical recruitment and collapse ('derecruitment') of alveolar units. Thus, tidal volumes are set at lower levels than have traditionally been thought necessary, the so-called lung protective approach. This reduces CO2 clearance, often resulting in a respiratory acidosis. A large multicentre trial in the United States of America demonstrated a convincing reduction in mortality (from 40% to 31% p = 0.007) associated with this ap- proach (using tidal volumes of 6 ml/kg ideal body weight and plateau pressure (end inspiratory pressure) <30 cm H2O) compared to con- ventional (12 ml/kg and plateau pressure <50 cm H2O) ventilation. Positive end-expiratory pressure High levels of positive end-expiratory pressure (PEEP) can also be used to ensure recruitment and retention of damaged lung units. Customarily, PEEP is increased transiently in a stepwise manner to high levels (e.g. 20–30 cmH2O) before a similar graded reduction to a maintenance level above the lower inflection point of the pressure- volume curve. CT tomograms taken during such manoeuvres (a) (b) Fig. 17.5.2 Plain chest radiograph (a) and CT (b) of patient with ARDS. Note greater detail provided by CT and dependent distribution of consolidation. ARDS by Berlin defining criteria Identify & manage precipitating cause Initial resuscitation (especially if septic) Ventilatory support (consider NIV) using protective strategy Adjunct assessments & monitoring (eg CT chest, echocardiography, infection screen) Act on findings (eg drain pneumothorax, start, inotropes/pressors) Initiate nutritional support, optimize fluid balance Yes Yes Oxygenation satisfactory (SaO2 > 88%) Stabilize 48 hr Consider weaning No Success Outpatient follow up Re evaluate precipitating cause, re assess with CT No Consider ECMO Consider prone positioning Consider inhaled nitric oxide Consider steroids Fig. 17.5.3 Protocol for management of patients with ARDS. NIV, noninvasive ventilation; P:F, PaO2:FiO2; PEEP, positive end-expiratory pressure; NMB, neuromuscular blockade; ECMO, extracorporeal membrane oxygenation.

17.5 Acute respiratory failure 3877 have demonstrated recruitment of atelectatic regions, especially in dorsal areas of the lung, which remain inflated after the PEEP is re- duced with an associated improvement in gas exchange. However, while higher PEEP may result in better oxygenation and possibly less ventilator-associated lung injury, circulatory depression and overdistension of recruitable lung units may also occur. The relationship between potentially recruitable lung (indicated by CT) and effects of PEEP has been explored in patients with ARDS and appropriate controls (healthy patients with unilateral pneumonia). Those patients with greater recruitability had greater calculated lung weight, poorer oxygenation, and respiratory system compliance, higher dead space, and higher rates of death. Thus, in this patient population the

percentage of recruitable lung is variable, but strongly associated with level of PEEP. Despite such knowledge, the appli- cation of varying levels of PEEP in clinical trials has not influenced outcome favourably. When patients with ARDS were randomized to low or high levels of PEEP using preset Fio2/PEEP (levels achieved in the two groups were 8.3 and 13.2 cmH2O, respectively), none of the study endpoints (mortality, days of unassisted breathing, inflamma- tory markers) differed between the two groups. A meta-analysis of three large recent randomized controlled trials found higher levels of PEEP in a subgroup of patients with ARDS, defined as a PaO2: FiO2 ratio of 200 mm Hg or less (equivalent to moderate ARDS with the new Berlin definition), conferred a mortality benefit. In contrast, a recent international trial, in which the majority of patients were re- cruited in Brazil, reported increased mortality when a protocol using recruitment manoeuvers and titrated PEEP was compared to a con- ventional low PEEP strategy. Further research is needed to elucidate the optimum strategy for PEEP in patients with ARDS. Prone positioning Mechanical ventilation in the prone position is frequently employed in the management of patients with ARDS, around 60% of whom respond to this manoeuvre with significant improvements in gas ex- change that may persist even after they are returned to the supine position. Since response cannot be predicted, a trial period is often used to identify those patients who are likely to benefit. While a large (>300 patients) study carried out in Italy demonstrated no survival benefit in response to at least 6 h prone ventilation per day, more prolonged 'proning' (e.g. 17 h per day) applied early to patients with more severe lung injury may reduce mortality. Moreover, a system- atic review and meta-analysis of published randomized controlled trials enrolling nearly 2000 patients suggested this manoeuvre re- duces mortality in those with the most severe hypoxemia. The results of a recent randomized control trial in patients with severe ARDS (PaO2/FiO2 <150 mm Hg with positive end-expiratory pressure of at least 5 mm Hg and FiO2 of >0.6) comparing early prone positioning (at least 16 hours a day) with nursing patients in the supine semi- recumbent position showed a significant reduction in both 28-day (16% versus 32.8%) and 90-day mortality (23.6% versus 41%). Both groups were ventilated with tidal volumes of around 6 ml per kg ideal body weight. All the ICUs in which the trial was conducted had routinely used prone positioning for more than five years. Turning critically ill patients from the supine to prone position and back is not without risk and requires experienced staff to perform safely. An instructional video made by the investigators is available, which accompanies the trial publication (http://www.nejm.org/doi/full/10.1056/NEJMoa1214103#t=article). High-frequency ventilation High-frequency ventilation (HFV) employs rapid respiratory rates (>4 times those used in conventional techniques). Tidal volumes are reduced, and are often smaller than the anatomical dead space. The two modes of HFV most widely used are high-frequency jet ventilation (HFJV) and high-frequency oscillatory ventilation (HFOV). HFJV in- volves the intermittent delivery of high pressure gas jets into the endo- tracheal tube, but optimal gas warming and humidification are difficult to achieve, which leads to problems with airway secretions and debris that, when coupled with a reliance on passive expiration, can lead to air trapping. HFOV involves the delivery of a continuous distending pressure to the endotracheal tube, which is then modified by the move- ment of a vibrating loudspeaker. Humidification and warming of the fresh gas flow are easier to achieve, and an active expiratory phase leads to less gas trapping. The only randomized controlled trial of HFJV in patients with severe acute respiratory failure did not show a signifi- cant improvement in gas exchange or a survival benefit. However, recent evidence suggesting that low tidal volumes reduce ventilator-associated lung injury, and that high levels of continuous airway pres- sure (PEEP) improve recruitment and retention of lung units, have led to renewed interest in HFOV. Two randomization controlled trials have been published comparing HFOV with conventional ventila- tion in patients

with moderate and severe ARDS (P:F ≤200 mm Hg (26.6 kPa). The OSCILLATE investigators compared the use of early HFOV with conventional ventilation using a low tidal volume and a high PEEP strategy. The trial was stopped early as HFOV was asso- ciated with higher in-hospital mortality than the control group (47% and 35%, respectively). The OSCAR study group found no difference in 30-day mortality between HFOV and usual ventilator care. As a re- sult, HFOV cannot be recommended as standard treatment in patients with moderate and severe ARDS and at most should be reserved for use by experienced operators in cases with refractory life-threatening hypoxaemia when conventional therapies fail and extracorporeal sup- port is not an option. Extracorporeal gas exchange Extracorporeal gas exchange is performed using a variety of tech- niques (e.g. venovenous or venoarterial bypass) either to completely replace or more commonly to accompany mechanical ventilation. Two historical randomized controlled trials of extracorporeal mem- brane oxygenation (ECMO) reported no survival advantage, but they did not take advantage of the main benefit of the technique by failing to decrease mechanical ventilation. A third recently com- pleted study using more advanced technology found a 16% survival benefit without severe disability among patients transferred to an ECMO centre compared to those who remained at the referral hos- pital and continued conventional ventilatory support. During the 2009 Influenza (H1N1) pandemic, ECMO was used to support patients who developed severe rapidly progressive ARDS and refractory hypoxia despite conventional ventilation with good results. A case series from Australia and New Zealand found 71% of those who received ECMO survived to ICU discharge. A UK-based cohort study in adult patients with suspected or confirmed H1N1 associated ARDS found those who were referred and transferred to an ECMO centre had a lower mortality than matched patients who were not referred for ECMO. This led to national commissioning of ECMO. services in the United Kingdom with standardized

Section 17 Critical care medicine 3878 referral and exclusion criteria (Box 17.5.4). By contrast, a recent French study found receiving ECMO for H1N1 associated ARDS conferred no mortality advantage over matched controls treated conventionally. Pharmacotherapy Fatty acids and antioxidants Initial research suggested that feeds rich in certain fatty acids and antioxidants may be of benefit in ARDS, presumably via changes in the host immune response. Eicosapentaenoic acid modulates production of proinflammatory eicosanoids, and γ-linoleic acid may suppress production of leukotrienes while itself being me- tabolized to prostaglandin E1. However, while one recent ran- domized controlled trial of eicosapentaenoic acid/γ-linoleic acid supplemented feeds in patients with ARDS showed improvements in oxygenation and shorter periods of ventilation and ICU stay, a more recent randomized controlled trial found no benefit from enteral feed supplemented with n-3 fatty acids, γ-linoleic acid and antioxidants in patients with ARDS: further investigation is required. Nitric oxide Nitric oxide (NO) is an endogenous vasodilator which can be given by inhalation at concentrations of up to 20 parts per million. It has been shown to improve oxygenation in patients with ARDS through effects on ventilation/perfusion matching, and to decrease pul- monary vascular resistance. However, only two-thirds of patients with ARDS benefit from inhaled nitric oxide (iNO), and random- ized controlled trials of iNO in ARDS have failed to show an im- provement in mortality or a reduction in the duration of mechanical ventilation. Moreover, improvements in oxygenation are only tran- sient, disappearing after 24 h of iNO therapy. Prostacyclin (PGI2) is another endogenous vasodilator that may have beneficial effects in ARDS. Like iNO it is thought to redistribute pulmonary blood flow to ventilated lung units, thus improving ventilation/perfusion matching. A sequential trial of iNO and PGI2 in patients with ARDS showed the two treatments to have identical effects on oxygenation and shunt flow, but as PGI2 is

easier to monitor and deliver than iNO, it is frequently used in its place. Surfactant administration Surfactant supplementation has proved effective in neonatal re- spiratory distress syndrome, and surfactant deficiency and dys- function has been demonstrated in adult patients with ARDS. However, several randomized controlled trials have failed to dem- onstrate an effect on mortality, or length of ventilation or intensive care unit stay in adults. A recent small trial has shown a survival benefit following use of bovine surfactant, but further large-scale trials are necessary. Neuromuscular blockade While neuromuscular blockade is frequently required to prevent ventilator dysynchrony in patients with ARDS, the use of paralysing agents have been limited due to concerns about causing or worsening long-term muscle weakness. However, a recent randomized con- trolled trial found the early use (within 48 hours) of cistatracurium in patients with moderate or severe ARDS (PF ratio, 150 mm Hg) in- creased time off the ventilator and improved 90 day survival without causing an increase in muscle weakness. Further trials are required to determine whether this is a reproducible class effect. Other pharmaceutical interventions Adult respiratory distress syndrome has considerable clinical and financial significance. While recently the association between prehospital treatment with anti-inflammatory agents (e.g. aspirin) and the incidence of ARDS has been explored, most investigations have evaluated the potential of both supportive and pharmaco- logical interventions in the established syndrome. Most of these interventions have targeted cellular and mediator-driven inflamma- tion. Although evaluated in large, randomized, placebo-controlled trials, all have failed to show a survival benefit. Corticosteroids Steroids have been used to treat ARDS since its first description in the 1960s. However, several multicentre trials in the 1980s failed to show a beneficial role for steroids either in the prevention of ARDS in at-risk groups, or in the treatment of established ARDS. Indeed, recent meta-analyses have concluded that steroids do not improve mortality in sepsis—a major group at risk of ARDS. However, des- pite this evidence, there has been a recent resurgence in enthusiasm for the use of steroids in the late (fibroproliferative) phase of ARDS. Early controlled data that appeared to support such therapy ran- domized patients on day 7 of ARDS to receive methylprednisolone or placebo for a further 32 days. A much larger randomized, double- blind trial compared corticosteroids to placebo in severe, late phase ARDS (7–14 days). There were two objectives; firstly, to determine if the administration of corticosteroids (methylprednisolone) in severe late-phase ARDS would reduce mortality and morbidity; and secondly, to evaluate the effects of steroids on markers of in- flammation and fibroproliferation. Methylprednisolone increased the number of ventilator-free and shock-free days during the first 28 days in association with an improvement in oxygenation, re- spiratory system compliance, and blood pressure, with fewer days of vasopressor therapy. There was no increase in the rate of infectious complications, but steroid therapy was associated with a higher rate of ICU-acquired weakness. These results do not support the routine use of steroids for persistent ARDS despite the improvement in car- diopulmonary physiology. In addition, starting methylprednisolone therapy more than 2 weeks after the onset of ARDS might have in- creased the risk of death. Antioxidants Oxidative stress is thought to be central to the pathogenesis of ARDS. Alveolar macrophages and recruited activated neutrophils Box 17.5.4 Indications and contraindications to the use of ECMO Referral criteria Acute, severe, potentially reversible, respiratory failure Lung injury score above 3 or hypercarbia, such that the pH is less than 7.20 despite optimized conventional mechanical ventilation Exclusion criteria Contraindication to limited anticoagulation (e.g. intracranial haemorrhage) Duration of high pressure and high FiO2 ventilation for over seven days (relative contraindication)

17.5 Acute respiratory failure 3879 release highly reactive oxygen species which cause injury through interactions with proteins, lipids, and DNA. It is thought that ex- cessive production of reactive oxygen species in ARDS overwhelms the endogenous antioxidant systems that normally regulate redox state within the lung. Attempts have therefore been made to intro- duce antioxidants to redress this balance, in particular using N-acetylcysteine, but none has shown a survival benefit or a repro- ducible effect on pulmonary physiology. Anti-inflammatory agents Ketoconazole is an imidazole used primarily for its antifungal ef- fects, but which also has immune modulating functions which may be of benefit in preventing the development of ARDS. Although a large multicentre trial showed that ketoconazole had no effect on mortality or duration of ventilation in patients with established ARDS, two smaller studies in critically ill surgical patients demon- strated a significant reduction in the incidence of ARDS. β-Agonists Experimental studies suggest that β-agonists might be beneficial in ARDS through several mechanisms, including the acceleration of alveolar fluid clearance. However, recent randomized controlled trials found no benefit from either nebulized albuterol (salbutamol) or intravenous salbutamol over placebo in patients with ALI/ ARDS, hence β-agonists cannot be recommended in this patient population. General supportive measures Pulmonary oedema in ARDS is caused by increased pulmonary vas- cular permeability in the face of apparently normal pulmonary ca- pillary pressure. Several studies have shown an association between a persistent positive fluid balance and poor outcome in ARDS, but it is not clear whether this represents administration of unnecessary fluid or greater haemodynamic instability in a group with a pre- existing poor prognosis. However, in a recent study of the safety and efficacy of ‘fluid conservative’ vs. ‘fluid liberal’ management strat- egies, applying interventions based on measurements of central venous or pulmonary artery occlusion pressures made at least every 4 h, the primary endpoint (death at 60 days) did not differ between strategies. Advantages in ventilator-free and organ failure-free (car- diovascular and central nervous system) days in favour of the fluid restricted group have to be balanced against suggestions of worse neurocognitive function at later follow-up. Transfusion of blood products, particularly those delivering large amounts of plasma from multiparous women, can cause ARDS—probably by preformed donor antibodies. Similarly, all blood products confer an increased risk of ARDS, nosocomial infection, and death on the recipient. Hence, the use of these products should be minimized. Wherever possible, feed should be administered via the enteral route, and the use of prokinetic drugs, avoidance of agents that im- pair gastric emptying (e.g. dopamine), and the use of postpyloric feeding tubes can all help achieve this aim. Prognosis and outcome Death rates attributable to ARDS are difficult to interpret, in that prognosis is determined in part by the nature of the precipitating illness. Thus, the mortality associated with ARDS complicating the sepsis syndromes is typically higher (40–60%) than that with trauma (14%), or following surgery using cardiopulmonary bypass (15%). Most patients with the established syndrome who die succumb to multiple organ dysfunction rather than as a direct result of respira- tory insufficiency. Recent controlled trials of putative therapeutic interventions in patients with ARDS have identified mortality rates of 25–40% in the control arms. Using the Berlin definition stages, mild, moderate, and severe ARDS were associated with mortality of 27%, 32%, and 45%, respectively. Survivors of ARDS have persistent functional disability five years after discharge from the intensive care unit despite normal or near normal lung function. Most patients have extrapulmonary condi- tions, with muscle wasting and weakness being most prominent. FURTHER READING Acute Respiratory Distress Syndrome Network (2000). 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, 342, 1301–8. British Thoracic Society

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17.6 Circulation and circulatory support in the cr

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ESSENTIALS Cardiovascular dysfunction is common in critically ill patients and is the primary cause of death in a vast array of illnesses. The prompt identification and diagnosis of its probable cause, coupled to ap- propriate resuscitation and (when possible) specific treatments, are cornerstones of intensive care medicine. Cardiovascular monitoring and diagnosis—cardiovascular per- formance can be assessed clinically at the bedside and through haemodynamic monitoring, and with therapeutic or other proactive interventions. Rapid assessment of shocked patients by bedside echocardiography is becoming increasingly popular in those insti- tutions where equipment and expertise are available. Diagnostic approaches or therapies based on data derived from invasive haemodynamic monitoring assume that specific patterns of de- rangement reflect specific disease processes, which will respond to appropriate intervention. Interpretation of haemodynamic variables—the various adaptive cardiovascular controls and varying metabolic demands make rules about specific haemodynamic variables of limited clinical utility. It is simply not possible to say that, when looking after a critically ill patient, the central venous pressure, or any other single measurable variable, must be kept at x or y. Key points in this context are: (1) tachycardia is never a good thing; (2) hypotension is always patho- logical; (3) there is no such thing as a normal cardiac output; (4) cen- tral venous pressure is only elevated in disease; and (5) peripheral oedema is of cosmetic concern. Oxygen delivery—while there is no level of cardiac output which is ‘normal’, there are oxygen delivery thresholds below which normal metabolism can no longer occur. One cardinal sign of increased cir- culatory stress is an increased O2 extraction ratio, which manifests it- self as a decreasing mixed venous O2 saturation (Svo2): a value of less than 70% connotes circulatory stress, less than 60% identifies signifi- cant metabolic limitation, and less than 50% frank tissue ischaemia. Pathophysiology of shock Circulatory shock can be defined as a decreased

