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The Royal College of Anaesthetists

Faculty of Pain Medicine

The Hong Kong College of Anaesthesiologists

College of Anaesthetists of Ireland

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Cover caption: Illustration of the structure of the Lobule of Liver. This illustration is from Asklepios Atlas of the Human Anatomy. Credit: ASKLEPIOS MEDICAL ATLAS/SCIENCE PHOTO LIBRARY.

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Cover caption: Portrait of Austrian physicist Christian Johann Doppler (1803–1853), discoverer of the Doppler effect. Doppler was educated in mathematics at the Vienna Polytechnic. He obtained a professorship in mathematics in Prague in 1841, then took the post of professor of experimental physics at Vienna in 1850. He is famous for the Doppler effect, proposed in 1842. This states that a stationary observer listening to a sound source will hear the sound at a higher pitch if the source is approaching, and a lower pitch when receding, than when the source is still. He later discovered this effect with light waves; Doppler shift measurements are used in modern cosmology. Credit: SCIENCE PHOTO LIBRARY.

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Cover caption: Sir Humphry Davy (1778–1829) experiencing, with members of the Clifton Pneumatic Institute, the euphoric effects of inhaling nitrous oxide to which Davy gave the name 'laughing gas'. He was head of the laboratory of the Institute which had been established to study the medical effects of recently discovered gases. Davy described the delirium induced as being characterised by extraordinary gaiety, significant enhancement of the intellectual faculties and an anaesthetic effect. His 1799 account of his experiments noted that nitrous oxide was 'capable of destroying physical pain and may possibly be used in surgical operations' but public suspicion of pneumatic chemistry and the opposition of the medical profession (pain being an important part of surgery) stopped the development of anaesthesia until 1844, and Davy moved on to his pioneering work in electrochemistry. Credit: SHEILA TERRY/SCIENCE PHOTO LIBRARY.

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Cover caption: Blood platelet, coloured scanning electron micrograph (SEM). Platelets (thrombocytes) are part of the blood. When a blood vessel is damaged, the platelets become activated and secrete chemicals that cause the formation of a fibrin mesh. This mesh traps platelets and red and white blood cells, forming a clot that seals the damaged blood vessel. Magnification: × 11,000 when printed at 10 centimetres across. Credit: SCIENCE PHOTO LIBRARY.

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Cover caption: Colour portrait of the German experimental physicist Wilhelm Konrad Roentgen, 1845-1923, discoverer of X-rays. While using a discharge tube (in which an electric discharge is passed through a gas at low pressure) in a darkened room, he noticed that a card coated with barium platinocyanide glowed when the tube was switched on. The effect was not blocked by an intervening wall, or even a thin sheet of metal. Roentgen termed this newly discovered phenomenon X-ray radiation, & suggested that it consisted of electromagnetic rays with a shorter wavelength than light. He was awarded the first Nobel Prize for physics, in 1901. Credit: SCIENCE PHOTO LIBRARY.

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Cover caption: Pneumococcal pneumonia. Coloured frontal X-ray of a section through the chest of a 60-year-old male patient with pneumococcal pneumonia affecting the upper lobe of the right lung (left). Pneumococcal pneumonia is a form of pneumonia caused by infection with Streptococcus pneumoniae (pneumococcus) bacteria. Credit: Pr Michel Brauner/SCIENCE PHOTO LIBRARY.

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Cover caption: Erythropoietin hormone complex. Computer model showing the secondary structure of a molecule of the human hormone Erythropoietin (EPO), complexed with an erythropoetin receptor molecule. Erythropoietin regulates blood oxygen levels in the body. When levels are low (hypoxia) it is released by the kidneys and travels to the bone marrow, where it stimulates red blood cell precursor cells to mature into red blood cells (erythrocytes). This allows the blood to carry more oxygen. Because of this role it is sometimes used illegally as a performance-enhancing drug by athletes. Credit: ALFRED PASIEKA/ SCIENCE PHOTO LIBRARY.

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Cover caption: Animal-human blood transfusion. 17th-century artwork showing blood transfusion from a dog (right) to a human. The first documented experiments involving transfusing animal blood into humans took place in the 1660s, including a transfusion performed in 1667 by French physician Jean-Baptiste Denys. Transfusing animal blood into humans was soon banned, as it often killed the patients. Artwork from 'Armamentarii Chirurgici' (Amsterdam, 1671) by Johannes Schultes (1595-1645). Credit: NATIONAL LIBRARY OF MEDICINE/SCIENCE PHOTO LIBRARY.

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Cover caption: Abraham Lincoln. Portrait of Abraham Lincoln (1809-1865), 16th president of the USA and a sufferer of Marfan's syndrome. Marfan's syndrome is a hereditary disorder characterized by excessive tallness, long slender fingers and heart defects. Lincoln's leaness, thin head and sunken breast were because of his condition. Lincoln is best known as the president who led his country through the Civil War (1861-1865) and who liberated the southern slaves. He was assassinated by the actor John Wilkes Booth whilst at the theatre.

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Cover caption: Red blood cells. Coloured scanning electron micrograph (SEM) of red blood cells or erythrocytes. These biconcave, disc-shaped cells transport oxygen from the lungs to all the cells of the body. They also remove carbon dioxide produced by cells in respiration and transport it back to the lungs, where it is exhaled. The red colour is due to haemoglobin, a protein compound that binds reversibly with oxygen. Red blood cells are the most abundant cell in vertebrate blood. Magnification: x4175 at 6x7cm size.

Credit: POWER AND SYRED/SCIENCE PHOTO LIBRARY.

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Cover caption: Heart pacemaker. Coloured X-ray of the chest of a patient, showing a fitted heart pacemaker. This electronic battery-run device is seen above the ribcage, with a yellow lead which connects it to the heart. The heart lies at lower right (yellow), taking up part of one lung field. A pacemaker supplies electrical impulses to the heart to maintain the heartbeat at a regular rate. It may be external (worn on a belt) or internal (implanted in the chest). They are fitted in patients suffering a heart block disrupting heart rhythm. Heart pacemakers may provide a fixed rate impulse or discharge only when a heartbeat is missed.

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Cover caption: Scanning electron micrograph of the head of a human femur (thigh bone), showing various degrees of damage to the surface caused by rheumatoid arthritis. The cartilage which covers the head of the bone is severely eaten away with only patches of normal, smooth surface remaining. The bone was removed at a hip joint replacement operation. Magnification: x70 at 8x10 inch size.

Credit: MOREDUN ANIMAL HEALTH LTD/SCIENCE PHOTO LIBRARY.

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Pain after thoracotomy

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Key points

- Poorly managed thoracotomy pain can result in postoperative pulmonary complications.
- The multifactorial pathophysiology of thoracotomy pain mandates a multimodal approach to analgesia.
- Paravertebral infusion provides similar analgesia to thoracic epidurals with less respiratory complications and hypotension.
- Chronic pain after thoracotomy can affect more than 50% of patients.

Thoracotomy is considered the most painful of surgical procedures and providing effective analgesia is the onus for all anaesthetists. Ineffective pain relief impedes deep breathing, coughing, and remobilization culminating in atelectasis and pneumonia. This article reviews the mechanisms of acute and chronic thoracotomy pain, the risk factors, current analgesic options, and the role genetics may increasingly play in the management of thoracotomy pain.

Pathophysiology of thoracotomy pain

Pain after thoracotomy arises from *nociceptive* and *neuropathic* mechanisms which may originate from somatic and visceral afferents. Pain can also be *referred*.

Nociceptive somatic afferents are conveyed by the intercostal nerves after skin incision, rib retraction, muscle splitting, injury to the parietal pleura, and chest drain insertion to the ipsilateral dorsal horn of the spinal cord (T4–T10). The afferents are then transmitted to the limbic system and somatosensory cortices via the contralateral anterolateral system of the spinal cord. *Nociceptive visceral* afferents are conveyed by the phrenic and vagus nerves after injury to the bronchi, visceral pleura, and pericardium.

In response to this tissue injury, inflammatory mediators, such as prostaglandins, histamine, bradykinin, and potassium, are released. These mediators directly activate nociceptors, enhance their activity, and reduce the pain threshold. This amplified response to pain is called primary sensitization and leads to intensified pain on breathing or coughing after operation.

Continued nociception during the perioperative period leads to hyperexcitability of the dorsal horn neurones and higher pain centres through activation of *N*-methyl-D-aspartate (NMDA) receptors in response to substance P, calcitonin gene-related peptide, and glutamate, which causes central sensitization. This, along with the development of neuropathic pain, can herald the onset of chronic pain which is defined as pain that persists or recurs along the site of the thoracotomy incision at least 2 months after the procedure.

Neuropathic pain, after intercostal nerve injury, develops via the mechanisms shown in Figure 1, and results in the paradox of reduced sensory input (from touch, temperature, and pressure) with hypersensitivity (dysaesthesia, allodynia, hyperalgesia, and hyperpathia).[1]

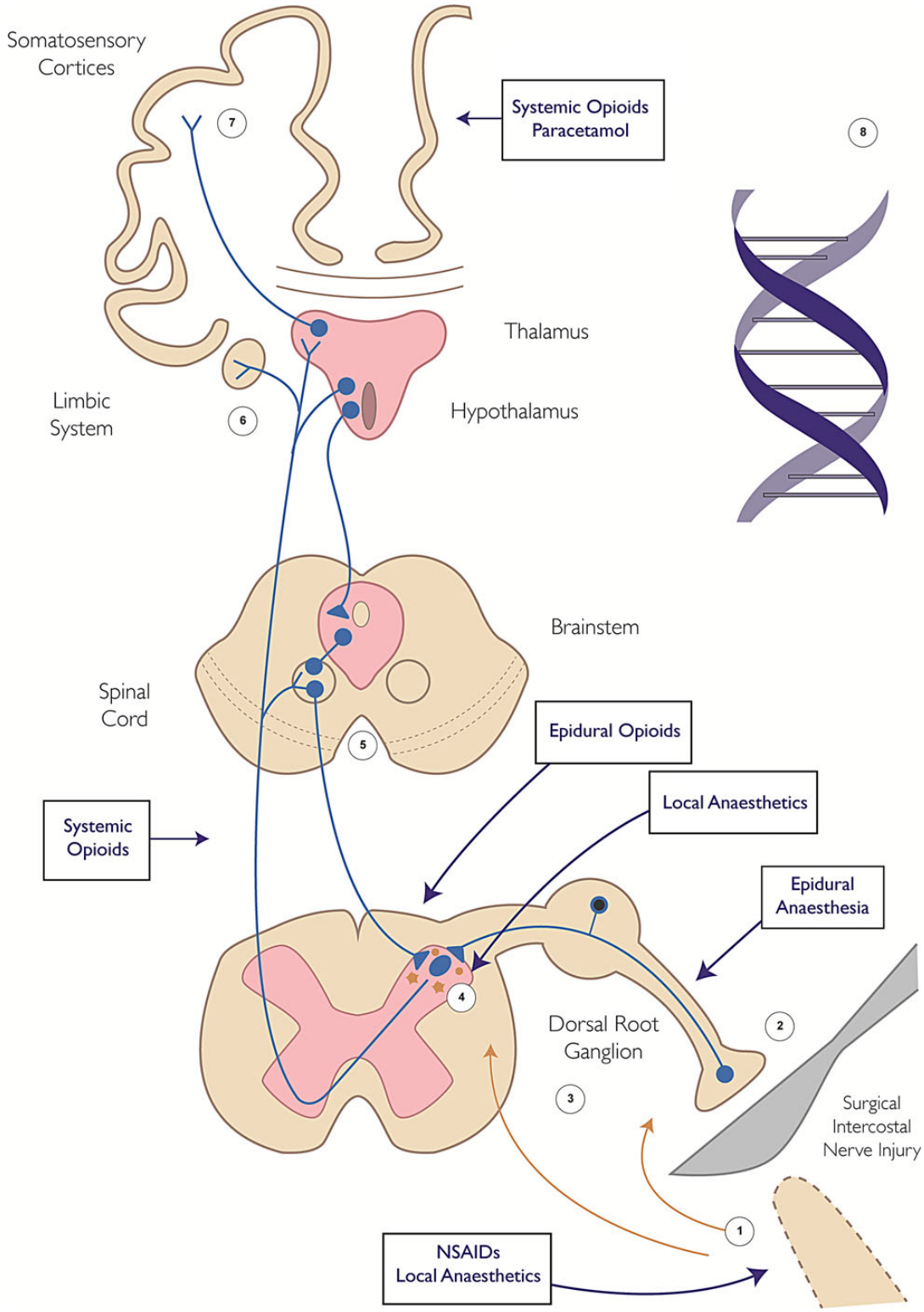

Fig 1 Pain pathway showing mechanisms of neuropathic pain and sites of analgesic action. (1) Denervated Schwann cells and infiltrating macrophages distal to nerve injury produce local and systemic mediators that drive pain signalling. (2) Neuroma at the site of injury is a source of ectopic spontaneous excitability in sensory fibres. (3) Changes in gene expression in dorsal root ganglion alter excitability, responsiveness, transmission, and survival of sensory neurones. (4) Dorsal horn is the site of altered activity and gene expression, producing central sensitization, loss of inhibitory interneurons, and microglial activation, which together amplify sensory flow. (5) Brainstem descending controls modulate transmission in the spinal cord. (6) The limbic system and hypothalamus contribute to altered mood, behaviour, and autonomic reflexes. (7) Sensation of pain generated in the cortex (past experiences, cultural inputs, and expectations converge to determine what patient feels). (8) Genomic DNA predispose (or not) the patient to chronic pain and affect their reaction to treatment. Reprinted from Kehlet and colleagues,[1] © 2006, with permission from Elsevier.

Referred pain to the ipsilateral shoulder is common after thoracotomy and can often be unresponsive to the effects of thoracic epidural analgesia (TEA). Studies have demonstrated a reduction in shoulder pain by infiltrating local anaesthetic to block the phrenic nerve at the level of the pericardial fat pad, or alternatively by interscalene block. This suggests that irritation of the visceral pleura and pericardium, referred to the shoulder by the phrenic nerve, is the most likely source of this pain. As the nerves arise from C3 to C5, TEA is ineffective in blocking this pain. The phrenic nerve may also convey referred pain from transection of a major bronchus or irritation of the pleura from a chest drain placed too far into the apex of the hemithorax.[2]

Factors affecting thoracotomy pain

Surgical factors

The posterolateral approach to thoracotomy provides the best surgical access. However, it involves dividing the latissimus dorsi, and at times the serratus anterior and trapezius muscles, resulting in one of the most painful surgical incisions. Many surgeons now use alternative muscle-sparing approaches where incision of the muscles is replaced with dissection and reflection onto the ribs. The reduced field of view, however, may lead to excessive rib retraction, fracture, dislocation, costovertebral disruption, and damage to the intercostal nerves. These incisions may also span multiple dermatomes as opposed to the single dermatome of the posterolateral approach; for example, the axillary incision extends vertically downwards. Alternatively, an increasing number of video-assisted thoracoscopic surgery (VATS) is performed which may reduce acute pain if intercostal nerve damage is avoided by limiting the number and size of intercostal ports used. However, the incidence of chronic pain appears to be similar to open thoracotomy.[3]

Patient factors

Although studies from the general surgical population suggest that patients who are young, of female gender, with a history of depression and anxiety and who are poorly informed about their management plan are more likely to experience acute post-surgical pain,[4] these risks have not been demonstrated in thoracotomy patients.

Treatment of post-thoracotomy pain

The multifactorial nature of acute thoracotomy pain precludes the use of any single analgesic technique to block all the pain afferents described above. Success is more likely with a multimodal approach that targets multiple sites along the pain pathway (Fig. 1), and incorporates regional anaesthesia with non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and other parenteral adjuncts.

Regional anaesthesia

Thoracic epidural analgesia

TEA is a widely used analgesic technique for thoracotomy.[5] Insertion of a thoracic epidural *before* general anaesthesia facilitates patient feedback on improper placement and permits the assessment of its efficacy. The insertion point is usually midway along the dermatomal distribution of the thoracotomy incision at the level of T5–T6. Difficulty in locating the epidural space is often encountered due to the steep caudal angulation of the spinous processes at this level; therefore, some anaesthetists prefer a paramedian approach which avoids the spinous processes (Fig. 2).

A combined local anaesthetic/opioid epidural solution is most commonly used. Local anaesthetics synergistically increase bioavailability of opioids in the cerebrospinal fluid (CSF), increase their binding to μ-receptors, and block the release of substance P in the substantia gelatinosa of the dorsal horn of the spinal cord. The choice of opioid depends on its lipophilicity, which influences its rate of systemic absorption. A sample regimen involves a test dose of 3 ml 0.5% l-bupivacaine followed by 0.1 ml kg^{-1} of 0.25% l-bupivacaine to establish the block. An infusion can then be commenced of 0.1–0.125% l-bupivacaine + 2–5 μg ml^{-1} fentanyl at 0.1 ml kg^{-1} h^{-1}. The dose can be reduced in the elderly who exhibit increased epidural spread.

Paravertebral analgesia

The paravertebral space is a potential space lateral to the vertebral column that lies posterior to the parietal pleura and anterior to the costotransverse ligament through which the spinal nerves (including their anterior and posterior rami and white and grey rami communicantes) pass *en route* from the intervertebral

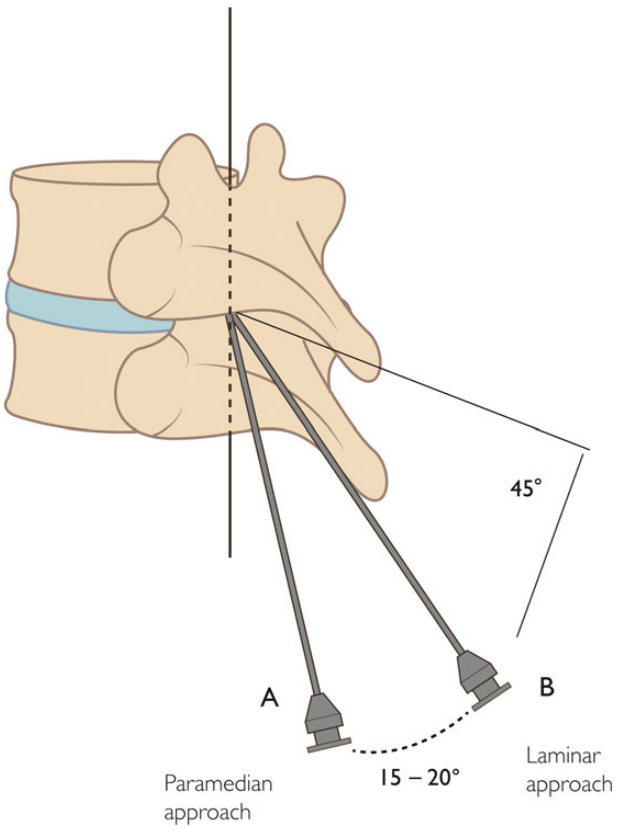

Fig 2 Insertion of paramedian thoracic epidural. The needle is inserted 1 cm lateral to the superior tip of the spinous process and then advanced perpendicular to all planes to contact the lamina of the vertebral body immediately below. The needle is 'walked' up the lamina at an angle rostrally (45°) and medially (20°) until the rostral edge of the lamina is felt. The needle is advanced over the edge of the lamina, seeking a loss of resistance on entering the epidural space after transversing the ligamentum flavum. The laminar approach (B) is favoured by other practitioners. The needle is inserted next to the rostral edge of the spinous process and advanced straight without any angle from the midline. Diagram adapted with permission from Anaesthesia for thoracic surgery, Slinger, PD, Campos, JD. In: *Miller's Anesthesia*, 7th Edn, Miller, RD, and colleagues, eds, 1819–88, © Elsevier 2009.

foramen to the intercostal space (Fig. 3). The lack of a surrounding fascial sheath facilitates *unilateral* nerve block using either a percutaneous loss of resistance technique or preferably an open technique where the surgeon incises and dissects the parietal pleura overlying the paravertebral gutter, threads a catheter, and sutures the pleura closed (Fig. 3). Alternatively, it can be done percutaneously under thoracoscopic or ultrasound guidance.

Although comparable with TEA, paravertebral analgesia (PVA) is less familiar and may fail due to misplacement of the catheter, inadequate dermatomal spread, or failure to maintain local

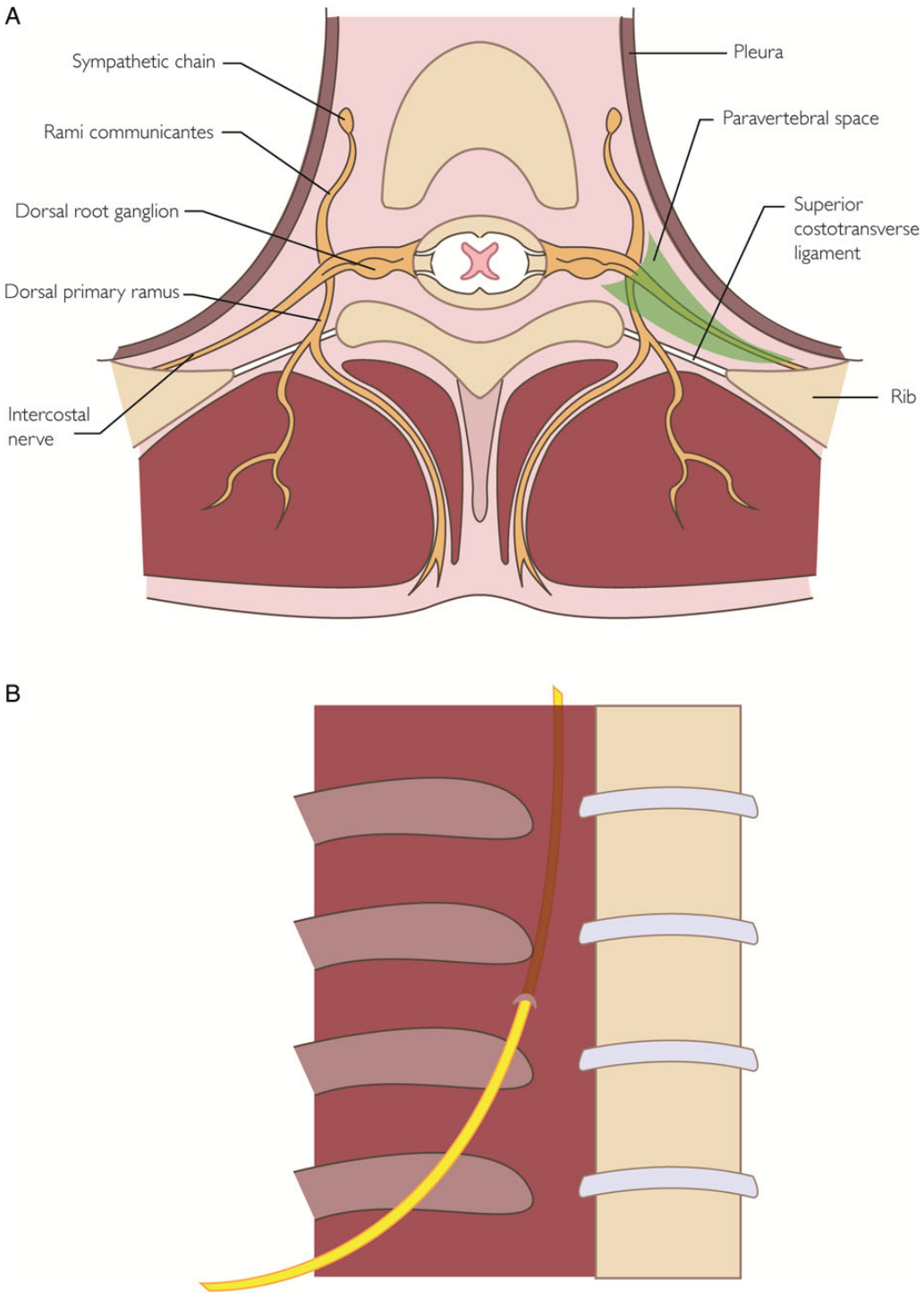

Fig 3 (A) The paravertebral space. (B) Open direct-vision placement of a paravertebral catheter intraoperatively. The epidural catheter is passed into the paravertebral space through a small defect created in the extrapleural (endothoracic) fascia. The proximal end of the catheter is then brought out of the chest through a separate needle puncture in an intercostal space near the chest drains. Diagram adapted with permission from Anaesthesia for thoracic surgery, Slinger, PD, Campos, JD. In: *Miller's Anesthesia*, 7th Edn, Miller, RD, and colleagues., eds, 1819–88, © Elsevier 2009.

anaesthetic within the paravertebral space if the pleura is not intact. The paravertebral space also lacks opioid receptors; therefore, local anaesthetic infusions may require supplementation with i.v. opioids. A sample regimen involves percutaneously placing 10 ml 0.25% l-bupivacaine at T3, T5, and T7 before skin incision, followed by an infusion of 0.125% bupivacaine at 0.2 mg kg^{-1} h^{-1} through a catheter placed by the surgeon under direct vision.

Intrathecal opioids

Intrathecal preservative-free opioids produce analgesia with doses much smaller than the epidural and i.v. routes via a multicompartmental mechanism.[6] On injection, opioids simultaneously spread cephalad within the CSF, bind to non-specific sites within white matter of the spinal cord and to opioid receptors in the dorsal horn, traverse the dura to enter the epidural space where they bind to epidural fat and enter the systemic circulation through vascular uptake. The speed of onset, duration of action, and degree of rostral spread depend on the effects of the lipophilicity of the opioid in each of these compartments. Morphine, a hydrophilic opioid, is commonly used in thoracotomy. It traverses the dura slowly, binds little to epidural fat, and entry to the systemic circulation is delayed. Morphine thus remains in relatively large concentrations in the CSF resulting in an onset of action within 1–2 h of administration and lasting up to 24 h. The technique can be combined with a paravertebral local anaesthetic infusion as an alternative to TEA. Patients must be observed for delayed respiratory depression, urinary retention, and must have an analgesic plan that extends beyond the duration of action.

Other regional techniques

When neuraxial analgesia is not feasible, intercostal nerve block coupled with systemic parenteral analgesia remains an option. The block is simple to perform either percutaneously or under direct vision intraoperatively. However, its limited duration of action (~6 h) necessitates repeating the block at multiple levels or starting an infusion. This increases the risk of systemic toxicity from the highly vascular intercostal space. Incomplete analgesia is also a problem since the dorsal rami supplying the back are not blocked, which is relevant in posterolateral thoracotomies, and the lateral cutaneous branch may also be missed if the block is performed too anteriorly.

Intrapleural analgesia, where local anaesthetics are injected between the layers of the parietal and visceral pleura, is not recommended. Surgery increases the volume of the interpleural space with blood and air which dilutes the spread of local anaesthetics. Systemic absorption of local anaesthetics is also considerable.

Systemic analgesia

Opioids

Epidural analgesia has been shown to be superior to i.v. morphine via patient-controlled analgesia (PCA) devices. Furthermore, the doses of opioids required to produce comparable analgesia when used as sole agents also produce significant respiratory depression; therefore, opioids are mainly relegated to adjuncts to a regional technique.

Non-steroidal anti-inflammatory drugs

The role of NSAIDs in thoracotomy is two-fold, to reduce opioid requirements and to treat ipsilateral shoulder pain resistant to TEA. NSAIDs reduce the inflammatory response to surgery by inhibiting the cyclooxygenase enzyme (COX) and consequently prostaglandin synthesis.[7] However, they should be used with care in the elderly who are especially vulnerable to renal dysfunction. NSAIDs may also reduce the effectiveness of pleurodesis procedures. Paracetamol shares the opioid-sparing and shoulder pain roles of NSAIDs with less side-effects.[7] Its analgesic effect with NSAIDs is additive.

Management of chronic post-thoracotomy pain

Chronic pain after thoracotomy afflicts up to 57% of patients at 3 months and 47% at 6 months.[8] This incidence has not improved since the 1990s despite improvements in perioperative care.[8] Patients present to the pain clinic describing a burning, numbness, or a cutting sensation along the thoracotomy scar, which may be constant or intermittent, and may be evoked by non-painful stimuli such as changes in temperature or donning clothing.

Perioperatively, the management of chronic post-thoracotomy pain (CPTP) should ideally begin with a review of any modifiable risk factors. A number of small studies have shown a reduction in chronic pain after TEA.[9] However, the concept of pre-emptive analgesia, where analgesics are administered before the noxious stimulus to prevent the peripheral and central sensitization implicated in chronic pain, has thus far little evidence to support it in the context of CPTP.[9]

Once a patient has developed CPTP, it is important to exclude other differential diagnoses such as malignancy recurrence or the effects of radiotherapy and chemotherapy. A multidisciplinary personalized plan incorporating behavioural therapies, pharmacological agents, and nerve blocks should then be devised. Agents used include NSAIDs, amitriptyline, gabapentin, opioids, and ketamine. The underlying goal of all these agents is to reduce the peripheral and central sensitization that has occurred. Non-pharmacological treatments used have shown varying success and include transcutaneous electrical nerve stimulation, cryoanalgesia, radiofrequency ablation, and spinal cord stimulation.

Epidural, paravertebral, or intrathecal morphine?

In a systematic review by the Procedure Specific Postoperative Pain Management working group (PROSPECT), paravertebral and thoracic epidural continuous infusions of opioid-free local anaesthetic were found to be comparable, but PVA was associated with less respiratory complications and hypotension.[10] Furthermore, in a Cochrane Review by the authors, PVB was found to be associated with lower rate of major complications including chest infection and acute confusion and minor complications such as low blood pressure, nausea and vomiting, itching and urinary retention when compared to TEA.[11] A single bolus of intrathecal opioid before operation was also comparable with both techniques. However, the duration of analgesia was limited to 24 h.[10]

Based on the review, PROSPECT recommend that either TEA with local anaesthetics and an opioid or continuous PVA with local anaesthetics combined with parenteral paracetamol and an NSAID should be used as first-line analgesia for thoracotomy. Where these techniques are not possible, or are contraindicated, intrathecal opioid or intercostal nerve block are recommended, which requires the use of supplementary systemic analgesia. The PROSPECT recommendations are summarized in Figure 4.

Although VATS is associated with less acute pain than open thoracotomy, it may still be significant if intercostal nerves are compressed by twisting instruments and the need for an incision to extract lobes. If the patient has poor respiratory reserve or their disease increases the likelihood of conversion to thoracotomy, TEA is advisable. Otherwise, the combination of PVA with i.v. PCA is a suitable alternative.[12]

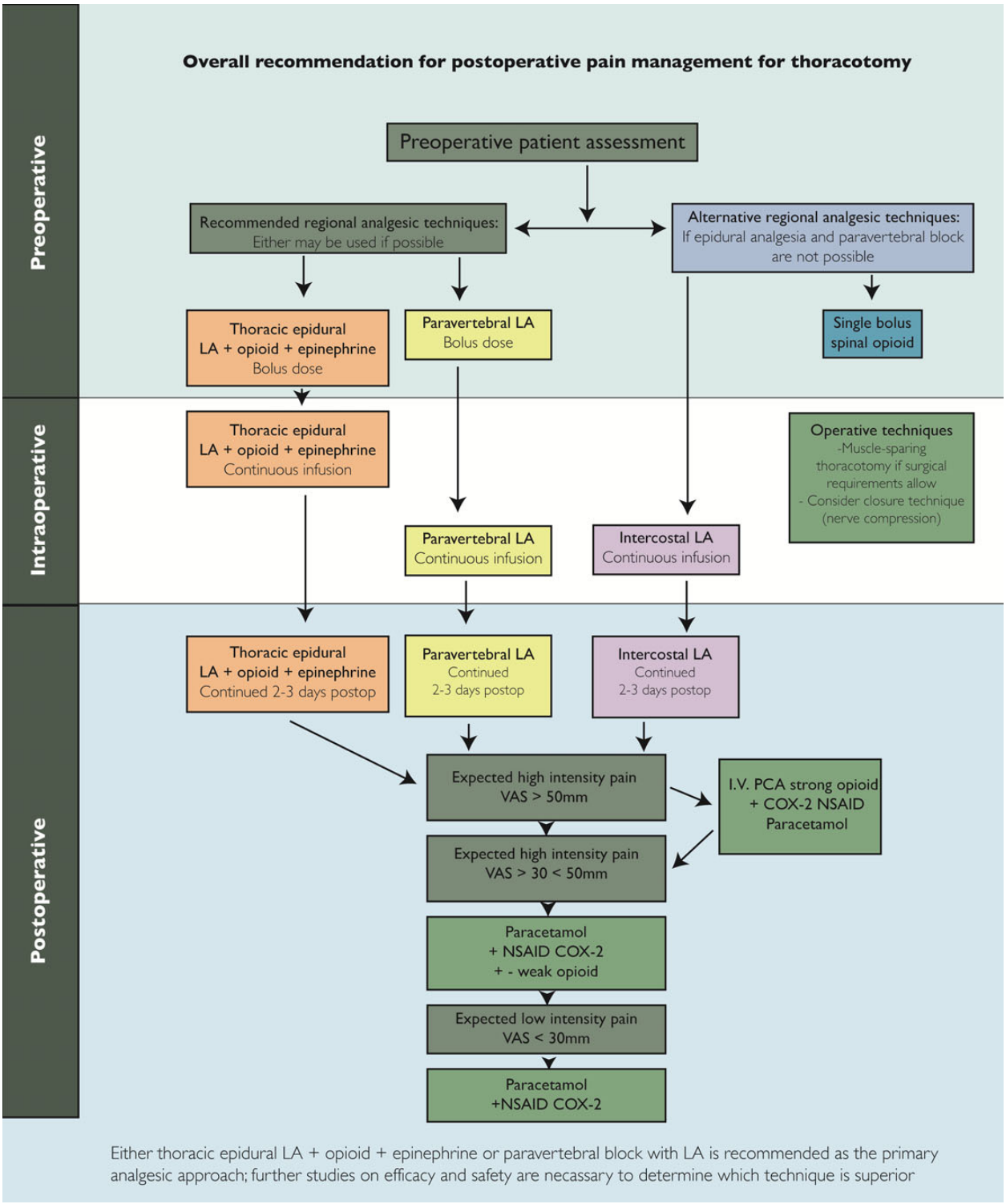

Fig 4 Algorithm proposed by the PROSPECT Working Group for pain management after thoracotomy. COX-2, cyclooxygenase 2; LA, local anaesthetic; VAS, visual analogue scale.

Genetics and thoracotomy pain

A patient's genes can change how he or she experiences thoracotomy pain. In addition to the effect on analgesic pharmacokinetics, genetic polymorphisms can have a profound influence on the sensation of thoracotomy pain such that the patient may be especially sensitive or conversely insensate to pain. For example, a mutation in the gene SCN9A, which encodes a sodium channel (NaV1.7), causes either a gain of function resulting in erythermalgia or loss of function resulting in the inability to sense pain.[13]

In addition to the purely genetic causes of altered nociception, epigenetic modifications may also play a role in CPTP. Epigenetics

is the way in which the environment changes gene expression through altering the chemical or physical structure of DNA. For example, the surgical injury may trigger a cascade of events that alter the structure of DNA by either methylation or histone modification which culminates in a change in gene expression leading to increased postoperative pain.

Preclinical studies have shown a reduction in the hypersensitivity that accompanies nerve injury by using histone deacetylase inhibitors to prevent histone deacetylation. This is particularly significant for surgery where there is a high risk of nerve damage such as thoracotomy. Other laboratory studies inhibiting DNA methyltransferase in an inflammatory pain model showed a reduction in hypersensitivity and reduced methylation in the prefrontal cortex and amygdala, which modulate feelings of depression, anxiety, and chronic pain.[14] These epigenetic processes therefore represent a target for future analgesic development.

Conclusion

The management of pain after thoracotomy requires a multimodal approach incorporating regional and systemic analgesia. The selection of an analgesic option should always be a balance between the risks and benefits of an individual technique and is a decision which should be tailored to the patient's comorbidities and wishes, the extent of surgery, and the local facilities available.

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Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Developments in the management of diabetic ketoacidosis in adults: implications for anaesthetists

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Key points

- Diabetic ketoacidosis (DKA) is a medical emergency and bedside capillary ketone testing allows timely diagnosis and identification of successful treatment.
- 0.9% saline with premixed potassium chloride should be the main resuscitation fluid on the general wards and in theatre; this is because it complies with National Patient Safety Agency recommendations on the administration of potassium chloride.
- Weight-based fixed rate i.v. insulin infusion (FRIII) is now recommended rather than a variable rate i.v. insulin infusion (VRIII).
- The blood glucose must be kept above 14 mmol litre^{-1} with the FRIII.
- Precipitating factor(s) needs to be identified and treated. Surgery and also critical care may be indicated to manage the patient presenting with DKA.

Diabetic ketoacidosis (DKA) is a medical emergency. The diagnostic triad is:

(i) Ketonaemia ≥3.0 mmol litre^{-1} or significant ketonuria (more than 2+ on urine sticks)
(ii) Blood glucose >11.0 mmol litre^{-1} or known diabetes mellitus
(iii) Bicarbonate <15.0 mmol litre^{-1}, venous pH <7.3, or both.

DKA can occur in both type 1 and type 2 diabetes mellitus and, although preventable, it remains a frequent and life-threatening complication. Errors in the management of DKA are not uncommon and are associated with significant morbidity and mortality. The majority of mortality and morbidity in DKA are attributable to delays in presentation and initiation of treatment. Rapid recognition and treatment of DKA is critical.

To overcome these concerns and to highlight current management strategies, the Joint British Diabetes Societies (JBDS) published guidelines in 2010. This was updated in consultation with the Intensive Care Society in September 2013.[1]

This article will review the pathophysiology of DKA and highlight the modern management of DKA that is relevant for anaesthetists. A summary of the JBDS guidelines pertinent to intensivists has been published.[2]

Epidemiology

In England in 2010, there were 14 375 admissions to acute NHS trusts where DKA was the primary diagnosis. Subsequently, it was estimated that 13% of these patients were admitted to Intensive Care Units (2% of all general ICU admissions).[3] Furthermore, the National Diabetes Inpatient Audit 2012 found that 0.5% of inpatients with diabetes actually developed DKA as an inpatient whilst in hospital.[4]

The mortality rate has decreased in some patient populations; however, in the elderly and in patients with comorbidities, it remains >5%.

Pathophysiology

DKA results from a relative or absolute insulin deficiency with a concomitant increase in counter regulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone. Hyperglycaemia ensues because of increased gluconeogenesis, accelerated glycogenolysis, and impaired glucose utilization by peripheral tissues.

This is magnified by transient insulin resistance because of the hormone imbalance itself. The combination of insulin deficiency and increased counter regulatory hormones leads to the release of free fatty acids and their unrestrained oxidation in the liver to ketones. These ketones include acetone, 3-beta-hydroxybutyrate, and acetoacetate. The predominant ketone in DKA is 3-β-hydroxybutyrate. Hydrogen ions produced by the dissociation of the ketone bodies causes the metabolic acidosis.[5]

Hyperglycaemia causes osmotic fluid shifts from intracellular to extracellular compartments. The glucose load in the glomerular tubules exceeds the renal threshold leading to glucosuria and an obligatory osmotic diuresis. This diuresis causes a loss of sodium, potassium, and phosphate along with water and glucose.

Causes

The three most common causes are:

(i) An underlying infection
(ii) Missed insulin treatment
(iii) First presentation of diabetes mellitus.[6]

Inadequate insulin therapy is the recognized cause of hospital-acquired DKA. This may be caused by inadequate prescription or administration of insulin, or insufficient monitoring of capillary blood glucose (CBG).

The cause may occasionally necessitate emergency surgical treatment (e.g. appendicitis; infarcted bowel; incision and drainage of abscess; ectopic pregnancy).

Clinical presentation

DKA occurs predominantly in patients with type 1 diabetes, but it can also develop in patients with ketone prone type 2 diabetes. There is a wide clinical spectrum in the presentation of DKA. DKA is a recognized cause of the acute abdomen, and this in itself can actually result in unnecessary emergency surgery. Presentation in type 2 diabetes is the same as in type 1 diabetes; however, some studies have found there to be a different biochemical presentation with a less severe acidosis and a tendency for normal initial serum potassium levels.[7]

Investigations

Initial investigations fall into three categories:

(i) Establish diagnosis of DKA
(ii) Baseline investigations
(iii) Identify cause.

Ongoing investigations are then required to monitor the effect of treatment, and to ensure successful and safe treatment.

Investigations to establish diagnosis of DKA

As DKA is the triad of:

(i) Ketonaemia ≥ 3.0 mmol litre^{-1} or significant ketonuria (more than 2+ on urine sticks)
(ii) Blood glucose >11.0 mmol litre^{-1} or known diabetes mellitus
(iii) Bicarbonate <15.0 mmol litre^{-1}, venous pH <7.3, or both.

The following investigations are mandatory.

(i) Capillary ketone levels/urinalysis for ketones
(ii) Blood sugar
(iii) Blood gas for pH, bicarbonate, or both.

Fig 1 GlucoMen blood glucose meter

Ketone meters

In the past, diagnosis and successful treatment of DKA was guided by CBG with the erroneous assumption that correction of hyperglycaemia would be a marker for suppression of ketogenesis and successful reversal of acidosis. However, CBG is both a poor determinant of severity and a poor surrogate marker for successful treatment. Euglycaemic ketoacidosis is possible depending on the hepatic glycogen stores before the onset of DKA. This demonstrates the necessity for ketone monitoring.

Ketone meters (Fig. 1) are now available for rapid testing for β-hydroxybutyrate at the bedside. Handheld ketone meters are operated in an identical fashion to bedside CBG meters. Results are available within 10 s allowing immediate differentiation between simple hyperglycaemia and ketotic states.

Trials have found that the utilization of blood ketone testing is more effective than urine acetoacetate testing in improving diagnosis and their use is associated with a reduced time to recovery from DKA and shorter hospital stay.[8]

Blood gas

To make the diagnosis, a blood gas is essential for the assessment of the acidosis and serum bicarbonate levels. Recent evidence has shown little difference between arterial and venous pH and bicarbonate.[9] These small differences are inconsequential to the diagnosis or management of DKA, and therefore the JBDS guidelines recommend the use of venous blood gases if the patient is managed on the ward, in order to prevent repeated arterial punctures.

Baseline investigations

These include full blood count, urea, creatinine, potassium, sodium, chloride, CRP, and liver function tests.

Investigations to identify cause

It is imperative to discover the cause of the DKA and investigations should be based on the clinical findings. Common investigations include ECG, blood cultures, amylase, and pregnancy test.

Ongoing investigations

To assure safe response to treatment, the following should occur hourly till resolution of the ketosis:

(i) CBG/arterial blood glucose (if arterial line sited)
(ii) Capillary blood ketones.

To assure metabolic stability, the following should occur at a minimum of 2 hourly intervals until resolution of the ketosis:

(i) pH
(ii) bicarbonate
(iii) potassium.

Initial management

DKA is a life-threatening condition and resuscitation along with initial treatment must occur simultaneously with clinical assessment. Appropriate history, examination, and investigations should be undertaken to diagnose the condition, identify the severity, and identify the cause.

Initial management should focus on:

(i) Airway protection, if required
(ii) Fluid resuscitation
(iii) Insulin administration
(iv) Assessment of severity
(v) Identification of cause.

Resuscitation

An airway, breathing, circulation, disability, exposure (ABCDE) approach will provide structure to the initial resuscitation. Appropriate venous access must be obtained.

Fluid resuscitation

The most important initial therapeutic invention in DKA is fluid replacement followed by insulin administration. It is now universally agreed that crystalloids with a sodium concentration in the range of 130–154 mmol litre^{-1} should be used as the resuscitation fluid. In the UK, this is generally either 0.9% saline or Hartmann's solution. There is ongoing debate on which crystalloid is superior. There is evidence to suggest that the use of balanced crystalloid solutions are associated with a faster resolution of the metabolic acidosis and less hyperchloraemic metabolic acidosis.[10 11] However, balanced solutions such as Hartmann's solution contains insufficient potassium, and under NPSA rules, 3% potassium chloride should not be stored/added to fluids on the general wards.[12] Therefore, the use of 0.9% saline with premixed potassium chloride is advocated for ward and theatre use. Critical care can both administer concentrated potassium centrally, and add potassium to Hartmann's solution. Thus, critical care may choose to use Hartmann's solution as the primary fluid for resuscitation.

Table 1 is an example of a typical fluid replacement regimen for a previously well 70 kg adult. However, the exact rate of infusion should be formulated after clinical assessment of the individual patient. If the patient is shocked, the patient should receive an initial bolus of 500 ml over <15 min, and further fluid boluses dependent on clinical re-assessment.

Table 1 Typical fluid replacement regimen for a previously well 70 kg adult on the general ward

Fluid number	Fluid	Rate
Initial bag	1 litre 0.9% saline	1000 ml h^{-1}
2nd bag	1 litre 0.9% saline with premixed potassium chloride	500 ml h^{-1}
3rd bag	1 litre 0.9% saline with premixed potassium chloride	500 ml h^{-1}
4th bag	1 litre 0.9% saline with premixed potassium chloride	250 ml h^{-1}
5th bag	1 litre 0.9% saline with premixed potassium chloride	250 ml h^{-1}
6th bag	1 litre 0.9% saline with premixed potassium chloride	150 ml h^{-1}
Further fluid	1 litre 0.9% saline with premixed potassium chloride	Clinical assessment
With regular re-assessment		

Insulin administration

Administration of i.v. human soluble insulin is mandatory. Classically the insulin has been titrated against the surrogate marker of the blood glucose using a variable rate i.v. insulin infusion (VRIII). The term 'variable rate i.v. insulin infusion' has now replaced the ambiguous and obsolete term 'sliding scale'. It is now recognized that glucose levels are a poor surrogate marker for resolution of ketosis, and using the blood glucose as a marker to guide insulin therapy may (and does) lead to the erroneous action of reducing insulin whilst the patient is still highly ketotic. A fixed rate administration of i.v. insulin whilst the patient remains ketotic avoids this risk. Thus, recent evidence and guidelines suggest that a weight-dependent fixed rate i.v. insulin infusion (FRIII) should be administered, rather than the variable rate i.v. insulin infusion (VRIII). Table 2 summarizes the advantages and disadvantages of an FRIII.

Preparation and administration of the fixed rate i.v. insulin infusion

The FRIII is administered via an infusion pump. The FRIII is constituted by adding 50 units of human soluble insulin (Actrapid®, Humulin S®) to 0.9% sodium chloride to make a final volume of 50 ml (1 unit ml^{-1}). Ideally this should be provided as a ready-made infusion. The FRIII is then administered at a fixed rate of 0.1 unit kg^{-1} h^{-1} (i.e. 7 ml h^{-1} if weight is 70 kg). Weight should be estimated if not available, and pregnant patients should have their current weight used.

Metabolic targets for the continuation of the current fixed rate insulin infusion are:

(i) Reduction of blood ketone concentration by >0.5 mmol litre^{-1} h^{-1}
(ii) If blood ketone measurement is not available, the venous bicarbonate should increase by 3.0 mmol litre^{-1} h^{-1}
(iii) Reduction in CBG by 3.0 mmol litre^{-1} h^{-1}.

If the above targets are not being achieved, it is necessary to reassess the patient and consider the causes of non-successful treatment. This may include:

Table 2 Advantages and disadvantages of an FRIII

Advantages	Disadvantages
(i) Faster resolution of DKA (ii) No titration of the insulin against the false surrogate marker of capillary glucose (iii) Complete resolution of DKA provided the FRIII is turned off once the ketone levels are <0.6 mmol litre^{-1}	Risk of hypoglycaemia if CBG is not measured hourly and additional glucose containing solutions not administered once CBG <14 mmol litre^{-1}

(i) Non-administration of the insulin for any reason (e.g. tissued cannula, pump not running, anti-syphon valve not used, etc.).
(ii) Ongoing co-morbidity that will need senior review
(iii) Insufficient insulin.

If it is deemed that unsuccessful treatment is secondary to insufficient insulin, the FRIII will need to be increased in increments of 1 unit h^{-1} until the targets are met. A maximum rate of 15 units h^{-1} is recommended.

Safe cessation of the FRIII

The FRIII should be continued until resolution of the ketosis. Resolution of DKA is defined as:

(i) pH >7.3
(ii) bicarbonate >15.0 mmol litre^{-1}
(iii) blood ketone level <0.6 mmol litre^{-1}.

Before stopping the FRIII, it is necessary to administer insulin in another form; otherwise, the patient will re-develop ketosis. The patient can either be recommenced on their usual regimen (if they are eating and drinking) or converted to a variable rate i.v. insulin infusion with concurrent administration of 5% dextrose in 0.45% saline with 0.15% potassium chloride. This transition should ideally be managed by the diabetes specialist team.

To aid the transition from i.v. insulin to subcutaneous insulins, it now advised that the long-acting analogue insulins are continued. The long-acting analogue insulins are Levemir®, Lantus®, and Tresiba®. Some units are also beginning to experiment with the continuation of the long-acting human basal insulins such as Humulin I®, Insulatard®, and Insuman Basal®. Continuation of the long-acting insulins avoids rebound hyperglycaemia when the i.v. insulin is stopped and may subsequently reduce the length of stay.[13]

Management of blood glucose <14 mmol litre^{-1}

The FRIII should be continued until there is resolution of the ketosis; however, it may cause hypoglycaemia before resolution of the ketosis. Therefore, it is mandatory to perform hourly CBGs and to be prepared to give additional glucose once the CBG is <14 mmol litre^{-1}. It is recommended that 10% glucose at 125 ml h^{-1} should be administered. In theatre, 20% glucose at 50 ml h^{-1} or 50% glucose may be administered. The rate of the primary resuscitation fluid may need to be altered to prevent fluid overload.

Management of continuous subcutaneous insulin infusion (CSII) pumps

Because of erratic and unpredictable insulin absorption, these devices should probably be stopped and disconnected during an episode of DKA, and only reinstated with diabetes specialist team input.

Critical care referral

Patients should be considered for critical care referral if any of the following criteria are present:

(i) Glasgow Coma Score (GCS) <12 or abnormal AVPU (alert, voice, pain, unresponsive) scale
(ii) Blood ketones >6 mmol litre^{-1}
(iii) Bicarbonate level <5 mmol litre^{-1}
(iv) Venous/arterial pH <7.0
(v) Hypokalaemia on admission (<3.5 mmol litre^{-1})
(vi) Oxygen saturation <92% on air (assuming normal baseline respiratory function)
(vii) Systolic BP below 90 mmHg
(viii) Pulse over 100 or below 60 beats min
(ix) Anion gap >16 [Anion gap = $(Na^+ + K^+) - (Cl^- + HCO^{3-})$].

It is often necessary to admit emergency surgical patients to a level 2 or 3 facility, both pre- and post-surgery.

DKA complications

Mortality from DKA in the UK has fallen significantly in the last 20 yr from 7.96 to 0.67%.[1] Hypokalaemia, acute lung injury, and co-morbid states such as pneumonia, sepsis, and myocardial infarction are associated with increased mortality. Cerebral oedema remains the most common cause of death in DKA in children. The exact mechanism is uncertain; however, it is felt that cerebral oedema may be related to cerebral *hypoperfusion before treatment*, with subsequent vasogenic oedema occurring during DKA treatment as a result of *reperfusion of previously ischaemic brain tissue* (i.e. the osmotic fluctuations during DKA treatment do not play the primary causal role).[14]

Table 3 summarizes the risk factors, signs and symptoms, immediate treatment and also the different strategies that are utilized by paediatricians to reduce the risk of cerebral oedema.[15]

Further management

Monitoring and replacement of electrolytes

Initial serum potassium may be normal, raised or low in DKA. However, there is a total body potassium deficit. Potassium loss is caused by a shift from the intracellular to extracellular space in exchange for hydrogen ions which accumulate in acidosis. The extracellular potassium is then lost through osmotic diuresis.

The initial litre of fluid should not have potassium added. Provided the serum potassium is <5.5 mmol litre^{-1}, and the patient is not oliguric, subsequent fluids should have 40 mmol litre^{-1} of potassium chloride.

Adequate fluid, potassium and insulin therapy will resolve the acidosis in DKA, but there may be disturbances of other electrolytes including bicarbonate, sodium, and phosphate.

Table 3 Summary of risk factors, signs and symptoms, initial treatment of cerebral oedema, and the strategies used to minimize the risk of cerebral oedema in children

Risk factors for cerebral oedema	Signs and symptoms	Initial treatment of cerebral oedema	Major differences in treatment of paediatric DKA to minimize risk of cerebral oedema
(i) Younger age (ii) New onset diabetes (iii) Longer duration of symptoms (iv) Greater hypocapnia at presentation after adjusting for degree of acidosis (v) Increased serum urea nitrogen at presentation (vi) More severe acidosis at presentation (vii) Bicarbonate treatment for correction of acidosis (viii) An attenuated increase in measured serum sodium concentrations during therapy (ix) Greater volumes of fluid given in the first 4 h (x) Administration of insulin in the first hour of fluid treatment	(i) Headache (ii) Slowing of heart rate (iii) Change in neurological status (restlessness, irritability, increased drowsiness, incontinence) (iv) Specific neurological signs (e.g. cranial nerve palsies) (v) Increase in blood pressure (vi) Decreased O_2 saturation	(i) Immediate i.v. mannitol or hypertonic 3% saline (ii) Reduce fluids by 1/3 (iii) Intubation and ventilation and avoidance of aggressive hyperventilation (iv) CT to rule out other pathology	(i) No i.v. boluses of insulin (ii) Commencement of i.v. insulin after 1 h of fluid treatment (iii) Gradual rather rapid restoration of normovolaemia (>48 h) (iv) Use of 0.9% saline initially (1st 4–6 h) and then consideration of saline with tonicity >0.45% according to serum sodium and osmolality.

Table 4 Typical fluid and electrolyte deficits in adults with DKA

Water	100 ml kg^{-1}
Sodium	7–10 mml kg^{-1}
Chloride	3–5 mmol kg^{-1}
Potassium	3–5 mmol kg^{-1}

Generally, these electrolyte imbalances improve as the DKA is treated effectively. Typical fluid and electrolyte deficits are summarized in Table 4.

Nasogastric tube

Ketosis causes delayed gastric emptying; therefore, the use of nasogastric tube may help protect the airway in those patients with an altered mental state, and those who require surgery and anaesthesia.

Urinary catheter

A urinary catheter should be inserted in all patients with an altered mental state, those in a critical care setting or undergoing anaesthesia for monitoring of urine output and fluid balance. Oliguria is a sign of acute kidney injury.

Venous thromboembolism risk assessment and prophylaxis

All patients should receive appropriate venous thromboembolism (VTE) risk assessment and subsequent prophylaxis. Dehydrated patients with DKA are at high risk of VTE. Both chemical (e.g. low-molecular-weight heparin) and physical (e.g. antiembolic stockings) thromboprophylaxis should be considered.

Antibiotics

If infection is suspected appropriate antibiotic therapy should be commenced according to local policy.

Involvement of diabetes specialist teams

The diabetes specialist team must be involved in the care of those with DKA as soon as possible in the acute phase. Their involvement has been shown to reduce the length of stay and improve patient safety.

Perioperative management of DKA

If a surgical cause is identified, senior multidisciplinary review to discuss the optimal timing of surgery is required. It is also important to try and ensure that the clinical picture of an 'acute abdomen' is not secondary to the DKA in order to prevent needless surgery. The Royal College of Surgeons (RCS) document 'Emergency Surgery, Standards for unscheduled surgical care' provides a useful framework that promotes timely surgery but allows time for accurate diagnosis, initial treatment, and resuscitation.[16] The standards are summarized below.

Timeframe to theatre as suggested by Royal College of Surgeons

(i) Patients with ongoing haemorrhage require immediate surgery.
(ii) Patients with septic shock who require immediate surgery are operated on within 3 h of the decision to operate as delay increases mortality significantly.

(iii) Patients with severe sepsis (with organ dysfunction) who require surgery are operated on within a maximum of 6 h to minimize deterioration into septic shock.
(iv) Patients with sepsis (but no organ dysfunction) who require surgery should have this within a maximum of 18 h.
(v) Patients with no features to indicate systemic sepsis can be managed with less urgency but in the absence of modern and structured systems of care, delay will result in unnecessary hospital stay, discomfort, illness, and cost.

Each patient must be managed individually, including the optimal time to operate. Unless the patient requires immediate surgery, preoperative resuscitation should occur with correction of the hypovolaemia, the metabolic acidosis, and the electrolyte imbalances.

Preoperative preparation

Preoperative management should be focused on optimizing the patient for surgery. Furthermore, the senior anaesthetist must decide whether a VRIII or a FRIII will be used intra-operatively. If the anaesthetist decides to use the FRIII intraoperatively, as a minimum, provision must be made to have sufficient vascular access for the following:

(i) Administration of the fixed rate i.v. insulin infusion via a pump
(ii) Administration of the DKA resuscitation fluid (0.9% saline with 0.3% premixed potassium chloride via a pump may be the most appropriate) at the rate as guided by Table 1.
(iii) Administration of the intra-operative resuscitation fluid
(iv) Administration of anaesthetic bolus drugs
(v) Administration of 20% glucose at 50 ml h^{-1} if the CBG is <14 mmol $litre^{-1}$.
(vi) Ability to check blood glucose, potassium, and pH at regular intervals (minimum hourly).

Central venous access should be obtained to guide fluid therapy and to facilitate the administration of multiple drugs and fluids.

Conduct of anaesthesia

Patients should be anaesthetized with full monitoring, with an arterial line *in situ*, and in theatre to facilitate continuous blood pressure monitoring post induction. An arterial blood gas (ABG) should be obtained before induction to give an indication of the degree of acidosis, and to ensure no hyperkalaemia, as succinylcholine is often used to facilitate intubation as part of a rapid sequence induction. Because of gastric stasis, the nasogastric tube should be aspirated before induction of anaesthesia.

Patients should be intubated with a rapid sequence induction with cricoid pressure. In view of the hypovoalemic state and the acidosis, anaesthesia must be induced with a combination of drugs that promote cardiovascular stability.

Regular (minimum hourly) monitoring of ABGs and blood glucose is mandatory. Patients should be ventilated to ensure no iatrogenic respiratory acidosis. Potassium needs to be kept within the normal range, and replaced as indicated. Blood glucose needs to be kept >14 mmol $litre^{-1}$ whilst the patient is being treated with the FRIII.

Consideration should be given to flow/cardiac output directed guided fluid therapy given the complex intra-operative fluid requirements of the surgical patient with DKA.

Postoperative care

After operation patients should receive nursing care in a level 2/3 environment until resolution of the DKA. The patient should receive their normal long-acting insulin analogue at the normal time. The Diabetes specialist teams will be able to assist in the transition from i.v. insulin to subcutaneous insulin and can provide further education and reinforce the 'sick day rules' to the patient.

Summary

(i) DKA is a life-threatening medical emergency characterized by the biochemical triad of ketonaemia, hyperglycaemia, and acidaemia.
(ii) Bedside monitoring of capillary ketones, glucose, blood gases, and electrolytes should be used to make the initial diagnosis and guide subsequent management.
(iii) Weight based fixed rate i.v. insulin infusion (FRIII) is now recommended rather than a variable rate i.v. insulin infusion (VRIII), and the blood glucose must be kept >14 mmol $litre^{-1}$ with the FRIII.
(iv) 0.9% Saline with premixed potassium chloride should be the main resuscitation fluid on the general wards and in theatre. This is because it complies with National Patient Safety Agency recommendations on administration of potassium chloride.
(v) Balanced electrolyte solutions are associated with a faster resolution of acidosis, but contain insufficient potassium to justify their safe use except in critical care.
(vi) The cause of the DKA must be sought and surgery may be required.
(vii) Critical care may be required.
(viii) Continuation of long acting insulins may reduce complications during transition from i.v. to subcutaneous insulin.
(ix) Early involvement of diabetic specialist teams is mandatory.

Declaration of interest

N.L. is a member of the writing group for JBDS DKA guidelines.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Computed tomography of the chest—II: clinical applications

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Key points

- Computed tomography (CT) scans can detect pathology that may be missed on a conventional chest radiograph and is the initial investigation of choice for major trauma.
- A systematic approach for reviewing a CT scan of the chest minimizes the risk of missing significant pathology.
- Chest CT may be used in the planning of airway management such as in thyroid goitre, tracheo-oesophageal fistulae, or for double-lumen tube placement.
- Lung parenchyma can be more accurately assessed with CT than conventional chest radiographs.
- Significant cardiac pathology may be detected on CT scans.

In the previous article in this edition of the journal, the authors stated a systematic approach to the process of reviewing a computed tomography (CT) scan of the chest is vital not to miss potentially subtle pathology. This article, the second of two concerning CT chest, will examine the clinical applications of chest CT and the various pathologies that may occur in relation to anatomical areas of interest. The clinician reviewing the scans must have an accurate history and pertinent examination findings to focus attention on likely areas of pathology. The lung parenchyma, pleurae, and mediastinum must all be comprehensively examined so as to minimize the risk of missing pathology when reviewing chest CT scans. This article will explore these three specific anatomical areas initially and then focus on the role of CT chest in trauma and in the diagnosis of certain cardiovascular pathologies.

Lung parenchyma and airways

Inspect the lung parenchyma, bronchi, and distal airways assessing their patency and diameter. Ground glass opacification of the lungs refers to the appearance of a hazy opacity that does not obscure the associated pulmonary vessels (Fig. 1). This appearance from parenchymal abnormalities is seen with either: alveolar wall inflammation or thickening, partial air-space filling, or with some combination of the two (Fig. 2). Common causes include pulmonary oedema; adult respiratory distress syndrome; viral, mycoplasmal, and pneumocystis pneumonias; pulmonary haemorrhage; and other diffuse interstitial lung diseases.

Early interstitial pulmonary oedema is demonstrated by the loss in definition of subsegmental and segmental vessels, the appearance of Kerley lines, and pleural effusions. Further, oedema will migrate centrally with progressive blurring of vessels, first at the lobar level and later at the level of the hilum. At this point, lung radiolucency decreases markedly, giving a ground glass appearance (Fig. 3).

Thereafter, a sudden extension of oedema into the alveolar spaces creates small nodular or acinar areas of increased opacity that coalesce into consolidation. These areas can display a

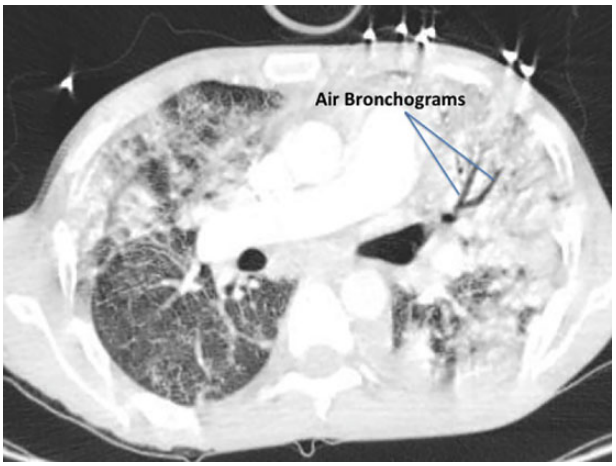

Fig 1 Consolidation of the left lung parenchyma with air bronchograms located within and patchy ground glass changes in the right lung.

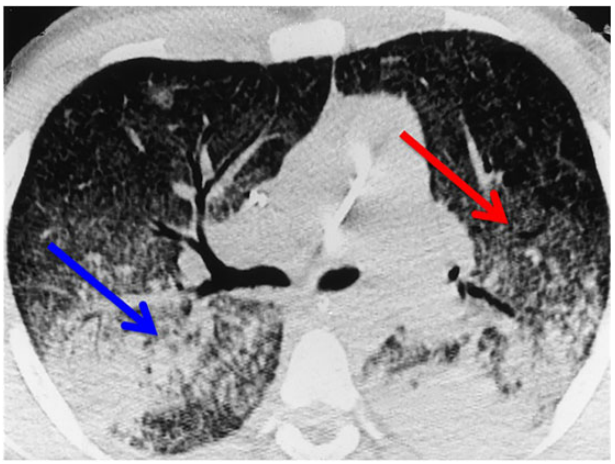

Fig 2 Adult respiratory distress syndrome with areas of parenchymal consolidation (blue arrow) in the dependent areas and ground glass opacification (red arrow) in the non-dependent areas.

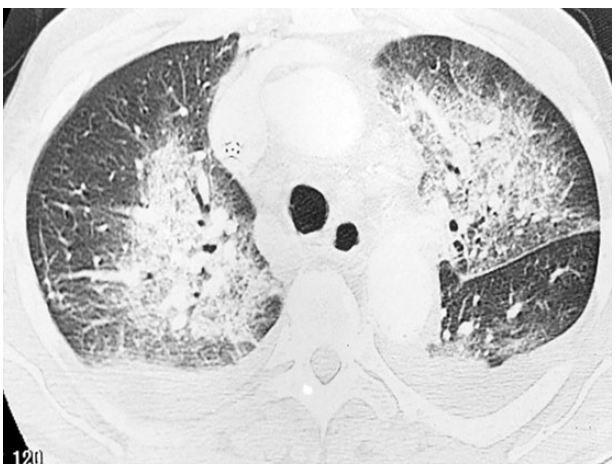

Fig 3 Pulmonary oedema.

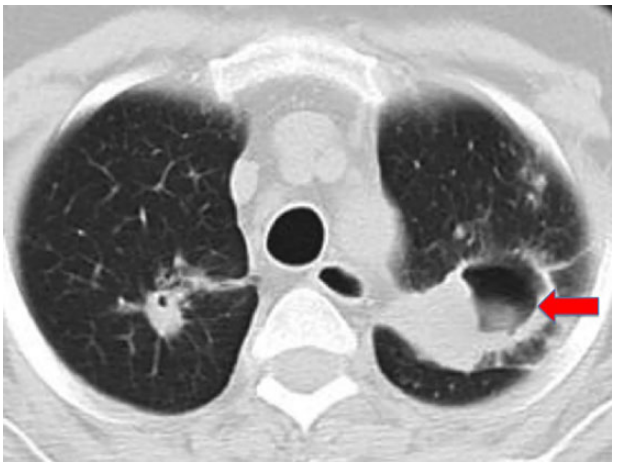

Fig 4 Left upper lobe cavitating lesion (red arrow)—differentials would include infective causes (mycobacterium or bacterial), septic pulmonary emboli, or malignancy.

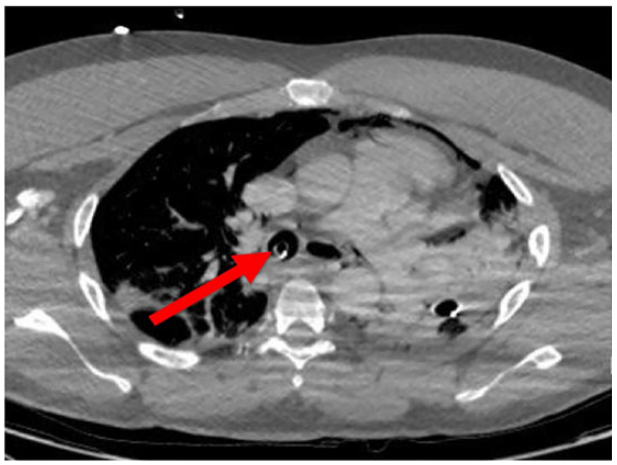

Fig 5 Right endobronchial intubation—the tracheal tube is seen within the right main bronchus (red arrow).

gravitational antero-posterior gradient. With cardiac causes of pulmonary oedema, left atrial or ventricular enlargement, such as in longstanding severe mitral regurgitation, may be seen.[1] Inspection of the parenchyma and airways should be methodical and comprehensive (Fig. 4). The airway can usually be followed from the glottis down to the segmental bronchi which may reveal structural abnormalities, masses, foreign bodies or misplaced endotracheal tubes (Fig. 5).

Pulmonary pleurae

Pleural disease encompasses pneumothoraces, effusions, infection, and tumours. Normally, the pleural fissures are seen as a distinct line, or their position could be recognized as a relatively avascular zone within the lung. In disease states, one may be able to observe pleural thickening and accumulation of fluid, such as blood or pus, in the dependent portions of the lung. CT scan will detect and may distinguish simple pleural effusion and empyema. Supine chest X-rays have an extremely low sensitivity (<25%) in detecting pneumothoraces—especially in supine patients—but these may be readily identified by CT (Figs 6–9).

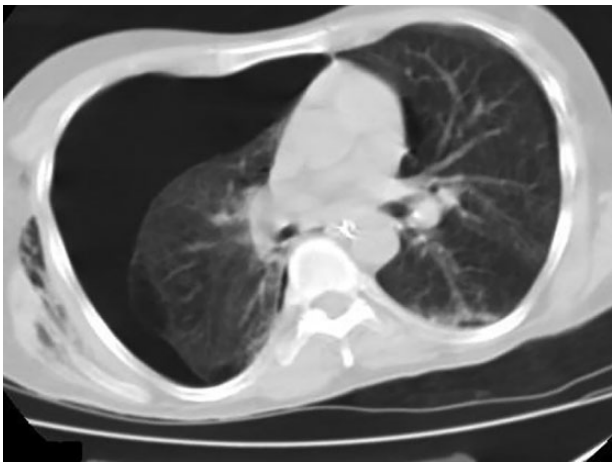

Fig 6 Left pneumothorax with mediastinal shift.

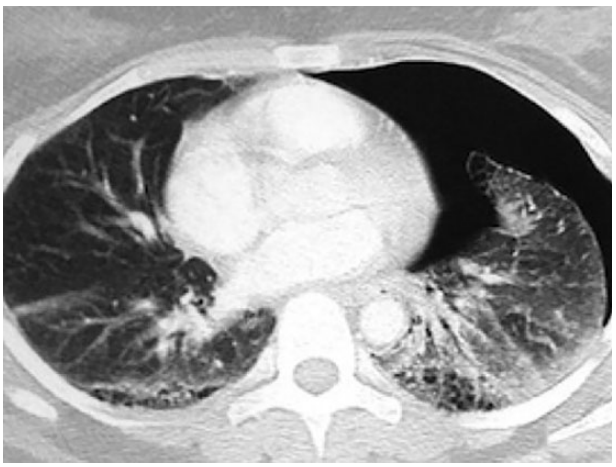

Fig 7 Left anterior pneumothorax.

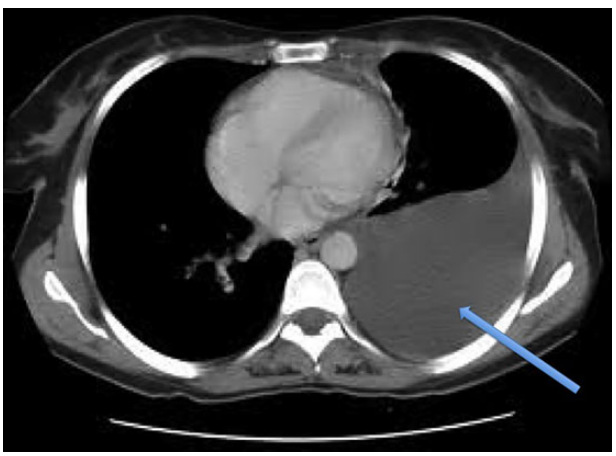

Fig 8 Pleural effusion (blue arrow) noted within the left pleural cavity.

Mediastinum

Structures contained within the mediastinum include the thymus, oesophagus, tracheo-bronchial tree, and lymph nodes.

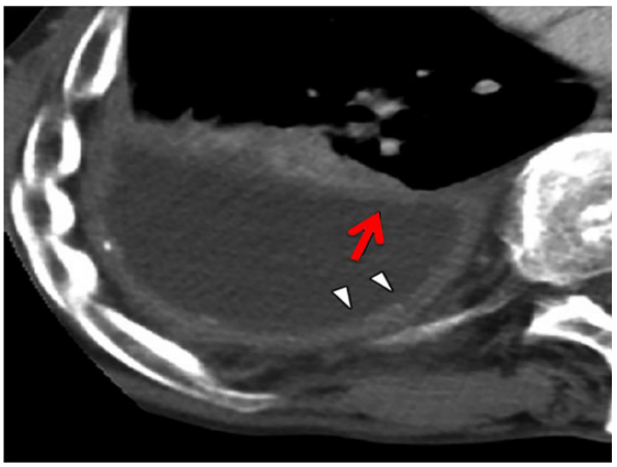

Fig 9 Split pleura sign—contrast-enhanced CT scan demonstrates thickening of the visceral (red arrow) and parietal pleura (white arrow heads) separated by fluid. The split pleura sign is seen mainly in empyema but may also be seen in haemothorax.

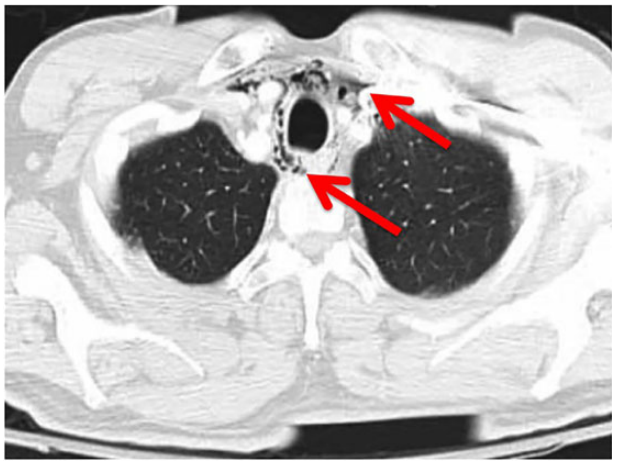

Fig 10 Pneumomediastinum—there is free gas within the mediastinum as highlighted by the arrows. This can be from either intrathoracic air (emanating from the trachea, major bronchi, oesophagus, or pleural space) or extrathoracic air (originating from the head and neck or the abdomen).

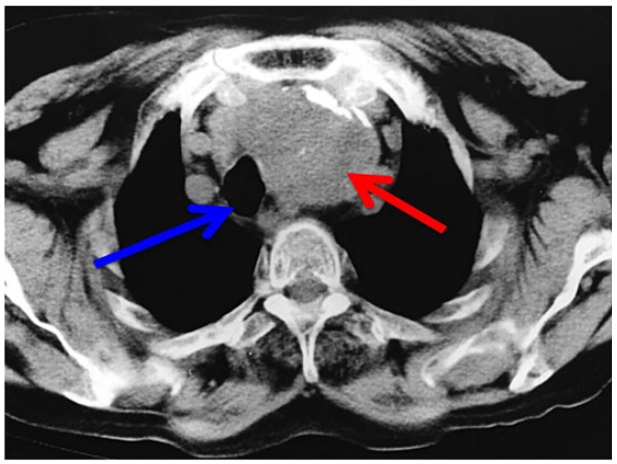

Fig 11 Retrosternal goitre (red arrow) causing significant tracheal deviation (blue arrow).

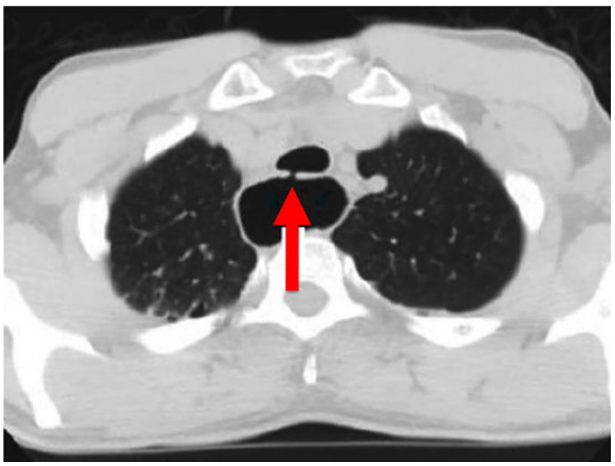

Fig 12 Tracheo-oesophageal fistula evidenced by the defect highlighted (red arrow).

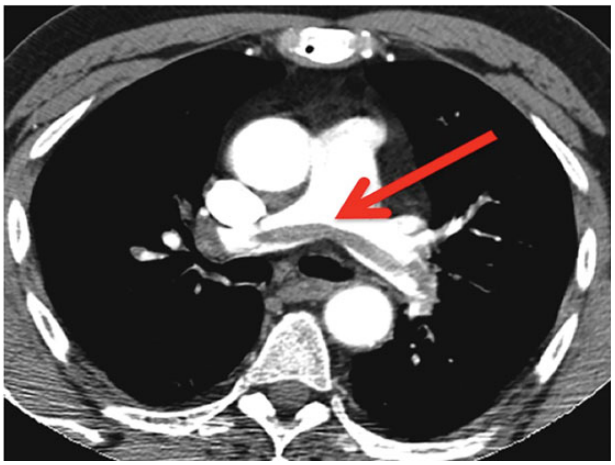

Fig 13 Saddle embolus noted within the pulmonary bifurcation.

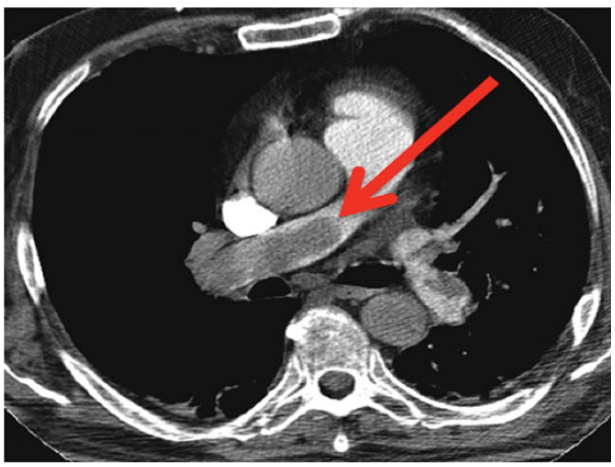

Fig 14 Embolus within the right main pulmonary artery.

Chest CT may therefore be useful in the planning of airway management such as in thyroid goitre, tracheo-oesophageal fistulae, or for double-lumen tube placement (Figs 10–12).

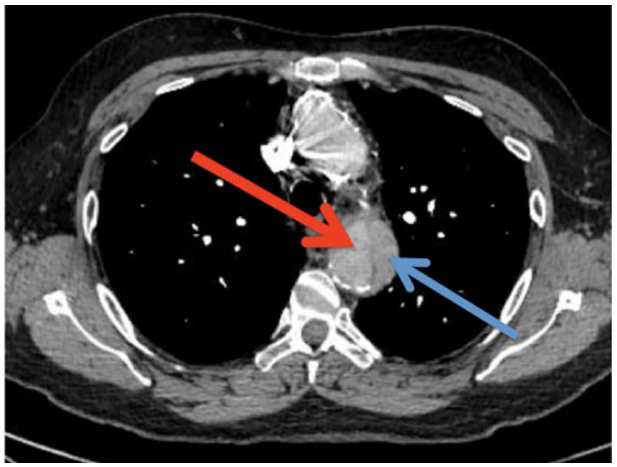

Fig 15 Descending thoracic aortic dissection with the true arterial lumen highlighted by the red arrow and the false lumen by the blue arrow.

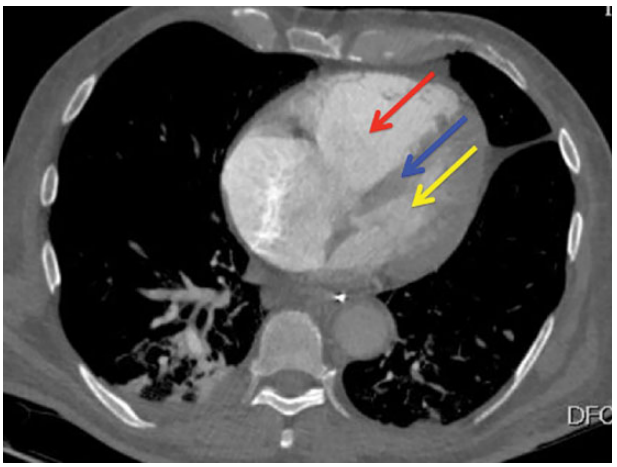

Fig 16 Dilated right ventricle (red arrow) with flattening of the interventricular septum (blue arrow) and compression of the left ventricle (yellow arrow) indicating right-sided volume or pressure overload. This picture may be seen in acute massive pulmonary embolus.

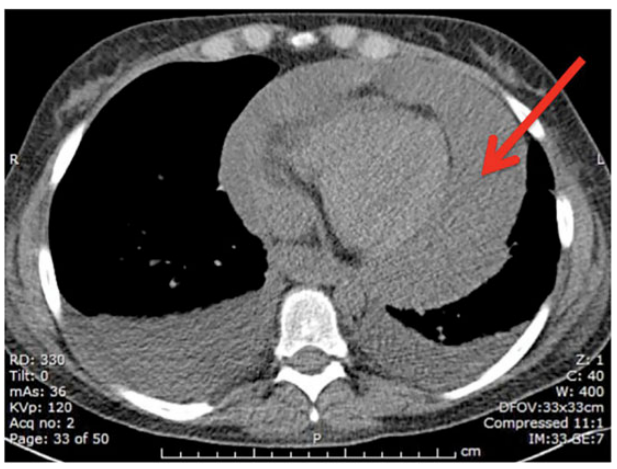

Fig 17 Large pericardial (red arrow) and pleural effusions.

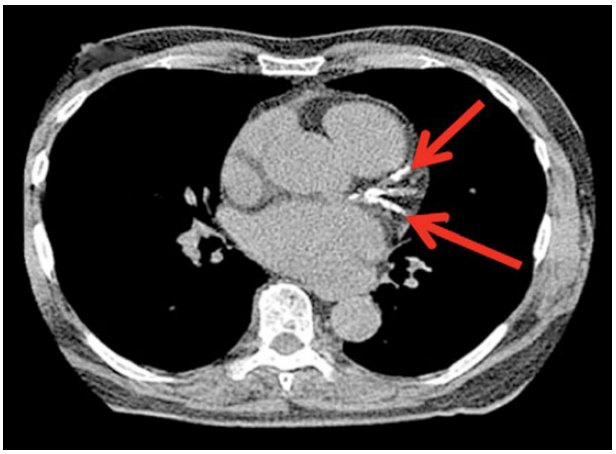

Fig 18 Coronary artery calcification—CT coronary angiogram can be used as an alternative to coronary angiography. It is utilized in those patients with a low risk of coronary artery disease and a low level of coronary artery calcification, measured using the CT calcium score, within the vessels.

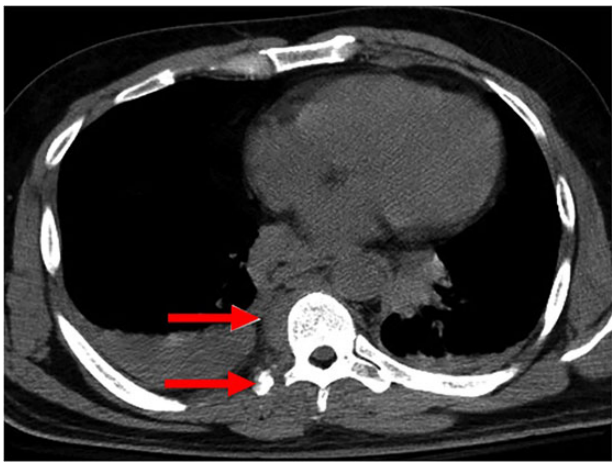

Fig 19 Large mediastinal haematoma (red arrows) from a right-sided transverse process fracture of the thoracic spine and an associated right-sided haemothorax in a trauma patient.

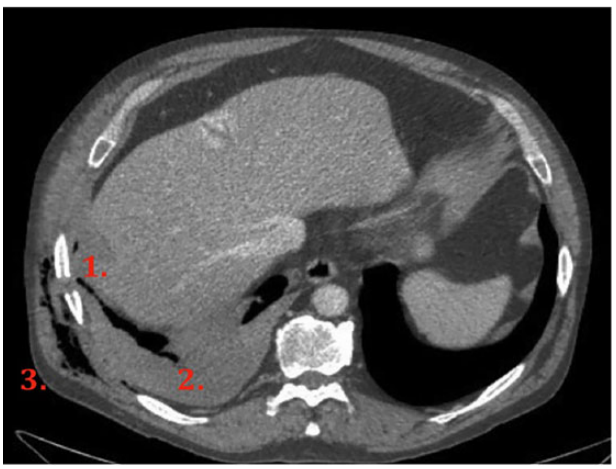

Fig 20 Fractured right 9th rib (1), haemopneumothorax (2), and subcutaneous emphysema (3).

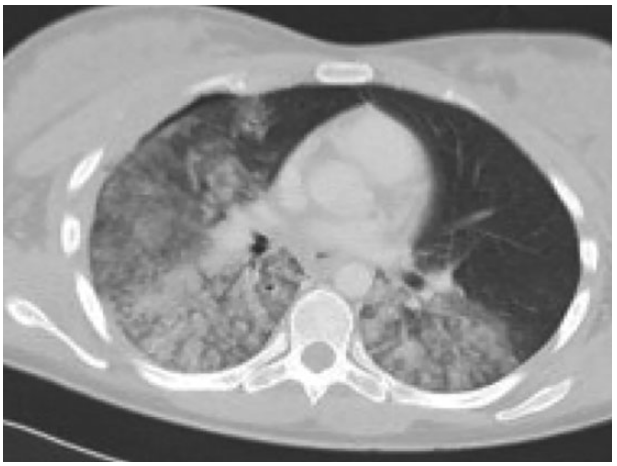

Fig 21 Lung contusions appear dense and are usually peripheral, non-segmental, and non-lobar. The increased lung density seen in the lung periphery is due to haemorrhage and oedema.

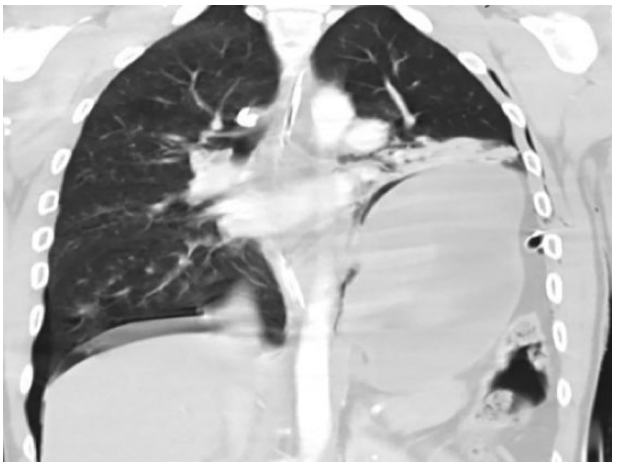

Fig 22 Left-sided traumatic diaphragmatic defect with herniation of the abdominal contents into the thoracic cavity and compression of the left lung parenchyma. There is also a right-sided pneumothorax.

Cardiovascular pathology

A contrast CT can identify vascular anomalies within the thorax, such as emboli and large vessel intimal disruption. Signs of right ventricular dilatation on CT may be used to grade the severity of pulmonary embolus (Figs 13–15).[2]

The coronary vasculature, cardiac chambers, and pericardial space can also be assessed but beat-to-beat motion leads to limitations in assessment (Figs 16–18).

Trauma

When assessing the trauma CT of the thorax, it is important to again work systematically through the components of the thoracic cavity to ensure completeness, using all three windows (lung, mediastinal, and bone) (Figs 19–22).

Summary

This article is an introduction to both clinical applications of chest CT and some of the pathology that it can be used to

diagnose. It is important for both intensive care physicians and anaesthetists to have some basic skills in the interpretation of chest CT, but close liaison with experts in the radiology department is essential.

Acknowledgement

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Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Anaesthetic implications for liver disease in pregnancy

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Key points

- The most common causes of serious hepatic complications during pregnancy are haemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome and acute fatty liver of pregnancy (AFLP).
- Management of AFLP includes assessing for encephalopathy, treating coagulopathy, and hypoglycaemia.
- Pregnant women at risk of developing hepatic failure should be referred to their nearest liver unit early.
- A lactate >2.8 mg dl^{-1} and the presence of encephalopathy are poor prognostic indicators of severe liver disease in pregnancy.
- Regional anaesthesia is suitable in mild, stable disease upon assessment of the risks and benefits to mother.

Liver disease in pregnancy is not common but can be a significant cause of maternal and fetal morbidity and mortality, frequently appearing in the triennial confidential enquiries (Table 1). Fulminant hepatic failure is very rare and poses major challenges to the anaesthetist, although it is more common to see women with varying degrees of liver dysfunction, classically considered as occurring specific to pregnancy and incidental to pregnancy.[1] The obstetric anaesthetist may be involved with the care of these women either at delivery or during an admission to the obstetric high dependency unit (HDU).

Hepatic physiological changes in pregnancy

Normal pregnancy induces physiological and biochemical changes because of an increase in oestrogen and progesterone. The upper limit of the normal range for transaminases is reduced by about 25% in all three trimesters, while alkaline phosphatase (ALP) tends to increase in the third trimester due to placental production. Changes in liver function are also present in the postnatal period with increases in both transaminases and γ-glutamyltransferase (GGT). These normal changes must be distinguished from abnormalities seen with liver disease. Clinically, it can be difficult to differentiate stigmata of liver disease, such as spider naevi and palmer erythema, as these features may be seen in healthy pregnant women in response to increased oestrogen levels.

The likely diagnosis of a woman presenting with new hepatic dysfunction in pregnancy was reported by Ch'ng and colleagues (Table 2).[2] In advanced liver disease, the liver is unable to synthesis enzymes such that a wide range of abnormal liver function may be seen at diagnosis. A differential diagnosis of liver dysfunction should always be considered as the presenting features may be confusing leading to misdiagnosis.

Hepatic disorders specific to pregnancy

Most women will present with disorders specific to pregnancy and of those women requiring intensive care admission, one study showed that 7% were related to the syndrome of haemolysis, elevated liver enzymes, and low platelets (HELLP), while 3% were due to acute fatty liver of pregnancy (AFLP).[3]

Hypertensive disorders: pre-eclampsia, eclampsia, HELLP syndrome

The high maternal mortality associated with pre-eclampsia (PET) and eclampsia is reducing. HELLP syndrome, a severe form of PET, affects 4–20% of women with PET. The condition usually presents in the late third trimester but can also present post-partum. Maternal mortality is <1%, but the condition makes up a disproportionate number of maternal deaths in the confidential

Table 1 Number of deaths related to liver disease, including hepatic complications secondary to pre-eclampsia and eclampsia 1997–2008. *One death as a result of fulminant hepatic failure secondary to hepatic rupture, despite receiving a portocaval shunt. †One death due to liver rupture secondary to a complication of type IV Ehlers–Danlos syndrome; three cases of liver failure: one caused by alcohol abuse; one due to chronic active hepatitis that had caused acquired antithrombin deficiency; and one secondary either to AFLP or to the antiretrovirals they were taking to manage HIV infection. ‡Two deaths from bleeding due to portal hypertension; one death due to a liver abscess and peritonitis; one death due to intra-abdominal bleeding, possibly due to spontaneous tearing of liver–spleen adhesions, secondary to focal nodular hyperplasia

		Triennium			
		1997–1999	2000–2	2003–5	2006–8
Maternal deaths *directly* related to pregnancy	Cause of death due to eclampsia and pre-eclampsia (overall total)	16	14	14	19
	Syndrome of haemolysis, elevated liver enzymes, and low platelets (HELLP)	5	8	8	8
	Hepatic				
	Rupture	2	0	0	1
	Failure/necrosis	0	0	1	2
	Other	5	4	3	2
	Subtotal	7	4	4	5
	Acute fatty liver of pregnancy (AFP)	4	3*	1	3
Maternal deaths *indirectly* related to pregnancy	Liver disease			4†	4‡
	Hepatic cancer		2		

enquiries. Patients should be managed in an HDU setting as the syndrome is unpredictable and can progress slowly or rapidly.

Clinical features include 'hepatic angina' (epigastric or right upper quadrant pain) that may precede deranged liver function and it is worth repeating blood tests due to this delay. Patients may present with symptoms suggestive of pulmonary embolus, that is, they may complain of chest pain and have tachypnoea due to an associated metabolic acidosis. Nausea and vomiting is common, while hypertension and proteinuria may only be mild. The low-grade haemolysis is not usually severe enough to cause anaemia. Low or decreasing platelets must be monitored. Disseminated intravascular coagulation occurs in about 20% of cases. Acute renal failure is more common in HELLP syndrome than in other forms of PET. Morbidity is often associated with acute kidney injury but is also higher the lower the platelet count. A platelet transfusion is only required if the patient is actively bleeding, to permit insertion of invasive lines or operative delivery. Other complications include placental abruption, pneumonia, liver haematoma, pulmonary oedema, and intracerebral haemorrhage.

Treatment is that for severe PET, that is, to stabilize the patient and deliver the fetus. Timing of delivery is usually a balance between reducing maternal risk with fetal risk from a premature delivery. Liver function usually recovers before the thrombocytopenia.

Hepatic haematoma or rupture are rare complications that are associated with high mortality (16–60%). Cardiovascular shock is present in half of these patients. Patients with HELLP syndrome complaining of right upper quadrant pain must be scanned (ultrasound, CT, or MRI) to make a rapid diagnosis. Treatment may involve interventional radiology or surgery.

Acute fatty liver of pregnancy

This condition is arguably a variant of pre-eclampsia tending to present in the late third trimester. AFLP is more common in women with multiple pregnancies and lower BMI, and women with the condition are more likely to have children with disorders of β-fatty acid oxidation. AFLP is of particular importance as it is associated with high maternal mortality with recent confidential enquiries reporting on average one death per year. A recent UKOSS study suggests management is improving with 60% of women admitted to an intensive therapy unit (ITU) and a mortality rate of <2% or five cases per 100 000 for their case series of 57 patients.[4] Perinatal mortality is high reported to range between 20% and 50%. As it is a rare but significant cause of maternal mortality, it is worth developing a protocol for the management of these women.

The diagnosis of AFLP is made when at least six of the clinical features described by the Swansea criteria are present in the absence of another explanation (Table 3).[2] Imaging with CT or MRI, a liver biopsy or fat stain may support this. Women will often complain of feeling unwell for a few weeks before presenting usually with non-specific symptoms such as nausea, vomiting, and malaise. There may be associated hypertension and proteinuria. Pruritus should not be confused with obstetric cholestasis. Renal impairment develops in about 90% of patients. Fulminant hepatic failure can occur and patients may develop hepatic encephalopathy, coagulopathy, and profound hypoglycaemia. Metabolic acidosis and elevated lactate are not part of the diagnostic criteria but are also important features. Pancreatitis and adult respiratory distress syndrome are other rare complications.

Delivery must be expedited once the patient is stabilized due to the high fetal mortality. Specific concerns for the anaesthetist are to correct hypoglycaemia and coagulopathy before delivery. Platelet function tends to remain stable unlike in HELLP syndrome. Uneventful regional anaesthesia has been reported and may improve hepatic blood flow, but the technique is often precluded by the presence of coagulopathy.[5]

Symptoms can deteriorate post-partum with worsening liver, renal function, and coagulopathy for 48 h and as such patients require careful management of the complications.

Obstetric cholestasis

Pregnancy can cause an impairment in the excretion of bile acids causing pruritis typically affecting hands and feet that can be severe but rarely requires admission to an obstetric HDU. Vitamin K malabsorption can occur and patients require an assessment of coagulation before proceeding with regional anaesthesia. Neuraxial opioids may worsen pruritis but this must be balanced against the need for effective pain control. Obstetric cholestasis

Table 2 Likely diagnosis in a pregnant woman with deranged liver function as modified by C Williamson OAA Maternal Critical Care: Hepatic Problems in the Maternity HDU Presentation, October 2013.[2] BA, bile acids

Likely diagnosis	Pattern of LFT changes	Estimated proportion with each diagnosis
Intrahepatic cholestasis of pregnancy	↑ ALT (×1.5–8) ↑ BA (×1.5–15) Bilirubin usually normal	17%
Pre-eclampsia with hepatic impairment	↑ ALT (×2–5) BA usually normal Bilirubin usually normal	49%
HELLP syndrome	↑ ALT (×2–30) BA usually normal Bilirubin (×1.5–10)	22%
Acute fatty liver of pregnancy	↑ ALT (×3–15) BA usually normal ↑ Bilirubin (×4–15)	4%

Table 3 Swansea criteria for diagnosis of AFLP: at least six or more of the features described must be present in the absence of another explanation[2]

Vomiting	Leucocytosis
Abdominal pain	Ascites/bright liver on US scan
Polydipsia/polyuria	Elevated transaminases
Encephalopathy	Elevated ammonia
Elevated bilirubin	Renal impairment
Hypoglycaemia	Coagulopathy
Elevated urate	Microvesicular steatosis on liver biopsy

can be a marker of other liver disease, such as AFLP or hepatitis, and therefore, the collection of symptoms should be considered.

Hepatic disorders incidental to pregnancy

Hepatic disorders that occur incidental to pregnancy are much less common than gestational-related conditions. Nevertheless, when women do present with these problems, they can be a significant cause of maternal morbidity and mortality. Pre-pregnancy counselling should be offered to all women with established severe liver disease.

Viral hepatitis

Viral hepatitis is the most common cause of hepatic dysfunction and jaundice in pregnancy worldwide. A number of viruses can cause hepatitis including hepatitis A, B, C, D, E, and G, along with herpes simplex virus (HSV), cytomegalovirus, and Epstein–Barr virus. Hepatitis B affects about 350 million people globally and nearly 5% of the population are chronic carriers of hepatitis B with one-quarter of these patients at risk of serious liver disease, including cirrhosis and hepatocellular cancer. Vertical transmission to the fetus can be reduced with active and passive immunization. Hepatitis C by comparison is less common.

The clinical features are no different from the non-pregnant population (fever, nausea, jaundice) except for those infections caused by hepatitis E and HSV that have a worse course in pregnant women. Pregnant women are more likely to develop acute viral hepatitis than non-pregnant women, with the majority of women having hepatitis E.[6] Hepatic encephalopathy and hepatorenal syndrome caused by viral hepatitis have a higher incidence during pregnancy. Fulminant hepatic failure in the context of hepatitis E is more common in pregnancy with a mortality rate of about 30%.[6] There is an associated high rate of obstetric complications with premature rupture of membranes, intrauterine growth restriction, and premature delivery and also a high rate of perinatal mortality through vertical transmission. A high viral load is associated with a worse prognosis.

Herpes simplex is a rare cause of viral hepatitis accounting for <1% of acute viral hepatitis in pregnant women. Typically, women will present with a prodromal illness of fever and respiratory or gastrointestinal symptoms. Patients can have very high levels of aminotransferases and develop a coagulopathy. Oral or genital lesions are absent in about 50% of cases. Treatment is with acyclovir and liver transplant has been reported in pregnancy.

Autoimmune hepatitis

As with many other autoimmune conditions, autoimmune hepatitis (AIH) generally improves during pregnancy. Management is with immunosuppressive therapy and it is important this is continued throughout the pregnancy. Azathioprine, cyclosporine, and tacrolimus are considered safe, whereas mycophenalate is teratogenic and contraindicated. In the absence of cirrhosis, maternal and fetal outcomes are usually favourable.[7]

Drug-induced liver injury

If the cause of liver disease is uncertain, drug-induced liver damage should always be considered. The pattern of injury may help to ascertain the causative agent. Paracetamol, methyldopa, and highly active antiretroviral therapy can cause hepatocellular damage with raised transaminases and sometimes elevated bilirubin. A cholestatic picture with raised ALP and GGT can be due to oestrogens, progesterones, amoxicillin, and psychotropic drugs. A mixed picture with both hepatocellular and cholestatic damage may implicate trimethoprim, nitrofurantoin, or carbamazapine.

Cirrhosis, portal hypertension, and oesophageal varices

Women with cirrhosis rarely become pregnant, but when they do, there is an associated high mortality rate of up to 10%. Portal hypertension worsens during pregnancy and oesophageal varices present a major risk for bleeding. This may be as high as 90% if diagnosed during pregnancy decreasing to 10% if the varices are treated beforehand with banding or sclerotherapy. Concerns over variceal rupture due to the increased venous pressure associated with straining in labour often make Caesarean section the preferred mode of delivery. Other complications

of cirrhosis in pregnancy include decompensation, ascites, hepatic encephalopathy, and maternal death. Prognosis can be predicted using a scoring system consisting of the most recent serum bilirubin, creatinine, and international normalized ratio (INR) measurements before pregnancy.[8]

Liver transplant

Women who have successfully undergone a liver transplant can be treated as healthy parturients, providing their liver function and coagulation is normal. Outcomes are generally favourable with a 70% live birth rate; however, the incidence of pre-term delivery, low birth weight, PET, and gestational diabetes are increased.[9] Immunosuppression must be continued throughout the pregnancy and the teratogenic risk appears low with commonly used agents. The potential for side-effects complicating anaesthesia such as neuropathy or electrolyte imbalance must also be considered. Pregnancy in the context of graft rejection is uncommon and outcomes are poor.

Budd–Chiari

Budd–Chiari syndrome is characterized by hepatic venous outflow obstruction and presents with ascites and hepatomegaly with or without right upper quadrant pain.

In 75% of cases is due to thrombosis for which pregnancy is a risk factor. The same prothrombotic conditions that predispose to Budd–Chiari make early fetal loss common.

Management of liver disease during pregnancy

Pregnant women with severe hepatic disease will require an individualized care plan with multidisciplinary team (MDT) input and HDU/ITU care. Liaise early with your nearest liver unit before significant complications develop. Patients must be monitored carefully for complications and part of the role of the obstetric anaesthetist is to identify patients at risk of developing fulminant hepatic failure. Low-grade encephalopathy may be subtle with irritability, forgetfulness, and sleep disturbance. In advanced liver disease, pseudonormalization of liver enzymes may occur and will not correlate with a clinical improvement. Worsening synthetic liver function may be indicated by prolonged INR, hypoglycaemia, hypoalbuminaemia, and a lactic acidosis. If a patient develops fulminant hepatic failure or encephalopathy, the nearest liver unit will need to be contacted for consideration of liver transplantation. Consider involving haematologists when treating an associated coagulopathy. *N*-acetylcysteine improves outcomes in non-pregnant acute liver failure and while its use in pregnancy is unproven, there is no evidence it causes harm. Decisions regarding timing and mode of delivery will require MDT input with a careful evaluation of the risks to the mother of continuing with the pregnancy.

Prediction of deterioration of liver function

A retrospective analysis by Westbrook and colleagues[10] of 54 intensive care admissions with severe liver disease found there were four deaths associated with the 18 admissions due to AFLP and three deaths in the subgroup of 32 patients with hypertensive-related disease. The overall survival rate for the cohort was 87%. The authors found that the best predictor for deterioration necessitating liver transplant or resulting in death were a lactate >2.8 mg dl^{-1} in combination with encephalopathy.

Specific anaesthetic considerations

The anaesthetic considerations for patients with liver disease have been described previously.[11] Advanced liver disease alters the body's handling of drugs as there are changes to protein binding secondary to reduced synthesis, impaired metabolism, and modified excretion. An associated impaired renal function may also delay excretion of drugs. These all act to prolong drug half-lives, but this has few practical implications for the conduct of general anaesthesia for Caesarean section where multiple dosing or prolonged infusions are rare. Relatively normal doses are thus required for induction of anaesthesia.

The action of thiopental is terminated by redistribution so is a safe choice as an induction agent. Propofol has normal pharmacokinetics in cirrhosis, does not reduce hepatic blood flow, and is an acceptable alternative. Succinylcholine is safe to use and prolonged neuromuscular block due to reduction in plasma cholinesterase is not clinically significant. Atracurium and cisatracurium are the non-depolarizing neuromuscular blocking agents of choice. The duration of action of rocuronium is unpredictable in the presence of liver disease and may be prolonged however can still be reversed with sugammadex. Isoflurane, sevoflurane, desflurane, and nitrous oxide are all safe and the anaesthetist should use what they are familiar with. Non-steroidal anti-inflammatory drugs are best avoided due to the high incidence of concomitant renal dysfunction and gastrointestinal bleeding. Morphine can be given in a standard dose and whilst prolonged metabolism may increase its duration of action, this should not preclude administration for treatment of breakthrough pain. Oxytocin, ergometrine, and carboprost all undergo hepatic metabolism but should be given in the standard dose for control of uterine haemorrhage. The i.m. route should be used with caution in the presence of coagulopathy. There are no contraindications to intraoperative cell salvage specific to non-oncological liver disease and its use should be encouraged where available. Infusions of propofol and fentanyl are suitable for sedation of intubated patients.

Regional anaesthesia is not contraindicated in the presence of liver disease but needs careful consideration of the risks and benefits to the mother. In rapidly progressive or advanced disease, the presence of coagulopathy in conjunction with the need for resuscitation and organ support often make regional techniques unsuitable. In mild or stable disease, laboratory tests of coagulation maybe minimally affected and mothers may be procoagulant on functional testing as demonstrated by thromboelastography (TEG). While TEG is useful for guiding administration of blood products, its role in assessment of safety for regional anaesthesia is less defined. The presence of gestational hyperfibrinogenaemia is reassuring. The decision to perform neuraxial techniques in the presence of borderline values for platelet count and INR should always be undertaken by an experienced anaesthetist who should themselves perform the procedure and may wish to consider administration of replacement blood components immediately before siting.

Epidural analgesia in labour should be reserved for mild, stable disease, so catheter removal can be undertaken without further intervention and to avoid toxicity from local anaesthetics which all undergo hepatic metabolism.

Summary

Liver disorders are a relatively rare complication during pregnancy. Patients presenting with new liver dysfunction may have non-specific symptoms and a broad differential diagnosis

should be maintained. The most common causes of serious morbidity are pregnancy-specific, namely HELLP syndrome and AFLP. Management for all hepatic disorders that require admission to HDU/ICU should involve an MDT.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Rib fracture management

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Key points

- Traumatic rib fractures are common, resulting from significant forces impacting on the chest, and are associated with significant morbidity and mortality.
- Respiratory complications, including pneumonia, are common occurring in up to 31% of patients.
- Prompt multi-modal analgesia incorporating regional analgesia, i.v. opioids, and oral adjuncts are essential to reduce complications.
- Operative fixation is indicated in some instances.

Trauma is a major cause of morbidity and mortality worldwide, and the leading cause of death in the first four decades of life. Rib fractures are very common and are detected in at least 10% of all injured patients, the majority of which are as a consequence of blunt thoracic trauma (75%) with road traffic collisions being the main cause. The remaining 25% are due to penetrating injuries. Rib fractures are associated with significant morbidity, with patients frequently requiring admission to the intensive care unit (ICU), and mortality rates as high as 33%.[1]

Pathophysiology

This morbidity and mortality associated with rib fractures is caused by three main problems: hypoventilation due to pain, impaired gas exchange in damaged lung underlying the fractures, and altered breathing mechanics.

Pain associated with rib movement reduces the tidal volume and predisposes to significant atelectasis. This can further lead to retention of pulmonary secretions and pneumonia.

An injury severe enough to fracture ribs, especially if so significant as to cause a flail segment, will invariably cause a substantial contusion to the underlying lung. The lung becomes oedematous with varying degrees of haemorrhage and necrosis. The damaged lung is poorly compliant and will not take part in gas exchange, leading to intrapulmonary shunting and a decrease in Pa_{O_2}.

In the presence of a flail segment, the generation of negative intrapleural pressure produces paradoxical movement of the flail, causing it to move inward, while the rest of the ribcage moves outward. This means that the underlying lung does not expand and as a result, the tidal volume decreases; this has been demonstrated clinically, although an increase in the respiratory rate means that Pa_{CO_2} remains normal. This inefficient breathing results in higher oxygen consumption and has been shown to reduce Pa_{O_2}.

Ventilatory management

Ventilatory management of patients with rib fractures begins with supplementary oxygen. This should be humidified to loosen secretions and help sputum clearance improving patient comfort. Nebulized saline may also help reduce sputum retention. Respiratory physiotherapy can also be useful, but the patient's ability to cooperate will often be limited by discomfort.

If, despite supplementary oxygen, the Pa_{O_2} cannot be maintained, continuous positive airway pressure can be useful. Positive pressure will act to reduce atelectasis, reduce intrapulmonary shunting, and will reduce the paradoxical movement of a flail segment, if present. However, it can be uncomfortable for the patient and may make expectoration more difficult.

Ultimately, if other measures fail, sedation and invasive ventilation may be necessary. This is extremely undesirable and should be avoided where possible in patients without other injuries. Pain management therefore plays a key role in managing these patients. Once ventilated, early weaning from a ventilator is paramount.

Rib fracture scoring

The number of ribs fractured correlates with the severity of the injury and together with age, they are the most important

determinants of morbidity and mortality.[2,3] Four or more fractured ribs are associated with higher mortality rates and seven or more have a mortality rate of 29%.[4] The presence of a flail chest alone has a reported mortality rate of 33%, since the paradoxical chest movement further inhibits effective ventilation.[5]

The elderly are particularly susceptible to rib fractures and the associated complications, with pneumonia rates as high as 31%.[6] Ribs fracture more easily and are often a result of only moderate trauma. This is as a consequence of osteoporosis, cartilage degeneration, and reduced elasticity. Respiratory mechanics are affected due to a reduced muscle mass, a weakened diaphragm, and intercostal muscles, along with a loss of alveoli. These changes culminate in a reduced lung volume, decreased lung function, and impaired gas exchange with a poor respiratory reserve. All these alterations, along with other co-morbidities, make the elderly patient with rib fractures at increased risk of hypoventilation, atelectasis, pneumonia, and subsequent ventilation.

With these factors in mind, Easter created a formula to determine which adult patients are at higher risk and therefore in need of a higher level of care:[4]

$$\text{Rib fracture score} = (\text{breaks} \times \text{sides}) + \text{age factor}$$

'Breaks' is the total number of fractures to the ribs and not the number of ribs fractured, for example, two fractures in one rib scores 2. For 'sides', unilateral fractures scores 1 and bilateral 2. Age is factored into the equation due to the aforementioned increased risk of complications, with different age groups scoring between 0 and 4.

In a study by Maxwell and colleagues,[7] they found the scoring system did not have a strong statistical validity as a predictor, but it was a useful screening tool to heighten awareness of increased risk. We have used the scoring system as a decision-making tool to decide on the appropriate level of analgesia required for each patient (Fig. 1).

Analgesia for rib fractures

The associated pain is notoriously difficult to manage, but effective analgesia started promptly prevents hypoventilation, enables deep breathing, adequate coughing with clearance of pulmonary secretions, and compliance with chest physiotherapy. Overall, this reduces secondary pulmonary complications, including atelectasis, pneumonia, respiratory failure, and the need for respiratory support.

Patients presenting to the emergency department after blunt chest wall trauma may require urgent intervention, including intubation and ventilation, but others may show little or no respiratory compromise. However, pulmonary complications often only become evident 48–72 h after the injury.

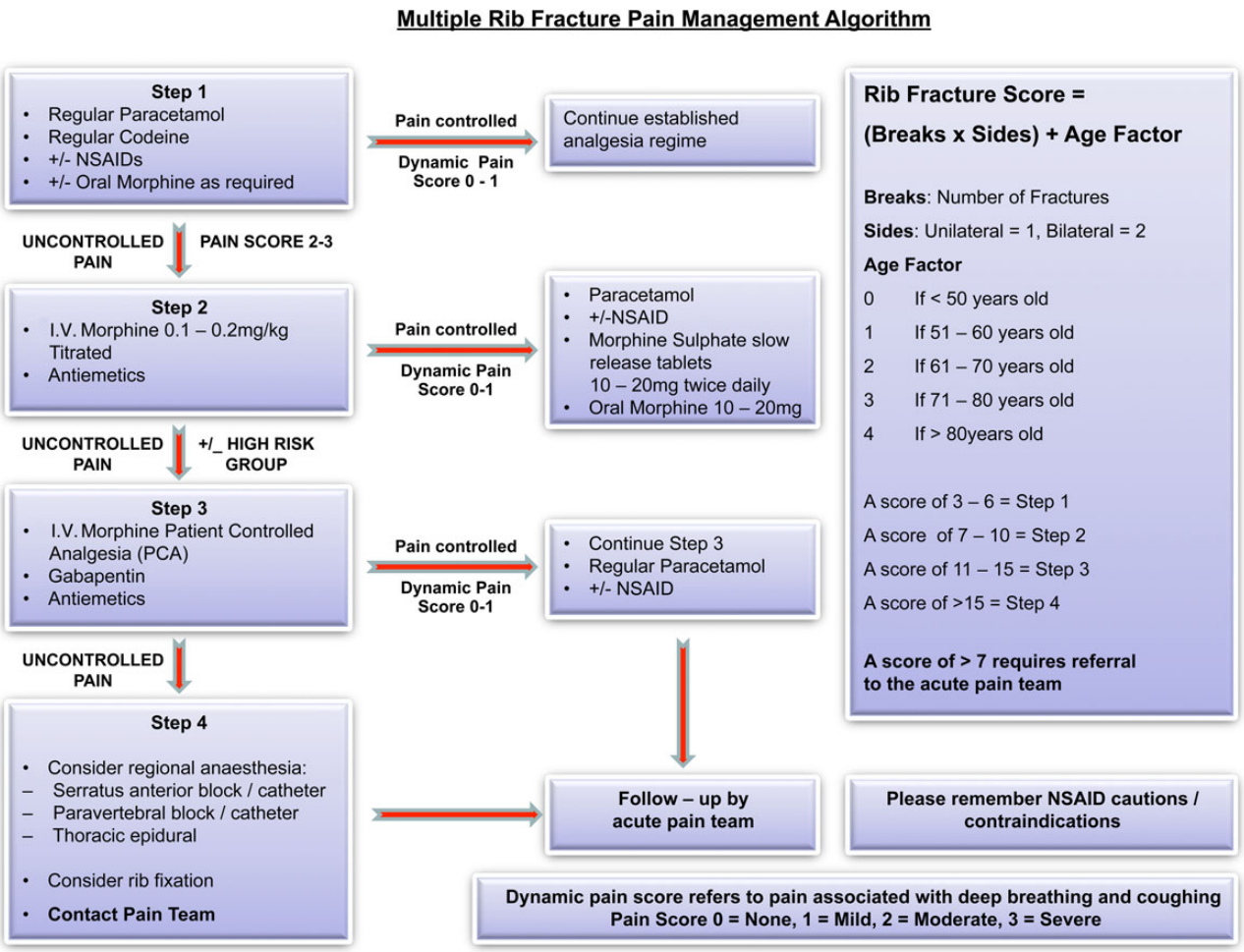

Fig 1 Multiple rib fracture pain management algorithm.

It is therefore imperative that effective analgesia is started promptly, preferably in the emergency department upon admission, not just for analgesia and patient comfort, but also to try and prevent the complications that ensue over the subsequent days.

Opioids were previously the mainstay of treatment, but with significant side-effects, including respiratory depression, depressed cough reflex, and delirium; multi-modal analgesia is now more commonly used, which incorporates regional nerve blocks and thoracic epidural analgesia.

Figure 1 is our current working rib fracture algorithm that incorporates Easter's scoring system to help identify those patients at greatest risk for morbidity and mortality and provide an analgesic pathway to most suit their needs.

Step 1: simple analgesics

The analgesia prescription for a patient should include regular simple analgesia, for example, paracetamol, a weak opioid, a non-steroidal anti-inflammatory drug (if not contraindicated), and a strong opioid for breakthrough pain. If adequate analgesia is achieved then the patient can be continued on this regime.

Step 2: opioids

If the pain is not controlled with the interventions in Step 1, then i.v. morphine can be titrated to effect with slow boluses of up to 0.1–0.2 mg kg^{-1}. Once adequate analgesia is achieved, a strong opioid (e.g. a slow-release morphine sulphate or oxycodone) can be added to the regular prescription in place of the weak opioid in Step 1. Side-effects of strong opioids such as nausea and vomiting and constipation need to be addressed with the relevant antiemetic and laxative prescriptions.

Step 3: i.v. patient-controlled analgesia

If the pain remains uncontrolled, or multiple morphine boluses are required, then a morphine i.v. patient-controlled analgesia should be started, providing the patient can successfully operate one. The addition of gabapentinoids should be considered due to their analgesic properties and opioid-sparing effects.

Step 4: regional anaesthetic techniques and operative fixation

Thoracic epidural

Epidural analgesia has become the standard of care when opioid analgesia is inadequate or initial presentation requires it, although it is an underutilized resource. Patients with higher rib fractures, multilevel or bilateral fractures, flail chests, intercostal drains, and functional respiratory compromise secondary to pain benefit most from epidurals.[8]

Multiple retrospective reviews and prospective trials have demonstrated improved pulmonary function, including tidal volume and maximal inspiratory force, enhanced analgesia, with overall better clinical outcomes when compared with treatment with systemic opioids.[8] The improved pulmonary function reduces the incidence of pneumonia, number of ventilator days, and mortality, especially those sustaining five or more rib fractures.[2,9]

When performing a thoracic epidural to provide analgesia for multiple rib fractures, the vertebral level of insertion should ideally be that of the middle fractured rib. Choice of local anaesthetic and loading doses, along with the infusion regime, are very much down to the operator and local policy. Our local policy is described in Table 1. The addition of opioids, for example, diamorphine, can prove highly beneficial, especially in an inadequate epidural. However, number of ribs fractured, co-existing injuries, age, co-morbidities, and haemodynamic status will all have an impact on the volume of local anaesthetic used, addition of opioids, and the starting rate of the infusion. Throughout the duration of the thoracic epidural, the extent of the block (both sensory and motor) need to be monitored and the patient requires regular (4 h) nursing observations, including arterial pressure and pulse and oxygen saturations.

Table 1 Local thoracic epidural regime

Loading dose	0.25% bupivacaine, 7.5–12 ml
Infusion	0.1% bupivacaine+2 μg ml^{-1} fentanyl, 5–15 ml h^{-1}
Breakthrough pain	Bolus infusion mixture, 5–10 ml, or Bolus 0.25% bupivacaine, 5–10 ml Consider bolus of epidural diamorphine 2–3 mg, once daily only

Although thoracic epidurals provide excellent analgesia for the management of rib fractures, they are limited to a certain population due to patient factors and side-effects. Many trauma patients have other injuries which contraindicate the use of epidurals, or which prevent positioning for insertion.

Contraindications[6]

Absolute

- Patient refusal
- Spinal cord injury
- Epidural or spinal cord haematoma
- Thoracic vertebral body fracture
- Spinal injury awaiting assessment
- Coagulopathy (platelets <50×10^9 $litre^{-1}$, INR>1.5)
- Local infection or sepsis
- Allergy to local anaesthetic

Relative

- Inability to position patient due to associated injuries
- Severe traumatic brain injury
- Unstable lumbar or cervical spinal fractures
- Anticoagulant therapy
- Platelet count 50–100 × 10^9 $litre^{-1}$
- Hypotension
- Hypovolaemia

There are disadvantages to thoracic epidural analgesia. They are technically challenging to insert, with a risk of dural puncture or spinal cord injury. Adverse effects include hypotension, and if opioids used, urinary retention and pruritus. Patients can develop a motor block and are unable to mobilize with an epidural *in situ*.

Paravertebral block

Injection of local anaesthetic into the thoracic paravertebral space produces unilateral sensory, motor, and sympathetic block. The spinal nerves are not initially bound by a fascial sheath, therefore enhancing uptake of local anaesthetic. The paravertebral space communicates with the epidural space medially and the intercostal space laterally, but with adequate volume, the majority spreads caudally and cranially covering at least five sensory dermatomes.[10] One catheter can cover up to

six consecutive fractured ribs, but a second catheter can be inserted for more than six levels, or for bilateral fractures, if a thoracic epidural is contraindicated. The vertebral level of insertion should ideally be at the height of the middle fractured rib.

Ensuring not to exceed the maximum local anaesthetic dose, we recommend a bolus of 40 ml of 0.25% levobupivacaine, followed by an infusion of 0.1% levobupivacaine at 5–10 ml h^{-1} via an elastomeric pump. The infusion can be continued for up to 7 days. Multiple or bilateral blocks can be performed, but ensure local anaesthetic doses are within safe limits.

Evidence suggests that paravertebral blocks are as effective as thoracic epidurals without many of the contraindications, complications, and side-effects seen with epidurals.[11] A relatively safe and technically easy procedure that is ideally performed under ultrasound guidance, it can be inserted in the unconscious patient. Sympathetic blockade is not seen when compared with thoracic epidurals due to limited epidural spread. Importantly, patients can also mobilize with a catheter *in situ*.

Contraindications

Absolute

- Patient refusal
- Allergy to local anaesthetic
- Local infection or sepsis

Relative

- Inability to position the patient
- Transverse process fractures at the level of the intended block
- Unstable vertebral fractures
- Anticoagulated patients/deranged clotting

Complications

- Failure
- Inadvertent epidural or intrathecal injection
- Epidural spread and hypotension
- Pneumothorax
- Intrapleural injection
- Vascular puncture
- Local anaesthetic toxicity

Serratus plane block

A regional anaesthetic technique first described in 2013 by Blanco and colleagues[12] for surgery performed on the anterolateral chest wall, serratus plane blocks aim to provide anaesthesia of the hemithorax. It has been used in patients with rib fractures as an alternative to thoracic paravertebral blocks and thoracic epidurals.[13,14]

Anatomy

The serratus anterior muscle originates on the anterior surface of ribs 1–8 and inserts on the medial border of the scapula. A potential space exists both superficial and deep to the serratus anterior muscle. The latissimus dorsi muscle lies superficial to serratus anterior, with the ribs and thoracic intercostal nerves lying deep to, but also piercing the serratus muscle. This therefore enables the thoracic intercostal nerves to be blocked when injecting local anaesthetic in the potential space around the serratus muscle, providing analgesia to the anterolateral part of the thorax, with paraesthesia from T2 to T9.[12] Local anaesthetic can be infiltrated either superficial or deep to serratus anterior, but Blanco and colleagues found a greater duration of action from superficial placement.

Indications/contraindications

Suitable for all rib fractures, there are very few contraindications to inserting a serratus plane block, with patient refusal, allergy to local anaesthetics, and local infection the only standard absolute reasons.

Relative contraindications are associated with distorted anatomy making landmarks difficult to identify by ultrasound, for example, surgical emphysema, intercostal drain placement, and previous surgery at the insertion site.

Recommended technique

Preparation

Informed consent should be obtained from the patient, and the block performed with a trained assistant in an area where full resuscitation equipment is available. Standard non-invasive monitoring should be applied and an i.v. cannula inserted. Aseptic precautions should be maintained throughout the procedure.

Procedure

As described by Blanco and colleagues, the block is performed with the patient in the supine position and the arm abducted. Using a high-frequency linear ultrasound probe set between 6 and 13 MHz, place the probe in the sagittal plane and identify the fifth rib in the mid-axillary line. Latissimus dorsi and serratus anterior muscles are now easily identifiable overlying the fifth rib (Fig. 3). The planes can be found between a depth of 1–2 cm from the skin, with the thoracodorsal artery passing in the superficial plane to serratus anterior (Fig. 2).

After local anaesthetic infiltration, using a 50 mm 18 G Tuohy catheter needle, insert the needle in-plane superficial (recommended and demonstrated in Figs 3 and 4) or deep to the serratus anterior muscle (Figs 5 and 6). Inject local anaesthetic and confirm good spread between latissimus dorsi and the serratus muscle, or deep to serratus. Ensuring not to exceed the maximum local anaesthetic dose, we recommend a bolus of 40 ml of 0.25% levobupivacaine. Immediately insert a catheter 2–3 cm into the space, tunnel, and secure in place. Correct catheter placement can be confirmed by demonstrating further local anaesthetic spread under ultrasound visualization. Commence an infusion of local anaesthetic, again weight dependent, but 0.1%

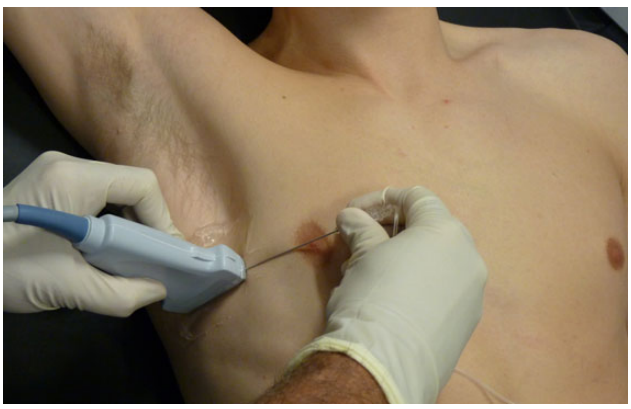

Fig 2 Ultrasound probe and needle orientation.

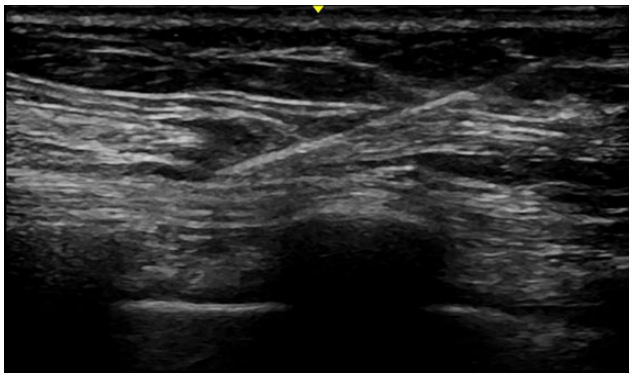

Fig 3 Ultrasound image of a superficial serratus plane block.

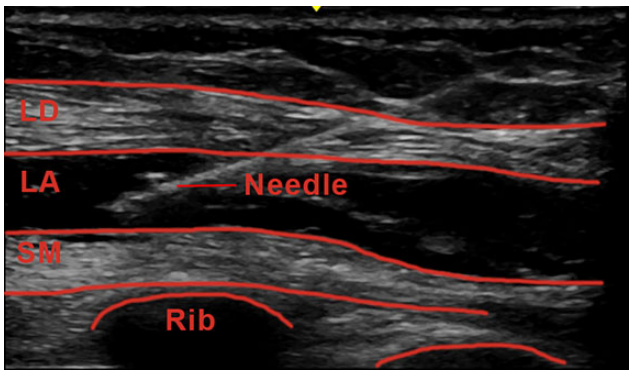

Fig 4 On injection of local anaesthetic (LA), good separation is demonstrated between latissimus dorsi (LD) and the serratus muscle (SM).

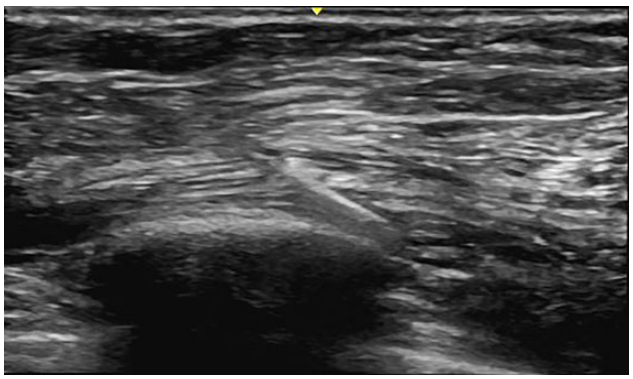

Fig 5 Ultrasound image of a deep serratus plane block.

levobupivacaine at 5–10 ml h^{-1} via an elastomeric pump is optimal, and can be kept running for up to 7 days if no signs of infection. Bilateral blocks can be performed, but ensure the maximum dose of local anaesthetic is not exceeded.

Static and dynamic pain scores, along with incentive spirometry and patient satisfaction, can confirm the adequacy of the block.

Advantages

- Technically easy and superficial block
- Performed with patients supine, therefore particularly useful when other injuries prevent patients rolling laterally or sitting to perform either a thoracic epidural or paravertebral block

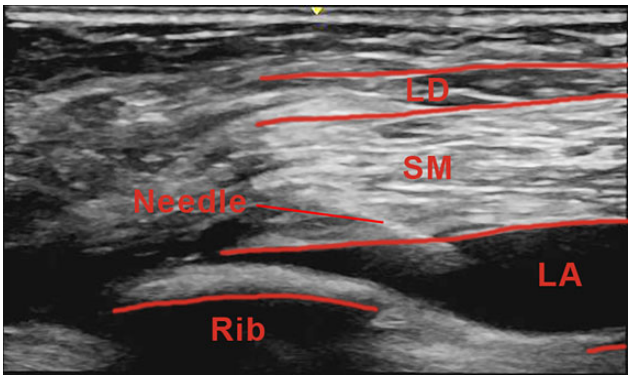

Fig 6 Good spread of LA is seen deep to SM, above ribs 4 and 5.

- Suitable for rib fracture patients with associated spinal trauma or head-injuries where paravertebral and epidural blocks are contraindicated
- Can be inserted in anticoagulated or thrombolysed patients
- Patients can mobilize with catheter *in situ*

Complications

- Pneumothorax
- Vascular puncture
- Nerve damage
- Failure/inadequate block
- Local anaesthetic toxicity
- Infection

Interpleural block

This has fallen out of favour as it provides suboptimal pain relief for patients with rib fractures.[11] Local anaesthetic can be injected via the chest drain, however, before absorption, it can drain out via the chest tubing. Large volumes are required and with rapid absorption, local anaesthetic toxicity is a risk. The distribution of the local anaesthetic is influenced by gravity and therefore patient positioning may prevent the correct intercostal nerves being targeted leading to an inadequate block. Blood or fluid in the pleural cavity will also dilute the local anaesthetic. Occluding the drain before and after injection can cause its own complications and may not be clinically safe. Infection can be introduced into the pleural cavity and an empyema can develop.

Intercostal block

Although correctly placed intercostal blocks can be very effective, providing effective analgesia for 4–24 h, reducing morbidity and length of stay, they involve multiple injections with a risk of pneumothorax and intravascular injection with every injection (http://www.trauma.org/archive/thoracic/CHESTflail.html).[11] The risk of local anaesthetic toxicity increases with every injection due to its rapid absorption. Palpation to determine the appropriate site for injection causes patient discomfort. Catheters have been placed in the intercostal space which provides spread of local anaesthetic to adjacent intercostal spaces providing analgesia to several dermatomes.

Operative fixation

Management of rib fractures by stabilizing the chest has been around for centuries, but has gone in and out of fashion.

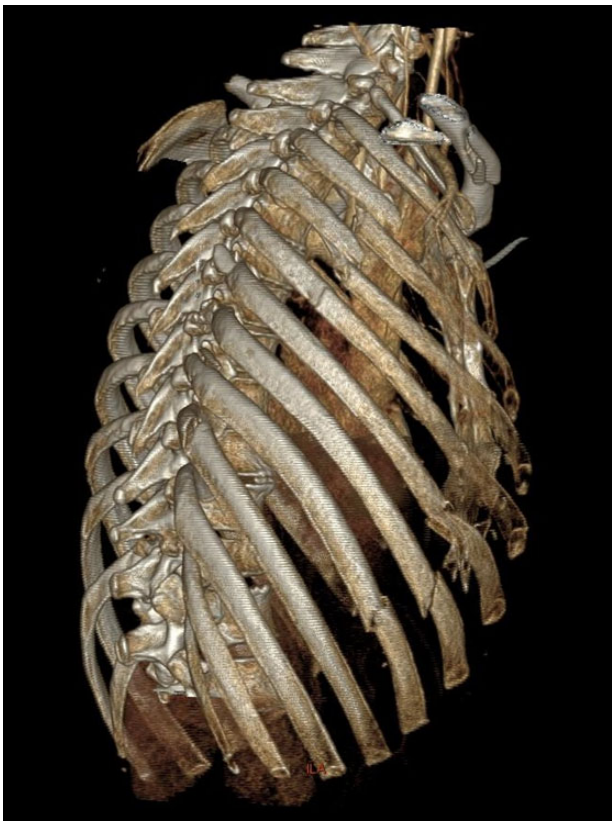

Fig 7 Three-dimensional CT reconstruction showing unilateral fractures to ribs 2–8 on the right, with a flail segment involving ribs 4–8.

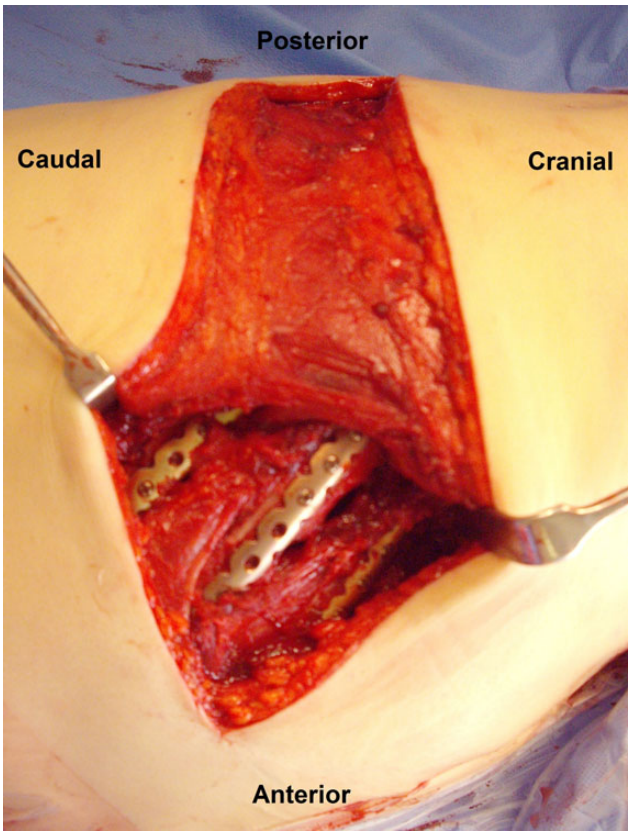

Fig 8 Subsequent operative fixation of ribs 4–8 with plates and locking screws.

However, more recently, rib fracture fixation has made a resurgence with evidence suggesting it is beneficial for a certain group of patients. Intubated patients with a flail chest, respiratory failure, and prolonged ventilation, or non-intubated patients with a flail with deteriorating pulmonary function, are now considered for operative fixation.[15] The aim is to stabilize the chest to restore pulmonary mechanics and reduce pain. Other indications include rib fractures refractory to conventional pain management, rib fracture non-union, and during a thoracotomy performed primarily for other injuries.[5]

Surgical repair is technically challenging due to the nature of the ribs. They have a conical and twisted shape with a thin cortex and often fracture obliquely. This results in poor cortical screw purchase. Individual ribs do not tolerate stress well and each fixation must tolerate the repetitive movement of at least 20 000 breaths day^{-1}.

A 3D CT reconstruction of the chest wall is necessary before surgery to plan the incision (Fig. 7). Although the skin incision is very similar to that of a thoracotomy, most centres have started using a muscle-sparing approach which avoids incising the latissimus dorsi muscle. Some centres are also practising minimally invasive surgery where small incisions are strategically placed to provide access to at least two or more rib fractures. Ultrasound can be used to mark the fracture site and subsequent incision before the operation.

The procedure is usually performed in the lateral position under general anaesthesia with a thoracic epidural, paravertebral, or serratus block for postoperative analgesia. Standard monitoring is applied as per AAGBI guidelines with invasive monitoring in the form of an arterial line, and a central venous catheter if required. The use of a double-lumen tube enables inspection of the lung at the time of rib fracture fixation, although not all centres opt for this. Intercostal drains inserted before the operation in close proximity to the surgical incision should be removed to prevent infection.

Anterior, anterolateral, and posterolateral rib fractures can be fixed with plates, although intramedullary splints are available for posterior fractures. The first aim of fracture fixation is to address the flail segment. Most surgeons aim to fix both ends of the flail segment. However, some posterior rib fractures are difficult to access without causing significant muscle stripping.

Once accessed, the fracture is reduced and a plate of appropriate length, usually 6–10 holes, is applied. The majority of plates are pre-contoured for different rib levels, although sometimes additional moulding is required. Two to three locking screws are then inserted on either side of the fracture (Fig. 8). At all times, the underside of the rib is avoided to prevent damage to the intercostal neurovascular bundle. No imaging is required intraoperatively, but an AP X-ray should be performed after the operation to demonstrate fracture fixation and lung expansion. A separate chest drain is inserted before closure.

In 2010, the National Institute for Health and Clinical Excellence (NICE) produced guidance on the insertion of metal rib reinforcements to stabilize a flail chest wall. Recognizing the evidence for operative stabilization lacks quantity, but consistently shows efficacy, NICE recommend a multidisciplinary approach to patient selection by critical care specialists, chest physicians, and thoracic surgeons, with appropriate training and experience.

Randomized control trials report significantly reduced rates of pneumonia in surgical fixation compared with those treated with mechanical ventilation. Overall critical care stay is less with fewer ventilator days, and reduced mortality.[1,16] Studies show opioid requirements are reduced and operative fixation is cost-effective.[1]

Chronic pain and disability

Chronic pain and disability are significant contributors to diminished quality of life after trauma. Little is known about the prevalence of chronic pain and disability after rib fractures, but a recent prospective follow-up of 203 patients with rib fractures found a prevalence of chronic pain of 22% and disability of 53%.[17] Acute pain intensity in the first 2 weeks predicted chronic pain; however, associated injuries, bilateral fractures, number of fractures, and injury severity score were not predictive of the development of chronic pain. Only acute pain intensity and bilateral fractures predicted disability. With operative fixation, forced vital capacity at 12 months is greater, more people return to work, and the incidence of chronic pain reduced.[15]

Conclusion

Rib fractures are common in trauma and associated with significant morbidity and mortality. The key to managing these patients is early recognition of those at risk of deterioration, prompt and effective analgesia, early mobilization, and respiratory support where indicated. This will enable deep breathing, coughing, and compliance with chest physiotherapy to try and prevent the associated complications that ensue.

Local pathways and scoring systems help to determine an appropriate initial analgesic plan with subsequent options if suboptimal. Regional analgesia should be considered, and although thoracic epidurals have previously been the gold standard, ultrasound-guided paravertebral and serratus plane blocks are possible alternatives. Operative fixation plays a role in patients with a flail chest and respiratory compromise, especially those un-intubated with deteriorating pulmonary function, or if there is difficulty weaning patients from a ventilator. Overall, results demonstrate reduced morbidity and mortality.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Hypertension in pregnancy

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Key points

- Chronic hypertension predisposes adverse pregnancy outcomes in the mother and baby.
- Blood pressure control is essential for prevention of intracerebral haemorrhage in pre-eclampsia.
- Magnesium sulphate is first-line therapy for prevention and treatment of eclamptic seizures.
- Haemolysis, elevated liver enzymes, and low platelets (HELLP) is a severe form of pre-eclampsia that often results in significant maternal morbidity and mortality.
- Echocardiography is emerging as a useful tool for the management of pre-eclamptic patients.

Hypertensive diseases in pregnancy comprise chronic hypertension, gestational hypertension, and pre-eclampsia. They are a significant cause of morbidity and mortality in the UK and worldwide, with effects on both mother and baby. Pre-eclampsia in particular results in major perinatal, and long-term, complications. In the most recent triennial report 2009–2012,[1] it was responsible for the death of 9 women, making it the fourth leading direct cause of maternal death. Many deaths are related to poor management of severe hypertension and eclampsia where the anaesthetist can have a significant role. Fetal implications include increased incidence of placental abruption, preterm delivery, and fetal growth restriction where the anaesthetist must provide timely safe anaesthesia to improve outcomes. These risks are not exclusive to pre-eclampsia, and it has become clear that pre-existing chronic hypertension is also associated with adverse pregnancy outcomes. This review will describe the pathophysiology, diagnosis, management, and recent advances in care of these patients with the primary focus on pre-eclampsia, where the anaesthetist is most involved.

Chronic and gestational hypertension

Chronic hypertension is defined as hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) present at the booking visit or before 20 weeks' gestation, or if the patient is already taking antihypertensive medication. It complicates between 1 and 5% of pregnancies. With advances in fertility techniques, increasing maternal age, and increasing obesity, this percentage is expected to increase. Its importance cannot be underestimated with a recent meta-analysis[2] demonstrating increased relative risk for numerous adverse outcomes; superimposed pre-eclampsia, preterm delivery, Caesarean section, low birth weight, admission to neonatal unit, and perinatal death. Gestational hypertension is hypertension presenting after 20 weeks' gestation without significant proteinuria and affects ~6% of pregnancies. Blood pressure should be controlled to <150/100 mm Hg in both groups (unless there is end-organ damage where target blood pressure is <140/90 mm Hg), and oral labetalol is the first-line therapy if the mother can tolerate it. Alternative agents include nifedipine and methyldopa. Women with pre-pregnancy hypertension already taking antihypertensives should be switched to one of these agents as early as possible, preferably pre-conception, because of their improved safety profile in pregnancy. Renal function should be regularly monitored with quantification of any proteinuria using spot protein:creatinine ratio. Delivery is not usually indicated until 37 weeks' gestation provided blood pressure is <160/110 mm Hg, the fetus is growing well, and the mother does not get superimposed pre-eclampsia. Timing of delivery often requires multidisciplinary discussions between obstetricians, anaesthetists, and neonatologists to optimize fetal maturity whilst taking into account fetal growth and maternal morbidity, such as renal dysfunction.[3]

Pre-eclampsia

Definition and diagnosis

Pre-eclampsia is defined as hypertension presenting after 20 weeks' gestation with significant proteinuria (spot urinary

protein:creatinine ratio >30 mg mmol^{-1} or a 24-h urine collection with >300 mg protein).[3] Proteinuria signifies endothelial damage characteristic of pre-eclampsia. The dependence of normal kidney function on adequate blood flow and selective glomerular filtration makes it vulnerable to these endothelial changes. Pre-eclampsia can be superimposed on women who have hypertension or proteinuria before 20 weeks' gestation and diagnosis can be more problematic in these patients. Worsening disease may be indicated by a sudden increase in blood pressure, new onset or worsening proteinuria, or evidence of involvement of other organ systems such as elevated liver enzymes or thrombocytopenia.[4] Pre-eclampsia is classified as severe when there is proteinuria with severe hypertension (≥160/100 mm Hg) or mild to moderate hypertension (140/90–159/109 mm Hg) with any of the features listed in Table 1.