effectiveness of cir- culatory blood flow to meet the metabolic demands of the body. Four basic functional aetiologies are recognized. (1) Hypovolaemic shock (e.g. haemorrhage, dehydration)—effective circulating blood volume is inadequate to sustain a level of cardiac output necessary for normal function without supplemental sympa- thetic tone or postural changes to ensure adequate venous return. (2) Cardiogenic shock (e.g. myocardial infarction)—pump dysfunc- tion can be due to either left ventricular or right ventricular failure, or both. Left ventricular failure is usually manifest by an increased left ventricular end-diastolic pressure, left atrial pressure and (by exten- sion) pulmonary artery occlusion ('wedge') pressure, which must exist to sustain an adequate left ventricular stroke volume. (3) Obstructive shock—mechanical obstruction of blood flow (e.g. pulmonary embolism) or of ventricular filling (cardiac tamponade). In the acute setting, neither pulmonary vascular resistance nor mean pulmonary artery pressure need be grossly elevated for right ven- tricular failure to occur. In cardiac tamponade, the cardinal sign is diastolic equalization of all pressures, central venous pressure, pul- monary arterial diastolic pressure, and pulmonary artery occlusion ('wedge') pressure. (4) Distributive shock—loss of blood flow regulation occurs as the end stage of all forms of circulatory shock, but as the initial pre- senting process it is common in sepsis, neurogenic shock, and ad- renal insufficiency. The haemodynamic profile of resuscitated sepsis is one of increased cardiac index, normal pulmonary artery occlusion ('wedge') pressure, elevated Svo2, and a low to normal arterial pres- sure, consistent with loss of peripheral vasomotor tone. Circulatory support of the haemodynamically unstable
patient If the cause of hypotension is intravascular volume loss, either ab- solute or relative, then cerebral and coronary perfusion pressures must be maintained while fluid resuscitation is begun, otherwise car- diac pump failure may develop and limit the effectiveness of fluid resuscitation. Pharmacotherapies for cardiovascular insufficiency—these are directed at the pathophysiological processes that either induce or compound the problem. They can be loosely grouped into one of three types: (1) vasopressor therapy—agents that increase vascular smooth muscle tone include noradrenaline (norepinephrine), adrenaline (epineph- rine), dopamine, and phenylephrine; (2) inotropic support—agents that increase cardiac contractility include dobutamine, dopexamine, levosimendan and phosphodiesterase inhibitors; (3) vasodilator therapy—agents that decrease smooth muscle tone include sodium nitroprusside and glyceryl trinitrate (nitroglycerine). It is important to 17.6 Circulation and circulatory support
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Section 17 Critical care medicine 3882 recognize that most inotropes and vasopressors in clinical use are sym- pathomimetics that have direct effects on the adrenoreceptor system, and there is a quantitatively unpredictable variation in adrenoreceptor density and function in many pathophysiological states, hence agents acting upon them need to be titrated to effect rather than being given at a defined infusion or dose rate. Resuscitation strategies—the only prospective clinical trials documenting benefit from particular interventions were applied early in the course of sepsis or in high-risk surgical patients. However, it makes physiological sense to prevent organ ischaemia by maintaining blood flow, hence the following strategies seem warranted. (1) Loss of vasomotor tone requires both fluid resuscitation to achieve the increased vascular volume needed to restore an effective pressure gradient for venous return, and increased α-adrenergic tone via sympathomimetic agents to restore arterial and venous vaso- motor tone. Targets for resuscitation are an Svo2 greater than 70% with a mean arterial pressure greater than 65 mm Hg. (2) Impaired contractility requires afterload reduction, as toler- ated, up to a decrease in mean arterial pressure to approximately 70 mm Hg, targeting pulmonary artery occlusion ('wedge') pressure (if measured)

less than 18 mm Hg and Svo2 greater than 70%. Inotropic support is often required. In sepsis, Svo2 is usually elevated following fluid resuscitation, hence reasonable resuscitation targets are a mean arterial pressure greater than 65 mm Hg and normalizing serum lac- tate concentration. (3) In right ventricular failure, maintaining a mean arterial pressure greater than pulmonary arterial pressure is essential to minimize right ventricular myocardial ischaemia. Introduction Cardiovascular dysfunction is common in critically ill patients and is the primary cause of death in a vast array of illnesses including sepsis, pulmonary embolism, and acute respiratory failure, as well as in those with cardiac disease. The prompt identification of car- diovascular dysfunction, the diagnosis of its probable cause, and ap- propriate specific treatments (when possible) coupled to appropriate resuscitation and restorative management are cornerstones of inten- sive care medicine. Cardiovascular performance can be assessed at the bedside and through haemodynamic monitoring and therapeutic or other pro- active interventions. Diagnostic approaches or therapies based on data derived from invasive haemodynamic monitoring assume that spe- cific patterns of derangement reflect specific disease processes, which will respond to appropriate intervention. Why such constellations of measured abnormalities occur is due to the underlying cardiovascular interactions that define normal and pathological states, hence it is es- sential that the practising clinician be well versed in the underlying principles of cardiovascular physiology and pathophysiology in order to appropriately diagnose and then treat the critically ill. Principles of cardiovascular homeostasis Physicians often consider disease states as involving only one organ, such as the heart, during acute coronary ischaemia or the circulation during haemorrhage. However, no organ system operates in the body without numerous and redundant feedback processes which both amplify and inhibit the specific response of the organ and the rest of the body to stress, disease, and treatment. These interactions form the basis of haemodynamic profile pattern recognition. Specific combinations of changing cardiovascular and metabolic variables better reflect specific disease processes than do individual values for specific variables. Furthermore, the change in these variables in re- sponse to time and treatment define the progression or resolution of disease, its severity, and subsequent responsiveness to therapy. Although specific combinations of haemodynamic variables often reflect certain disease states, there may be considerable overlap of haemodynamic data sets among markedly different pathological states, which may require different therapies. These vagaries reflect individual patient differences, complex cardiovascular interactions not considered in the original logic, and also inaccuracies in the measures themselves and incorrect assumptions as to what the pri- mary force is, and what is its response. This confusion can be minim- ized, however, by performing an experiment at the bedside to force the cardiovascular system into doing one thing or another. This is the essence of a ‘clinical trial’ of positive pressure breathing, passive leg raising, fluid therapy, diuresis, or increased inotropy. Thus, by examining the specific haemodynamic response of the individual to a specific therapy, the clinician at the bedside can gain essential in- sight into the process that is dysfunctional and also tailor therapy to the individual. Let us first consider normal cardiovascular physi- ology, then pathophysiology, and finally how to diagnose and treat. Ventricular pump function Frank–Starling relationship Our understanding of cardiac pump function has evolved greatly since the initial studies of Frank and Starling in the 1890s. Frank, a German physiologist, noted that when cardiac muscle strips were stretched they (unlike skeletal muscle strips) increased their force of contraction. Starling used these data to reason that since the left ventricular (LV) cavity approximated a sphere, increases in LV end- diastolic volume (EDV) should proportionally increase LV myocar- dial fibre stretch. Thus, he explained the observation that the force of LV contraction was related to left ventricular end-diastolic volume (LVEDV). Based on this

construct, increasing left ventricular end- diastolic volume when LV function is normal will increase LV stroke volume and—for a constant heart rate—cardiac output as well. However, if LV pump function is impaired, then for the same in- crease in left ventricular end-diastolic volume stroke volume will not increase as much, if at all. Most studies of ventricular func- tion revolve around LV function, assuming that the right ventricle follows suit. The Frank–Starling relationship is central to most diagnostic and therapeutic protocols used to assess cardiac function. In fact, clinically, the immediate treatment of acute cardiovascular insuffi- ciency and arterial hypotension is to increase intravascular volume. If arterial pressure increases, then the subject is said to be 'preload-responsive' and the presumptive diagnosis of hypovolaemia is made. However, this common therapeutic response of fluid resuscitation will only increase cardiac output in half the patients who are haemo- dynamically unstable, hence understanding better the determinants

17.6 Circulatory support in the critically ill 3883 of cardiovascular insufficiency and how to assess them are important goals in the training of critical care physicians. When modelling LV pump function, one assesses both stroke volume and pressure work, or stroke work, needed to cause that flow. LV stroke volume varies inversely with outflow pressure (ar- terial pressure) for a constant left ventricular end-diastolic volume and LV contractility, whereas stroke work will remain constant. Thus, LV stroke work, rather than stroke volume, is often used to as- sess LV functional status because it is relatively pressure (afterload) independent. If stroke work is less for the same left ventricular end- diastolic volume, then LV contractility is also said to be less under this condition (Fig. 17.6.1). The measure of LV function best used to assess cardiovascular status is highly dependent on the question being asked. If the ques- tion is the adequacy of LV output to meet the metabolic demands of the body, then stroke volume and cardiac output are the relevant measures. However, if the question is 'what is the functional status of the heart, and can it be counted on to sustain blood flow as ejection pressures rise?', which in essence is asking 'what is the level of myo-cardial contractile reserve, independent of the level of blood flow?', then the change in LV stroke work relative to the change in left ven- tricular end-diastolic volume is a better index. LV pressure–volume loop LV pump behaviour is best described using the LV pressure–volume relation, wherein a single cardiac cycle is described as a loop with LV volume on the x-axis and pressure on the y-axis (Fig. 17.6.2). In this construct no time units are used. Filling occurs during diastole when LV chamber pressure decreases to less than left atrial pressure. The slope of the passive LV distention is diastolic compliance. At end- diastole, defined by the electromechanical coupling of contraction, the pressure/volume ratio is at its minimum. This point is often used to assess diastolic compliance, but is influenced by external forces independent of the LV, such as the pericardium, lungs, and right ventricle. Left ventricular end-diastolic volume is synonymous with LV preload as applied to the Frank–Starling relationship. With mechanical contraction, the LV intracavitary pressure rises, forcing mitral valve closure and changing the shape of the LV from an elongated ellipsoid into more of a sphere. As contraction progresses, intracavitary pressure rises as the end-diastolic blood volume is trapped in the LV. Once intracavitary pressure exceeds aortic pressure, the aortic valve passively opens and ejection begins. In a subject with a normal heart, the point where ejection occurs represents the maximal LV wall stress, itself the product of radius of curvature and developed pressure. Thus, diastolic arterial pressure is a major determinant of LV wall stress, and this LV wall stress is the LV afterload. Any therapy which selectively decreases diastolic arterial pressure will then reduce LV afterload more than therapies which selectively decrease systolic arterial pressure. Similarly, if an inovasodilator, such as dopexamine, were given that decreased left ventricular end-diastolic volume but increased LV stroke volume and ejection

pressure, one may erroneously conclude that LV afterload increased, when in fact it decreased. Ejection occurs as LV volume decreases and both LV pressure and aortic pressure rise. Due to the filling characteristics of the aorta, aortic pressure increases most towards the end of ejection as the distensible volume of the aorta is finally reached. Thus, most of the increase in arterial pressure occurs when the LV volume is already small. As a result, the maximal LV wall stress usually occurs at the start of ejection and the LV unloads itself during ejection. That the left ventricle unloads itself during ejection has important clinical implications. First, systolic hypertension is better tolerated without much increase in myocardial oxygen demand (MVo2) than is dia- stolic hypertension. However, if left ventricular end-diastolic volume is increased such that LV volumes do not decrease much during ejection (as is the case in congestive heart failure), then systolic pres- sure will be a major contributor to both LV wall stress and MVO2. Accordingly, in dilated heart failure states, the LV performance is sensitive to changes in systolic arterial pressure, and end-systolic volume (ESV) then is a function of both afterload and contractility. As such, increases in afterload will increase ESV, whereas increases in contractility will decrease ESV. LV relaxation occurs once ejection has finished. Diastolic re- laxation or lusitropy is an energy-dependent process, causes LV intracavitary pressure to decrease faster than would be predicted by passive relaxation alone, and is impaired by myocardial ischaemia. Impaired active diastolic relaxation is the earliest manifestation of myocardial ischaemia and can be readily identified by echocardi-ography and as an S3 gallop on cardiac auscultation. Since coronary artery blood flow occurs primarily in diastole, when LV wall stress is low and perfusion pressure is high, any process which impairs dia- stolic relaxation will decrease coronary blood flow. LV ejection phase indices: Hypereffective Ejection fraction stroke volume stroke work LV dP/dt VCF Preload (end-diastolic volume) Hypoeffective Normal Fig. 17.6.1 Relationship between left ventricular (LV) end-diastolic volume (preload) and LV ejection phase indices, including ejection fraction, stroke volume, stroke work, rate of change of LV pressure
(dP/dt), and velocity of circumferential fibre shortening (VCF). Shown in the example are three curves of varying performance referred to as hypereffective, normal, and hypoeffective performance. Each ejection phase index is affected to a greater or lesser extent by changes in afterload and contractility. Ejection End-systole Aortic valve opening LV volume (ml) LV pressure (mm Hg) Isometric contraction Isometric relaxation Diastolic filling End-diastole Mitral valve opening Fig. 17.6.2 The LV pressure–volume relationship describing all aspects of the cardiac cycle.

Section 17 Critical care medicine 3884 Time-varying elastance The entire LV contractile process can be understood better from the perspective, not of a single pressure–volume loop, but of the pressure–volume domain of contraction. In this context, as time progresses from the start of contraction to end ejection, the left ventricle becomes progressively more stiff (e.g. more elastic), such that the pressure may increase and the volume may decrease inde- pendent of preload and afterload characteristics, but where on the pressure–volume domain this point lies is a function of the stiffness or elastance of the ventricle. Time-varying elastance (E(t)) describes the progressive stiffening through systole and then its relaxation in diastole in the pressure–volume domain. It can be calculated as a plot of the slopes of the isochronic (similar point in time) pressure– volume relations during ejection as end-diastolic volume is rapidly varied (Fig. 17.6.3) by either rapid volume loading or occlusion of venous drainage. The slopes of these sequential pressure–volume lines reflect the obligatory LV pressure–volume domain that must be followed during systole. The end-systolic elastance (Ees) is usually calculated from the re- gression line of the end-systolic pressure–volume data pairs of re- petitive LV pressure–volume loops, as either preload or afterload

are rapidly varied. Ees is also referred to as the LV end-systolic pressure–volume relationship (ESPVR). Maximal elastance (Emax) is the maximal LV pressure–volume ratio and usually occurs just after end-systole due to the inertial and impedance hydrodynamic characteristics of the arterial tree. Increased contractility results in both a more rapid rise of (E(t)) to Ees and a higher Ees value. Using this construct, it becomes clear that the Frank–Starling relationship is the unidimensional description of the mechanical quality of ven- tricular ejection as described by time-varying elastance. Applied cardiac physiology at the bedside The preload-dependent nature of LV performance is central to the understanding of applied cardiac physiology. In fact, documenting that left ventricular end-diastolic volume is above some minimal value, despite cardiac output and stroke work both being depressed, is essential for the diagnosis of cardiac pump dysfunction. Similarly, demonstrating that left ventricular end-diastolic volume is reduced in the setting of haemodynamic instability presumes the diagnosis of inadequate circulating blood volume as the most likely cause of the haemodynamic instability, even though other aetiologies, such as tamponade, cor pulmonale, and restrictive cardiomyopathies can coexist and require different treatments. However, knowing left ventricular end-diastolic volume does not predict if LV stroke volume will increase in response to volume loading. Since a fundamental aspect of haemodynamic monitoring is to predict which patients will be preload-responsive, meaning that their cardiac output will increase in response to a fluid challenge, this lack of concordance between right atrial pressure, pulmonary artery occlusion pressure (‘wedge’ pressure), and even ventricular volumes, and subsequent changes in cardiac output in response to volume challenge can be disquieting. Still, it is a reality. However, there are three techniques of proven utility in defining preload re-sponsiveness: the classic volume challenge, noting the magnitude of (1) the arterial pulse pressure, or (2) left ventricular stroke volume variation during fixed tidal volume positive pressure ventilation, and (3) noting the change in mean cardiac output in response to a passive leg raising manoeuvre. For either pulse pressure variation (PPV, the ratio of maximal minus minimal pulse pressure to mean pulse pressure over five or more breaths) or stroke volume variation (SVV, the ratio of maximal minus minimal stroke volume to mean stroke volume over five or more breaths) to reflect preload respon- siveness, the tidal volume must be fixed during unassisted positive pressure breathing and the sequential R-R intervals must be con- stant (i.e. no arrhythmias). In patients who are breathing spontan- eously, and those with arrhythmias, the mean increase in flow 20 s after a passive leg raising to 30° gives a similar predictive value. In all cases, having a PPV greater than 13% or a SVV or mean increase in flow of more than 10% accurately predicts preload responsiveness as validated by many independent studies. PPV can be measured from the arterial pressure waveform and SVV calculated using numerous devices that assess beat-to-beat stroke volume using the arterial pressure waveform. Arterial pressure and the vascular circuit Organ perfusion is dependent on organ perfusion pressure and local vasomotor tone. Local vasomotor tone varies inversely with local tissue metabolic demand. For most organs, except the kidneys and heart, independent changes in arterial pressure above some min- imal value are associated with increased vasomotor tone to main- tain organ perfusion constant, hence this is essentially independent of cardiac function and cardiac output. In this circumstance, car- diac output is only important to allow parallel circuits to maintain flow without inducing hypotension, and cardiac function is only important in sustaining cardiac output and a given output pressure without causing too high a back pressure in the venous circuits. Operationally, mean arterial pressure (MAP) is the input pres- sure to all organs other than the heart. Diastolic aortic pressure is the input pressure for coronary blood flow. Usually, mean ar- terial pressure is equal to the diastolic pressure plus one-third the pressure pulse between diastole and systole. If, in a previously nonhypertensive subject,

mean arterial pressure decreases below 65 mm Hg, then tissue perfusion will decrease independent of meta- bolic demand. Hypotension directly reduces organ blood flow and is synonymous with cardiovascular instability and is the essence of circulatory shock. However, the assumption is often false that be- cause mean arterial pressure is the major central determinant of LV volume LV pressure 20 ms 40 ms 60 ms 80 ms 100 ms 140 ms 200 ms ESPVR Vo Fig. 17.6.3 Multiple LV pressure–volume relations over time with isochronic pressure–volume domains (time-varying elastance) drawn for all ventricles ending at the end-systolic pressure–volume relationship (ESPVR). Isochronic lines at 20-ms intervals. Note that LV time-varying elastance increases progressively from end diastole to end systole.