Risk factors

Numerous risk factors for the development of pre-eclampsia have been identified including nulliparity, previous pre-eclampsia, multiple pregnancy, maternal age >40 yr, BMI ≥35 kg m^{-2} before pregnancy, family history of pre-eclampsia, pre-existing diabetes, hypertension, renal disease, antiphospholipid syndrome, and an inter-pregnancy gap of >10 yr.[5] A genetic contribution has been hypothesized but there is, as yet, no evidence to support the role of any particular gene.[4]

Pathogenesis

Several pathogenic mechanisms for pre-eclampsia have been proposed. It is generally accepted that impaired trophoblastic cell invasion results in failure of spiral artery dilatation, leading to placental hypoperfusion, and consequently hypoxia. In response to hypoxia, the placenta releases cytokines and inflammatory factors into the maternal circulation triggering endothelial dysfunction. The subsequent increase in vascular reactivity and permeability, and coagulation cascade activation, results in organ dysfunction.[4]

Prevention

The significant morbidity caused by pre-eclampsia has led to considerable interest in preventative measures. Progress has been hindered by an incomplete understanding of pathogenesis, but some evidence exists in favour of a number of interventions.

Aspirin

The National Institute for Health and Clinical Excellence recommends 75 mg aspirin daily from 12 weeks' gestation until 36–37 weeks' gestation for any woman with one high, or two or more moderate, risk factors (Table 2).[3] This is based on the results of a meta-analysis showing a 50% relative risk reduction for the development of pre-eclampsia in high-risk women (identified by abnormal uterine artery Doppler in the first trimester of pregnancy) who started taking aspirin before 16 weeks' gestation.[6] The proposed mechanism of action is a reduction in platelet production of thromboxane relative to prostacyclin and hence reduced vasoconstriction.

Calcium

In populations with low dietary calcium, calcium supplementation can reduce the incidence of pre-eclampsia. Owing to the rarity of calcium deficiency in the developed world, calcium supplementation is not currently recommended in the UK despite the low risk of harm.

Bariatric surgery

Obesity is strongly associated with hypertensive disorders of pregnancy, and there is evidence that bariatric surgery decreases the incidence of hypertension in pregnancy in obese women by ~75%.[7] It is uncertain whether weight loss by other methods can confer similar risk reductions.

Folic acid

The ongoing Folic Acid Clinical Trial (FACT) is a phase III, double-blinded, randomized, placebo-controlled trial assessing the effect of high-dose folic acid (4 mg day^{-1}) on the incidence of pre-eclampsia in women deemed high risk. It is based on several cohort studies that have suggested a protective effect. Recruitment is attributable to finish in 2015.

Management

Blood pressure

The principal aim of blood pressure control in pre-eclampsia is the prevention of intracerebral haemorrhage. It is recommended to aim for systolic and diastolic blood pressures of <150 and 80–100 mm Hg, respectively, although rapid reductions in blood pressure may result in complications to both mother and fetus. The rate of reduction should be ~1–2 mm Hg every minute. Oral labetalol is often first choice, but alternatives include nifedipine and methyldopa. Nifedipine should be used cautiously with magnesium sulphate as a result of the possible toxic effects of a calcium-channel blocker with magnesium therapy. In cases of severe hypertension, oral therapy may be inadequate, and more reliable control achieved with i.v. labetalol or hydralazine. Hydralazine can cause maternal tachycardia and sudden hypotension, and it may be necessary to cautiously preload women with 500-ml crystalloid solution. Once the mother requires

Table 1 Features of severe pre-eclampsia[3]

Severe headache
Visual disturbance such as flashing lights or blurring
Vomiting
Subcostal pain
Papilloedema
Clonus (≥3 beats)
Liver tenderness
Thrombocytopenia (<100×10^9 litre^{-1})
Abnormal liver enzymes (asparate transaminase or alanine transaminase >70 iu litre^{-1})
HELLP syndrome (haemolysis, elevated liver enzymes and low platelets)

Table 2 High and moderate risk factors for development of pre-eclampsia[3]

High risk factors	Moderate risk factors
Hypertensive disease in previous pregnancy	First pregnancy
Chronic kidney disease	Age ≥40 yr
Autoimmune disease (e.g. antiphospholipid syndrome)	Pregnancy interval ≥10 yr
Type 1 or 2 diabetes mellitus	Family history of pre-eclampsia
Chronic hypertension	Multiple pregnancy

i.v. antihypertensive therapy with fluid restriction, the option of invasive blood pressure monitoring in a high dependency area should be considered, and also regular urine output monitoring and 6-hourly blood tests to monitor platelet count, renal function, and liver enzymes. Continuous fetal monitoring should be carried out until blood pressure is stable.

Seizures

Eclamptic seizures are a significant cause of mortality in pre-eclampsia, and are associated with intracerebral haemorrhage and cardiac arrest. Magnesium sulphate is first-line therapy for treatment and prevention of eclamptic seizures, and has been shown to reduce the incidence of seizures in patients with severe pre-eclampsia by >50%. The Collaborative Eclampsia Trial recommended a loading dose of 4–5 g over 5 min followed by an infusion of 1 g h^{-1} for 24 h through a volumetric infusion pump. Recurrent seizures are treated with further 2 g boluses. Despite some antihypertensive effects, magnesium sulphate does not normally adequately lower blood pressure in pre-eclampsia, and is therefore not recommended as the sole antihypertensive agent, although the additive effect of repeated bolus doses of magnesium sulphate with recurrent seizures can cause significant hypotension. Where preterm delivery within the next 24 h is anticipated, magnesium sulphate provides the additional benefit of rapid fetal neuroprotection and reduced risk of cerebral palsy.[8] Patients receiving magnesium sulphate should be regularly monitored for evidence of toxicity, as indicated by diminished reflexes, low respiratory rate or low oxygen saturations, and progressive paralysis. Renal impairment with low urine output may predispose to magnesium toxicity, and if suspected administration should cease and serum magnesium levels be checked. The treatment for magnesium toxicity is calcium gluconate (10 ml of 10% solution over 10 min). Magnesium sulphate causes a reduction in the normal sympathetic tone of the fetus, reducing variability in the cardiotocograph, and making interpretation difficult for the obstetrician.

Pulmonary oedema

Acute pulmonary oedema occurs in up to 3% of cases of pre-eclampsia with the potential to cause maternal mortality. The majority of cases (~70%) occur after delivery and are often associated with heart failure and excess fluid administration. Consequently, fluid restriction to 80 ml h^{-1} (oral, drugs and i.v. fluid combined) is recommended for women with severe pre-eclampsia, provided there are no ongoing fluid losses.[3] Diagnosis is based on clinical findings, chest radiograph (even if the mother is still pregnant), and in severe cases an urgent echocardiogram to assess ventricular function. First-line treatment is with oxygen, fluid restriction, furosemide boluses of 20–60 mg, and urgent delivery of the fetus. Sufficient oxygen delivery may require non-invasive or invasive ventilatory support. The role of morphine (in boluses of 2–5 mg) is now more controversial, with the potential benefits of mild systemic venodilatation, reduced anxiety and dyspnoea potentially outweighed by reduced ventilatory drive. In severe cases, usually associated with renal impairment, the response to furosemide may be inadequate. In these rare circumstances, glyceryl trinitrate may be required,[9] and should be given as an infusion starting at 5 μg min^{-1} increased as necessary every 3 to 5 min to a maximum of 100 μg min^{-1}.

Haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome

Haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome is diagnosed by the presence of elevated liver enzymes (aspartate transaminase >70 iu $litre^{-1}$, or alanine transaminase >70 iu $litre^{-1}$, or gamma-glutamyltransferase >70 iu $litre^{-1}$), thrombocytopenia (platelet count <100×10^{-9} $litre^{-1}$), and either hypertension, proteinuria or haemolysis (lactate dehydrogenase >600 iu $litre^{-1}$, total bilirubin >20 mmol $litre^{-1}$, or on blood film). A variant without haemolysis is known as elevated liver enzymes, low platelets (ELLP) syndrome. In the UK, HELLP and ELLP have incidences of 1.6 and 1 per 10 000 pregnancies respectively, and are associated with significant maternal and fetal morbidity. Although the most common complaint is epigastric or right upper quadrant abdominal pain, patients are often very unwell at presentation with disseminated intravascular coagulation (DIC), placental abruption, or hepatic haematoma, rupture or infarction. In the presence of severe maternal disease or non-reassuring fetal parameters, urgent delivery is indicated. Where a delay in delivery may be beneficial (e.g. administration of corticosteroids to aid fetal lung maturation) a delay of up to 48 h may be appropriate, but it should be borne in mind that disease progression is often extremely rapid. The thrombocytopenia, in particular, can be rapidly progressive and a full blood count within the preceding 2 h is vital before performing central neuraxial blockade. The presence of thrombocytopenia or rapidly decreasing platelet count, and risk of DIC often precludes the use of regional techniques, and so general anaesthesia is often required should operative delivery be indicated. Additionally, these patients have a relatively high incidence of eclampsia, and so magnesium sulphate should be strongly considered.[10]

Analgesia

The majority of women with severe pre-eclampsia will benefit from neuraxial analgesia in labour, through prevention of the hypertensive response to pain, and the resulting sympathetic block contributing to the overall anti-hypertensive strategy. In addition, an indwelling epidural catheter enables the provision of surgical anaesthesia should operative delivery become necessary. The contraindications specific to pre-eclampsia are thrombocytopenia, rapidly decreasing platelets, or more rarely disseminated intravascular coagulation. For this reason full blood count and coagulation studies are required within 6 h in all cases, and 2 h in severe cases, before performing central neuraxial blockade. It has been suggested that central neuraxial blockade should not be performed below a platelet count of 75–100×10^{-9} $litre^{-1}$ with extra care required for rapidly decreasing counts. Pre-loading with fluid is not usually required for pre-eclamptic patients receiving low-dose central neuraxial analgesia but careful blood-pressure monitoring with small doses of a vasopressor may be necessary, as sudden decreases in blood pressure can be poorly tolerated by the fetus. When central neuraxial blockade is contraindicated, i.v. opioids provide an appropriate alternative, with remifentanil patient controlled analgesia gaining popularity. Postpartum analgesia will vary depending on mode of delivery but may include intrathecal or i.v. opioids, abdominal wall nerve blocks or wound infiltration, and simple analgesics such as paracetamol. Non-steroidal anti-inflammatory drugs should be avoided until a postpartum diuresis with normal renal function is confirmed.

Anaesthesia

Central neuraxial blockade is the anaesthetic technique of choice for the majority of pre-eclamptic women requiring operative delivery. Spinal, epidural and combined spinal-epidural are all used successfully with no evidence in favour of one particular technique. Hypotension secondary to regional anaesthesia, although less common than in non pre- eclamptic patients, can still occur

and should be managed with boluses of phenylephrine or ephedrine, titrated to effect. Alternatively, phenylephrine infusions may be used, provided adequate care is taken due to the increased sensitivity to these drugs. Invasive blood pressure monitoring is useful especially if the mother is already requiring magnesium sulphate and i.v. anti-hypertensives. General anaesthesia may be necessary if regional techniques are contraindicated due to clotting abnormalities. The hypertensive response to laryngoscopy must be actively managed as this has been directly linked with maternal deaths. This can be achieved with a number of pharmacological agents including alfentanil, remifentanil, lidocaine, esmolol, labetalol, magnesium sulphate and a combination of the aforementioned. No drug has been shown to be superior, and so the anaesthetist should choose that with which they are most familiar. Hypertension on emergence from anaesthesia is also common and repeat boluses of the above drugs may be necessary. The upper airway oedema of the pre-eclamptic patient may necessitate a smaller than predicted tracheal tube diameter and care on extubation is also required. The action of succinylcholine is unaffected by magnesium sulphate although the appearance of the characteristic fasciculations may be reduced. All the non-depolarizing neuromuscular blocking agents are potentiated by magnesium sulphate, and a smaller dose than usual may be required with careful monitoring of adequate reversal into the postoperative period.

Postpartum haemorrhage

Pre-eclampsia is a recognized risk factor for postpartum haemorrhage (PPH) possibly due to the associated thrombocytopenia, liver disease with reduced clotting factor production, DIC, and the restricted use of uterotonics. Syntocinon 5 units given as a slow i.v. or i.m. injection is first-line pharmacological treatment which can be repeated if necessary and continued as an infusion of 10 units h^{-1}. Care should be taken not to exceed fluid restrictions and preparation in smaller than usual volumes may be required. Ergometrine is generally contraindicated due to its liability to increase blood pressure, and so second-line treatment is with carboprost 250 μg intramuscularly or misoprostol 1000 μg rectally.[11] Only in extreme unresponsive atonic haemorrhage with delayed access to surgery, should ergometrine be considered. If required it should be given either intramuscularly in divided doses or very small i.v. doses after dilution. There is a significant risk of pulmonary oedema when managing a pre-eclamptic patient with postpartum haemorrhage and monitoring central venous pressures may be helpful. Continuous oxygen saturation monitoring for the first 24 h post-delivery is sensitive to developing pulmonary problems.

Recent advances

Echocardiography

As a consequence of the considerable cardiopulmonary morbidity and mortality in pre-eclampsia, a significant amount of recent research has focused on ways to optimize this aspect of management. Echocardiography is emerging as an extremely useful tool investigation, with recent studies shedding new light on the cardiovascular changes in pre-eclampsia. It has been demonstrated that patients with severe pre-eclampsia have increased cardiac output, increased contractility and mild vasoconstriction, all of which contribute to hypertension. The increase in cardiac output results from an increased stroke volume as a consequence of increased contractility, rather than increased left ventricular end-diastolic volume. In addition, it has been shown that there is diastolic dysfunction due to a combination of increased left ventricular mass and pericardial effusions, hence the predisposition to pulmonary oedema.[12] Echocardiography can also be used to aid management of women with pre-eclampsia by enabling more informed decisions regarding need for fluid therapy and choice of antihypertensive agent.[13] It may also be possible to use echocardiography as an additional intra-operative and post-operative monitoring tool. Echocardiography is now a relatively routine investigation in the non-pregnant hypertensive patient as it provides a robust evaluation of cardiac function. It seems likely that its use in the hypertensive pregnant patient will become more widespread in the near future.

Placental growth factor

The diagnosis of pre-eclampsia is currently based on the presence of hypertension and proteinuria indicating organ dysfunction. There has been considerable effort to identify other markers that may aid in an earlier diagnosis to enable closer monitoring of the mother and fetus with the potential to improve outcomes. Placental growth factor (PlGF) is an angiogenic factor produced by the placenta, with peak concentrations occurring between 26 and 30 weeks' gestation. Maternal levels of PlGF have been shown to be reduced in women with pre-eclampsia, with the lowest levels corresponding to earlier onset and increased disease severity. A recent study which recruited women with suspected pre-eclampsia (but without the diagnostic combination of hypertension and proteinuria), from 20 weeks' gestation onwards, demonstrated that low levels of PlGF (<100 pg ml^{-1}) are highly sensitive in predicting the need for delivery due to pre-eclampsia within 14 days. The importance of this novel biomarker lies in its ability to diagnose pre-eclampsia before the onset of hypertension and proteinuria, thus allowing earlier treatment and multidisciplinary planning for delivery. Levels of PlGF naturally decline during the third trimester, and so the test becomes less reliable after 35 weeks.[14] Randomized controlled trials are required to assess whether diagnosing pre-eclampsia with PlGF rather than current methods can improve maternal and/or fetal outcomes.

Conclusion

Hypertensive disorders of pregnancy are common and remain a significant cause of maternal and fetal morbidity. An understanding of the pathophysiology and management is vital in enabling provision of the highest quality of care. As part of a multidisciplinary team, anaesthetists are responsible for providing these patients with safe analgesia and anaesthesia, and in severe cases, critical care and resuscitation, playing a vital role in optimizing outcomes for mother and baby.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Practical approach to lung ultrasound

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Key points

- Lung ultrasound (LU) relies on direct visualization of structures and artifact interpretation.
- A curvilinear probe is the best 'all-rounder'.
- LU has a very high diagnostic accuracy.
- A comprehensive point-of-care scan can be done in <5 min.
- A training structure and competencies specific to critical care in the UK have been developed.

Critically ill patients need rapid access to accurate and reproducible imaging techniques to diagnose pathology, implement, and monitor treatment. Point-of-care ultrasound (US) has become firmly established in acute and critical care settings (FAST, vascular access, echocardiography) and is now emerging as an important tool in the assessment of the lungs.

Lung ultrasound (LU) can be performed quickly and easily in critically ill patients. It has a higher diagnostic accuracy than physical examination and chest radiography combined.[1] It enhances safety by avoiding ionizing radiation and the need for potentially dangerous transfers within the hospital. LU can also be used to guide fluid management, weaning, and therapeutic procedures such as thoracocentesis.

LU is relatively quick to learn with a steep learning curve. By attaining competencies with appropriate training, the Intensivist can effectively utilize LU as a point-of-care investigation.

This article will take the reader through the physics and physiology of LU, outline how to perform a scan, describe the US appearances of normal and pathological lung conditions, and put these in the context of the intensive care setting.

Physics: air, water, and echoes

The appearances of LU are based on the relative amounts of air and fluid in the lung because of the phenomenon of acoustic impedance (Z). This is a measure of the resistance of particles in a medium to mechanical vibrations. Resistance increases in proportion to the density of the medium and the propagation velocity of US in the medium. When US hits a relatively large and flat boundary between mediums with different impedances, some of the sound is transmitted across the boundary and some is reflected (an echo). The greater the difference in Z, the greater the reflection. Fluid has a constant Z resulting in no echoes and so appears black. Soft tissues have very similar values of Z resulting in minimal reflection. Interfaces between bone and soft tissue reflect about 40% of US energy. Soft tissue and air reflect 99.9% rendering this interface virtually impenetrable to US.

This means structures below the pleura in an air filled lung cannot be visualized—only artifacts will be seen. LU relies on the interpretation of artifacts in conditions where the lung is predominantly aerated. These artifacts will vary depending on the ratio of air and fluid. If the lung is highly fluid filled, then it can be directly visualized. Pneumothorax consists of only air below the parietal pleura while a pleural effusion is only fluid. There is a range between these two extremes of normal lung (98% air), interstitial syndrome (IS; 95% air), alveolar syndrome (10% air), and atelectasis (5% air), all with different US appearances ranging from specific artifacts to true structure visualization.[1] It is important to remember that because of gravity fluid is usually dependent and air non-dependent.

Probe selection

US machines available in critical care settings are likely to have either a linear (vascular access probe), curvilinear (abdominal probe) or phased array (echo probe), or a combination. A great advantage of LU is that useful images can be obtained with each of these. Each probe has pros and cons.

Linear probe (8–12 MHz)

These high-frequency probes give good resolution of superficial structures. As the anterior pleura is relatively superficial, excellent images of the pleura and lung sliding can be obtained. The poor penetration of high-frequency US and the narrow sector width mean deeper structures are poorly imaged.

Curvilinear probe (3–5 MHz)

This is the best all-round probe for LU. Lung sliding can be easily visualized as can IS. Effusions, consolidated lung, and the diaphragm are also well imaged because of the good penetration and large sector width. The large footprint of the probe means some angulation is needed to avoid the ribs when scanning postero-laterally.

Phased array (3–4.5 MHz)

These probes have a useful footprint for getting in between the ribs. They can be used to demonstrate all the signs of LU but the clarity of the images is not as good.

General points

The clearest images are obtained by having the image as shallow as possible with the focus point at the level of interest. The frequency can be adjusted to enhance the image, depending on the depth. Increasing the frequency on a curvilinear probe will improve the appearance of lung sliding whilst worsening the appearance of a consolidated lung base.

How to perform a scan

US convention is that the left side of the image (as you look at it) should correspond with either the right side of the patient (if transverse) or cephalad (if longitudinal). A comprehensive examination can be performed on supine patients. There are several systems that have been described in the literature to examine the thorax. One is a 3-point examination of each lung.[1] This is quick and simple and there is convincing evidence that this technique yields a high diagnostic accuracy. It is therefore an excellent starting point for a novice.

Method

Apply two hands side by side (without your thumbs) over the anterior chest with your wrists in the anterior axillary line and your upper little finger resting along the clavicle. Your lower little finger will be aligned with the lower border of the lung (the phrenic line) (Fig. 1). For each point the probe should be placed at 90° to the skin, looking into the lung, with the left of the screen cephalad and the right caudad. All views are longitudinal and not transverse.

Upper anterior point

This corresponds to the base of the middle and ring fingers on the upper hand. It lies over the upper lobe.

Lower anterior point

This is the middle of the palm on the lower hand (close to the nipple in a man). It lies over the middle or lingular lobe. These points will miss the heart on the left.

Postero-lateral point

From the lower anterior point move laterally and posteriorly as far as possible behind the posterior axillary line (limited by the bed). It lies over the lower lobe. With a curvilinear probe rib shadows can then be minimized by rotating the probe slightly to lie between the ribs (cephalad will still be on the left of the image).

More comprehensive scanning techniques have also been described and are recommended for advanced practitioners.

Normal appearance

All signs in LU arise from the pleural line except for subcutaneous emphysema which will abolish it (as there is air above it). Rib shadows will be seen (as the sound is reflected back to the probe) and in between them the bright white pleural line about 0.5 cm below the rib line. Centre this in your image and you will see the 'bat sign' with the ribs as the wings (Fig. 2 online video).

Air below the pleural line reflects most US back to the transducer. This is itself a reflector, meaning some of the US waves will bounce back and forth between the pleura and transducer generating artifacts called *A lines*. They are horizontal lines below the pleura with the same spacing as the distance between

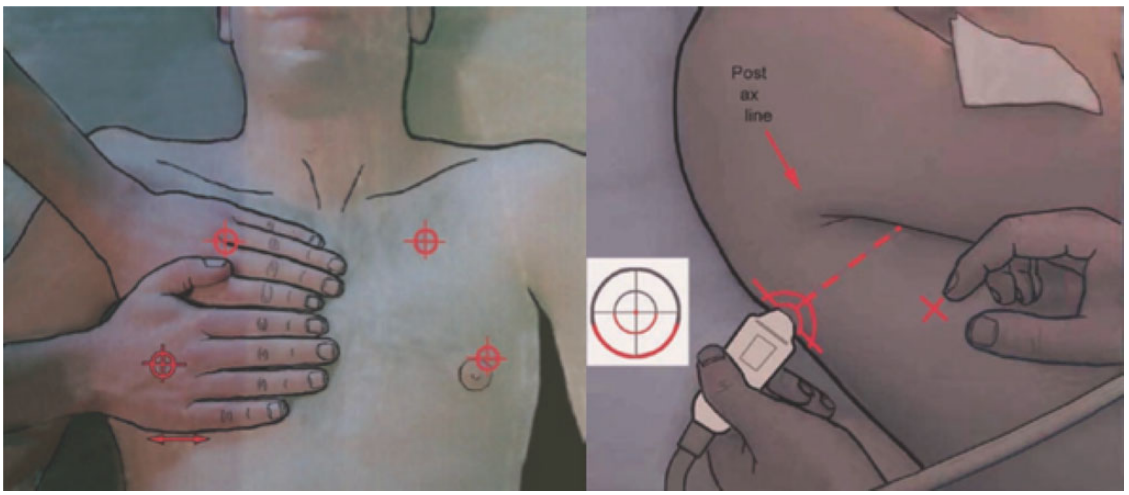

Fig 1 Probe positioning (reproduced from Whole Body Ultrasonography in the Critically Ill by D. Lichtenstein with kind permission from Springer.)

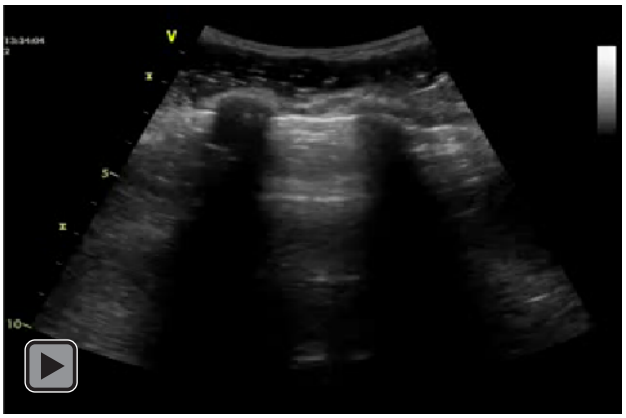

Fig 2 Online video The 'bat sign'. If reading the pdf online, click on the image to view the video.

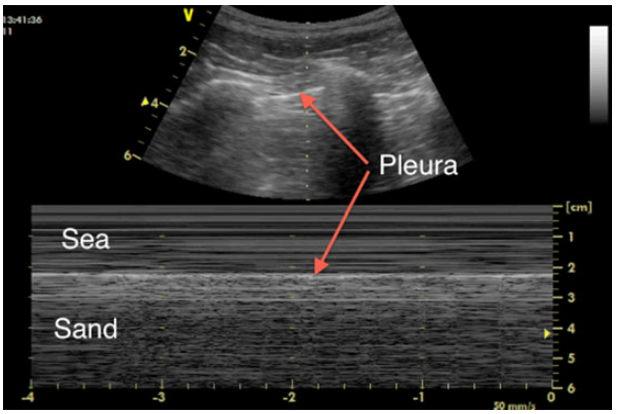

Fig 3 M-mode image of lung sliding (the 'seashore sign').

the probe and the pleural line. Because they demonstrate the presence of air below the pleura, they are present both in normal lungs and in pneumothorax. Turning the probe transversely will abolish the rib shadows so more of the pleural line can be seen. The danger of this is that an inexperienced user may interpret a rib as the pleural line and incorrectly diagnose absent lung sliding.

Lung sliding

The visceral and parietal pleura are normally closely opposed with a minute amount of fluid between them and slide over one another with respiration. The appearance of this is backwards and forwards movement of the pleura (often with little blebs appearing to move up and down the pleural line). Small artifacts (white or black lines) projecting a few millimetres below the pleural line move with sliding. These are more commonly seen with high-frequency probes and have no clinical significance. They are not B lines (see later). Any B lines present will move to and fro with lung sliding. The whole of the sub-pleural space between the ribs will shimmer (Fig. 2 online video).

An M-mode image (using a single scan line to demonstrate echoes plotted against time) with lung sliding present will show the 'seashore sign'. Subcutaneous tissue above the pleural line generates horizontal straight lines while there will be a sandy appearance below the pleural line created by the movement of lung sliding (Fig. 3).

Lung sliding will be reduced with low tidal volumes or in hyper-inflated lungs. It will be absent in any condition in which the pleura are either not directly opposed (pneumothorax, effusion), are stuck together (pneumonia, ARDS, pleurodesis), or in absent respiration (pneumonectomy, one lung intubation). The appearance of this on M-mode is horizontal straight lines—the 'stratosphere sign' (also termed barcode sign) (Fig. 4). It should not be necessary to use M-mode to demonstrate the presence or absence of sliding—2D is sufficient.

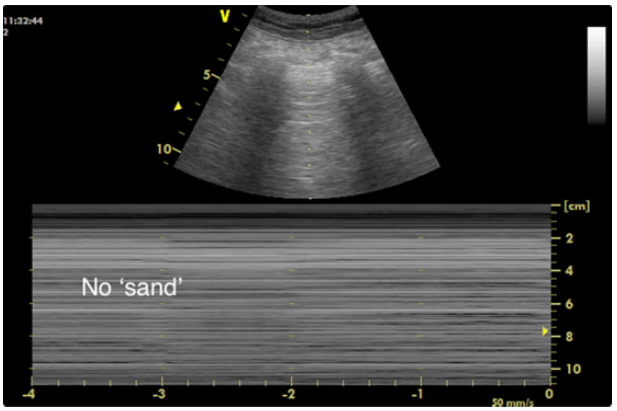

Fig 4 M-mode image of absent sliding (the 'stratosphere sign').

Interstitial syndrome

IS is a sonographic entity caused by

- Pulmonary oedema—either haemodynamic (fluid overload, cardiac failure) or permeability-induced (ALI/ARDS).
- Interstitial pneumonia or pneumonitis.
- Lung fibrosis.

Clinical examination and supine radiography have poor sensitivity for detecting interstitial oedema. The sensitivity and specificity of US approaches 100% when compared with CT. The US feature of IS is *B lines* (Fig. 5). These are artifacts generated by the juxtaposition of alveolar air and septal thickening (from fluid or fibrosis). Their characteristics are

- They arise from the pleural line.
- They are long, vertical hyperechoic lines which continue to the depths of the image.
- They look like comet tails (an old name for them).
- They erase A lines.
- They move with lung sliding.

Occasional B lines can be seen in normal lungs (especially at the bases). Up to two between two adjacent ribs can be considered normal. Three or more between rib spaces (or close together in a transverse image) are pathological. They can be localized, disseminated, homogenous, or non-homogenous depending on the pathology. They are present in any disease affecting the interstitium. The commonest cause is pulmonary oedema where they are the equivalent of Kerley B lines. When oedema becomes more severe (ground-glass appearance on CT) B lines become more numerous and closely spaced. Very severe oedema causes them to fuse with a hyperechoic confluent pattern that fills the space between two ribs (white lung). LU can distinguish between causes of IS.[2] A detailed explanation is beyond the scope of this article as it is not a core-level competence; however, Table 1 outlines the main features distinguishing cardiogenic from non-cardiogenic pulmonary oedema.

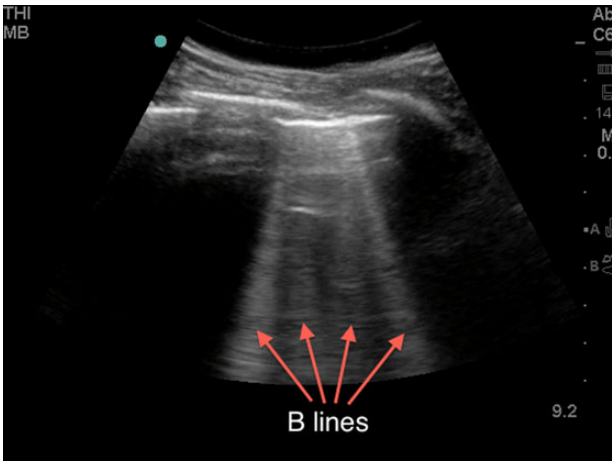

Fig 5 B lines demonstrating IS.

Table 1 Interstitial syndrome

Ultrasound features	Cardiogenic	ALI/ARDS
Lung sliding	Normal	Reduced or absent
Pleural line	Normal	Irregular, thickened, coarse. Often multiple small anterior subpleural consolidations
Distribution	Homogenous. Spread from postero-lateral to anterior with increasing severity. No spared areas.	Spared areas (normal pleura, no B lines). More severe in dependent areas
Consolidation	No consolidation	Dependent consolidation
Lung pulse	Absent	Present in areas of reduced sliding
Pleural Effusion	Common	Less common

Differentiating between cardiogenic and non-cardiogenic pulmonary oedema.

Pneumothorax

LU is nearly as good as CT for ruling a pneumothorax in or out. It takes less than a minute with US (Fig. 6).

The features of a pneumothorax are abolished sliding, absence of B lines, absence of the lung pulse, and presence of the lung point.[3] Air, being non-dependent, will collect anteriorly in a supine patient. Placing the probe on the highest point of the anterior chest and demonstrating lung sliding will rule out a pneumothorax in only a few seconds. The presence of any B lines means that the pleural layers are opposed at that point ruling out pneumothorax even if there is no sliding.

If there is no sliding and no B lines, then the 'lung point' should be sought. This is the point at which the two pleural layers rejoin one another. It will be more lateral with increasing pneumothorax size and so should be looked for by moving the probe laterally. This point will move with lung inflation and deflation resulting in an area at which sliding will appear and disappear (Supplementary data, Video).

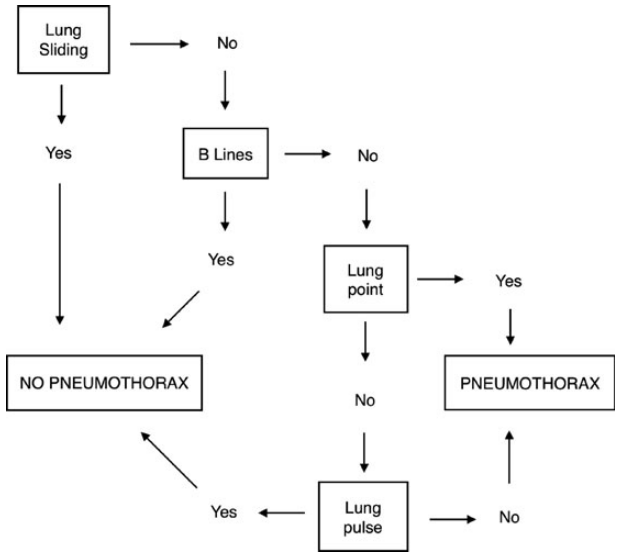

Fig 6 Flowchart to assess for a pneumothorax (adapted from a diagram with kind permission from Intensive Care Medicine.)

If the lung point cannot be found (it usually can) then the 'lung pulse' should be sought. If the pleural layers are still adjacent to one another, then cardiac pulsation will be transmitted to the pleura by the lung. This results in a very small amount of motion in 2D in time with the heartbeat. It is easier to see in M-mode where it produces *T lines*. These are vertical lines running from the pleural line to the bottom of the image in time with cardiac pulsation (Supplementary data, Fig. S1).

Alveolar syndrome

The sonographic entity of alveolar syndrome encompasses alveolar consolidation and atelectasis.

Consolidation

Consolidations are highly fluid filled, and over 95% reach the pleura,[4] so US can image the pathology directly. Three US patterns are typical with consolidation.

Anterior consolidations

These are (usually small) echo poor areas beneath the pleura. Peri-lesional B lines and comets deep to the far margins are common. The margins of pneumonic consolidation are indistinct (Fig. 7).

Tissue-like sign

When the lung is highly fluid filled, it resembles the liver in echogenicity—it becomes hepatisized. Extensive consolidation will allow the opposite pleural line to be seen (8–11 cm deep) with mediastinum deeper still with the aorta or IVC visible (Fig. 8). Severe consolidation will often be accompanied by a pleural effusion.

Shred sign

If consolidations are less extensive, and the percentage of air therefore greater, it looks as if chunks have been taken out of the lung (echo poor areas). These areas will be bordered by aerated lung identified by sliding and comets. The border of

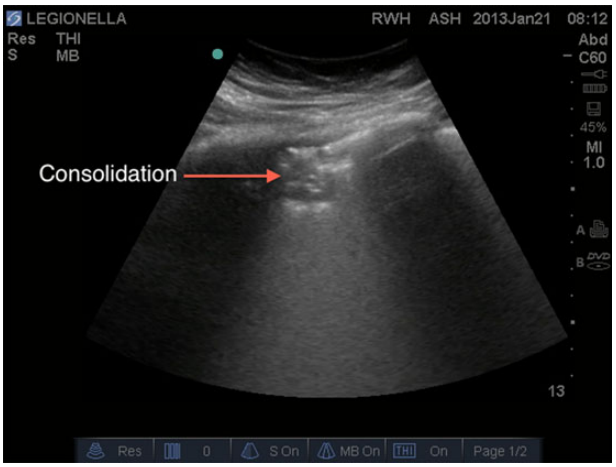

Fig 7 A small anterior consolidation with indistinct margins.

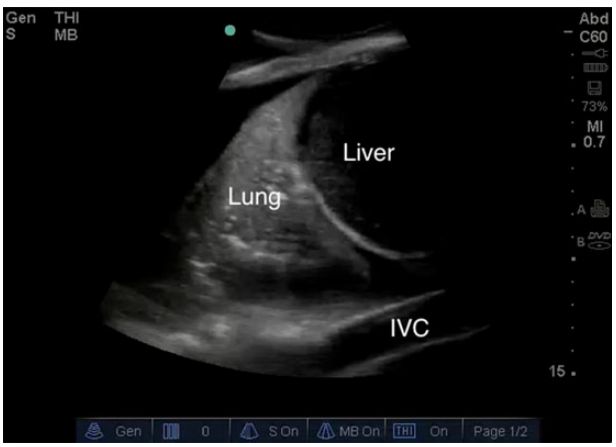

Fig 8 A fully consolidated lung base surrounded by an effusion.

consolidated and aerated lung is not sharp. This sign is highly suggestive of pneumonia (Supplementary data, Fig. S2).

Air and fluid bronchograms

Air bronchograms appear white while fluid bronchograms are black. They are punctiform if transverse to the beam and linear if longitudinal (Fig. 9 online video). Fluid bronchograms are specific to pneumonia. They can be distinguished from vessels with colour Doppler and by the angulation of their branches. An air bronchogram which moves with respiration excludes bronchial obstruction and helps distinguish between consolidation and atelectasis. Dynamic air bronchograms make pneumonia more likely; static or no air bronchograms make atelectasis more likely (Fig. 9 online video).

Atelectasis

Atelectasis and consolidation are difficult to tell apart with US. Bronchograms are suggestive as above but have a low specificity. If there is a very large pleural effusion, then compression atelectasis is more likely. A small effusion makes consolidation much more likely. If there is significant collapse, then associated signs such as a raised hemidiaphragm will be present. Virtually all pleural effusions in critical ill patients have underlying consolidated/atelectatic lung underneath. The only sure way to distinguish compression atelectasis from consolidation is to drain the effusion and see if the lung re-aerates.

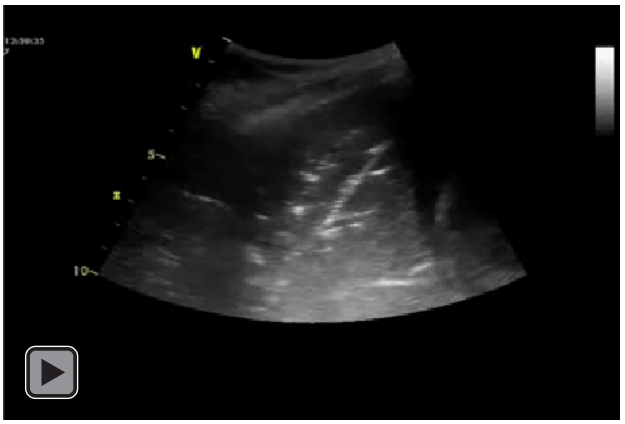

Fig 9 Online video Linear air bronchograms (white and branching) within a consolidated lung base. If reading the pdf online, click on the image to view the video.

Diaphragm

The diaphragm is easily visualized if there is basal consolidation or an effusion (Supplementary data, Fig. S3). It is mostly obscured by aerated lung (unless looked at from below through the liver), but its position will be identified by air above (on the left of the screen) and abdominal organs below (on the right). The diaphragm is raised if above the normal phrenic line. The normal inspiratory amplitude longitudinally is between 15 and 20 mm. Low amplitude reflects atelectasis, low tidal volume, raised intra-abdominal pressure, and muscle weakness. Paradoxical movement indicates phrenic nerve palsy.

Pleural effusion

Up to 500 ml of fluid is easily missed with chest radiography. The sensitivity and specificity of US approach 100%. US will reveal septations and can help distinguish between transudates and exudates. Effusions are dependent because of gravity so collect caudad and posteriorly in ICU patients. They are easily identified between the diaphragm and lung postero-laterally. The lung will float on top of an effusion.

The quad sign—with the diaphragm out of view an effusion will be seen as a rectangular shape (usually anechoic) whose borders are the ribs cephalad and caudad and the parietal and visceral pleura at the top and bottom. It is imperative not to confuse an A line for the visceral pleura. The lung moves towards and away from the probe with respiration which can be visualized in 2D or M-mode (the sinusoid sign) (Supplementary data, Fig. S4). This is important for distinguishing pleural thickening from an effusion as is colour Doppler which will identify fluid movement within an effusion. With the diaphragm in view a significant effusion will be seen surrounding the basal lung and separating it from the diaphragm. Atelectatic or consolidated lung base is usually seen floating around.

Size

There are a number of published sizing techniques for effusions which vary significantly as an accurate volume is difficult to define with US. It is more practical and clinically relevant to classify an effusion volume as small, moderate, or large. As a rule of thumb, an effusion depth of >4–5 cm at the widest point will mean an effusion of >1000 ml.

Transudates and exudates

Transudates and exudates are defined biochemically, but the nature of effusions can be suggested by LU.[5] An anechoic effusion may be a transudate, exudate, or acute haemothorax. Echoic effusions (uniform or particles) signify an exudate or subacute haemothorax. A septated effusion is a result of inflammation so is an exudate (Supplementary data, Video).

Thoracocentesis

Thoracocentesis can be done in real time (in or out of plane) or the site can be marked. If marked, then the patient should not be moved before the procedure. If done in real time, then the curvilinear probe makes needle visualization easiest (with minimum depth and highest frequency settings) as the needle will be at 90° to the probe. The site selected should be where the effusion is largest and as far removed as possible from other structures (lung, diaphragm, etc.). It is advisable to remain anterior to the posterior axillary line to avoid the intercostal vessels. There should be a reasonable distance between the pleura in inspiration to avoid pneumothorax (minimum 1 cm depending on skill). It is essential that the needle is inserted at the same angle as the US beam. Tapping can be done with a green needle. Evacuation can be achieved with a 14G cannula or a small Seldinger drain.

Pulmonary emboli

A normal LU is a very sensitive but not specific sign of PE. Small, peripheral infarcts can sometimes be seen which are wedge shaped with defined margins. The main strength of LU in PE is to rule out other causes of respiratory failure—it should not be used in place of normal imaging techniques if PE is suspected. Identification of peripheral emboli is not a core competence.

COPD/asthma

As these conditions affect the airways, LU will be normal (if no pneumonia is present). LU is particularly useful in distinguishing between pulmonary oedema, pneumonia, and a COPD exacerbation in patients in whom the diagnosis is not clear.

Acute respiratory failure (the BLUE protocol)

For patients presenting acutely with respiratory failure, LU provides a diagnostic accuracy of 90.5% (compared with about 75% for physical examination plus chest radiography) with a scan that takes <5 min.[1] The scan requires the operator to seek lung sliding anteriorly and look for B lines at two anterior points on each hemithorax. If a diagnosis is not reached, then the operator scans the leg veins for a deep venous thrombosis (DVT). If there is no DVT, then consolidation is looked for postero-laterally. This simple protocol has the ability to greatly enhance the speed and accuracy of diagnosis in patients with acute respiratory failure (Supplementary data).

Intensive care setting

Diagnosis and treatment

The BLUE protocol was designed for spontaneously breathing patients with acute respiratory failure. Other studies confirm the very high diagnostic accuracy of LU in ventilated intensive care patients.[6,7] Expert practitioners can distinguish between cardiogenic and non-cardiogenic pulmonary oedema and other interstitial diseases. The high diagnostic accuracy allows appropriate treatment to be instituted (diuretics, antibiotics, thoracocentesis, etc.).

Fluid management

The absence of B lines can reassure that fluid will not be detrimental to gas exchange. Their presence should, in most circumstances, dissuade you from giving further fluid. B lines appear with interstitial oedema (before alveolar oedema). It has been proposed that the appearance of B lines be the stopping point when giving a fluid challenge with B lines corresponding to the flat portion of the Starling curve.[8] B lines will disappear with treatment of pulmonary oedema.

Lung aeration, PEEP, and weaning

Lung re-aeration can be assessed after pleural drainage. LU has been used to assess lung recruitment with PEEP (it is important to note that hyperinflation cannot be assessed).[9] Loss of aeration assessed by LU during a spontaneous breathing trial (SBT) predicts post extubation distress.[10] Crucially this applies to patients who pass the SBT.

Training

Publications by the Royal College of Radiologists and a joint document by the Association of Anaesthetists of Great Britain and Ireland, Intensive Care Society and Royal Collage of Anaesthetists provide guidance for training non-radiologists in US. The Intensive Care Society has recently launched an accreditation pathway, Core Ultrasound in intensive Care (CUSIC) which includes all the key aspects of LU outlined in this article. Information can be found at www.ics.ac.uk. It is anticipated that lung US will be incorporated into the ICM syllabus in the future.

Supplementary material

Supplementary material is available at *BJA Education* online.

Online videos

The videos associated with this article can all be viewed from the article in *BJA Education* online.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Quantitative Doppler echocardiography

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Key points

- Doppler and 2D imaging provide objective haemodynamic data to quantify ventricular function and grade valve lesion severities.
- Parallel alignment of Doppler ultrasound beam to the direction of blood flow is of paramount importance to avoid errors.
- Velocity–time integration of Doppler traces through valves, using area under the curve analysis, provides the basis for the majority of calculations.
- Pulse-wave Doppler measures slower velocities at a specified depth, whereas continuous-wave Doppler measures any velocity shift but without knowing where on the scan line they come from.
- The simplified Bernoulli equation can convert Doppler velocity to pressure, using $P=4V^2$.

Echocardiography provides information regarding volumes [e.g. stroke volume (SV), ejection fraction], flows [e.g. cardiac output (CO), shunt fractions], and pressures (e.g. gradients across valves). As the only directly measurable variables are length (using 2D imaging) and velocity (using spectral Doppler), quantitative haemodynamic data is acquired using extrapolation of these two modalities. Area can also be measured directly using planimetry in most systems. This review demonstrates how the physical principles behind Doppler echocardiography can be used to calculate volumes, flows and pressures. Systolic and diastolic ventricular function, filling status, and valve pathology can all be quantified, providing depth and accuracy to decision-making processes.

Principles of Doppler

$$f=\frac{2v f_0 \cos\theta}{c}$$

where f is Doppler shift frequency, v velocity of red cell target, f_0 frequency of transmitted ultrasound beam, θ angle between the ultrasound beam and vector of the red blood cell flow and c is velocity of ultrasound in blood.

The Doppler effect is the change in frequency of a reflected sound wave for an observer moving relative to its source. In blood flow, the frequency shifts relate to red blood cell velocities. If the source moves towards the observer, the observed frequency increases (and thus, wavelength decreases). If the source is moving away from the observer, the opposite occurs. The observer and source must be parallel to each other. As the angle between them becomes more perpendicular, the Doppler shift falls, until at 90° there is no shift. An angle >20° produces unacceptable error in Doppler velocity measurements. In general, all measurements should be done by using data from a minimum of three cycles (more with arrhythmias) and from more than one view. In 2D imaging, the ultrasound beam should be perpendicular and passing through the centre of the structure of interest to reduce measurement errors. The measurements are taken from inner-to-inner edge.[1]

Continuous-wave Doppler

Two separate crystals are used, one to transmit and one to receive ultrasound signals. Every single velocity along the line of interrogation is recorded, thus the trace appears filled in (see echo inset in Fig. 2). Continuous-wave (CW) Doppler can measure very high velocities, but it is unable to pinpoint where on the scan line they come from. For measurement, the outer edge of the velocity envelope is used.

Pulse-wave Doppler

A single crystal is used, both to transmit and receive ultrasound signals. By knowing the velocity of ultrasound in body tissue (~1540 m s^{-1}), the crystal is able to wait a defined period of time for the reflected signal to return, and thus interrogate a specified area. The trace appears hollow and for measurement the

outer edge of the brightest portion of the velocity tracing is used. A drawback to pulse-wave (PW) Doppler is that the further away the sample volume, the longer the round trip the signal has to take resulting in a lower pulse repetition frequency. If the blood flow being measured is fast, then the blood cells will have moved a long way between pulses and the direction of flow will not be able to be determined. This phenomenon is called *aliasing*. A visual example of aliasing is vehicle wheels appearing to rotate the opposite way when viewed on television as a result of the frame rate at which they are filmed. The maximum Doppler frequency that can be measured unambiguously is half the pulse repetition frequency (as sound waves have to be measured at least twice per wavelength to measure wavelength accurately). This maximum velocity is known as the *Nyquist limit*, above which aliasing occurs. In colour flow Doppler (a form of pulse-wave Doppler) this means the colour may change from red to blue (or vice versa), despite the blood flow continuing in the same direction, giving the false impression of turbulence. With velocity tracings, any velocities above the Nyquist limit will be displayed on the opposite side of the baseline. Aliasing can be reduced in a number of ways including shifting the baseline of the velocity tracing, decreasing the frequency, increasing the angle of incidence and by sampling at two points. For colour Doppler it can be minimized by adjusting the colour Doppler velocity scale and decreasing the width and depth of the sample volume.

Colour Doppler

A form of PW Doppler whereby single crystals both emit and receive signals but instead of focusing on a single point, multiple sample volumes are evaluated along each individual sampling line. The velocities detected are colour coded such that blue signifies velocities away from the transducer and red towards it. (Blue Away, Red Towards—'BART'.)

Tissue Doppler

Myocardial wall motion velocities can be interrogated as well as the blood velocities listed above, where the cursor is aligned over the ventricular wall rather than within a cavity. This provides additional information on the extent and timing of diastolic wall motion.

Calculations rely on several vital factors and also make several assumptions.[2]

Vital factors:

1. The Doppler beam must be parallel or within 15–20° of the direction of blood flow. An angle >20° produces an unacceptable error in Doppler velocity shift. At 20° the error is 6%, at 60° it is 50%.
2. Areas must be measured accurately. Errors in measuring cylinder diameters will be exponentially compounded in calculations. This is particularly relevant with calculating ejection fraction and SV.
3. No two heart beats are identical; therefore, several separate measurements should be averaged. This is time-consuming.

Assumptions:

1. *Blood flow is laminar with a flat velocity profile*. This may be true through the left ventricular outflow tract (LVOT) but cannot be said for a diseased valve or in a great vessel, where flow is more parabolic and turbulent in shape.
2. *For each equation, variables are measured simultaneously*. This is rarely possible as different modalities are used for areas and velocities.
3. *Cross-sectional areas (CSA) are circular* (e.g. oesophageal Doppler calculations). This is rarely, if ever, completely accurate.
4. *Area sizes are fixed*. Changes in CSA will occur during any flow period.

These are only 'ideals' but not necessarily achievable or practical in many clinical situations.

Pressure gradients

Pressure gradients quantify severity of stenotic lesions and can estimate unknown pressures from known pressures. Pressure and flow are integrally related but neither can be measured directly with echocardiography. Pressure (*P*) can be estimated from velocity (*V*) using the simplified Bernoulli equation: $P=4V^2$.

Total energy in a closed system is a constant (Newton's law of conservation of energy). When blood flows through a stenotic valve, kinetic energy increases and potential energy decreases proportionately to maintain constant total energy. Velocity increases through an orifice and pressure decreases. This explains why post-stenotic dilatation of the aorta is seen in severe aortic stenosis. The modified Bernoulli equation states:

$$\Delta P = 4(V_2^2 - V_1^2)$$

where V_1 is velocity pre-orifice and V_2 is velocity post-orifice. V_1^2 is significantly less than V_2^2 in most physiological conditions and can be ignored, thus: $\Delta P=4V^2$. In aortic stenosis, peak pressure gradient is 4×(peak velocity)^2 through the valve. If V_1 (LVOT) velocity is abnormally high, such as in obstructive cardiomyopathy (>1 m s^{-1}), the full equation should be used. If V_1 is <1 m s^{-1} (most common in clinical practice), then the simplified version is used.

Stenotic valve gradients

Pressure gradients across stenotic valves correlate with invasive, cardiac catheterisation data, particularly with the aortic valve (AV). Cardiac catheterisation measures the arithmetic difference between peak LV pressure and peak aortic pressure, which is non-simultaneous. Doppler measures velocities simultaneously and thus the pressure gradient may be slightly greater. True gradients are generally overestimated and this is exaggerated (pressure recovery)[3] if there is a small aortic root, prosthetic valves or aortic coarctation, where the pressure can increase post narrowing. The pressure recovery phenomenon can be responsible for gradients that are substantially higher, and valve areas that are lower, than those measured invasively. In practice, kinetic energy gained proximal to the stenotic orifice is converted to thermal energy or recovered as pressure energy (known as pressure recovery) distal to stenosis. Doppler underestimates the pressure gradient rather than overestimating it because of sampling errors from poor beam alignment.

Right Ventricular systolic pressure

Right Ventricular systolic pressure (RVSP) is commonly estimated using peak tricuspid regurgitation (TR) velocity (in m s^{-1}) and central venous pressure (CVP). RVSP correlates with pulmonary artery systolic pressure in the absence of RV outflow obstruction or pulmonary stenosis.

$$\mathrm{RVSP} = 4 \times \mathrm{TR}_{(\text{jet velocity})}{}^2 + \mathrm{CVP}$$

By using the same principle, an instantaneous pressure gradient across a ventricular septal defect (VSD_{PG}) can be measured and

RV systolic pressure can be calculated from the known LV systolic pressure.[4]

$$\text{RVSP} \approx \text{LVSP} - \text{VSD}_{\text{PG}}$$

Pulmonary artery (PA) pressures

In diastole, right atrial and ventricular pressures are equal if the tricuspid valve is normal. If pulmonary regurgitation (PR) is present, Continuous-wave Doppler can be applied to the jet to estimate PA diastolic pressure.

$$\text{PA}_{\text{end-diastolic pressure}} = 4 \times \text{PR}_{(\text{jet velocity})}{}^2 + \text{CVP}$$

Similarly, PA systolic pressure is estimated by using the velocity jet of a patent ductus arteriosus if present.

Left heart pressures

Left atrial pressure (LAP) and left ventricular end-diastolic pressure (LVEDP) can be estimated from mitral regurgitant (MR) and aortic regurgitant (AR) jets (in m s^{-1}), respectively:

$$\text{LAP} = \text{LVSP} - 4 \times \text{MR}_{(\text{jet velocity})}{}^2$$

$$\text{LVEDP} = \text{aortic diastolic pressure} - 4 \times \text{AR}_{(\text{end-diastolic jet velocity})}{}^2$$

Left heart pressures are included here for completeness but are more theoretical and not used in clinical practice.

Left ventricular diastolic assessment

Symptomatic heart failure with preserved ejection fraction suggests diastolic dysfunction, which is most readily identified using mitral valve inflow Doppler interrogation. PW Doppler at the mitral valve annulus produces two periods of forward blood flow from LA to LV during diastole, the first (*E* wave) corresponding to passive early filling of the ventricle and the second (*A* wave) corresponding to late diastolic atrial contraction. The ratio between the two changes as diastolic dysfunction worsens. In addition, the *E* wave velocity can be coupled with the mitral annulus velocities (measured with tissue Doppler, *E′*) to create an *E*/*E′* ratio, which is one of the more reliable ways of differentiating the aetiology of diastolic dysfunction. Thus, $E/E' < 8$ indicates normal filling pressures, whilst $E/E' > 12$ indicates elevated filling pressures. Diastolic function and dysfunction are covered in detail in a previous *CEACCP* article.[5]

Stroke volume and cardiac output

During one cardiac cycle the entire CO and SV pass through the LVOT and AV, making them ideal areas to interrogate, although other locations within the heart and great vessels can be used. Oesophageal Doppler uses the same principles for calculating CO from the descending aorta.

SV and CO can be derived as follows, using the AV as an example:

$$\text{SV} = \text{area} \times \text{length} = \text{CSA}_{\text{AV}} \times \text{SD}$$

where CSA_{AV} is cross-sectional area of AV and SD is stroke distance.

CSA_{AV} is easily measured using 2D imaging. A short-axis view of the AV is achieved, then the area calculated by tracing around the opened leaflets during mid-systole. The machine calculates the area bound by the line traced. This is known as planimetry. Descending aorta and the LVOT are assumed to be cylindrical and the area is calculated using πr^2, where r is the radius of the cylinder. Oesophageal Doppler acquires this area using nomograms from patient height and weight data correlated to aortic size from historical CT scan slices from multiple patients. Of importance, error in basic measurement can be exponentially compounded in further analysis. πr^2 is often seen written as $0.785 \times d^2$, as diameter (d) is usually measured, rather than radius.

$$\pi r^2 = \pi \times \left(\frac{d}{2}\right)^2 = 3.14 \times \frac{d^2}{2^2}.$$

In mid-systole, the normal open AV resembles an equilateral triangle. Thus, CSA can also be calculated using the formula:

$$\text{CSA}_{\text{AV}} = 0.433 \times S^2$$

where S is the length of one side (leaflet base).

Stroke distance cannot be measured directly. It is a theoretical concept equivalent to the distance that blood travels with each heartbeat. Doppler measures velocity (distance/time). The area delineated by a velocity/time curve gives the distance travelled for a given time. So, tracing the area under the curve of the Doppler flow velocity profile [known as the velocity–time integral (VTI)] yields SD. Thus

$$\text{SV} = \text{CSA}_{\text{AV}} \times \text{VTI}_{\text{AV}}$$

This integration of velocity and time by calculating areas under curves is a fundamental way in which 2D imaging and Doppler can achieve volume and CO measurements.

In practice, SV calculation is more commonly done using LVOT interrogation rather than AV, which may be diseased. It is paramount to place the PW Doppler sample volume at the same point as where the diameter of the LVOT is measured to ensure accuracy.

Whilst CO can be calculated from the SV above, Doppler can also be used to measure it directly, as follows.

$$\begin{aligned}\text{Flow (Q)} &= \text{volume/time} \\ &= (\text{area} \times \text{length})/\text{time} \\ &= \text{area} \times (\text{length/time}) \\ &= \text{CSA}_{\text{AV}} \times \text{velocity}_{\text{AV}}\end{aligned}$$

When CW Doppler is aligned through the AV, the predominant velocities reflect aortic ejection. By measuring the maximum velocity (V_{max}) during mid-systole, the equation for CO becomes as follows:

$$\text{CO} = \text{CSA}_{\text{AV}} \times \text{V}_{\text{max}_{\text{AV}}}$$

Calculation of pulmonary-to-systemic flow ratio (Q_P/Q_S)

It is possible to quantify the magnitude of shunt that exists from abnormal cardiac foramina such as atrial septal defect or ventricular septal defect or from a patent ductus arteriosus.

Q_P/Q_S normally equals 1 as the CO from left and right ventricles is equal. In the presence of a pathological shunt, Q_P increases. The ratio is important as $Q_P/Q_S>1.5$ may indicate the need for clinical intervention.

Q_S is calculated from the CO formula above, from measurements either at the LVOT or AV. Similarly, Q_P can be calculated using CO calculations from the RVOT or main pulmonary artery. It is important to make several measurements as errors in calculating both outputs may make the resultant ratio even more inaccurate (e.g. overestimating one whilst underestimating the other).

The continuity equation

The continuity equation expands upon the concepts of SV and CO calculation above and has many applications. It is the most widely used method of calculating AV area in aortic stenosis, where calcium deposition makes planimetry inaccurate. It is simply conservation of mass, in that flow or volume through the LVOT in systole must equal that through the AV in the same cardiac cycle.

Thus, using flow

$$CSA_{LVOT} \times V_{max-LVOT} = CSA_{AV} \times V_{max-AV}$$

CSA_{LVOT} can be measured directly with 2D echo. The diameter is measured in cm, then πr^2 applied, assuming it to be cylindrical. $V_{max\text{-}LVOT}$ is measured using PW Doppler aligned with aortic outflow and the cursor in the LVOT. $V_{max\text{-}AV}$ must be measured with CW Doppler as the velocity exceeds the Nyquist limit. AV area can then be calculated (Fig. 1).

Alternatively, using SV:

$$CSA_{LVOT} \times VTI_{LVOT} = CSA_{AV} \times VTI_{AV}$$

where VTI_{LVOT} is the area under the curve using PW Doppler at the LVOT. VTI_{AV} is the same, using CW Doppler aligned with aortic outflow.

It may be possible to use CW Doppler alone to calculate AV area. In correct alignment with aortic outflow a 'double envelope' may be seen, where the two predominant Doppler velocities of LVOT and aortic outflow are seen. This has the advantage of knowing that the velocities through LVOT and AV were from the same heartbeat, although they may not be as accurate. Because LVOT and aortic ejection occur in the same phase of the cardiac cycle, the continuity equation is accurate in the presence of aortic regurgitation. It can also be used to calculate other valve areas. For example, flow through the mitral valve in diastole must equal flow through the AV in systole, but the method must factor in any aortic and mitral regurgitation. This becomes a more time-consuming and complicated calculation, with the possibilities of inaccuracies from multiple measurements.

Calculation of regurgitant volumes

Regurgitation is the flow of blood backwards through an incompetent valve. Quantification of regurgitant volume and its fraction of SV provides objective information on severity and guides the clinician on the need for intervention. Regurgitant volume and fraction are validated for grading severity of mitral and aortic regurgitation, but are seldom used for tricuspid and pulmonary valve pathology.

Volumetric method:

$$\text{Systemic SV} = \text{Total SV} - \text{regurgitant volume (RV)},$$

where the total SV is forward flow through the regurgitant valve.

Thus, for mitral regurgitation:

$$SV_{LVOT} = SV_{MVI} - RV_{MV}$$

where MVI is mitral valve inflow and SV_{LVOT} is the systemic (true) SV.

This demonstrates conservation of mass as the passage of blood has only two options; forward through the LVOT or backwards through the incompetent mitral valve.

In practice, whilst possible, this method is seldom used because of the challenges involved in accurately measuring mitral valve area, which is more complex in shape than the AV and changes in shape during atrial systole. The presence of aortic regurgitation is a compounding problem as it is in the same phase as mitral inflow and thus erroneously increases total SV.

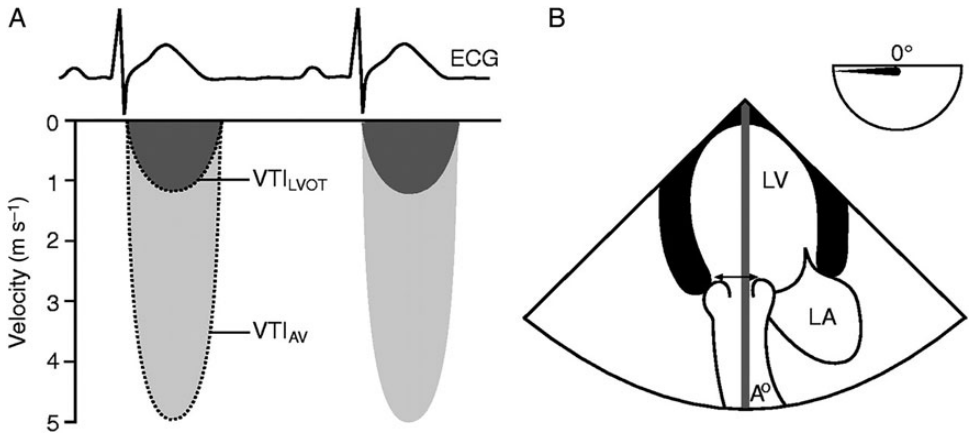

Fig 1 CSA_{LVOT} is measured from the diameter of LVOT, given as an arrow in the 2D echo image in (B). A 'double envelope' signal is obtained from the CW Doppler of LVOT and AV. The thick darker envelope represents low velocity flow through LVOT and the lighter envelope represents flow through stenotic AV in (A). The software calculates peak and mean gradients for each signal and the velocity–time integral (VTI) for AV VTI_{AV} and LVOT VTI_{LVOT} signals. SV is calculated by the equation $CSA_{LVOT} \times VTI_{LVOT}$. AV area is calculated from the equation $CSA_{LVOT} \times VTI_{LVOT}/VTI_{AV}$. (Reproduced after permission from Morgan-Hughes.)[6]

For aortic regurgitation, the equation is as follows:

$$SV_{MVI} = SV_{LVOT} - RV_{AV}$$

where SV_{MVI} is the systemic (true) SV after the removal of the aortic incompetent component from the LVOT ejection. Again, this process is seldom used as it is time-consuming and has the same error potential as that with the mitral valve. Similarly, mitral regurgitation will underestimate the aortic regurgitant volume and invalidate the calculation.

The regurgitant fraction can be calculated by dividing the regurgitant volume by total SV and is a gauge of severity. Quantification of all valve lesions is given in Table 1.

Proximal isovelocity surface area measurement

Proximal isovelocity surface area (PISA) is the term used to explain the phenomenon that occurs as blood flows through an orifice, whereby all equidistant points towards the orifice exhibit the same velocity. The velocity increases as blood nears the orifice. This creates the illusion of multiple concentric hemispheres of flow convergence, with each hemisphere having the same velocity, the smallest of which is the fastest. PISA can be used in all valves, but its commonest application is in mitral valve pathology. PISA hemispheres are seen using colour flow Doppler analysis.

Regarding the mitral valve, PISA hemispheres occur on the ventricular side of the valve during systole for mitral regurgitation, and on the atrial side of the valve during diastole for mitral stenosis. Thus, for mixed mitral valve disease, PISA hemispheres can be seen on both sides of the valve throughout the cardiac cycle.

PISA size can be artificially changed to suit the interrogation simply by altering the Nyquist limit, with no loss of accuracy. Reducing the Nyqyist limit increases the size of the PISA.

For mitral regurgitation, the flow rate through any proximal hemisphere equals regurgitant flow rate through the mitral valve during systole.

Using the same equation from above, flow=CSA×velocity and the law of conservation of mass (as in the Continuity Equation), the following equations must be true:

$$\text{PISA flow rate} = \text{Regurgitant flow rate}$$
$$CSA_{PISA} \times \text{velocity}_{PISA} = EROA_{MV} \times \text{velocity}_{MR}$$

where EROA is the effective regurgitant orifice area and MR is mitral regurgitant jet peak velocity.

CSA_{PISA} is assumed to be hemispherical, thus the area is $2\pi r^2$ (surface area of a sphere is $4\pi r^2$). The radius is the length of the PISA from the valve orifice and the velocity is simply the Nyquist limit set by the investigator. If the PISA angle (θ) is <180°, then the CSA should be multiplied by $\theta/180°$.

Once the $EROA_{MV}$ is known (in itself a marker of MR severity), the regurgitant volume can be calculated in the same way that SV was calculated in the previous section.

$$\text{Regurgitant volume (MR)} = EROA_{MV} \times VTI_{MR}$$

CW Doppler aligned through the MR jet is used both for peak velocity to calculate EROA and the area under the curve (VTI) to calculate regurgitant volume.

The above process is used regularly in formal echocardiography but is time-consuming in the operating theatre. An abbreviated method of calculating $EROA_{MR}$ uses the following equation:

$$EROA_{MR} = \frac{r^2}{2}$$

where r is the PISA radius (Fig. 2).

This can only be done if the Nyquist limit is set to 40 cm s^{-1}, the PISA is a complete hemisphere, r is the radius of the first PISA seen and the MR peak velocity is 5 m s^{-1}. Whilst much simpler, errors are often small and acceptable. PISA radius alone at 40 cm s^{-1} can be used as a marker of MR severity.

PISA can also be used to calculate mitral valve area (MVA) in mitral stenosis:

Thus

$$PISA_{MV-inflow} \times \text{velocity}_{PISA} = MVA \times VTI_{MV-inflow}$$

Pressure half time (PHT)

PHT is a simple Doppler method for assessing MVA and the severity of aortic regurgitation, and uses the concept of pressure deceleration.

Mitral stenosis

The pressure gradient between LA and LV increases in mitral stenosis, with longer time required for blood to fill the LV through the stenotic valve. The early diastolic, transmitral Doppler velocity (E-wave) deceleration is subsequently prolonged. PHT

Table 1 Quantification of valve lesions

	Mild	Moderate	Severe
Aortic regurgitation			
Jet width/LVOT width (%)	<0.25	<0.25–0.64	>0.64
Vena contracta width (cm)	<0.3	0.3–0.6	>0.6
Jet area/LVOT area (%)	<4	4–60	>60
$P^{1/2t}$ (ms)	>500	500–200	<200
Regurgitant volume (ml $beat^{-1}$)	<30	30–59	>60
Regurgitant fraction	<30	30–49	>50
EROA (cm^2)	<0.10	0.10–0.29	0.3
Aortic stenosis			
Jet velocity (m s^{-1})	<3	3–4	>4
Mean gradient (mm Hg)	<25	25–40	> 40
Valve area (cm^2)	1.5–2.0	1.0–1.5	<1.0
Mitral regurgitation			
Jet area/LA area (%)	<20	20–40	> 40
Vena contracta (mm)	<3.0	3–6.9	>7
PISA radius (mm)	<4	4–10	>10
Regurgitant volume (ml)	<30	30–59	>60
Regurgitant fraction (%)	<30	30–49	>50
EROA (cm^2)	<0.2	0.2–0.4	>0.40
Mitral stenosis			
Mean gradient (mm Hg)	<5	5–10	>10
PHT (ms)	71–139	140–219	>219
MVA (cm^2)	1.5–2.0	1.0–1.5	<1
Tricuspid regurgitation			
Jet area (cm^2)	<5	5–10	>10
PISA radius (mm)	<5	6–9	>9
Vena contracta (mm)	–	<7	>7
Pulmonary stenosis			
Peak velocity (m s^{-1})	<3	3–4	>4
Pressure gradient (mm Hg)	<36	36–64	>64
LV dysfunction			
dP/dt (mm Hg s^{-1})	1200	800–1200	<800

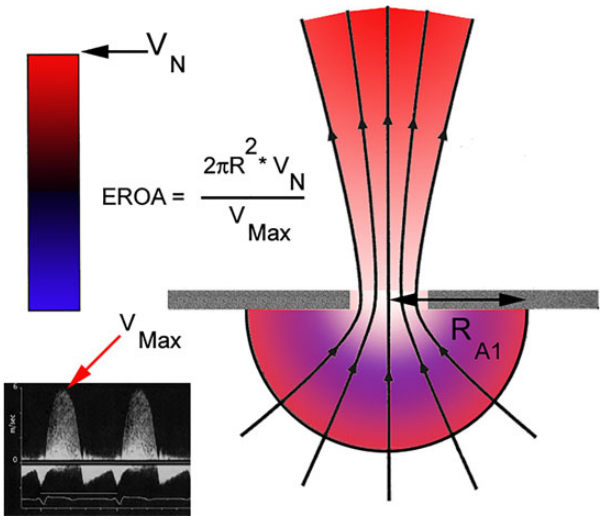

Fig 2 Proximal isovelocity surface area (PISA) principle applied to stenotic or regurgitant orifice area. EROA refers to effective regurgitant orifice area; $2\pi R^2$ surface area of hemispheric shell derived from the proximal flow convergence radius (R) in cm^2; V_N velocity at the radius of hemispheric shell (colour aliased velocity or Nyquist limit) (cm s^{-1}); V_{max} peak velocity across the stenotic orifice. (Figure belongs to A. Pybus. Reproduced with permission from ipad app; https://itunes.apple.com/gb/app/papworth-hospital-mcq-learning/id679626718?mt=8.)

measures the rate of decrease of the pressure gradient between LA and LV and is the time required for the peak pressure gradient to decline to 50% of its original value (in milliseconds). As stenosis increases in severity, the PHT increases. From before, pressure has to be extrapolated from Doppler velocities:

$$P_{half} = \frac{1}{2} \times P_{peak}$$

from Bernoulli $\Delta P = 4V^2$

$$4(V_{half})^2 = \frac{1}{2} \times 4(V_{peak})^2$$

Simplifying the above, we obtain

$$V_{half} = V_{peak}/\sqrt{2}$$

or more simply

$$V_{half} = V_{peak} \times 0.707$$

Thus PHT is the time taken for the initial peak mitral inflow velocity to decrease by 30% (Fig. 3).