17.6 Circulatory support in the critically ill 3885 organ perfusion pressure, then organ perfusion must be adequate if mean arterial pressure exceeds some minimal value. Intraorgan vascular resistance and venous outflow pressure are the two other determinants of organ blood flow. Furthermore, in severe stress situations, such as shock states, normal homeostatic mechanisms functioning through carotid body baroreceptors vary arterial vas- cular tone to maintain mean arterial pressure relatively constant despite varying cardiac output, this vasoconstriction being done to maintain cerebral and coronary blood flow at the expense of the remainder of the body. In subjects with normal renal function, im- mediate oliguria is the manifestation of this adaptive response, re- flecting marked reduction in renal blood flow and solute clearance by the kidneys despite persisting normal arterial blood pressure, hence normotension does not ensure haemodynamic sufficiency. Indirect measures of sympathetic tone, such as heart rate, respira- tory rate, and peripheral capillary filling and peripheral cyanosis, are better estimates of cardiovascular status than is mean arterial pressure. Despite the lack of sensitivity of mean arterial pressure to reflect haemodynamic sufficiency, measures of it are essential in the as- sessment and management of haemodynamically unstable subjects for several reasons. Measures that increase mean arterial pressure will also increase organ perfusion pressure. Hypotension causes coronary hypoperfusion, impairing cardiac function and cardiac output. Vasoconstrictor therapies will increase vasomotor tone in nonvital peripheral organs, but will maintain flow to the cerebral and coronary beds. It is also important to remember that the normal mechanism allowing autoregulation of blood flow distribution is local changes in organ inflow resistance, such that organs with in- creased metabolic demand vasodilate to increase their blood flow. If there is hypotension, then local vasodilation will not result in in- creased blood flow because the pressure gradient for that flow will also be reduced. Thus, hypotension impairs autoregulation of blood flow distribution. Vasopressor therapy can reverse systemic hypo- tension, but at a price: the only way that it can increase MAP is by reducing blood flow through vasoconstriction. Importantly, cere- bral and coronary vascular circuits have minimal α-adrenergic re- ceptors so their beds will not constrict. Regrettably, in hypovolaemic states vasopressor support may improve transiently both global blood flow and MAP, but at the expense of worsening local non- vital blood flow and hastening tissue ischaemia. Initial resuscitative efforts should therefore always include an initial volume expansion component and fluid challenge or other diagnostic approaches that identify preload-responsive shock states, before relying on vasopres- sors alone to support the unstable patient. Cardiac output, oxygen delivery, and oxygen consumption To support cellular metabolism, the circulation must deliver ad- equate amounts of oxygen (Do2) and blood flow (cardiac output) to support oxidative phosphorylation. Do2 is the product of cardiac output and arterial O2 content. Within this construct, cardiac output and Do2 are often used interchangeably, primarily because the greatest gain in Do2 comes from varying cardiac output, not arterial O2 content. However, like

all simplification constructs, this one is also limited. Nonmetabolic blood flow, such as renal and splanchnic and skin blood flow, are essential to normal homeostasis. All of these processes need to be maintained under normal conditions and cannot be excluded for long in stress states without inducing marked end-organ dysfunction. Haemodynamic homeostasis Since the primary goal of the cardiorespiratory system is to continu- ously maintain adequate Do2 to meet the metabolic demands of the tissues, how can one assess its adequacy? As described here, neither LV preload nor MAP are sensitive or specific measures of adequacy of cardiovascular function. Although the best measure of circulatory sufficiency is the maintenance of normal bodily functions, this ana- lysis is often difficult to assess accurately at the bedside during states of stress. Furthermore, since metabolic demand can vary widely, there is no value of cardiac output or Do2 that ensures circulatory sufficiency. Under normal conditions, Do2 and metabolic demand vary in parallel. However, as metabolic demands start to exceed Do2 limits, either because of increased metabolic demand (e.g. seizures, fever, fighting the ventilator) or decreased delivery (e.g. circula- tory shock and respiratory failure), the ability of the cardiovascular system to sustain O2 consumption is stressed. One cardinal sign of increased circulatory stress is an increased O2 extraction ratio, which manifests itself as a decreasing mixed venous O2 saturation (Svo2). However, even this concept is useful only in limited conditions. Muscular activity effectively extracts O2 from the blood because of the set-up of the microcirculatory flow patterns and the large concentration of mitochondria in these tis- sues. Thus, normal vigorous muscular activity can be associated with a marked decrease in Svo2 despite a normal circulatory system. Muscular activities, such as moving in bed or being turned, ‘fighting the ventilator’, and breathing spontaneously increase O2 consump- tion. In the patient with an intact and functioning cardiopulmonary apparatus, this will translate into an increase in both Do2 and O2 consumption and a decrease in Svo2. However, in a sedated and ven- tilated patient, Svo2 is a very sensitive marker of circulatory stress. There is no level of cardiac output which is ‘normal’, but there are Do2 thresholds below which normal metabolism can no longer occur. Using Svo2 as a sensitive but nonspecific marker of circula- tory stress, values less than 70% connote circulatory stress, less than 60% identify significant metabolic limitation, and values less than 50% frank tissue ischaemia. The various adaptive cardiovascular controls and varying meta- bolic demands make rules about specific haemodynamic vari- ables of limited clinical utility. It is simply not possible to say that, when looking after a critically ill patient, the central venous pres- sure, or any other single measurable variable, must be kept at x or y. Table 17.6.1 lists some haemodynamic monitoring key points rele- vant to critically ill patients. Pathophysiology of shock The heart, vascular integrity, vasomotor tone, and autonomic con- trol all interact to sustain circulatory sufficiency. Circulatory shock reflects a failure of this system and results in an inadequate perfu- sion of the tissues to meet their metabolic demand, which can lead to cellular dysfunction and death. Numerous disease processes can result in circulatory shock, displaying surprisingly similar gross

 phenotypic expressions despite being caused by divergent processes whose treatments are equally different. Weil and Shubin defined circulatory shock in 1968 as a decreased effectiveness of circulatory blood flow to meet the metabolic de- mands of the body. Four basic functional aetiologies of circulatory shock can be defined: (1) hypovolaemic, due to inadequate venous return (haemorrhage, dehydration); (2) cardiogenic, due to inad- equate ventricular pump function (myocardial infarction); (3) ob- structive, due to vascular obliteration (pulmonary embolism or tamponade); and (4) distributive, due to loss of vasoregulatory con- trol (sepsis). Tissue hypoperfusion is common in all forms of shock, with the possible exception of

hyperdynamic septic shock. This results in tissue hypoxia and associated hyperlactataemia and metabolic acidosis. However, hyperlactacidaemia, per se, is not a marker of ongoing tissue hypoperfusion because lactate clearance is often de- layed or impaired in shock states, and processes such as exercise (seizure activity) can induce hyperlactacidaemia without cardio- vascular insufficiency. Sustained circulatory shock results in cellular damage, not from anaerobic metabolism, but from an inability to sustain intermediary metabolism and enzyme production necessary to drive normal mitochondrial performance. Metabolic failure due to sustained tissue hypoxia may explain why preoptimization and early goal-directed therapy can improve outcome, whereas aggres- sive resuscitation after injury is not effective at reducing mortality from a variety of insults. As stated here, measures of cardiac output, mean arterial pres- sure, and their changes in response to both shock and its treatment poorly reflect both regional and microcirculatory blood flow. Since most forms of haemodynamic monitoring measure global param- eters like arterial pressure, heart rate, other vascular pressures, and cardiac output, it is clear that assessment of severity of shock and its initial response to therapy is often limited if monitoring is limited to these variables alone. Potentially, measuring Svo2 or the differ- ence between tissue Pco2 and arterial Pco2, referred to as the Pco2 gap, would allow one to assess effective tissue blood flow since de- creases in capillary blood flow initially causes CO2 from aerobic metabolism to accumulate. Gastric tonometry describing Pco2 gaps identifies gastric ischaemia and may be useful in guiding resuscita- tion in critically ill patients: sublingual Pco2 gaps are much easier to measure and offer a readily simple bedside monitoring approach. However, gastric tonometry is confounded by CO2 production from nonoxidative phosphorylation, and sublingual Pco2 is not yet valid- ated as a routine measure. Thus, at the present time, characteristic groupings of abnormalities of global measures of circulatory func- tion are often used to determine which of the four shock categories is the most likely cause of organ dysfunction; this is referred to as haemodynamic profile analysis. More recently the availability in many countries of relatively simple and portable cardiac ultrasound machines, combined with formalized training programmes, has resulted in widespread use of rapid bedside echocardiography in the initial and ongoing as- sessment of shocked patients. Echocardiography can be used to decide when fluid resuscitation should be stopped, for example, if there is evidence of right ventricular overload (e.g. paradoxical septal shift, increased tricuspid regurgitation). Echocardiographic imaging can quantify both right and left ventricular contractility, the presence of mechanical causes of cardiac pump failure (e.g. pericardial effusion and tamponade, acute and severe valvular dis- ease, acute right ventricular dilatation and failure due to massive pulmonary emboli). Hypovolaemic shock Hypovolaemia is the cardiovascular state in which the effective cir- culating blood volume is inadequate to sustain a level of cardiac output necessary for normal function without supplemental sym- pathetic tone or postural changes to ensure adequate venous return. It is a relative process and can occur through absolute blood loss as with haemorrhage, or fluid and electrolyte loss, as with massive diuresis, diarrhoea, vomiting, or evaporation from large burn sur- faces. The normal reflex response to hypovolaemia is increased sym- pathetic tone, vasoconstriction, and tachycardia. Cardiac output is often sustained by these mechanisms such that heart rate is in- creased and stroke volume decreased, whereas blood flow distribu- tion is diverted away from the skin, resting muscles, and gut. Lactic acidosis develops and has been considered as a marker of tissue an- aerobic metabolism, although increased lactate production due to β-adrenergic stimulation may be the dominant or only mechanism. Thus, hypovolaemia initiates as tachycardia, reduced arterial pulse pressure, and (often) hypertension with a near normal resting car- diac output, followed by signs of organ hypoperfusion (oliguria, confusion) as cardiac output decreases. Systemic hypotension is the final presentation of

hypovolaemic shock and—if the clinician waits for this before acting—ischaemic tissue injury is almost always present. Table 17.6.1 The critically ill patient: haemodynamic monitoring key points Key point Explanation Tachycardia is never a good thing Tachycardia defines stress or an adaptation to stress. It may be necessary to sustain adequate blood flow, as in heart failure, but it still reflects heart failure. Hypotension is always pathological Hypotension impairs blood flow distribution and thus any patient with a MAP <65 mm Hg is impaired. They may have hepatic cirrhosis with adequate tissue blood flow at rest, but they have a markedly limited ability to adapt to increased metabolic demand. There is no such thing as a normal cardiac output Since blood flow is regulated to meet the metabolic demand of the body, and that metabolic demand can vary widely and rapidly, there is no value of total cardiac output that guarantees adequate tissue perfusion. Blood flow is either adequate or inadequate, no matter what the absolute value is. Central venous pressure is only elevated in disease Under most conditions, the central venous pressure is very close to zero as the heart pumps all venous return immediately back to the body. The CVP will rise if either right or left sided heart failure develops, or fluid overload (e.g. renal failure or iatrogenic). The presence of an elevated CVP before medical intervention connotes disease of some sort. Peripheral oedema is of cosmetic concern Tissue perfusion is independent of interstitial fluid accumulation. Since the primary concern is maintenance of organ perfusion, which requires an adequate venous return and MAP, restricting fluid resuscitation in an unstable patient because of peripheral oedema is illogical and should be avoided. CVP, central venous pressure; MAP, mean arterial pressure.

17.6 Circulatory support in the critically ill 3887 Cardiogenic shock Cardiac pump dysfunction can be due to either LV or right ven- tricular (RV) failure, or both. LV failure, as just described, is usually manifest by an increased LV end-diastolic pressure, left atrial pressure, and (by extension) pulmonary artery occlusion (‘wedge’) pressure, which must exist to sustain an adequate LV stroke volume. Tachycardia is universal in the patient who is not β-blocked. The most common cause of isolated LV failure in a critically ill patient is acute myocardial infarction. Usually, LV stroke work is re- duced and heart rate increased. In chronic heart failure both car- diac output and systemic vasomotor tone may be normal, whereas in acute LV failure states both may be reduced. These combined haemodynamic interactions lead Forrester and colleagues to use a pulmonary artery occlusion (‘wedge’) pressure of 18 mm Hg and a cardiac index of 2.2 as the cut-off to define heart failure states fol- lowing acute myocardial infarction. However, neither cardiac output nor systemic vascular resistance is a sensitive marker of LV failure until cardiogenic shock develops. Since pulmonary artery occlusion (‘wedge’) pressure is the back pressure to pulmonary blood flow, increases associated with LV failure may lead to pulmonary oedema and hypoxaemia, and secondary pulmonary hypertension may sub- sequently impair RV ejection, inducing biventricular failure, peripheral venous hypertension, and peripheral oedema formation, the so-called ‘backward failure’. The normal adaptive response of the host to impaired LV con- tractile function is to increase sympathetic tone, induce tachycardia, activate the renin-angiotensin system, retain sodium by the kid- neys, and thus increase the circulating blood volume. Fluid reten- tion takes time, whereas acute impairments of LV contractility can occur over seconds in response to myocardial ischaemia. Thus, the haemodynamic profile of acute and chronic LV failure can be dif- ferent. Acute LV failure is manifest by increased sympathetic tone (tachycardia, hypertension), impaired LV function (increased filling pressure and reduced stroke volume), with minimal RV ef- fects (normal central venous pressure), and increased O_2 extrac- tion manifest by a low Svo_2. Cardiac output need not be reduced and may in fact be elevated, owing to the release of catecholamines as part of the

acute stress response; vascular resistance is increased. By contrast, in chronic heart failure, although sympathetic tone is elevated, the heart rate is rarely over 105/min, and filling pressures are elevated in both ventricles consistent with combined LV failure and fluid retention. Again, cardiac output is not reduced except in severe heart failure states, but a cardinal finding is the inability of the heart to increase output in response to a volume load or metabolic stress (exercise). Furthermore, owing to the increased sympathetic tone, splanchnic and renal blood flows are reduced and can lead to splanchnic or renal ischaemia. Obstructive shock Obstruction in this context means mechanical obstruction of blood flow or ventricular filling. The most common cause of obstructive shock is pulmonary embolism leading to acute RV failure, but iso- lated RV dysfunction can occur in the setting of an acute inferior wall myocardial infarction, also as a consequence of pulmonary vascular disease (chronic obstructive pulmonary disease, primary pulmonary hypertension). Acute RV distension and failure due to massive pulmonary embolism has a characteristic appearance, and bedside echocardiography aids in rapid diagnosis and decision-making about treatment (Fig. 17.6.4 and 17.6.5). When RV dys- function predominates and is induced by pulmonary parenchymal disease, it is referred to as cor pulmonale, which is associated with signs of backward failure, elevated RV volume and pressures, sys- temic venous hypertension, low cardiac output, as well as reduced renal and hepatic blood flow. LV diastolic compliance decreases as the right ventricle dilates due to ventricular interdependence, either from intraventricular septal shift or absolute limitation of biventricular volume due to pericardial restraint. Thus, pulmonary Fig. 17.6.4 Transthoracic echocardiogram of acute pulmonary embolism. A four chamber view reveals a dilated right heart. The echo- free space in front of the heart represents a pericardial fat pad. PF, pericardial fat; RA, right atrium; RV, right ventricle. From Galiuto et al. (ed) (2011). The EAE Textbook of Echocardiography. © European Society of Cardiology, by permission of Oxford University Press. Fig. 17.6.5 Transthoracic echocardiogram of acute pulmonary embolism. Cross-section of the right pulmonary artery from the suprasternal view reveals masses in the lumen, consistent with thrombi (arrow). Ao, aorta; RPA, right pulmonary artery. From Galiuto et al. (ed) (2011). The EAE Textbook of Echocardiography. © European Society of Cardiology, by permission of Oxford University Press.

Section 17 Critical care medicine 3888 artery occlusion (‘wedge’) pressure is often elevated for a specific LV stroke work, giving the erroneous appearance of impaired LV con- tractility, but if left ventricular end-diastolic volume were measured, it is possible that no change in LV function would be seen if this were plotted against LV stroke work. Neither pulmonary vascular resistance nor mean pulmonary ar- tery pressure need be grossly elevated for RV failure to be present. Indeed, and importantly, if pulmonary arterial pressures are greater than 30–35 mm Hg, then pulmonary hypertension is probably chronic in nature because acute elevations of pulmonary arterial pressures above this level are not consistent with life. Elevations in central venous pressure of more than 12 mm Hg also reflect fluid retention, suggesting further that there is a state of compensated RV failure. Cardiac tamponade can occur from either (1) ventricular dilation limiting biventricular filling due to pericardial volume limitation, (2) acute pericardial effusion due to either fluid (inflammation) or blood (haemorrhage), which needs not be great in quantity, and (3) hyperinflation, which can act like pericardial tamponade to limit biventricular filling. The first two aetiologies are rarely seen, whereas the third commonly occurs. The cardinal sign of tamponade is dia- stolic equalization of all pressures, central venous pressure, pul- monary arterial diastolic pressure, and pulmonary artery occlusion (‘wedge’) pressure. Since RV compliance is greater than LV compli- ance, early on in tamponade there may be selective reduction in RV filling.

The presence of a pericardial effusion is often obvious on bed- side echocardiography (Fig. 17.6.6). Distributive shock Loss of blood flow regulation occurs as the end stage of all forms of circulatory shock, but as the initial presenting process it is common in sepsis, neurogenic shock, and adrenal insufficiency. Sepsis is a sys- temic process characterized by activation of the inflammatory medi- ators and generalized endothelial injury, but it is not clear that tissue ischaemia is an early aspect of this process. At its onset, sepsis is as- sociated with increased sympathetic activity (tachycardia, diaphor- esis) and increased capillary leak with loss of intravascular volume. Before fluid resuscitation this combination of processes resembles simple hypovolaemia, with decreased cardiac output, normal to in- creased peripheral vasomotor tone, and very low Svo2, reflecting systemic hypoperfusion. LV function is often depressed, but only in parallel with depression of other organs, and this effect of sepsis is usually masked by the associated hypotension that maintains low LV afterload. However, most patients with such a clinical presentation receive fluid resuscitation, after which the clinical picture of resusci- tated sepsis is a hyperdynamic state rather than hypovolaemia; this has been referred to as ‘warm shock’ in contrast to all other forms of shock. The haemodynamic profile of sepsis is one of increased car- diac index, normal pulmonary artery occlusion (‘wedge’) pressure, elevated Svo2, and a low to normal arterial pressure, consistent with loss of peripheral vasomotor tone. Acute spinal injury, spinal anaesthesia, general anaesthesia, and central nervous system catastrophe all induce a loss of sympa- thetic tone. The resulting hypotension is often not associated with compensatory tachycardia, hence systemic hypotension can be profound and precipitate cerebral vascular insufficiency and myo- cardial ischaemia. Since neurogenic shock reduces sympathetic tone, biventricular filling pressures, arterial pressure, and cardiac output all decrease. Treatment consists of reversing the primary pro- cess and supporting the circulation with infusion of an α-adrenergic agonist, such as phenylephrine or noradrenaline. Acute adrenal insufficiency can present with hyperpyrexia and circulatory collapse. This is more common than might be guessed, based on the epidemiology of adrenal cortical disease, because many patients are receiving chronic corticocosteroid therapy for the management of systemic and localized inflammatory states, such as asthma or rheumatoid arthritis, and in such cases the added stress of trauma, surgery, or infection can precipitate sec- ondary adrenal insufficiency, as can the abrupt discontinuation of long-term steroid treatment. Presentation is with nausea and vomiting, diarrhoea, confusion, hypotension, and tachycardia. Cardiovascular collapse is similar to that seen in neurogenic shock, except that the vasculature is not as responsive to sym- pathomimetic support. Accordingly, failure to respond to vaso- active pharmacological support in a patient who is hypotensive should suggest the diagnosis of adrenal insufficiency, when giving stress doses of corticosteroids usually reverses the unresponsive nature of the shock process. Circulatory support of the haemodynamically unstable patient If the cause of hypotension is intravascular volume loss, either ab- solute, as would occur with haemorrhage or massive diarrhoea, or relative, as would occur with loss of vasomotor tone or increased capillary endothelial permeability, then cerebral and coronary per- fusion pressures must be maintained while fluid resuscitation is begun, otherwise cardiac pump failure may develop and limit the effectiveness of fluid resuscitation. Infusions of vasoactive agents will increase both cardiac output and mean arterial pressure at the expense of the remaining vascular beds, hence fluid resuscitation to achieve an adequate intravascular blood volume is essential for Fig. 17.6.6 Transthoracic echocardiogram of cardiac tamponade. A parasternal short-axis view demonstrates a large amount of pericardial fluid and diastolic right ventricular collapse, indicating tamponade physiology. Ao, aorta; PE, pericardial effusion; RV, right ventricle. From Galiuto et al. (ed) (2011). The EAE Textbook of Echocardiography. © European Society of Cardiology, by permission of Oxford

University Press.

17.6 Circulatory support in the critically ill 3889 sustaining isolated vasopressor therapy in the setting of systemic hypotension. Many pathological states and acute stress conditions are associated with either adrenergic exhaustion or blunted respon- siveness to otherwise adequate circulating levels of catecholamines (e.g. diabetes, adrenal insufficiency, hypothermia, hypoglycaemia, and hypothyroidism). Furthermore, acute sepsis and systemic in- flammation are associated with reduced adrenergic responsiveness. Thus, even if the host makes an otherwise adequate sympathetic re- sponse, the vasomotor and inotropic response may be inadequate, requiring transient use of potent sympathomimetic agents to sustain cardiovascular homeostasis. Pharmacotherapy for cardiovascular insufficiency is directed at the pathophysiological processes that either induce or com- pound it. These therapies can be loosely grouped into one of three processes: (1) those that increase vascular smooth muscle tone (vasopressor therapy); (2) those that increase cardiac contractility (inotropic support); and (3) those that decrease smooth muscle tone (vasodilator therapy). Infusion of vasopressor agents are indicated to sustain a MAP greater than 60 mm Hg to prevent coronary or cerebral ischaemia, while other resuscitative measures, like volume resuscitation, and specific treatment of the underlying condition are ongoing. This level of MAP is clearly arbitrary since some patients maintain adequate coronary and cerebral blood flow at lower MAP levels, whereas others—notably those with either pre-existent sys- temic hypertension or atherosclerotic cerebrovascular disease—may not tolerate MAP decreasing more than 30 mm Hg from their base- line values. Once an adequate MAP has been achieved and intra- vascular volume losses corrected, care shifts towards maintaining adequate blood flow to metabolically active tissues to sustain organ performance. Several recent studies have underscored the principles described here. Three large prospective randomized trials comparing early goal-directed therapy (EGDT based on targeting ScvO2) to usual care reported that standard care based on maintaining good fluid resuscitation and bedside assessment was as good as targeted EGDT, and mortality rates were lower than predicted from historical con- trols. Similarly, a large prospective study showed that in previously nonhypertensive patients, targeting a mean arterial pressure of 65–75 mm Hg was as good if not better than targeting a mean ar- terial pressure 80–85 mm Hg. Finally, a large retrospective study of Australia and New Zealand ICU care from 2000 to 2012 demon- strated a clear progressive decline in mortality in all patient groups over this period with equal trends across all age groups and treat- ment settings. These progressive improvements in clinical outcomes have occurred without the use of new and proven treatment modal- ities. Thus, attention to detail, preventing complications, and with- drawing unneeded therapies and instrumentation reflect the new standard for patient care. Adrenergic receptor physiology and the role of vasopressin Most inotropes and vasopressors in clinical use are sympatho- mimetics that have direct effects on the adrenoreceptor system. Adrenoreceptors are complex membrane glycoproteins whose intracellular signal transduction is commonly, although not ex- clusively, mediated through G proteins and adenylate cyclase in an amplification-type system. Adrenoreceptors are classic- ally subtyped into six functional classes: myocardial β1 and smooth muscular β2, postsynaptic α1 and dopamine1 (DA1), and presynaptic α2 and DA2. Despite several recent reports indicating that there are more classes of adrenoreceptors, conceptually the six subtypes serve clinicians well, with most functional issues relating only to α and β adrenergic receptor modulation. Importantly, there is a quantitatively unpredictable variation in adrenoreceptor density and function in many pathophysiological states, hence agents acting upon them need to be titrated to effect rather than being given at a defined infusion or dose rate.

Vasopressor agents Phenylephrine The only noncatecholamine sympathomimetic used, phenylephrine differs chemically from other sympathomimetics by the absence of a hydroxyl group on position 4 of the benzene ring. This deletion reduces its potency relative to other sympathomimetics. It acts as a moderately potent α1-agonist and is used in those patients in whom hypotension is due to decreased arterial elastance (it only activates β-adrenoreceptors at high doses). A modest direct coronary vasoconstrictor effect appears to be offset by autoregulatory mechanisms in the absence of flow-limiting coronary disease. It is not metabolized by catecholamine O-methyltransferase (COMT), which metabolizes catecholamines, and therefore its absolute half-life is considerably longer than catecholamine sympathomimetics. Noradrenaline (norepinephrine) Noradrenaline has significant activity at α and β1-adrenoreceptors, resulting in a positive vasoconstrictor and inotropic effect. Its β1 activity makes it the α1-agonist of choice in patients with hypotension and known LV dysfunction. Its positive vasopressor effect may enhance renal perfusion and indices of renal function in haemodynamically stable patients, and this effect may also be seen at higher doses when noradrenaline is used as a vasopressor in those with sepsis. Both observations are likely related to elevation of MAP, the input pressure for organ perfusion. Adrenaline (epinephrine) Adrenaline is a very potent catecholamine sympathomimetic that has markedly increased β2-adrenoreceptor activity compared with its molecular substrate, noradrenaline. Adrenaline has potent chronotropic, inotropic, β2-vasodilatory, and α1-vasoconstrictor properties. Its net vasopressor effect is the end result of the balance between adrenaline-mediated β2 and α1 adrenoreceptor stimulation. At low doses this balance may result in no net pressor effect, with a fall in the diastolic blood pressure. Additionally adrenaline, unlike noradrenaline, has marked metabolic effects mediated through β2-adrenoreceptor stimulation that includes inducing a transitory, but apparently harmless, hyperlactataemia. Clearance rates are variable and mediated by both the COMT and monoamine oxidase systems. Vasopressin Vasopressin exerts its vasomotor effects by stimulating V1 receptors to cause an increase in intracellular calcium, and by potentiating the effects of β adrenergic receptor stimulation. In normal conditions the vasomotor effect is weak, but in shocked states—especially in septic shock, when vasopressin desensitization commonly occurs—vasopressin may act as a powerful vasopressor. In many

Section 17 Critical care medicine 3890 pressor-dependent patients with septic shock, adding low-dose arginine vasopressin (0.01–0.02 μg/kg/min) may markedly improve the patient's vascular responsiveness. Indeed, several authors in this field recommend that when vasopressors are withdrawn in patients treated with norepinephrine and vasopressin, that the norepinephrine be decreased first as the vasopressin is acting more like a stress hormone than an actual vasopressor. This is an important concept, because if vasopressin is given in higher doses it may cause profound vasoconstriction on its own, and indeed it is used for this purpose as a treatment to cause splanchnic ischaemia in oesophageal variceal bleeding. Whether the addition of vasopressin to norepinephrine, or use of vasopressin instead of norepinephrine, results in improved outcomes in patients with septic shock has been investigated in blinded randomized trials. These have shown no significant difference in organ dysfunction, mortality, or adverse events, suggesting that while vasopressin is as safe as norepinephrine, it has not yet been proven to be superior. Further investigation of arginine vasopressin and vasopressin analogues is ongoing. Dopamine Dopamine is the most controversial of the clinically utilized catecholamine sympathomimetics. This stems largely from claims for selective, dose-dependent, splanchnic, and renovascular vasodilatory properties. Its dopaminergic properties do not reduce the incidence of renal failure in patients with

shock when compared to noradren- aline. Dopamine stimulates the release of noradrenaline from sym- pathetic nerve terminals in a dose-dependent manner, with this indirect noradrenaline effect accounting for up to half of dopamine's clinically observed physiological activity. Cardiomyocyte noradren- aline stores are finite, accounting for tachyphylaxis to the positive inotropic effects of dopamine observed after approximately 24 h in patients with acute myocardial infarction. Recent clinical trials have compared the effect of dopamine versus noradrenaline as first line agents for the treatment of shock. Dopamine use resulted in no survival benefit overall, an increased incidence of cardiac arrhyth- mias, and it may increase mortality in patients with cardiogenic shock. As a result of these findings, dopamine is now much less com- monly used than in the past. Synthetic angiotensin II Recently synthetic human angiotensin II has been licensed for use in humans after it was shown to increase blood pressure in a trial in adult patients with vasodilated shock who were being treated with high-dose noradrenaline or equivalent vasopressors. The trial was not designed to assess important patient centred outcomes but reported no significant difference in adverse events or mortality. Whether adding angiotensin II as an alternative or supplementary vasopressor improves outcomes for critically ill patients requires further study. Inotropic agents Dobutamine Dobutamine is a synthetic analogue of dopamine. It is adminis- tered by continuous intravenous infusion as a positive inotrope, with the improvement in cardiac output noted to potentially in- crease renal blood flow, creatinine clearance, and urine output. As a β1-agonist it will increase myocardial oxygen consumption, although autoregulatory increases in coronary blood flow usually fully compensate in the absence of flow-limiting coronary artery disease. A noted problem with dobutamine is the development of tachyphylaxis with prolonged (as little as 72 h) infusions, suggested to be due to the down-regulation of β1-adrenoreceptors. Dopexamine Dopexamine is a synthetic dopamine analogue with significant β2- adrenoreceptor agonist activity. Its splanchnic blood flow effects and positive inotropic activity have led to enthusiasm for potential utility outside its primary indication, acute heart failure syndromes with hypertension and oliguria. Randomized controlled clinical inves- tigations have demonstrated improvement in morbidity and mor- tality outcomes when dopexamine was used as the pharmaceutical of choice in achieving goal-oriented oxygen delivery values in peri- operative critically ill patients. Phosphodiesterase inhibitors These agents are variably used in the management of circula- tory shock, with the two most commonly employed agents in this class being amrinone and milrinone. Both are bipyridines, and the class of drugs is otherwise known as 'inodilators', with reference to the two predominant dose-dependent modes of action iden- tified. Conventional wisdom is that these agents are much more potent vasodilators than inotropes, with the difference in potency approaching 10–100-fold. Milrinone has a shorter half-life and is a more potent (10–15-fold) inotropic agent than amrinone, but from all other aspects they are similar agents. Both are eliminated by conjugation, with amrinone's biological half-life known to be extended in the presence of congestive heart failure. Their mech- anism of action is not precisely known, but at least part of their ac- tivity is related to inhibition of phosphodiesterase type 3, found in high concentrations in cardiomyocytes and smooth muscle cells, and they may activate a sodium-dependent calcium channel. The end result is an increase in intracellular cAMP and calcium, with the physiological effect being an improvement in diastolic myocar- dial function, and for this reason these agents are felt to be posi- tive lusiotropes. Clinically, they are used as positive inotropes, given by continuous intravenous infusion following a loading dose, with their catecholamine-independent mechanism of action making them theoretically attractive as inotropic support of choice in pa- tients with potential β1-adrenoreceptor down-regulation. Levosimendan Levosimendan is a calcium sensitizing agent that has positive ino- tropic effects and additionally

causes vasodilatation by acting on vascular ATP-dependent potassium channels. Because its action is distal to calcium flux, there is no increased cardiac muscle oxygen demand. This feature is attractive in managing cardiac failure states in which coronary blood flow is either limited or cannot increase further. Levosimendan has been compared to dobutamine in pa- tients with severe low output heart failure, and in this patient group it provides no clear mortality benefit. Some trials have shown ad- vantage over dobutamine in other critically ill patients, but a limi- tation is that levosimendan's action requires its uptake into the cell and thus it has a slower onset of action and longer wash-out time compared with catecholamines and other agents, making it

 less titratable, and limiting its use in acute care situations. In pa- tients with sepsis, a recent well-conducted trial found that adding levosimendan to standard care decreased neither severity of organ dysfunction or risk of death, reduced the likelihood of suc- cessful weaning from mechanical ventilation, and increased risk of supraventricular arrhythmias. Vasodilators Afterload reducing vasodilators act via vascular smooth muscle re- laxation. Vascular dilatation is mediated by both nitric oxide (NO) and non-NO-based mechanisms, nitric oxide being a powerful, lo- cally acting vascular smooth muscle relaxant. Among commonly used vasodilators in haemodynamically unstable patients, both sodium nitroprusside and glyceryl trinitrate (nitroglycerine) func- tion as nitric oxide donors. Numerous other nonnitric oxide donor vasodilating agents are available, with hydralazine, clonidine, and inhibitors of the renin-angiotensin system being the most com- monly employed nonnitric oxide-based vasodilators in patients with cardiovascular instability. A simple approach to the pharmacotherapy of circulatory shock Loss of vasomotor tone requires both fluid resuscitation to achieve the increased vascular volume needed to restore effective venous re- turn, and increased α-adrenergic tone, usually via sympathomimetic agents, to restore arterial and venous vasomotor tone. Accepted targets for resuscitation are an Svo2 greater than 70% with a mean arterial pressure greater than 65 mm Hg. Impaired contractility re- quires afterload reduction, as tolerated, up to a decrease in mean ar- terial pressure to approximately 70 mm Hg, targeting an Svo2 greater than 70%. Since pulmonary arterial catheterization is now used less often, bedside echocardiographic evaluations are often substituted for it. Fluid resuscitation should be stopped if there is echocardio- graphic evidence of right ventricular overload (e.g. paradoxical septal shift, increased tricuspid regurgitation). Echocardiography can quantify both right and left ventricular contractility, the pres- ence of mechanical causes of cardiac pump failure (e.g. pericardial effusion and tamponade, severe valve disease, acute right or left ven- tricular failure). In sepsis, Svo2 is usually elevated following fluid resuscitation, hence resuscitation usually focus on restoration of end-organ function (e.g. urine output, improved sensorium) with individualization of resuscitation to achieve adequate end-organ perfusion pressure and the absence of evidence of hypoperfusion. Regrettably, the only prospective clinical trials documenting benefit from such resuscitation strategies were applied early in the course of sepsis or in high-risk surgical patients. However, it makes physio- logical sense to prevent organ ischaemia by maintaining adequate blood flow, hence strategies such as those described here are war- ranted while awaiting confirmation through the conduct of ran- domized trials. FURTHER READING Angus DC, et al. (2015). A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. Intensive Care Med, 41, 1549–60. Annane D, et al. (2007). Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. Lancet, 370, 676–84. Bellomo R, et al. (2000). Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care

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17.7 Management of raised intracranial pressure 38

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ESSENTIALS Normal intracranial pressure is between 5 and 15 mm Hg in supine subjects. Intracranial hypertension (ICP >20 mm Hg) is common in many central nervous system diseases and in fatal cases is often the immediate cause of death. Aetiology and pathogenesis—increases in intracranial volume and hence—given the rigid skull—intracranial pressure may be the consequence of (1) brain oedema, (2) increased cerebral blood volume, (3) hydrocephalus, and (4) space-occupying lesions. Brain perfusion depends on the cerebral perfusion pressure, which is mean arterial pressure minus intracranial pressure. The normal brain autoregulates cerebral blood flow down to a lower limit of cerebral perfusion pressure of about 50 mm Hg in healthy subjects, and perhaps 60–70 mm Hg in disease. Cerebral perfu- sion pressure reduction to below these values results in cerebral ischaemia. Clinical features—the cardinal symptom of intracranial hyper- tension is headache, which may be accompanied by vomiting, visual disturbance, and alterations in mental function or con- scious state. Papilloedema is the classical sign, but may be absent. Severe elevation of intracranial pressure can result in brady- cardia and hypertension (Cushing's response), abnormalities of breathing (Cheyne–Stokes respiration, central neurogenic hyper- ventilation, 'ataxia of breathing'), and various forms of cerebral herniation. Investigation—computed tomography or magnetic resonance imaging is the investigation of choice; if lumbar puncture is con- sidered (e.g. for diagnosis of meningitis), imaging must be done first and lumbar puncture avoided if the basal cisterns are effaced by cerebral oedema. Management—this involves (1) ensuring normoxia and normocapnia (Pao2 >11 kPa, Paco2 4.5–5 kPa), with tracheal in- tubation and ventilatory support where required; (2) treating precipitating factors such as seizures, fever, and electrolyte ab- normalities; (3) treating raised intracranial pressure with mannitol, dexamethasone (for tumours), hyperventilation (if pupillary dilata- tion/clinical picture merits); and (4) monitoring intracranial pres- sure if appropriate (e.g. trauma). Introduction The normal intracranial pressure (ICP), measured at the level of Monro's foramen, is between 5 and 15 mm Hg in supine subjects. Intracranial hypertension (ICP >20 mm

Hg) is a common accom- paniment of many central nervous system (CNS) diseases. In many of these situations intracranial hypertension is the most important cause of symptoms and determinant of outcome, and in fatal cases is often the immediate cause of death. Epidemiology Intracranial hypertension is a pathophysiological mechanism common to many diseases. Acute intracranial pressure elevation is commonly encountered in traumatic brain injury, haemorrhagic and large ischaemic strokes, and intracranial infection. Subacute and chronic intracranial hypertension are seen in intracranial tu- mours. Less commonly, intracranial hypertension may be observed without any underlying cause—the syndrome of idiopathic intracra- nial hypertension. Pathophysiology The cranial cavity contains brain (80%), blood (10%), and cere- brospinal fluid (CSF; 10%). These incompressible contents are bounded by a rigid skull with a fixed capacity. Consequently, an in- crease in volume of any of these contents, or the presence of any space-occupying pathology, results in an increase in intracranial pressure unless one of the other constituents can be displaced or its volume decreased (Fig. 17.7.1). This principle is referred to as the Monro–Kellie doctrine. Increases in intracranial volume may be the consequence of: • Brain oedema, which may have different pathogenic mechanisms: ■ Cytotoxic oedema occurs as a result of cell swelling, most com- monly due to ischaemic energy depletion and increases in intracellular Na+ and water. 17.7 Management of raised
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17.7 Management of raised intracranial pressure 3893 ■ Vasogenic oedema results from an increased permeability of the blood-brain barrier with an expansion of the extracellular fluid compartment. ■ Interstitial oedema occurs in the context of hydrocephalus, where increased intraventricular cerebrospinal fluid pressures result in permeation of cerebrospinal fluid into adjacent brain, typically in the frontal periventricular regions. ■ Vascular engorgement that results from increased cerebral blood volume. This may be due to the vasodilatation that accompanies normal or abnormal (e.g. epileptiform) neuronal activity. In other situations vasodilatation may be due to loss of vasoregulation, either due to disease (vasoparalysis), or due to the effect of potent physiological (carbon dioxide) or pharma- cological (nitrates and other nitric oxide donors) cerebral vasodilators. • Hydrocephalus, which may be noncommunicating (where an ob- struction prevents the ventricular system communicating with the subarachnoid space), or communicating (where there is a defect in cerebrospinal fluid reabsorption). • Space-occupying lesions (SOL), which may be either chronic (e.g. intracranial tumours) or acute (e.g. intracranial haematomas associated with trauma). Temporal patterns of intracranial pressure change Initial increases in intracranial volume are buffered by displace- ment or reduction in volume of other contents. Thus, cerebral oedema may result in compression of the ventricles, with trans- location of cerebrospinal fluid to the spinal subarachnoid space, and compression of cerebral vasculature. Over longer time periods, normal brain may be compressed and cerebrospinal fluid produc- tion diminished. The relationship between intracranial volume (ICV) and intra- cranial pressure is commonly depicted as a hyperbolic curve, with an initial flat part during which compensatory mechanisms are effective, a knee that represents their progressive exhaustion, and a steep phase when even small increases in intracranial volume produce large increases in intracranial pressure. However, the ex- tent and efficiency with which these mechanisms buffer increases in volume depend on the speed of progression of disease. Given these considerations, it is more appropriate to depict the evolution of pathophysiology as a family of curves, with variable rates of pro- gression (Fig. 17.7.2). It is important to make three further points in this context: • First, a precipitating factor may suddenly increase the speed of progression of a relatively slow pathophysiological process, and be the

proximate cause of symptomatic decompensation. • Secondly, acute changes in cerebrovascular physiology are an important cause of such deterioration. Both hypoxia and hypercarbia can cause cerebral vasodilatation and elevate intra- cranial pressure. While severe hypertension may result in cere- bral oedema, it is far more common to find that relatively minor reductions in mean arterial pressure compromise cerebral per- fusion and trigger reflex vasodilatation and secondary increases in intracranial pressure. Such haemodynamic instability may be the underlying cause of phasic increases in intracranial pressure (Fig. 17.7.3). (a) AV FM SSAS ICP 100 Arterial Venous CSF CP Brain 0 Sol Pressure transducer (b) AV SSAS ICP 100 Arterial Venous CSF CP Brain 0 Pressure transducer Fig. 17.7.1 Schematic diagram showing intracranial contents in the normal brain (a) and with elevated intracranial pressure (b). Note that cerebrospinal fluid (CSF) is produced by the choroid plexus (CP), circulates freely, passing through the foramen magnum (FM) into the spinal subarachnoid space (SSAS), before absorption by arachnoid villi (AV) in the cerebral venous sinuses. Increases in intracranial pressure may be due to brain oedema, vascular engorgement, space-occupying lesions (SOL), or impaired CSF circulation or absorption. Compensatory mechanisms include translocation of CSF to the SSAS, and compression of cerebral vascular beds. The intracranial pressure trace shows a higher mean value, and the inability of the noncompliant brain to cope with increased blood during each systole results in an increased pulsatility of the intracranial pressure waveform. 40 ICP (mmHg) 30 20 10 0 Rate of rise of ICV X Intracranial volume Slow Fast Fig. 17.7.2 Intracranial volume/pressure curves. Increases in intracranial volume (ICV) are initially buffered by compensatory mechanisms, but eventually result in intracranial pressure (ICP) elevation. The ability to buffer ICV increases depends on the speed at which pathology develops. Gradually progressive increases in ICV (such as those produced by a slow growing tumour) may be well compensated, until a precipitating factor (e.g. the development of hydrocephalus, denoted by X in the diagram) shifts the relationship to a steeper curve.