PHT is quick to do and independent of CO, mitral regurgitation, and heart rate. It is thus very useful in mitral stenosis with coexistent mitral regurgitation. Conversely, in low CO status, severity of mitral stenosis can be underestimated by low transmitral pressure gradients.

From experimental models, a PHT of 220 ms equates to a MVA of 1.0 cm^2.[7]

Thus, MVA equals 220/PHT (shorter PHT = bigger valve area).[8]

Limitations of using PHT to calculate MV area

Any condition that alters the diastolic compliance of the LA or LV can affect flow velocity and pressure half time. It is not useful in the estimation of normal mitral valve area because it reflects only the compliance of the ventricle when there is no stenosis. It is inaccurate if the compliance of the ventricle is abnormal. Pressure half time method is not validated in calculating prosthetic mitral valve areas.[9] It is unreliable with severe aortic regurgitation because of rapid equilibration of LA and LV pressures and also because the mitral inflow and aortic back flow may be difficult to differentiate with Doppler. Sinus tachycardia, first-degree block and atrial flutter with fast atrial rates can affect deceleration slope by altering the mitral inflow E wave and artificially shorten the PHT and overestimate the MVA. Pressure half time method is also not accurate in the presence of an atrial septal defect.

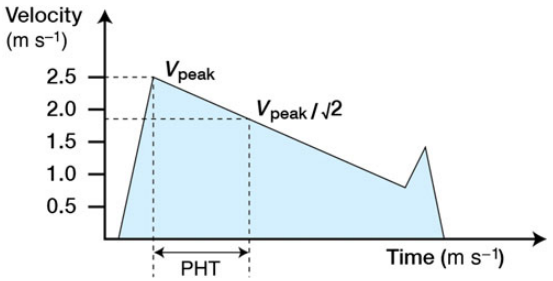

Fig 3 The method of measuring pressure half time from the Doppler velocity spectrum. PHT equals the time taken for the peak velocity (V_{peak}) to decrease to a value equitant to $V_{peak}/\sqrt{2}$. In this example, PHT equals the time taken for the velocity to decrease from 2.5 to 1.77 m s^{-1}. (From Anderson.[11] Reproduced with permission from MGA Graphics.)

Aortic regurgitation

In aortic regurgitation, CW Doppler velocity profile during diastole denotes the pressure decrease between aorta and left ventricle and the velocity at which the pressures equilibrate reflects severity of regurgitation. With mild disease, the early diastolic gradient is initially high and declines slowly over time. The gradual decrease in aortic diastolic pressure creates a small increase in left ventricular diastolic volume. In severe aortic regurgitation, the drop in pressure gradient during diastole occurs suddenly as a result of the rapid decrease in aortic diastolic pressure, with an associated increase in left ventricular end-diastolic volume (PHT < 300 ms). PHT is most useful in acute aortic regurgitation, which commonly manifests as a rapid increase in LVEDP and short PHT. PHT is not validated for estimating severity of aortic regurgitation in the presence of significant mitral disease.

Ventricular systolic function (dP/dt)

Many of the methods above calculate LV function during ejection and are thus influenced by preload and afterload. Using the mitral regurgitation jet (CW Doppler), dP/dt advantageously measures the rate of increase of ventricular pressure during the isovolumetric phase of contractility (units mm Hg s^{-1}). The MR jet is measured at 1 and 3 m s^{-1} (which corresponds to a pressure increase from 4 to 36 mm Hg, using the simplified Bernoulli equation) and the time interval between 1 and 3 m s^{-1} on the mitral regurgitation jet is measured to calculate dP/dt.[10]

$$\frac{dP}{dt} = \frac{32}{\Delta t}$$

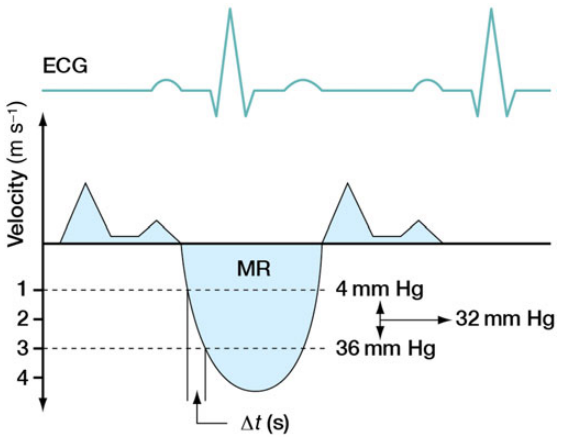

Fig 4 Measurement of the dP/dt from the mitral regurgitation Doppler signal. For explanation, please refer to text. (From Anderson.[11] Reproduced with permission from MGA Graphics.)

(i.e. time interval taken for the velocity to change from 1 to 3 m s^{-1}) (Fig. 4).

Normal values are 1000–1200 mm Hg s^{-1}.

It can also be used to assess right ventricular systolic function, usually between 0 and 2 m s^{-1}.

Conclusions

Echocardiography is not only used for evaluating cardiac anatomy but can also provide objective haemodynamic information about valve areas, pressure gradients, intra-cardiac volumes, ventricular systolic and diastolic function and cardiac output. These assessments guide clinicians and their advice to patients on treatment options and need for intervention, such as grading aortic stenosis and the need for valve replacement. However, they are measurements which require accuracy and expertise and have complex limitations in the presence of other cardiac pathologies and thus should be used in conjunction with other modalities in the final decision-making process.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Update on the intraoperative management of adult cadaveric renal transplantation

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Key points

- In the UK in 2013, 1930 renal transplantations were undertaken: a 50% increase since 2005. NHS Blood and Transplant initiatives suggest that this number is set to increase.
- Chronic renal failure patients have severe comorbidities necessitating close attention to preoperative assessment.
- Patients on regular dialysis present the anaesthetist with significant challenges from complex fluid shifts, electrolyte disturbances, and rapid scheduling of emergency surgery.
- Achievement of physiological goals intraoperatively is associated with improvement in clinical outcomes.
- New immunosuppression regimes, particularly those including monoclonal antibodies, may be started perioperatively. They have side-effects which anaesthetists must be aware of.

Renal transplantation is increasing with 1930 transplants undertaken in the UK in 2013 compared with 1308 in 2005. This increase follows the NHS Blood and Transplant (NHSBT) 'Organs for Transplant' initiative, and should continue rising as part of their 'Taking Organ Transplant to 2020' programme. Renal transplantation confers almost immediate improvements in quality of life and improves morbidity and mortality compared with dialysis. There are also fiscal gains to the healthcare provider: renal transplantation being cheaper than ongoing dialysis. However, graft implantation is a complex surgical procedure with both short- and long-term outcomes directly attributable to intraoperative physiological status.[1,2] In future there will be a need to anaesthetize more elderly recipients, with more extensive comorbidities.

This article will discuss anaesthesia for implantation of cadaveric kidneys; alternative sources within this journal have discussed live related donor surgery in detail.[3]

Preoperative investigation and optimization

Comorbid illness

The commonest aetiology of renal dysfunction in the UK is diabetes mellitus, with an increasing prevalence since 2006 and projected to be 14 000 patients in 2014–15. This and other causes of end-stage renal failure (ESRF), such as IgA nephropathy and hypertension, each pose their own anaesthetic challenges.

Chronic kidney disease (CKD) is classified using glomerular filtration rate (GFR) to quantify the extent of failure. CKD Stage 1 disease (GFR >90 ml min^{-1} 1.73 m^{-2}) describes normal function but with urinary or structural renal abnormalities. Stage 2 (GFR 60–89 ml min^{-1} 1.73 m^{-2}), Stage 3 (GFR 30–59 ml min^{-1} 1.73 m^{-2}), and Stage 4 (GFR 15–29 ml min^{-1} 1.73 m^{-2}) describe mild, moderate, and severe impairment, respectively. CKD Stage 5 is defined as a GFR of <15 ml min^{-1} 1.73 m^{-2}. In this article, ESRF will refer to patients whose kidney disease is severe enough to warrant transplantation, typically a GFR <20 ml min^{-1} 1.73 m^{-2}, including both CKD Stage 4 and 5 patients.

Preoperative assessment of potential renal transplant recipients occurs as part of the listing process. This assessment identifies patients with scope for optimization and excludes patients with contraindications to transplantation. Though most patients will be adequately optimized, some travel significant distances to the transplant centre so investigations may not be readily available. Most will be in ESRF and dialysing, although some undergo pre-emptive transplantation before starting dialysis.

The commonest co-morbidity in adults with ESRF is ischaemic heart disease (IHD). This is accelerated in ESRF because of the complex interaction between CKD and risk factors for IHD such as diabetes mellitus, hypercholesterolaemia, and hypertension; and also through independent risk factors such as modulation of systemic inflammatory processes by dialysis, renal osteodystrophy, and hyperhomocysteinaemia.

Preoperative investigations

Patients are frequently anaemic, so a full blood count is mandated before operation with a group and save serum. Blood loss during renal transplantation is typically <500 ml, but unanticipated brisk bleeding is possible so transfusion should be consented for.

A raised white cell count is of concern and a source should be sought; the most likely foci being the chest, urinary tract, dialysis line, or peritoneal catheter. A decision must be made to proceed or cancel surgery as immunosuppression may render the patient susceptible to overwhelming sepsis.

An ECG should have been acquired at listing and a repeat preoperative ECG ensures there are no electrocardiographic sequelae from electrolyte imbalance, and provides a baseline should perioperative cardiac embarrassment occur. Many high risk or symptomatic patients will have more extensive preoperative cardiac investigations such as stress echocardiography, coronary angiography, or cardio-pulmonary exercise testing available.

A preoperative chest X-ray is essential to correlate with clinical evaluation of fluid status and to assess for radiological evidence of progressive heart disease.

Medication

Typically recipients are hypertensive and receiving antihypertensive therapy comprising an angiotensin receptor blocker or an ACE inhibitor. Hypertension is often refractory and patients may take several additional drugs such as calcium-channel antagonists, alpha antagonists, or beta-blockers. This impairs autoregulation and undermines their ability to respond to hypovolaemia under anaesthesia.

High doses of ACE inhibitors should be withheld perioperatively, unless there is evidence of left ventricular dysfunction. In contrast, beta-blockers, aspirin, and statins should not be stopped perioperatively.[4] Diuretics should not be stopped, as this may compromise native renal function after operation, and these patients must have serum potassium, chloride, and bicarbonate levels evaluated immediately before operation.

Although platelet number may be normal, the uraemic state and frequent use of antiplatelet drugs in this population may impair platelet function and prolong bleeding times without abnormalities in the coagulation profile.

Dialysis assessment

Volume status, acid–base, and electrolyte balance can be assessed from blood samples taken before and after dialysis, noting the volume of fluid removed at each session and the patient's native urine output. An anuric patient will be fluid restricted, and will have more fluid removed during dialysis to manage their water balance. This causes large fluid shifts and relative dehydration with possible cardiovascular instability under anaesthesia. Peritoneal dialysis patients undergo comparatively smaller fluid shifts.

An important decision is whether to dialyse a patient before transplantation. Absolute indications aside (hyperkalaemia, fluid overload, uraemia, acidosis), a subtle balance must be struck. Dialysis will reduce plasma potassium, correct acidosis, and potentially avoid the need for postoperative dialysis, even if graft function is delayed. However, it will render the patient intravascularly deplete necessitating greater i.v. filling to optimize conditions for graft implantation. Though dialysis renders the patient transiently anticoagulated, the short half-life of heparin obviates this problem perioperatively. Most transplant anaesthetists operate by the idiom: 'if in doubt dialyse'.

Anaesthetic techniques

Induction of anaesthesia

Good peripheral venous access is essential before induction, as there may be a requirement to give large volumes of fluid rapidly but insertion may be challenging because of previous repeated venepunctures.

Induction may proceed with a combination of an i.v. induction agent and a strong opioid, considering the renal elimination of the drugs used. Fentanyl is a suitable choice of opioid, as is remifentanil. Morphine is predominantly metabolized by the liver but its metabolites, which have analgesic properties, are excreted in the urine. This should not affect intraoperative morphine requirements (patients with ESRF require the same plasma concentration of morphine for analgesia), but maintenance doses should be reduced. Propofol is a safe choice of hypnotic agent, and thiopental is a suitable alternative (the dose of thiopental should be reduced in uraemia to correct for changes in its plasma protein binding). Both drugs cause severe hypotension if given in excess in this population.

Muscle relaxation

Neuromuscular block is mandated to facilitate tracheal intubation and allow modulation of acid–base status. An elevated Pa_{CO_2} will increase serum potassium concentrations. Rapid sequence induction (RSI) should be considered, particularly in patients who display autonomic dysfunction, as gastric emptying may be delayed. Should RSI be indicated, succinylcholine should be avoided in cases where the serum potassium is >5.5 mmol l^{-1}. Rocuronium 0.9 mg kg^{-1} provides a suitable alternative with only a slightly longer onset of action than succinylcholine. This dose will have a clinical duration in this patient population of around 90 min as rocuronium is 30% eliminated by the kidney.

Muscle relaxation can otherwise be achieved with drugs that are eliminated in the presence of renal failure, such as atracurium and cisatracurium which undergo Hofmann degradation and ester hydrolysis. Although rocuronium may be reversed with sugammadex at the end of surgery, excretion of the rocuronium–sugammadex complex is renally dependent (Fig. 1). It is not yet recommended on the product data sheet for these patients until further research has been carried out.[5]

Monitoring and positioning

A central venous cannula should be inserted after induction, to guide fluid administration and allow use of potent vasoactive

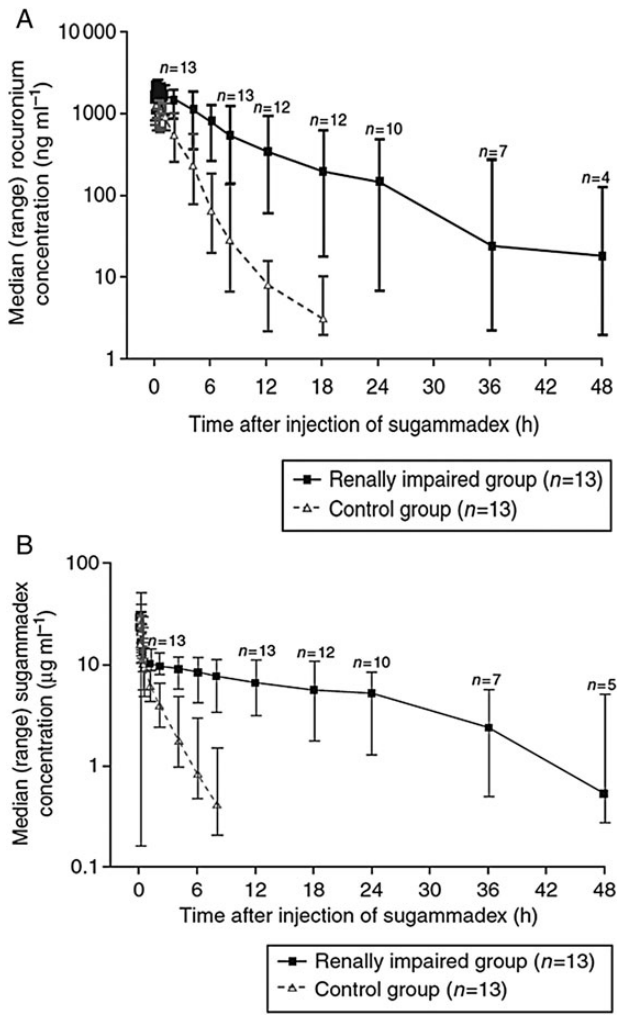

Fig 1 Semilog plots of the plasma concentrations of rocuronium (A) and sugammadex (B) in health and chronic renal failure.[5] Both drugs persist in the plasma for up to 48 h in patients with renal dysfunction.

medication such as metaraminol, ephedrine and norepinephrine. It may be appropriate to site a haemodialysis catheter at this stage for postoperative use in anticipation of delayed graft function; an assessment best made by the transplant surgeon. Ultrasonographic assessment of the central vasculature before attempting cannulation is essential as there is a high incidence of pre-existing venous stenosis from the use of long-term indwelling catheters (particularly at subclavian and internal jugular sites). Central venous cannulae should not be sited where there is a potential for steal from an established arteriovenous fistula (AVF), or where post-procedural stenosis may undermine future attempts to form one.

Monitoring of cardiac output may be warranted in cases where cardiovascular instability is expected, particularly if there is evidence of significant cardiac co-morbidity or large volume fluid administration is anticipated. There is little evidence to guide therapy using oesophageal Doppler in this cohort, but it remains the most useful tool in practice. Avoidance of unnecessary arterial cannulation renders pulse contour analysis devices less appropriate. If there is a strong comorbid indication for arterial cannulation (e.g. severe valvular heart disease or poor ventricular function), then a site should be selected that will not impede future AVF formation, or undermine existing fistula function. Femoral cannulation is contraindicated because of surgical vascular access concerns, and the increased incidence of catheter-related bloodstream infection.

Care of the AVF is of paramount importance perioperatively and involves avoiding cannulating the AVF limb, wrapping it with cotton wool, and carefully positioning it alongside the patient or on an arm board to prevent traction and compression injuries. Positioning is typically supine with lateral roll as necessary with the arms easily accessible using boards. Patient and fluid warming should proceed according to NICE Clinical Guidance 65 standards.

Maintenance of anaesthesia

Anaesthesia may continue using inhalation agents, with sevoflurane being the agent of choice for shorter, uncomplicated cases. Isoflurane is an alternative and neither drug has been shown to be associated with postoperative renal dysfunction, despite peak plasma fluoride levels in excess of 50 μM litre^{-1} having been documented with use of sevoflurane. Should anaesthesia run to over 4 MAC hours then desflurane has a more favourable emergence profile and results in less fluoride ion production (although this has not been shown to be clinically significant).[6] Total i.v. anaesthesia is a suitable alternative technique using target-controlled propofol and remifentanil infusions. Safety is ensured as esteratic metabolism of remifentanil is renally independent.

Intraoperative analgesia

This can be provided with i.v. paracetamol, and incremental doses of morphine (0.05–0.1 mg kg^{-1}) or fentanyl (up to 1.0 mcg kg^{-1}). Non-steroidal anti-inflammatory drugs are contraindicated because of deleterious effects on kidney function by interruption of blood flow in the renal vasa recta. Given the nature of the surgical technique and incision site, transverse abdominus plane blockade, either post induction or surgically under direct vision, provides a useful opiate-sparing effect.

Neuraxial techniques may be suitable depending on the anticipated duration of surgery. The increased risk of haematoma formation in these patients must always be appreciated. Use of spinal anaesthesia with local anaesthetic agents will provide dense intraoperative analgesia, reducing initial opioid requirements. Addition of intrathecal opioids may aid postoperative analgesia. Epidural catheter techniques are less appropriate because of the possibility of dialysis and anticoagulation in the immediate postoperative period.

Physiological goals under anaesthesia

A mean arterial pressure (MAP) of 90 mm Hg is warranted for all patients undergoing renal transplantation (adjusted upwards for untreated hypertensives).[1] This preserves residual renal function and reduces delayed graft function and the need for postoperative dialysis. Normotension at the time of graft arterial clamp removal is essential to optimize graft perfusion.

I.V. fluids

Fluid balance during renal transplant surgery is contentious. Fluid loading to maintain cardiac output, optimize renal perfusion, and reduce blood viscosity (to improve rheology) may improve outcomes.[2] However, sensible goals should be set, as postoperative pulmonary oedema must be avoided.

There is good evidence that a CVP of 12–14 cm H_2O at the time of graft perfusion leads to improvements in graft survival and

function.[2] One trial suggested that fluid regimes where <2500 ml were administered intraoperatively seem to have better outcomes.[1] Therefore, a liberal fluid administration strategy at the beginning of surgery is likely to be beneficial, whilst avoiding high total infusion volumes. Cardiac output monitoring allows more accurate assessment and management of the fluid regime. Several trials have suggested that normal saline in this population is detrimental to postoperative serum potassium indices and acid–base balance, and instead a balanced crystalloid such as Hartmann's solution should be used.[7] Hydroxyethyl starch must be avoided due to the risk of renal injury. Alternative colloids include gelatins and human albumin solution (which has a growing evidence base).

Mannitol

Mannitol is used as an adjunct to intraoperative fluid therapy: combining a well-established colloid with a free radical scavenging effect, but there is little evidence of improved graft survival.[8] Many centres infuse mannitol 0.5 g kg^{-1} at the time of arterial clamp removal. This should be accounted for when planning fluid administration.

Dopamine

Dopamine is used by a diminishing number of centres during renal transplantation, as there is no evidence to support improvements in patient or graft outcomes after use of this drug.

Blood transfusion

A transfusion target of 70 g $litre^{-1}$ should be used before operation, in line with current critical care recommendations. Though the recently dialysed patient will be volume deplete and blood transfusion may seem appropriate to reduce haemodilution and improve oxygen delivery to the graft, such improvements are not immediate. Other risks of transfusion include hyperkalaemia, increased blood viscosity, allosensitization, and transmission of infection. Consequently, transfusion of allogenic CMV negative blood should be used judiciously and, in cases of high blood loss, consideration should be given to intraoperative cell salvage.

Immunosuppressant regimes

Early immunosuppressant regimes for renal transplantation were reliant on corticosteroids and azathioprine. They were superseded in the 1980s by cyclosporin, which has a more acceptable side-effect profile. Current immunosuppressant regimens comprise two phases: induction and maintenance. The induction phase is typically administered pre- and intraoperatively.

If induction of immunosuppression begins after induction of anaesthesia, it should be agreed with the transplant surgeon before operation, and recognized during the WHO surgical safety 'sign in'. Modern intraoperative regimes include a biological agent and high dose methylprednisolone.

Methylprednisolone is a potent i.v. corticosteroid, administered around the time of venous anastomosis. Whilst many centres avoid use of long-term steroids for maintenance immunosuppression, almost all induction regimes include a perioperative dose.

Biological immunosuppressants

There is good evidence that induction of immunosuppression with a biological agent reduces the incidence of early cellular rejection,[9] but this is balanced against the risks of these extremely potent drugs, which are summarized in Table 1.

Table 1 Recognized complications of depleting biological immunosuppressants (e.g. alemtuzumab)

Infusion-related side-effects
Fever
Nausea and vomiting
Anaphylactoid effects
Pruritus
Rash
Dyspnoea and bronchospasm
Angioedema
Hypotension, both transient and sustained
Cytokine release syndrome
Cardiac effects
Angina
Arrhythmia
Heart failure
Cardiac tamponade
Cutaneous effects
Stevens–Johnson syndrome
Toxic epidermal necrolysis
Infectious complications
Susceptibility to opportunistic infection
Hepatitis B infection and reactivation
Tuberculosis reactivation
Progressive multifocal leucoencephalopathy

Agents may be divided into two groups: T-cell depleting and non-depleting agents. Lymphocyte depletion is associated with cytokine release and potential drug reactions. It results in chronic immunosuppression in some patients putting them at risk of infectious complications and malignancies in the longer term.[10] For this reason, depleting agents are used when potent immunosuppression is required (e.g. ABO or HLA incompatibility between donor and recipient, in young recipients with potent alloreactivity or where there are adverse pro-inflammatory graft factors).

Depleting agents

The commonest depleting agents in transplant practice are antithymocyte globulin (ATG) and alemtuzumab. Both cause profound lymphocyte depletion.[11] ATG is first line in the USA, with alemtuzumab being the agent of choice in the UK. Intraoperatively, alemtuzumab 30 mg is given by i.v. infusion over at least an hour, or by subcutaneous injection.

Non-depleting agents

These drugs do not cause lymphocyte depletion but oppose the pathways that result in alloreactive T-cell activation. They include the CD-25 (IL-2 receptor) antagonist basiliximab. The benefit of non-depleting agents is reduced immunoparesis and improved side-effect profile whilst reducing the risk of acute rejection compared with regimens where induction agents are not used.[12] Intraoperatively, basiliximab 20 mg is given by slow i.v. injection.

Anaphylaxis

Biological agents are manufactured after inoculation of animals with human T cells. The polyclonal sera produced are purified, chimerized and humanized, to a greater or lesser degree, but all carry a risk of anaphylaxis and cytokine release syndrome. This syndrome, characterized by bronchospasm, hypotension, and tachycardia initially indistinguishable from anaphylaxis, can cause vasodilatation and bronchospasm lasting for many hours or days. Survival after cytokine release syndrome is variable but severe reactions are

associated with poor outcomes. Management is initially that of anaphylaxis, with ongoing organ support as required.

Biological agents are also associated with cardiac events intra- and after operation, ranging from coronary work perfusion mismatching (cardiac ischaemia) to idiosyncratic cardiac tamponade.

Postoperative management

Analgesia

A patient-controlled analgesia (PCA) device is appropriate for pain control. As renal function may improve only slowly after operation a reliable regime is morphine 0.5 mg boluses with 5 min lockouts. The inherent safety of a PCA means that standard dosing regimes should be safe but the risk of respiratory depression is greater than in healthy patients due to the renal excretion of active metabolites of morphine. Other suitable pain management strategies utilize oxycodone (19% excreted unchanged in urine) or fentanyl (despite increased risks of respiratory depression).

Fluid balance

Monitoring of CVP after operation can guide fluid administration but evidence suggests that suboptimal MAP rather than suboptimal CVP increases the incidence of DGF.[13]

Level of care

There is no indication to admit transplant recipients to Level 2 or 3 care routinely, although this should be considered if there are perioperative concerns. A dedicated post-transplant unit is essential and staff who routinely care for this cohort are vital to early identification and prevention of postoperative complications.

Summary

Renal transplantation is a complex surgical procedure. Anaesthesia for these cases is challenging and optimal physiology can significantly improve graft and patient outcomes. Many of these cases occur outside of normal working hours, but senior anaesthetic input is essential.

Immunosuppression commences in the pre- and intraoperative phase and it is imperative that anaesthetists have an awareness of the agents used. Immunosuppressant drug selection should be discussed by the anaesthetic and surgical team, and units must have strict protocols regarding drug handling and administration.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Anaesthesia for paediatric lower limb surgery

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Key points

- Musculoskeletal disorders can be manifestations of a systemic disease.
- There may be relative or absolute contraindications to the use of non-steroidal anti-inflammatory drugs or central neuraxial block.
- Blood loss can be substantial unless a tourniquet is used.
- Many conditions are associated with difficult airway management.
- Some co-morbidities are associated with a hypermetabolic state that can be confused with malignant hyperpyrexia.

Musculoskeletal problems in children account for about one-third of all congenital abnormalities. Many, such as clubfoot and hip dysplasia may be isolated in otherwise healthy children but a significant number of patients present for surgery with a musculoskeletal aspect of their multi-system disease. The anaesthetic care and management of the child requiring lower limb orthopaedic surgery may range from the straightforward to the very complex and this is largely dependent upon the child's pre-existing condition for which they require the corrective surgery. This article will focus on the assessment and anaesthetic management of children requiring surgery to correct their lower limb problems.

Associated conditions

Children with some underlying medical conditions frequently require orthopaedic intervention and these include:

Spina bifida

Caused by incomplete closure of the embryonic neural tube, spina bifida has a range of clinical presentations, from *spina bifida occulta* to meningocele and Arnold–Chiari malformation associated with hydrocephalus. The total incidence of spina bifida is 5.8 per 10 000 total births but the incidence of elective termination in affected pregnancies is ~72%, so incidence in live births is much lower. Ten year survival now exceeds 80%.[1]

Myelomeningocele is a sac containing meninges and neural elements bulging through a vertebral defect and which is closed surgically shortly after birth, but the underlying spinal cord damage remains. Abnormal lower limb growth and denervation can lead to developmental abnormalities such as hip dysplasia and talipes equinovarus (clubfoot). Neuromuscular imbalance occurs when spastic or unopposed muscles work against flaccid muscles, causing joint deformity. Surgical intervention in the form of soft tissue release and bone realignment is then required to preserve mobility.

Arthrogryposis multiplex congenita

Occurring in 1:3000 live births, arthrogryposis consists of multiple, non-progressive symmetrical rigid joint contractures, worsening distally. Children have normal intellectual function and nearly normal life expectancy. Orthopaedic intervention may be required for clubfoot, hip dysplasia, dislocated patella, and scoliosis. Surgical treatment aims to correct all lower limb deformities with soft tissue releases and osteotomies before the age of 2 yr to facilitate mobilization.

Developmental dysplasia of the hip

Developmental or congenital dysplasia of the hip (DDH) is prolonged displacement of the fetal femoral head from the acetabulum. Incidence is ~1:1000, with girls affected four times more commonly than boys.

Infants under 6 months of age generally have joint subluxation without associated bony deformity and are treated non-surgically in a Pavlick harness for up to 8 weeks until both hips are stable. Children over 6 months of age or those with inadequate reduction after conservative treatment require open or fluoroscopically guided closed manipulation and reduction under general anaesthesia, with application of a hip spica cast to maintain the correct joint position until the hip becomes stable. After 18 months of age, open reduction is the treatment of choice. Generally no specific anaesthetic precautions are required as these tend to be otherwise healthy children.

Cerebral palsy

For a full discussion of this condition please refer to the *CEACCP* article 'Cerebral palsy and anaesthesia'.[2]

Surgery is performed to prevent or improve defects such as the classical *windswept deformity* of hips or knees—an abduction and external rotation position of one joint with the opposite joint in adduction and internal rotation, caused by a combination of contractures, immobility, gravity, and time. Surgery can facilitate function or mobility, including ability to sit in a wheelchair. Common procedures include soft tissue releases, tendon transfers, tenotomies, and botox injections. These patients are frequently listed for simultaneous correction of multiple deformities.

Osteogenesis imperfecta

This autosomal dominant condition with four major variants is caused by a defect or reduction in the production of type I collagen with an incidence of 1:20 000 live births. Bones are osteoporotic, brittle, and easily fractured, joints are hypermobile and frequently dislocated. Patients with Type I osteogenesis imperfecta (OI) have characteristic blue-grey sclerae and craniofacial disproportion. Fractures may occur during nappy changes and application of a non-invasive blood pressure cuff.[3] Type II is most severe (OI congenita) and is usually lethal at birth because of multiple fractures sustained during delivery. If the neonate survives to childhood they may develop micrognathia, restrictive thoracic deformity and severe fragility of long bones. Death is frequently as a consequence of respiratory failure because of restrictive lung disease.

Children with OI present for emergency treatment of fractures and correction of deformities, including multiple site osteotomies.

Dwarfism

The most common form of dwarfism is *achondroplasia*, affecting 1.5 per 100 000 live births but there are over 100 osteochondrodysplasias and mucopolysaccharidoses characterized by disproportionate short stature (<157 cm in adults) and limb abnormalities. Common orthopaedic procedures include limb-lengthening techniques, joint replacement, and limb realignment.

Preoperative evaluation

Preoperative assessment concerns vary with the age and medical condition of the child. Planning is best done in conjunction with the surgeon to be aware of the location of the incision site (to plan regional techniques) the length of the procedure and any individual surgical preferences. The surgeon may also plan multiple interventions in one session and this significantly extends the duration of surgery and potentially increases analgesic requirements.

Related conditions

A thorough history of related diagnoses is essential. Important co-morbidities include scoliosis and restrictive pulmonary disease, congenital or acquired cardiac lesions, craniocervical and facial abnormalities, hydrocephalus, dental disease, and obesity. Pre-existing neurological deficits, contractures, deformities, and fractures should also be carefully documented to aid the planning of positioning and handling.

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is especially common in dwarfism, either secondary to cervico-medullary cord compression (central OSA), or as a result of thickened pharyngeal and laryngeal structures, narrowed nasal passages, micrognathia, pharyngeal hypoplasia, and tracheal narrowing. An element of airway obstruction may be present even when awake and great care should be taken when considering sedative pre-medicants, especially in obese patients. Sleep studies are frequently performed to assess for apnoeas. Children with OSA have an increased incidence of perioperative complications such as airway obstruction, desaturation, and laryngospasm. They are also more likely to need postoperative critical care.

Children with OSA and systemic disease affecting the skeleton should also be carefully examined for upper motor neurone lesions secondary to craniocervical instability or foramen magnum stenosis and if a lesion is suspected imaging should be discussed with a paediatric radiologist.

Cardiorespiratory disease

Arthrogryposis, achondroplasia, and OI are frequently associated with congenital cardiac lesions. ECG, echocardiogram, chest radiograph, and cardiological review may guide anaesthetic technique and decision-making.

Developmental diseases of the skeleton can lead to thoracic cage deformities, scoliosis, and consequent restrictive lung disease. Pulmonary hypertension and hypoplasia can then progress to cor pulmonale and right heart failure. In children, symptoms of right heart dysfunction are non-specific and may include shortness of breath and fatigue during physical exertion or difficulty in feeding for infants.

Significant cardiorespiratory disease can lead to difficulties with extubation and postoperative self-ventilation. The risks and benefits of surgery must be carefully weighed by the multidisciplinary team and include a planned extubation strategy. There should be a low threshold for postoperative ventilation and discussion of the possibility for temporary or permanent tracheostomy with long-term ventilation. It may be necessary to decide that the procedure is contraindicated if the child has very severe cardiorespiratory disease.

Airway assessment

A thorough evaluation of the airway is imperative to highlight any increased risk for inadequate mask ventilation and difficult tracheal intubation, and to plan an airway management strategy. For example, in OI there may be craniocervical instability, brittle teeth, a cleft palate, and pre-existing facial fractures. In arthogryposis, there may be micrognathia, gastro-oesphageal reflux, and limited neck movement because of contractures.

Laboratory tests

Abnormalities in full blood count or coagulation studies should be discussed with the surgical team and consideration given to postponing the procedure until the abnormality is corrected. If the starting haemoglobin is low (our institution would consider the lower limits of safety to be 70 g litre^{-1}) or significant blood loss is anticipated, cross-matched blood should be available before starting the procedure. In open procedures where a tourniquet is not used the potential for blood loss is significant and the requirement for preoperative blood typing or cross-matching should be discussed with the surgeon. Preoperative blood testing should also include screening for sickle cell disease where appropriate, especially if tourniquet use is planned.

Up to 30% of children with OI have bleeding diathesis in the presence of normal platelet count as collagen is involved in platelet aggregation.[3] Platelet function tests available as part of bedside thromboelastography may be helpful but a normal result does not predict straightforward control of intra-operative bleeding. The risks and benefits of regional anaesthesia should be considered and cross-matched platelets should be available before the start of major surgery.

Communication

Some children who have systemic co-morbidities will require several procedures from a young age, with the involvement of multiple clinical teams. They may have varying experiences of hospital care (including perioperative care) and this can be challenging for the child, their whole family and the multi-disciplinary team. It is important to remember that every child has the right to have their views taken into consideration in all matters affecting their care[4] and so the child must be placed at the centre of the decision-making process whenever possible.

It is extremely important to note that many patients with severe systemic disease, including one-third of patients with cerebral palsy (CP) are of normal intellect and may understand much more than they are able to communicate. Some children use simple signing techniques such as Makaton and may require the parent/carer to be present as interpreter for accurate assessment of pain. A preoperative anxiolytic may be necessary as these children can become very distressed.

Perioperative management

Most conventional anaesthetic techniques will be suitable for most children and procedures, including laryngeal mask airway for shorter procedures in the supine position. Some clinicians would advocate the use of total i.v. anaesthesia (TIVA) for longer cases when immediate extubation is planned but the speed of emergence with TIVA can be experience dependent so this choice is left to the individual.

Areas of particular anaesthetic concern for the related conditions described above or where technique modification may be required are discussed below.

Vascular access and monitoring

For patients with significant cardiorespiratory disease invasive pressure monitoring should be considered for all but the shortest and least invasive of procedures. In addition, for those with OI it may avoid the risk of fractures from non-invasive blood pressure cuffs.

In arthrogryposis vascular access can be difficult because of limb contractures and thin subcutaneous tissues with scanty vessels that are small and fragile. Pre-induction i.v. cannulae should be inserted at sites of sensory loss in the child with spina bifida, to minimize discomfort. Finally, the use of intraosseous needles is contraindicated in OI.

Airway management

Children with dwarfism, OI, and arthrogryposis present some of the most challenging airway management problems in paediatric anaesthesia.

In arthrogryposis mask ventilation and intubation can be difficult or impossible as the temporomandibular joint and cervical spine can be stiffened by contractures that worsen with increasing age. Micrognathia is an associated feature that may further compound the difficulties with airway management.

Complications from difficult mask ventilation and intubation are a significant cause of morbidity and mortality in children with dwarfism, who may also have cervical spine instability, thickened pharyngeal and laryngeal structures, narrowed nasal passages, pharyngeal hypoplasia, and tracheal narrowing.[5]

In OI, the airway requires minimal manipulation during mask ventilation and intubation to prevent fractures. Care must be taken with brittle teeth, neck, atlanto-axial joint, jaw, and base of skull.

In cases where airway management is known or suspected to be difficult, strongly consider inhalation induction and a strategy involving advanced airway equipment (such as video laryngoscope and fibre-optic intubation). Airway patency can be dramatically improved by changing the head position but this must be done very cautiously as catastrophic intra-operative spinal cord ischaemia can result from a hyperextended neck. Manual cervical stabilization during laryngoscopy may be necessary. Some children will be of short stature for their age so the usual formulae for calculating tracheal tube size should be modified to take this into account. Using a smaller-diameter paediatric cuffed tube may help to avoid the need for repeated tracheal intubation.

Although many of these children suffer gastro-oesophageal reflux, it is not usually of clinical significance at induction. Cricoid pressure should be avoided in OI.

Airway obstruction can also occur postextubation so extended pulse oximetry monitoring in a critical care setting is recommended for children at increased risk.

Neuromuscular blocking agents

Many of the diseases discussed above have a neurological or metabolic component and therefore these children have altered responses to neuromuscular blocking agents.

Succinylcholine is frequently avoided as it may cause catastrophic hyperkalaemia:

(i) In arthrogryposis with an underlying myopathy.
(ii) In achondroplasia with an upper motor neurone lesion.
(iii) In OI (in addition fasiculations and use of neuromuscular monitoring may cause fractures).

In arthrogryposis, most children have a reduced population of anterior horn cells throughout a smaller-diameter spinal cord. This can lead to an altered response to neuromuscular relaxants. Short-acting non-depolarizing agents with neuromuscular monitoring should ideally be used.[6]

Positioning

Positioning on the operating table is of utmost importance, both for surgical access and to support fragile bones, thin skin and

reduced muscle mass. For children with contractures ensure each joint is carefully supported to prevent pressure sores and accidental dislocation. In OI padding should be carefully applied to prevent further fractures. Avoid overextension of joints during positioning as this can cause dislocation. The use of adhesive tape should be minimized where skin is thin and fragile.

Special operating tables are sometimes required such as a radiolucent table for fluoroscopy work, a fracture table, or a spica table. The surgeon may require the patient to be positioned at the extreme end of the operating table to allow access to the lower limbs from three sides of the table.

Multiple positions are used in lower limb surgery including prone positioning for clubfoot and some ankle surgery. The lateral position allows the surgeon to access the front and back of the limb without re-positioning and re-draping. Tracheal intubation is recommended to maintain a secure airway if the patient is to be repositioned from supine.

Hypermetabolic states

Arthrogryposis and OI are associated with a hypermetabolic state under anaesthesia in ~33% of cases.[7] An increase in body temperature is accompanied by tachycardia, increased end-tidal carbon dioxide, and acidosis. This state is distinct from malignant hyperthermia (MH) in that the only treatment usually needed is active cooling. Dantrolene is not required. The hypermetabolic state occurs even in the absence of MH trigger agents, does not manifest with muscle rigidity, urinary myoglobin is not detectable and *in vitro* muscle contracture testing is negative. Intra-operative temperature should be carefully monitored and the usual paediatric perioperative warming strategies discontinued as necessary.

Tourniquets

The benefits of tourniquets in lower limb surgery are a bloodless operating field and limited intra-operative blood loss. They can potentially be used for any operative site distal to the mid-thigh and are widely used for ankle procedures. It is important to accurately size the tourniquet with a width greater than half the limb's diameter in order to safely distribute pressure. In children the recommended inflation pressures are determined by blood pressure and limb size – for the lower limb 150 mm Hg above systolic blood pressure is sufficient.

The use of tourniquets in patients with sickle cell anaemia or trait is controversial but there is no absolute contraindication provided that the benefits outweigh risk on a per-patient basis.[8] It is important to ensure adequate haemoglobin correction, patient warming, hydration, oxygenation, and maintenance of acid–base balance to prevent subsequent localized sickle crisis in the operative limb. The limb should be carefully exsanguinated and then reperfused in stages to avoid triggering a generalized sickle crisis by the release of a large load of hypoxic, acidotic blood into the circulation.

Tourniquets are inadvisable in OI because of the risk of fracture as the tourniquet is inflated. Patients with thin skin, contractures, and reduced muscle mass need very careful padding under the tourniquet if it is considered necessary.

On exsanguination and inflation of the tourniquet up to 15% of circulating blood volume is redistributed. This may increase blood pressure by up to 30%, with a parallel increase in central venous pressure.

Prolonged use of bilateral tourniquets (>90 min) is associated with an increase in core temperature (1–2°C) and tachycardia so intra-operative warming may need to be discontinued. There is no evidence-based or consensus opinion to suggest a maximum safe inflation time but steps should be taken to keep this to a minimum in order to reduce the risk of irreversible cellular ischaemic damage.

Fig 1 Picture of a child undergoing an orthopaedic procedure. In this case, application of a plaster jacket to aid correction of spinal scoliosis. Written parental permission obtained.

Minute ventilation should be increased for 5 min after tourniquet deflation to compensate for an increase in Pa_{CO_2} as venous stasis resolves.

If a tourniquet is not used either for clinical reasons or because the site is too proximal—for instance in hip surgery—substantial blood loss may occur. Cell-salvage techniques can dramatically reduce the requirement for cross-matched blood, but it is still important to have blood available. Some clinicians give additional fluids early in the procedure to lower haematocrit and reduce red cell loss.

Anaesthetic implications for common paediatric orthopaedic procedures

Spica casts

Typically used after hip surgery or to treat DDH, this procedure can take up to 90 min. The name originates from Latin 'ear of grain' referring to the figure-of-eight appearance of plaster bandage wrappings. Spica casts immobilize one or both lower limbs generally with knees in flexion and hips in flexion, abduction, and external rotation. A fibreglass cast is applied to envelop the mid and lower chest, the hips, the thighs, and one or both legs to the ankle (Fig. 1).

The child is positioned on a spica table by several assistants with one support under the shoulders, one under the pelvis, and a post at the perineum. Care with the airway is required during positioning on the spica table, especially if a supra-glottic airway is used.

A towel is placed under the cast during moulding to allow chest expansion and a window is cut to allow for abdominal breathing. When the surgeon applies the abdominal and chest components pay close attention to ventilation—a ventilator

loop display is invaluable as an early indicator of over-tight wrapping. Epidurals are generally avoided as the lumbar spine is inaccessible once the spica cast has been applied.

Osteotomies

Osteotomies are used extensively to allow repositioning and realignment of limbs. The two cut ends of bone are rejoined and held together with metalwork, usually K-wires. They vary from simple wedge osteotomy—where a wedge-shaped section of bone is removed for correction of congenital hallux valgus, to the multi-level rotational osteotomy and intramedullary rodding performed to realign and reinforce the long bones in children with OI. These procedures are painful and if performed without tourniquet can yield significant blood loss. They can also predispose to painful postoperative muscle spasm.

Epiphysiodesis

This involves fusion of the growth plate (epiphysis) to correct limb length inequality. The epiphysis is ablated with drills and curettes under image-intensifier guidance. The small incisions give a good cosmetic result and minimize skin pain which can be controlled with local anaesthetic injection. Despite the small incision, bleeding can be extensive from exposed cancellous bone so a pro-coagulant foam may be applied to the exposed bone by the surgeon.

Tendon surgery

This is used to correct imbalance of muscle forces in joint deformity and/or improve gait. Tendon transfers detach a partial or full tendon from its point of insertion, retain its innervation and vasculature and re-attach it to another bone or tendon point. Lengthening procedures involve two tendon cuts offset from one another and tendon releases or *tenotomies* completely detach the tendon from the insertion point. The child may be placed in a cast after operation to encourage healing in the desired joint position. The cast also limits movement and therefore reduces analgesic requirements, which can be substantial. Common sites for tendon manipulation include the hip via groin incision, hamstrings via posterior thigh incision (prone/lateral positioning) and the ankle. Painful postoperative muscle spasm is common after tendon manipulation.

Limb lengthening

The Ilizarov method is used to preserve height in limb length inequality caused by unequal growth, trauma, or osteomyelitis. It is a lengthy and painful process of cortical osteotomy (corticotomy) distraction and fixation. Operations are prolonged (typically 10 h or more) and technically difficult as an external fixator is placed around the osteotomy to retain distraction of the bone. The fixator is periodically tightened with approximately 1 cm of new bone growth for each month of therapy.

After operation, transient nerve palsies are possible so carefully document any pre-existing conditions. These children can be at high risk of compartment syndrome, especially with tibial lengthening. The procedure is very painful but neuraxial techniques are often avoided as there is a need to closely monitor nerve and vascular recovery and to detect compartment syndrome. High-dose opioids via patient- or nurse-controlled analgesia may then be the best option and it is worth discussing a short course of NSAIDs with the surgical team. A child with a previous experience of painful fixator may need an epidural in order to agree to undergo the procedure.

Therapeutic botulinum toxin use

An i.m. injection is used in spasticity and dystonia to improve motor function, promote longitudinal muscle growth, and decrease painful spasms. Specific indications include spastic equinus (toe walking), hip subluxation, and spastic diplegia. The site of injection can be localized by the surgeon using landmark technique, ultrasound, or electrical stimulation.

Botulinum toxin is produced by some strains of Clostridium bacteria. Seven serogroups (A–G) exist of which two (A and B) have therapeutic licences. Group A (BTA) is most commonly used in paediatric work.

The toxin creates a localized muscle paralysis by highly specific irreversible binding to pre-synaptic, cholinergic peripheral nerve terminals. Neurotransmission recovers when the axon terminal sprouts new nerve endings and forms new synaptic contacts on adjacent muscle fibres. A reduction in tone can be seen in 2–3 days with maximum effect at 2 weeks. On average recovery occurs within 3 months.

Therapeutic botulinum toxin injection has an excellent safety profile. Less than 1% of children have systemic side-effects including generalized weakness and fatigue. Dystonias and anaphylaxis have been reported in the literature. Procedure-related complications can also occur such as haematoma and damage to anatomical structures adjacent to the injection site.

Pain management

Minor procedures such as botox injection require only simple analgesia.

Procedures involving bone or tendons can be extremely painful so it is important to provide multi-modal analgesia including consideration of regional or local techniques, paracetamol and NSAIDs. A multi-modal approach reduces opioid use, limiting the increased side-effect profile known to occur in children. Preoperative single-dose gabapentin has insufficient evidence to support routine use in paediatric orthopaedic surgery but has been shown to significantly decrease postoperative pain and rescue analgesic requirements in adults who undergo lower limb orthopaedic surgery.[9]

It is important to use an age and ability appropriate pain scale for postoperative assessment such as Wong-Baker Faces for children aged over 3 yr, FLACC (Face, Legs, Activity, Cry, Consolability) for children aged 2 months to 7 yr, or revised FLACC for children with developmental impairment.[10]

Patients with communication difficulties such as in CP may find it difficult to express postoperative pain so regular (rather than as required) analgesia used in combination with careful monitoring of pain score may be preferable (Fig. 2).

Regional anaesthesia can become an increasing challenge as the child with musculoskeletal disease ages beyond infancy. A secured difficult airway may be jeopardized by repositioning for central neuraxial block. Caudal or lumbar epidurals are highly recommended for major procedures but can be contraindicated in OI-related platelet dysfunction and the abnormal spinal anatomy of spina bifida. They can be technically challenging because of patient positioning, bone condition and scoliosis. The spread of injectate can be difficult to predict in children with skeletal abnormalities. There may be fears that the block would mask compartment pain in procedures with a significant risk of postoperative compartment syndrome.

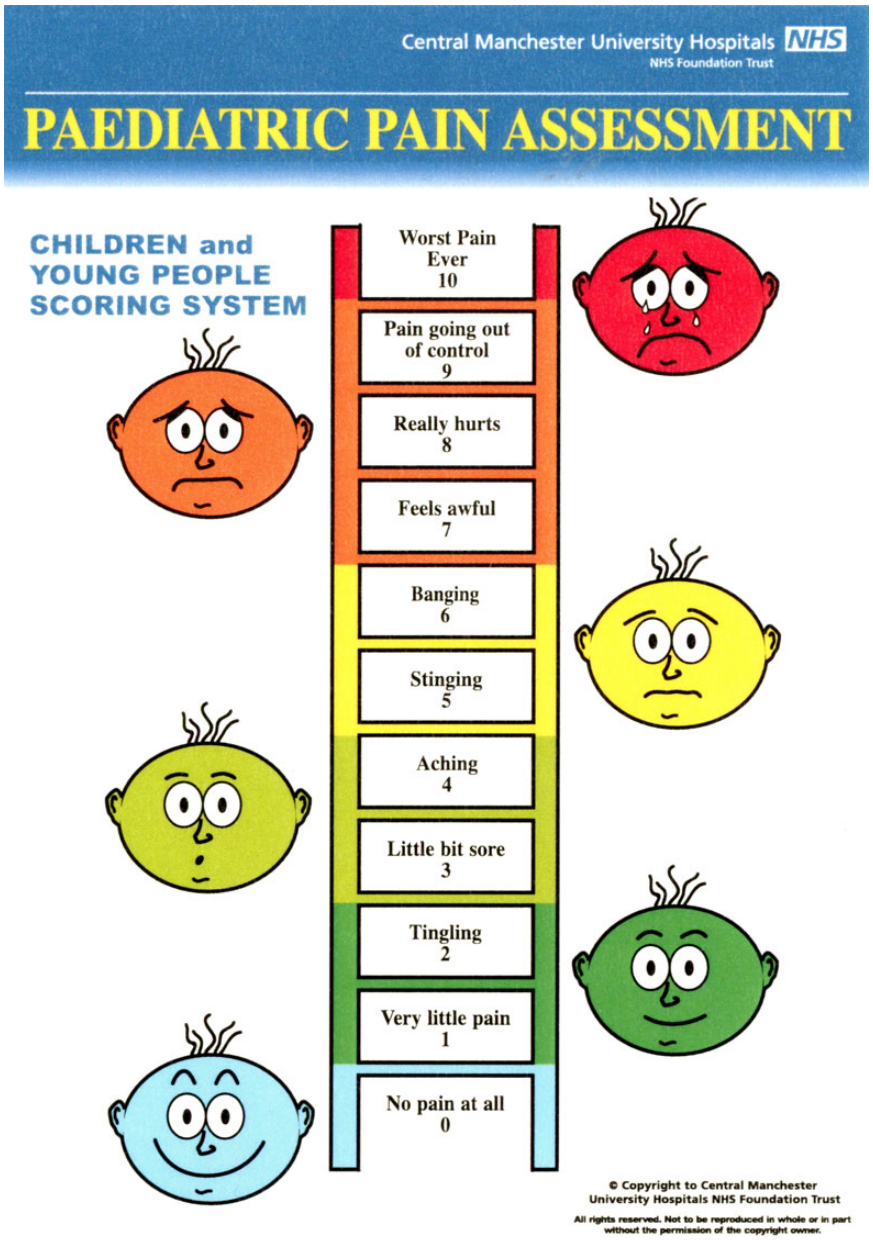

Fig 2 Faces scale. Reproduced with permission from Royal Manchester Children's Hospital, CMFT.

Dense sensory loss around the operative site in spina bifida may significantly reduce analgesia requirements (Table 1).

Compartment syndrome and regional anaesthesia

Certain procedures such as Ilizarov limb-lengthening carry a risk of postoperative compartment syndrome distal to the operative site in ~2% of patients.[11] Some teams may therefore wish to avoid regional anaesthesia on the basis that it potentially masks the pain of compartment syndrome. Children as a group may be at increased risk of developing compartment syndrome as their physiological mean arterial pressure (MAP) is lower, giving a reduced compartmental perfusion pressure (Δp = MAP – compartment pressure). Compartment pressure can be measured using a standard invasive arterial pressure monitoring set connected to a cannula in the compartment at risk. A compartment perfusion pressure of <30 mm Hg may indicate a diagnosis of compartment syndrome and the need for fasciotomy.

A 2009 review showed no cases of patients aged <18 yr where epidural analgesia had completely masked the pain of compartment syndrome or caused delay in diagnosis[12] and a literature search by the authors did not find any more recent reports to March 2014.

The most important aspect of early detection of compartment syndrome is clinical vigilance for disproportionate pain, swelling, paresthaesia, and paralysis of the operative limb.[13] If called to assess a child with uncontrolled postoperative pain despite good provision of analgesia, jointly review with a surgeon and examine the painful site. Consider pain distal to the site of surgery and/or increasing pain that is unresponsive to analgesia as compartment syndrome until proven otherwise. Encourage a low surgical threshold for compartment pressure monitoring.

Table 1 Suggested analgesia options for commonly performed paediatric lower limb orthopaedic procedures. *In agreement with the surgical team

Surgical procedure	Paracetamol	NSAIDs*	Caudal	Epidural infusion	PCA/ NCA	Popliteal and saphenous block	Sciatic block	Femoral block
Ilizarov limb lengthening	X	X	X*	X*	X		X*	X*
Long bone osteotomy	X	X	X	X	X		X	X
Percutaneous pinning	X	X						
Tendon surgery	X	X				X	X	X
Epiphyseodesis	X	X	X				X	X
Ankle surgery	X	X			X	X		
Spica casting (without invasive procedure)	X							
Therapeutic botulinum toxin injection	X							

Other strategies for limiting compartment syndrome can be surgical such as prophylactic fasciotomies at time of procedure, or anaesthetic (e.g. using low concentration local anaesthesia to avoid dense sensory, motor, and vasomotor block).

With careful postoperative observation, epidural anaesthesia can be offered appropriately to patients who are not at high risk of developing compartment syndrome. This involves good training of recovery and ward nurses in red flag signs and symptoms. It is important to remember that theoretically even patient- or nurse-controlled opioid analgesia can mask the early stages of compartment syndrome (Box 1).

Box 1 Red flag signs of acute compartment syndrome

Increasing or uncontrolled pain despite good provision of analgesia
Pain remote to site of surgery
Paresthaesia or paralysis not attributable to analgesia, and not resolving despite cessation of local anaesthetic infusion
Reduced perfusion of areas distal to painful site
Tight swelling
Pain on passive movement of the site

NSAIDs and healing

NSAIDs provide excellent analgesia as part of a multi-modal regime. They significantly spare opioid usage and may also reduce the incidence of chronic pain but their use in orthopaedic practice is controversial because of conflicting accounts of inhibition of bone healing in adults. They block cyclooxygenase and hence reduce the creation of prostaglandins from arachidonic acid. Prostaglandins have a direct stimulatory effect on osteoclasts and increase multiplication and differentiation of osteoblasts.[14] The published paediatric studies show no evidence for delayed bone healing in children. An international survey reported that 59% of anaesthetists routinely use oral ibuprofen or i.v. ketorolac (72% of respondents) for scoliosis surgery for 3–4 days after operation.[15]

Many of the laboratory-based studies use supra-maximal doses of NSAID and few studies directly examine juvenile bone healing. However, lack of evidence does not necessarily imply a lack of any adverse effect so anaesthetists should discuss the use of NSAIDs with their surgeon. It would seem sensible to avoid them in patients at high risk of poor bone healing.[16]

Postoperative muscle spasms

Many children with co-morbidities such as CP will suffer chronic spasticity. Their anti-spasticity treatment should be continued perioperatively to prevent withdrawal and worsening of symptoms. In addition, surgical procedures such as osteotomy or tendon lengthening pre-dispose to painful postoperative muscle spasm.

Acute postoperative spasms are best managed in a critical care environment by control of pain with the techniques described above and then the addition of i.v. benzodiazepine with careful monitoring for excessive sedation and respiratory depression. Suggested regimens include diazepam 0.1 mg kg^{-1}, or midazolam infusion 10–30 $\mu g\,kg^{-1}\,h^{-1}$. Baclofen or dantrolene are also sometimes used as sole agents or in conjunction with benzodiazepines.

Postoperative care

Many minor procedures can be performed as day cases but limited mobility, airway abnormalities, blood loss and the need for significant analgesia may require several nights of in-patient care. In addition, children with co-morbidities including upper airway abnormalities or significant cardiorespiratory disease and those having long or complex surgery with significant blood loss will require postoperative critical care.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Splanchnic circulation

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Key points

- The arterial supply to the splanchnic bed comprises three divisions of the abdominal aorta; the coeliac artery; and the superior and inferior mesenteric arteries.
- Under physiological conditions, blood flow in the splanchnic circulation is controlled via intrinsic (myogenic and metabolic) and extrinsic (autonomic and humoral) mechanisms.
- The splanchnic bed forms an important circulatory reservoir, which can be mobilized during periods of physiological stress.
- Disorders of the splanchnic circulation may contribute to the multi-organ dysfunction syndrome and vice versa.
- A number of techniques used in anaesthesia and critical care influence the distribution of blood flow in the splanchnic circulation.

The splanchnic circulation is a complex system. A number of important functions depend on its normal operation, including digestion and absorption within the gut, maintenance of the mucosal barrier, and successful healing of surgical anastomoses, but we have little quantitative information about its physiology because routine measurement in humans is so difficult. This article outlines some basic science and describes how influential the splanchnic circulation might be in our clinical practice.

Anatomy

The term 'splanchnic circulation' describes the blood flow to the abdominal gastrointestinal organs including the stomach, liver, spleen, pancreas, small intestine, and large intestine. It comprises three major branches of the abdominal aorta; the coeliac artery; superior mesenteric artery (SMA); and inferior mesenteric artery (IMA) (Fig. 1). The hepatic portal circulation delivers the majority of the blood flow to the liver.

Coeliac artery

The coeliac artery is the first major division of the abdominal aorta, branching at T12 in a horizontal direction ~1.25 cm in length. It shows three main divisions such as the left gastric artery, common hepatic artery, and splenic artery and is the primary blood supply to the stomach, upper duodenum, spleen, and pancreas.

Superior mesenteric artery

The SMA arises from the abdominal aorta anteriorly at L1, usually 1 cm inferior to the coeliac artery. The five major divisions of the SMA are the inferior pancreaticoduodenal artery, intestinal arteries, ileocolic, right colic, and middle colic arteries. The SMA supplies the lower part of the duodenum, jejunum, ileum, caecum, appendix, ascending colon, and two-thirds of the transverse colon. It is the largest of the splanchnic arterial vessels delivering >10% of the cardiac output and therefore has significant implications for embolic mesenteric ischaemia.

Inferior mesenteric artery

The IMA branches anteriorly from the abdominal aorta at L3, midway between the renal arteries and the iliac bifurcation. The main branches of the IMA are the left colic artery, the sigmoid branches, and the superior rectal artery. It forms a watershed with the middle colic artery and supplies blood to the final third of the transverse colon, descending colon, and upper rectum.

Physiology

Resting splanchnic blood flow (SBF) is typically 30 ml min^{-1} 100 g^{-1} of tissue, which equates to 25–30% of the cardiac output.

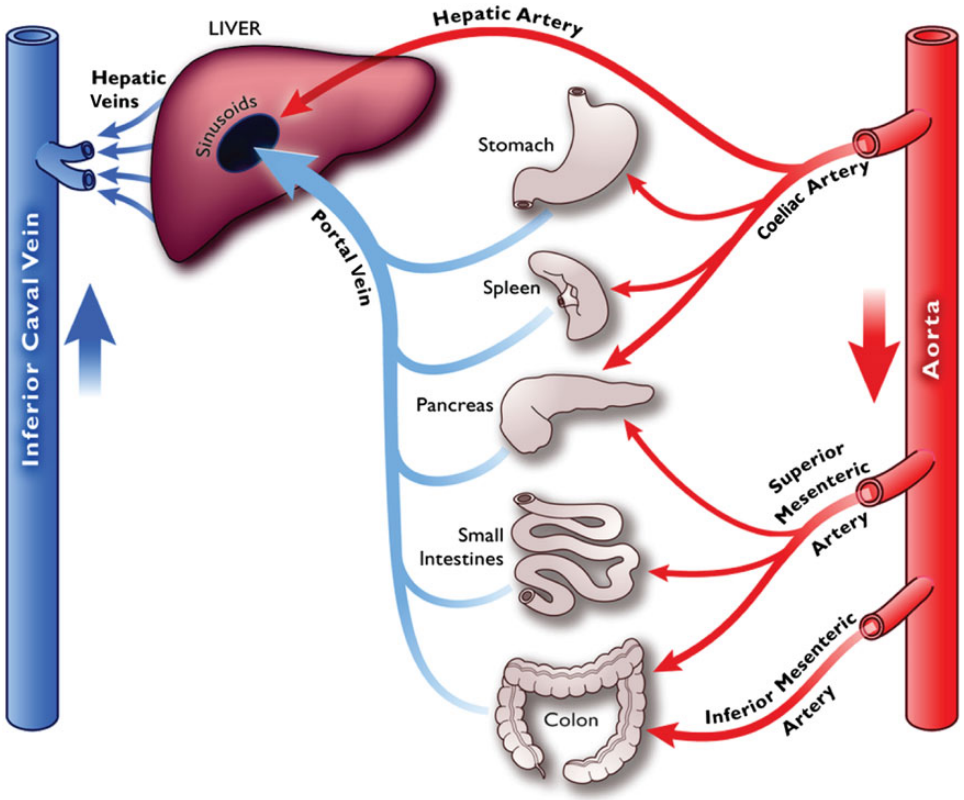

Fig 1 Schematic representation of the splanchnic circulation.[1]

This may decrease to <10 ml min^{-1} 100 g^{-1} in low cardiac output states or peak locally at 250 ml min^{-1} 100 g^{-1} after a meal. The splanchnic circulation must therefore be highly adaptive. The mechanisms of physiological regulation of SBF are complex but the academic debate focuses primarily on three circulatory determinants: intrinsic (local metabolic *vs* myogenic), extrinsic (autonomic nervous system), and humoral (local or circulating vasoactive substances).

Intrinsic control

The splanchnic vascular bed demonstrates an autoregulatory capacity similar to that seen in other vascular beds such as the renal and cerebral circulations. This ensures that a constant blood flow can be maintained across a wide variety of perfusion pressures. There are two proposed mechanisms: metabolic and myogenic control.

The metabolic hypothesis focuses on the balance between oxygen supply and demand rather than blood flow. Accumulation of metabolites such as H^+, K^+, adenosine or CO_2, during periods of poor supply and tissue hypoxia serve to produce vasodilation, thereby restoring blood flow. Alternatively increased delivery of oxygen to the tissues will result in vasoconstriction.

The myogenic hypothesis describes the mechanism by which vessels respond to an increase in transmural pressure or stretch by constricting, thereby restoring blood flow to baseline levels. This is mediated through opening of mechano-sensitive cation channels, principally sodium (Na^+). The resulting depolarization activates voltage-gated calcium (Ca^{2+}) channels elevating intracellular Ca^{2+} concentrations, thereby inducing smooth muscle contraction. Conversely the vessels relax and reduce their tone in response to a reduction in transmural pressure.

Extrinsic control

All of the splanchnic vasculature with the exclusion of the capillaries receive sympathetic innervation. The postganglionic fibres from the coeliac, superior mesenteric, and inferior mesenteric ganglia follow the path of the corresponding arteries. Sympathetic stimulation exerts a direct effect through the release of noradrenaline mediating α-adrenergic vasoconstriction. Alterations of blood flow in response to sympathetic stimulation follow a triphasic pattern. Initial reductions in flow return to near normal within minutes of stimulation followed by a reactive hyperaemia on cessation of activity. Sympathetic vasoconstriction plays an important role in the distribution of blood volume throughout periods of both physiological and pathological stresses such as exercise and major haemorrhage.

Parasympathetic innervations from the vagal and pelvic nerves synapse with postganglionic fibres in the gut wall. Parasympathetic stimulation increases intestinal motility and secretions, which indirectly increase blood flow. Release of nitric oxide (NO) upon activation of muscarinic receptors (M1) by acetylcholine in the endothelial layer leads to vascular smooth muscle relaxation and an increase in mucosal blood flow.

Humoral control

Circulating vasoactive mediators of the splanchnic circulation are legion and may be exogenous or endogenously produced (Table 1). The complex interplay of factors is evident during postprandial hyperaemia. Local production of vasodilator metabolites such as adenosine and CO_2 secondary to increased mucosal metabolic activity and consumption of O_2 lead to increased blood flow. In addition, the hyperosmolar conditions

Table 1 Vasoactive mediators of the splanchnic circulation

Vasodilators	Vasoconstrictors
Parasympathetic tone	Sympathetic tone
↑ P_{CO_2}	↓ P_{CO_2}
↓ P_{O_2}	↑ P_{O_2}
↓H^+	↑H^+
Acetylcholine	Vasopressin
Bradykinin	Angiotensin II
Adenosine	Prostaglandins
Gastrin	Peptide YY
Secretin	Neuropeptide Y
Cholecystokinin	
Vasoactive intestinal polypeptide	
Substance P	
Prostaglandins	
Gastric inhibitory polypeptide	
Leukotrienes	
Nitric oxide	
Dopamine	

exerted by the absorption of nutrients directly increases blood flow. Intracellular Na^+ concentrations increase because of hyperosmaolar intraluminal conditions. This results in activation of the Na^+/Ca^{2+} exchanger, increasing intracellular Ca^{2+} concentration, which in turn stimulates NO-mediated relaxation of vascular smooth muscle via activation of nitric oxide synthase.[2] Many of the peptide hormones, including cholecystokinin, secretin, and gastrin, have vasodilatory properties. They are released locally during digestion and increase blood flow and gut motility.

Disorders of the splanchnic circulation

Ischaemia-reperfusion injury and the gut origin hypotheses

Hypoperfusion is a common feature in anaesthesia and critical illness. Examples include low cardiac output states, vasodilatory or hypovolaemic shock, and abdominal compartment syndrome (ACS). In such situations, perfusion of other vital organs is often maintained at the expense of the splanchnic circulation. This renders the gut particularly vulnerable to non-occlusive mesenteric ischaemia. Reperfusion triggers a sequence of events beginning with the formation of reactive oxygen metabolites causing tissue damage and the activation and endothelial adhesion of polymorphonuclear neutrophils. The resulting increase in vascular permeability and release of inflammatory mediators into the systemic circulation is important in the development of the systemic inflammatory response syndrome (SIRS) and ultimately the pathophysiology of multi-organ dysfunction syndrome (MODS).

MODS is an important clinical syndrome associated with significant systemic insults such as trauma, pancreatitis, and sepsis, with a mortality in excess of 40%.

The majority of patients who develop MODS secondary to an insult will at some point in the process exhibit a septic response; however, it is recognized that in a significant proportion no precipitating bacterial focus will be identified.

The gut origin hypothesis describes the situation in which splanchnic hypoperfusion and loss of gut barrier function may occur during the initial systemic insult. This hypothesis gained prominence with experimental evidence demonstrating that bacterial translocation during laparotomy or in pancreatitis is associated with an increase in infective complications. The link between bacterial translocation and ARDS/MODS is less conclusive with bacteria and endotoxin being identified in the portal blood of only 2% of trauma patients who later went on to develop MODS.[3]

The suggestion that bacterial translocation and liberation of pro-inflammatory mediators may be independent of the disruption of gut barrier function is supported by the observation that in MODS, progressive dysfunction often begins with pulmonary changes, with acute lung injury being the initial clinical picture. This is contrary to the expectation that the liver may be the initial victim if gut derived bacteria or endotoxins were carried in the portal blood. The gut-lymph hypothesis attempts to resolve this paradox. In this model, pro-inflammatory mediators from the stressed or ischaemic gut are delivered to the systemic circulation via the mesenteric lymphatics in the thoracic duct bypassing the liver to the subclavian vein and then the lungs. This theory is endorsed by experimental data.[4]

SBF in SIRS/sepsis

It is accepted that sepsis and acute intra-abdominal inflammatory conditions influence the SBF; however, the mechanisms are controversial. Microcirculatory conditions appear to be mediated by local metabolic and paracrine factors, indeed redistribution of blood between mucosal and muscularis layers has been demonstrated. On the other hand, macrocirculatory flow is influenced predominantly by systemic circulatory conditions such as SVR and CO. Therefore, the precise circulatory milieu is a complex and dynamic process, the evolution of which is dependent on stage of disease (early or late), severity, or therapeutic intervention.

Systemic and microcirculatory disturbance is a prominent feature of severe acute pancreatitis (SAP) and is a key factor in the pathogenesis, progression, and outcome of the disease. At presentation, haemodynamic disturbance is a common feature. Circulating volume is reduced due to increased capillary permeability and third space losses while systemic vasodilatation has a profound influence. These features are common to all severe inflammatory conditions; however, they can be replicated by i.v. infusions of pancreas-derived enzymes such as trypsin, chymotrypsin, and elastase in the animal model.[5]

Evaluation of the splanchnic microcirculation is complicated by the inability to directly measure blood flow and oxygenation in human disease. However, the impairment of the pancreatic microcirculation is recognized as an important factor in the pathogenesis and evolution of necrotizing pancreatitis. It occurs earlier and with greater severity than in self-limiting oedematous pancreatitis and appears to herald progression from mild to severe forms of the disease. Early vasoconstriction leads to reductions in blood flow, capillary stasis, and a loss of capillary density. Furthermore, endothelial dysfunction with activation and adhesion of leucocytes contributes to micro-vessel occlusion, while loss of endothelial barrier function results in increased capillary permeability. This allows migration of large molecules such as activated proteases into the pancreatic tissue causing further cellular destruction. Several therapeutic modalities have been identified which target the pancreatic microcirculation, including reducing the viscosity of blood, anticoagulation, and epidural anaesthesia. However, the influence on morbidity and mortality in clinical trials is inconsistent.[6]

The splanchnic circulation in liver disease

The classic disruption of the splanchnic circulation secondary to liver disease is portal hypertension (PH). This is most commonly

a result of cirrhosis; however, associated conditions include venous thrombosis, hepatic fibrosis, granulomatous disease (sarcoidosis, miliary tuberculosis), schistosomiasis, and right heart failure. The gold standard for assessing severity is the hepatic venous pressure gradient (HPVG), which is the difference between the free hepatic venous pressure and the wedged hepatic venous pressure. PH occurs when the HPVG exceeds 5 mm Hg. In the later stage of the condition in addition to PH patients with liver disease often have a hyperdynamic circulation characterized by vascular vasodilatation, plasma volume expansion, and increased cardiac output which maintains and exacerbates PH. The pathophysiology of vasodilatation in the hyperdynamic circulation is multifactorial but is ultimately secondary to an elevated production of vasodilators and an abnormal response to vasoconstrictors.[7]

Patients with PH may present acutely with a number of complications such as ascites, hepatic encephalopathy, hepatorenal syndrome, or spontaneous bacterial peritonitis, which generally are a result of blood that would normally be processed in the liver being shunted into the systemic circulation. Patients may also present with life-threatening haemorrhage from porto-systemic shunts such as gastric or oesophageal varices. These form not only as a direct effect of the increased pressure forcing blood into existing collaterals but also via revascularization under the influence of vascular endothelial growth factor.

The splanchnic circulation in anaesthesia and critical care

Inhalation and i.v. agents

Volatile anaesthetic agents have well recognized effects on systemic haemodynamics, but may also cause regional changes in blood flow to the splanchnic circulation. Despite the obvious importance of these changes, there is limited evidence regarding the effects of individual agents. Propofol and many of the volatile anaesthetics have vasodilatory properties, potentially increasing SBF. The literature does not report a consistent relationship between other i.v. anaesthetics (e.g. etomidate or thiopentone) and SBF. The degree to which changes occurs depends on the agent which is being used. There are no data to link these findings with more significant outcomes, and firm conclusions regarding which agent is superior are impossible to make.

Ventilation and IPPV

Intermittent Positive pressure ventilation (IPPV) has well-described effects on the cardiovascular system, which may include a fall in cardiac output principally via a reduction in preload, predictably reducing splanchnic perfusion. The splanchnic circulation is also susceptible to more direct effects of positive pressure ventilation. The use of very large tidal volumes, high levels of positive end expiratory pressure, and high inspiratory pressures have been shown to reduce splanchnic perfusion. These effects appear to be due to increased hepatic venous pressures and mesenteric vascular resistance, with reduced portal blood flow. At normal ventilator pressures, adverse effects appear to be minimal. Sustained recruitment manoeuvres have been associated with a worsening in splanchnic oxygen delivery, despite improving arterial oxygenation. Spontaneous breathing efforts during airway pressure release ventilation have been shown to improve both cardiac output and splanchnic perfusion. Prone ventilation does not affect splanchnic perfusion, provided care is taken to avoid intra-abdominal hypertension. Permissive hypercapnia helps to maintain splanchnic perfusion.[8]

Sympathomimetic agents

Administration of vasoactive medications is a core component of treatment for a variety of conditions in which splanchnic perfusion may already be at risk. The variety of studies and end-points of investigation make it difficult to draw clear conclusions about vasoactive medication use. Several receptor systems and their subtypes are important for the regulation of blood flow in the splanchnic circulation. In general, $\alpha 1$ stimulation causes vasoconstriction to a greater degree than $\alpha 2$, and $\beta 2$ effects appear to be vasodilatory. Dopamine receptors are also present in the gut, principally DA1 and DA2, activation of which results in vasodilation.

Norepinephrine (mainly $\alpha 1$ and $\beta 1$ agonist) is the commonest drug used for augmenting the circulation in sepsis. Its effects on splanchnic perfusion appear to be minimal. Within the treatment of sepsis a further increase in mean arterial pressure (MAP) beyond 65 mm Hg did not improve or impair splanchnic perfusion. Phenylephrine (mainly $\alpha 1$) and epinephrine ($\alpha 1$ and $\beta 1$) have been shown to reduce SBF, and also gastric markers of perfusion.[9]

Dobutamine ($\beta 1$ and $\beta 2$), dopexamine (DA1, some $\beta 2$) and low-dose dopamine (DA1 and DA2, $\beta 1$ and $\beta 2$, $\alpha 1$ in high dose) all have vasodilatory effects on the splanchnic circulation, and have been shown to improve markers of perfusion. For many years, low-dose infusions of dopamine were used as a prophylactic and therapy for acute renal failure, using the logic that DA1- and DA2-mediated vasodilation in renal and splanchnic beds would be protective. This was supported by the observation that dopamine promoted a diuresis; however, this is now widely acknowledged to be primarily a result of increased cardiac output due to dopamine's $\beta 1$ and $\beta 2$ effects. Concerns over the potential harmful side-effects of dopamine including thyroid and pituitary dysfunction and immunosuppression and the lack of consistent data from the literature supporting its efficacy has meant that the routine use in high-risk surgery has become less widespread. In addition, from the available data, it would seem that the addition of dobutamine rather than dopamine to a noradrenaline infusion is superior for augmenting mesenteric blood flow.[10]

Vasopressin is utilized as a second line agent in the treatment of septic shock. It exerts its effect via G-protien coupled receptors (V1), and has been shown to be a vasoconstrictor in the splanchnic circulation. This property of vasopressin analogues is useful in the treatment of variceal bleeding and hepatorenal failure, but it is unclear what effect this may have in the treatment of a septic patient.

Regional anaesthesia

The relationship between regional anaesthesia (RA), in particular thoracic epidural anaesthesia (TEA) and SBF, is poorly characterized. This is of particular interest in colorectal surgery as many clinicians are concerned that direct reductions in tissue perfusion and worsening of tissue oedema as a consequence of fluid resuscitation while managing systemic hypotension might compromise vulnerable bowel anastomoses. Evidence suggests that TEA does not increase the risk of anastomotic leak and may in fact be beneficial.[11] Human experimental data are limited, because of primarily difficulties with direct measurement. Furthermore, outcome data are conflicting. Sympathetic block might logically improve flow by reducing splanchnic vascular

resistance, while reductions in systemic vascular resistance and cardiac output might offset this beneficial effect. In fact, Gould and colleagues demonstrated that TEA caused a reduction in blood flow in the IMA that was associated with a decrease in systemic MAP. This reduction in flow could not be corrected by increasing the cardiac output with fluids but required a vasopressor (methoxamine) to fully restore flow in the IMA.[12]

TEA used as a therapeutic intervention for sepsis is theoretically attractive. Microcirculatory disturbance plays an important role in the pathogenesis of sepsis, and as such moderating this with regional sympathetic block might influence morbidity and mortality. Unfortunately research in humans is hampered by methodological difficulties; however, in experimental models of sepsis, TEA has been shown to reverse microcirculatory disturbance.[13] The use of TEA in sepsis, either as a therapeutic intervention or to manage pain, is controversial. The accepted wisdom states that the use of TEA in sepsis will increase the incidence of potentially devastating complications such as epidural abscess. Despite this, a convincing association is yet to be demonstrated.

TEA has also been identified as having therapeutic potential in SAP. Experimental models of the disease have identified improvements of pancreatic microcirculation and oxygenation that have been translated to significant survival outcomes. The use of TEA for SAP in the critical care scenario does pose a number of clinical concerns, even in the absence of an identified focus of infection. Patients with SAP represent a cohort at greater risk of sepsis and coagulopathy, who may require prolonged treatment and in whom monitoring of complications is challenging. Nevertheless, this technique was shown to be safe in a group of 121 patients with SAP admitted to ICU with a mortality of 2.5%.[14]

Laparoscopic surgery and the pneumoperitoneum

Normal intra-abdominal pressure (IAP) is 5–7 mm Hg although this varies during the respiratory cycle and may be as high as 14 mm Hg in the obese patient. Intra-abdominal hypertension is defined as an IAP >12 mm Hg while ACS occurs at pressures >20 mm Hg.[15]

The haemodynamic effect of laparoscopic surgery is principally determined by a number of factors including the insufflation pressure and the gas used. It is also worth noting however that laparoscopic surgery is more likely to use extremes of patient position such as head up or down for prolonged periods.

Clinical and experimental studies, with outcomes measured directly and indirectly, demonstrate that perfusion of the splanchnic organs is inevitably compromised by the pneumoperitoneum. The degree of this compromise is directly proportional to the pressure used. Typically insufflation pressures between 12 and 15 mm Hg are used during laparoscopic surgery, although this is tailored according to a variety of factors, and is a compromise between surgical access and potential haemodynamic compromise. It is of interest to note that deep neuromuscular block has been shown to facilitate laparoscopic cholecystectomy to be performed at lower insufflation pressures and was associated with better operating conditions when compared with moderate neuromuscular block.[16]

The most widely used gas to establish pneumoperitoneum is CO_2. It has a number of favourable qualities because it is inexpensive, readily available, easily absorbed, and non-flammable. Argon and helium have been used as replacements for CO_2. These gases appear to have benefits experimentally; however, concerns over the potential for gas embolism and pneumothorax of non-absorbable gases mean that they are unlikely to be accepted as viable alternatives.

Laparoscopic surgery is well tolerated in fit patients, the majority of case reports of mesenteric ischaemia after operation have occurred in patients with significant cardiovascular comorbidities. In this group, a number of strategies that aim to limit the impact of pneumoperitoneum have been advocated. The 'dial-down' approach uses standard inflation pressure which is sequentially reduced to find the lowest acceptable point. Alternatively, gas can be intermittently released from the abdomen during the procedure. Finally, the reverse Trendelenburg position should be avoided where possible because reduced venous return may compromise cardiovascular stability.[17]

Monitoring and measurement

Splanchnic perfusion can be measured in a variety of ways; however, because of a variety of issues, monitoring has not become common in clinical practice. The use of indicator dilution with Indocyanine green (ICG) was first described more than 40 yr ago. This original application of this technique required hepatic venous catheterization to measure the post-hepatic concentration of ICG. From this the application of the Stewart–Hamilton equation (originally applied to calculate cardiac output using dye dilution) can be used to calculate an SBF; flow equals the amount of injectate divided by the area under the post-hepatic concentration curve. ICG is eliminated from the blood solely by hepatocytes. This process can be monitored non-invasively using the principle of pulse spectrophotometry and the optical absorption of ICG with a transcutaneous probe, allowing for assessment of liver function and splanchnic perfusion.

Gastric tonometry has been extensively studied as a monitor of splanchnic perfusion. This technique requires a gastric catheter to measure the concentration of carbon dioxide within the stomach and arterial measurements of carbon dioxide and bicarbonate. Using the Henderson–Hasselbalch equation the gastric intramucosal pH (pHi) can be calculated. Alternatively the concentration difference between gastric and arterial carbon dioxide concentration ($PgCO_2$) can be calculated. Both pHi and $PgCO_2$ are prognostic indicators in the critically ill. Although not directly part of the splanchnic circulation assessments of the sublingual circulation have now been developed. This utilizes its greater accessibility within the gastrointestinal tract. The use of sublingual capnometry allows sublingual CO_2 to be measured ($PslCO_2$) which has been correlated with lactate concentrations and outcomes.[18] At present, this remains an area of interest for the future without any clear evidence to support its widespread use. Laser Doppler flowmetery utilizes the frequency shift (Doppler principle) in a laser beam to measure flow. This has been used in trials to establish colonic blood flow, as have ultrasound-based Doppler measurements.

Supplementary feeding

Enteral nutrition has been established as an important part of the management of critically ill patients. Expert guidelines recommend that enteral feeding should be commenced early (<24 h) in all patients not expected to tolerate a full oral diet within 3 days.[19] Under physiological conditions, oral alimentation results in a 'postprandial hyperaemic response', mediated primarily by local humoral and mechanical factors. The fact that this response is mirrored in critically ill patients receiving enteral nutrition raises safety concerns in the haemodynamically unstable patient. The first being the potential for triggering bowel ischaemia by an increase in oxygen demand exceeding supply, the second being the potential for the steal phenomenon whereby gut

blood flow increases at the expense of other 'vital' organs. Despite these anxieties, the benefits of early enteral nutrition appear to be apparent even in patients requiring vasopressor support. In contrast, SBF appears to be reduced during parenteral nutrition. This may be due to an increase in systemic basal metabolism resulting in diversion of blood towards systems with a higher basal metabolic rate.[20]

Conclusion

Much of what we know about the physiology of the splanchnic circulation has been extrapolated from experimental studies because routine assessment of SBF in humans is impractical. Techniques for direct measurement are invasive while reliability issues hamper indirect alternatives. As such a thorough understanding of the splanchnic circulation during the perioperative period and critical illness remains elusive. Despite these problems, manipulation of splanchnic physiology is a fascinating area of research and therapeutic techniques for targeting the splanchnic circulation, such as RA in sepsis or SAP merit further investigation.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Analgesia in intensive care: part 1

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Key points

- Despite evidence of adverse impacts because of suboptimal pain management, pain still remains poorly assessed and treated in intensive care.
- In choosing the ideal analgesic drug in the critically ill, the interplay between altered drug pharmacokinetics and pharmacodynamics, organ dysfunction, and side-effect profile must be considered.
- Sedation protocols in intensive care should focus on analgesia first. The aim should also be to avoid prolonged continuous infusions and encourage targeted titration to specific individualized goals.
- Opioids remain the mainstay of analgesia management but wherever possible, multimodal approach should be considered.
- The synergistic action of the analgesic adjunct drugs has the potential to minimize the side-effects, while maintaining effectiveness.

Patients in intensive care experience distress because of a multitude of factors and a significant proportion is attributable to pain.[1] A vast majority of patients report moderate to severe pain at some point during their intensive care stay. Pain can be caused or provoked by many pre-existing conditions: acute medical, surgical, or routine aspects of intensive care (Table 1).

Pain is widely regarded as the fifth vital sign, and it induces a myriad of deleterious physiological changes in most organ systems. Severe pain induces a stress response and sympatho-adrenergic stimulation causing tachycardia, hypertension, increased myocardial oxygen consumption, and can induce myocardial ischaemia in susceptible patients. Poorly managed pain from abdominal incisions reduces diaphragmatic function, causes hyperventilation and atelectasis. Pain especially in sedated patients can present as agitation, delirium and when badly managed can have psychological sequelae like post-traumatic stress disorder,[2] depression, and anxiety or it can progress to chronic pain. Systemic deleterious effects of pain include systemic inflammatory response syndrome, hyperglycaemia, immunosuppression, impaired wound healing, hypercoagulability, and increased catabolism. All these detrimental effects can lead to an increased length of intensive care and hospital stay, and mortality.

Despite overwhelming evidence of adverse clinical impact, pain still remains infrequently assessed and poorly managed in the intensive care unit (ICU).[3] Patients who had regular assessments for pain are more likely to have lighter levels of sedation, an increase in the use of non-opioid multimodal analgesic therapies and pre-emptive analgesia before painful procedures. This in effect has been shown to decrease the duration of mechanical ventilation and ICU stay.[3]

There are numerous barriers to pain management in the ICU and surveys have revealed wide national and international variations in assessment, monitoring, drugs, protocols and algorithms used for sedation, and analgesia. The objective of this article is to discuss the key principles of pain management in ICU and the commonly used systemic analgesics and adjuvants; the role of regional analgesia in ICU is covered in a subsequent article.

Recognition of pain in ICU

Recognition of pain in ICU patients is the important first step in its management. However, verbal reporting is not always

Table 1 Causes of pain in intensive care. SCI, spinal cord injuries; GBS, Guillain–Barre syndrome; MS, multiple sclerosis

Constant background pain (requiring infusion of opioids/adjuncts)	Postoperative: surgical incision, abdominal/chest drains Pre-existing: exacerbation of chronic pain, arthritis Neurological conditions: phantom limb pain, SCI, demyelinating neuropathy-GBS, MS Trauma: amputations, fractures, soft tissue injuries, burns, pressure sores
Intermittent/periprocedural pain (requiring boluses of opioids/adjuncts)	Invasive procedures: central/arterial line placement, tracheal tubes, nasogastric tubes, catheters Routine care: position change, physiotherapy, tracheal suctioning, mobilization, wound/burn dressing changes

possible because of difficulties in communication (e.g. sedation, delirium, tracheal intubation, neuromuscular block and weakness). Physiological parameters, which are usually related to pain, can be caused or masked by various other factors in the ICU setting (e.g. arrhythmias, sepsis, inotropic therapy, beta-blockade, and other pharmacological interventions).

Pain assessment

Less than 50% of intensive care professionals assess pain, and even when done, it is only done infrequently.[3] Lack of training in the assessment is a frequently cited factor for poor pain management. The main principles of pain assessment in the critically ill are to:

(i) Understand and identify the causes of distress, most common, but not all, of which is attributable to pain.
(ii) Assess pain, sedation, and delirium using validated scales, regularly and accurately, and use all the information in conjunction.
(iii) Appreciate that vital signs should not be used alone in the assessment of pain, but may be used as a cue to begin further assessment.[4]

Pain scales

Self-reporting of pain is considered as gold standard[4, 5] and wherever possible, healthcare professionals should try and rate patient's self-reported pain using validated scales. Pain scales can be continuous or discrete, unidimensional or multidimensional, subjective or objective. Commonly used pain scales in the ICU are unidimensional and are quite useful in the assessment of pain and measuring the response to treatment.

Pain scales for patients able to communicate.

(i) *Visual Analogue scale (VAS)*: Patients mark their pain on a 100 mm line, with verbal descriptors at each end (0: no pain; 100: very severe pain). The score is obtained by measuring the distance in millimetres from the left end of the line.
(ii) *Numerical Rating Scale (NRS)*: Patients rate pain on an 11-point scale (0: no pain; 10: severe pain).
(iii) *Verbal Rating Scale (VRS)*: 4-point scale, in which the pain can be rated as 1: absent, 2: mild, 3: moderate, and 4: severe.

Pain scales for patients unable to communicate.

(i) *Behavioural Pain Scale (BPS)*: this scale uses clinical observations of facial expression, upper limb movements, and synchrony with mechanical ventilation. BPS ranges from 3 to 12, scores >6 require pain management (Table 2).[6]
(ii) *Critical Care Pain Observation Tool (CPOT)*: the scale uses a four-component clinical observation of: facial expression, body movements, muscle tension, and compliance with the ventilator for intubated patients or vocalization for extubated patients. Each component has a score of 0–2, and total score ranges from 0 to 8. A score of >2 has a high sensitivity and specificity for predicting significant pain in post-operative ICU patients exposed to a painful procedure.[4,5]

Table 2 The behavioural pain scale.[6] Reproduced with kind permission from Wolters Kluwer Health

Clinical observation	Score
Facial expression	
Relaxed	1
Partially tense	2
Totally tense	3
Grimace	4
Movement of upper limbs	
Relaxed	1
Partially flexed	2
Totally flexed	3
Totally contracted	4
Mechanical ventilation	
Tolerating movements	1
Coughing but tolerating most of the time	2
Fighting the ventilator	3
Impossible to control ventilation	4

Principles of pain management in the ICU

The basic principles in management of pain in the ICU are very similar to the perioperative setting:

(i) Ensuring a holistic approach to pain management by using a combination of non-pharmacological and pharmacological interventions (systemic analgesia and loco-regional techniques).
(ii) Using multimodal approach to management of pain so as to improve the quality of analgesia and reduce side-effects.

The important modifications are:

(i) Emphasis on analgesia before sedation ('analgesia first: A1') and daily planned interruption of sedation. Consider distress because of anxiety and delirium after pain has been adequately managed (Appendix).
(ii) Titration of analgesia to specific individualized goals with reassessments and avoidance of continuous prolonged infusions.[4,7]
(iii) Understanding that drugs can cause organ dysfunction and also organ dysfunction can influence the choice of drugs and dosages: needing an individually adapted analgesic regimen.

Greater use of sedatives (Sedo-analgesia) is associated with cardiovascular depression, increased duration of mechanical

ventilation and intensive care stay, delirium, and cognitive dysfunction. Algorithms emphasizing adequate analgesia before sedation [Analgo-Sedation or analgesia first (A1)] reduces the requirements for sedatives, duration of mechanical ventilation without increasing the incidence of accidental extubations, or post-traumatic stress disorder. Wherever possible pain should be pre-empted and treatment initiated before potentially painful procedures.[4] Evidence shows that an algorithm-based approach to sedation and pain management improves outcomes and whatever the algorithm used, analgesia should be goal directed and titrated to effect. Hence, guidelines and protocols should be made available in every unit (e.g. Appendix).

Specific problems in intensive care patients

These patients usually have multiple physiological derangements, which influences the pharmacokinetic and pharmacodynamic profile of the drugs. It is paramount to recognize that these factors are also likely to change or develop newly in the dynamic setting of intensive care. Some of these factors are:

(i) *Ileus*: unpredictable absorption of orally administered drugs.
(ii) *Altered protein binding*: increase in free drug fractions in hypoalbuminaemia.
(iii) *Deranged acid–base balance*: affects the ionized and bound fractions of drugs.
(iv) *Altered splanchnic blood flow*: reduces phase 1- and 2-dependent metabolism (i.e. in patients with shock, inotropes, or both).
(v) *Organ dysfunction*: hepatic and renal dysfunction reduces metabolism and excretion of drugs and their active metabolites.
(vi) *Drug induced worsening of organ dysfunction*: NSAIDs may worsen renal function.
(vii) *Drug interactions*: influences both metabolism and effectiveness (synergism or antagonism) of concomitantly administered drugs.
(viii) *Pharmacodynamic effects*: alterations in the blood brain barrier can result in increased sensitivity to the effects of drugs (opioids and respiratory depression; CNS toxicity to local anaesthetics).

Modalities of management

The modalities available for pain management include both systemic and regional analgesia.

Systemic analgesia

There is no evidence to support the superiority of one analgesic over another in ICU. Intravenous (I.V.) administration of medication is preferred to enteral and other parenteral routes of administration because of potentially decreased or erratic absorption that can occur in low perfusion states. Additionally, the i.v. route also has the benefits of faster onset of action, higher bioavailability and is easily titratable to effect.

Ideal analgesic

The ideal analgesic agent must have:

(i) Rapid onset, offset, and be titratable.
(ii) Predictable dose response.
(iii) High therapeutic index.
(iv) Short context sensitive half-time.
(v) Less accumulation in organ dysfunction.
(vi) No interactions.
(vii) Minimal adverse effects.
(viii) Cost-effectiveness.

Multimodal analgesia and synergism

Pain pathways are numerous and complex, and involves various receptors. Simultaneous use of different classes or modes of drugs to modulate the different pathways and receptors to provide best benefit is called the multimodal approach. The actions of analgesics can be additive or synergistic; hence, multimodal approach reduces dose requirements, side-effects, and complications.

Analgesics classification

The variety of drugs available to treat pain reflects the varied and complex nature of pain that is seen in critically ill patients. The drugs available can be classified into:

(i) Opioid analgesics.
(ii) Non-opioid analgesics.
(iii) Analgesic adjuncts: neuropathic drugs.

Opioid analgesics

Opioids are considered to be the mainstay for treatment of acute pain in critically ill patients. Opioids act by stimulating μ-, κ-, and δ-opioid receptors, which are widely distributed within the central nervous system and throughout the peripheral tissues. All opioids are considered to have equivalent analgesic efficacy when titrated to same pain intensity endpoints without any difference in clinical outcomes. The dosages, routes of administration, interactions, and considerations in organ dysfunction are summarized in Tables 3 and 4.

Management of background pain is best achieved by an initial bolus followed by an infusion (Tables 3 and 4). For infusion regimes, generally a step-up approach is recommended, where the opioid is started at a lower dose and increased by 15–20% of the initial dose until adequate pain control is achieved. This minimizes the incidence of side-effects because of inter-individual variability. Continuous infusions of conventional opioids can lead to drug accumulation and prolonged duration of action. Hence, emphasis must be placed on regular assessment of pain and titrating down the infusion rates if the pain goals are achieved; the infusion rates can be decreased in a stepwise fashion by 25%.

The prolonged use of opioids has been associated with high incidence of side-effects like tolerance and withdrawal. This does not differ between the different opioids, the route, or the regimen used. The adverse effects of opioids include hypotension, bradycardia, ileus, nausea/vomiting, urinary retention, constipation, delirium, hallucinations, and hyperalgesia. Rare side-effects include immunosuppression, seizures, and muscle rigidity.

Non-opioid analgesics

The simple analgesics like paracetamol and the non-steroidal anti-inflammatory drugs (NSAIDs) are both effective for treating mild nociceptive pain.

Paracetamol. The mechanism of action of paracetamol is not well understood. Paracetamol can be given through many routes, including oral, i.v., and rectal. Paracetamol reduces opioid requirements, and so unless contraindicated should be considered as a first line drug in management of mild to moderate pain and should be included as part of the multimodal regimen in treatment of severe pain. Dosing of paracetamol in patients with low body weight, reduced glutathione stores (i.e. malnutrition or comorbidity) should be done cautiously as paracetamol may potentially cause liver injury even within normal recommended doses.

Table 3 Pharmacokinetics of commonly used opioids. Doses below are guides and vary widely for individual patients. B, bolus; I, infusion; PCA, patient-controlled analgesia; ESRF, end stage renal failure; IBW, ideal body weight; M3G, morphine-3-glucouronide; M6G, morphine-6-glucouronide. *Bolus doses are titrated in aliquots for achieving pain relief

Opioid	Onset after iv bolus	Half-life ($t_{1/2}$)	Dosage*	Important considerations
Fentanyl	1–2 min	2–4 h	B: 1–2 μg kg^{-1} I: 1–10 μg kg^{-1} h^{-1} PCA: 10–25 μg bolus, lock out: 5–15 min, 4 h limit 400–800 μg Patches: 25–100 μg h^{-1}	Metabolized in the liver with no active metabolites. Accumulation in hepatic impairment. Less likely to accumulate in ESRF. Less hypotension than with morphine. Highly lipid soluble, duration of action is significantly increased when continuous infusions are used for prolonged periods. Transdermal patches used in palliative care and opioid rotation
Morphine	5–10 min	3–4 h	B: 0.1–0.2 mg kg^{-1} I: 0.05–0.1 mg kg^{-1} h^{-1} PCA: 1–3 mg bolus, lock out: 5–15 min, 4 h limit: 30–70 mg Enteral: 5–20 mg fourth hourly	Metabolized by glucouronidation, active metabolites: M6G and M3G. Oral bioavailability poor 15–65%. M6G is more potent than morphine and accumulates in renal impairment and M3G can cause delirium. Caution in both hepatic and renal impairment. Morphine causes histamine release
Alfentanil	1–2 min	1.6 h	B: 10–30 μg kg^{-1} I: 20–60 μg kg^{-1} h^{-1}	Less lipid soluble, quick onset and offset. Dose related, short duration respiratory depression, elderly patients particularly sensitive. Clearance prolonged in hepatic impairment (cirrhosis) but unaffected in renal impairment
Remifentanil	1–3 min	3–10 min	B: 1 μg kg^{-1} I: 0.05–2 μg kg^{-1} min^{-1}	Hydrolysis by plasma esterases. No active metabolites. No accumulation in hepatic/renal failure. Use IBW in obese individuals. Used more often in the neuro-intensive care for early neurological assessment

Table 4 Pharmacokinetics of less common opioids used under special circumstances. *Bolus doses are titrated in aliquots for achieving pain relief

Opioid	$t_{1/2}$	Dosage*	Important considerations
Oxycodone	4–6 h	s.c. 2.5–5 mg fourth hourly Enteral: 5–10 mg fourth hourly	Predictable and higher oral bioavailability 60–87%, caution in hepatic and renal impairment. Used both in acute pain and in cancer/palliative pain
Diamorphine	3–4 h	I.V. bolus: 0.05–0.1 mg kg^{-1} s.c: 5–10 mg fourth hourly Enteral: 5–10 mg fourth hourly	Metabolized to active components monoacetyl morphine and morphine by esterases. Highly lipid soluble, less likely to cause respiratory depression when administered intrathecally. Mainly used for cancer pain and palliative care as subcutaneous infusions
Tramadol	4–6 h	I.V.: 50–100 mg fourth to sixth hourly Enteral: 50–100 mg fourth to sixth hourly	High oral bioavailability, only partial antagonism by naloxone, causes less respiratory depression. Accumulates in renal and hepatic impairment. Caution in patients with epilepsy. Contraindicated with concomitant use of mono amino oxidase inhibitors
Codeine	4–6 h	Enteral: 30–60 mg fourth hourly	50% oral bioavailability, 10% undergoes O-demethylation to morphine, less effective against severe pain. CYP 2D6 polymorphisms produce unpredictable effects. Poor metabolizers have inadequate pain relief; ultra-rapid metabolizers may have respiratory depression

Non-steroidal anti-inflammatory drugs. NSAIDs work by inhibition of the cyclooxygenase (COX) enzymes COX-1 and COX-2. They regulate production of prostaglandins and thromboxane from arachidonic acid with varying ratio of COX-1 *vs* COX-2 inhibition. NSAIDs have analgesic, anti-pyretic, and anti-inflammatory properties. The analgesic property of NSAIDs has not been well studied in critically ill patients, so it is unclear whether the potential benefits (e.g. reduced time of mechanical ventilation or decreased duration of ileus) outweigh potential risks (i.e. renal dysfunction, gastrointestinal bleeding). In a retrospective cohort study on patients admitted to ICU after rib fractures, ketorolac use was associated with decreased pneumonia, increased ventilator, and ICU-free days. The rates of acute kidney injury, gastrointestinal haemorrhage, and fracture non-union were not different.[8]

NSAIDs should be avoided in patients at risk of renal dysfunction (hypovolaemia and inotrope dependent shock), GI bleeding (mechanical ventilation, burns, and alcoholic liver disease) and in patients with platelet abnormalities, coagulopathy, concomitant angiotensin-converting enzyme inhibitor therapy, congestive heart failure, cirrhosis, or aspirin sensitive asthma. Even selective COX-2 inhibitors have a similar effect to non-selective NSAIDs on reducing renal blood flow. Apart from the stable postoperative patient, NSAIDs find limited usage in ICU and are in general avoided. However, NSAIDs do have a place in critical care due their inhibition of prostaglandin synthesis (e.g. closure of patent ductus arteriosus in preterm neonates; hypothermic sepsis).

Analgesic adjuncts

There is abundant evidence to support the perioperative use of adjunctive drugs in reducing postoperative pain intensity and opioid consumption but there is paucity of evidence to support their routine use in critical care, except under specific circumstances. In general, pre-existing adjuvant drugs like gabapentinoids and tricyclic antidepressants (TCA) should be continued in ICU as cessation can precipitate withdrawal states.

Neuropathic pain is poorly treated with opioids and is best treated with analgesic adjuncts like the gabapentinoids, TCAs, or both.[4] Established neuropathic pain is very refractory to treatment, hence patients who are at a high risk of developing neuropathic pain should be started on the adjuvant medications early.

Adjuvant drugs (Table 5) lower opioid consumption and in addition to improving the quality of analgesia they also lower sedative requirements. They aid pain management in opioid tolerant individuals, facilitate opioid rotation and are useful in opioid and alcohol withdrawal.

Gabapentinoids. Gabapentin and pregabalin work by binding to the $\alpha_2\delta$ subunits of voltage dependent calcium ion channels. They reduce the development of hyperalgesia and central sensitization and are useful adjuncts in the treatment of neuropathic pain. Up to 89% of patients experience pain after demyelinating immune polyradiculoneuropathies like Guillain–Barre syndrome (GBS); the pain can be severe during the acute phase and up to a third may progress to develop chronic pain.[9]

Pain management in patients with conditions like GBS, multiple sclerosis (MS) or spinal cord injuries (SCIs) can be complicated and refractory. Gabapentin compared with carbamazepine or placebo reduces pain intensity in patients with GBS without increasing adverse side-effects. In a recent meta-analysis, both gabapentin and pregabalin have a moderate to large effect in reducing pain after SCI in the short and long term. In addition, they improve secondary measures like sleep, anxiety and depression and are now the first line drugs for post-SCI neuropathic pain.[10] Gabapentin has been used for pain management in the post-burn period and after surgical debridement.

The gabapentinoids are only available in the enteral formulation. Bioavailability of gabapentin is inversely related to the dose. Gabapentin is absorbed in a relatively small part of the duodenum and has a lower bioavailability compared with pregabalin, which is absorbed throughout the small intestine. Hence, gabapentin will be ineffective in patients on jejunal feeding. Side-effects of gabapentinoids include somnolence, dizziness, confusion, convulsions, and ataxia.

Tricyclic antidepressants. Amitriptyline is not licensed in the UK for treatment of acute pain but is useful for management of chronic and neuropathic pain. Specific circumstances relevant to intensive care where TCAs should be considered are neuropathic pain secondary to malignancy, diabetes, HIV, porphyrias, SCI, GBS, and MS. Side-effects of TCA include dry mouth, sedation, blurred vision, arrhythmias, and postural hypotension. TCAs must be avoided in patients with QT_c prolongation.

α_2-Agonists. Clonidine and dexmedetomidine are α_2-adrenoceptor agonists, which provide both analgesia and sedation. Dexmedetomidine has eight times more affinity for α_2-receptors compared with clonidine. Despite the well-known synergistic property of α_2-agonists and opioids, there is limited evidence to support their routine use for their opioid sparing properties in intensive care.

In contrast to clonidine, which has found a place as a perioperative analgesic adjunct, dexmedetomidine is more commonly used as an analgo-sedative in the intensive care setting. Dexmedetomidine infusion has been shown to reduce the prevalence and duration of confusion and delirium when compared with the use of morphine and midazolam.[11]

Both clonidine and dexmedetomidine have been used to treat opioid, benzodiazepine and alcohol withdrawal. Iatrogenic opioid withdrawal syndrome is a well-recognized entity both in the adult and paediatric intensive care (PICU) and occurs in up to 57% of PICU patients for which α_2-agonists are useful second line agents.[12] α_2-Agonists are used to improve quality of analgesia and aid opioid rotation in opioid tolerant individuals (e.g. burns, substance abuse). The side-effect profile of both α_2-agonists includes bradycardia and hypotension, which may limit the dose that can be safely administered. Abrupt cessation of α_2-agonists can cause rebound hypertension and can rarely cause a withdrawal syndrome.

Ketamine. Ketamine is an *N*-methyl-D-aspartate (NMDA) antagonist that is effective both as an analgesic and also a sedative agent. It improves the quality of analgesia with a tolerable neuropsychiatry side-effect profile. Ketamine is used more commonly as an analgo-sedative in PICU but it is reserved for special situations in the adult ICUs. In a study of patients admitted to the surgical intensive care after major abdominal surgery, low-dose ketamine infusion ($\leq$0.12 mg kg^{-1} h^{-1}) reduced cumulative PCA morphine requirements by up to 25% despite having similar VAS scores at rest and mobilization.[13] Low-dose infusions of ketamine ($\leq$0.25 mg kg^{-1} h^{-1}) with midazolam (0.5–1 mg h^{-1}) have been found to be effective in the management of pain in sickle cell crisis with improved pain scores and reduced morphine

Table 5 Adjuvant drugs. B, bolus; I, infusion

Drug	$t_{1/2}$	Dosage	Important considerations
Ketamine	2.5–3.5 h	B: 0.1–1 mg kg^{-1}; I: 0.125–0.5 mg kg^{-1} h^{-1}	Metabolite nor-ketamine is less potent and has hypnotic effect. Oral bioavailability 20%. Caution in patients with raised ICP, ischaemic heart disease, significant hypertension and psychotic states
α_2-Agonists			
clonidine		B: 2–5 μg kg^{-1}; I: 0.3 μg kg^{-1} h^{-1} Enteral: 50–150 μg	Reduced myocardial ischaemia, sedation, and hypotension at higher doses
dexmedetomidine		B: 1 μg kg^{-1}; I: 0.2–1 μg kg^{-1} h^{-1}	Not available orally
Gabapentinoids			
gabapentin	4.8–8.7 h	Enteral: 900–3600 mg day^{-1} in 3 divided doses	Bioavailability of gabapentin inversely related to dose. Both gabapentinoids have no hepatic metabolism and are excreted largely unchanged in the urine. Dose adjustment in renal impairment
pregabalin	5.5–6.7 h	Enteral: 50–300 mg day^{-1} in 2–3 divided doses	
Amitriptyline		Enteral: 10–100 mg	Useful in neuropathic pain. Caution in elderly, start at night-time at low dosage. Avoid in heart blocks and QT_c prolongation
Magnesium		B: 40 mg kg^{-1} I: 10 mg kg^{-1} h^{-1}	Delayed tendon reflexes in high doses/prolonged infusions. Prolongs duration of action of neuromuscular blockers

use. Addition of ketamine provides an opioid sparing effect in burns and opioid dependent/tolerant patients.

Pain and stress response because of tracheal suctioning (TS) causes increases in mean arterial pressure (MAP), intracranial pressure (ICP), mean cerebral blood flow velocity (mCBV), and cerebral perfusion pressure (CPP); acute rises of these parameters can be deleterious in head injured and neurosurgical patients. In a small observational study in patients sedated with propofol and remifentanil, addition of an infusion of ketamine at 0.1 mg kg^{-1} min^{-1} for 10 min before TS reduced cough scores and inhibited the increase in MAP, CPP, and mCBV but not ICP. Similarly in neurosurgical patients, infusions of S(+) ketamine compared with fentanyl for analgesia showed no differences in pain scores, cerebral haemodynamics or rates of developing ileus but patients who had S(+) ketamine showed a trend of decreasing norepinephrine requirements.[14] Ketamine is used as a useful adjunct in analgesic drug rotation and facilitating weaning from long-term opioid therapy in ICU. Ketamine's sedative and bronchodilatory properties have been used in refractory status epilepticus and status asthmaticus respectively. Side-effects of ketamine include delirium, hallucinations, nausea, and vomiting.

Magnesium. Magnesium causes blockade of NMDA receptors and acts as a useful perioperative adjunct by reducing analgesic requirements without major haemodynamic complications. In ICU, there is no evidence to support its use for analgesia or opioid sparing effect but its use is limited to management of atrial fibrillation, prevention of vasospasm after aneurysmal subarachnoid haemorrhage and for management of blood pressure in pre-eclampsia or eclampsia.

Alternative therapy

Other modalities of pain management like transcutaneous electrical nerve stimulation, acupuncture, and aromatherapy have a very weak evidence base in acute pain management and in intensive care, but should be considered as their side-effect profile is low.

Renal and hepatic dysfunction

The incidence of renal dysfunction in the mixed intensive care population is ~20%[15] and the incidence of liver dysfunction remains unknown as there is no universal definition for liver dysfunction. Most analgesic drugs depend on hepatic and renal clearance of either the parent drug, its metabolites (toxic or active), or both. Moreover, some drugs may aggravate pre-existing or cause new liver (e.g. amitriptyline, carbamazepine, and valproate) or renal dysfunction (e.g. NSAIDs). In general, short-acting drugs with very rapid clearance and no/minimal active metabolites (fentanyl, alfentanil, sufentanil, remifentanil, buprenorphine, paracetamol, and ketamine) can be used safely in renal failure. Drugs like morphine, oxycodone, tramadol, amitriptyline, clonidine, and gabapentin have been used in renal dysfunction, but require dosage adjustment based on the estimated glomerular filtration rate. In liver dysfunction, most drugs have significantly impaired clearance and higher oral bioavailability because of the reduced first pass metabolism. Drugs with short half-life and independent of hepatic clearance (e.g. remifentanil) must be considered.

Conclusion

Pain is a common problem in intensive care and remains poorly assessed and managed. Pain adversely affects multiple organ systems and inadequately managed pain has a direct impact on outcomes. When managing pain, emphasis must be placed on regular assessment and using a protocol-based multimodal analgesic regimen. The decision on the choice of the analgesic drugs must take into the account the varied physiological derangements that can also occur in ICU and also the potential for these drugs to cause organ damage.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Appendix

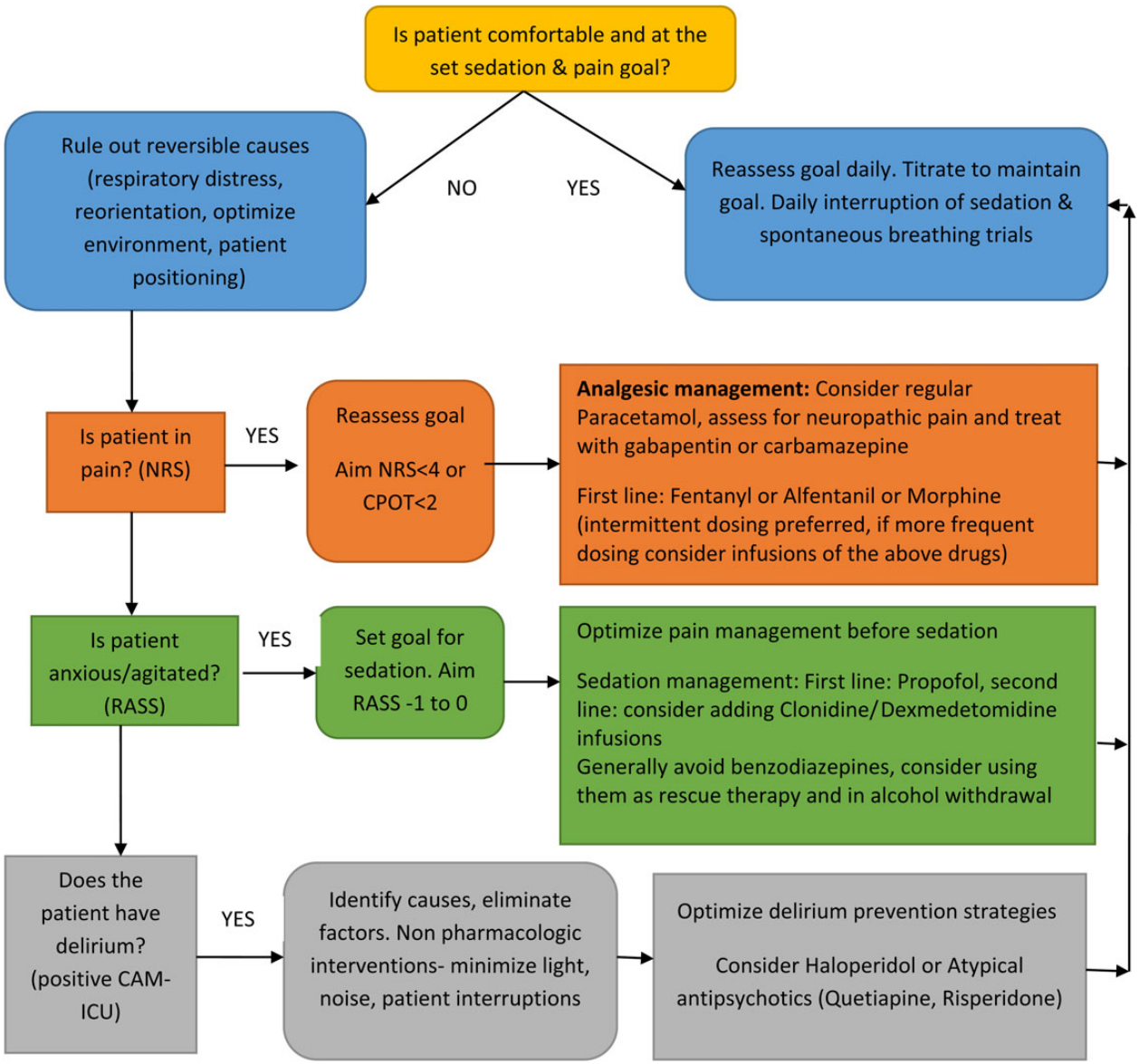

Fig A1 Composite pain, agitation and delirium management guideline in mechanically ventilated adult ICU patients. NRS, numerical rating scale; CPOT, critical care pain observation tool; RASS, Richmond agitation and sedation scale; CAM-ICU, confusion assessment method for ICU. Adapted from Barr and colleagues.[4]

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'Medical skin loss': Stevens–Johnson syndrome/toxic epidermal necrolysis and staphylococcal scalded skin syndrome

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Key points

- Severe exfoliative skin conditions leading to major skin loss are rare, yet associated with significant morbidity and mortality, and often necessitate critical care input.
- These conditions are complex and need a multidisciplinary approach to management with input from intensivists, plastic surgeons, dermatologists, ophthalmologists, dieticians, psychologists, and physiotherapists.
- Skin failure from widespread skin loss constitutes another organ failure. It should be treated like a major burn.
- Strict attention to fluid and electrolyte balance, temperature management, eye care, wound care, pain control, nutrition, and prevention of infection are key.
- Early referral with subsequent transfer to a burns centre for specialist wound management is highly recommended and improves outcomes.

Several acute exfoliative skin conditions lead to major skin loss and require critical care treatment. Although rare, these conditions have high mortality rates, long critical care stays, and are associated with significant chronic morbidity. Included in this group are Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and staphylococcal scalded skin syndrome (SSSS). Widespread skin loss from these conditions leads to 'acute skin failure' which is comparable with any other major organ dysfunction. It is characterized by pain, loss of water, electrolytes and protein, altered thermoregulation and immune function, hypermetabolism, and increased cardiac output.[1] Understanding the structure and function of skin improves our ability to care for these patients.

Many of the challenges associated with managing these conditions are similar to those seen in patients with a major burn. Hence, these cases are most appropriately managed in specialized burns centres with access to multidisciplinary expertise including intensivists, plastic surgeons, dermatologists, ophthalmologists, dieticians, psychologists, and physiotherapists. Early input from other disciplines optimizes long-term outcomes.[2]

Current burns data suggest 60–80 cases of SJS/TEN and SSSS are admitted to burns critical care units in the UK per annum over the past 5 yr. In addition, intensive care national audit and research centre data recorded 132 cases admitted to general adult critical care units between 1995 and 2006.[3] Compared with average general adult critical care patients, these patients had a higher mortality rate and longer critical care stay. The relative rarity of these conditions makes it difficult for individual clinicians to gain experience in managing these cases. This article, therefore, aims to cover the main critical care and anaesthetic considerations with regard to major skin loss during critical care admission.

Other infective skin conditions such as necrotizing fasciitis and dermatological malignancies are beyond the scope of this article.

Skin structure and function

The skin is the largest organ of the body, accounting for 15% of total body weight and has a surface area of 1.7 m^2 in the average adult. Human skin consists of three layers; the epidermis, dermis, and the supporting hypodermis or 'subcutis' (Fig. 1).

Epidermis

This is a stratified squamous epithelium derived from embryonic ectoderm. The keratinocyte is produced in the basal layer of the epidermis. These immature cells proliferate and differentiate as they migrate towards the surface forming several well-defined layers that are constantly replenished. The outermost layer, the stratum corneum, consists of flattened keratinized cells (corneocytes) that are shed every 2–3 weeks. Transmission of biochemical messages to lower layers in response to injury regulates their activity.

Dermis

This is a layer of connective tissue composed mainly of collagen (70%), elastin, and a semi-solid matrix of glycosaminoglycan. This connective tissue matrix provides strength, structure, and elasticity to the dermis and is formed by fibroblasts. Nerves and free nerve endings responsible for transmission of pain, itch, and temperature are found in the dermis in addition to specialized sensory receptors. There is also a rich vascular plexus located within the dermis.

Regeneration of the epidermis requires the presence of the dermis. If the dermis is totally destroyed such as with a full thickness burn, skin is unable to heal.

Specialized cells of the skin

Skin contains a variety of specialized structures referred to as epidermal appendages. These include hair follicles, arrector pili muscles, sebaceous glands, eccrine and apocrine sweat glands, melanocytes, Merkel cells, and Langerhans cells.

Functions of skin

The skin is a complex organ with many functions, which are crucial to survival.[1] These are given in Table 1.

Stevens–Johnson syndrome and toxic epidermal necrolysis

SJS and TEN are severe muco-cutaneous reactions characterized by erythema, extensive epidermal necrosis, and widespread bullous epidermal detachment. They are most commonly triggered by drugs and affect all age groups.

SJS and TEN are variants of the same disease spectrum, but distinguished chiefly by severity. SJS is the less severe form, affecting <10% total body surface area (TBSA). TEN is more severe and affects >30% TBSA. Cases which affect 10–30% are referred to as SJS/TEN overlap.

In total, 90% of cases involve mucous membranes of the mouth, eyes, and genital tract. This rare condition has an annual estimated incidence of 0.4–1.2 cases million^{-1}.[4]

Causes

The common drugs that trigger TEN are listed in Table 2. The onset of symptoms is typically 4–28 days after introduction of the drug, but can be delayed. Infection with Cytomegalovirus and Mycoplasma are the next most common triggers of TEN.

Other predisposing factors include:

(i) Human immunodeficiency virus infection
(ii) Malignancy or bone marrow transplantation
(iii) Genetic susceptibility (e.g. human leukocyte antigen B×1520).

Pathophysiology

The mechanism of TEN is not fully understood. However, it is characterized histologically by keratinocyte apoptosis and

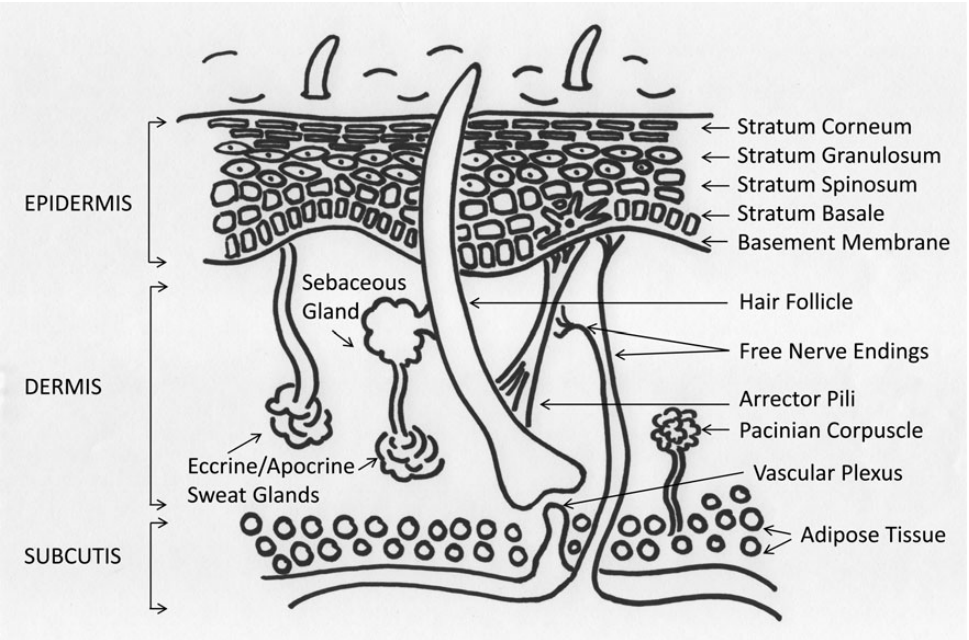


Fig 1 The structure of skin.

Table 1 Functions of skin

Protection	Barrier function of stratum corneum protects against environmental, chemical, and microbial hazards
	Limitation of inward and outward passage of water and electrolytes ensures the conservation of the internal milieu
	Durability and elasticity of dermis contributes to protection against physical injury
	Melanin production protects against ultra-violet radiation
Regulation	Temperature homeostasis is maintained by alteration of skin blood flow, sweating, and pilo-erection
	Minor role in maintaining fluid balance by avoiding excessive evaporative water loss that would otherwise cause dehydration and cooling
Immune	Dynamic role in innate and acquired defence systems.
Metabolic	Role in Vitamin D synthesis
	Capability in transformation of some drugs
Neurosensory	Terminal fibres of sensory nerves and specialized sensory receptors lying within the dermis enable skin to act as a large sensory organ
Social interaction	Visible portion of body covering

Table 2 Medication associated with high risk of TEN[4]

Medication associated with high risk of TEN
(i) Allopurinol
(ii) Carbamazepine
(iii) Lamotrigine
(iv) Phenobarbital
(v) Phenytoin
(vi) Cotrimoxazole
(vii) Sulfadizine
(viii) Oxicam NSAIDs
(ix) Nevirapin

separation of the epidermis from the dermis at the dermo-epidermal junction. This leads to extensive epidermal destruction. This process is thought to be mediated by cytokines including fas-fas ligand and tumour necrosis factor alpha either by triggering an immune reaction involving CD8+ lymphocytes or from a direct toxic effect of the drug or its metabolite.

Clinical features

The onset of TEN is typically preceded by a prodrome for 2–3 days of fever, flu-like illness and malaise before the development of skin blistering, erosions, and tenderness of the skin. Mucous membranes of the eyes, nose, mouth, and genitalia are commonly affected early in the course of the disease and result in an erosive and haemorrhagic mucositis. Involvement of the respiratory and gastrointestinal (GI) tract epithelium can also occur.

The early cutaneous lesions tend to be atypical target like lesions. The erythematous macules with purpuric centres then become diffuse and confluent reaching a maximum over the next 5–7 days. Bullae and skin sloughing result in large areas of

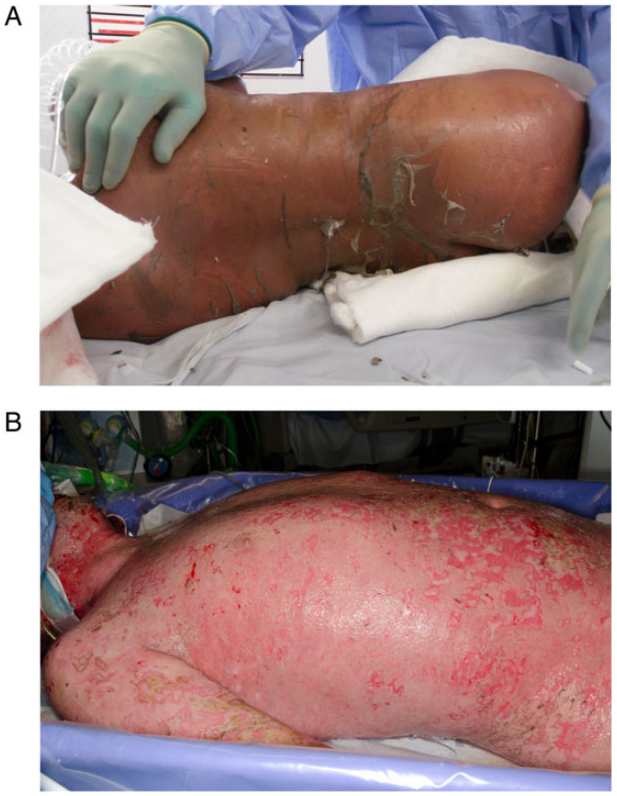


Fig 2 (A) Nikolsky sign. (B) Large area of denuded skin in TEN.

denuded epidermis. Nikolsky's sign is present, where gentle lateral pressure results in sheet-like epidermal detachment (Fig. 2A). Separation of this necrotic epidermis leaves areas of exposed, raw, dark red dermis that readily bleeds (Fig. 2B).

History of introduction of a drug associated with a high risk of SJS/TEN within 4–28 days is classical.

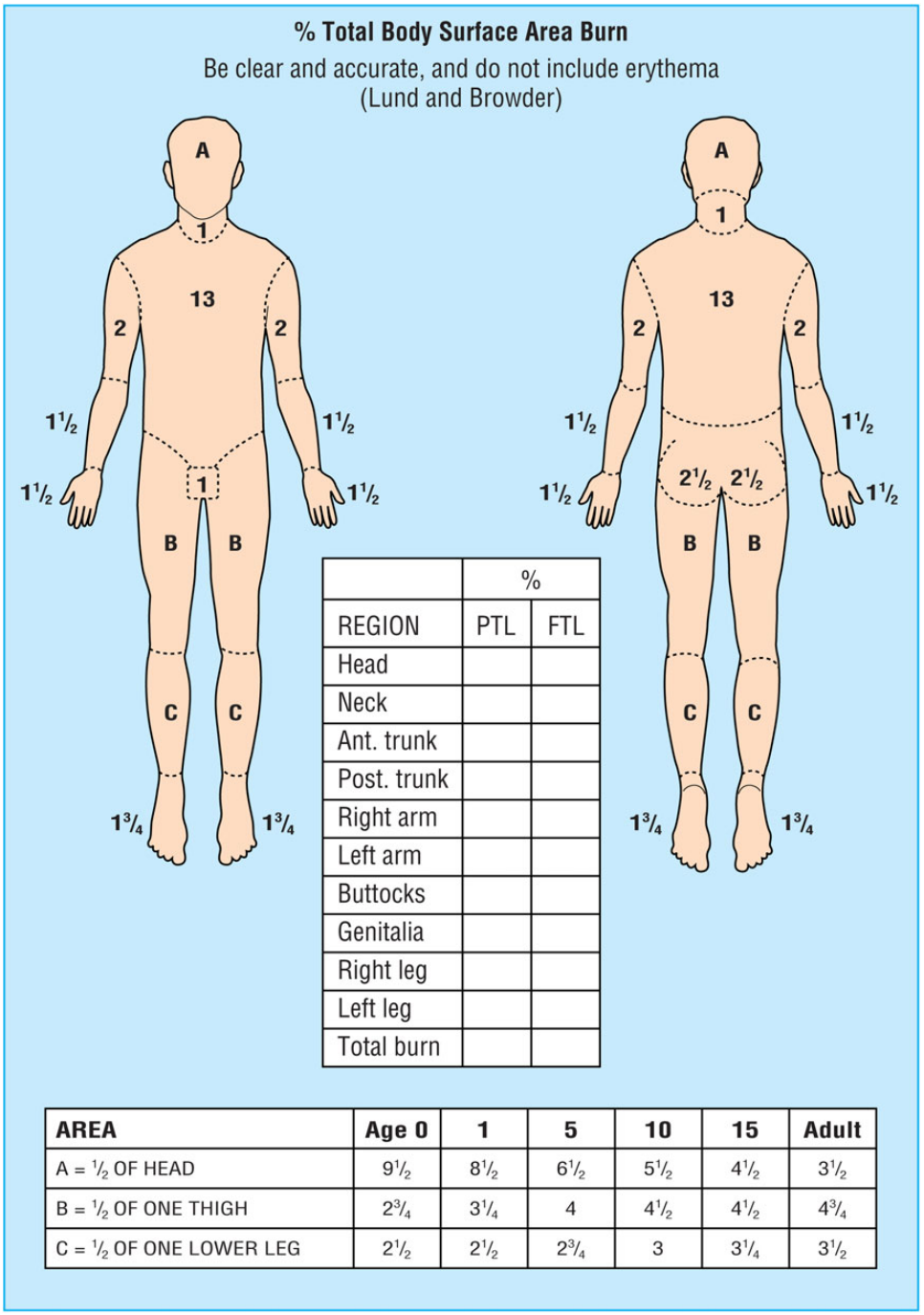
Estimation of skin involvement can be done using the Wallace rule of nines or the Lund and Browder chart as a rough guide, though often affected areas are non-confluent and patchy (Fig. 3).

Diagnosis is suggested by the clinical picture, but skin biopsy demonstrating variable epidermal loss and vesicle or bulla formation in the basal layer is useful to support the diagnosis and exclude other blistering skin disorders.

Specific management: TEN

Early recognition and withdrawal of any potentially causative agent is crucial. These drugs require reporting to the medicines and healthcare products regulatory agency. Careful consideration needs to be given to minimizing medication and limiting introduction of new medicines to prevent complications (e.g. deep vein thrombosis prophylaxis, GI protection).

Although there is no definitive treatment for TEN, several adjunctive immunomodulating therapies have been trialled. These include the use of immunoglobulins, corticosteroids, and ciclosporin. However, as a result of the rare nature of SJS/TEN, studies are limited and evidence-based standards are difficult to define. This is reflected in variable treatment practices across burns centres over the past two decades. In Maher and colleagues[5] review of 20 studies, 8 studies reported using i.v. immunoglobulin in the course of treatment and 6 studies reported the use of systemic corticosteroids.



	%	
REGION	PTL	FTL
Head		
Neck		
Ant. trunk		
Post. trunk		
Right arm		
Left arm		
Buttocks		
Genitalia		
Right leg		
Left leg		
Total burn		

AREA	Age 0	1	5	10	15	Adult
A = ½ OF HEAD	9½	8½	6½	5½	4½	3½
B = ½ OF ONE THIGH	2¾	3¼	4	4½	4½	4¾
C = ½ OF ONE LOWER LEG	2½	2½	2¾	3	3¼	3½

Fig 3 Lund and browder chart.

Thalidomide use in TEN has been studied in a randomized control trial but found to be harmful. The use of plasmapheresis and TNF inhibitors has been reported in a few case series.

Immunoglobulin

The use of i.v. immunoglobulin (IVIG) was first studied by Viard and colleagues[6] in 1998. Its proposed mechanism of action is based on its antagonizing effect on fas ligand activity, which has a role in mediating keratinocyte apoptosis in TEN. Since 1999, the use of IVIG for TEN remains controversial because of the limited evidence base.[7,8] However, use has become more frequent in the past decade and the Department of Health lists TEN as a condition for which IVIG use is appropriate in the short term. Adverse effects include renal impairment, haemolysis, and thrombotic complications.

The St Andrew's Centre currently use IVIG in suspected cases of TEN at a dose of 1 g kg^{-1} (ideal body weight) for 3 days. Current data suggest that IVIG treatment is more effective if used early.

Systemic corticosteroids

Sub-analysis of patients from the EuroSCAR and RegiSCAR trials have not shown any benefit from steroid therapy in TEN,

though some studies have initially shown values in reducing inflammation and, in particular, reducing ocular complications. There is a theoretical risk of increased sepsis and impaired re-epithelialization leading to increased mortality. I.V. corticosteroids are currently not recommended.

Ciclosporin

The immunosuppressant effects of ciclosporin are directed towards T-cell function, which play a role in the propagation of keratinocyte apoptosis in TEN. Studies use a dose of 3–5 mg kg^{-1} for 8–24 days. Adverse effects include hypertension, worsening renal function, and infection. There has been no firm conclusion regarding benefits because of the small number of published studies.

Prognosis

The overall mortality rate for SJS is 10%, but increases to 30–50% in TEN. The main cause of in-hospital mortality is multi-organ failure from sepsis. Age and extent of skin involvement are major prognostic factors. The SCORTEN (severity of illness score for TEN) is a validated scoring system, which predicts mortality from TEN based on seven clinical parameters.[9] This should be scored within 24 h of admission. Each parameter scores 1 point (Fig. 4).

Staphylococcal scalded skin syndrome

This is a staphylococcal toxin-mediated exfoliative dermatitis that can result in major skin loss because of widespread splitting of the granular layer of the epidermis. It primarily affects children <6 yr with low renal maturity and hence reduced metabolism and decreased excretion of staphylococcal toxin. Adults who are affected commonly have underlying disease that increases their susceptibility to staphylococcal infection.

Pathophysiology

SSSS is caused by two distinct epidermolytic exotoxins, ETA and ETB. These exotoxins cause cleavage of the desmoglein 1 complex, a desmosomal adhesion molecule responsible for the anchoring of keratinocytes. This results in the formation of fragile tense bullae. These toxins are also implicated in bullous impetigo. Widespread splitting of the epidermis results in superficial diffuse sheet-like desquamatization.

Although the diagnosis is clinical, skin biopsy will classically show cleavage of the stratum granulosum.

- Age ≥ 40 yr
- Malignancy
- Initial area of epidermal detachment ≥10% TBSA
- Heart Rate ≥120 bpm
- Serum Urea >10 mmol l^{-1}
- Serum Glucose >14 mmol l^{-1}
- Serum Bicarbonate <20 mmol l^{-1}

Score	Predicted Mortality (%)
0-1	3.2
2	12.1
3	35.3
4	58.3
5 or more	90

Fig 4 SCORTEN.

Clinical features

SSSS presents with a prodromal illness of fever, malaise, irritability, sore throat, or conjunctivitis. Blistering of the skin develops over the next 48 h. Lesions often affect the flexures initially before generalized scaling and sheet-like desquamatization over the next few days (Fig. 5). Nikolsky's sign can be present revealing a moist erythematous dermal base. Mucosal lesions are rare.

Estimation of skin loss can be done in children using the Lund and Browder chart (Fig. 3).

Specific management: SSSS

Antibiotic therapy directed at staphylococci along with supportive therapy and good wound care is the mainstay of treatment. Cultures should be taken from blood, urine, nasopharynx, skin lesions, and any site of potential infection.

Prognosis

In the absence of systemic complications, complete healing without scarring or altered pigmentation can occur in 10–14 days.

Mortality from SSSS is 4% in children. The main cause of morbidity and mortality are sepsis and electrolyte imbalance. In adults, the mortality rate is up to 60% because of underlying disease.

General management of major skin loss

Meticulous supportive care forms the mainstay of treatment for major skin loss. Management in a critical care unit or specialized burns unit for optimal wound care is appropriate for skin involvement of >10%. Wound infection is a major threat to wound healing by deepening of the skin loss, but can also be life-threatening because of resultant bacteraemia and multi-organ failure. Where possible, lines should be inserted through unaffected skin.

Fluid management

Fluid resuscitation is often required in the early stages as many patients present with fluid deficit from poor oral intake and increased transcutaneous fluid loss. Initial requirements are less (by a third/quarter) than that required for a burn of similar size as predicted by the Parklands formula; 4 mg kg^{-1} (% burn)$^{-1}$. Maintenance fluid needs to account for variable, but often significant ongoing insensible losses from skin and should be guided by clinical parameters aiming for urine output of 0.5 ml kg^{-1} h^{-1}

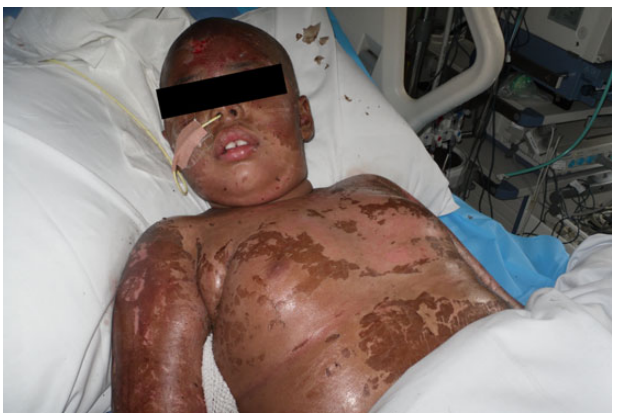


Fig 5 Staphylococcal scalded skin syndrome.

(1 ml kg^{-1} h^{-1} in children). The use of vasopressors may be required, but should be avoided if possible as they may reduce blood flow to the skin and limit wound healing.

Children with skin involvement >15% require catheterization.

Temperature management

Significant heat loss from radiation and evaporation occurs from skin loss. Patients should be nursed in a side room where ambient temperature can be raised to 25–28°C and humidity can be adjusted. The use of warming devices, such as warming blankets, is recommended. Both core and peripheral temperature should be monitored to maintain a core—peripheral temperature gradient of <2°C.

Wound care

There are several approaches to skin care. Surgical debridement to remove the detached skin and necrotic tissue is the main approach in many burns units and reflects the current approach to care of burns patients. This requires a general anaesthetic. Other centres advocate more conservative management and restrict aggressive debridement. Currently, there is no evidence to suggest that either approach is superior. Subsequent coverage of the wounds is essential to reduce infection and to promote effective wound healing. The St Andrew's Centre wound management algorithm is shown in Figure 6. It includes the use of versajet hydrosurgery in patients who present late (>2 days) or whose wounds appear infected.[10]

Ideal dressings should maintain a moist environment, be permeable to gas exchange and impermeable to bacteria. They should provide a degree of thermal insulation and be able to be removed without trauma. Non-adherent nanocrystalline silver dressings (e.g. Acticoat™) have good antimicrobial efficacy and has been successfully used as the primary dressing. Dressings impregnated with silver sulfadiazine should be avoided in cases of TEN triggered by a sulfonamide. Biosynthetic skin substitutes such as Biobrane® have also been used as a primary dressing. It is effective in reducing pain and exudative losses and limits microbial colonization. It remains intact for up to 7 days before becoming detached and hence can decrease the frequency of painful dressing changes. This also minimizes disruption to the healing skin. Application requires a general anaesthetic.

Gentle skin handling and limitation of trauma to the skin from blood pressure cuffs, adhesive electrocardiogram electrodes, and line dressings is required. Day-to-day care is best undertaken by specialist nurses who are familiar with managing fragile skin.

Infection

Wound infection with Pseudomonas, Staphylococcus, and Enterobacter is common and can limit recovery by impairing re-epithelialization and contributing to sepsis and multi-organ failure. Sterile handing where possible and regular use of antimicrobial solutions for disinfection such as Octenisan® are recommended. Frequent wound swabs for culture are required for microbiological surveillance and to guide antimicrobial therapy. There is no indication for the prophylactic use of systemic antibiotics in patients with SJS/TEN as this may increase skin colonization with Candida.

The use of bowel management systems is useful to prevent soiling of wounds from faeces.