 • Finally, since patients with significant intracranial hypertension operate on the steep part of the ICV/ICP curve, even small de- creases in intracranial volume (e.g. a 5 ml decrease in cerebral blood volume produced by mild hyperventilation) can have grati- fyingly large effects on intracranial pressure. Why treat intracranial hypertension? Brain perfusion depends on the cerebral perfusion pressure (CPP), the difference between mean arterial pressure (MAP) and intracra- nial pressure. While the normal brain autoregulates cerebral blood flow across a large range of CPP values, the lower limit of such autoregulation is about 50 mm Hg in healthy subjects, and may be sig- nificantly higher (60–70 mm Hg) in disease. CPP reduction below the lower limit of autoregulation results in cerebral ischaemia, and even minor reductions in CPP may trigger reflex vasodilatation and increase intracranial pressure in a noncompliant intracranial cavity. Such cere- bral ischaemia is important in its own right. For instance, intracranial hypertension may be the direct cause of neurocognitive deficits in sur- vivors of traumatic brain injury. It is very likely that both the severity and duration of ICP elevation contribute to the ‘dose’ of intracranial hypertension that is responsible for its adverse effect on outcomes. An expanding focal mass can generate pressure gradients within the intracranial cavity, and the resulting displacement of brain against rigid structures, and protrusion (herniation) of brain through narrow openings between intracranial compartments can press on vital structures and result in death (Fig. 17.7.4). Prolonged intracranial hypertension may result in permanent damage to critical structures. Thus, benign intracranial hyperten- sion rarely results in herniation syndromes, but if left untreated, fre- quently results in optic atrophy. Clinical features Symptoms The symptoms that accompany intracranial pressure elevation can be nonspecific and insensitive. The cardinal feature

of intracranial hypertension is headache, which may be described as severe (‘worst ever’) and explosive in onset in the setting of intracranial haemor- rhage. The headache of intracranial tumour is often progressive, worst on awakening (possibly due to intracranial pressure elevations associated with the supine position and Paco2 elevation in sleep), and is exacerbated by coughing and straining. However, it may be indistinguishable from common tension headache, and dangerous intracranial hypertension may occur without headache. The headache is often accompanied by vomiting, which is classic- ally described as projectile and not preceded by nausea. Visual dis- turbances are often reported, which may be attributable to optic or oculomotor nerve compression (with accompanying visual failure or diplopia, respectively). Alterations in mental function or con- scious state may be observed, ranging from impaired concentration, through increased irritability, impaired cognition and memory, and altered personality, to increased somnolence and deep coma. Signs While papilloedema is the classical sign associated with intracra- nial pressure elevation, it is not seen with acute intracranial hyper- tension, and may be absent even with large intracranial masses. Pressure on cranial nerves may result in weakness of ocular move- ment. The abducens nerve is often involved in such a process due its long intracranial course, and the resultant diplopia provides the CPP ICP CBV 140 [A] 120 MAP (mmHg) 100 60 45 40 5 min 25 5 ICP (mmHg) 80 [B] Cerebral vasodilatation CPP (mmHg) CBV Cerebral vasoconstriction CPP ICP Fig. 17.7.3 Intracranial pressure (ICP) traces show phasic variations which may last several minutes (Lundberg A waves; (A)) or may be more transient (Lundberg B waves; (B)). ICP elevations are often initiated by reductions in mean arterial pressure (MAP), which trigger compensatory vasodilatation and increase cerebral blood volume (CBV) and ICP. This vicious cycle may be terminated by spontaneous hypertension associated with a Cushing’s response (arrow in MAP and ICP traces), or by therapeutic elevation of MAP, which triggers compensatory cerebral vasoconstriction and reductions in ICP. Note that a period of stable MAP greater than 100 mm Hg is associated with a low, stable ICP. Modified from Rosner MJ (1993). Pathophysiology and management of increased intracranial pressure. In: Andrews BT (ed) Neurosurgical intensive care, p. 75. McGraw-Hill, New York. 1 2 3 4 Fig. 17.7.4 Cerebral herniation may be (1) subfalcine (beneath the falx cerebri), (2) transtentorial (through the tentorial hiatus with compression of the midbrain and posterior cerebral artery), (3) tonsillar (where the cerebellar tonsils herniate through the foramen magnum and compress the lower brainstem upper cervical cord), or (4) transcalvarial (through a traumatic or surgical defect in the roof of the cranial cavity). Modified from Fishman RA (1975). Brain edema. New Engl J Med, 293, 706–11.

 classical example of a false localizing sign. Lesions that irritate the posterior fossa dura can produce neck stiffness. Progressive increases in intracranial pressure result in bradycardia and hypertension, which constitute the Cushing’s response and sig- nify stimulation of brainstem autonomic nuclei. Worsening brain stem compression and/or ischaemia result progressively in Cheyne– Stokes respiration, central neurogenic hyperventilation, and ir- regular respiratory patterns (‘ataxia of breathing’). Both neurogenic pulmonary oedema and the adult respiratory distress syndrome have been associated with intracranial hypertension; sudden mas- sive increases in ICP, such as occur with a high grade subarachnoid haemorrhage, cause a ‘catecholamine storm’ with severe acute sys- temic arterial hypertension that causes both pulmonary vascular and myocardial damage. Severe elevation of intracranial pressure may result in hernia- tion of the temporal lobe through the tentorial notch (Fig. 17.7.4). This produces clinical features due to pressure on the ipsilateral oculomotor nerve (ipsilateral pupillary dilatation), pyramidal tract (contralateral weakness), and brainstem (Cushing’s

response and abnormal respiratory patterns followed by circulatory collapse and respiratory arrest). The posterior cerebral artery is frequently com- pressed by the herniating temporal lobe, and successful resuscita- tion from threatened or early transtentorial herniation may leave a patient with an ipsilateral occipital infarction. Clinical investigation Imaging The most informative standard imaging in patients with intracra- nial hypertension is computed tomography (CT), which may reveal subarachnoid or intracerebral blood, contusions, or a tumour. In addition, cerebral oedema may be manifest by loss of sulci, com- pression of the third and lateral ventricles, and effacement of the perimesencephalic and suprasellar cisterns. Unilateral lesions may result in midline shift (which can occur without pupillary asym- metry), compression of the ipsilateral lateral ventricle, and in some cases dilatation of the contralateral ventricle due to obstruction of Monro's foramen. It is important to recognize that overt ventricular dilatation may be absent when hydrocephalus coexists with cere- bral oedema. Indeed, the presence of normal sized ventricles in the context of intracranial hypertension (demonstrated by intracranial pressure monitoring) should suggest the possibility of coexisting hydrocephalus and trigger the consideration of cerebrospinal fluid drainage as a means of therapy. Magnetic resonance imaging may provide better definition of underlying pathology, particularly in the posterior fossa, and its multiplanar capability may provide a better appreciation of the ex- tent of space-occupying lesions. Modern imaging methods can also detect patients who may have relatively normal intracranial pres- sure, but are at high risk of severe intracranial hypertension. For example, patients with a middle cerebral artery (MCA) territory in- farction are at high risk of severe brain swelling if more than 50% of the MCA territory is hypodense. Lumbar puncture A lumbar puncture offers the opportunity to directly measure cere- brospinal fluid pressure, and can be the defining investigation in meningitis, subarachnoid haemorrhage, or benign intracranial hypertension. However, in the context of clinical features that sug- gest intracranial hypertension, a lumbar puncture must be preceded by CT, and avoided if the basal cisterns are effaced by cerebral oe- dema. Removal of cerebrospinal fluid from the lumbar subarach- noid space under these circumstances can markedly increase the pressure differential between the infratentorial and supratentorial compartments, or the intracranial and spinal compartments, and precipitate transtentorial or cerebellar herniation, respectively. At the extreme it can be fatal. Monitoring intracranial pressure The clinical evaluation of intracranial hypertension is diffi- cult due to its nonspecific clinical picture and phasic variations. Management may therefore be greatly facilitated by direct moni- toring of intracranial pressure using intraparenchymal or ven- tricular monitoring devices. Such monitoring is most commonly used in severe intracranial hypertension and in sedated or deeply unconscious patients, in whom changes in clinical signs do not provide an alternative means of assessing progress and response to therapy. Although authoritative guidelines recommend such an ap- proach, the one randomized clinical trial that evaluated intracranial pressure monitoring in traumatic brain injury found no outcome benefit when compared to a protocol based on clinical evaluation and serial imaging. This trial was conducted in South America, as intracranial pressure monitoring in patients with moderate to se- vere traumatic brain injury is considered a standard of care in many high-income countries. Strategies for therapy Management focuses on four areas, which are described next. Monitoring progression of disease and response to therapy Monitoring will depend on the clinical context. Repeated clinical examination with regular charting of the Glasgow Coma Scale may suffice in many cases. Patients with benign intracranial hyperten- sion may require regular visual field assessment, while those with traumatic brain injury, intracranial haemorrhage, or severe cerebral oedema may benefit from direct intracranial pressure monitoring. The value of intracranial pressure monitoring may be substantially enhanced by the use of other monitoring modalities such

as brain tissue oximetry. Maintenance of stable physiology and removal of precipitating factors Hyponatraemia and low plasma osmolality will tend to worsen cerebral oedema by favouring water entry into the brain, and should be vigorously corrected. Maintenance of cerebral perfusion pressure with fluid resuscitation and vasoactive agents will prevent cerebral ischaemia. Comatose patients should have arterial blood gas analysis, and intubation and ventilatory support provided if airway protection is required or gas exchange is impaired. While hyperventilation has been widely used to control intracranial pres- sure in the past, there is increasing concern regarding the induc- tion of critical cerebral ischaemia by hypocapnic vasoconstriction.

Section 17 Critical care medicine 3896 Current recommendations suggest that near normal Paco2 levels (4.5–5 kPa) should be maintained, with moderate hyperventilation (Paco2 4.0–4.5 kPa) guided by brain tissue or jugular bulb oxim- etry; and more profound reductions in PaCO2 reserved for control of acute episodes of severe intracranial hypertension, evidenced by monitoring or clinical signs (such as pupillary dilatation). Intensive glucose control targeting a blood glucose concentration of 4.5– 6.0 mmol/litre significantly increases the risk of inducing moderate and severe hypoglycaemia, but the effects on clinical outcomes are currently unclear. Most current recommendations are to treat blood glucose when it is greater than 10 mmol/litre, with a target range of 6.0–10.0 mmol/litre. Attention should also be paid to treating epilepsy and significant fever, both of which can precipitate rises in intracranial pressure, and to discontinuing or mitigating the cardiorespiratory effects of drugs such as opioids, which may be responsible for physiological derangements that precipitate intra- cranial pressure elevation. Treatment of the underlying condition Early neurosurgical evaluation and operative therapy may be life- saving if a patient has an acute intracranial haematoma, a large tumour, or established hydrocephalus. Specific antimicrobial therapy may be required for meningitis, encephalitis, or brain ab- scess. Systemic hypertension commonly accompanies intracranial hypertension, and should generally not be treated because it may be needed to preserve cerebral perfusion. If therapy is needed for extreme hypertension or for hypertensive encephalopathy, then it is best to avoid nitric oxide donors such as nitrates or sodium nitroprusside, which can cause cerebral vasodilatation and further increase intracranial pressure. Table 17.7.1 Treatment of intracranial hypertension CPP augmentation (by increasing MAP) Maintenance of CPP >60–70 mm Hg prevents ischaemia, and further increases (90–100 mm Hg) may reduce ICP by autoregulatory cerebral vasoconstriction. Efficacy demonstrated in traumatic brain injury. Corticosteroids Reduce vasogenic oedema by restoring BBB integrity. Particularly effective in peri-tumoural oedema and benign intracranial hypertension. No outcome benefit in trauma. Prophylactic use may reduce incidence of hydrocephalus and other sequelae in tuberculous and acute bacterial meningitis. Diuretics Furosemide used to potentiate mannitol. Acetazolamide and thiazide diuretics used in benign intracranial hypertension. Osmotic agents Mannitol is effective in emergencies and can be used repeatedly if effective and plasma osmolality ≤325 mOsm/litre. Hypertonic NaCl (3–30%) may reduce ICP either as first line agent or when mannitol is ineffective and tends to cause less problems with major fluid shifts. Hyperosmotic agents may be less effective when there is widespread disruption of the blood–brain barrier. Reduction of cerebral blood volume Sedation and treatment of seizures can produce reductions in CBF and CBV that are coupled to reduction of neuronal metabolism. Hyperventilation has been commonly used to reduce CBV by inducing cerebral vasoconstriction, but can produce critical reductions in CBF. Needs to be used with care and with monitoring of cerebral oxygenation (usually with brain tissue or jugular bulb oximetry). Hypothermia Mild to moderate hypothermia (32–36oC) is neuroprotective in experimental models, but clinically unproven. The neuroprotective benefit of

hypothermia following cardiac arrest has been challenged by more recent data that show no benefit when compared to avoidance of hyperthermia. Hypothermia is effective at controlling refractory intracranial hypertension by multiple mechanisms, including metabolic suppression and anti-inflammatory effects, but outcome benefits have not been demonstrated. Indeed, when used early as an ICP lowering intervention in TBI, it may result in worse outcomes. CSF drainage Ventriculostomy provides emergency drainage of CSF in trauma, acute hydrocephalus (subarachnoid haemorrhage, tumours). Ventriculoperitoneal, ventriculoatrial, and lumboperitoneal shunts provide chronic CSF diversion in idiopathic or secondary hydrocephalus. Endoscopic third ventriculostomy provides communication between ventricular and cisternal CSF in noncommunicating hydrocephalus. May remove the need for shunts and the associated risk of shunt malfunction and sepsis. Surgical decompression In TBI, early decompressive craniectomy worsens outcome in the absence of severe intracranial hypertension; used for the treatment of refractory intracranial hypertension it reduces mortality, but increases the number of survivors with severe disability or in a vegetative state. Decompressive craniectomy improves survival, and probably functional outcome, in 'malignant' MCA stroke with severe cerebral oedema. In traumatic brain injury, early decompression results in worse functional outcomes. When used in refractory intracranial hypertension, it can increase survival and the proportion of survivors at least independent at home, but with some increase in severely disabled survival. Optic nerve decompression may prevent visual deterioration in benign intracranial hypertension. BBB, blood–brain barrier; CBF, cerebral blood flow; CBV, cerebral blood volume; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; ICP, intracranial pressure; MAP, mean arterial pressure; MCA, middle cerebral artery; TBI, traumatic brain injury Fig. 17.7.5 Management of the unconscious patient with intracranial hypertension. CPP, cerebral perfusion pressure; MAP, mean arterial pressure.

17.7 Management of raised intracranial pressure 3897 Specific treatment of intracranial hypertension Several therapies can be used to reduce intracranial pressure, and their application will depend on the cause and severity of intracranial pressure elevation. Commonly used interventions and their indica- tions are outlined in Table 17.7.1, but it must be pointed out that few of these have been assessed by good quality outcome studies. Treatment pathways for the emergency management of an uncon- scious patient with suspected intracranial hypertension are outlined in Fig. 17.7.5. FURTHER READING Andrews PJ, et al. (2015). Eurotherm3235 Trial Collaborators: hypo- thermia for intracranial hypertension after traumatic brain injury. N Engl J Med, 374, 1385. Brain Trauma Foundation (2016). Guidelines for the Management of Severe Traumatic Brain Injury, 4th edition. https://braintrauma.org/ uploads/03/12/Guidelines_for_Management_of_Severe_TBI_4th_ Edition.pdf Chesnut RM, et al. (2012). A trial of intracranial-pressure monitoring in traumatic brain injury. N Engl J Med, 367, 2471–81. Cooper DJ, et al. (2011). Decompressive craniectomy in diffuse trau- matic brain injury. N Engl J Med, 364, 1493–502. Hofmeijer J, et al. (2009). Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]):
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17.8 Sedation and analgesia in the ICU 3898 Michae

17.8 Sedation and analgesia in the ICU 3898 Michael C. Reade

ESSENTIALS Patients undergoing mechanical ventilation or other forms of inva- sive organ support in an intensive care unit should ideally be free of pain, anxiety, and delirium, sufficiently cooperative or sedated to en- able safe delivery of essential aspects of their care, sufficiently awake such that tracheal extubation is not unnecessarily delayed, and left with few or no unpleasant memories of their illness and treatment. This ideal is often not achieved. Management should be based on an analgesia-first, delirium- control, sedation-minimization approach. Identifying intensive care unit-associated delirium is not straightforward: most delirious pa- tients are not agitated, and 'hypoactive' delirium can mask substan- tial psychological distress. Various assessment scales can be used to quantitate, monitor and communicate sedation and sedation goals, and similar tools can be employed to identify delirium. The most common choice of drugs for pain control, delirium control and sed- ation varies markedly around the world, and is determined more by familiarity and traditional local practice than by evidence from com- parative effectiveness trials. However, the widespread application of a systematic approach offers a significant prospect of patient and hospital efficiency benefit compared to current practice in many in- tensive care units. Introduction Patients undergoing mechanical ventilation or other forms of inva- sive organ support in an intensive care unit (ICU) should ideally be: • free of pain, anxiety and delirium; • sufficiently cooperative or sedated to enable safe delivery of essen- tial aspects of their care, in particular with a low risk of removal of their endotracheal tube or intravascular catheters; • sufficiently awake such that tracheal extubation is not unneces- sarily delayed; and • left with few or no unpleasant memories of their illness and treatment. When properly applied, modern pharmacotherapy along with nonpharmaceutical techniques should be able to achieve these goals in most patients. This is helped considerably by technical advances in organ-support technologies such as microprocessor- controlled ventilators that are sensitive to the patient's respiratory effort, minimally-invasive cardiovascular monitoring, and better use of regional analgesia that acts without affecting cognitive function. Where patients were once thought to require deep sed- ation

to tolerate various aspects of ICU care, most can now remain interactive and indeed begin their physical and psychological re- habilitation while still requiring mechanical ventilation and other invasive organ support. Very few patients require deep sedation, which is indicated only to reduce intracranial pressure, control seizures, or prevent awareness during neuromuscular blockade. However, despite this optimistic outlook, contemporary observa- tional studies consistently find that most critically ill patients re- call substantial pain and anxiety, often accentuated by distressing hallucinations. Clearly there is a gap between optimal and actual practice. Central to optimizing ‘sedation and analgesia in the ICU’ is understanding the interplay of causes of pain, agitation (and un- pleasant awareness) and delirium in a particular patient, and also the interactions of drugs used for each of these indications. Much like the ‘triad of anaesthesia’ (hypnosis, analgesia, and muscle re- laxation) reminds anaesthetists that a balanced anaesthetic using specific drugs reduces the adverse effects of ‘overdosing’ any one drug category, the ‘ICU triad’ (Fig. 17.8.1) emphasizes the benefit of targeted treatment. Drug choices for sedation, analgesia,
and delirium control Drugs in common use are listed in Table 17.8.1. The most common choice in each drug category varies markedly around the world, and is determined more by familiarity and trad- itional local practice than by evidence from comparative effective- ness trials. Analgesics The principal reason for treating pain is to relieve the patient’s dis- tress. Pain also intensifies the hormonal and cytokine stress response, worsens delirium, and may interfere with essential patient care. 17.8 Sedation and analgesia in the ICU Michael C. Reade

17.8 Sedation and analgesia in the ICU 3899 Pain Endotracheal tube Tissue injury (e.g. surgery, trauma, pressure areas) Vascular access Affective component (e.g. ‘this pain means I’m more likely to die’) Elements of routine ICU care (e.g. turning, physical therapy) Advanced age Severity of illness Medical co-morbidity Pre-existing mental impairment Neurologic diagnosis (e.g., head injury) Observable and occult metabolic abnormalities Withdrawal from chronic psychoactive medications (e.g. benzo- diazepines, opioids) Sleep deprivation Substance abuse or withdrawal Noise Sedatives Delirium Agitation; unpleasant awareness Anxiety (appropriate or pathologic) Frustration Lack of homeostasis (e.g. thirst, hunger, dyspnoea) Ventilator dyssynchrony Inability to communicate Physical restraint Fig. 17.8.1 The ‘ICU triad’ highlighting interactions of the causes of pain, agitation/unpleasant awareness, and delirium in the management of critical illness. From New England Journal of Medicine. Reade M.C. and Finfer S., Sedation and Delirium in the Intensive Care Unit, 370, 444–454. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.
Table 17.8.1 Sedatives, analgesics, and antidelirium drugs in common use in the ICU Drug Mechanism Typical adult dose Pharmacokinetics Adverse effects 1. Sedatives Midazolam GABAA agonist Bolus 1–5 mg; infusion
1–5 mg/hr Half-life 3–11 hours. Active metabolite accumulates with prolonged infusion. Metabolized by hepatic oxidation, with renal excretion of active metabolite Possibly a higher risk of delirium and tolerance than nonbenzodiazepine sedatives Hypotension (less than propofol) Respiratory depression Lorazepam GABAA agonist Bolus 1–4 mg; infusion
1–5 mg/hr Slower onset (5–20 mins, compared to 2–5 mins with midazolam and diazepam). Half-life 8–15 hours Metabolized by hepatic glucuronidation, with no active metabolites. Offset is more predictable than midazolam in critical illness Possibly a higher risk of delirium and tolerance than nonbenzodiazepine sedatives Hypotension (less than propofol) Respiratory depression Propofol GABAA agonist, with other effects including on glutamate and cannabinoid receptors 50–200 mg/hr (or 1–3 mg/kg/hr) Half-life 30–60 minutes after infusion; longer after prolonged infusion due to

redistribution from fat stores. Metabolized by hepatic glucuronidation and hydroxylation Vasodilatation/negative inotropy causing hypotension/bradycardia. Propofol infusion syndrome (lactic acidosis, arrhythmia, and cardiac arrest), mostly associated with prolonged infusion rates

> 4–5 mg/kg/hr Respiratory depression Hypertriglyceridemia (due to carrier solution) Pancreatitis (continued)

Section 17 Critical care medicine 3900 Drug Mechanism Typical adult dose Pharmacokinetics Adverse effects Dexmedetomidine α-2 agonist 0.2–1.5 mcg/kg/hr Half-life 2 hours. Does not accumulate with prolonged infusion. Metabolized by hepatic glucuronidation and oxidation, with no active metabolites Transient hypertension, then hypotension Bradycardia (may be profound) Dry mouth Nausea Remifentanil Mu agoinst (also with kappa agonist effects). NB: Typically considered an 'analagosedative' as at typical doses has a sedating as well as analgesic effect 0.05–2 mcg/kg/hr Loading doses of
0.4–0.8 mcg/kg may be considered Half-life 3–4 minutes. Does not accumulate with prolonged infusion. Metabolized by plasma esterases and so unaffected by organ function Nausea Constipation Respiratory depression Bradycardia 2. Analgesics Fentanyl Mu agoinst (also with kappa agonist effects) 20–100 mcg/hr Loading dose of 50–100 mcg may be considered Half-life 1.5–6 hours. Highly fat-soluble, so rapid onset but accumulates with prolonged infusion. Metabolized by hepatic oxidation. No active metabolite Nausea Constipation Respiratory depression Skeletal muscle rigidity with large bolus doses Morphine Mu agoinst (also with kappa and
δ-agonist effects) 1–5 mg/hr
Loading dose of 2–5 mg may be considered Half-life 3–7 hours. More water soluble, so slower onset than fentanyl with less accumulation. Metabolized by hepatic glucuronidation to M-6-glucuronide (10%) (20× as active as parent drug) and M-3- glucuronide (90%) (inactive as an analgesic, but causes neuroexcitation, at least in animal models), glucuronides excreted via kidney Nausea Constipation Respiratory depression Histamine release and consequent vasodilation and hypotension (with large doses) and pruritus Hydromorphone Mu agoinst (also with kappa and δ-agonist effects) 0.04–0.4 mg/hr Loading dose of 0.4–1.5 mg may be considered Half-life 1.5–3.5 hours. 7–11 times more potent than morphine. Metabolized by hepatic glucuronidation to H-3-glucuronide, with similar effects to M-3-glucuronide Nausea Constipation Respiratory depression Ketamine NMDA antagonist, with weak mu and kappa agonist action and inhibition of reuptake of serotonin, dopamine, and noradrenaline 5–15 mg/hr Half-life 2.5 hours. Hepatic metabolism to a variety of compounds, one of which (norketamine) which is 1/6 as active as ketamine Hallucinations Delirium Hyper- or hypotension (but little effect at analgesic doses) Paracetamol Mechanism of action is not fully understood, but in part acts by inhibition of cyclooxygenase-2 1 g q6hr IV or PO Half-life 2.7 hours. Hepatic metabolism to inactive metabolites. Notably, one metabolite (N-acetyl-p-benzoquinone imine; NAPQI) irreversibly conjugates with glutathione, which in overdose can cause potentially fatal hepatic damage by oxidative stress Gastrointestinal (GI) upset Increased liver function tests (LFTs), with hepatotoxicity at high doses or prolonged regular use (especially in malnourished patients). Pyroglutamic acidosis (thought to be rare) Nonsteroidal
anti-inflammatory drugs Cyclooxygenase- 2 inhibition (thereby reducing prostaglandins and

thromboxanes and producing anti-inflammatory, analgesic and antipyrectic effect) +/- cyclooxygenase- 1 inhibition (producing gastrointenstinal ulceration) Varies by drug (e.g. ibuprofen, 400 mg PO q6hr) Varies by drug (e.g. ibuprofen 2 hours. Hepatic metabolism to inactive metabolites) GI ulceration Renal impairment Bronchospasm Bleeding though an antiplatelet effect Tinnitus Rebound headache Table 17.8.1 Continued

17.8 Sedation and analgesia in the ICU 3901 Adequate treatment of pain can avoid the need for any other drug therapy. A multimodal approach to analgesia is best, beginning with • reducing painful stimuli (e.g. reducing needless dressing changes); • continuous regional or neuraxial analgesia (now substantially fa- cilitated by ultrasound-guidance of catheter placement), specific treatment of neuropathic pain; and • nonopioid analgesic drugs. ■ Regular (rather than as-required) paracetamol should be given to every patient without contraindications requiring treatment of somatic pain. ■ Nonsteroidal anti-inflammatory drugs are often contraindi- cated in critical illness due to their renal, coagulation, and gastrointestinal effects, but are nonetheless useful in patients at otherwise low risk of these complications. ■ Ketamine is usually thought of as a cardiovascularly stable an- aesthetic induction agent and retains this utility in the ICU; however at the doses required for continuous sedation it usu- ally causes problematic hallucinations and so is not used for this indication. However, low-dose ketamine by continuous infu- sion is a very effective opioid-sparing analgesic that is thought to work mainly by modulating transmission of pain at the level of the dorsal horn of the spinal cord. At low doses, problem- atic hallucinations are uncommon, and if present can usually be treated with low-dose benzodiazepines. Notwithstanding, opioids are the main analgesics used in the ICU. Virtually no mechanically ventilated ICU patients should receive sedative drugs without also receiving opioid analgesia. In one ran- domized trial, properly addressing analgesia with opioids was found to remove entirely the requirement for sedation in 82% of patients. Attempting such a ‘no sedation’ strategy, compared to conventional sedation, was also associated with a shorter ICU stay and a near- significant trend to reduced ICU mortality with no increase in adverse events such as self-extubation. There is little evidence to guide choice of opioid, but pharmacokinetic and pharmacodynamic rationale suggest that any differences would be clinically insignificant. Sedatives Several observational studies have found associations between benzodiazepine-based sedation, delirium, and longer ICU admis- sion, but these associations are confounded by indication with benzodiazepines typically being chosen for less haemodynamically stable patients, who are expected to need more prolonged ventila- tion. Several large comparative trials have found dexmedetomidine to be superior to benzodiazepines in terms of delirium and length of mechanical ventilation, while these differences were not evident in a comparison of dexmedetomidine to propofol. Despite more than 90 other comparative trials, no sedative is clearly superior for all patients. Antidelirium agents Delirium should be sought actively in all ICU patients. The evidence underpinning specific drug treatment of delirium is less robust than that for the other arms of the ‘ICU triad’, but optimized drug selec- tion and dosing have nonetheless been associated with better out- comes. The term ‘antidelirium agent’ is preferable to ‘antipsychotic’ when using the drugs in Table 17.8.1 to treat ICU-acquired delirium, which has similarities to but is distinct from psychosis. Nonetheless, all these drugs were originally described as antipsychotics for use in the chronic treatment of mental illness. Options for delirium con- trol vary markedly in their pharmacokinetic and dynamic proper- ties. Quetiapine is the most sedating option, and was found superior to placebo in a randomized trial. Dexmedetomidine has also been found to be superior to placebo in the management of patients who cannot be extubated due to agitated delirium. Small antidelirium drug/drug comparative trials are essentially inconclusive.

A major Drug Mechanism Typical adult dose Pharmacokinetics Adverse effects 3. Antidelirium agents Haloperidol Predominant dopamine-2 receptor antagonist 0.5–2.5 mg IV bolus repeated as required; typical maximum 50 mg/day Half-life 12–38 hours. Metabolized by hepatic oxidative N-dealkylation to inactive metabolites Somnolence Neuroleptic malignant syndrome Extrapyramidal effects (more common with PO administration) QT prolongation/torsades de pointes Quetiapine Predominant histamine-1 receptor antagonist, with very little antidopaminergic effect 25–100 mg PO bd Half-life 7 hours. Metabolized by hepatic cytochrome p450 to inactive metabolites Somnolence Dizziness Dry mouth Extrapyramidal effects QT prolongation in very high doses/ overdose Risperidone Predominant 5HT2A receptor antagonist 1–3 mg PO bd (also available as an orally disintegrating tablet) Half-life 3–17 hours, determined in part by genetic variation Metabolized by hepatic cytochrome p450 partly to active metabolites Insomnia Agitation Extrapyramidal effects Neuroleptic malignant syndrome Olanzapine Predominant muscarinic receptor antagonist with moderate anti- 5HT2A action 5–10 mg PO daily (also available as an orally disintegrating tablet) Half-life 33 hours Metabolized by hepatic conjugation and oxidation to largely inactive metabolites Somnolence Anticholinergic effects (dry mouth, urinary retention, constipation, fever) Extrapyramidal effects Table 17.8.1 Continued

Section 17 Critical care medicine 3902 flaw of many such trials is the grouping together of patients with both hyper and hypoactive delirium, a factor that logically would be expected to influence response to drugs with different sedating properties. Dosing targets and strategies The goal of minimizing sedation and optimizing analgesia and delirium control has been pursued using several dosing strat- egies (Fig. 17.8.2). Compared to conventional physician-directed dosing, a strategy of daily interruption of all sedatives (+/- spon- taneous breathing trials) resulted in shorter ventilation and ICU stay, and in one trial, increased survival. However, daily sedative interruption was found not superior to a protocol that minim- ized sedation by giving bedside nurses substantial autonomy in ti- trating sedatives to agreed goals. The best choice for each ICU will rest on factors such as nurse:patient ratios, physician availability, and the autonomy with which nurses are permitted to act. In many ICUs, communicating and monitoring sedation goals is facilitated by the use of sedation monitoring scales, such as those listed in Table 17.8.2. Identifying ICU-associated delirium is complex, as by definition the condition fluctuates and has protean manifestations. Most deli- rious ICU patients are not agitated, and this ‘hypoactive’ delirium can produce a misleading appearance of calm that masks substan- tial psychological distress. The two diagnostic tools in commonest use are the Confusion Assessment Method for the ICU (CAM- ICU), which involves an active assessment of the patient at a single time point, and the Intensive Care Delirium Screening Checklist (ICDSC), which asks the clinician to observe several features of delirium over a period of time (Table 17.8.3). As defined and con- ventionally used, both scales dichotomize delirium as ‘present’ or ‘absent’, and neither distinguish hypo- from hyper- active delirium. Status epilepticus intracranial hypertension severe respiratory failure with or without neuromuscular blockade Assess pain and treat with opioid or other drug or technique Assess pain and treat with opioid or other drug or technique Specific indication for sedation Pain controlled Pain controlled Assess for delirium Mainly hypoactive delirium No delirium Mainly hyperactive delirium Yes Treat with antidelirium medication (or nonpharmacologic measures) Treat with nonpharmacologic measures (e.g. physical therapy, earplugs or quiet room, cognitive stimulation, repeated reorientation) Delirium controlled Yes Assess need for sedative medication to achieve target RASS score of –2 to 0 (lightly sedated but responsive at least to voice) Reassess analgesic, antidelirium, and sedative requirement regularly (e.g. every 4 hr or with observed change) Do not use sedative medication Target sedation

to RASS score of –2 to 0 Yes No No Yes No No Yes Target sedation to indication: Seizure control Acceptable intracranial pressure Tolerance of hypercarbia or necessary ventilator settings No awareness when being treated with neuromuscular blocking agent Regularly assess the need for this level of sedation The target sedation level is likely to be best communicated using the RASS scale Fig. 17.8.2 A suggested algorithm that implements the analgesia-first, delirium-control, sedation-minimization approach supported by modern ICU clinical trials. From New England Journal of Medicine. Reade M.C. and Finfer S., Sedation and Delirium in the Intensive Care Unit, 370, 444–454. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.

17.8 Sedation and analgesia in the ICU 3903 Another major concern with delirium detection is the interaction of sedative medications with assessment. Deeply sedated patients cannot be assessed, but light or recently discontinued sedation can produce a positive test result that does not portend the adverse con- sequences associated with persistent delirium. Having identified delirium, a logical dosing strategy (supported by some trial evidence) is quickly to gain control of delirium using an as- required prescription (most commonly of the only commonly-used drug available in parenteral form, haloperidol) along with institu- tion of a regularly scheduled low-dose (but titratable) enteral longer- acting drug: in theory quetiapine or olanzapine for agitated delirium and respiridone for hypoactive delirium. Recently, a large trial tested the hypothesis that prophylactic low dose haloperidol would reduce mortality in ICU patients considered at high risk of delirium. The trial also examined the effect of haloperidol on 15 secondary outcomes including incidence of delirium, and duration of ICU treatment and Table 17.8.2 ICU sedation scales Riker Sedation Agitation Scale (‘Riker’ or ‘SAS’) 7 Dangerous agitation Pulling at endotracheal tube (ETT) tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side 6 Very agitated Requiring restraint and frequent verbal reminding of limits, biting ETT 5 Agitated Anxious or physically agitated, calms to verbal instructions 4 Calm and cooperative Calm, easily rousable, follows commands 3 Sedated Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again 2 Very sedated Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously 1 Unarousable Minimal or no response to noxious stimuli, does not communicate or follow commands Richmond Agitation-Sedation Scale (RASS) +4 Combative Overtly combative, violent, immediate danger to staff +3 Very agitated Pulls or removes tube(s) or catheter(s); aggressive +2 Agitated Frequent nonpurposeful movement, fights ventilator +1 Restless Anxious but movements not aggressive vigorous 0 Alert and calm Alert and calm –1 Drowsy Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds) –2 Light sedation Briefly awakens with eye contact to voice (<10 seconds) –3 Moderate sedation Movement or eye-opening to voice (but no eye contact) –4 Deep sedation No response to voice, but movement or eye-opening to physical stimulation –5 Unrousable No response to voice or physical stimulation Table 17.8.3 ICU delirium identification tools Confusion assessment method for the ICU (CAM-ICU) Patient must be sufficiently awake (RASS score ≥–3) to be able to be assessed. The following criteria are assessed: Positive or negative

1. an acute change from mental status baseline OR fluctuating mental status during the past 24 hours (must be true to be CAM-ICU positive);
2. more than 2 errors in a 10-point test of attention to voice or pictures (must be true to be CAM-ICU positive);
3. If the RASS is not 0 and the previous two criteria are positive, the patient is delirious.

4. If the RASS = 0 and the previous two criteria are positive, test for disorganized thinking using 4 yes/no questions and a 2-step command. >1 error means the patient is delirious; ≤1 error excludes delirium. Intensive Care Delirium screening Checklist (ICDSC) Patient must show at least a ‘response to mild or moderate stimulation’. Then score one point for each of the following features observed, as assessed in the manner thought appropriate by the clinician: A score of ≥ 4 is positive for delirium (scores of 1–3 are ‘subsyndromal delirium’)
5. Anything other than ‘normal wakefulness’
6. Inattention
7. Disorientation
8. Hallucination
9. Psychomotor agitation
10. Inappropriate speech or mood
11. Sleep/wake cycle disturbance
12. Symptom fluctuation

Section 17 Critical care medicine 3904 mechanical ventilation. The trial reported no detectable beneficial ef- fect from the prophylactic administration of haloperidol. While the diagnosis of delirium is associated with worse outcomes for ICU pa- tients, a causal relationship has not been established and the assump- tion that treating delirium, particularly hypoactive delirium, leads to improved outcome is not yet proven. Monitoring of brain electrical activity Various simplified forms of electroencephalogram (EEG) moni- toring have become established methods for monitoring depth of anaesthesia, which is particularly useful for patients requiring neuromuscular blockade as paralysis can mask signs of awareness. However, such devices have not been adopted in most ICUs as depth-of-sedation monitors, for several reasons. First, prevention of awareness is not the goal in most ICU patients and at lighter levels of sedation the processed EEG signal correlates poorly with observed clinical signs. Second, muscle relaxants are rarely indicated in the ICU, and the muscle activity of nonparalysed and lightly sedated pa- tients interferes with the EEG signal. Third, of the small trials that have been performed, most have found no suggestion of patient benefit when sedatives are titrated to an EEG signal rather than con- ventional clinical endpoints. Nonpharmacological techniques and ‘complex interventions’ addressing pain, agitation, and delirium Optimizing patient comfort (by positioning, frequent turning, and min- imizing painful procedures), minimizing sleep disruption, facilitating environmental stimulation (for example, with windows, lighting, spec- tacles, and hearing aids) but not overstimulation (e.g. by reducing am- bient noise or using earplugs or headphones), repeated reorientation, maximizing the presence of familiar trusted people, addressing meta- bolic derangements, and of course addressing the underlying critical illness are all low-risk, low-cost components of good holistic care that at least some evidence suggests reduce the need for pharmacological control of pain, agitation, and delirium. The most robust evidence sup- ports a strategy of early mobilization, even for patients still dependent on mechanical ventilation. In comparison to standard care, this has re- sulted in less delirium and less time mechanically ventilated, with more patients functionally independent at the time of hospital discharge, none of which came at the cost of more adverse events. Combining nonpharmacologic techniques with both tailored drug selection that recognizes the importance of very early interven- tions adjusted as required by illness progression (rather than policy- based drug A vs. drug B trials) and a dosing strategy that facilitates maximum drug titratibility in the physician/nursing/organizational context is a ‘complex intervention’ that is only recently starting to

be tested in clinical trials. Special circumstances Substance abuse or dependence on medically indicated psycho- active medications is common in patients admitted to an ICU. Even patients who were previously drug-naive can manifest with- drawal syndromes after discontinuation of ICU sedatives and other medications. The commonest withdrawal syndromes are from alcohol, nicotine, GABA-agonists, and opioids. Classic fea- tures of withdrawal from sedating drugs include agitation, sym- pathetic activation, and delirium. Somnolence might be expected during withdrawal from nicotine but is often overshadowed by irritability and anxiety. • Benzodiazepines are the time-honoured treatment for both al- cohol and GABA-agonist withdrawal, but the association of benzodiazepines used as an ICU sedative with delirium suggests that other agents might be superior. Very little trial evidence sup- ports the theoretical advantages of alternatives. • Clonidine (an α-2 receptor agonist) is the popular choice for opioid withdrawal, combining reduction of sympathetic activity with a sedative action similar to that of dexmedetomidine. • Nicotine withdrawal is typically treated with transcutaneous nico- tine replacement. However, the evidence underpinning each of these strategies is largely anecdotal, with few comparative trials. One pivotal trial found that early severe acute respiratory distress syndrome is a special circumstance that should be the exception to the modern approach of light or no ICU sedation. Patients random- ized to receive muscle relaxation for the first 48 hours of their ICU stay had a significantly lower 28-day mortality than those treated according to usual care. Most clinicians feel that muscle relax- ation without sufficient sedation to prevent awareness is needlessly distressing to the patient. Prognosis/outcome There is substantial evidence from observational studies and clin- ical trials that selection of drugs to provide sedation, analgesia, and delirium control, along with optimizing their mode of delivery and concurrent use of nonpharmacological interventions, affects both hospital efficiency (e.g. duration of mechanical ventilation and ICU length of stay) and patient-centred outcomes (e.g. time spent in pain or with dysphoric delirium, long-term cognitive, and functional outcomes and mortality). Early concerns that a light- or no- sedation strategy in mechanically ventilated patients might produce more adverse events (such as self-extubation or removal of vascular access catheters) or more long-term psychological morbidity (such as post-traumatic stress disorder) have proved unfounded. Guidelines Several research groups and professional societies have published evidence-based guidelines for the management of cognitive func- tion in the ICU. Principal among these are the ‘Clinical practice guidelines for the management of pain, agitation and delirium in adult patients in the intensive care unit’, published by the American College of Critical Care Medicine in 2013. This document, with 472 references (the result of reviewing over 19 000 references) contains 54 statements and recommendations.