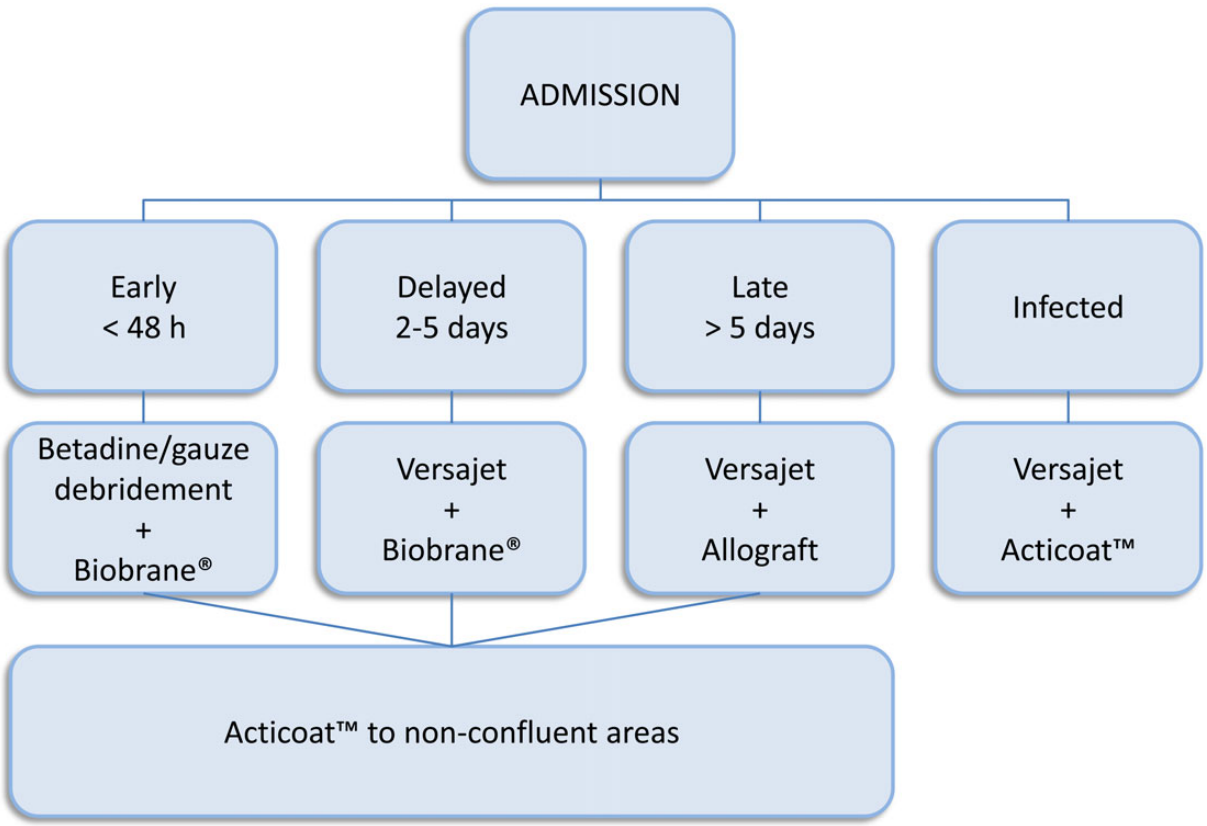


Fig 6 St Andrew's Centre wound management algorithm.

Patients often require critical care therapy for prolonged periods and are at risk of usual critical care infections. General critical care precautions in infection control including strict barrier nursing is required to prevent cross contamination and nosocomial infections.

Mouth and airway involvement

Mucosal involvement of the lips, tongue, and palate is frequent (Fig. 7). When severe, haemorrhagic erosions can extend to affect the oropharynx, oesophagus, larynx, and respiratory tree. Fibre-optic bronchoscopy may demonstrate bronchial epithelial detachment in the proximal airways. Subsequent development of pulmonary infiltrates, bronchial obstruction, and hypoxaemia may prompt the need for mechanical ventilation. Washout of necrotic bronchial epithelium during fibre-optic bronchoscopy is useful.

Intubation and mechanical ventilation may be required in the absence of respiratory involvement to facilitate the general management of patients with severe skin loss. In the acute stages, it may be required to enable safe transfer, aids with effective pain relief and airway protection from excessive epithelial necrosis, and haemorrhagic erosions of the upper airway.

Pain management

Major skin loss is painful and a holistic approach is required. Inadequate pain control leads to psychological trauma and has a marked adverse effect on long-term psychological outcome.

Patients generally require opioids to maintain adequate background analgesia. Additional analgesics are necessary for the increased pain associated with positioning and wound handling. Sedation may also be required for procedures such as dressing changes. Options for this include the use of ketamine, propofol, midazolam, and remifentanil.

Regular use of analgesic adjuncts such as ketamine, clonidine, and gabapentin are useful in combination with opioids because of their opioid-sparing effects. However, careful consideration is required before using gabapentin in patients with SJS/TEN triggered by anticonvulsants. These adjuncts can be reduced and adapted during the course of healing.

Nutrition

Poor oral intake in combination with increased calorie requirements can result in weight loss. Calories in addition to those required to sustain basal metabolic rate are required for the increased energy expenditure from the stress factor because of skin loss and hypermetabolism. This is not to the same extent as that seen with burns. Input from a dietician for assessment of calorie requirements is important and requires adjustment from the early catabolic phase to the anabolic recovery phase.

Continuous nasogastric or ideally nasojejunal feed should be established as soon as practical to support metabolic disturbances. Regular weighing is recommended to monitor nutritional state.

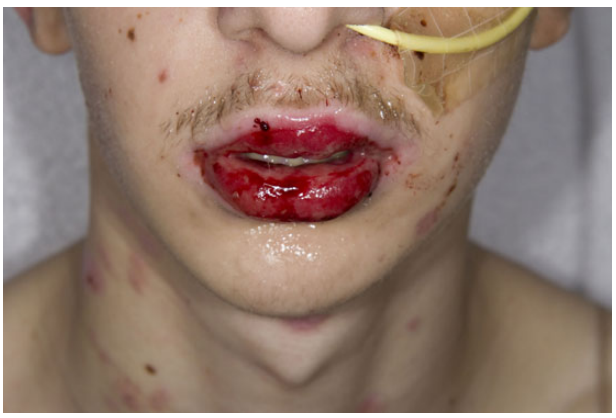


Fig 7 Mucosal involvement in TEN.

Eye care

Immediate and regular ophthalmology review is necessary to assess for ocular involvement and secondary ophthalmic complications in SJS/TEN. Early effective management can reduce the severity of chronic eye disease including permanent visual impairment and blindness. Patients require frequent eye lubricants and topical preservative free antibiotics in the presence of corneal ulceration or proved ocular infection. Ocular hygiene including glass rodding to prevent against adhesions is required on a daily basis.

Prevention of urogenital and vulvovaginal sequale

Examination of the urogenital tract should form part of the initial and subsequent daily assessment of SJS/TEN as blistering and erosions occur. Long-term urinary and sexual dysfunction can result from urethral strictures and vaginal adhesions. In women, formal gynaecological review is recommended for consideration of the use of vaginal dilators or vaginal moulds to prevent against vaginal synaechiae. Application of corticosteroid creams, antimicrobial creams, and white soft paraffin ointment to involved areas is appropriate and coverage with a non-adherent dressing such as gelonet or Mepitel™. Uncircumcized males need to be checked for preputial retractability.

Summary

Major skin loss from exfoliative dermatoses is rare but life threatening and often necessitates critical care input. It is associated with marked physiological abnormalities, which lead to higher mortality and longer critical care stays than average for adult patients. The resulting ‘skin failure’ should be regarded as a distinct entity analogous to any other organ failure.

The rarity of SJS/TEN and SSSS leads to difficulty in gathering high-quality evidence on specific immunomodulating treatment options. Hence, there is a lack of consensus among clinicians and varied treatment practice. Above all, withdrawal of the culprit drug in cases of SJS/TEN and early appropriate antibiotic therapy in cases of SSSS is required in combination with meticulous supportive care. This is best carried out in a specialized burns unit with expert multidisciplinary input.

Declarations of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Nitrous oxide in modern anaesthetic practice

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Key points

- Nitrous oxide is an *N*-methyl-D-aspartate receptor antagonist and may reduce the incidence of chronic post-surgical pain.
- Nitrous oxide oxidizes Vitamin B12 and can precipitate sub-acute combined degeneration of the cord with chronic use or in patients with folate/B12 deficiency.
- Nitrous oxide expands air spaces and is contraindicated in patients with pneumothorax or recent (up to 4–6 weeks) ocular surgery using intraocular gas.
- Nitrous oxide has global warming and ozone depletion potential and its concentration in the theatre environment is regulated.
- The ENIGMA-II trial showed that nitrous oxide does not increase the risk of death or cardiovascular complications.

Nitrous oxide (N_2O) was first isolated by Joseph Priestly in 1772 and subsequently recognized for its analgesic properties by Humphrey Davy in 1799.

> Davy has actually invented a new pleasure, for which language has no name. Oh Tom! I am going for more this evening; it makes one strong, and so happy!. . .Tom, I am sure the air in heaven must be this wonder-working gas of delight!
>
> — Robert Southey, *Letter to Thomas Southey*, July 12, 1799

Although noted by Davy that it 'may probably be used with advantage in surgical operations' and some initial use in dentistry by Horace Wells in 1845, it was firmly established as an anaesthetic agent by Gardner Quincy Colton in the 1860s and promoted around North America and Europe.

Because of a diverse range of concerns, the use of N_2O as an anaesthetic is declining in Western countries. It was used in 33% of operations in the USA in 2009 and had reduced to 21% in 2011.[1] Sadly, its recreational use is increasing, outpacing cocaine, ecstasy, and ketamine. In the UK, 470 000 people aged between 16 and 59 used nitrous oxide in the past year compared with 100 000 in 2013.[2]

This review will examine the physical and pharmacological properties of nitrous oxide and the controversies regarding its current use.

N_2O manufacture and environmental impact

At temperature 170–240°C, ammonium nitrate breaks down in an exothermic reaction to form nitrous oxide and water by the following equation:

$$NH_4NO_3 \rightarrow N_2O + 2H_2O$$

By-products including nitrogen (N_2), nitrogen dioxide (NO_2), and nitric acid (HNO_3) are removed by scrubbing agents and base/acid gas washes.

Nitrous oxide has a global warming potential (GWP) of 310 (CO_2 is the standard with a GWP of 1) and is regulated under the Kyoto Protocol (1997). It is the third greatest contributor to the greenhouse effect in the UK. However, because of the formation of NO_x intermediates under the influence of ultraviolet radiation in the stratosphere, it also has ozone-depleting potential (ODP). As an essential medical gas, it is unregulated by the Montreal Protocol (1987). Nitrous oxide has an ODP 1/60th of the standard chlorofluorocarbon (CFC)-11, but because of the effectiveness of the Montreal Protocol in reducing CFC emissions and the scale of natural and man-made nitrous oxide, nitrous oxide will remain one of the greatest contributors to ozone depletion during the 21st century.

Physiochemistry, storage, and supply

Nitrous oxide is a colourless gas with a slightly sweet odour and taste at room temperature and pressure (Table 1). It is stored in a cylinder, compressed as a liquid/vapour below its critical temperature (36.5°C). The saturated vapour pressure (SVP) is temperature sensitive (Gay-Lussac's law). At standard temperature (0°C) the SVP is 35 bar (3500 kPa) and at room temperature (20°C) it is 52 bar (5200 kPa). The filling ratio in the UK is 0.75 (i.e. the weight of nitrous oxide in a full cylinder is three-quarters the weight of water that would fill the cylinder). This is reduced in tropical climates to 0.67 because of the increased vapour pressures exerted at higher temperatures. As nitrous oxide is discharged from a cylinder, it vapourizes, requiring energy in the form of heat (latent heat of vapourization). This process cools the cylinder, reducing the SVP and cylinder pressure. The pressure recovers when the cylinder is closed and it warms back to environmental temperature. Cylinder pressure does not accurately indicate the filling status of the cylinder, as the SVP will only decrease when all the liquid nitrous oxide is consumed and the tank is almost empty.

Hospitals often supply piped nitrous oxide at a pressure of 4 bar to theatre environments. These are supplied by large cylinders (e.g. size-J) in a system that automatically switches cylinder when the previous one is empty.

A 50:50 mixture of nitrous oxide/oxygen (Entonox, British Oxygen Company) is used as an inhalation analgesic. Gaseous oxygen bubbled through liquid nitrous oxide increases the vapour pressure of the mixture to form a gas at pressures far exceeding those capable of liquidizing nitrous oxide alone (Poynting effect). Because of this effect, Entonox has a pseudocritical temperature of –6°C at a cylinder pressure of 137 bar (13700 kPa) and is therefore a compressed gas during storage at room temperature. It must not be stored below its pseudocritical temperature or it will separate under a process called 'lamination'. This will leave oxygen gas above a layer of liquid nitrous oxide. When used, pure oxygen will be delivered first and the delivered mixture will become increasingly concentrated until pure nitrous oxide is delivered with hypoxic consequences to the patient. Pipeline Entonox at 4 bar has a pseudocritical temperature of –30°C and is safer in this respect.

Table 1 Properties of nitrous oxide

Molecular structure	$N\equiv\overset{+}{N}-O^{-} \longleftrightarrow {}^{-}N=\overset{+}{N}=O$
Molecular weight	44
Boiling point	–88°C (309 K)
Critical temperature	36.5°C
Critical pressure	72 bar
Cylinder colour (UK)	Blue
Cylinder phase	Liquid/vapour at <36.5°C
Cylinder pressure at 15°C	44 bar (4400 kPa)
Filling ratio	0.75 (UK) 0.67 (tropical)
Pipeline pressure	4 bar (400 kPa)
Mechanism of action	NMDA receptor antagonist
MAC	105%
Blood: gas partition coefficient	0.47
Oil:gas partition coefficient	1.4
Nitrous oxide: air 50%:50%	
Cylinder colour	White or blue with blue and white shoulders
Cylinder pressure	137 bar (13 700 kPa)
Pseudocritical temperature –6°C	
Pipeline pressure	4 bar (400 kPa)
Pseudocritical temperature –30°C	

Theatre environment

Nitrous oxide may reduce fertility[3] and increase the rate of spontaneous abortion in female workers with chronic exposure. Rare cases of myelopathy have been recorded in the past from occupational exposure. Therefore, nitrous oxide is controlled under the Control of Substances Hazardous to Health (COSHH) regulations. Exposure is assessed over an 8- or 10-h period and recorded as an average exposure level. The limit in the UK (COSHH) is 100 ppm (parts per million) and in the USA (National Institute of Safety and Health) 25 ppm. Areas that do not use anaesthetic gas scavenging systems or have inadequate ventilation, such as recovery, dental suites, and radiology, are at risk of exceeding these exposure limits.

Pharmacodynamics

Anaesthesia and pain

Mechanism of action

Nitrous oxide acts as an N-methyl-D-aspartate (NMDA) receptor antagonist. This is different from other volatile anaesthetic agents that modulate (usually potentiate) the activity of gamma-amino butyric acid-A ($GABA_A$) receptors and inhibit neuronal potassium channels (TREK-1) among other suggested targets. The NMDA receptor is a glutamate binding, non-selective ion channel involved in synaptic plasticity and memory formation. The $GABA_A$ receptor is the main inhibitory, chloride-ion selective, ligand-gated channel of the central nervous system (CNS). Through different mechanisms, nitrous oxide and $GABA_A$ modulators act synergistically to induce amnesia and hypnosis. Thus nitrous oxide is often referred to as a 'volatile-sparing agent'.

Awareness and cerebral function monitoring

The 5th National Audit Project (NAP5) from the Association of Anaesthetists of Great Britain and Ireland estimated the incidence of patient-reported awareness as ~1:19 000 anaesthetics, with a wide variation between settings, the highest being in cardiothoracic (1:8600) and Caesarean section under general anaesthetic (1:670).[4] The NAP5 project found that nitrous oxide was used in 27.7% of 'Class A' (certain or probable) awareness cases but this exactly correlated with the frequency of nitrous oxide use in all anaesthetics (28.6%), suggesting that it does not influence the risk of awareness. The use of nitrous oxide was associated with a lower incidence of awareness in Caesarean section under general anaesthesia and its use is recommended in this setting by NAP5.[4]

NMDA antagonists such as nitrous oxide and ketamine do not suppress the cortical electroencephalogram in the same manner as $GABA_A$ modulators and therefore their effects are not correlated with cerebral function monitoring (e.g. bispectral index). Using cerebral function monitoring in regimes containing nitrous oxide may lead to inappropriately deep anaesthesia.

Pain

Nitrous oxide releases proenkephalin in the CNS. While single agent 66–70% nitrous oxide provides an analgesic effect similar to a whole blood concentration of remifentanil of 2 ng ml^{-1},[5] it seems that volatile anaesthetic agents or strong opioids are not synergistic with nitrous oxide and may in fact negate some of the analgesic effects of nitrous oxide during co-administration. With the advent of short-acting opioids and volatile agents, the role of nitrous oxide in the delivery of analgesia in balanced anaesthesia is of decreasing importance.

However, it seems that the NMDA antagonism of nitrous oxide may offer a significant benefit in the reduction of chronic post-surgical pain and opioid-induced hyperalgesia. NMDA receptors are involved in synapse plasticity and the development of central and peripheral sensitization leading to chronic post-surgical pain. Sub-group analysis of the ENIGMA-I trial showed a significant reduction in the incidence of chronic pain with the use of nitrous oxide.[6] This effect has been examined by the ENIGMA-II trial and will be reported on shortly.

Speed of onset, second gas, and concentration effects

Nitrous oxide has low anaesthetic potency, with a concentration of 105% required for single minimum alveolar concentration (MAC) anaesthesia, a clearly unreasonable proposition at atmospheric pressure. However, its low solubility in blood (blood:gas partition coefficient) leads to a rapid equilibration of partial pressures between blood and inspired gas and rapid onset and offset of action (Fig. 1).

Nitrous oxide also improves the speed of onset of volatile agents by the 'second gas effect'. Nitrous oxide transfers across the alveolus rapidly because of its high lipid solubility. This leads to concentration of the remaining gases in the alveolus (volatile agent, oxygen, and nitrogen), increasing the driving pressure of volatile anaesthetic agent into the blood. Also the loss of volume associated with nitrous oxide uptake leads to an augmentation of ventilation. Providing a higher concentration of nitrous oxide or volatile anaesthetic agent further increases this effect. This is referred to as the 'concentration effect'. The second gas and concentration effects work to increase the speed of onset of anaesthesia when using nitrous oxide (Fig. 1).

Diffusion hypoxia

The rapid transfer of nitrous oxide across the alveolus occurs in reverse during wake-up. In the case of low ventilation with air, nitrous oxide will quickly transfer into the alveolus, down its concentration gradient, diluting the concentration of oxygen, and impairing oxygen transfer across the alveolus into the blood, leading to hypoxia. Maintaining adequate minute ventilation and supplementing oxygen during the brief washout phase of nitrous oxide prevent this.

Diffusion into closed cavities

Because of the higher blood solubility of nitrous oxide than nitrogen, nitrous oxide transfers faster into closed gas cavities than nitrogen is removed, leading to expansion of air or low-solubility gas-filled cavities. These cavities can be divided into compliant and non-compliant. Compliant cavities, such as pneumothorax, pneumoperitoneum, bowel gas, and air emboli, will increase in volume with transfer of nitrous oxide whereas non-compliant cavities such as the cranium, middle ear, and eye will increase in pressure.

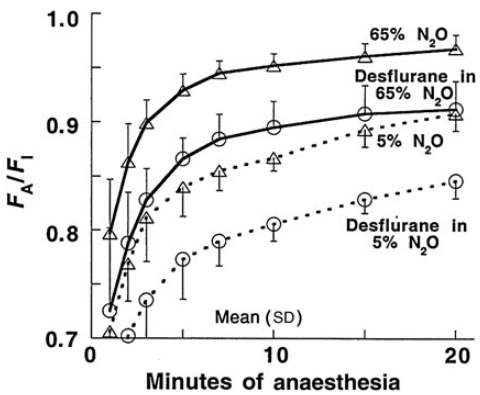

Fig 1 Ratio of alveolar (end-tidal) concentration (F_A) to inspiratory concentration (F_I) over time. Because of low blood solubility, 65% nitrous oxide alone has a faster onset than desflurane in 5% nitrous oxide. Increasing the concentration of nitrous oxide from 5 to 65% increases the speed of onset of desflurane[7]

In compliant cavities, the maximum expansion is related to the alveolar percentage of nitrous oxide for equilibration. Therefore, 50% nitrous oxide will lead to a maximum two-fold expansion, and 75% nitrous oxide will lead to a four-fold expansion. In dogs, 75% nitrous oxide led to a two-fold increase in volume over 10 min and a three-fold increase in volume in 30 min.[8]

Volume expansion can take place over seconds for an air embolus in a circulation containing nitrous oxide. The lethal volume of air in rabbits breathing 75% nitrous oxide is 30% less than in those not receiving nitrous oxide.[9] The use of nitrous oxide for neurosurgery in the sitting position does not increase venous air embolism (VAE) risk, but if VAE is suspected, nitrous oxide use should be discontinued.[10] Increases in bowel volume can lead to difficult surgical conditions and an inability to close the abdomen after surgery or high intra-abdominal pressures during laparoscopy.

Nitrous oxide should be avoided during or after eye surgery using intraocular gas (SF_6 or C_3F_8). With 75% nitrous oxide a three-fold[11] increase in size of the bubble can occur within the eye with a resultant increase in intraocular pressure, and a reduction in retinal perfusion pressure and visual loss. SF_6 remains *in situ* for 7–10 days and C_3F_8 for 4–6 weeks or more. Pressure changes of 20–50 mm Hg can also occur in the ear, affecting post-operative hearing and worsening surgical conditions.

Nitrous oxide might expand an already present pneumocephaly, converting to a tension pneumocephaly. A recent review suggests waiting 6–8 weeks after open dura surgery before using nitrous oxide, as intracranial air persists for several weeks after intracranial surgery.[10] However, its use in open brain surgery does not show an increase in intracranial gas post-craniotomy and may in fact reduce intracranial pressure (ICP) because of the rapid washout of nitrous oxide after closure of the dura and wake-up.

Because of these concerns, nitrous oxide is relatively contraindicated in bowel, laparoscopic, middle ear, and eye surgery with caution advised in neurosurgery. Patients with pneumothorax should avoid nitrous oxide and information should be sought from patients before operation to exclude the possibility of recent eye surgery or details of the gas used. Attention must also be paid to the potential effects of increased volume in air-filled spaces such as the tracheal cuff, laryngeal mask, and pulmonary artery catheter cuff if used.

Physiological systems

Metabolic and haematological systems

Nitrous oxide irreversibly oxidizes the cobalt ion at the centre of Vitamin B12 (cyanocobalamin). Vitamin B12 is required as a co-factor for the enzyme methionine synthetase. This crucial enzyme of one-carbon chemistry transfers the methyl group from 5-methyl tetrahydrofolate (THF) to homocysteine, to form THF and methionine. THF is involved in thymidine synthesis and DNA production. After several hours of nitrous oxide anaesthesia, activity levels of methionine synthetase are very low. Mild megaloblastic changes (associated with B12 deficiency) are present after 12 h and are marked after 24 h. After several days, complete bone marrow failure is expected.

Methionine is required for the methylation of myelin sheath phospholipids. B12 or folate deficiency leads to sub-acute combined degeneration of the cord—presenting as limb weakness, numbness and tingling with imbalance. Patients with subclinical B12 deficiency, because of illness, pernicious anaemia, or nutritional deficiency, and patients with methylene-tetrahydrofolate-reductase deficiency are especially at risk. Preoperative B12 followed by folate supplementation is recommended or nitrous oxide should be avoided.

Cardiovascular systems

Nitrous oxide leads to mild adrenergic stimulation with a slight increase in heart rate, venous tone, and pulmonary vascular resistance. It has a mild negative ionotropic effect that seems to be offset by the adrenergic stimulation. On balance, when given to reduce the concentrations of volatile anaesthetic agent, nitrous oxide improves haemodynamic performance compared with volatile alone. It is not cardioprotective and has no effects on the coronary circulation.

Nitrous oxide increases plasma homocysteine concentrations, a marker of cardiovascular disease. The ENIGMA-I trial demonstrated a trend to an increased risk of myocardial infarction (MI) in the nitrous oxide group and a statistically significant increase in the risk of MI over a 3.5-yr follow-up.[12,13] However, sub-group analysis of the PeriOperative ISchaemic Evaluation trial of perioperative β-blockade showed no link between nitrous oxide and cardiovascular death.[14] This has been confirmed by the recent release of the ENIGMA-II trial, a 7112 patient, international, multicentre, randomized controlled trial of nitrous oxide in equivalent oxygen concentrations (Table 2). This showed no increased risk of death or cardiovascular complications with nitrous oxide use.[15]

Neurological systems

Increasing concern is being placed on the effects of anaesthesia on the developing brain, using either NMDA antagonists or $GABA_A$ agonists. A variety of animal experiments demonstrating apoptosis or dendrite growth failure, followed by observational cohort studies of neonates or young children who have received multiple anaesthetics shows a link with poorer neurological outcomes (reviewed in Ref.[16]). However, from this study design, it is impossible to determine whether children who require multiple anaesthetics are by their nature more at risk of learning difficulties, rather than this being caused by anaesthesia. Supporting this are data suggesting that single anaesthetic episodes do not increase the risk of developing learning difficulties. Finally, brief episodes of nitrous oxide exposure to mothers in the delivery suite or to medical personnel have never been significantly linked with developmental problems. Its use for labour analgesia is therefore considered safe.

The ageing brain is also at risk of postoperative cognitive dysfunction after anaesthesia and the onset of Alzheimer's disease has been linked to cumulative anaesthetic exposure before the age of 50. The same trial methodology issues exist for these studies as in the paediatric population and nitrous oxide itself has not demonstrated any significant worsening of cognitive decline when compared with volatile agents. Minimizing the depth of anaesthesia in patients who need surgery at the extremes of age seems an obvious suggestion that is already followed by best clinical practice.

Nitrous oxide, when administered alone, increases the cerebral blood flow (CBF), cerebral metabolic rate, and ICP. However, i.v. anaesthetic agents reduce these effects. When administered with volatile agents, an equi-MAC mixture of volatile and nitrous oxide increases CBF when compared with volatile alone. Further discussion of the extensive evidence is outside the scope of this review, but interested parties may wish to read a recent comprehensive review.[10]

Respiratory systems

Nitrous oxide is slightly sweet smelling and does not cause airway irritation. It is, thus, an ideal agent for inhalation induction with a suitable volatile agent. It has a minimal effect on minute ventilation and therefore reduces the ventilatory depression induced by volatile agents when used as part of balanced anaesthesia. It does not cause bronchodilation similar to volatile agents.

Wound infection

The ENIGMA-I trial demonstrated a significant increase in the risk of wound infection with exposure to nitrous oxide.[12] The role of hyperoxia in wound infection is controversial and effects may have been caused by the different amounts of oxygen

Table 2 Summary of the ENIGMA-II trial[15]

Design	International multicentre, randomized controlled trial. Intention-to-treat analysis
Inclusion criteria	Major non-cardiac surgery. ≥45 yr old at risk of cardiovascular complications—history of coronary disease, heart failure, cerebrovascular disease, peripheral vascular disease, ≥70 yr with other comorbidities
Exclusion criteria	Planned $F_{I_{O_2}} > 30\%$ including thoracic surgery involving one-lung ventilation, patients with substantially impaired gas exchange
Groups	Intervention: 70% nitrous oxide 30% oxygen after induction and intubation until the end of surgery Control: oxygen and air to achieve $F_{I_{O_2}}$ of 30%
Primary outcome	Composite of death and cardiovascular events (non-fatal MI, cardiac arrest, pulmonary embolism, and stroke) within 30 days of surgery
Selected secondary outcomes	Non-fatal MI, surgical site infection Severe PONV (for others see Ref.[15])
Power calculation	7000 patients for 0.05 type I and 0.1 type II error detection of increased risk of primary outcome from 6 to 8%
Enrollment	10 102 eligible patients, enrolled 7112
Primary outcome result	Primary outcome in 283 (8%) of nitrous patients and 296 (8%) of control patients (RR: 0.96, 95% CI: 0.83–1.12, P=0.64)
Secondary outcomes result	Surgical site infection 321 (9%) nitrous and 311 (9%) control Severe nausea and vomiting 506 (15%) nitrous and 378 (11%) control
Sub-group analysis	Increased PONV risk with nitrous reduced with prophylactic antiemetics Without antiemetics RR 1.75 (95% CI: 1.43–2.13; interaction P=0.001) With antiemetics RR 1.12 (95% CI: 0.95–1.32)

PONV, post-operative nausea and vomiting; RR, relative risk; CI, confidence interval.

delivered to the trial groups. The ENIGMA-II trial in moderate to high-risk surgical patients delivered equal oxygen fractions with or without nitrous oxide and demonstrated no difference in wound infection rates between the trial groups.[15]

Postoperative nausea and vomiting

The ENIGMA-I study demonstrated a significantly increased risk of post-operative nausea and vomiting (PONV) with nitrous oxide anaesthesia. This has been confirmed by other non-randomized studies and guidelines suggest avoidance in patients at high risk of PONV. Increased rates of PONV have also recently been shown in the ENIGMA-II trial. However, this trial demonstrated that with prophylactic antiemetic treatment, the relative risk (RR) of severe nausea, and vomiting reduced from RR 1.75 [95% confidence interval (CI): 1.43–2.13] to RR 1.12 (95% CI: 0.95–1.32).[15]

Conclusion

Nitrous oxide has been a staple of anaesthetic practice for more than 150 yr. Basic science studies have often questioned its use, but plausible mechanisms of harm have not always proved to be clinically significant. With the arrival of recent studies such as ENIGMA-II, some important controversies regarding its use have been resolved.

There are other anaesthetic agents and methods that increasingly enable us to avoid nitrous oxide. However, with 150 yr of experience, this valuable analgesic and anaesthetic agent should not be discarded.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Principles of total intravenous anaesthesia: basic pharmacokinetics and model descriptions

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Key points

- Competency in total i.v. anaesthesia (TIVA) allows safe management of general anaesthesia in patients with malignant hyperthermia risk.
- Poor understanding of the pharmacokinetics of target-controlled infusion (TCI)/TIVA practice has contributed to accidental anaesthetic awareness as reported by NAP5.
- There is no defined 'ideal' TIVA technique, but co-administration of propofol and remifentanil by TCIs approaches this goal.
- A variety of pharmacokinetic models for propofol and remifentanil have been described, but only a few have been implemented in commercial infusion devices.
- All models incorporate assumptions and elements of inaccuracy in the prediction of plasma and effect-site targets. However, inter-individual variability in pharmacodynamic response represents a more challenging aspect of using TIVA.

Total i.v. anaesthesia (TIVA) describes the maintenance of general anaesthesia without inhaled hypnotics. Some indications for TIVA are given in Table 1. Competency in TIVA is vital for safe management of patients with malignant hyperthermia risk who require general anaesthesia.

Any combination of hypnotics (with or without analgesics) can be used to achieve a desired clinical endpoint. This heterogeneity confounds the interpretation of TIVA outcome data as no technique defines 'ideal' TIVA. Suboptimal techniques are often included in outcome analyses, but the results are generalised to all methodologies.[1–3] Poor understanding of the pharmacokinetics underlying TIVA has caused accidental awareness as documented in the Fifth National Audit Project on accidental awareness during general anaesthesia (NAP5) report.[3]

Choice of agents

Drugs with fast onset and offset times are most useful for balancing adequate hypnosis/analgesia with rapid recovery. The decline in the plasma concentration of most i.v. agents slows as the duration of infusion increases ('context-sensitive half-time'—CSHT) and impairs recovery. Propofol and remifentanil demonstrate short or minimal CSHT unlike other i.v. agents. For this article, 'ideal' TIVA constitutes the co-administration of these agents by target-controlled infusion (TCI). This approach exploits their known synergy in obtunding responses to noxious stimuli.[4]

The three-compartment model

After an i.v. bolus, the plasma concentration of a typical drug follows an exponential decline in three distinct phases (Fig. 1). These observations are explained by distribution of drug between a central compartment (V_1, principally plasma) and two compartments which equilibrate rapidly (V_2, well-perfused tissue like muscle) and slowly (V_3, mainly fatty tissue) (Fig. 2).

Table 1 Indications for using TIVA

- Malignant hyperthermia risk
- Long QT Syndrome (QTc≥500 ms)
- History of severe PONV
- 'Tubeless' ENT and thoracic surgery
- Patients with anticipated difficult intubation/extubation
- Neurosurgery—to limit intracranial volume
- Surgery requiring neurophysiological monitoring
- Myasthenia gravis/neuromuscular disorders to avoid NMBs
- Anaesthesia in non-theatre environments
- Transfer of anaesthetised patient between environments
- Day-case surgery
- Trainee teaching
- Patient choice

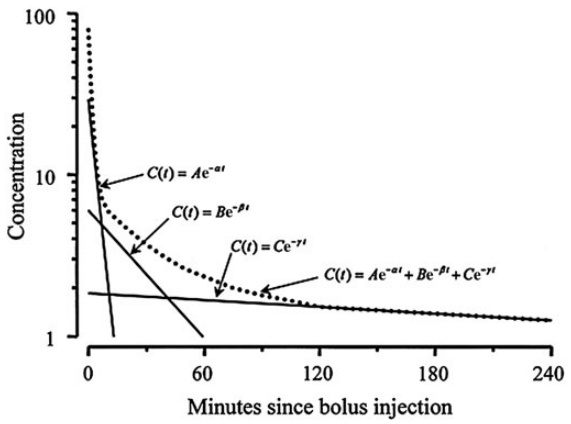

Fig 1 Plasma concentration *vs* time curve demonstrating tri-exponential decline after a bolus injection. In conventional pharmacokinetic terminology, these are phases A–C. The plasma concentration at time *t*(Ct) may be derived from $C(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$, where *t* is time since i.v. bolus. *C*, concentration after a bolus dose. A–C represent the phase coefficients which sum to the plasma concentration after an i.v. bolus. α, β, and γ represent phase rate constants. e, natural logarithm.

Mathematical analysis allows the compartment volumes and rate constants for drug transfer between them to be calculated.[5] Detailed discussion of the modelling process has been published in this journal.[6,7]

Target-controlled infusions

Adequacy of TIVA depends on the maintenance of brain propofol and remifentanil concentrations which are clinically appropriate and in equilibrium with levels in the plasma. The best way to achieve this state is by TCI from dedicated pharmacokinetic pumps. These devices solve the complex equations which describe the distribution of agents between compartments and allow for rapid adjustments in targets to achieve the desired clinical effect. Manual infusion regimes are prone to errors in the calculation and implementation of the required changes in infusion rate as reported by NAP5.[3]

Principles of TCI

A bolus/elimination/transfer (BET) principle is used to approximate a constant plasma level of drug (however, the algorithms in pharmacokinetic pumps use more exacting analytical solutions). Once compartment V_1 is filled by the bolus, the subsequent infusion rate compensates for rapid and slow transfer of drug to V_2 and V_3, and drug elimination from V_1 as described by the rate constant K_{10} (rate constant for drug elimination from the central compartment in a pharmacokinetic model). When the three compartments reach steady-state concentration (>20 h for propofol), the infusion rate slows to match elimination only. Without an appropriate bolus, a constant propofol infusion at 10 mg kg^{-1} h^{-1} requires 40–90 min (dependent upon which kinetic model is used for calculation) to achieve a clinically useful plasma concentration of 4 μg ml^{-1} in an 85 kg adult male. It is likely that an inadequate clinical effect would be observed in the interim as was reported by NAP5.[3]

The TCI system

The key components are:

- User interface
- Microprocessor(s) with pharmacokinetic software
- Infusion pump which delivers up to 1200 ml h^{-1}
- Visual and audible safety systems and alarms

A typical system calculates the bolus dose and speed of subsequent infusion required to maintain the targeted plasma drug concentration (Cpt). Calculations are repeated every 10 s and the infusion rate adjusted until Cpt is achieved. Diffusion of drug from plasma to brain occurs exponentially with a first-order rate constant (k_{e0}, see below). The half-time ($T_{1/2}$) for the process is calculated as $T_{1/2} = [\ln(2)/k_{e0}]$ and equilibration occurs after 4–5 half-times.[8] If Cpt is subsequently increased, an additional bolus is given to fill V_1 and the infusion rate increases to match additional transfer and elimination at the higher concentration.

When Cpt is decreased, the infusion stops until the plasma concentration declines to the new target and is restarted at a lower rate. Diffusion of drug from the brain occurs with the same half-time.

Common TCI models

The differences in published models for propofol and remifentanil result from methodological aspects and limitations of the original studies. Relatively few of these solutions are implemented in commercial infusion devices (Table 2). Currently, there is no evidence to support the use of one model in preference to another and all have proved reliable in clinical practice. All have similar performance in terms of the accuracy and stability of predicted plasma (Cp) and effect-site (Ce) concentrations.

Propofol

The key pharmacokinetic parameters for the adult Marsh and Schnider plasma-targeting models are shown in Table 2. The major difference is the volume of V_1 (Marsh 19.4 litre *vs* Schnider 4.27 litre for an 85 kg individual), and therefore a bolus administered as mg kg^{-1} causes a four-fold difference in calculated peak plasma concentrations (Fig. 3).

The Marsh model ignores age and scales the volumes of V_{1-3} linearly to patient weight. An identical bolus dose is administered to all patients of a given body mass for any chosen Cpt. This delivery contrasts with non-TIVA practice where the anaesthetist usually adjusts dosage for patient age and likely pharmacodynamic response. Age is input to the TCI pump only to ensure

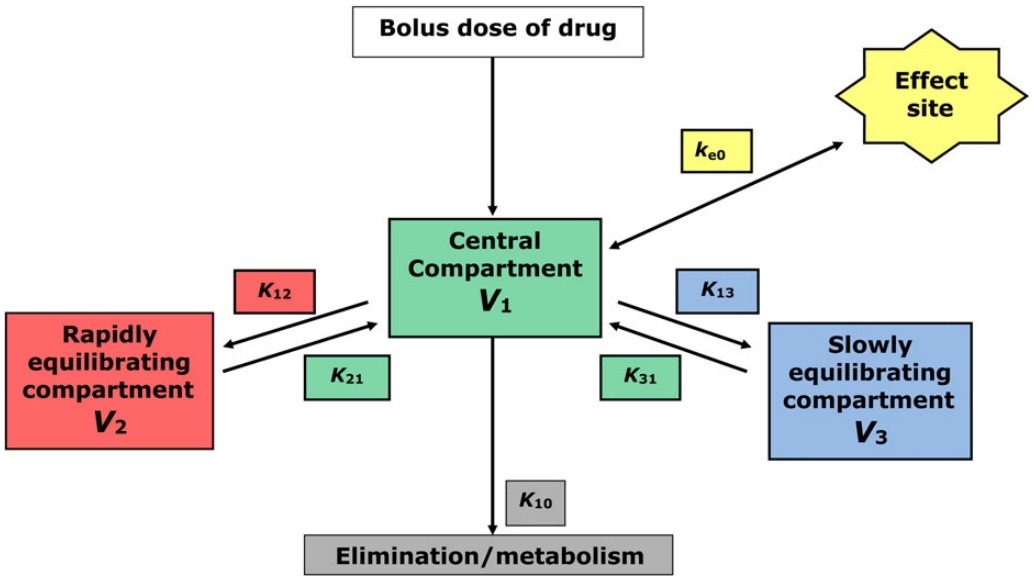

Fig 2 Three-compartment model showing the various compartments and their associated rate constants. V_{1-3} represents the compartment volumes. K_{12} represents the rate constant between V_1 and V_2, K_{21} between V_2 and V_1, etc. K_{10} represents the rate constant for drug elimination from the central compartment. k_{e0} is the rate constant for equilibration between plasma and effect-site concentrations.

Table 2 Comparison of the pharmacokinetic parameters for the main TCI models implemented in commercial infusion devices. V_1, central compartment; V_2, rapidly equilibrating compartment; V_3, slowly equilibrating compartment; K_{10}, rate constant for drug elimination from the central compartment in a pharmacokinetic model; K_{xy} and K_{yx}, rate constants for drug transfer from compartment x to compartment y or the reverse direction; LBM, lean body mass

Model	Fixed parameters	Variable parameters	Parameter determined by
Marsh	All rate constants	$V_{1,2,3}$	Weight
Schnider	V_1 = 4.7 litre	V_2	Age
	V_3, K_{13}, K_{31}	K_{12}, K_{21}	Age
		K_{10}	Age, weight, LBM
Paedfusor	All rate constants except K_{10}	$V_{1,2,3}$	Weight
		K_{10}	Weight
Kataria	All rate constants	$V_{1,2,3}$	Weight
Minto	V_3 = 5.42 litre	V_1 and V_2 and rate constants	Age, LBM

that the patient is ≥16 yr and that the use of this model is appropriate. For less robust patients, it is better to start the pump at a lower Cpt and increase the target incrementally until a desired clinical effect is obtained.

Although the Schnider model adjusts some of the pharmacokinetic parameters for age (Table 2), this does not necessarily constrain the patient's pharmacodynamic response. A sex-specific lean body mass (LBM) is calculated and used to adjust the elimination rate constant K_{10}. Because a small fixed volume for V_1 is used, lower doses of propofol are required to achieve a given Cpt compared with Marsh (Table 3). In many instances, this bolus is inappropriately small and results in an inadequate clinical effect. Consequently, the Schnider model can only be recommended for use in effect-site targeting mode (see below) as larger bolus doses are utilised.

Small differences between the Paedfusor and Kataria paediatric models are shown in Table 2. Both use weight as the key patient characteristic for scaling the volumes of V_{1-3}. The Kataria model is validated for use in patients aged 3–16 yr with a minimum weight of 15 kg. The Paedfusor model is a variant of the Marsh kinetics for patients 1–16 yr of age, and also uses weight to calculate the elimination constant K_{10}. It features non-linear scaling of V_1 volume as age exceeds 12 yr. Extrapolation of these models to patients outside of the described patient characteristics is not recommended due to increased pharmacokinetic differences, but is commonly practised.

A recently described allometric scaling model promises improved utility in propofol administration.[9] Allometry relates biological activity to proportional rather than absolute changes in body size. In the new model, 10 927 blood propofol concentrations were aggregated from 660 subjects (500 patients, 160 healthy volunteers) recruited to 21 separate studies. This contrasts with the limited data used to generate the Marsh and Schnider kinetics. Body composition in the new model is reflected in the calculation of the volumes of V_2 and V_3 which in turn are the primary determinants of their associated rate constants, not absolute body mass. This complex analysis allows the model to be used for patients aged 3 months to 88 yr and weighing 5–160 kg, but needs further clinical validation before it becomes commercially available.

Remifentanil

The Minto model for remifentanil is popular because it is applicable to a wide range of patient characteristics. Age is used for calculation of pharmacokinetic parameters (Table 2) but in common with the Schnider model, this adjustment does not influence pharmacodynamic response. A sex-specific LBM is calculated and used to fine tune some of the parameters to the patient.

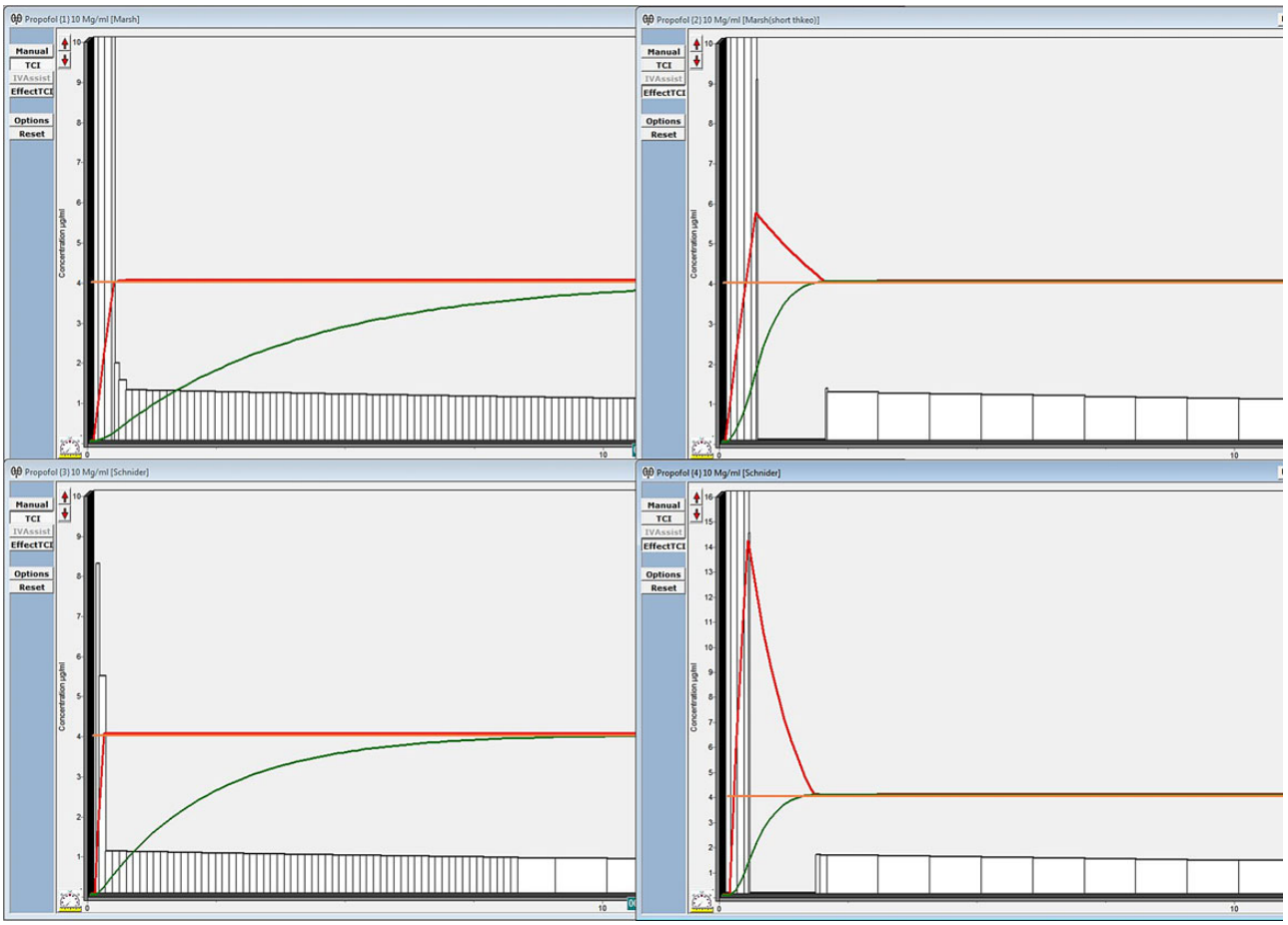

Fig 3 Comparison of propofol concentrations predicted for a 40-yr-old male, 178 cm tall, and weighing 85 kg by the Marsh (upper panels) and Schnider (lower panels) models using Tivatrainer 9 software (www.eurosiva.eu). Left-hand panels show plasma targeting (Cpt) mode; right-hand panels show effect-site targeting (Cet). The target was set at 4 μg ml^{-1} and all diagrams have the same time scale in minutes on the *x*-axis. Note the major difference in plasma concentration predicted in Cet modes—this is largely due to the difference in the volume of the central compartment V_1 assumed by each model. Differences in the time to equilibration of the plasma and effect-site concentrations for the Marsh model are due to the different k_{e0} utilised in each calculation. The k_{e0}s used in the effect-site models are based on a TTPE of 1.6 min after the bolus dose. Red line, plasma concentration; orange line, chosen target level; green line, effect-site concentration; vertical white lines represent the infusion rate of TCI pump.

Effect-site targeting

Propofol

Clinicians regularly but unintentionally use effect-site targeting in non-TIVA practice to rapidly achieve unconsciousness. The high plasma concentration generated by a large bolus of propofol causes fast diffusion of drug into the brain and rapid onset of the desired effect. However, propofol diffusion continues until the brain concentration has equilibrated with the diminishing plasma level (Fig. 3, right-hand panels). This occurs 1.6–3.9 min after injection irrespective of the size of the bolus dose[9] (the 'time to peak effect', TTPE, as predicted by the Schnider and Marsh models, respectively). Depending on the patient's idiosyncratic sensitivity to propofol, this peak brain level can cause unwanted cardiovascular instability (reflecting an effect-site overshoot). Effect-site targeting achieves unconsciousness rapidly without effect-site overshoot provided that the target effect-site drug concentration (Cet) is appropriate for the patient's physical status.

A peak blood concentration (called the plasma overshoot) generates the desired Cet at equilibrium (Fig. 3, right-hand panels) and can in theory be calculated from the rate constant for drug transfer into the brain. The bolus dose required to produce this plasma overshoot is governed by the volume of V_1 used in the calculation and hence the model chosen. Once the bolus is given, the TCI pump stops infusing until equilibration occurs at the relevant TTPE and then re-starts at a rate matching inter-compartmental transfer and elimination (also right-hand panels in Fig. 3).

However, brain propofol concentrations cannot be measured *in vivo* and the rate constant required for direct calculation of plasma overshoot is unknowable. Instead, drug concentration in a theoretical surrogate called the effect-site is used for mathematical analysis of effect and prediction of plasma overshoot.[10] This virtual compartment is assumed to have negligible volume compared with V_1 and causes little perturbation in plasma concentration at equilibrium. A rate constant called k_{e0} (Fig. 2) describes equilibration of effect-site concentration with plasma propofol levels but has to be derived indirectly in experimental studies.

A measure of dynamic anaesthetic effect, typically a processed EEG signal, is recorded simultaneously with measured plasma propofol concentrations in volunteer subjects. A numeric value for k_{e0} can then be derived to match the timing of the

Table 3 Comparison of the dose of propofol administered to a 40-yr-old male, 178 cm tall, and 85 kg in weight when a 4 μg ml^{-1} target concentration is set. The table shows the initial bolus dose, the time to equilibration of plasma and effect-site concentrations, and the cumulative doses at two time points. Time to equilibration is equivalent to TTPE with effect-site targeting. Data derived from Tivatrainer 9 software (www.eurosiva.eu). Greyed areas show non-applicable data

Comparison of adult propofol models								
Model	Plasma targeting Cpt				Effect-site targeting Cet			
	Initial bolus (mg)	Time to equilibrium (min)	Cumulative dose		Initial bolus (mg)	Time to equilibrium (min)	Cumulative dose	
			At equilibrium (mg)	After 30 min of infusion (mg)			At equilibrium (mg)	After 30 min of infusion (mg)
Marsh	86	16	360	570				
'Modified Marsh'					119	1.6	119	574
Schnider	18	9.8	142	414	73	1.6	73	444

calculated peak Ce to the observed maximum EEG effect. This k_{e0} is linked to rate of decay of drug concentration in V_1 and hence to the specific pharmacokinetic model used to administer the agent. Once established, k_{e0} allows manipulation of plasma overshoot to achieve a particular Cet.

For any given pharmacokinetic model, a large numeric value of k_{e0} will predict a more rapid increase in Ce and allow a smaller initial bolus dose to be given. Similarly, the decline in Ce to a level representing recovery from anaesthesia will be predicted to occur more quickly.

Effect-site targeting is the only approach recommended for the Schnider model as larger bolus doses are required to achieve plasma overshoot (Table 3). Because this model incorporates more patient characteristics, it has been recommended for use in the elderly and less robust patient. However, it is always better to start at a low Cet in frail individuals and increase the target incrementally until the desired response is obtained.

The original description of the Schnider Cet model matched peak kinetic and dynamic parameters at a TTPE of 1.6 min and allowed for small variations in k_{e0} between individuals based on their idiosyncratic pharmacokinetics.[10] It is also possible to use the 'average' k_{e0} published in this study as a fixed parameter and allow small variations in TTPE between patients.[11] Pump manufacturers implement one particular approach in their equipment. Consequently, a clinician using different pump brands may observe some differences in the bolus dose administered for a desired Cet in similar individuals.[12] Care must be taken to ensure that the expected clinical response is actually obtained.

The original 'Diprifusor' Marsh Cpt model did not have a k_{e0} and could not be used in the Cet mode. Subsequently, a k_{e0} was assigned to allow calculation of Ce for information only, and the selected value predicts a TTPE of 3.9–4.5 min after a typical 2–3 mg kg^{-1} bolus. This timing may seem lengthy, but the prediction of Ce by this model has been validated in a patient study.[13] Attempts have been made to find the 'best' k_{e0} for enabling the Marsh model in the Cet mode, and a variety of solutions have been published. A method using a TTPE of 1.6 min to derive k_{e0} has been implemented in some commercial TCI devices as the 'Modified Marsh' model.[14]

For both Marsh and Schnider models, larger bolus doses of propofol are used in the Cet mode at any given numeric target compared with the same model in the Cpt mode. Marsh always administers a larger bolus dose than Schnider in either mode principally due to the significant difference in the volume of V_1 used in calculations. However, the absolute mass of agent may seem small compared with that used in non-TIVA practice (Table 3) where unwanted effect overshoot is common. The propofol TCI models described above prove highly effective in combination with remifentanil TCI.

Remifentanil

The Minto model for remifentanil can be used in the Cet mode, but the k_{e0} used is derived from studies of EEG parameters as a measure of effect. It must be remembered that an EEG parameter does not necessarily equate with the onset of analgesic action. The increased plasma remifentanil concentrations required in the Cet mode can be associated with a higher likelihood of chest wall rigidity and severe bradycardia via non-vagal mechanisms, so an incremental approach to remifentanil Cet may be a reasonable technique.

Conclusion

Currently, there is no 'best' TCI model for propofol. The clinician should become familiar with the model which matches the patient characteristics of their usual patient population. All pharmacokinetic models have inherent assumptions which generate elements of inaccuracy in prediction. However, inter-individual variability in pharmacodynamic response represents a more challenging aspect of using TIVA. Close clinical monitoring of the patient remains an important part of the anaesthetist's role.

Educational video

The European Society for Intravenous Anaesthesia (EuroSIVA) provides an educational video on the basic pharmacokinetics of a simple infusion at the following link: https://www.youtube.com/watch?v=6U_K-ToHRvs (accessed 1 May 2015).

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Declaration of interest

D.M. is a member of the Committee of SIVA, the UK Society for Intravenous Anaesthesia (www.siva.ac.uk) (accessed 1 May 2015).

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Anaesthesia for nephrectomy

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Key points

- Preoperative assessment must take into account the effect that nephrectomy will have on the patient's postoperative renal function.
- Positioning the patient whether open or laparoscopic requires good communication and a robust approach to ensure that iatrogenic injuries are avoided.
- Nephron-sparing surgery (partial nephrectomy) should be considered in patients with limited renal reserve.
- Adequate venous thromboprophylaxis is essential, particularly in those patients with a renal malignancy.
- Renal malignancy with extension into the renal vein and inferior vena cava will necessitate a different approach that requires careful forward planning with multiple specialities and should only be performed in specialist centres.

This paper will summarize the perioperative anaesthetic considerations for patients undergoing nephrectomy for both non-neoplastic and neoplastic disease of the kidney. It does not include the management of patients undergoing living donor nephrectomy.

Indications for nephrectomy

Nephrectomy for patients with renal cell carcinoma (RCC) was first described in 1969.[1] Surgical treatment varies with the pathology. Simple nephrectomy is the preferred option for those with non-neoplastic disease (e.g. trauma, non-functioning kidney with chronic infection) with radical nephrectomy being preferred in those with neoplastic disease. Radical nephrectomy implies resection of the whole of Gerota's fascia, including the perinephric fat, lymphatics, and the ipsilateral adrenal gland.

The vast majority (~90%) of solid renal masses are RCC; the remainder comprising mainly of transitional cell carcinoma or Wilm's tumour (in children). RCC accounts for between 1% and 3% of all visceral malignancies. It is twice as common in men when compared with women and most commonly presents in the seventh decade of life. The main environmental risk factor is cigarette smoking, contributing to one-third of all cases. Other important risk factors include obesity, hypertension, asbestos exposure, and acquired polycystic kidney disease. If symptomatic, presentation is usually with haematuria, loin pain, and a palpable mass. Non-specific symptoms such as malaise, weight loss, fever, and night sweats are relatively common. Small localized tumours are often asymptomatic and present with microscopic haematuria identified often through routine urinalysis.

Approximately 40% of RCCs are detected as an incidental finding on abdominal imaging. Tumour size is frequently small and confined to the kidney; however, ~25% of cases present with distant metastases commonly in the lung, bone, liver, and brain. Metastases do not preclude surgery, nephrectomy still improving symptoms, quality of life, and prognosis. Five-year survival rates for RCC in the UK have improved over the last two decades with survival rates for grade I, II, III, and IV being 87%, 88%, 72%, and 46%, respectively. Tumour extension into the renal vein and/or inferior vena cava (IVC) is seen in up to 25% of cases and can present with severe pulmonary congestion and pulmonary embolism. Less than 10% will present with thrombus inside the IVC, with fewer than 2% with thrombus and tumour at the border of the right atrium. This group does gain a survival benefit from surgery despite the extensive involvement of the IVC and are discussed later in the paper.

Surgical approach

The surgical approach is individualized and largely determined by surgeon preference and by the disease stage (Table 1), location of the pathology, the presence of multiple or bilateral pathology, baseline renal function, differential renal function, and history of a hereditary kidney cancer syndrome.

Radical nephrectomy is considered for cancer patients with stage I, II, and III disease. However, those patients with metastatic disease, at risk of developing severe renal impairment, and those with bilateral tumours are likely to be considered for nephron-sparing surgery.

The incision varies depending on the kidney location, tumour characteristics, body habitus, and surgeon's preference. The most commonly used incisions are flank, thoraco-abdominal, and trans-abdominal (chevron or anterior subcostal). Most kidneys can be removed safely via a transperitoneal subcostal approach. Radical nephrectomy can be undertaken using a laparoscopic technique in tumours which measure no more than 10 cm in diameter. Results appear to demonstrate similar survival, recurrence, and renal impairment rates regardless of technique or surgical approach.

Partial nephrectomy is performed in those patients with tumours smaller than 7 cm in diameter, those at risk of future significant renal impairment, tumours in a peripheral position (e.g. at one pole), those with bilateral tumours, and those with a solitary kidney. In selected patient groups, they have similar oncological outcomes. They can be performed using advanced laparoscopic techniques which require a great deal of technical skill. This may result in increased warm ischaemic times and as such, open partial nephrectomy may be preferable in certain circumstances (e.g. solitary kidney). Conversion from partial to radical nephrectomy is likely if a synchronous tumour or extension into the renal vein is discovered during surgery.

Laparoscopic nephrectomy has proven benefits of reduced analgesic requirements and reduced length of stay.[2] Further developments have emerged in laparoscopy, including hand-assisted procedures and robotic technology. In all such operations, particular attention needs to be paid to the cardiovascular and respiratory systems, given the need for pneumoperitoneum and the use of steep Trendelenburg. A laparoscopic approach may not be appropriate for those with severe ischaemic or valvular heart disease, given the haemodynamic instability or in patients with increased intracranial pressure. However, an attempt at laparoscopy combined with a low threshold for conversion to open surgery may be a reasoned approach.[3]

Table 1 Staging of renal malignancy

TNM staging system for kidney cancer			
Primary tumour (T)			
T1	Tumour 7 cm or less confined to the kidney		
T1a	<4 cm		
T1b	>4 cm		
T2	Tumour >7 cm confined to the kidney		
T2a	Less than or equal to 10 cm		
T2b	>10 cm		
T3	Tumour extends into major veins or perinephric tissues but not into adrenal gland or beyond Gerota's fascia		
T3a	Extends into renal vein or branches or perirenal sinus fat but not beyond Gerota's fascia		
T3b	Extends into vena cava below the diaphragm		
T3c	Extends into vena cava above the diaphragm or invades the wall of the vena cava		
T4	Tumour invades beyond Gerota's fascia including into the adrenal gland		
Regional lymph nodes			
N0	No regional lymph node metastasis		
N1	Metastasis in regional lymph node		
Distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 or T2	N1	M0
	T3	N0 or N1	M0
Stage IV	T4	Any N	Any M
	Any T		M1

Preoperative assessment

In addition to providing a rigorous preoperative assessment, the anaesthetist needs to be cognizant of the impact surgery will have on the renal function in the immediate postoperative period. Cancer-specific survival for patients with certain grade and stage of renal cortical tumours is extremely good (e.g. 5 yr survival of males with stage 1 renal cancer is ~84%, when compared with 5% with stage 4 disease) and hence consideration will be given to nephron-sparing surgery (partial nephrectomy), particularly in patients with chronic kidney disease. After a radical nephrectomy, one-third of patients will be left with significantly reduced renal reserve, that is, a glomerular filtration rate (GFR) of <45 ml min^{-1} (~CKD Stage 3B). This may impact upon subsequent management and prognosis during any future healthcare treatment. Serum creatinine, a calculation of estimated GFR (eGFR) in conjunction with an assessment of differential renal function using computerized isotope renography, is advocated. The results of which will influence the final choice of surgical approach and perioperative management.

Preoperative assessment should attempt to assess functional capacity and assess for cardiorespiratory disease severity and should always take into account the degree of urgency for intervention. Patients are usually in their seventh decade of life and as such, the anaesthetist should make an attempt to exclude significant occult cardiorespiratory disease in those without prior history. Chemotherapy is not routine preoperative therapy as tumours are generally unresponsive to chemotherapy agents. Hence, unlike many other patients presenting for major surgery with malignant disease, an assessment of the impact of preoperative chemotherapy is generally not required.

Further investigations such as non-invasive cardiac stress tests, resting transthoracic echocardiogram, and static pulmonary function tests may be appropriate after initial clinical examination and history. This is particularly the case in the older, frailer patient to assist in appropriate perioperative medical optimization.

Cavo-atrial disease

Extension of disease into the IVC is apparent in 4–10% of all RCCs and has major anaesthetic and surgical implications. It is described in four stages (Table 2) by Novick and is helpful in determining the surgical conduct and approach.[4]

Patients with cavo-atrial involvement may present with significant morbidity relating to the thrombus and will need

Table 2 Novick classification of cavo-atrial tumour extension in patients with RCC[4]

Level 1	Thrombus into IVC but <2 cm above the renal vein
Level 2	Thrombus below the intrahepatic vena cava
Level 3	Thrombus involves the intrahepatic vena cava but below the diaphragm
Level 4	Thrombus involves the right atrium

anticoagulation with heparin therapy before, during, and after the surgery. The thrombus needs detailed imaging to determine the stage and degree of IVC involvement typically using CT or magnetic resonant imaging. It is vital the imaging is up to date at the point of surgery as thrombus extension towards the heart in the interim before surgery will significantly change the management. The use of transoesophageal echocardiography (TOE) is extremely valuable in these scenarios and can provide more detailed information than CT or MRI when imaging retrohepatic tumour thrombus.

A typical case will require angio-emboliation of the kidney to be removed and insertion of a saline-filled balloon into the IVC (proximal to the tumour) to prevent embolization of tumour and thrombus into the heart. After a chevron or roof-top incision and dissection onto the renal bed, the vascular surgeon will usually perform the cavotomy. This can only be performed once control is possible from below and above the tumour. A hepatobiliary surgeon will assist with dissection and removal of tumour from the intra and retro-hepatic regions of the IVC.

In most cases, preoperative arterial embolization of the kidney will facilitate surgery by allowing early ligation of the renal vein and its collaterals, thereby reducing excessive blood loss. This is associated with an angio-infarction syndrome of pain, nausea, hypertension, and fever. Ideally, the angio-embolization should be performed after induction of anaesthesia. At the author's institution, angio-embolization of the kidney occurs in a purpose-built hybrid theatre and after induction of anaesthesia for the comfort of the patient. In the past, many patients had IVC filters inserted. This is still done for palliative patients who are not due to have the tumour removed surgically but is no longer routine. If they are thought necessary, they should be fitted within 48 h of the operation so to avoid thrombi infiltrating the filter.

A multi-speciality approach consisting of radiology, anaesthesia, urology, vascular, and hepato-billiary specialists is essential. Cardiothoracic input will be required for those in which tumour thrombus extending up to the level of the diaphragm. For level 4 and occasionally level 3 tumour extent, the patient will need to go onto cardiopulmonary bypass to allow safe removal of the tumour. The decision to use CPBP in level 3 disease is made by balancing the advantages of better surgical access, control of bleeding, and reducing the impact on venous return against the risks associated with CPBP (i.e. in particular renal impairment, stroke, and air emboli). Deep hypothermic circulatory arrest is occasionally used in level 4 disease and those with more technically difficult surgery where the tumour is adherent to the cava wall. Supra-hepatic tumours that do not extend to the mouth of the right atrium may on occasion be approached via a small sternotomy with control of the IVC being achieved via a small incision in the pericardium.

Transfusion requirements can be huge and as such planning for major haemorrhage management including communication with the blood transfusion service is essential. Monitoring of coagulation parameters with modalities such as thromboelastography, blood gas analysis, and activated clotting time are all an essential part of management.

General intraoperative management

The appropriate vascular access is in part determined by the surgical approach. For a standard radical nephrectomy (open, laparoscopic, partial, or full) in a patient without significant co-morbidities, we would advocate a minimum of one wide gauge peripheral i.v. cannula. If the patient is to be positioned in the lateral position, it is ideal to place i.v. access in the ipsilateral limb to the kidney being removed. The authors have a very low threshold for insertion of invasive arterial cannula, allowing earlier detection and treatment of fluctuation in the patient's haemodynamic status. Many clinicians advocate additional non-invasive monitoring of the cardiac output in any major surgery and nephrectomy is no exception. Assistance in optimizing intravascular fluid therapy through stroke volume optimization is becoming more common practice. TOE is essential in those with stage 3 or 4 cavo-atrial disease. TOE is of particular importance in visualizing the most distal extension of the tumour/thrombus within the cava. The imaging is of excellent quality and is essential in confirming that complete resection of the thrombus has been achieved.

Prevention of hypothermia through active warming should be initiated early with a forced-air warmer, heated mattress, and warmed i.v. fluids. A rigorous approach to venous thormboprophylaxis is very important, with the use of graduated stocking, low molecular weight heparin therapy, and pneumatic calf compression devices being considered mandatory. Bladder catheterization is routine, but the routine administration of prophylactic antibiotics is not. Antibiotics are only administered in certain higher risk patients such as those with significant renal dysfunction or infection within the renal tract. In these cases, a broad-spectrum antibiotic is usually administered such as co-amoxiclav with or without an aminoglycoside such as gentamicin (3–5 mg kg^{-1}) before knife to skin.

Cell salvage is generally advocated in uro-oncological surgery, despite early concerns of it theoretically being associated with an increased risk of tumour recurrence. These concerns have not been supported by the current literature and it appears a safe practice to adopt. In 2008, NICE published guidance on the issue but recommend the use of a leucocyte depleting filter as routine. Blood loss during nephrectomy is seldom over a litre, although many patients may present with an anaemia. As such, cell salvage is not usually a routine consideration. However, in those with caval involvement, it is not clear whether the use of cell salvage is associated with tumour recurrence or not. In view of the potential for massive blood loss, the authors recommend the use of cell salvage under these circumstances only.

Positioning needs consideration as both open and laparoscopic nephrectomy are commonly performed in the lateral position with varying degrees of tilt and flexion at the waist. This type of positioning is associated with an increased risk of pressure sores, nerve damage, venous pooling, corneal abrasion, and venous congestion. Both laparoscopic and the more extensive procedures (e.g. cava thrombectomy) may involve changing position intraoperatively. Care should be taken to assess new pressure points are adequately protected and to ensure that the tracheal tube and indwelling vascular access and monitoring is protected.

Lateral positioning and/or a degree of the Trendelenburg will generally further reduce FRC, increase ventilation–perfusion mismatch, and is associated with the development of atelectasis.

Table 3 Dermatomes requiring regional anaesthesia blockade after nephrectomy according to incision used

Incision	Dermatomes
Flank	T9–T11
Thoraco-abdominal	T7–T12
Trans-abdominal	T6–T10

Table 4 Complications after nephrectomy

Immediate	Early	Late
Vascular injury	Acute renal failure	Chronic renal failure
Splenic injury	Bowel obstruction	Incisional hernias
Bowel injury	Peritonitis	Wound infection
Pneumothorax	DVT and pulmonary embolus	

In the laparoscopic approach, a pneumoperitoneum may further aggravate respiratory function but may also have a deleterious effect on the venous return and cardiac output, particularly if intra-abdominal pressures increase above 20 mm Hg. Hence, laparoscopic surgery may not be well tolerated in patients with significant systolic dysfunction or those with co-existing coronary artery disease with ventricular hypertrophy.

A combination of general and a loco-regional technique usually combine well. Low thoracic epidural analgesia, paravertebral block, or the use of wound catheters and local infiltration all have roles in the approach to analgesia. Open nephrectomy is associated with a significant degree of acute pain and will require opioid analgesia if regional analgesia is avoided or not successful. Transversus abdominis plane block and paravertebral blocks are known to reduce opioid requirements without the hypotension associated with epidurals, but their role in nephrectomy is less well established. The dermatomes that require coverage with regional anaesthesia are dependent on which incision is used (Table 3). Increasingly, wound infusion catheters are being effectively used to complement opioid patient-controlled analgesia (PCA). Regional anaesthesia is usually avoided in those with cavo-atrial involvement due to the ongoing anticoagulation and also the extensive blood loss may cause them to become coagulopathic.

Although laparoscopic nephrectomy has proven reduced analgesic requirements, patients will still require regular strong opioids either in the form of an infusion or a PCA pump and also regular simple analgesics such as paracetamol. The use of drugs which rely on renal metabolism and excretion should be used cautiously in those with preoperative evidence of poor renal reserve and complete avoidance of non-steroidal anti-inflammatory diseases is recommended.

For level 3 cava disease operated on without CPBP, there is likely to be the use of both the Pringle manoeuvre and cross-clamping of the vena cava. This will cause a decrease in venous return and subsequent cardiac output. Such haemodynamic instability can be very poorly tolerated, but the haemodynamic response is poorly predicted. The effect will largely depend upon whether the patient has complete occlusion of the IVC at presentation for surgery and the extent to which a collateral circulation has developed. One option is to see how well cross-clamping is tolerated before proceeding with surgery on the vena cava. If problems arise, veno-venous bypass or full cardiopulmonary bypass may need to be considered.

Operative-specific complications have decreased significantly with advancement in surgical practice; however, they are still significant and listed in Table 4. Mortality after radical nephrectomy is considered to be <0.5% and is usually due to complications such as pulmonary embolism and myocardial infarction.

Postoperative

Postoperative care can be delivered with level 1 surgical ward care for a standard radical nephrectomy (open or laparoscopic). There should be a low threshold for arranging a higher level of care for individuals with significant co-morbidities and those planned to have continuous thoracic epidural analgesia in the immediate postoperative period. Those with cavo-atrial disease should all be cared for after operation in a critical care environment, although the exact level of care will be dictated by the magnitude of surgical trauma and whether veno-venous or cardiopulmonary bypass has been required.