17.8 Sedation and analgesia in the ICU 3905 Likely future developments The key to optimal sedation, analgesia, and antidelirium practice is almost certainly the type of ‘complex intervention’ described here, but several (easier to test) hypotheses and questions are likely to be answered over the coming years: • Understanding the importance of very early (i.e. immediately after intubation to 24–48hrs) sedation/analgesia strategy in influencing later outcomes; • Evaluating established sedative drugs in use in anaesthesia in well- designed pragmatic comparative effectiveness trials (including remifentanil, inhaled halogenated anaesthetic vapours and xenon); • Evaluating patient-controlled sedation and other novel approaches to mode of administration of sedative/analgesic/antidelirium agents, such as better communication and modification of goals and the optimal degree of autonomy that should be held by the bedside nurse; • Describing a delirium detection tool that accounts for the fluctuating nature of the condition, its hypo and hyperactive manifestations, and the influence of sedating medications; then validating the utility of

this tool in guiding treatment that im- proves outcomes; and • Better comparison of the clinical effects of the various antidelirium drug options, taking into account their different sedative properties and thus likely different effects on hyper and hypoactive delirium. Benefits associated with these points are likely to be incremental rather than revolutionary, but widespread application of the well- founded recommendations listed in this chapter offers a significant prospect of patient and hospital efficiency benefit compared to what appears to be current practice in many ICUs.

FURTHER READING

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chronic critical illness 3906 Eva Boonen and Greet

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ESSENTIALS Critical illness, an extreme form of severe physical stress, is charac- terized by important endocrine and metabolic changes. The devel- opment of critical care medicine has made possible survival from conditions that were previously rapidly fatal, and as a result many patients now enter a prolonged phase of chronic or persistent crit- ical illness. Acute endocrine adaptations are directed towards providing en- ergy and substrates for the vital fight or flight response in the context of exogenous substrate deprivation. Distinct endocrine and meta- bolic alterations characterize the chronic phase of critical illness, which seems to no longer be solely beneficial and may hamper re- covery and rehabilitation. The hypothalamus-anterior pituitary axes respond to critical illness in a bi-phasic manner, or a tri-phasic manner if recovery is included as the third ‘phase’. Onset of the stressful event causes an acute activation of pulsatile hormonal release from the anterior pitu- itary, followed by suppression in the chronic phase of illness, ultim- ately resolving to normality if recovery occurs. Thyroid function—plasma concentrations of triiodothyronine (T3) are acutely lowered and plasma concentrations of reverse T3 (rT3) increase. When patients remain critically ill for several weeks, the low plasma T3 concentration coincide with low T4 concentration and low or low-normal thyroid-stimulating hormone concentra- tion. The acute ‘low T3 syndrome’ is likely an adaptive response to fasting, but the low T4 and T3 levels during the prolonged phase of critical illness are likely to be at least partially maladaptive. Whether interventions to normalize T4 and T3 levels produce clinical benefit remains unproven. Adrenal function—during critical illness, increased cortisol (achieved by reduction in the breakdown of cortisol and decrease in plasma cortisol binding globulin levels) is considered to prioritize energy pro- vision to vital organs via its catabolic effects on metabolism and by switching off anabolism. ‘Relative adrenal failure’ is frequently treated with hydrocortisone (200–300 mg per day), but whether such high doses are needed has not been well investigated. Blood glucose control—the endocrine response to severe illness is assumed to guarantee availability of glucose for those organs and tissues that rely on this as metabolic substrate. Hyperglycaemia in critically ill patients

has a J-shape association with risk of death, with the lowest risk in patients who remain normoglycaemic. Following recent clinical trials targeting normoglycaemia is not currently recommended for general daily clinical practice, but not tolerating pronounced hyperglycaemia has become the standard of care. Introduction The term ‘critical illness’ refers to any life-threatening condition re- quiring support of vital organ functions to prevent imminent death. Critical illness can be evoked by a variety of insults including mul- tiple trauma, complicated surgery, sepsis, and other severe medical illnesses. Critical illness is thus an example of pronounced physical stress, and all the immediate biological responses evoked by other stressful events are assumed to be of a greater magnitude in critic- ally ill patients. These immediate stress responses comprise orchestrated endocrine and metabolic adaptations that are presumed to be directed towards providing enough energy for the ‘fight or flight’ response in a context of temporary food deprivation. Alterations within the different hypothalamic-pituitary axes generate a ‘cata- bolic’ effect, in order to provide metabolic substrates, and to pri- oritize energy consumption for those processes essential for acute survival. With modern intensive care, survival from previously rapidly fatal conditions is now possible. However, full recovery is often not rapid and, when the triggering event has resolved, patients enter a chronic phase of critical illness during which they can re- quire vital organ support for weeks. This chronic phase is charac- terized by distinct endocrine and metabolic alterations which may no longer be solely beneficial and could potentially hamper re- covery. Recovery means renewal of cells that have a fast turnover, such as most epithelial and blood cells. For cells with a long half- life, such as neurons and myofibers, recovery requires removal of intracellular damage. This chapter summarizes recent insights with a specific focus on the hypothalamus-pituitary-thyroid and hypothalamus-pituitary- adrenal axes, the role of fasting in the acute stress response, and the impact of the hyperglycaemic response on recovery from critical illness. 17.9 Metabolic and endocrine changes in acute and chronic critical illness Eva Boonen and Greet Van den Berghe

17.9 Metabolic and endocrine changes 3907 Hypothalamic-pituitary axes The hypothalamus-anterior pituitary axes respond to critical illness in a bi-phasic manner, or a tri-phasic manner if recovery is included as the third ‘phase’ (Fig. 17.9.1). Onset of the stressful event causes an acute activation of pulsatile hormonal release from the anterior pituitary, followed by suppression in the chronic phase of illness, ultimately resolving to normality if recovery occurs. Although the concept applies to all hypothalamus-pituitary axes, recent studies have focused on the hypothalamus-pituitary thyroid axis and the hypothalamus-pituitary adrenal axis. The hypothalamus-pituitary-thyroid axis Responses to acute and prolonged critical illness Acute illnesses have an immediate effect on circulating thyroid hor- mone levels (Fig. 17.9.2). Plasma concentrations of triiodothyronine (T3) are acutely lowered and plasma concentrations of reverse T3 (rT3) increase, due to an immediate inactivation of thyroid hormone in peripheral tissues such as the liver, mediated by a suppressed activity of the type-1 deiodinase (D1) and/or an activated type-3 deiodinase (D3) (Fig. 17.9.2). In contrast, plasma concentrations of thyroxine (T4) and thyroid-stimulating hormone (TSH) increase briefly after onset of acute surgical stress. Thereafter, plasma TSH and T4 con- centrations return to ‘normal’. This constellation of low plasma T3 concentrations and elevated rT3 is referred to by different names: the acute low-T3 syndrome, the euthyroid-sick syndrome, or the non- thyroidal illness syndrome. There are several candidate mediators of this acute decrease in plasma T3 concentrations including cytokines, hypoxia-triggered signalling, and lack of nutrition. Acute reduction in the plasma concentrations of thyroid hormone binding proteins and the inhibition of hormone binding, transport, and metabolism by ele- vated free fatty acid and

bilirubin concentrations also play a role. When patients remain critically ill for several weeks the alterations within the thyroid axis become different. In this phase of critical illness, low plasma T3 concentration coincide with low T4 concentration and low or low-normal TSH concentration (Fig. 17.9.2). Moreover, the pulsatility of TSH secretion is largely lost and reduced pulsatile TSH secretion correlates with low plasma thyroid hormone concentra- tions, a constellation that resembles central hypothyroidism (Fig. 17.9.2). In line with central hypothyroidism postmortem studies demonstrate suppressed expression of thyrotropin-releasing hor- mone (TRH) gene in the hypothalamic paraventricular nuclei. Suppressed expression of the TRH gene correlates positively with the low plasma concentrations of TSH and T3. Thus, in prolonged critical illness, the production and release of thyroid hormones from the thyroid gland appears reduced due to diminished hypothalamic stimulation of the pituitary thyrotropes. Recovery is preceded by hypothalamus-pituitary reactivation with an increase in TSH levels followed by an increase in thyroid hormone concentrations. The mechanisms underlying suppressed hypothalamic TRH ex- pression during prolonged critical illness are incompletely under- stood. There appears to be a ‘resetting’ of the set point for feedback inhibition, via a local increase in type-2 deiodinase (D2) activity in the hypothalamus, which could elevate local thyroid hormone levels. Local cytokine effects within the hypothalamus, but also effects of endogenous dopamine or cortisol may play a role. Additionally, during prolonged critical illness peripheral tissues respond to low T3 levels by mechanisms capable of increasing local hormone avail- ability and effects. The monocarboxylate transporters, responsible for thyroid hormone uptake, were are overexpressed in skeletal muscle, liver, and kidney during prolonged critical illness (Fig. 17.9.3). The upregulation of these transporters is reversible by thy- roid hormone treatment. D2-expression and activity is upregulated in skeletal muscle and upregulation of D2 in the lung is an adap- tive response to lung injury. At the level of the thyroid hormone re- ceptor (TR), an inverse correlation is observed between the ratio of active TR-1 over inactive TR-2, a surrogate marker of thyroid hor- mone sensitivity, and the T3/rT3 ratio in liver biopsies of prolonged critically ill patients. Together, the available evidence suggest that in prolonged critical illness, the production of thyroid hormones falls whereas peripheral tissues protect themselves by increasing thyroid Acute phase Chronic phase Recovery phase Normal level Serum concentration or secretion Cortisol Anterior pituitary hormones Target-organ hormones Fig.17.9.1 Schematic overview of the pituitary-dependent changes during the course of critical illness. In the acute phase of illness, the secretory activity of the anterior pituitary is essentially maintained or increased, whereas anabolic target organ hormones are suppressed. Catabolic cortisol levels are elevated presumably driven by a brief increase in adrenocorticotropic hormone (ACTH). In the chronic phase of critical illness, the secretory activity of the anterior pituitary appears uniformly suppressed coinciding with reduced circulating levels of target organ hormones. Cortisol is a notable exception, the circulating levels of which remain elevated because of suppressed breakdown. Figure reproduced from Van den Berghe G, de Zegher F, Bouillon R (1998). Clinical review 95: Acute and prolonged critical illness as different neuroendocrine paradigms. J Clin Endocrinol Metab, 83(6), 1827–34. Copyright © 1998, by permission of Oxford University Press.

 hormone transporters, local activation of thyroid hormone and gene expression of the active TR isoform. What are the consequences of low plasma T3 concentrations in protracted critical illness? Low T3 levels correlate inversely with markers of muscle breakdown and of bone loss in prolonged critic- ally illness. This correlation may reflect either an adaptive and pro- tective response against catabolism or a causal maladaptive reaction.

As the cause of the low thyroid hormone levels is suppressed ex- pression of TRH in the hypothalamus, the optimal way to address the question of causality is by assessing the effect of TRH treatment. A continuous infusion of TRH can increase plasma T4 and T3, but also increases rT3 concentration. However, when TRH is combined with a growth hormone (GH)-secretagogue, no rT3 increase occurs which was explained by a GH-mediated suppressive effect on the inactivating D3 enzyme. As this treatment also induces an anabolic response during prolonged critical illness, it can suggest a causal relationship between low thyroid hormone levels and impaired an- abolism in chronic critical illness. Treatment with releasing factors has the advantage that negative feedback inhibition by thyroid hor- mones on thyrotropes is maintained, and thus overstimulation of the thyroid axis is prevented. Diagnostic implications The changes that occur within the thyroid axis during critical illness complicate the diagnosis of pre-existing thyroid disease. Indeed, patients with pre-existing primary hypothyroidism would nor- mally have high plasma TSH concentrations, but when primary hypothyroidism and severe nonthyroidal critical illness coincide, even more so when iatrogenic factors such as treatment with dopa- mine are involved, TSH levels may be lower than anticipated, even completely suppressed. Hence a low TSH during critical illness does not exclude the presence of primary hypothyroidism. As the low T4 and T3 levels in patients with severe hypothyroidism and crit- ical illness can be indistinguishable from those values observed in prolonged nonthyroidal critical illness, this further complicates such a diagnosis. Repeated thyroid function tests after recovery are re- quired to confirm a suspected diagnosis of thyroid disease. Elevated plasma T4 and T3 concentrations are so unusual during critical illness that they should always raise concern about pre-existing hyperthyroidism. The undetectable TSH expected with primary hyperthyroidism loses all diagnostic value during critical illness. Therapeutic implications The currently available evidence suggests that the acute ‘low T3 syn- drome’ is likely an adaptive response to fasting. Hence, it is highly unlikely that treatment would be beneficial. In contrast, the low T4 and T3 levels during the prolonged phase of critical illness are likely to be at least partially maladaptive. Indeed, in prolonged crit- ical illness in patients who are receiving nutrition, the low T3 syn- drome can be reversed by infusion of hypothalamic releasing factors leading to an anabolic response. However, no studies have yet inves- tigated the effect of such treatment on morbidity and mortality and the clinical implications of these experimental findings are currently unclear. Normalizing plasma concentrations of thyroid hormones by treatment with T4 and/or T3 has proven very difficult during crit- ical illness. While a high dose of T4 could normalize plasma T3 con- centrations it may result in supranormal T4 levels and even higher rT3. A high dose of T3 can normalize plasma T3 but suppresses TSH and T4 to subnormal levels via negative feedback inhibition. In com- bination, the risk of overtreatment is even higher. It remains equally controversial when and how to treat primary hypothyroidism during critical illness. It appears common sense to TRH Hypothalamus Pituitary Plasma levels & tissue metabolism Peripheral tissue level & effects TSH TSH secretion pulsatile pattern diurnal rhythm Healthy subjects Critical illness T4 T2 T3 rT3 Binding proteins & binding Peripheral TH uptake TR expression D1, D2 D1, D2 D3 D3 TRH Acute phase Chronic phase TRH Plasma TSH ↑/ = Pulsatility = No diurnal rhythm Normal TRH expression Binding proteins & binding ↓ Peripheral TH uptake ↓ TR expression ? T4↑/ = T2 T3↓ rT3↑↑ D1↓ D2 = D1↓ D2 = D3↑ D3↑ 0 7 21h 06h TSH (mU/l) TRH expression ↓ Plasma TSH ↓ Pulsatility ↓↓ No diurnal rhythm 21h 06h Binding proteins & binding = Peripheral TH uptake ↑ TR expression ↑ T4↓↓ T2 T3↓↓ rT3↑= D1↓ D2↑ D1↓ D2↑ D3↑ D3↑ Fig.17.9.2 Simplified changes in the central and peripheral components of the hypothalamic-pituitary- thyroid axis during acute and prolonged critical illness, as compared with healthy status.

17.9 Metabolic and endocrine changes 3909 continue the maintenance dose of thyroid hormone for patients who were receiving this treatment prior to critical illness. When a patient presents with myxedema coma, it is current practice to administer parenteral thyroid hormone. For this endocrine emergency, many clinicians prefer an IV loading dose of 300–500 μg of T4 to quickly reach 50% of the euthyroid value of T4, followed by 50–100 μg of IV T4 daily until oral intake is possible. Some experts have suggested the use of a coinfusion of T3 with T4. Whether and how symptom- atic patients with low T3 and T4 during prolonged critical illness, but without a proven history of hypothyroidism, should be treated remains unknown. The experimental protocol of the author's insti- tution advises administering one 100–150 μg bolus of T4 intraven- ously per 24 hours alone or, when required to also increase plasma T3, combined with T3 at 0.6 μg/kg ideal body weight per 24 hours by continuous intravenous infusion, adapting the dose based on clinical assessment, frequent monitoring, and targeting serum thy- roid hormone levels in the low-normal range. When patients start to recover, a prompt tapering of this dose is usually required. The need for treatment of primary hyperthyroidism may also be affected by concomitant critical illness. Indeed, theoretically, treatment re- quirements could be lower as thyroid hormone metabolism is high during critical illness. Furthermore, when patients are receiving ac- tive treatment for hyperthyroidism when becoming critically ill, po- tential toxicity of the medication and interaction with other drugs should be taken into account. The hypothalamus-pituitary-adrenal axis The response to acute and prolonged critical illness Cortisol is the stress hormone, considered to be a key player in the 'fight or flight' reaction to illness and trauma. It is generally accepted that all types of stressful events activate the hypothalamic-pituitary- adrenal (HPA) axis via the hypothalamic release of corticotropin- releasing hormone (CRH) and arginine vasopressin (AVP), which stimulate the anterior pituitary corticotrophs to secrete adrenocor- ticotropic hormone (ACTH) (Fig. 17.9.4). During critical illness, in- creased cortisol is considered to prioritize energy provision to vital organs via its catabolic effects on metabolism and by switching off anabolism. Also, cortisol optimizes the haemodynamic response to severe illnesses by intravascular fluid retention and by enhancing inotropic and vasopressor effects of catecholamines and angiotensin II. Furthermore the anti-inflammatory properties of cortisol prevent excessive inflammation in response to critical illness. Traditionally, it is assumed that a several-fold increased produc- tion rate of cortisol in the adrenal cortex, driven by high circulating ACTH, brings about the elevated plasma cortisol concentrations during critical illness. However, most studies could not document elevated plasma ACTH concentrations in critically ill patients, ex- cept very transiently. In a recent study, plasma ACTH concentra- tions were suppressed, in the face of high plasma cortisol, from the first day in the intensive care unit (ICU) and remained lower than normal throughout the first week of critical illness. Low plasma ACTH in the presence of high plasma cortisol concentrations has been interpreted as non-ACTH-driven cortisol production, in which direct adrenocortical effects of cytokines could play a role. However, no study had ever provided direct evidence for an increased cor- tisol production during critical illness. Recent work that used a state of the art cortisol tracer technique showed that daytime cortisol production during critical illness was only slightly higher or equal to that of healthy subjects (Fig. 17.9.5). Even more surprisingly, nocturnal cortisol secretion rates were found to be lower than in matched healthy subjects. In a recent study cortisol breakdown was found to be substantially reduced, attributable to suppressed expres- sion and activity of A-ring reductases in the liver and by suppressed activity 11β-hydroxysteroid dehydrogenase type 2 in kidney. The exact cause of the suppression of these enzymes remains unclear, but data point to a possible role of bile acids, which are elevated during critical illness and potent inhibitors of the cortisol metabolizing en- zymes (Figs. 17.9.4 and 17.9.5). The concept of

increased bioavailability of cortisol during the stress of severe illnesses via reducing its breakdown, can be inter- preted as a highly ‘cost-effective’ way to maintain increased cortisol Human patients Rabbit model Plasma hormone concentrations Tissue expression 2.0 ∗ TT3 (nmol/l) 1.5 1.0 0.5 0.0 160 ∗ 120 80 40 0 TT4 (nmol/l) Liver Muscle MCT8 mRNA 2.0 3.0 1.0 0.0 ∗ ∗ MCT10 mRNA 2.0 3.0 1.0 0.0 2.0 3.0 1.0 0.0 ∗ ∗ 2.0 3.0 1.0 0.0 ∗ 2.0 MCT8 mRNA 1.5 1.0 0.5 0.0 ∗ 12 10 8 6 4 2 0 ∗ ∗ Fig.17.9.3 The upper panel represents the circulating thyroid hormones in acutely stressed (light blue bars, n = 22) and chronically ill patients (dark blue bars, n = 64). The white horizontal bars indicate the normal ranges. The central panel shows the relative monocarboxylate (MCT8 and MCT10) mRNA expression levels measured in liver and skeletal muscle of acutely stressed (light blue) and chronically ill (dark blue) patients. The lower panels show the relative expression levels of MCT8 and MCT10 in liver and muscle of healthy control rabbits (white bar), saline treated prolonged ill rabbits (light blue), and T3+T4 treated (dark blue bar) ill rabbits. Data are expressed as mean ± s.e.m. *p <0.05 versus acute values. Figure reproduced from Boonen E, Van den Berghe G (2014). Endocrine Responses to Critical Illness: Novel Insights and Therapeutic Implications. J Clin Endocrinol Metab, 99(5), 1569–82. Copyright © 2014, by permission of Oxford University Press.

Section 17 Critical care medicine 3910 Fig. 17.9.4 Simplified cartoon of the changes in the hypothalamus-pituitary-adrenal axis during critical illness, as compared with during health. Figure adapted from Boonen E, Bornstein SR, Van den Berghe G (2015). New insights into the controversy of adrenal function during critical illness. Lancet Diabetes Endocrinol, 3(10), 805–15, copyright © 2015, with permission from Elsevier. Fig. 17.9.5 Panel (a) depicts cortisol production in critically ill patients with the systemic inflammatory response syndrome (SIRS) (N = 7; dark blue bar) and no systemic inflammatory response syndrome (N = 4; light blue bar) compared to controls (N = 9; white bar). Based on these results, 24 h cortisol production (mg/day) was estimated and depicted with the arrows. Panel (b) depicts cortisol plasma clearance as assessed with a small dose of deuterated cortisol tracer. Bar charts represent means and standard errors. Panel (c)-(e) show mRNA and protein expression of 5β-reductase in liver of 20 controls (white bar) and 44 patients (blue bar) and the relation to plasma total bile acid concentrations. Bar charts represent means and standard errors. The mRNA data are expressed, normalized to glyceraldehyde 3-phosphate dehydrogenase (GAPDH), as a fold difference from the mean of the controls. Protein data are expressed normalized for CK-18 protein expression, as a fold difference from the mean of the controls. Figure reproduced from Boonen E, Van den Berghe G (2014). Endocrine Responses to Critical Illness: Novel Insights and Therapeutic Implications. J Clin Endocrinol Metab, 99(5), 1569–82. Copyright © 2014, by permission of Oxford University Press.

17.9 Metabolic and endocrine changes 3911 levels and to prioritize the consequences thereof to those tissues and cells that produce the metabolizing enzymes. Other cost-effective mechanisms are low plasma cortisol binding globulin levels in crit- ical illness, causing increased levels of biologically active free cortisol, and possibly tissue-specific effects, regulated at the level of gluco-corticoid receptor (GR) expression. GR expression is suppressed in white blood cells of critically ill children, which may safeguard an effective innate immune response and protect the host against in- fections in the presence of hypercortisolism, the latter generating its effects primarily in those tissues with a normal or perhaps even increased GR expression. This novel concept of tissue-specific regu- lation of glucocorticoid activity during critical illness requires fur- ther investigation. The new insight that during critical illness cortisol metabolism is suppressed could explain low

plasma adrenocorticotropic hormone concentrations via negative feedback inhibition at the level of the pituitary gland and/or the hypothalamus, but studies assessing this at the tissue level are currently lacking. Post-mortem studies in pa- tients after prolonged critical illness demonstrate clear signs of im- paired adrenocorticotropic hormone signalling in the adrenal gland. It is thus possible that sustained suppression of ACTH secretion causes adrenal atrophy in the prolonged phase of critical illness. This would explain the reported 20-fold higher incidence of symptomatic adrenal insufficiency in critically ill patients being treated in the in- tensive care unit for more than 14 days. Diagnostic implications Fifteen years ago, the term ‘relative adrenal insufficiency’ was launched in the context of critical illness. The term refers to the con- dition of a critically ill patient, in which, despite a maximally ACTH- activated adrenal cortex, cortisol production is still insufficient to generate enough glucocorticoid and mineralocorticoid receptor ac- tivation to safeguard hemodynamic stability. The large association studies pioneering this concept suggested that this condition is iden- tifiable by an insufficient increase (<9 μg/dl: 250 nmol/l) in plasma cortisol following a bolus injection of 250 μg ACTH, irrespective of the baseline plasma cortisol concentration, which is usually much higher than in healthy humans. In such a condition of insufficiently increased cortisol production, a very high plasma ACTH concen- tration would be expected. However, the recent robust finding that ACTH plasma concentrations are suppressed rather than increased, that cortisol production rate is not much elevated if at all, and that instead reduced cortisol breakdown plays a major role during crit- ical illness, further complicates the issue of diagnostic criteria for ad- renal failure in this setting. Moreover, in critically ill patients cortisol responses to a bolus of ACTH correlate positively with both cor- tisol production rate and with cortisol clearance. Patients who have the lowest cortisol response to ACTH, below the level that is seen in patients suffering from absolute adrenal failure, are those with the most suppressed cortisol breakdown while their plasma cortisol levels are identical to those with a higher response to adrenocor- ticotropic hormone. These findings suggest that a low cortisol re- sponse to an ACTH injection during critical illness mostly reflects the degree of negative feedback inhibition exerted by high levels of circulating cortisol, a finding that is quite similar to what is ob- served in patients treated with exogenous glucocorticoids for an extended time. Whether this low cortisol response to adrenocor- ticotropic hormone during critical illness also indicates that cortisol availability would be ‘insufficient’ to cope with the stress of illness, and thus requires treatment with corticosteroids, remains highly debated. Furthermore, circulating total cortisol concentrations do not necessarily reflect the amount of glucocorticoid effect. Evidence from both animal and human experiments suggests that there is tissue-specific regulation of glucocorticoid receptor expression during critical illness, thus conclusions about ‘adequacy’ of cortisol availability and function are not easily drawn from measurements of plasma cortisol concentration. Therapeutic implications It is standard practice for patients with an established diagnosis of primary or central adrenal failure, or patients treated with systemic glucocorticoids prior to critical illness, to be treated with supple- mental ‘stress doses’ of hydrocortisone, commonly 200–400 mg/ day. Also, patients suffering from an acute Addisonian crisis in the ICU are treated with high doses of corticosteroids. However, this therapeutic strategy is based on the assumption of a several-fold in- creased cortisol production during critical illness and whether such high doses are truly needed and whether lower doses may suffice with fewer side effects has not been well investigated. The dose of hydrocortisone currently recommended to treat ‘relative adrenal failure’ is controversial. The proposed dose of 200–300 mg of hydrocortisone per day, referred to as ‘low dose’ in the literature, in fact represents approximately 10-times more than that produce by a healthy human per day, and about three to six times more than the production which has now been quantified in critically ill patients (Fig.

17.9.5). In view of the substantially re- duced cortisol breakdown during critical illness, these doses may be too high and it is unclear for how long such a treatment should be given. During critical illness treatment with corticosteroids in a too high dose for too long time could contribute to lean tissue wasting, to my- opathy and prolonged need for intensive care. Based on the results of stable isotope studies, a dose of +/-60 mg of hydrocortisone, equiva- lent to about a doubling of the normal daily cortisol production, may be sufficient and merits further investigation. In all cases, tapering to the lowest effective dose as soon as the patient has been stabilized is advisable to limit side effects. The role of fasting in the acute stress response Critically ill patients cannot feed normally by mouth and establishing full feeding by the enteral route takes time and generally results in a substantial macronutrient deficit. Until recently, it was unclear what part of the acute endocrine/metabolic stress response is brought about by this obligatory fasting, and to what extent the coupling be- tween the responses to the stressful event and those to the lack of food may affect recovery. Fasting and the hypothalamus-pituitary-thyroid axis response to critical illness In healthy subjects, the low plasma T3 concentrations induced by fasting have been shown to mediate adaptive, beneficial effects counteracting the catabolic consequences of lack of macronutrients. Whether or not the acute decrease in circulating levels of thyroid hormone in response to critical illness is brought about by lack of

 macronutrients and also reflects an adaptive attempt to reduce en- ergy expenditure, in which case it should be left untreated, was not clear. A recent large randomized controlled trial (RCT) investigated the impact of adding early parenteral nutrition to supplement en- teral feeding to reach normal nutritional targets as compared with tolerating the pronounced macronutrient deficit that accompanies enteral feeding alone. This trial provided indirect evidence that the acute low T3 syndrome of acute critical illness is an adaptive re- sponse as the patients who received intravenous nutrition in the acute phase of their critical illness had worse rather than improved outcome. Furthermore, the increase in T3 and in the ratio of T3 over rT3 with early forceful feeding explained statistically the worsening of the clinical outcome. These data thus suggest that at least part of the acute decrease in T3 concentration during critical illness is evoked by the concomitant fasting and that this part of the low T3 syndrome is likely adaptive and beneficial. Possible benefits include the expected reduction in energy expenditure but also the direct ef- fect of increased D3 activity locally in granulocytes could optimize bacterial killing. Fasting and the hypothalamus-pituitary-adrenal axis response to critical illness Given the catabolic effects of increased cortisol availability, and the possible role of bile acids in mediating hypercortisolism during critical illness, an interaction between the HPA axis stress response and macronutrient availability is possible. Although eating and the infusion of glucose tend to increase plasma cortisol, more pro- longed caloric restriction activates the HPA axis. Hence, tolerating macronutrient deficit early during critical illness could evoke higher plasma ACTH and cortisol concentrations and early administra- tion of nutrition during critical illness may suppress this response and increase the need for steroid treatment. In the recent RCT dis- cussed here, intravenous administration of macronutrients did not affect the suppressed plasma concentration of ACTH or the elevated plasma cortisol concentration. The impact of hyperglycaemia on recovery from critical illness Association between high blood glucose and poor outcome of critical illness In humans, the endocrine response to severe illness is assumed to guarantee availability of glucose for those organs and tissues, such as the brain and the blood cells, which rely on glucose as metabolic sub- strate. In young and lean acutely ill patients, who do not suffer from comorbidities such as diabetes and are not receiving macronutri- ents or glucocorticoids, this stress response will

maintain normogly- caemia. However, when patients are older, overweight, suffer from chronic comorbidity, receive drugs that affect insulin sensitivity and receive enteral/parenteral nutrition, circulating glucose concentra- tion usually increases quickly above the upper limit of normality. In the condition of prolonged critical illness, hyperglycaemia may be quite severe and persistent. Hyperglycaemia in critically ill pa- tients has a J-shape association with risk of death, with the lowest risk in patient who remain normoglycaemic. In critically ill patients with established diabetes mellitus the J-shaped curve is significantly blunted in the hyperglycaemic zone and the nadir is shifted to higher blood glucose levels. This hyperglycaemia of critical illness could be adaptive or maladaptive. Hyperglycaemia and adverse outcome of critical illness: cause or consequence? Determining whether treating hyperglycaemia is beneficial or harmful during critical illness has been investigated in several RCTs. The first RCT on blood glucose management was performed in an adult surgical ICU in Belgium. In this study patient were randomly assigned a blood glucose target of strictly normal fasting blood glucose, (80–110 mg/dl, 4.4–6.1 mmol/litre) or contemporaneous usual care which was to tolerate hyperglycaemia up to 215 mg/dl (11.9 mmol/litre). The study was highly standardized, resulting in a strong internal validity. Targeting strict normoglycaemia reduced ICU and in-hospital mortality and reduced morbidity by preventing organ failure. In a second study using the same targets in the medical ICU of the same hospital, these morbidity benefits were confirmed, although mortality was not significantly affected. The same inves- tigators subsequently assigned critically ill children to a target of normal fasting glucose concentration for age, compared with toler- ating hyperglycaemia up to 215 mg/dl (11.9 mmol/litre), and found that targeting normoglycaemia reduced ICU morbidity and mor- tality and had long-term beneficial effects on neurocognitive devel- opment. Other investigators reported that targeting an adult range for fasting blood glucose in young infants in the ICU did not alter blood glucose concentration or patient outcomes. These results sug- gest that targeting the ‘normal’ fasting level for blood glucose may be key to prevent acute toxicity of hyperglycaemia during illness in each age group. The underlying mechanisms of hyperglycaemia- induced toxicity may involve cellular damage in those cells that do not require insulin for glucose uptake, such as hepatocytes, renal tubular cells, the endothelium, immune cells, and neurons. Soon after the first Belgian study was published, the interven- tion was swiftly implemented in clinical practice worldwide. After several smaller studies, a large multicentre international study compared tight blood glucose control to a normoglycaemic target (4.5–6.0 mmol/litre) with an intermediate target of less than 10.0 mmol/litre. This study reported that targeting normoglycaemia increased mortality. As this pragmatic trial had high external val- idity, targeting normoglycaemia is not currently recommended for general daily clinical practice. However, not tolerating pronounced hyperglycaemia has become the standard of care. Additionally, it now seems clear that targeting a narrow range for blood glucose requires accurate tools to measure blood glucose and that training and experience is crucial to avoid (undetected) episodes of hypogly- caemia. Profound, prolonged/undetected hypoglycaemia can have serious consequences and may result in death. How to deal with hyperglycaemia in clinical practice? With the available technologies, tight blood glucose control cannot be recommended for every ICU. Post-hoc analyses of the Belgian studies revealed that most of the benefit for mortality, to be achieved by blood glucose control, comes from avoiding excessive hyperglycaemia (Fig. 17.9.6). Thus, avoiding excessive hyperglycaemia and targeting blood glucose to +/-150 mg/dl (c.8 mmol/litre) is a reasonable com- promise. In a highly standardized environment, more can be gained by further tightening the glycaemic control, but it requires a substantial investment in training and technology to do this safely. Additionally,

17.9 Metabolic and endocrine changes 3913 avoiding early parenteral nutrition improves outcomes and reduces the requirement of insulin to prevent hyperglycaemia. Hence, to what extent forceful feeding contributes to the toxicity of hyperglycaemia during critical illness also requires further investigation. FURTHER READING Annane D, et al. (2002). Effect of treatment with low doses of hydro- cortisone and fludrocortisone on mortality in patients with septic shock. JAMA, 288, 862–71. Boonen E, et al. (2013). Reduced cortisol metabolism during critical illness. N Engl J Med, 368, 1477–88. Boonen E, et al. (2014). Impact of duration of critical illness on the adrenal glands of human intensive care patients. J Clin Endocrinol Metab, 99, 4214–22. Boonen E, et al. (2014). Reduced nocturnal ACTH-driven cortisol secretion during critical illness. Am J Physiol Endocrinol Metab, 306, E883–92. Boonen E, Bornstein SR, Van den Berghe G (2015). New insights into the controversy of adrenal function during critical illness. Lancet Diabetes Endocrinol, 3, 805–15. Casaer MP, et al. (2011). Early versus late parenteral nutrition in critic- ally ill adults. N Engl J Med, 365, 506–17. Casaer MP, Van den Berghe G (2014). Nutrition in the acute phase of critical illness. N Engl J Med, 370, 1227–36. Finfer S, et al. (2009). Intensive versus conventional glucose control in critically ill patients. N Engl J Med, 360, 1283–97. Finfer S, et al. (2012). Hypoglycemia and risk of death in critically ill patients. N Engl J Med, 367, 1108–18. Fliers E, et al. (2015). Thyroid function in critically ill patients. Lancet Diabetes Endocrinol, 3, 816–25. Gielen M, et al. (2012). Effect of tight glucose control with insulin on the thyroid axis of critically ill children and its relation with out- come. J Clin Endocrinol Metab, 97, 3569–76. Kosiborod M, et al. (2009). Relationship between spontaneous and iat- rogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. JAMA, 301, 1556–64. Langouche L, et al. (2013). Impact of early nutrient restriction during critical illness on the nonthyroidal illness syndrome and its rela- tion with outcome: a randomized, controlled clinical study. J Clin Endocrinol Metab, 98, 1006–13. Meersseman P, et al. (2015). Effect of early parenteral nutrition on the HPA axis and on treatment with corticosteroids in intensive care pa- tients. J Clin Endocrinol Metab, 100, 2613–20. Mesotten D, et al. (2012). Neurocognitive development of children 4 years after critical illness and treatment with tight glucose con- trol: a randomized controlled trial. JAMA, 308, 1641–50. Sprung CL, et al. (2008). Hydrocortisone therapy for patients with septic shock. N Engl J Med, 358, 111–24. Van den Berghe G (2014). Non-thyroidal illness in the ICU: a syn- drome with different faces. Thyroid, 24, 1456–65. Van den Berghe G, de Zegher F, Bouillon R (1998). Clinical review 95: acute and prolonged critical illness as different neuroendocrine paradigms. J Clin Endocrinol Metab, 83, 1827–34. Van den Berghe G, et al. (2001). Intensive insulin therapy in critically ill patients. N Engl J Med, 345, 1359–67. Van den Berghe G, et al. (2006). Intensive insulin therapy in the med- ical ICU. N Engl J Med, 354, 449–61. Vanhorebeek I, et al. (2006). Cortisol response to critical illness: effect of intensive insulin therapy. J Clin Endocrinol Metab, 91, 3803–13. Vlasselaers D, et al. (2009). Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet, 373, 547–56. Days Cumulative risk in-hospital mortality Expected outcomes for ranges of blood glucose based on Belgian trials .3 .2 .1 0 0 100 200 300 400 500 600 Blood glucose >150 mg/dl (>8.4 mmol/litre) Blood glucose 110–150 mg/dl (6.2–8.4 mmol/litre) Blood glucose <110 mg/dl (<6.2 mmol/litre) Fig. 17.9.6 The dose response for blood glucose ranges versus mortality is shown for the aggregated adult studies in Leuven. Reproduced from G. Van den Berghe (2012). Intensive insulin therapy in the ICU–reconciling the evidence. Nat Rev Endocrinol., 8, 374–378, with permission.