Conclusion

Perioperative management varies significantly and there is a wide spectrum of disease and patient groups who may present for nephrectomy. The anaesthetist must be cognizant of the various surgical approaches and be prepared to assist surgical colleagues and patients in agreeing the best approach to their disease based on the findings at preoperative assessment and staging of malignant disease. These findings influence preoperative optimization, referral to allied specialities, determine the optimal timing of surgery, and allow the team to provide an individualized approach. Comprehensive imaging, MDT discussion, and preoperative planning are frequently necessary between several specialities and as such nephrectomy in the 21st century still remains a potentially challenging case for the anaesthetist.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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The clinical use of methadone in cancer and chronic pain medicine

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Key points

- Methadone is a synthetic opioid used in the management of cancer pain, chronic pain, and opioid addiction.
- It has multiple pharmacological modes of action, but it predominantly works via antagonism of the μ-opioid receptor.
- Conversion to and from methadone and other long-term opioids is problematic, and no universally accepted equianalgesic dosing regimen exists.
- Perioperative management of patients taking long-term methadone is similarly problematic, and is discussed.

Methadone is an opioid invented in Germany during the Second World War. Clinical trials were initiated in the USA in 1947, and methadone was originally marketed as Dolophine, with etymological origins from the Latin words dolor (pain) and fins (end). It was recognized in 1964 that it could be used to diminish or prevent the symptoms of craving and withdrawal in heroin users, and continues to be widely used in the management of opioid addiction. During the last 50 years it has also found a place in the management of cancer and chronic pain.

Pharmacology

Methadone is a synthetic phenylheptylamine μ-opioid agonist with a molecular weight of 345.9. It is lipophilic and has a volume of distribution of 4 l kg^{-1}. It has pK_a of 9.2, and so at physiological pH only 1% of the drug is ionized.[1] It is presented as a racemic mixture of *R*- and *S*-methadone, with the *R*-enantiomer being primarily accountable for μ-receptor agonism and therefore analgesia. The *S*-enantiomer is responsible for N-Methyl-D-Aspartate (NMDA) antagonism, having an affinity at the NMDA receptor similar to ketamine, and serotonin and norepinephrine reuptake inhibition.[2] This NMDA antagonism may help to prevent opioid tolerance, withdrawal, and opioid-induced hyperalgesia. Finally, methadone may also interact with Na channels in a similar manner to local anaesthetics. A summary of the pharmacokinetic characteristics of the drug are summarized in Table 1. In the UK, methadone is available as 5 mg tablets, and in solutions of 1, 10, and 20 mg ml^{-1}.

Methadone is usually administered orally. Parenteral preparations are also available in the UK but are less-commonly used.

Absorption and bioavailability

Methadone has a generally high but variable oral bioavailability of 35–100%, with plasma concentrations peaking 2 h after administration.[3] This large variation is in part explained by genetic polymorphism in the cytochrome p450 3A4 enzyme system, along with the possible auto-induction of hepatic first-pass metabolism with long-term use. Oral absorption is also influenced by gastric motility, gut perfusion and pH.

Rectal administration of methadone results in a bioavailability of 76% but has been associated with proctitis.

Distribution

Methadone binds primarily to α-1 acid glycoprotein and also albumin. In the presence of cancer, debilitating illness and opioid dependency, α-1 acid glycoprotein may be elevated as an acute-phase reactant, so reducing the free fraction of active

Table 1 Pharmacokinetic characteristics of methadone

		Range
Bioavailability (%)	75	35–100
Time to max. plasma conc. (h)	2.5–4	1–5
Volume of distribution (l kg^{-1})	4	1.9–8
Protein binding (%)	89	81–97
Half-life (h)	20–35	5–130

drug. Methadone crosses the placenta with concentrations in amniotic fluid similar to that of maternal plasma.

Metabolism and elimination

Methadone is metabolized by oxidative biotransformation to inactive metabolites. It is demethylated to 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine, 2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline, methadole, or normethadole, before renal and faecal excretion.[4] In patients with normal renal function, 20–50% of metabolites are renally excreted, but this proportion diminishes as estimated glomerular filtration rate decreases, and excretion occurs almost entirely via the enteral route in anuric patients. In light of this, there is considerable controversy about whether dosage intervals should be increased in renal failure.[5] Peritoneal dialysis or haemodialysis only removes ~1% of the total daily dose.

Methadone is sequestered in lipid-rich peripheral tissues and released back into the plasma slowly during redistribution and elimination. It therefore exhibits a highly variable half-life depending on the degree of saturation of peripheral tissues, increasing with the length of therapy and cumulative dose. Values of between 5 and 130 h are reported, with a mean of 35. Inter-individual variation of up to 24 h is well recognized. However, it is also possible that, in patients on chronic therapy, hepatic enzyme auto-induction may inconsistently reduce half-life. The unpredictable nature of methadone's pharmacokinetics implies that caution must be exercised when using this drug in the clinical context.

Drug interactions

There is considerable potential for interaction with CYP 3A4 inducers and inhibitors. Inducers, such as carbamazepine, phenytoin, rifampicin, and St John's Wort have the potential to lower plasma concentrations of methadone. Inhibitors, such as fluoxetine, antifungals, and HIV-1 protease inhibitors may do the opposite. It should be noted that many methadone-related deaths recorded in the literature are due to drug interactions rather than methadone alone.[6] In addition, some antipsychotics may precipitate methadone withdrawal symptoms via an unknown mechanism.

Precautions and adverse effects

Methadone has a similar range of side-effects to other opioids. However, when compared with morphine, methadone readily accumulates with repeated dosing, and the development of withdrawal symptoms is more insidious and prolonged. Opioid toxicity develops unpredictably during dose titration and may continue long after the drug is discontinued, requiring several days of naloxone treatment.

Table 2 Risk factors for QTc prolongation in patients taking methadone

Methadone dose >100 mg (24 h)$^{-1}$
Concomitant administration of other QTc prolonging drugs (e.g. antipsychotics, antidepressants, antiarrythmics)
Female gender
Structural or ischaemic heart disease
Electrolyte imbalances, including hypokalaemia, hypomagnesaemia and hypocalcaemia
Congenital long QT syndrome
Liver impairment
Renal impairment

QTc prolongation and torsades de pointes

In doses of 100 mg (24 h)$^{-1}$ or greater, corrected QT interval (QTc) interval prolongation and torsades de pointes have been reported. Methadone prolongs the QTc interval by binding to cardiac human ether-a-go-go related gene (hERG) potassium ion channel KVE 11.1, prolonging cardiac depolarization in a dose-dependent manner. Chlorambutanol, the preservative in parenteral methadone, also blocks the hERG channel and may act synergistically with methadone to cause QTc prolongation. Methadone should therefore be used with caution in at-risk patients, including those with cardiac or hepatic disease, electrolyte imbalances or a family history of sudden cardiac death. ECG monitoring is recommended before and at 7 days after titration of doses above 100 mg. Maudsley guidelines recommend annual ECG monitoring in patients on long-term methadone treatment over 100 mg (24 h)$^{-1}$ or in those with other risk factors for QTc prolongation[7] (Table 2).

Prospective studies have shown that QTc prolongation with methadone is less significant than was originally thought. Indeed, *in vitro* studies may underestimate the protein binding of methadone in human plasma and thus overestimate the potential for hERG channel interaction and QTc prolongation.[8] However, some data indicate that sudden cardiac death may occur even with normal therapeutic concentrations.[9]

Rationale for use in pain medicine

Methadone has a number of properties that make it useful in the settings of cancer and chronic non-malignant pain, including long half-life, good oral bioavailability, delayed withdrawal, low cost, and convenient dosing schedule. Its use in the UK is governed by the Misuse of Drugs Act 1971.

However, due to unpredictable pharmacokinetics and dose–response relationship, it tends to be used as a second- or third-line opioid. It may be particularly suited to treatment of mixed nocioceptive/neuropathic pain states due to opioid and NMDA receptor antagonism together with catecholamine reuptake inhibition, although such theoretical pharmacodynamic advantages have not been borne out in rigorous empirical studies.[10]

Please see Table 3 for a summary of the advantages and disadvantages of methadone use in cancer and chronic non-malignant pain.

Practical aspects of methadone prescribing

Conversion to methadone in opioid-tolerant patients

The conversion of methadone from and to other opioids is considerably more complicated than conversions between other opioids. The principles of conversion remain the same, however,

Table 3 Advantages and disadvantages of methadone in comparison with other opioids

Advantages	Disadvantages
Inexpensive	Unpredictable half life
High oral bioavailability	QTc prolongation and torsade de pointes in high doses and in risk groups
Long acting, with stable interdose plasma levels and slow onset to withdrawal	Interaction with other drugs metabolized by the cytochrome P450 enzyme system
Serotonin and norepinephrine reuptake inhibition and NMDA antagonist activity	Potential for accumulation with unpredictable, delayed and prolonged opioid toxicity
Lack of active and toxic metabolites	Unpredictable equianalgesic dose conversion with other opioids
Little accumulation with renal impairment	Variable protein binding and free levels of drug in illness and addiction
Constipation develops slowly and may be less marked than with other opioids	Subcutaneous use can produce local tissue reactions
	Not cleared by renal replacement therapy

- ***Day 1***: Previous opioid stopped. Fixed dose of methadone started on a 3 hourly prn basis. This fixed dose is calculated as 1/10th of the 24 h OME e.g. 20 mg prn 3 hourly for patients with an OME of 200 mg/24 h. This must not be more than 30 mg of methadone 3 hourly;
- ***Day 6***: Mean taken of Days 4 and 5 24 h methadone usage. This mean is halved to give the bd maintenance dose;
- Further dose titration may be required following this if inadequate analgesia or opioid toxicity is experienced;
- 1/10th of the total daily methadone dose may continue to be used on a 3 hourly prn basis.

Fig 1 The ad libitum, UK conversion strategy from other opioids to methadone.

and rely on a series of steps using published opioid equivalence ratios to estimate an appropriate equianalgesic starting dose:

(i) Convert existing opioid to *oral morphine equivalent* dose (OME) (e.g. oral oxycodone:oral morphine ratio is estimated at 1:2).
(ii) Further convert OME to new opioid (e.g. OME to subcutaneous diamorphine ratio is estimated at 3:1).
(iii) Introduce a safety margin by the reduction of calculated equivalent dosage by 33–50% to allow for inherent inaccuracy in equivalence ratio and unpredictability in patient response to new opioid (due to incomplete cross-tolerance).

It can be seen that each step has the potential to introduce significant inaccuracy, with early inaccuracies becoming amplified by later calculations. Published equianalgesic ratios may vary to some extent, and they are usually derived from single dose studies in healthy, opioid-naïve patients, potentially limiting their applicability in most clinical situations in which they are actually used.

For example, to convert a patient taking oxycodone 50 mg bd to a subcutaneous diamorphine infusion, a ratio of 1:2 suggests an OME of 200 mg (24 h)$^{-1}$. Further, a ratio of 3:1 OME: subcutaneous diamorphine gives an estimated 24 h diamorphine dose of 66 mg. Introducing an appropriate safety margin, it would be reasonable to start an infusion at 1.5 mg h^{-1} while monitoring the patient for analgesic efficacy, opioid toxicity, and withdrawal symptoms and adjusting infusion rate accordingly.

When converting opioid-tolerant patients to methadone, however, the equianalgesic dose ratio varies depending on current opioid dose, becoming relatively more potent in patients taking larger amounts of existing opioid. This is reflected in published conversion regimes, with, for example, Mercadante reporting a strategy utilizing a 4:1 conversion ratio in patients receiving <90 mg day^{-1} of OME, 8:1 for 90–300 mg day^{-1}, and 12:1 in >300 mg day^{-1}.[11]

Conversion strategies to methadone can be divided into two broad groups: by the clock (Edmonton model) and ad libitum. There are no studies comparing the efficacy of one method with the other. The Edmonton method relies on an overlapping approach with the previous opioid over 3 days, with sequential 30% reductions in existing opioid and replacement with 8 hourly methadone at an OME conversion ratio of 10:1. The ad libitum method involves stopping the previous opioid on Day 1 with replacement by a fixed dose of methadone on a 3 hourly prn basis. This is the most-commonly used method in the UK. Figure 1 gives further details of the ad libitum strategy.

During the first week of therapy it may be necessary to provide other immediate-release short-acting opioids for breakthrough pain, but this should be avoided where possible as it may prolong the titration phase. Other strategies such as non-opioid analgesia and non-pharmacological interventions should be tried first.

At the start of methadone titration, the duration of analgesia may be very short, at ~6 h, despite the prolonged terminal

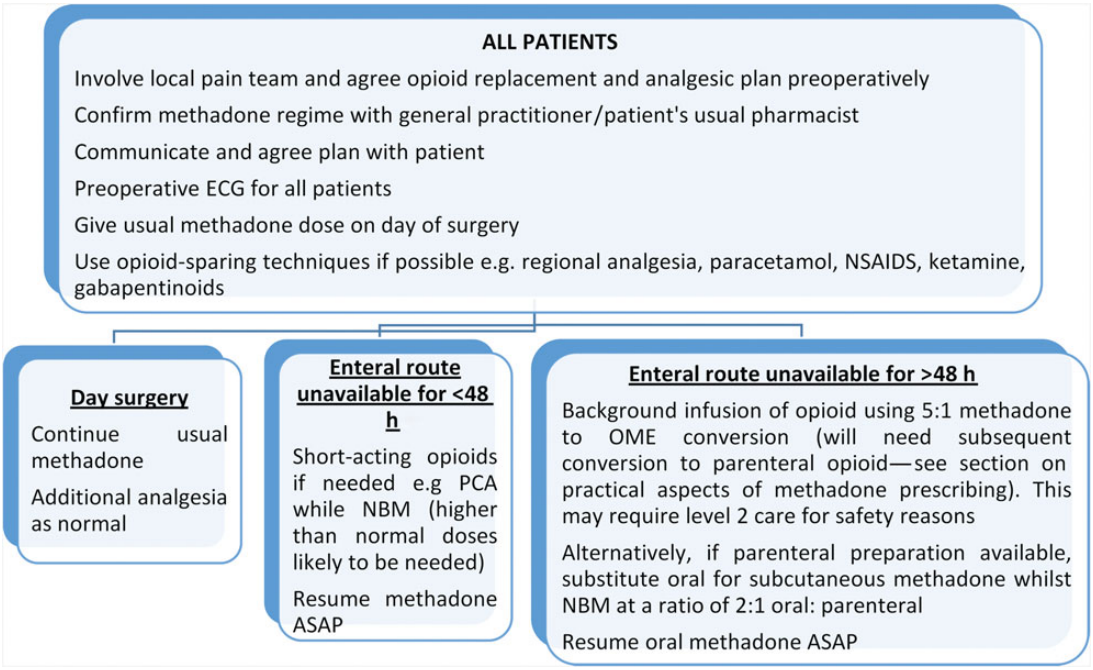

Fig 2 Suggested algorithm for the perioperative management of patients on long-term methadone.

elimination half-life. This is due to rapid redistribution after oral administration, resulting in plasma levels decreasing below the minimum effective analgesic concentration. With chronic dosing, peripheral tissues serve to maintain plasma levels and may prolong analgesic effect.

If an in-progress methadone switch needs to be abandoned due to e.g. inadequate analgesia or QTc prolongation, the original opioid should be recommenced at 66% of the previous dose and retitrated.

Starting methadone in opioid-naïve patients

It is very unusual to administer methadone in opioid-naïve patients with chronic or cancer pain, but if done, an oral prn 3 hourly dose of 2.5 mg in an adult (less in the elderly) might be considered a reasonable starting point, with conversion on Day 6 to a bd dose as per the ad libitum regime.

Conversion from methadone to other opioids

The conversion of methadone to other opioids may be more problematic than the conversion of other opioids to methadone as no published guidance exists for this. Some authors report successful conversion using a 1:4.7 methadone to OME ratio, but this is not universally accepted, and others suggest a ratio significantly lower than this (e.g. 1:3).[12] Pragmatically, it may be necessary to convert to a relatively low OME (e.g. three times daily methadone dose) with adequate breakthrough opioid analgesia and prn low-dose methadone to treat any withdrawal symptoms that do not respond to the new opioid.

Special populations

Controversy exists as to whether the dose of methadone should be decreased in renal failure. As excretion in patients with kidney disease is predominantly faecal (70%), it has been suggested that dose reduction is unnecessary. However, certain studies have stated that dosing intervals should be increased in moderate renal failure. Maintenance doses do not need to be altered in patients with stable chronic liver disease.[13]

During pregnancy patients may require higher doses and shorter dosing intervals. This is due to reduced absorption and increased elimination.[14] Neonatal opioid administration may be required to prevent opioid withdrawal.

Methadone is permitted in breastfeeding mothers, although the dose should be as low as possible and the infant monitored to avoid sedation.

General considerations

In light of the above considerations and pitfalls, methadone administration in the context of chronic and cancer pain should be overseen by clinicians experienced in its use. It is the authors' opinion that conversion to and from methadone should be done in an inpatient setting due to the unpredictable nature of its effects. Serial ECGs should be performed as above, and if QTc prolongation is demonstrated, consideration should be given to reducing methadone dose or converting to an alternative opioid. Clear and regular communication with other healthcare professionals in both primary and secondary care is essential.

Managing acute pain in patients on methadone

Anaesthetists may encounter patients on long-term methadone treatment in the perioperative setting. Here, the goals of treatment should be to prevent opioid withdrawal and to treat acute pain effectively. Underlying principles are similar to managing patients on other long-term opioids in this context. This includes:

(i) adequate explanation and communication with the patient, including allaying potential fears about long-term opioid re-escalation when other opioids are given;
(ii) provision of usual maintenance opioid or equivalent throughout perioperative period; and

(iii) provision of further analgesia on top of maintenance to treat acute pain, using opioid-sparing techniques where possible, and bearing in mind that higher opioid doses may be necessary to achieve clinical effect.

Many of the characteristics that favour the use of methadone in chronic non-malignant and cancer pain complicate its management and use in the perioperative period. Such characteristics include the high degree of inter-individual variability in dose–response, numerous medication interactions and long half-life. In addition, parenteral methadone preparations are not routinely stocked by many UK institutions, and no simple bioequivalent conversion ratio exists as detailed above. This may create significant problems if the enteral route becomes unavailable for more than 2 days perioperatively.

There is no published guidance on the management of methadone in the perioperative period. A suggested algorithm is shown in Figure 2.

It should be remembered that many patients on long-term methadone express their dosage in millilitres rather than milligrams. Some use a fixed, individually prepared volume of 100 ml containing a variable concentration of drug. Where possible, methadone dose should be confirmed with primary care colleagues. A preoperative ECG is warranted to establish the QTc before administration of anaesthesia, and if prolonged, consideration should be given to the avoidance of other QTc prolonging drugs and early correction of relevant electrolyte abnormalities.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Pain after amputation

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Key points

- Good quality postoperative analgesia is essential for limb amputation.
- Pain management after amputation can be challenging due to the presence of mixed nociceptive and neuropathic pain.
- Thorough pain assessment is required to establish the aetiology of post-amputation pain.
- Prolonged analgesia via continuous perineural blockade provides optimal analgesia for early management of stump and phantom pain.
- Salmon Calcitonin and Memantine can be useful in the acute management of phantom limb pain.

Amputation of a limb is one of the oldest recorded surgical procedures. Traumatic amputation and use of a prosthesis is found written in Sanskrit texts dating from 1800 to 3500 BC. Today, amputation remains a commonly performed surgical procedure with ~5500 lower limb amputations carried out in England alone every year.[1] Complications from peripheral vascular disease and diabetes are the leading medical causes of amputation although worldwide a vast number are as a consequence of trauma. Internationally, accurate numbers of limb amputations performed are very difficult to estimate as there is no recognized database or organization collecting this information.

Regardless of the indication for surgery, pain management after amputation is challenging. Amputation of a limb is one of the most severe pains in the human experience. This is attributable to the magnitude of the tissue injury involved and the varying loci of centres responsible for pain generation; comprising peripheral, spinal, and cortical regions. Pain after amputation involves nociceptive pain, due to bone and soft tissue injury, and neuropathic pain from direct neural trauma and central sensitization. This leads to a complicated, mixed, form of pain and a highly varied array of different postoperative pain syndromes. The burden of pain after amputation is therefore considerable, not just in the short term, but also in the years and decades after surgery. Severe post-amputation pains from phantom limbs have been recorded in survivors from World War II, some 50 yr after loss of a limb.[2]

Pain management is often complicated in surgical amputees due to the presence of polypharmacy and severe co-morbidity including ischaemic heart disease and renal compromise. Furthermore, for these reasons, amputees remain a high-risk patient group with a 22% thirty-day mortality from emergency surgery.

This article will discuss the different pain phenomena encountered after limb amputation and its management. This will include stump pain, acute phantom limb pain, and back pain. Different perioperative treatment modalities will be discussed aiming to inform practice in achieving optimal acute pain control and potentially preventing the chronicity of acute pain.

Pain following amputation

Acute pain management has been identified as a key priority in the management of patients undergoing amputation by a recent NCEPOD report. In achieving good quality analgesia it is important to strike a balance between effective pain control and excess morbidity as a result of interventional or pharmacotherapy. However, failure to optimize acute pain control not only leads to a detrimental pathophysiological stress response but impacts on a patient's psychology, functional recovery and predisposes to chronic stump and phantom pain.

A number of different pain syndromes can present after amputation. These shall be discussed as stump pain, phantom pain, and mechanical pain. It should be borne in mind however that

each pain rarely exists in isolation and frequently contribute to one another. A full assessment must therefore be made of each patient to try and identify the predominant pain at the time.

Stump pain

The immediate aftermath of limb amputation in the first post-operative days is dominated by surgical wound pain. This pain is readily identifiable and confined to the surgical site. Surgical stump pain is often described as sharp, aching, and severe. It is primarily a nociceptive form of pain due to the extensive tissue trauma involved, however, the inevitable direct neural injury that occurs results in a significant neuropathic component to the presentation. This neuropathic component may be part of the reason for the relative analgesic failure seen if single modality, anti-nociceptive, pharmacotherapy is used.

In the absence of regional anaesthesia, the severity of the stump pain requires management with strong opioids as a baseline. Opioids used in isolation are however often insufficient and require to be taken in such quantities as to cause significant sedative side-effects. Consequently, adjuvant analgesics such as i.v. Ketamine are frequently required.

Acute stump pain would be expected to resolve in the first few weeks after amputation, however, ~10% of patients will go on to experience persistent stump pain[3] although some studies quote a far higher incidence than this. The differential diagnosis for persistent stump pain is varied. It is therefore important to take a full history as well as visually inspecting, palpating, and performing sensory testing of the stump to identify any tender points, dysaesthetic areas and any possible pathology.

Some potential causes of persistent stump pain are listed in Table 1.

Three particular causes of persistent stump pain are worth specific mention; infection, neuroma, and heterotopic ossification.

Infection

Infection is relatively common after amputation. Higher rates of infection are seen in below knee compared with above knee amputations, in diabetic patients, patients with poor nutritional status, ongoing vascular compromise or if there has been pre-existing infection in the amputated limb. Infections at a stump include cellulitis, abscess, or osteomyelitis. Clinical evidence of infection includes erythema, swelling, purulent exudate, or wound breakdown.

If a stump infection is suspected it must be treated early and aggressively. Baseline investigations include white cell count, CRP, blood and wound cultures. X-ray, magnetic resonance imaging (MRI), or bone scan may be required if osteomyelitis is suspected. Prolonged antibiotic treatment is often required. If a stump infection is not controlled, early serious systemic sepsis can result in addition to wound dehiscence that occasionally requires surgical debridement or revision of a stump to a higher level.

Table 1 Aetiology of persistent stump pain

Infection
Wound breakdown
Arterial insufficiency
Osteomyelitis
Bone spur
Haematoma
Insufficient myoplasty covering
Poorly fitting prosthesis

Stump neuroma

After a nerve has been severed, an intense immune-cell mediated inflammatory reaction is observed. This of itself causes pain and peripheral sensitization but also initiates a process by which free endings of unmyelinated A-delta and C-fibres sprout to form a tangled end at the cut surface of the nerve bundle. Neuromas display altered sodium channel function with reduced activation thresholds and spontaneous firing. This leads to unprovoked pain and contact sensitivity in the region of the neuroma. There is a close association between the presence and severity of stump neuroma pain and phantom limb pain.

Neuromas take time to develop and are not usually seen in the first few weeks after amputation. Features suggestive of neuroma formation include a focal point of pain at the stump, spontaneous pain, and localized sensory changes.

Heterotopic ossification

This is a phenomenon rarely considered as a cause for acute or persistent stump pain. It has only been characterized recently due to the upsurge in patients suffering traumatic amputation in military conflict. Heterotopic ossification essentially involves the deposition of calcium in the soft tissues of the stump. The incidence is unknown in medical amputees but has been found in up to 63% of patients after traumatic amputation.[4] Interestingly, the presence of traumatic brain injury significantly increases the risk of heterotopic ossification.

There is no definitive means of preventing heterotopic ossification. Some centres have used a bisphosphonate (such as Etidronate) to prevent heterotopic ossification but good evidence for this practice is lacking. Non-steroidal anti-inflammatory medication may be helpful but this class of drug is frequently contra-indicated in many amputees. COX-2 inhibitors may offer a slightly safer alternative although, again, there is no good evidence to support routine use of these drugs in this circumstance.

In the sub-acute or chronic setting, a patient presenting with persistent stump pain should have this diagnosis considered and investigated by way of an X-ray of the stump. There are no well described, definitive, treatments for this condition. Heterotopic ossification can be managed conservatively in many cases but further surgery may be indicated if ossification is severe.

Management of acute stump pain

Systemic opioids delivered via patient controlled analgesia (PCA) are commonly used for post-amputation pain management in the acute phase. This can provide reasonably satisfactory analgesia and has a number of advantageous features including ease of titration, reliable systemic delivery, minimal invasiveness, and relatively low associated morbidity. Morphine is commonly used however there is no good evidence to indicate it is superior to any other opioid in the circumstance. The patients' clinical condition or past experience may make another opioid more preferable, e.g. fentanyl may be more appropriate if there is significant renal impairment (eGFR <30 ml min^{-1} 1.73 m^{-2}).

Acute stump pain, in the absence of other pathology, would normally be expected to have subsided by the time of discharge from hospital such that strong opioids were no longer required. If stump pain is still severe enough to require strong opioids at the point of discharge, continuing causative factors or pathology

should be sought and referral made to Out-patient Pain Services for follow-up and monitoring of analgesia.

Other pharmacological modalities are often used in the management of acute stump pain. Ketamine given via a low-dose continuous i.v. infusion at up to 15 mg h^{-1} is often helpful. Gabapentinoids are frequently utilized and present a rational choice due to their effect on nociceptive as well as neuropathic pain. Pregabalin is a good choice due to its superior pharmacokinetic profile with more reliable enteric absorption, faster onset, and relatively low incidence of side-effects. A starting dose of 25–75 mg per day is recommended depending on renal function and clinical condition.

The gold standard for management of post-amputation acute stump pain is regional anaesthesia. This can be accomplished either with central neuraxial blockade, usually via an epidural infusion, or peripheral nerve block. It should be noted that there is no good evidence to indicate that commencing central neuraxial or perineural blockade for a prolonged period before operation confers any advantage in terms of minimizing acute, or chronic, stump or phantom pain. Preoperative regional anaesthesia is only clearly indicated in cases of severe, treatment refractory, ischaemic pain before re-vascularization or amputation. In this circumstance regional anaesthesia is highly effective in controlling pain, alleviating distress, decreasing opioid related morbidity and even improving peripheral perfusion.

Epidural analgesia

This has been the most widely discussed and researched technique for post-amputation analgesia. For management of stump pain, epidural analgesia can be effective and versatile offering a number of advantages over systemic pharmacological techniques. For example, epidural analgesia can be started before operation to provide analgesia for ischaemic pain; can be converted to provide anaesthesia for surgery and continued after operation.

Opioid related morbidity, particularly respiratory complications, can be minimized with central neuraxial blockade but there has been no consistent or clear advantage demonstrated to date on preventing chronic pain, including phantom pain, with the use of epidural analgesia for amputation. This is somewhat surprising but methodological problems with the design of many studies, particularly the early discontinuation of epidural analgesia after operation, is important in interpreting the validity of these findings.

Although epidural analgesia can be very effective for the management of acute surgical pain, there are limitations to the technique in this patient group. Specifically, many vascular patients require therapeutic anti-coagulation thus either contra-indicating or substantially increasing the risk of epidural haematoma. Furthermore, epidural analgesia can have a failure rate approaching 10%; the potential for infection is higher with prolonged use of epidural blockade particularly in the diabetic population and adequate critical care facilities, staffing and monitoring are required. Consequently, resources may not be available in many hospitals to deliver epidural analgesia safely to this high-risk patient group.

Perineural blockade

Perineural blockade has been a major advance in pain management after amputation. The introduction of ultrasound guided neural blockade has made this technique more reliable particularly when identifying nerve supply to a non-viable limb or after traumatic amputation. Perineural blockade has been effectively utilized by the Armed forces for many years because continuous peripheral nerve block provides a relatively simple and highly effective means of providing prolonged, good quality analgesia, with low monitoring requirements that is virtually free of systemic side-effects.

When instituting regional anaesthesia for the lower limb, the relevant nerves should be blocked depending on the level of amputation. For below knee amputation a sciatic nerve block is sufficient while for above knee amputation, both the femoral and sciatic nerves should be targeted. Ideally, nerve blocks should be instituted immediately before surgery in addition to either general or central neuraxial anaesthesia. Anaesthetic placement of a perineural catheter may not be possible in all circumstances in which case a surgically placed sciatic catheter should be sought to be sited under direct vision providing there are no significant concerns regarding on-going local infection.

For postoperative analgesia perineural blockade can be initiated with a bolus dose and continued with elastomeric pumps delivering local anaesthetic at up to 10 ml h^{-1}. Ropivacaine is a good choice due to low cardiotoxicity; an important consideration particularly if two nerve catheters are placed. A typical perineural infusion lasts 40 h and is often discontinued at this point once the elastomeric pump runs out. For management of wound pain, this is too early as nociceptive pain is still maximal inside the first 72 h. Perineural blockade should be extended beyond 72 h whenever possible. Experience at our hospital indicates that perineural blockade can be continued safely to 80 h or more before discontinuing. This technique provides excellent analgesia in the first crucial days after amputation with low associated morbidity, results in minimal systemic opioid requirements and has a very low incidence of catheter related infections.

Phantom limb pain

Phantom limb pain is the most widely known post-amputation pain syndrome. The first written record of phantom limb pain dates to 1462 when Ambrose Paré, a French surgeon, reported the phenomenon in his book *Treatise on Surgerie*. It is a phenomenon that has largely remained a medical curiosity over the centuries as it defied satisfactory explanation and effective treatments remained elusive. It is only in recent years that we are gaining a clearer insight into this problem and how to manage it.

Phantom limb pain occurs in up to 80% of amputees. At least 75% of patients who develop phantom pain do so within the first week after amputation. The natural history of phantom pain is then variable. Many patients will show gradual improvement of phantom pain within the first year and some will resolve completely. Many patients however will have phantom pain for life.

Like other chronic post-surgical pain syndromes there are no definitive predisposing factors but some circumstances do make the chances of developing phantom pain higher. These are listed in Table 2.

There is no clear difference in the incidence of phantom pain between the sexes and psychological factors such as depression

Table 2 Risk factors for developing phantom limb pain

Severe preoperative pain
Bilateral amputation
Stump pain
Repeated limb surgeries
Increasing age

or anxiety are not predictive. It is important to note however that patients with significant psychological risk factors do tend to report more severe phantom pain with higher levels of disability and reliance on medication.

Phantom limb pain is typically felt in the distal extremity of the absent limb. Pain characteristics vary but are often described as being cramping, burning, or shooting in nature. It is not uncommon to observe that if a patient experiences severe pain in a limb before operation then the same pain will be experienced after removal of that limb. Phantom pains are usually episodic occurring in short bouts ranging from a few seconds to many hours. It is the minority of patients who have severe and unremitting phantom pain.

Patients may report other phenomenon from the missing limb such as tingling or itching. These non-painful phenomena are termed phantom sensations. Patients should be informed that these are normal and reassurance is provided. The phantom limb may also be felt to be in a different position, shape or size to the missing limb. Telescoping, where sensation from a missing extremity migrates in perceived position towards the stump, can occur but this is usually a finding in more established cases.

Pathophysiology

The precise mechanisms underlying phantom limb pain have been difficult to accurately elucidate. This is likely to reflect the fact that anatomically different pain centres can be involved in producing the phenomenon with one or more loci contributing at any one time. There are however three key areas that are implicated in phantom pain.

Peripheral nerves

Many patients presenting for amputation will already have a damaged and sensitized peripheral nervous system due to ischaemia. Further neural injury from surgical trauma leads to an inflammatory reaction and the release of pro-nociceptive factors such as cytokines, prostaglandins, and substance P. These factors cause a decrease in activation thresholds from nociceptors and spontaneous discharge leading to further sensitization. These changes occur in afferent nociceptive pathways emanating from the absent limb.

It is likely that during the early postoperative phase it is the intensity of the afferent peripheral nociceptive stimulus that initiates phantom pain and results in the changes seen subsequently upstream in the central nervous system (CNS). Neuroma formation is frequently cited as being the cause of phantom pain. While this may be true in the sub-acute or chronic phase, within the first week of amputation when the majority of phantom pains first present, a neuroma would not have had time to develop so cannot be responsible for acute phantom pain.

Spinal cord

The intense nociceptive barrage from the peripheral nervous system has a profound effect on pain pathways at the spinal cord. At this level the dorsal route ganglion is an important site as afferent pain signals can be substantially modified, either attenuated or enhanced. The N-methyl-D-aspartate (NMDA) receptor seems to be particularly important in this process for both modifying nociceptive signals and facilitating CNS plasticity. Specifically, the NMDA receptor is involved in the phenotypic switch and cross sprouting that occurs in afferent nerve fibres after amputation. This results in afferent non-painful stimuli being felt as painful and the widening of receptive fields from one neural pathway resulting in sensitivity extending beyond the dermatomal distribution of one nerve.

Somatosensory cortex

Considerable attention has been focused on the somatosensory cortex as a source of phantom limb pain. It has long been suspected that cortical structures were implicated in the generation of phantom limb pain however it has not been until the introduction of functional MRI scanning that this has been confirmed. The cortical changes after amputation are complex but not unique to phantom pain. Similar cortical reorganization is also seen in cases of Complex Regional Pain Syndrome and lower back pain.

In essence the cortical changes involve a compensatory migration into the representation of the absent limb from adjacent regions of the somatosensory cortex. This can be inferred clinically as patients with upper limb amputation can experience exacerbations of phantom pain on touching their face or, in the lower limb, experience phantom pain with a full bladder.

Prevention and treatment

Many therapies have been studied over the decades for phantom pain and are too numerous to cover in detail within the scope of this article. Only the most pertinent and promising interventional and pharmacological treatments are discussed. The use of strong opioids in this circumstance does require special mention. It must be emphasized that strong opioids have a very limited role in the management of either acute or chronic phantom limb pain. Strong opioids initiated to manage wound pain should not be continued without very good reason and with proven efficacy on a case-by-case basis for the management of phantom pain.

Perineural blockade

Perineural blockade provides excellent analgesia for surgical stump pain and in doing so can attenuate peripheral and central sensitization that may either prevent, or at least minimize, the impact of phantom pain. Many studies looking at the use of regional anaesthesia in the prevention of phantom limb pain discontinue neural blockade within 48 h of surgery. When considering that stump pain and the inflammatory process is still at its peak at this time, as stated previously, it is clear this is far too soon to discontinue therapy.

An interesting study by Borghi *et al.*[5] demonstrated a very significant reduction in the incidence of phantom limb pain with the use of prolonged perineural blockade. They reported only a 2% incidence of phantom pain by continuing neural blockade for up to 80 days after amputation. Prolonging perineural blockade to this extent is unlikely to be feasible in most hospitals but enhancing existing practice is possible.

In our hospital, continuous perineural blockade is commenced perioperatively with 400 ml of Ropivacaine 0.2% infused via an elastomeric pump at 10 ml h^{-1} if a single catheter is used or 5 ml h^{-1} per catheter if two infusions are required for above knee amputations. Perineural blockade is continued for a minimum of 80 h after amputation to get a patient beyond the crucial first days of maximal pain in order to minimize sensitization. Local experience indicates this is probably the single most important technique for acute pain management after amputation and is crucial in decreasing the likelihood of developing significant phantom limb pain.

Pharmacological treatment

Tricyclic antidepressants

This family of medication is frequently utilized in the management of neuropathic pain, however, they have little role in the acute management of phantom limb pain. Tricyclic antidepressants are of limited utility as they are frequently contra-indicated in surgical amputees due to patients' concurrent co-morbidities; the analgesic effect is of slow onset, of poor efficacy and side-effects frequently preclude dose titration.

Gabapentinoids

Gabapentinoids are agonists at the alpha-2-delta subunit of voltage dependent calcium channels and $GABA_B$ receptors in the CNS. This class of medication is increasingly recognized for its anti-nociceptive and anti-neuropathic effects. Gabapentinoids are an integral part of many enhanced recovery pathways for their opioid sparing effects and there is increasing evidence they can help prevent the development of chronic post-surgical pain.

Gabapentinoids have a good safety profile, few drug interactions, are well tolerated and have efficacy in both neuropathic and nociceptive pain. With regard to phantom limb pain the majority of published evidence only examines the use of Gabapentin in chronic, established, cases. Only one study by Nikoljsen *et al.*[6] examined early postoperative use of Gabapentin after amputation but did not find any benefit for stump or phantom pain. No studies to this time have been done examining Pregabalin in this context. Although there is no conclusive evidence, a Cochrane review identified a 'trend towards benefit' from Gabapentin in the management of phantom pain.[7]

Increasingly compelling evidence is emerging regarding the use of Gabapentin, and Pregabalin in particular, for preventing chronic post-surgical pain. Combining these two strands of evidence indicates that it is reasonable to initiate therapy with a Gabapentinoid perioperatively, as the clinical condition allows, continuing after operation for as long as felt to be clinically necessary.

Salmon calcitonin

Salmon calcitonin is a neuropeptide with a novel analgesic action. Its exact mechanism of action is not well defined but is postulated to be due to a combination of altered β-endorphin production, inhibition of prostaglandin and cytokine production and modulation of central serotonergic pathways. It is only available in parenteral form in the UK.

Salmon calcitonin has been found to have analgesic efficacy in a diverse range of pain disorders including pain from spinal cord injury and vertebral fractures. It was however first serendipitously found to have an analgesic action on phantom limb pain in a number of early case reports. A small study by Jaeger confirmed the benefits of a short treatment course of salmon calcitonin on phantom limb pain the effects of which were still evident on follow-up 1 yr later.[8] Unlike many therapeutic agents in pain management salmon calcitonin, when successful, abolished phantom limb pain.

Despite these promising early results, salmon calcitonin has seldom been studied and is infrequently utilized in acute pain management. Due to its good safety profile, low incidence of side-effects, and efficacy it should be considered for early treatment of acute phantom limb pain. A dose of 100 IU per day given subcutaneously as a treatment course for 5–7 days should be considered for acute presentations.

Clonidine

Clonidine is an agonist at α2-adrenoceptors which are primarily located in the CNS and are involved in central control of the cardiovascular system. α2-Adrenoceptors are also expressed on macrophages at the site of inflammation where they have a role in the expression of pro-inflammatory cytokines. Perineural clonidine has been found to prolong and enhance regional anaesthesia and reduce mechanical hypersensitivity after nerve injury.

There are no well conducted studies specifically examining the use of clonidine as an adjuvant to perineural blockade for amputation. Extrapolating the best evidence available and clinical experience indicates that the addition of clonidine to a continuous perineural infusion at a dose of between 10 and 20 $\mu g\,h^{-1}$ after amputation can be safe and effective. In our practice, perineural clonidine is reserved for patients whose block has not been complete or who are judged to be very high risk of severe stump or phantom pain.

NMDA antagonists

Ketamine is the most widely used NMDA antagonist. It has specific anti-neuropathic, anti-nociceptive and anti-hyperalgesic properties. It is commonly used perioperatively for amputation surgery but it does not prevent the development of phantom limb pain. Rather, Ketamine can decrease the severity of phantom pain experienced. I.V. Ketamine is probably the best means of administration as it ensures reliable systemic delivery (oral Ketamine has a bio-availability of only 20–40%), minimizes side-effects and ensures continuous blockade of the NMDA receptor in the crucial early postoperative period.

Memantine is another NMDA antagonist that is seldom considered in pain management. It has different binding characteristics at the NMDA receptor compared with Ketamine and, crucially, is relatively free of the psychotropic effects that frequently limit the use of Ketamine. Memantine has no active metabolites, is renally excreted and preferentially accumulates in the CNS where it has a half-life of 80 h. All these properties are advantageous in treating pain in amputees.

Memantine has been studied when given perineurally and orally. The conclusions reached from these studies and in subsequent reviews dismissed Memantine on the grounds of lack of statistical significance in treating phantom pain. Crucially, Memantine did display considerable *clinical* significance in these studies and the evidence available needs to be re-evaluated with this in mind. Local experience indicates Memantine is generally well tolerated and efficacious in the management of phantom pain.

Back pain

Back pain is a very common yet under recognized and seldom studied post-amputation pain problem. Back pain can arise *de novo* after amputation or pre-exist and be exacerbated by loss of a limb. Back pain may also occur as a result of prolonged bed rest after surgery but is more frequently encountered during the early rehabilitation phase during weight bearing on a prosthesis. Considerable bio-mechanical changes occur in the lower back and pelvis as a result of altered weight and force distribution and different muscle utilization.

Assessment of the clinical characteristics of back pain is essential to exclude any specific spinal or disc pathology. Following exclusion of spinal pathology, e.g. disc herniation or discitis, treatment can proceed on empirical grounds with attention paid to adequate prosthetic fitting and physiotherapy.

Pharmacological management should comprise simple analgesics, anti-inflammatories (where clinically appropriate), middle strength opioids, and non-benzodiazepine-based neuromuscular blocking agents. TENS machines and acupuncture are also useful in this setting. Strong opioids should be avoided if at all possible.

Conclusion

Post-amputation pain management remains a challenging area of clinical practice. A wide variety of pain problems present after operation which need careful clinical assessment to differentiate. Despite considerable advances in surgical and anaesthetic practices, pain related morbidity remains high after amputation.

The evidence base for optimal analgesic management is incomplete but it is wrong to use this reason as a basis for persevering with conventional treatment strategies that have proved ineffective. Best evidence, clinical experience, and pragmatism all indicate prolonged perineural blockade is the best analgesic technique post-amputation to attenuate both nociceptive and neuropathic pain. Continuation of perineural blockade for a minimum of 72 h post-amputation is essential in achieving this goal.

A multi-disciplinary, multi-modal approach to pain management must be emphasized comprising assessment and engagement in pain control from all team members involved in the care of amputees. Early treatment of acute phantom limb pain with novel analgesic agents such as salmon calcitonin and Memantine may offer the best chance of success to prevent chronicity alongside active physical and rehabilitation therapy.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Chemotherapy-induced peripheral neuropathic pain

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Key points

- Chemotherapy-induced peripheral neuropathy (CIPN) is not an uncommon sequelae after treatment with certain chemotherapy agents in cancer patients.
- CIPN is becoming one of the common causes for referral to pain clinics.
- Although newer agents are available, drugs that cause CIPN like platinum compounds, taxanes, and vinca alkaloids are still widely used in managing common cancers.
- CIPN causes not only pain, but also sensory, motor, and autonomic dysfunction that can result in severe disability.
- Despite better understanding of the mechanism of the neuronal toxicity, effective methods of prevention are lacking and the management of established CIPN is essentially symptomatic.

Chemotherapy-induced peripheral neuropathy (CIPN) is due to the toxicity of the chemotherapeutic drugs and mainly affects the peripheral nervous system. More than 50% of patients are surviving longer than 10 yr since their diagnosis of cancer and a good proportion of them have either disease-related or treatment-related chronic pain. The severity of the resultant neuropathy depends on the drugs used, duration of treatment, or nerve damage either by cancer itself or due to any pre-existing conditions such as diabetic or alcoholic neuropathy. There are no major differences in the incidence between the sexes. The objective of the article is to discuss the nature of the peripheral neuropathy associated with chemotherapeutic agents, their clinical features, evaluation, and subsequent clinical management.

The drugs most commonly associated with CIPN are platinum compounds (cisplatin, carboplatin, and oxaliplatin), taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine, vinblastine), epothilones (ixabepilone), bortezomib, and thalidomide along with its analogues. Combination of two or more of these agents can result in higher possibility of developing peripheral neuropathy. For example, when combined with cisplatin or carboplatin, paclitaxel neuropathy may be encountered in 70% of patients.

Chemotherapeutic agents

Platinum compounds

These are commonly used for lung, ovarian, and bowel cancers and the mechanism of action is by interacting with the DNA causing apoptosis (programmed cell death).

Cisplatin

Cisplatin can cause sensory neuropathy due to its effect on the dorsal root ganglion (DRG). The anti-neoplastic effect is partly due to its effect on tumour vasculature and therefore can cause damage to the vasa nervorum.[1] Neuropathy has been reported at dosages as low as 200 mg m^{-2}, but doses above 400 mg m^{-2} will almost always cause neuronal damage. It manifests predominantly as sensory neuropathy, presenting as distal paraesthesia, areflexia and sensory ataxia, dorsal column myelopathy, and bilateral jaw pain. Neurophysiological recovery is rare and is never complete.

Carboplatin

Moderate to severe toxicity is seen in 5% of patients with doses exceeding 1600 mg m^{-2} of carboplatin. The presentation is similar to cisplatin: painful paraesthesia, gait difficulties, and ataxia. The toxicity could be reduced if given along with pegfilgrastim (recombinant human granulocyte colony-stimulating factor) or trastuzumab (monoclonal antibody against HER/neu2 receptor).

Oxaliplatin

Oxaliplatin is a novel compound that differs significantly from cisplatin and carboplatin. It is used as a first-line chemotherapy agent for metastatic colorectal carcinoma and is also used in ovarian, breast, and lung cancers. It contains a 1,2-diaminocyclohexane carrier ligand, which leads to the formation of heavy platinum-DNA adducts that are more difficult to repair, causing impaired DNA synthesis and increased apoptosis. Unpleasant paraesthesia in the distal extremities, mouth, and throat are common adverse effects associated with acute administration. Sensory neuropathy with loss of sensation and dysaesthesias in the distal extremities are encountered with total doses exceeding 540–850 mg m^{-2}. Pharyngeo-laryngeal dysaesthesia may manifest as a sensation of dysphagia and is associated with jaw spasms. Neuropathy usually begins to resolve in 4–6 months, with complete resolution within 6–8 months in 40% of patients after cessation of the chemotherapy. Occasionally, neuropathy may flare up in some patients when oxaliplatin is stopped. 'Coasting' is the term used to describe this phenomenon in which there is progression of sensory loss even after cessation of chemotherapy and the symptoms can present as late as 3–6 months.

Vinca alkaloids

These are derivatives from the periwinkle plant *Catharanthus roseus* and exert their cytotoxic effect by destabilizing the mitotic spindle through the inhibition of tubulin polymerization into microtubules.[2] Vincristine is mainly used for treating solid tumours, lymphomas, and leukaemias. Neurological symptoms and signs are seen with cumulative doses higher than 12 mg. It affects axonal transport by binding with tubulin and blocks its polymerization into microtubules, thereby arresting mitosis in the metaphase. This produces microtubule disorientation causing accumulation of neurofilaments in the dorsal sensory ganglion. The earliest sign is the depression of deep tendon reflexes, especially the ankle reflex, progressing onto paraesthesias, dysaesthesias and numbness of the distal extremities, postural hypotension, urogenital dysfunction, and hyperesthesia. It induces a weak axonopathy, which leads to difficulty in walking on heels and loss of strength in the wrist extensors. The peak incidence is seen 2–3 weeks after administration and recovery is expected within 3 months of stopping the medication. Vincristine when given during childhood can mimic Guillain–Barré syndrome, presenting as autonomic nervous system dysfunction. Neuropathy is less common with other agents such as vindesine, vinblastine, vinflunine, and vinorelbine.

Taxanes

These are used for the treatment of solid tumours like ovarian, breast, and non-small cell lung cancer. They act by binding to the β-tubulin subunits, thereby interfering with microtubule dynamics and polymerization, resulting in inhibition of cell division and apoptosis.[3] The toxicity seen with taxanes is severe when co-administered in combination with cisplatin and also in those patients with pre-existing neuropathy such as diabetic neuropathy.

Paclitaxel is an effective anti-tumour agent isolated from the bark of the pacific yew tree, *Taxus brevifolia*. A single dose of 250 mg m^{-2} and a cumulative dose of 1000 mg m^{-2} or higher can induce a predominantly sensory axonopathy and painful sensory distal neuropathy. Risk factors for paclitaxel-induced CIPN include cumulative dose, a high single dose, rapid infusion time (<24 h), previous or concomitant chemotherapy, and pre-existing neuropathy. It acts by aggregation of intracellular microtubules, microtubule disorientation, and neurofilament accumulation causing disruption of axonal transport. The symptoms of paclitaxel-induced neuropathy are mostly peripheral and sensory in nature, consisting of mechanical allodynia, cold allodynia, persistent burning pain, tingling, and numbness. Light touch and vibration are the most commonly affected sensations. *In vivo* studies have shown that Cremophor EL, a vehicle used to formulate paclitaxel is toxic to the DRG. Nanoparticle albumin-bound (NAB) paclitaxel does not need a vehicle to deliver and hence is associated with a lower incidence and also early resolution of neuropathy. Abraxane (Celegene Corporation USA) is an albumin-stabilized nanoparticle formulation of paclitaxel. Its use has been associated with a lower incidence of hypersensitivity reactions, but with a higher incidence of CIPN. Patients with pre-existing neuropathy receiving high doses of paclitaxel are prone to motor and autonomic dysfunction. It can also cause an acute encephalopathy that can lead to coma and death. Docetaxel is a semi-synthetic analogue of paclitaxel and shows similar neurotoxicity, often manifesting as a symmetrical progressive, length-dependent sensory neuropathy.

Bortezomib

It is a boronic acid derivative belonging to the proteasome inhibitor family and is used mainly for the treatment of multiple myeloma. It is a dipeptide and 26S proteasome complex inhibitor that acts by disrupting various cell signalling pathways, thereby leading to cell cycle arrest, apoptosis, and inhibition of angiogenesis. Another proposed mechanism of causing CIPN is dysregulation of neuroproteins by inhibiting NF-κB activation, thereby blocking the nerve growth factor (NGF)-mediated neurone survival. Neuropathy occurs with a cumulative dose of over 30 mg m^{-2}. The clinical presentation is of distal sensory loss to all modalities including suppression of deep tendon reflexes and altered proprioception. Pain symptoms mostly manifest before the fifth treatment cycle.[4] Neuropathic pain is described mainly in the fingertips and toes and is associated with deficits of all three fibre types—Aβ, Aδ, and C primary afferent fibres. An increase in sharpness-detection threshold and lower skin temperature are demonstrated in painful areas when compared with the non-painful areas. The recovery is usually quick, but in some cases can take as long as 18 months.

Thalidomide

Thalidomide is a glutamic acid derivative used for severe cutaneous inflammatory disorders (erythema nodosum leprosum), cancers (relapsed/refractory multiple myeloma), and inflammatory conditions (Crohn's disease). The risk is low when <20 g of thalidomide is used, but higher doses may increase the risk of neuropathy.[5] It suppresses the production of tumour necrosis factor α and decreases the expression of selected cell surface adhesion molecules involved in leucocyte migration. Lenalidomide is an

analogue of thalidomide, which produces a similar, but a milder form of neurotoxicity.

5-Fluorouracil

This is an analogue of uracil and is used for treating cancers of head/neck, stomach, colon, rectum, and anus. Capecitabine, an oral formulation, is a pro-drug of 5-fluorouracil which was developed to achieve higher intra-tumour levels of 5-fluorouracil while causing less toxicity. Toxic effects include diarrhoea and hand–foot syndrome.

Suramin

Suramin is a polysulphonated napthylurea that has anti-tumour activity in hormone refractory prostatic carcinoma and is a potent reverse transcriptase inhibitor. Two distinct patterns of peripheral neuropathy have been reported: distal axonopathy and a demyelinating neuropathy. Distal axonopathy affects small and large sensory fibres and motor axons, and the earliest changes are registered in the sural and peroneal nerve amplitudes. Demyelinating neuropathy is often associated with lymphocytic inflammation.

Pathophysiology

The underlying pathophysiology of chemotherapy-induced neuropathy is not yet clearly understood. The damage may occur at different neural structures like microtubules, axons of DRG, myelin sheath, or supporting glial structures. Microtubules are responsible for axonal transport and are important for supply of trophic factors. Most of the agents causing CIPN cannot cross the blood–brain barrier,[6] and hence the main involvement is manifested at the DRG and the afferent and efferent axons, as they lack an effective blood–brain barrier. The commonly used chemotherapy agents and their mechanisms of action are summarized in Table 1.

Clinical features

CIPN manifests in several ways. It predominantly affects small diameter nerve fibres causing burning pain, hyperesthesia, and later on loss of pain and temperature sensations. Effects on large diameter nerve fibres cause loss of vibration sense, proprioception, and slowing of nerve conduction. The most common presentation involves sensory disturbances such as numbness, pain, paraesthesia, hypoaesthesia, and dysaesthesia. Neuropathy may simultaneously affect upper and lower extremities and also the cranial nerves. The diagnostic features are distal length dependency, symmetrical distribution, and temporal onset of the neuropathy. Predominantly, sensory modalities are involved with sparing of motor function except in oxaliplatin-induced neuropathy. The sensory changes may be permanent with little improvement over time because of loss of nerve cell bodies in the DRG.

Deep tendon reflexes, proprioception, vibration, two-point discrimination, and temperature sensation may be lost. Motor dysfunction is less common and when present is associated with severe sensory disturbances. Motor weakness may not be reported by the patient, but may be ascertained on clinical examination and is often associated with muscle weakness. Pure motor neuropathy is rarely seen and if present should suggest a diagnosis other than CIPN.

Autonomic dysfunction manifests as orthostatic hypotension, cardiovascular, erectile, or gastrointestinal disturbances. Patients with leukaemia or lymphoma may have lymphomatous infiltration of the peripheral nerves, presenting as neuropathy. The clinical course of CIPN starts during chemotherapy and usually tends to resolve once the therapy is completed. Most CIPN improves after the offending drugs are stopped (e.g. bortezomib, thalidomide), except for cisplatin and oxaliplatin with which CIPN may continue to progress even after the drug has been withdrawn.

Table 1 Chemotherapy

Chemotherapy	Mechanism
Vinca alkaloids (vincristine, vinblastine)	Binds to microtubules and causes cell cycle arrest
Taxanes (paclitaxel, docetaxel)	Prevent microtubule depolymerization and inhibits mitosis
Platinum agents (cisplatin, carboplatin)	Cross-linking of DNA strands causing impairment of cell division
Proteasome inhibitors (bortezomib)	Demyelination causing sensory neuropathy
Thalidomide	Toxicity of neuronal cell bodies

Diagnosis

The most reliable method of detecting CIPN is by taking a detailed history and conducting a neurological examination. The most sensitive neurological signs of CIPN are impairment of vibration, proprioceptive, and two-point discriminatory sensations. Quantitative sensory testing (QST) shows an increase in touch thresholds, abnormal cold pain thresholds, and reduction in sharpness detection. The accurate grading of CIPN has poor reliability as it is dependent on patient reporting, and thus QST may have a role to play in early identification of CIPN.

Electrophysiology

Clinical tests like nerve conduction tests and electromyography that are routinely used to assess neuropathy are insensitive during early stages even when the patients may be showing signs of motor or sensory neuropathy. Nerve conduction velocity (NCV) measures velocity and amplitude in the large diameter and fast conducting fibres and thus does not provide reliable data on the small fibres. NCV may reflect the status of surviving fibres and may not identify the state of the fibres affected.

Physician-based assessment methods are available as shown in Table 2. The most widely used scale is NCI-CTC.

Management

The management of CIPN remains largely ineffective; preventive measures are often adopted during the oncological treatment, but the management remains primarily supportive and symptomatic.

Preventive measures

The oncologists and chemotherapy nurses usually institute these preventive measures while the patient is receiving the chemotherapy and the pain clinician is seldom involved at this stage. Several compounds and physical measures like peripheral cooling during the chemotherapy infusion have been tried to reduce the incidence of CIPN, but a single effective preventive option is yet to be identified.[6] Magnesium and calcium infusions have been found to reduce the incidence of CIPN related to oxaliplatin by their action of chelation of oxalate, a metabolite of oxaliplatin.[11]

Table 2 Grading scales for CIPN. ECOG, Eastern Cooperative oncology group; NCI-CTC, National Cancer Institute common toxicity criteria

Type	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
WHO[7]	None	Paraesthesias, decreased tendon reflexes, or both	Severe paraesthesias, mild weakness, or both	Intolerable paraesthesias, marked weakness, or both	Paralysis
ECOG[8]	None	Decreased tendon reflexes, mild paraesthesias, mild constipation	Absent tendon reflexes, severe constipation, mild weakness	Disabling sensory loss, severe peripheral neuropathic pain, obstipation, severe weakness, bladder dysfunction	Respiratory dysfunction, secondary to weakness, obstipation requiring surgery, paralysis confining the patient to bed/wheelchair
NCI-CTC: sensory neuropathy[9]	None	Loss of deep tendon reflexes or paraesthesias (including tingling) but not interfering with function	Objective sensory loss or paraesthesia (including tingling) interfering with function, but not interfering with activities of daily living	Sensory loss or paraesthesia interfering with activities of daily living	Permanent sensory loss that interferes with function
NCI-CTC: motor neuropathy	None	Subjective weakness but no objective findings	Mild objective weakness interfering with function, but not interfering with activities of daily living	Objective weakness interfering with activities of daily living	Paralysis
Ajani sensory neuropathy[10]	None	Paraesthesia, decreased deep tendon reflexes	Mild objective abnormality, absence of deep tendon reflexes, mild to moderate functional abnormality	Severe paraesthesia, moderate objective abnormality, severe functional abnormality	Complete sensory loss, loss of function

Cisplatin causes accumulation of platinum adducts in the DRG, and vitamin E is suggested to reduce this toxicity via its anti-oxidant properties. Glutathione and *N*-acetyl cysteine is thought to decrease the incidence of CIPN by preventing and reducing the accumulation of platinum adducts in the DRG.[12] Glutamine is also shown to protect against oxidative injury at doses of around 500 mg kg^{-1} day^{-1} by up-regulating NGF.

Acetyl-L-carnitine acetylates intracellular tubulin, thereby increasing the availability of NGF and increased NGF expression promotes regeneration after nerve injury.[13] Acetyl-L-carnitine also blocks the abnormal firing of A-δ and C fibres.

Recombinant human leukaemia inhibitory factor is a cytokine that supports regrowth and has been shown to ameliorate the loss of large myelinated fibres when given with paclitaxel. The reduced rate of chemotherapy-induced neuropathy was observed in patients taking oxcarbazepine. Erythropoietin has also shown some efficacy as a neuroprotective agent in cisplatin-induced neurotoxicity. These findings are all based on small studies and should be validated in large carefully designed trials. Despite all the above-mentioned measures, there is an increasing incidence of chemotherapy-induced neuropathy in patients surviving the cancer.

Patients are often referred to the pain clinic for the management of symptoms either during the chemotherapy cycle, as the patient had developed intolerable symptoms compromising delivery of further chemotherapy. Patients are also referred after completion of the planned chemotherapy regime and who are now having problems with painful peripheral neuropathy. It is imperative to identify the difference between painful neuropathy from peripheral neuropathy without pain; there are more proprioceptive changes in the latter and it does not respond well to standard neuropathic pain treatments. Most clinicians follow the IASP (International Association for the Study of the Pain) or EFNS (European Federation of Neurological Societies) guidelines to manage the neuropathic pain associated with CIPN. Various agents and treatment options have been tried, but the evidence-base is not very strong in the use of established neuropathic agents for specifically managing CIPN.

Pharmacological

Anti-depressants

Tricyclic anti-depressants exert their effect through their interaction with the serotonin and norepinephrine neurotransmitter systems. Duloxetine is a serotonin–norepinephrine re-uptake inhibitor which has shown good efficacy if administered at doses of 30–60 mg day^{-1} for over 5 weeks.[14] Venlafaxine is another anti-depressant that has shown some benefit in managing chronic oxaliplatin and paclitaxel-induced neurotoxicity.

Anti-convulsants

In CIPN, as with other painful peripheral neuropathy, a number of changes occur in various channels that lead to neuronal hyperexcitability and anti-convulsants act by decreasing the excitability of these neurones.

Gabapentin and pregabalin reduce the neuronal excitability resulting from up-regulation of α2 δ1 subunit of the voltage-dependent calcium channels. The excitability is recorded in the DRG as a result of the nerve injury.

Ethosuximide, in a small study, has been shown to completely reverse paclitaxel-induced mechanical allodynia and hyperalgesia and also vincristine and paclitaxel-induced cold allodynia;[14] larger studies are required to validate this before using in mainstream clinical practice.

Eight per cent capsaicin patch has shown some efficacy in painful CIPN, particularly in reducing the pain and also in alleviating the pain and improving the mobility that was being restricted due to pain improving pain-induced restriction of mobility. This is the authors' personal experience and the 8% capsaicin patches have been used as a first-line treatment option in certain cases for rapid control of symptoms so that the chemotherapy regimen is not compromised by reduction in the dose or even cessation of the cancer treatment after discussions with the oncology team.

Alpha-lipoic acid has been shown to produce improvement in pain, burning, and numbness in diabetic neuropathy[15] and may be

a promising option for treating CIPN. Topical compounded creams with agents like ketamine, amitriptyline, and baclofen are being evaluated for its efficacy in managing CIPN, but the existing evidence is not robust for these treatment options.

Non-pharmacological

Physiotherapy input is advocated early to prevent muscle wasting and also to assist mobilization; walking aids like crutches or walking frame may be required in some patients. Studies have shown that acupuncture has some benefit in diabetic neuropathy by improving gait and sensation. There are centres that use acupuncture for CIPN, but no validated studies have proven its efficacy in established CIPN.

Neuromodulation is increasingly used for managing resistant neuropathic pain states and spinal cord stimulation has been used for managing painful diabetic neuropathy. There may be a role for spinal cord stimulation and DRG stimulation in the management of resistant CIPN, but currently, there is no evidence for supporting its use. Deep brain stimulation and motor cortex stimulation have also been suggested as potential options and evaluation of these technologies in the context of established CIPN are awaited.

Conclusion

Cancer and its treatment cause neuropathic pain, and CIPN is one of the more debilitating side-effects of certain agents. Modern chemotherapeutic agents are being developed with minimal side-effects, but platinum compounds, taxanes, and vincristine are still widely used in the management of common cancers resulting in chemotherapy-induced neuropathy. Healthcare services should also allocate more resources for research into this field to understand the mechanisms and develop effective preventive and management options as the incidence of cancer survivors and CIPN is increasing due to early screening and detection of cancers and effective oncological management.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Place of rapid sequence induction in paediatric anaesthesia

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Key points

- Preoxygenation may not prevent hypoxia during classical rapid sequence induction (RSI) in children.
- Cricoid pressure is effective at reducing gastric insufflation.
- The sequelae of aspiration are less severe in children.
- 'Controlled' RSI, with careful mask ventilation, may decrease the risks associated with the classical approach.

Stept and Safar[1] introduced the concept of rapid sequence induction (RSI) in 1970 after Snow and Nunn had found that the commonest cause of anaesthesia-related deaths in 1958 were because of aspiration.[2]

The perceived benefit of RSI in reducing the risk of aspiration, in high-risk patients, has led to it becoming the standard level of care, despite the lack of quality evidence.[3]

The development of the RSI technique is based upon adult practice. In children a 'classical' RSI may not always be the correct choice because of psychological, anatomical, and physiological differences. A survey of UK anaesthetists found that only around 50% would routinely perform an RSI for a child with a presumed full stomach despite having comparable aspiration risk as an adult.[4]

This article examines the evidence for the use of 'classical' RSI and its place in contemporary paediatric anaesthetic practice.

History of RSI

Pulmonary aspiration of gastric contents under anaesthesia was not described as a problem until Mendelson famously described its deleterious effects in 1946. However, practice at that time included many risks for aspiration: no routine fasting combined with placing patients in a 20° head down position, undoubtedly increased the number who suffered from passive regurgitation. The first neuromuscular blocking agent, tubocurarine, was invented in the early 1940s. Although not used widely in 1946, it is only fully effective after 2–3 min, thereby allowing a prolonged period without protective airway reflexes.

Despite the consideration of fasting times and gastric emptying taking a more prominent place since the 1940s and the invention of succinylcholine in 1951, aspiration was still the number one cause of adult anaesthetic related deaths in 1958.[2] Sellick described cricoid pressure in 1961, but it was not until 1970 that Stept and Safar combined the individual components to develop the concept of the 'classical' RSI, with the aim of reducing the risk of aspiration as it was designed to minimize the time the airway was unprotected.

What is perhaps surprising is that despite these advances aspiration is still a significant problem. The NAP-4 study showed that the risk of aspiration in adults was 1:2–3000 for elective surgery and as high as 1:6–800 for emergency surgery.[5] In paediatric anaesthesia, it appears that the risk of aspiration is slightly lower.[6]

Aspiration

A recent study from the UK investigated the incidence, risk factors, and outcomes from aspiration in paediatric patients.[6] It found an incidence of 1:5076 for elective and 1:4498 for emergency paediatric cases. Children who had aspirated suffered less severe sequelae than adults. Of the 24 patients who aspirated there was no deterioration in 8 patients, mild deterioration in 11 patients (requiring only basic medical management) and severe deterioration in 5 patients (all requiring intubation and

ventilation). The additional finding that all children who deteriorated after aspiration did so within 2 h concurred with previous studies.[7] No mortality was reported from pulmonary aspiration in either study.

Aetiology

Aspiration of gastric contents occurs either passively or by active vomiting.

Passive regurgitation occurs mainly because of a distended or incompetent lower oesophageal sphincter. Common causes for this are attributable to gastric distension during bag mask ventilation or after accidental oesophageal intubation. Other important causes of abdominal distension include intestinal obstruction, intra-abdominal tumours, and ascites.

Active expulsion of gastric content occurs mainly because of instrumentation of the airway before adequate depth of anaesthesia is reached, leading to coughing and vomiting. Cricoid pressure should be removed on active vomiting to avoid oesophageal rupture.

Risk of aspiration

Recent studies have highlighted a failure to recognize significant risk factors (Table 1) and use an RSI when indicated in such cases.[5,6]

Anatomical variations in children

There are several anatomical factors that predispose infants to gastro-oesophageal reflux (GOR). Infants have a shorter oesophagus, thereby the stomach is that much closer to the larynx. The angle of His (made by the oesophagus and the axis of the stomach) is obtuse in newborns but decreases as infants develop. Infants also have decreased gastric compliance, which is believed to lead to lower oesophageal sphincter relaxation at lower intra-gastric volumes. It was initially thought that infants have an immature lower oesphageal sphincter (LOS), which predisposes them to GOR, but it has now been shown that it is because of periods of transient lower oesophageal relaxation. Abdominal muscle contraction coinciding with an episode of LOS relaxation may increase the risk of aspiration.

Behavioural differences

Babies and older, distressed children may cry and scream, thereby swallowing air and predisposing to abdominal distension. This may compound the risk of regurgitation and aspiration.

Reducing the risk of aspiration

The pH and volume of gastric contents can be reduced by pharmacological treatments such as prokinetics, H_2 blockers, proton pump inhibitors and non-particulate antacids. However, there is no evidence to show any benefit in children.

Table 1 Risk factors for aspiration in the paediatric population,[6] in ascending order of importance of risk

Anxiety, inadequate/light anaesthesia
Gastric distension from bag valve mask ventilation
Increased intra-abdominal pressure
Difficult airway, GI pathology, obesity
GOR, oesophageal disease
Sepsis, renal failure, opioids before operation

Insertion of a nasogastric tube and aspiration of gastric contents, before commencement of anaesthesia, reduces the volume but does not reliably empty the stomach completely.

Fasting guidelines

Widely, although not universally, accepted fasting recommendations for children undergoing elective surgery are 6 h for solids, formula, and cow's milk, 4 h for breast milk, and 2 h for clear fluids. Children are more prone to gastric stasis with minimal trauma, opioid analgesia, and pain. In one study 49% of children who suffered trauma still had significant aspirates after 8 h of starvation.[8] These guidelines cannot be relied upon to produce complete gastric emptying in all non-elective cases. Additionally prolonged fasting period may lead to an irritable, uncooperative child at increased risk of hypoglycaemia and dehydration.

The 'classical' RSI

Classical RSI, as described in adults, consists of preoxygenation, application of cricoid pressure followed by induction with a predetermined dose of thiopental and succinylcholine. Avoidance of positive pressure ventilation together with rapid tracheal intubation with a cuffed tube before removal of the cricoid pressure swiftly follows. The success of this technique requires scrupulous attention to detail of each component.

Preoxygenation

Preoxygenation is designed to increase the reserves of oxygen within the lungs by denitrogenation of the functional residual capacity (FRC). This prolongs the apnoeic period before hypoxaemia ensues. The efficacy of preoxygenation can be measured by the end-tidal oxygenation fraction, which provides an approximation of the alveolar oxygen fraction. To achieve full denitrogenation of the lungs, an end-tidal oxygenation fraction of >0.9 is required. Maintenance of a patent airway during the apnoeic period allows oxygen to reach the alveoli by the process of bulk flow. This occurs as a result of differences in the volume of oxygen consumption and CO_2 production and their respective solubility in blood. During apnoea, it is estimated that CO_2 enters the alveoli at a rate of 0.12–0.25 ml kg^{-1} min^{-1} whilst O_2 is removed at a rate of 4–8 ml kg^{-1} min^{-1} in paediatric patients and 2–3 ml kg^{-1} min^{-1} in the adult population. This net removal of gas volume from the alveoli during periods of apnoea results in a reduction in barometric pressure in the alveoli that facilitates the bulk flow of oxygen from the upper airway to the alveoli. Studies in adults have shown that oxygen administered by nasal prongs and also by facemask, with a patent airway, prolongs the time to desaturation.

Owing to the negative pressure gradient that bulk flow causes, it is important to maintain the application of continuous positive airway pressure via a tight fitting mask, in order to reduce atelectasis. This is emphasized in children, as they are more prone to atelectasis and hypoxaemia on induction because of the combination of a reduced FRC, increased closing volume, and higher respiratory rate.

Time to complete preoxygenation is theoretically shorter in children because of a smaller lung volume and an increased respiratory rate, creating a faster 'turnover' of ambient respiratory gases. However, a non-compliant and sometimes combative child may make full denitrogenation and preoxygenation unobtainable whilst simultaneously increasing oxygen consumption. During apnoea in a term baby who is 1 month old, the rate of

decline of Pa_{O_2} is three times more rapid than in an adult. Infants tolerate even very short periods of apnoea badly and can desaturate after <100 s despite adequate preoxygenation.[9] Failure to achieve full preoxygenation/denitrogenation because of non-compliance from the child compounds this risk. Sedation to improve mask acceptance may be an option after careful consideration in a select few. This practice is not recommended routinely, as a small amount of sedation may cause respiratory depression.

In adults, preoxygenation may be best achieved with the patient in a 20–25° head up position. This had been shown to improve efficacy and consequently produce an increased time to desaturation.[10] Although such an effect is unproven in the paediatric population, it would seem sensible to consider its use more frequently in children.

Cricoid pressure

There has been much controversy about the benefits and risks of cricoid pressure recently in the literature. A recent survey showed that only 50% of anaesthetists would routinely apply cricoid pressure in paediatric patients aged 1–14 and only 40% if they were <1.[11]

Cricoid pressure relies on the alignment of the trachea and the oesophagus so that when the cricoid cartilage is depressed it is displaced backwards onto the oesophagus and occludes it, in order to stop aspiration of gastric contents. A study examined CT scans of the neck of 120 children to assess the alignment.[12] In children <8 yr old, 45% had lateral displacement of the oesophagus at the level of cricoid cartilage as opposed to only 15% of children over the age of 8. This questions the efficacy of cricoid pressure in children, particularly in younger children. In children the cricoid cartilage is smaller and more cephalad in position, making it harder to identify. In addition, when the cricoid cartilage is depressed, it decreases the lower oesophageal sphincter tone, predisposing to aspiration.

Application of forces as low as 7.7 N may adequately compress a child's airway, and higher forces (typically 30 N) as recommended for use in adult practice may worsen or obscure the view of the larynx.[13]

However, the use of cricoid pressure may prevent insufflation of the stomach during bag mask ventilation. Effectively applied cricoid pressure may prevent gastric insufflation up to a maximal pressure of 40 cm H_2O in children between 2 weeks and 8 yr old.[14]

Induction agents

The paediatric population exhibits different, age-related pharmacokinetic and pharmacodynamic activity compared with adults.

No single drug possesses all of the attributes as the agent of choice for RSI in children. All have undesirable side-effects and choice depends upon the specific clinical circumstance. Detailed discussion is beyond the scope of this article. The predominant agents used are thiopental and propofol although alternative agents may be preferred in haemodynamically unstable patients. Both require larger doses compared with adults. Thiopental has a faster onset of hypnosis than propofol. Issues with propofol include potentially significant hypotension and pain on injection (ameliorated by co-administration of lidocaine). One major advantage of propofol over thiopental is that it suppresses the laryngeal reflexes. On balance, in the haemodynamically stable patient, propofol is commonly the favoured drug of choice.

Very little is written about inhalation induction for a child with a full stomach. Many paediatric anaesthetists would recommend an inhalation induction for a child undergoing emergency surgery only in cases of difficult airway or difficult vascular access. Sevoflurane's non-irritant smell and rapid onset make it the agent of choice in such situations.

Neuromuscular blocking drugs

Traditionally succinylcholine, in a dose of at least 2 mg kg^{-1}, is used for RSI as it rapidly provides excellent intubating condition with a rapid offset in effect. The average recovery time from administration of succinylcholine to spontaneous breathing is 4.7 min.[15] Such an offset time cannot be relied upon as a mechanism to prevent desaturation even in fully preoxygenated small children.

Rocuronium in a dose of 1.2 mg kg^{-1} can provide similar intubating conditions to succinylcholine. Rapid reversal of rocuronium's effects required in a 'cannot intubate, cannot ventilate' situation requires the prompt use of 16 mg kg^{-1} sugammadex. Full reversal can take several minutes, in addition to any time required to locate and draw up the drug. Prevention of significant desaturation is not guaranteed, particularly in babies.

Premedication with atropine

The routine use of atropine before intubation in children, in an attempt to prevent bradycardia associated with administration of succinylcholine, manipulation of the airway or reflex bradycardia associated with hypoxia, has been advocated. A retrospective study examined the effects of atropine on the prevention of bradycardia during laryngoscopy.[16] The children who received atropine had a similar incidence of bradycardia and atropine did not prevent bradycardia in all children.

Risks of RSI

RSI has risks associated with it, perhaps even more pertinent in the paediatric population.

Frank *et al.*[17] tried to establish the risks associated with the 'classical' approach to RSI in children. A retrospective study of over a thousand children aged 3–12 yr showed an overall risk of hypoxia (saturations <90%) of 3.6% with 1.7% demonstrating severe hypoxaemia (saturations <80%). Children <20 kg were at greater risk.

The same study showed an incidence of hypotension (systolic <70 mm Hg) as 0.8% and bradycardia (heart rate <60 beats min^{-1}) of 0.5%. The incidence of these risks is higher than the published risks of aspiration.

RSI in children may differ in the following ways when compared with adults

- Classical RSI
  - Preoxygenation
    - Difficult to achieve in uncooperative children and even preoxygenation creates minimal reserve
  - Administration of induction agent
    - Difficult i.v. access
  - Application of cricoid pressure
    - Correct timing is difficult
    - Can distort airway
    - Conflicting evidence regarding efficacy
  - Administration of neuromuscular blocking agent
    - If succinylcholine is used a larger dose kg^{-1} is needed
  - Period of apnoea with no positive pressure ventilation
    - Even brief period of apnoea can lead to profound hypoxaemia

An alternative approach

Classical RSI in children presents the anaesthetist with a unique set of potential challenges. RSI with a desaturating child can be a very stressful time for the personnel involved. There is emerging evidence that the use of a 'controlled RSI (cRSI)', without the use of cricoid pressure may offer an effective and potentially safer alternative. By utilizing this technique, it allows the operator optimal conditions, with ideal respiratory and haemodynamic conditions.[17] Significant differences between RSI and cRSI include:

- Continuous aspiration of an NG tube if *in situ*. If no NG, then one should be inserted after the tracheal tube is secured.
- Patients in a 20° head up position during preoxygenation and induction.
- Titration of induction agent to produce hypnosis followed by administration of a non-depolarizing relaxant. Atracurium at 1 mg kg^{-1} is traditionally described in cRSI but any neuromuscular blocking agent may be used as it is more important to guarantee optimal relaxation, guided by monitoring of neuromuscular block.
- Gentle bag mask ventilation (insufflation pressure <12 cm H_2O) before intubation.
- Intubation only after there is no response to a train-of-four stimulus from a nerve stimulator, thus allowing time for a deep level of anaesthesia and complete muscle paralysis.

Summary

Children are at risk of aspiration of gastric contents under anaesthesia, particularly at induction. Classical RSI has been adopted from adult practice without any modifications required to allow for significant differences in risk factors in children. The adoption of a controlled RSI may reduce the potentially significant risks of hypoxaemia associated with classical RSI whilst providing rapid intubating conditions.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Perioperative care of children and young people with diabetes

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Key points

- Diabetes mellitus is the most common metabolic disorder in childhood and the worldwide incidence is increasing.
- Blood sugar control may be more difficult in the perioperative period due to disruptions in routine, emotional, physiological, and metabolic stress.
- The aim is maintenance of near-normal glycaemic control with optimal hydration and electrolyte balance.
- A pragmatic approach should be adopted to prevent iatrogenic hypoglycaemic episodes and regimes for use in the perioperative period should be simple and straightforward, avoiding insulin infusions when possible.
- Ideally, there should be good communication between the surgeon, anaesthetist, paediatric diabetes team, and ward staff, enabling individualized care planning.

Background

Diabetes mellitus affects an estimated 497 000 children globally between the ages of 0 and 14 yr, accounting for 0.02% of the total child population. This is likely to be a significant underestimate due to underdiagnosis, especially in areas of socio-economic deprivation. As in adults, diabetes is the most common cause of metabolic co-morbidity and the UK has the fifth largest population of Children and Young People (CAYP) with type 1 diabetes mellitus (T1DM) in the world. T1DM remains the most prevalent form of childhood diabetes, affecting 97% of British diabetic children. The incidence of T1DM is increasing, with the greatest increase in younger children. However, the peak age for diagnosis remains in the 10–14 age range. Additionally, the number of CAYP with type 2 diabetes mellitus (T2DM) is increasing, which is associated with the growth in childhood obesity and physical inactivity.[1]

Compared with the rest of Europe, the UK has some of the poorest outcomes of care in paediatric diabetes. The annual National Paediatric Diabetes Audit in England and Wales has repeatedly shown poor glycaemic control in CAYP with only 16% achieving the National Institute for Health and Care Excellence (NICE) target value of a glycated haemoglobin (HbA1c) of <58 mmol mol^{-1} (7.5%) in the 2012–3 period. Twenty-six per cent of children had an HbA1c of >80 mmol mol^{-1}, which is associated with a high rate of future complications. UK diabetic CAYP also have the highest rates of diabetic ketoacidosis (DKA).[2] Although there have been small improvements in the UK median HbA1c in children, there appears to be significant regional variation in standards of care and glycaemic control across the country.

Perioperative care of the diabetic child can be challenging alongside the various different therapeutic strategies and regimens that exist for ongoing maintenance of blood sugar. The current UK National Paediatric Diabetes Service Improvement Delivery Plan notes the importance of standardizing perioperative care to ensure best practice is shared throughout the country.

In general terms, the aim should be avoidance of complications and maintenance of near normal glycaemic control with optimal hydration and serum electrolyte balance, while avoiding

hypoglycaemia. Local/regional guidelines for the perioperative management of diabetes in CAYP should now be based on the International Society of Paediatric and Adolescent Diabetes (ISPAD) guidance, which was published in 2014.[3]

Classification

Diabetes mellitus involves a defect in insulin secretion, its action, or both. Insulin is the major anabolic hormone and deficiency leads to dysfunction in carbohydrate, fat, and protein metabolism. In T1DM, pancreatic β islet cell destruction occurs usually through an immune-mediated process or can be idiopathic, but always leads to an absolute insulin deficiency with a need for insulin therapy. T2DM results from a varying combination of insulin resistance and relative insulin deficiency. CAYP with T2DM are usually obese and have a positive family history and can be managed with insulin and/or oral hypoglycaemic agents. Other less common causes of diabetes are shown in Table 1.

Type 1 diabetes is frequently associated with other autoimmune diseases. Hypothyroidism and coeliac disease are the most common, occurring in 3–8% and 1–10%, respectively. Hyperthyroidism and Addison's disease, primary adrenal insufficiency, coexist less often with T1DM, but the latter can be life-threatening if missed and may reduce insulin requirements while increasing the risk of hypoglycaemic episodes.

Table 1 Aetiological classification of less common forms of diabetes mellitus (based on American Diabetes Association classification)

Genetic defects of β-cell function	
Maturity-onset diabetes of the young (MODY)—monogenic group of disorders, presenting in adolescence	
Mitochondrial disorders	Drug- or chemical-induced
	Steroids
Genetic defects in insulin action	Chemotherapeutic drugs
Type A insulin resistance	Thiazides
Leprechaunism	Phenytoin
Rabson–Mendenhall syndrome	
Lipoatrophic diabetes	Infections
	Congenital rubella
Diseases of the exocrine pancreas	Cytomegalovirus
Cystic fibrosis—20% will develop DM by age 20 yr	Enterovirus
Trauma/pancreatectomy	Uncommon forms of immune-mediated diabetes
Neoplasia	Autoimmune polyendocrine syndrome (APS) types I and II
Pancreatitis	Anti-insulin receptor antibodies
Haemochromatosis	'Stiff-man' syndrome
Fibrocalculous pancreatopathy	
	Genetic syndromes sometimes associated with diabetes
Endocrinopathies	Down syndrome
Autoimmune polyglandular syndrome	Klinefelter syndrome
Cushing's syndrome	Turner syndrome
Acromegaly	Wolfram syndrome
Phaeochromocytoma	Friedreich's ataxia
Hyperthyroidism	Huntington's chorea
Glucagonoma	Laurence–Moon–Biedl syndrome
Somatostatinoma	Myotonic dystrophy
Aldosteronoma	Porphyria
	Prader–Willi syndrome

Complications

The recognized long-term vascular complications of diabetes rarely manifest clinically in children. However, their severity in adulthood is influenced by disease duration and adequacy of glycaemic control in childhood and adolescence.

Autonomic neuropathy, with alterations in haemodynamic control including postural responses and heart rate regulation, has been described with subclinical manifestations in adolescence. This may lead to cardiovascular instability under anaesthesia.

Limited joint mobility syndrome is associated with poor glycaemic control and early microvascular complications. It primarily affects the hands and feet but can progress to involve the axial skeleton, including the cervical spine, and it has been described in adolescents. Joint extension is restricted and the overlying skin has a waxy appearance. However, this does not appear to have a clinical relevance in terms of predisposing to difficult intubation until adulthood.

The metabolic burden of surgery

The perioperative period can adversely affect blood glucose control. Preoperative starvation and the overuse of insulin infusions can predispose to hypoglycaemic episodes. Conversely, the neuroendocrine stress response to surgery, critical illness, or both results in suppression of insulin secretion and a surge in counter-regulatory hormones, which can lead to hyperglycaemia. In the diabetic patient with little or no endogenous insulin, the hepatic production of glucose and reduction in peripheral glucose uptake mediated by catecholamines, cortisol, growth hormone, glucagon, and cytokines such as tumour necrosis factor α continue unchecked. Substrates for gluconeogenesis are also mobilized from lipid and protein stores. Lipolysis produces glycerol and free fatty acids. The latter can be converted to another useful fuel source: ketone bodies.

While it is common practice to aim for tighter, near normal glycaemic control in critically ill adults to improve outcomes, it cannot be recommended either in the intensive care unit or the perioperative period for children. Children have physiological differences to adults such as lower glycogen reserves. The risks of both inducing hypoglycaemia and the deleterious effects of hypoglycaemia on the developing brain are potentially greater.[4]

Guidelines for perioperative management

Anaesthetic technique can moderate the stress response. Effective analgesia provided by opioids is known to suppress hypothalamic–pituitary hormone secretion and neuraxial block has been shown to reduce markers of stress including blood glucose levels in children.[5]

A perioperative target capillary blood glucose (CBG) of 5–10 mmol litre^{-1} is generally recommended for children. This range is in agreement with the recently revised adult guidelines for peri-operative care of diabetic patients chosen to decrease the risk of hyperglycaemia with associated osmotic diuresis, dehydration, potential metabolic acidosis, and electrolyte imbalance, and that of hypoglycaemia where clinical signs are absent or are easily missed in patients who are sedated from anaesthesia. Active treatment is only recommended if CBG <5 or >14 mmol

litre^{-1}. These allowances minimize the risk of interventions and of hypo- and hyperglycaemia. Guidance suggests that CBG should be monitored hourly as a minimum and in young children (<3 yr), those undergoing major surgery and where the CBG is <5 mmol litre^{-1}, it may be pertinent to monitor half-hourly.

Preoperative assessment

A collaborative approach should be established with good communication between the surgical team, anaesthetists, paediatric diabetes team, and ward staff, enabling individualized care planning. Management also depends on the type of surgery, anticipated timing, duration of expected starvation, and the child's usual insulin/oral hypoglycaemic regimen.

For planned surgery, communication between all members of the multidisciplinary team should take place as soon as a decision for surgery is made. An assessment of diabetic control should be undertaken with adjustments to improve glycaemic control if time allows. Usual insulin regimes are established and the child, and parents, should be counselled on alterations of these and when to stop food and fluid before operation. The history should include frequency of hypoglycaemic episodes and whether the child is aware of these. Any associated pathologies and diabetic complications should be considered. Investigations should include recent HbA1c, serum electrolytes, and current CBG and blood/urinary ketones. ISPAD consensus guidelines[3] recommend delaying surgery when possible if glycaemic control is poor or if metabolic derangement is apparent until these are corrected. As with adults, whenever possible, diabetic children should be scheduled to be first on a morning surgical/procedures list. Increasingly, anaesthetists are providing preoperative assessment clinics and much of the above can be brought together in such a setting. Children and their families are often very well informed about their disease and an opportunity to discuss the perioperative plan and make sure that all members of the multidisciplinary team are fully informed is essential.

In general, the period of time without oral intake should be minimized and the Association of Children's Diabetes Clinicians recommend (in common with other routine guidance before planned surgery in children):

(i) No solid food for 6 h
(ii) In infants, breast milk until up to 4 h before surgery and other milks up to 6 h. Thereafter, clear fluids should be given as in older children.
(iii) Children should be encouraged to drink clear fluids (including water, or if necessary dilute squash) up to 2 h before surgery.

Children having emergency surgery also need a multidisciplinary team approach. Weight, hydration status, serum electrolytes and glucose, blood or urinary ketones/β-hydroxybutyrate, and/or a blood gas if glucose or ketones are high are all essential investigations. DKA can be precipitated by acute illness (including surgical emergencies) and where possible, metabolic and circulatory status should be corrected before surgery, but may have to occur in parallel. Management of DKA is discussed below.

Management for elective surgery

In general and as in adult practice, the use of variable rate insulin infusion (VRII), titrating short-acting i.v. insulin to blood glucose levels, should be avoided where possible to reduce the risk of administration error with i.v. preparations.

For short anticipated starvation periods, generally <12 h and only missing one meal, the patient can generally be managed by modification of their usual subcutaneous insulin on the day of surgery only (shown in Fig. 1, summarizing points from regional[6] and national guidelines). In general, if children are on long-acting insulins, these should be continued while intermediate-acting insulin doses are halved before operation as are premixed doses of short/intermediate-acting insulins, depending on the time of day.

Some patients will be receiving continuous subcutaneous insulin infusions (insulin pump therapy). This involves delivery of a basal insulin infusion of rapid/short-acting insulin in addition to boluses administered through the pump before meals according to the predicted carbohydrate load. In the perioperative period, the indwelling catheter insertion site should be secured to prevent dislodgement. The basal infusion can be continued, but pre-meal boluses withheld during the starvation period. If the perioperative team is unfamiliar or uncomfortable with this regime and its management, the pump should be discontinued and a VRII can be used instead.

Children with T2DM treated with insulin follow the same plan as type 1 diabetics, depending on their insulin regime. Those on oral hypoglycaemics should follow the same preoperative starvation guidelines and CBG monitoring as T1DM and oral hypoglycaemics agents are adjusted as in Figure 1. Contrary to adult guidance, the advice is for metformin to be omitted for 24 h before operation.

If a procedure is very short (expected maximum anaesthetic time no more than 30 min with anticipated rapid recovery), a meal can be delayed rather than missed. The usual short-acting dose of insulin can be delayed or if on an insulin pump, this can be withheld for the procedure period only.

Some flexibility to this approach is required and exceptions include situations when the duration of surgery is longer than anticipated, or when there is a high risk of postoperative nausea and vomiting which delays return to a normal diet and insulin regime. On these occasions, a VRII may need to be commenced and generally the younger the child, the greater the need for caution as diabetic control may be particularly challenging in pre-school children.

A VRII is also required if the perioperative starvation period is expected to include more than one missed meal (Table 2 includes a guide to infusion doses and rates).[3] For elective procedures, usual insulin doses should be administered the day before and a VRII started on the morning of surgery and generally run alongside 5% dextrose in 0.45% saline containing 0.15% potassium chloride (KCl) (available in the UK as a pre-made bag) initially in maintenance amounts. Additional losses should be replaced with boluses of Hartmann's solution or other (generally isotonic) fluids depending on the anaesthetist's preference and composition of fluid lost. It is notable that published perioperative guidance for use in diabetic CAYP does not reflect the 2007 directive from the UK National Patient Safety Agency around routine use of isotonic fluids in children. ISPAD in particular quotes the use of 5–10% dextrose as maintenance but also notes that many centres are now using 0.45–0.9% saline with dextrose. We would agree with the need to consider isotonic fluids and would suggest that moderate fluid restriction may be appropriate as in other perioperative situations if i.v. fluids are continued into the postoperative period.[7] In particular, the anaesthetist should be cautious in prescribing hypotonic fluids for prolonged periods of time. There is a need for close liaison with surgical and paediatric colleagues and regular monitoring of clinical and biochemical status while i.v. regimes are required. As a minimum, daily electrolytes should be monitored while on a VRII and in the presence

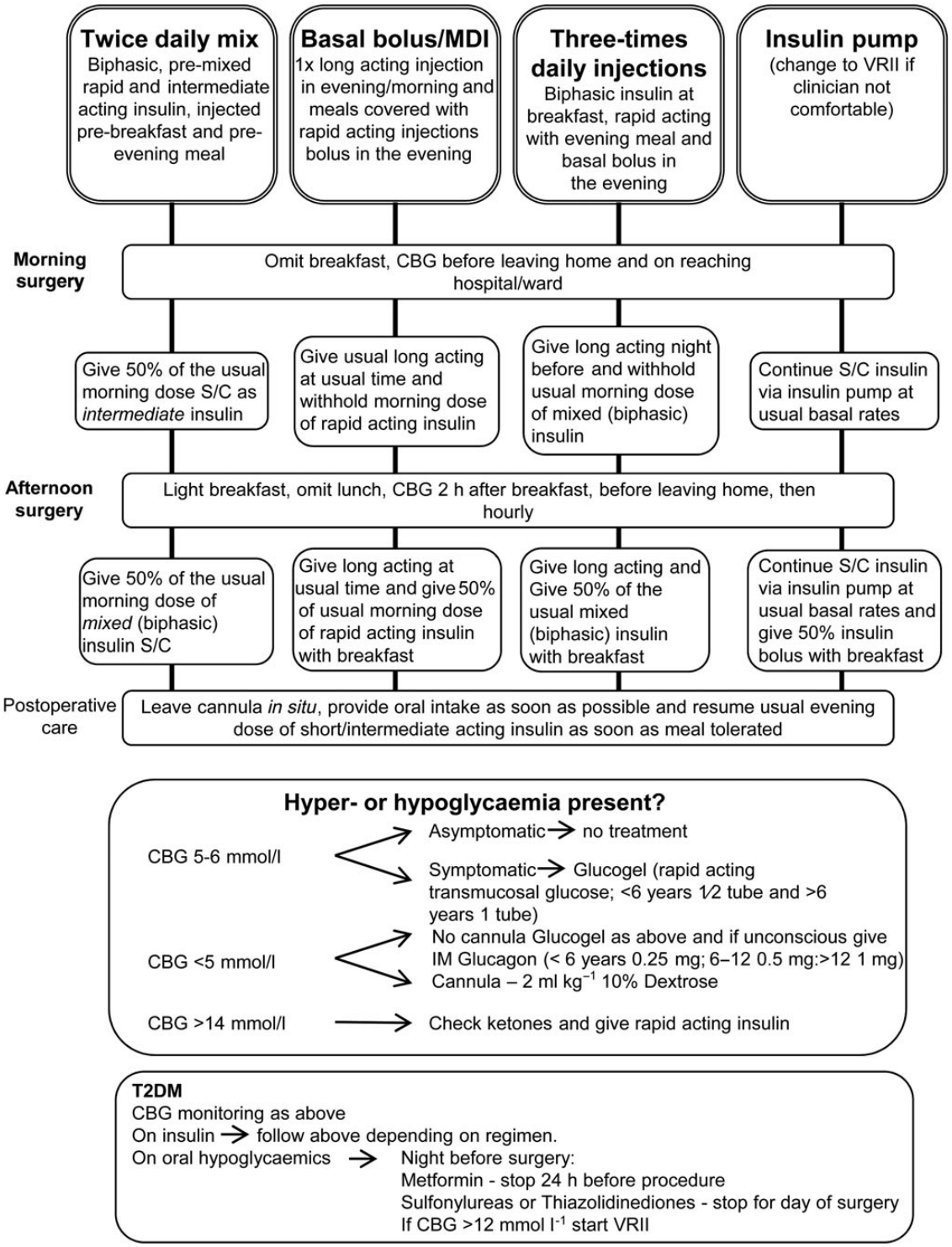

Fig 1 Perioperative care plan for patients undergoing elective surgery missing one meal (summary of points from regional and national guidelines).

of hyponatraemia, maintenance fluids should be changed to 5% dextrose in 0.9% saline with or without 0.15% KCl.

Commonly, insulin doses in VRII regimes for CAYP vary between 0.025 and 0.1 units kg^{-1} h^{-1} according to blood glucose (Table 2). It is extremely important when calculating these doses to avoid factor of 10 errors.

Modern perioperative diabetic regimes may also include calculation of an 'insulin sensitivity factor' which is a correction factor to estimate the dose of rapid-acting insulin needed to correct CBG>14 mmol $litre^{-1}$ and will vary according to the patient's (usual) daily dose of insulin.

Management for emergency surgery

These patients are generally treated with a VRII as described above. In a T2DM child, usually treated with metformin and if

Table 2 Infusion guide for surgical procedures (ISPAD 2014)[3]

Maintenance fluid guide

Dextrose

5% dextrose; 10% if there is concern about hypoglycaemia. If blood glucose is high (>14 mmol litre^{-1}, 250 mg dl^{-1}), use half-normal saline (0.45% NaCl) without dextrose and increase insulin supply but add 5% dextrose when blood glucose decreases below 14 mmol litre^{-1} (250 mg dl^{-1})

Sodium

There is evidence that the risk of acute hyponatraemia may be increased when hypotonic maintenance solutions (i.e. <0.9% NaCl) are used in hospitalized children. Many centres, therefore, use saline 0.45–0.9% (77–154 mmol Na litre^{-1}). A compromise would be to give 0.45% saline with 5% dextrose, carefully monitor electrolytes, and change to 0.9% saline if plasma sodium concentration is decreasing

Potassium

Monitor electrolytes. After surgery, add potassium chloride 20 mmol to each litre of i.v. fluid. Some centres add potassium routinely only if infusion is required for more than 12 h

Example of calculation of maintenance requirements

Body weight (kg) fluid requirement per 24 h

For each kilogram between 3 and 9: 100 ml kg^{-1}

For each kilogram between 10 and 20: add an additional 50 ml kg^{-1}

For each kilogram more than 20: add an additional 20 ml kg^{-1} (maximum 2000 ml female, 2500 ml male)

Insulin infusion

Add soluble (regular) insulin 50 units to 50 ml normal saline (0.9% NaCl), making a solution of 1 unit insulin ml^{-1}; attach to syringe pump and label clearly

Start infusion at 0.025 ml kg h^{-1} (i.e. 0.025 units kg h^{-1}) if blood glucose is <6–7 mmol litre^{-1}, 0.05 ml kg h^{-1} if 8–12 mmol litre^{-1}, 0.075 ml kg h^{-1} between 12 and 15 mmol litre^{-1}, 0.1 units kg h^{-1} if >15 mmol litre^{-1}

Aim to maintain blood glucose between 5 and 10 mmol litre^{-1} by adjusting insulin infusion hourly

Blood glucose must be measured at least hourly when the patient is on i.v. insulin

Do not stop the insulin infusion if blood glucose <5–6 mmol litre^{-1} as this will cause rebound hyperglycaemia. Reduce the rate of infusion

The insulin infusion may be stopped temporarily if blood glucose is <4 mmol litre^{-1} but not >10–15 min

this was taken <24 h before emergency surgery, perioperative i.v. fluids should be administered to maintain hydration and diminish the risk of lactic acidosis.

In the presence of DKA, correction of hydration, electrolyte, and metabolic parameters should occur before anaesthesia if possible, accepting that control is unlikely to be perfect and that some surgery must proceed with intensive intraoperative monitoring and care (see below).

Management of diabetic emergencies including DKA

Hypoglycaemia may be asymptomatic in individuals with a lack of awareness, such as young children and in poorly controlled diabetics. Symptoms and signs depend on age but relate to autonomic involvement (sweating, pallor) and neuroglycopenia (headache, confusion, lethargy, blurred vision, instability with walking, irritability, and combativeness). Its management is addressed in Figure 1.

As in adults, DKA occurs when counter-regulatory hormones are overwhelmingly high in the presence of absolute or relative insulin deficiency. The biochemical criteria for diagnosis are hyperglycaemia, acidosis, and ketonaemia or ketonuria. The blood glucose may not be particularly high initially (blood glucose >11 mmol litre^{-1}), but in association with acidosis (venous pH <7.3 or bicarbonate <15 mmol litre^{-1}) and ketonaemia/ketonuria, this may be indicative of DKA when it presents in the context of a typical clinical picture.

The management of DKA in children is covered in depth in a previous *CEACCP* article.[8] National and international guidelines[9,10] emphasize reducing the risk of cerebral oedema, which occurs in up to 1% of childhood DKA episodes but carries a very high mortality of ~25%. Younger children have less well-developed cerebral autoregulatory mechanisms and relatively less space in the skull vault, so are at particular risk of developing cerebral oedema, as are those presenting with severe metabolic derangement and dehydration.[11] Guidelines advocate less aggressive rehydration, caution in over-estimating fluid deficits, replacing deficits over the first 48 h, avoiding hypotonic i.v. solutions, particularly in the first 24 h by using 0.9% saline with or without dextrose, and introduction of a low-dose insulin infusion only after an hour of rehydration to prevent significant changes in osmolality. Correction of dehydration, glucose levels, and acid–base balance should take place very cautiously over 48–72 h.

Postoperative care

As in all situations adequate analgesia should be ensured, as this is likely to reduce the catabolic response to surgery. Prevention and active management of nausea and vomiting is also essential to enable the child to resume eating and drinking. The usual diabetic regimen should be recommenced as soon as the child tolerates normal oral intake. I.V. fluid may need to be continued or started in those unable to eat or drink. If CBG levels show a downward trend, 5% dextrose in 0.45% saline containing 0.15% KCl is recommended and CBG should continue to be monitored hourly. When the child is well enough for discharge, having eaten a normal meal and restarting their normal insulin regime, clear instructions should be given to guide future food and fluid intake, and continued administration of insulin. Closer CBG and possibly ketone monitoring is required for the next 24–48 h and especially if the child is feeling unwell. Symptoms and signs are more difficult to interpret in the pre-school child or, for example, due to postoperative pain, distress, and sedation. Families should have 'open access' if they feel re-admission is required and this should be made clear to them at discharge, particularly after day-case surgery.

Summary

Children and young people with diabetes commonly present for both routine and urgent surgery and procedures under general anaesthesia. While the focus is on improved long-term daily blood sugar control and routine insulin regimes are increasingly complex, the aim in the perioperative period should be (as in adults) to maintain normoglycaemia, prevent complications, and return to normal diet and maintenance therapy as soon as possible.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Anaesthetist's guide to the Coroner's Court in England and Wales

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Key points

- Coroners are independent judicial officers and have significant powers to request statements, call witnesses, and request post-mortems to fulfil their statutory duties.
- Anaesthetists are likely to be called to give evidence at an inquest at some point in their career.
- The new Coroner's Act provides scope for investigation of deaths rather than having an inquest.
- Closer scrutiny of deaths will lead to increased investigation and potentially more inquests.
- Advice and help is available from hospital legal teams and medical defence organizations.

Coroners have been part of the English Legal System since 1194 and have evolved from being a form of mediaeval tax gatherer to an independent judicial officer charged with the investigation of sudden, violent, or unnatural death. In the last 800 yr, the role of the coroner has changed substantially culminating in The Coroners and Justice Act 2009 (enacted July 2013). This is the result of many reports leading to fundamental reform of the Coronial service (Table 1). The reforms were instigated following the Luce report 2003[1] and the Shipman inquiry (The Shipman Inquiry) led by Dame Janet Smith. Coronial reform has been on the political agenda for many years but the UK's financial situation delayed the implementation. This article will update anaesthetists with the information needed to understand the reforms and to be able to understand what will be required if called as a witness at an inquest.

The new legal framework will ensure all 96 coronial jurisdictions in England and Wales will work to the same standards, ending the past inconsistencies of practice that led to criticisms of a postcode lottery with bereaved people in some areas facing long delays for inquests.

Coronial services are now being overseen by the first Chief Coroner of England and Wales, His Honour Judge Peter Thornton QC, and will be locally delivered to a framework of national standards designed to produce a more efficient system of investigations and inquests.

Who is a coroner?

There are 32 full time salaried and approximately 70 part-time Coroners in England, Wales, and Northern Ireland. A Coroner is a solicitor, barrister, or doctor of at least 5 yr standing. The majority (85%) are from a non-medical professional background. A Coroner appoints a deputy who can act in his/her place if they are unavailable. To become a senior Coroner it is usual to have been an Assistant or Deputy first. The new legislation will change the numbers of full time and area Coroners and jurisdictions will be amalgamated to streamline the service. Part of the new Coronial rules means that doctors can no longer be appointed as senior or assistant Coroners. The act also includes the introduction of a medical examiner system that would review all hospital deaths before the Coronial investigation starts. However, this has not been implemented to date.

A Coroner is a completely independent judicial officer who although employed, funded, and paid by local government, is not answerable to any authority except that of the Chief Coroner and the Lord Chancellor. Although decisions are open to Judicial Review only the Coroner is able to adjudicate on factual matters and their judgements can only be judicially reviewed by the High

Table 1 Key points from the Coroners and Justice Act 2009

Speed up the release of bodies after post-mortem. Coroners will be required to notify the deceased's next of kin or personal representative if the body cannot be released within 28 days
Permit less invasive post-mortem examinations
Require inquests to normally be completed within 6 months of the date on which the Coroner is made aware of the death
Require the Coroner to notify the bereaved within a week of setting the date for the inquest
Require the Coroner to report any cases that last more than a year to the Chief Coroner, and give reasons for any delays
Provide greater access to documents and evidence, such as post-mortem reports, before the inquest takes place
Provide new training requirements for Coroners

Table 2 Deaths that should be referred to the Coroner

Deaths that are violent or unnatural
Deaths related to trauma
Deaths related to self-harm, intentional or not
Related to neglect or failure of care by another person
Occurred as a result of poisoning, use of a controlled drug, medicinal product, or toxic chemical
When the identity of the deceased is unknown
Deaths of an unknown cause
Deaths in custody or otherwise in state detention, even of natural causes
Occurred as a result of a notifiable accident, poisoning or disease
Death as a result of anaesthesia or failure to recover from an anaesthetic

or Supreme Courts if there has been an error in interpreting the law. This ensures transparency and unbiased judicial decision but creates a tension surrounding Coronial accountability. The new act provides for a framework of legislation but the Coroner still has significant autonomy to decide the key facts and evidence in the case he/she is hearing.

Background

Up to 47% of all deaths in England and Wales are referred to a Coroner (UK Ministry of Justice. Coroners statistics England and Wales 2010). Some 222 371 deaths were reported to Coroners in 2011, a decrease of 8224 (3.6%) from the 2010 figure. Inquests were opened on 30 981 deaths, representing nearly 14% of all deaths reported. In England and Wales, Coroners are required, by law, to hold an investigation or inquest into violent, unnatural, sudden deaths of unknown cause, and those deaths that occur in prison or police custody. Many deaths reported for Coroners' investigations are now concluded without an inquest being held. The Coroner will have satisfied him- or herself, by means of a post-mortem examination or other investigation of the cause of death and there is no requirement to hold an inquest (Coroners Act 2009 part 1). This is a new power given formally to the Coroner in the new Act.

The Coroner is increasingly expected to look closely into hospital deaths as politicians and healthcare professionals strive towards achieving higher standards of care under increasing public and media led scrutiny. With the publication of the Francis report[2] and the recent publicity following the mortality review[3] carried out by the NHS Medical Director, Sir Bruce Keogh, it is likely that Coronial investigations, not necessarily inquests, will be more common and thorough.

Enquiries and investigations

An enquiry starts when the Coroner is notified of a body being within their jurisdiction and the Coroner will open a formal investigation or inquest if necessary. Coroners have the power to order a post-mortem examination if they feel this may shed any light on a death [Coroners Act 2009 S14(1)(b)]. Once an investigation or inquest has concluded the Coroner notifies the Registrar of the cause of death so that the death can finally be formally registered. Interim certificates are issued to allow for funeral or cremation if an inquest or investigation has been opened.

Which deaths must be referred to the Coroner?

The reasons for deaths to be reported to the Coroner are summarized in Table 2. Deaths that occur in the intensive care unit do not necessarily need to be referred but some of the causes may be applicable to critical care practice and would require referral. Discussion of the case with the Coroner or Coroner's officer would be prudent if there is doubt. Death after anaesthesia and 'on table' deaths should certainly be referred to the Coroner. Failing to recover from an anaesthetic is more difficult to define. Post-operative ventilation would mean that the patient had not 'recovered' but the legal definition is unclear. The prudent course would be to discuss the case and if in doubt refer to the Coroner for guidance.

What is the purpose of a Coroner's inquest?

The Coroner is looking to establish the answers to four main questions: who the deceased is and where, when and by what means the person died [Coroners Act 2009 s5(1)]. The inquest is held in the public interest and not for the benefit of any individual. These four questions give a Coroner wide scope to investigate as he or she sees fit. Specifically and crucially it is not to establish findings of blame or responsibility for the death. It can be easy for an anaesthetist attending an inquest to forget this and feel that they are going to be held to account for a death that they may well have done everything possible to prevent. The Coroner is not allowed, by law, to find any civil or criminal liability against a person or an organization.

Who is present in a Coroner's Court?

The court is a public hearing and anyone can attend. The Coroner, Coroner's officer, sometimes a jury, properly interested persons and their legal teams, witnesses, expert witnesses the media and general public can all be present.

A 'properly interested person' (PIP) is determined by law and with the new act gives a wider definition. A PIP will be confirmed as such by the Coroner and can be anyone, from the parent of a deceased child to the insurer of the deceased. A PIP can nominate friends to ask questions on their behalf (sometimes referred to as a 'McKenzie friend'). A McKenzie friend is somebody who accompanies a person to a court hearing for the purpose of assisting him/her in such matters as taking notes, helping to organize the documents, and quietly making suggestions (e.g. as to questions to put to a witness). Although the introduction of McKenzie friends was initially related to the family Court their use has been expanded to the Coroner's court as well as not all PIPs have legal representation, although some may have a solicitor or barrister to advise them. They have particular rights that are enshrined in the new act[4].

The county council employ Coroner's officers. Their role is to do much of the detailed administrative groundwork and investigation behind a case, as well as ensuring the smooth running of an inquest.

Anaesthetic and intensivist involvement in the Coroner's Court

It is likely that most anaesthetists and intensivists will be required to attend the Coroner's Court at least once in their career for a variety of reasons. For example, if a patient dies during an operation, within 24 h of admission to hospital (e.g. after a trauma call), where they have been involved in resuscitation efforts or a patient from the intensive care unit who dies will all be referred for investigation. Although not all ITU patients must be referred to the Coroner the likelihood is that with a significant number of the cases requiring critical care succumbing to sudden, unexpected, or violent death a large proportion will need to do so. As an anaesthetist you may be called as a witness of fact, or as an expert witness. You may be required to write a report, and can be questioned by the Coroner, the PIPs or their legal team. Although you may be cross examined you do not have to answer any question that might incriminate you and the Coroner will control the questions you are asked if they seem irrelevant or outside the scope of the inquest.

An *expert witness* is an independent expert, instructed by the Coroner, to prepare a report and give an opinion on a case to help the Coroner reach a verdict. An expert witness will not have been involved directly with the clinical management of the case he/she is providing comment upon. A 'witness of fact' or *professional witness* will have been directly involved with the case in hand and is giving evidence not opinions as to causation. All witnesses are summonsed to the Court and attendance is mandatory. Failure to attend is a criminal offence.

Who can assist you?

In most cases the hospital legal team will be your first port of call. Medical defence organizations such as the MPS and MDU have information sheets available to read[5]. The Ministry of Justice also produces a helpful guide to Coroners and Inquests (Ministry of Justice, Coroners and Burials Division, A guide to Coroners and Inquests, January 2010). The MDU/MPS may represent doctors at Coroner's inquests depending on the circumstances, especially if the reputation of a doctor or individual criticism is likely from relatives of the deceased.

It is vital to make contemporaneous notes of any events in which you are involved particularly if a death is likely to be reported to the Coroner and that the anaesthetic record is fully completed. It is advisable to also ensure that you retain copies of the relevant medical notes and the anaesthetic record. These should be stored in the hospital that the death occurred in to reduce the risk of breach of confidentiality. These actions will make any subsequent request to give evidence at an inquest much easier. Fifty per cent of cases are heard within 8 months, however some cases may not be heard until 2 or 3 yr after the death and a lack of good notes can make giving evidence extremely stressful. The adage 'if it is not written down you didn't do it' runs true and good documentation is crucial.

Preparing a report

This is best done with advice from the hospital's legal experts or from one of the medical defence organizations. It needs to be clear and well set out in numbered paragraphs. The report should confine itself strictly to the facts of the case and should not contain your personal opinions or suppositions. In addition your comments should not attribute blame to any individual or organization. Remember that your report may be used as evidence in any further legal action that may subsequently arise.

What happens at the inquest?

Once summoned to a Coroner's inquest, you must attend. Before the inquest read the case notes paying particular attention to your own documentation and reports. Even with prior preparation, appearing in front of a Coroner is stressful. However it is important to remember that even if a person is suspected of causing the death they will be protected by the Coroner from answering any question that may incriminate them (Coroners Act Rule 22 against self-incrimination). It is also important to remember that the Coroner's Court is convened to find the facts surrounding a death. It is not an adversarial trial and hence should not be confrontational.

The Coroner decides who is to be called and what order they will appear during the proceedings. All witnesses give evidence under oath. Witnesses are permitted to read from a statement and are allowed to take notes to the stand. Witnesses are first questioned by the Coroner, and then by anyone with a 'proper interest' in the case, either directly by them, or by their legal team. Questions should be sensible and relevant to establishing the facts surrounding the death. This will be guided by the Coroner who will prevent any non-relevant questions being asked.

The correct way to address a Coroner is Sir or Madam and on answering any questions all responses should be directed to them. You must answer honestly and concisely and answer only what is asked. Keep medical jargon out of your answers and speak slowly and clearly. The Coroner might not be able to understand your technical explanation and the relatives almost certainly will not!

What are the potential verdicts in a Coroner's Court?

After hearing the evidence, the Coroner has a range of findings that he may issue as to the cause of death. He/she can essentially draw any conclusions he/she wishes depending on the evidence but potential verdicts are summarized in Table 3.

Death by *natural causes* is the verdict if the evidence shows that it is 'probable (i.e. more likely than not) that the cause of death was the result of a naturally occurring disease process running its [full] course' ('Coroners and the Investigation of Deaths' Appendix C)[6]. To bring a verdict of *suicide* the Coroner has to be sure beyond reasonable doubt (i.e. the criminal level of proof that the person intended to take his or her own life).

An *open verdict* is reached when there is not enough evidence to know the exact cause of death. A *misadventure* verdict shares many similarities with an accidental death. One distinction is where a person deliberately undertakes a course of action that results in death, rather than inadvertent action causing the death. Medical misadventure is when the death has occurred because a known complication or event has occurred and the risks were known and had been discussed.

A *narrative verdict* is simply a recording of how the deceased met his death[7] and gives more detail of the circumstances surrounding the death and the conclusions reached in arriving at the verdict. A narrative verdict may apportion blame to a

Table 3 Potential verdicts issued by the Coroner

Natural causes
Suicide
Accidental death
Unlawful or lawful killing
Death due to an industrial disease (e.g. asbestosis)
Open verdict
Narrative verdict, including medical misadventure or contributed to by neglect

hospital/institution (e.g. the verdict of 'gross neglect' which has been applied in some recent cases).

Unlawful killing is a verdict that can be brought but still must not name the possible culprit. All elements of manslaughter must be proved to the criminal standard for a conclusion of unlawful killing. This finding will normally not be used in the Coroner's Court as it directly apportions blame to an individual. The case of Adomako [R v Adomako (1995) 1AC 171 HL] illustrates the gross negligence verdict of an anaesthetist in a criminal setting. The anaesthetist took over a case and did not notice that the ventilator tubing had become disconnected. The patient died due to this error. The error and omission was so gross that it amounted to negligence rather than a simple error. A finding of gross negligence can apply if an institution rather than an individual is to blame. Further information can be found in any medical law textbook.

If the Coroner concludes that there is a potential for the same cause of death to occur again and that this is preventable he/she is empowered to write a letter to draw public attention to this to some authority, such as a hospital Trust or other public body. This is called a rule 28 report (previously known as a rule 43 report). Anyone who receives such a report must send a written reply to the Coroner stating what is being done to prevent the same circumstances recurring within 56 days unless the Coroner allows an extension to this time limit. The majority of rule 28 reports occur after inquests. It is mandatory for the organization or individuals named in the report to respond within the stipulated period. A review of these reports demonstrates that the major issues contributing to investigated deaths in hospital to be inadequacies in staff training, absence of defined procedures and protocols or failing to follow such procedures and protocols, deficiencies in record keeping, and concerns about communication between healthcare professionals. Copies of all these recommendations and responses are sent to the Chief Coroner each year and are available online.

Scotland, Republic of Ireland, Australia, and New Zealand

In Scotland, the Crown Office and the Procurator Fiscal (PF) Service is responsible for investigating sudden and unexpected deaths. There are 11 PFs in Scotland. Once a crime or death occurs, agencies such as the police commence an investigation and report to the PF who decides if it is in the public interest and if there is any evidence to take further action via a *fatal accident enquiry* (which is a form of inquest unique to the Scottish legal system). The PF may decide to prosecute, impose a fiscal fine, or to take no further action. They report to the Sheriff, District, and Justice of the Peace courts.

The Irish Coroner's system has many similarities to the English and Welsh system. Irish Coroners are assisted by Garda Síochána in their investigative duties. Australia and New Zealand also run Coronial services, which are based on the UK system.

Conclusions

The Coronial system although ancient in its premise is still highly relevant today. Recent constitutional developments provide for a stronger role for Coroners and aim to encourage a more standardized and fair Coronial system in England and Wales, with a Coroner's Charter for relatives. With the increasing emphasis on quality of patient care and closer scrutiny of practice, it is likely that anaesthetists and intensivists will be called as witnesses in more cases referred to the Coroner. Although this can be stressful, a good knowledge of the case, the procedural system, and close liaison with the hospital's legal team will help. Crucially, good knowledge and understanding of this aspect of the legal system and the role of the Coroner will help considerably with any forthcoming witness testimony required of a doctor.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

Podcasts

This article has an associated podcast which can be accessed at http://www.oxfordjournals.org/podcasts/ceaccp_16.04.01.mp3.

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Platelets for anaesthetists—part 1: physiology and pathology

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Key Points

- Platelets in circulation are anucleate structures.
- Adhesion of platelets is the primary step in the platelet haemostasis followed by platelet activation and platelet aggregation.
- Von Willebrand disease is the most common inherited bleeding disorder.
- There are several tests available to diagnose qualitative platelet disorders and a haematologist should be consulted for advice on these patients and their management.
- An understanding of platelet physiology is essential to have an insight into perioperative haemostasis and the mechanism of action of antiplatelet agents.

Platelets are essential in the maintenance of haemostasis. Understanding the basic physiology of platelet function will enable anaesthetists to have an insight into the management of haemostasis in the perioperative period. This review will focus on basic physiology, testing, and disorders of platelet function.

Platelet production

Pluripotential haematopoietic stem cells present in bone marrow undergo differentiation into megakaryocytes. The platelets are released into the circulation by the fragmentation of megakaryocytes. Each megakaryocyte can produce 1000–5000 platelets. Various factors influence the production of platelets but the whole process is regulated such that the platelet count stays between 150 and 450×10^9 litre^{-1}. The most significant factor in the proliferation, differentiation, and maturation of megakaryocytes is thrombopoietin (TPO).[1]

TPO is produced in liver and kidneys constitutively at a constant rate.[2] Inducible TPO[1] (a very minor fraction) is produced by spleen and bone marrow during thrombocytopenia. Once produced, the ability of the TPO to stimulate the production of platelets depends upon the number of circulating platelets. The TPO receptor present on the surface of platelets binds to the released TPO and removes it from the plasma. The higher the number of circulating platelets, the lower the TPO. But if the circulating platelets are few, more TPO will be available to stimulate the production of platelets.[1] Approximately 100 billion platelets are produced every day.[3] About one-third of the total circulating platelets are stored in splenic sinusoids and are released into the circulation if necessary. The normal life span of platelets is ~10 days and influenced by the balance of pro- and anti-apoptotic factors in the platelet.[1]

Platelet structure

Platelets are small structures of ~2–4 μm diameter. As they are anucleate they cannot synthesize any new proteins. All the proteins stored in platelets are synthesized by the megakaryocytes and are packaged into granules to be released by the platelets into the circulation. If an antiplatelet agent irreversibly blocks

Table 1 Constituents of dense granules and alpha granules

Dense granules	α-Granules
ADP	Von Willebrand factor
Serotonin	PDGF, VEGF, TGF-b
ATP	Fibrinogen
Calcium	Platelet factor 4
Histamine	Fibronectin
Catecholamines	Thrombospondin
Various other platelet agonists	Various coagulation factors
	Vitronectin

Table 2 Glycoproteins and their ligands

Glycoproteins	Ligands
GP IIb–IIIa complex	Fibrinogen
GP Ib-IX–V complex	Von Willebrand factor
GP VI	Collagen
GP Ia–IIa	Collagen
GP Ic–IIa	Laminin, fibronectin

any of the protein receptors, the receptor will lose its function for the rest of the lifespan of that platelet. Apart from various cellular contents like mitochondrion, lysosomes etc., the two most important components in platelets are the α-granules and the dense granules[1] (Table 1).

Dense granules are ~3–8 in number per platelet.[3] These mainly contain mediators that recruit new platelets and activate more platelets. Upon stimulation these mediators can be released into the system very quickly.

α-Granules are ~50–100 in number per platelet.[3] These mainly contain various membrane receptors and proteins required for adhesion, aggregation, and coagulation.

Platelet membrane invaginates into the cytoplasm at various points to form an extensive canalicular system, which provides a large surface area on which membrane receptors and proteins are stored. This system helps the platelets to transform into various shapes and sizes during activation. They also form a membrane network called the dense tubular system which is a storage compartment for calcium and also a site for prostaglandin synthesis.[1]

Platelet receptor glycoproteins

The receptor glycoproteins are attached to the plasma membrane. Some glycoproteins are normally expressed and are attached to the surface, while other glycoproteins are attached to the canalicular system inside the platelet surface; they are then moved to the surface on platelet activation. Most of the surface receptors are in a form of complex with 2–3 glycoproteins. The major glycoproteins and their ligands are shown in Table 2.

Role of platelets in haemostasis

Platelets are pivotal in haemostasis. During the normal laminar blood flow in blood vessels, platelets tend to occupy the peripheral part of the blood column. This way they come in contact with any vessel injury relatively quickly and start the haemostatic process. Endothelium, which lines the vessel wall, is a crucial barrier in separating platelets and potent prothrombotic factors (collagen and subendothelial matrix) underneath the endothelium. In addition, the endothelium actively inhibits platelet activation by the production of prostacyclin and nitric oxide.

Within the haemostatic plug, platelets exist in predominantly two states of activation (fibrin coated and aggregating) caused by differences in local rheology, exposure to agonists, and anatomical factors, complicated by the presence of platelets in various stages of apoptotic activation.[4]

Platelet adhesion

An injury to the vessel wall exposes platelets to the subendothelial matrix. Platelets immediately attach to the exposed collagen on the injured vessel wall via the collagen receptor (GPVI). Platelets then undergo a change in shape and bind to the vessel wall. This may be sufficient under low shear conditions. For vessels with high shear conditions, Von Willebrand factor (VWF) is essential for the stabilization of the platelet adhesion.[1]

VWF is a large multimeric protein that is synthesized by the endothelium and megakaryocytes. The synthesized VWF is either released into circulation or stored in the Weibel–Palade bodies of endothelium and in the α-granules of platelets.[1] VWF essentially has two main functions: (i) it acts as a carrier protein for the circulating factor VIII and prevents it from proteolytic degradation; and (ii) it assists in platelet adhesion at the site of injury. When there is an exposure of subendothelial matrix, VWF binds to the collagen to create scaffolding for the platelets to adhere to them. The GP Ib-IX–V is the receptor that binds the platelets to the VWF.[5] In order for the GP Ib-IX–V receptor to bind with the VWF, the VWF should have already been bound to the collagen. Circulating VWF has a coiled structure, concealing the platelet-binding site. With subendothelial damage and consequent collagen exposure, VWF changes its shape, exposing the platelet-binding site to which platelets bind, via the GP Ib-IX–V receptor. This VWF–platelet binding is stabilized by the binding of GP VI receptor to the collagen or subendothelial matrix directly (Fig. 1). GP Ia–IIa receptor stabilizes this VWF–platelet binding in high shear conditions.

Platelet activation

The binding of platelets via GP Ib-IX–V with the VWF and GP VI receptors to the collagen stimulates a cascade of reactions releasing various mediators leading up to platelet activation (Fig. 2).

(i) Thromboxane A2: the activation of the cyclooxygenase system leads to the release of arachidonic acid from the platelet membrane and the formation of thromboxane A2 (TXA_2) in platelets. Platelets produce TXA_2 predominantly because they express more of thromboxane synthetase enzyme when compared with prostacyclin (PGI_2) synthetase. On the contrary, the endothelial cells produce PGI_2 (which inhibits platelet aggregation) as they express more of the PGI_2 synthetase. TXA_2 is a potent vasoconstrictor and activates further platelets present in the vicinity by binding to a thromboxane (TP) receptor (a G-protein-coupled receptor) present on the surface of platelets. Binding to the TP receptor leads to activation of phospholipase C which cleaves the phospholipid phosphatidylinositol 4,5-bisphosphate (PIP_2), present in the platelet membrane, leading to formation of diacyl glycerol (DAG) and inositol triphosphate (IP_3).[6] IP_3 causes the release of calcium ions stored in the dense tubular system. Both DAG and cytoplasmic calcium activates protein kinase C which causes protein phosphorylation and further degranulation of α- and dense granules.

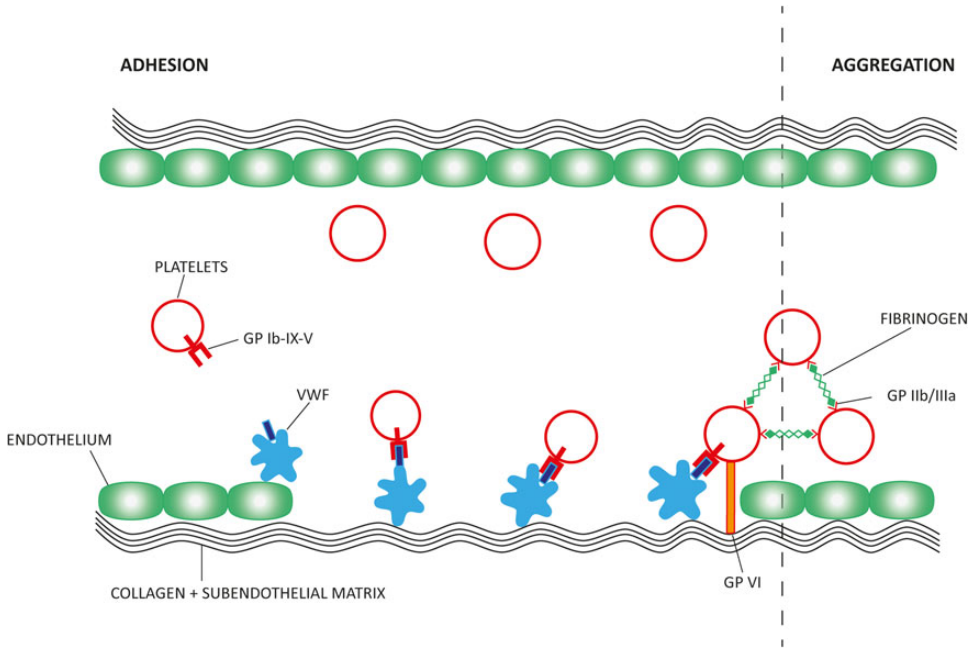

Fig 1 Schematic representation of platelet adhesion.

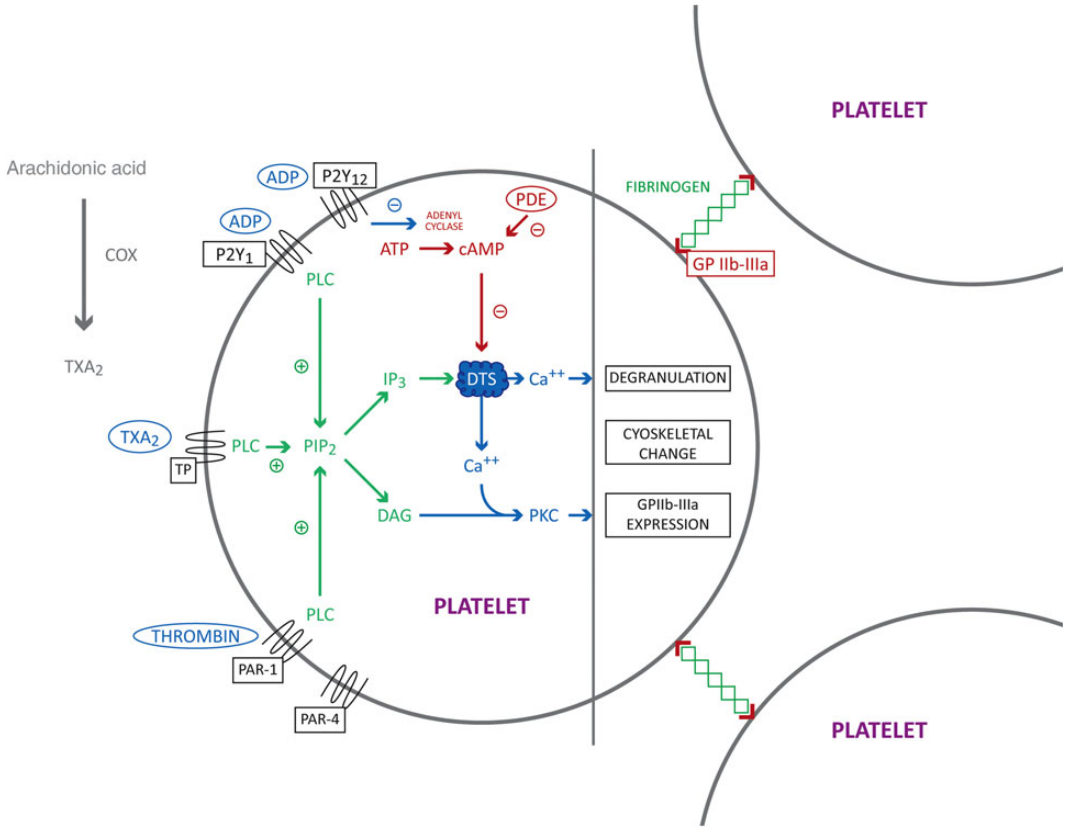

Fig 2 Platelet activation and aggregation. ADP, adenosine diphosphate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; COX, cyclooxygenase; DAG, diacyl glycerol; DTS, dense tubular system; IP_3, inositol triphosphate; PAR, protease activated receptor; PDE, phosphodiesterase; PIP_2, phosphatidylinositol 4,5-biphosphate; PKC, protein kinase C; PLC, phospholipase C.

(ii) Adenosine diphosphate (ADP). ADP stored in the dense granules is released upon initial activation of the platelets and they bind to the ADP receptor $P2Y_{12}$ predominantly and also to another ADP receptor $P2Y_1$ present on the surface of platelets. For a maximal response both the receptors have to be activated by ADP.[7] $P2Y_{12}$ receptors belong to the Gi group

of G-protein-coupled receptors. Binding of ADP to this receptor causes inhibition of adenylate cyclase resulting in decreased levels of cAMP enabling further release of calcium ions from the dense tubular system. $P2Y_1$ receptors belong to the Gq group of G-protein-coupled receptors. Binding of ADP to this receptor causes degranulation and activation of various other proteins through the phospholipase C pathway as described above.

(iii) Thrombin: thrombin generated through the coagulation pathway binds to the surface of platelets through PAR (protease activated receptor)—mainly PAR-1 and PAR-4 receptors.[6] The PAR is also a G-protein-coupled receptor having a similar second messenger system to the $P2Y_1$ receptor.[4]

Activated platelet

Platelet secretion occurs through receptor activation of some platelet and paracrine activation then triggers a chain reaction of further platelet activation. The platelet secretion varies within the haemostatic plug and can include the release of α-granules, dense granules, and lysosomal enzymes.[4] Phosphorylation of the proteins present in the cytoskeleton of platelets leads to a change in the shape of the platelets for aggregation. This leads to a population of (fibrin) coated platelets, supporting thrombin generation and aggregating platelets.[4]

Fibrin coated, activated platelets promote coagulation by providing a scaffold for the various stages of coagulation cascade. The thrombin generated through this mechanism creates a cyclical positive feedback to activate more platelets resulting in the generation of huge amounts of thrombin, called 'thrombin burst'. The thrombin converts fibrinogen to fibrin to form a clot. Also platelets release various factors from its granules for the stabilization of the clot.

Platelet aggregation

Aggregating platelets are predominantly important in clot retraction and express activated glycoprotein receptors.[4] A change in shape of the platelets is the primary response of platelets to the activation by ADP or thrombin or TXA_2. This is achieved through conformational changes in its cytoskeleton.[8] The effect of ADP, TXA_2, and thrombin leads to the activation and surface expression of the receptor GP IIb–IIIa. Fibrinogen acts as a ligand in bridging two platelets via glycoprotein receptor GP IIb–IIIa. Linking of several platelets leads to platelet aggregation.

Assessment of platelet count

This is a selection of the commonly available laboratory tests to help quantify platelet function. Current methods are designed to detect reduced platelet function with no consensus with regard to the interpretation of occasionally apparent increased platelet function. All functional methods become invalid when the platelet count is critically reduced with the thresholds varying between the different methods. Other than the full blood count a haematologist should be consulted to request and interpret the more differentiated platelet function tests.[9]

Full blood count

Platelets can be assessed by automated Coulter count which uses the changes to electric conductivity induced by platelets passing through a narrow channel to measure platelet size and number (impedance).[10] This method is universally available but can be flawed if there is artifactual platelet clumping (EDTA or other anticoagulant induced).[11] Where the patient is found to have an abnormally low platelet count that is unexpected this should be confirmed with a blood film. Where there is platelet clumping this should be discussed with the laboratory as an alternative anticoagulant such as citrate or ThromboExact® (Sartstedt, Sarstedt, Germany) and minimizing the time delay for the sample to get back to the laboratory may help overcome this.

Where platelets are unusually large the Coulter counters may be unable to quantify the number of platelets and a flow cytometry-based count may be helpful such as in gestational thrombocytopenia or some forms of idiopathic thrombocytopenic purpura.[12]

Assessment of platelet function

Light transmission aggregometry

This method is labour intensive and not well standardized and so should not be requested without the help and advice of a haematologist. In addition, it is the mainstay of the assessment of congenital platelet dysfunction and Von Willebrand disease (VWD).[9]

Point of care methods

PFA 100. The PFA 100® (Siemens, Frimley, UK) is a flow chamber-based test that assesses the time taken for whole blood to form a clot over a small opening in a membrane within a cartridge, in the presence of different agonists and collagen (e.g. epinephrine, ADP). It has been shown to be sensitive enough to detect some forms of VWD but is poorly predictive in some cases of platelet dysfunction and is therefore not routinely used. It is potentially useful in the assessment of haemostatic treatments such as DDAVP but caution is advised in its interpretation and ideally should be accompanied by haematological advice.[13]

Multielectrode aggregometry. Multielectrode aggregometry (MEA) (Multiplate®, Roche, Rotkreuz, Switzerland) is a technology that uses electrical impedance in whole blood after exposure of the patients' blood to specific platelet agonists. It is rapidly available and potentially at the point of care. As it is an open system, it can potentially be adapted to be used with a wide variety of platelet agonists. It is much more rapid than light transmission aggregometry as it can use the whole blood, however it is also more sensitive to changes in platelet count over time.

Its main application has been in assessing the patient's response to aspirin or clopidogrel. It is not validated to predict a clinical bleeding phenotype but its use is advocated by a number of experts in the perioperative setting.[14]

Platelet mapping. Thromboelastography (TEG) (Haemonetics®, Niles, NY, USA) can be modified to make the clot formation reaction dependent on the action of platelets in response to specific agonists such as ADP or arachidonic acid. There have only been a limited of number of studies and the test is not validated to predict a bleeding phenotype.[15]

Verify now. Verify now® (Douglasville, PA, USA) is a closed system that allows the assessment of platelet aggregation response to ADP and arachidonic acid and its use is therefore limited to assessment of aspirin or clopidogrel on patients. It is insufficiently validated to predict a patient's bleeding phenotype.

Flow cytometry. Flow cytometry can measure the response to ADP or the cell surface expression of markers of platelet activation.

Table 3 Causes of thrombocytopenia

Decreased platelet production	Increased platelet destruction
B12, folic acid deficiency	Immune related
Drugs	Idiopathic thrombocytopenic purpura
Bone marrow failure	Autoimmune diseases
Cancer, leukaemia, radiation	Infection—HIV, Dengue
Aplastic anaemia, Myelodysplastic syndromes	Drugs—Heparin, Post transfusion purpura
Infection—HIV	Non immune related
Myeloma	Disseminated intravascular coagulation
	Thrombotic thrombocytopenic purpura

Table 4 Causes of thrombocytosis

Primary thrombocytosis	Reactive thrombocytosis
Essential thrombocythaemia	Disseminated malignancy
Polycythaemia vera	Drugs
Myelofibrosis	Inflammation
Leukaemia	Surgery
	Iron deficiency
	Blood loss or haemolysis

Compared with the other assays samples are stable and dependent on assay for up to 48 h. A wide variety of different markers can be tested such as VASP or p-selectin expression. In addition, it remains a research tool. Flow cytometry-based platelet counting may be used to obtain a more accurate platelet count in patients with abnormally large platelets by using a platelet specific antibody (CD41, CD61) rather than platelet size and impedance (Coulter method) for platelet counting.

Platelet disorders

Quantitative platelet disorders

The normal platelet count is in the range 150–450 × 10^9 litre^{-1}. A platelet count of <150 × 10^9 litre^{-1} constitutes thrombocytopenia. Thrombocytopenia can be either due to decreased production or increased destruction of platelets as illustrated in Table 3. Other causes of low platelet count include increased platelet sequestration by the spleen due to hypersplenism and dilution of the blood volume by massive blood transfusion.

Treatment

Treatment was primarily aimed towards the management of the underlying cause. The options include platelet transfusion, immunosuppression with steroids, immunoglobulin, TPO stimulation with TPO agonists (romiplostim, eltrombopag), discontinuation of suspected drug or plasma exchange

High platelet count—thrombocytosis

High platelet count can either be due to primary (essential) bone marrow pathology or a reactive process secondary to a systemic condition. Table 4 illustrates some examples of thrombocytosis.

Treatment

Primary thrombocytosis: should be treated with aspirin. Cytoreductive treatment (e.g. hydroxycarbamide) to control platelet count should be considered in liaison with a haematologist as well as extended thromboprophylaxis with new oral anticoagulants or fractionated heparin.

Reactive thrombocytosis: treatment should be directed at the underlying cause (e.g. infection, iron deficiency, or inflammation). Extended thromboprophylaxis with fractionated heparin or new oral anticoagulants and/or aspirin should be considered.

Qualitative platelet disorders

Inherited: plasmatic defects associated with platelet dysfunction

Von Willebrand disease. It is the most common inherited bleeding disorder. Not a platelet disorder in the true sense of the word, but a disorder of the chief platelet adhesion factor: VWF. Note that the platelet function is normal (with the exception of type 3 VWD).

- Type 1 VWD (most common subtype)—mild-to-moderate quantitative deficiency with balanced reduction of activity and factor level.
- Type 2 VWD—qualitative defects in VWF structure and function, characterized by a discrepancy in antigenic level and functional activity (subtypes A, B, N, and M).
- Type 3 VWD—severe balanced quantitative deficiency of VWF activity and level.

Patients with this type of VWD have normal platelet count but poor platelet function. Patients also have reduced factor VIII levels (VWF is essential for the prevention of proteolytic degradation of factor VIII), which may in severe cases prolong the of activated partial thromboplastin time (aPTT). A normal aPTT does however not exclude a bleeding tendency in the presence of a significant bleeding history.

Treatment

Treatment must be guided by a haematologist experienced in the management of haemophilia. Therapeutic options include desmopressin (DDAVP) which stimulates the release of VWF stored in the Weibel–Palade bodies of the endothelium (mainly useful in mild type 1 VWD) and plasma derived factor VIII and VWF concentrates in severe forms. At present there is no commercially available recombinant VWF concentrate.

Inherited platelet disorders

(i) Defects in adhesion: Bernard–Soulier syndrome, an autosomal recessive disorder caused by deficiency of the GP Ib-IX–V complex, causing a symptomatic macrothrombocytopenia.[12]

(ii) Defects in platelet secretion: storage pool disease, a heterogeneous group of disorders caused by either due to lack of dense granules or poor release of the mediators from the granules (aspirin-like defect). Rare forms such as the grey platelet syndrome affect the α-granules.

(iii) Defects in platelet aggregation: Glanzmann's thrombasthenia characterized by the deficiency of platelet receptor GP IIb–IIIa resulting in failure of platelet aggregation with normal platelet count.[14]

(iv) Platelet release and retraction: myosin heavy chain-9 (MYH9) defects (Epstein syndrome, Fechtner syndrome, May—Hegglin syndrome, and Sebastian anomaly)—characterized by platelet contractility defects associated with their premature release from the bone marrow, macro thrombocytopenia, and sometimes associated with hearing loss, renal impairment, and presenile cataracts.

Treatment should be discussed with a haematologist. Patients usually have a special transfusion requirement for HLA matched platelets to avoid alloimmunization. Adjuncts such as tranexamic acid, DDAVP, and optimization of plasmatic coagulation may be useful when treating or preventing excessive bleeding.

Acquired qualitative platelet disorders

Iatrogenic causes of acquired platelet disorders include the use of antiplatelet agents and extra corporeal circuits. The use of antiplatelet agents is one of the commonest causes of acquired platelet disorders. Use of extra corporeal circuits initially causes platelet activation and secretion leading to severe depletion of its granular contents on prolonged use. These circuits also cause extensive physical trauma to the platelets. Uraemia (end-stage renal disease) causes acquired defects in platelet function. The pathogenesis of the platelet dysfunction is multifactorial and complex secondary to defects in platelet adhesion, aggregation, and secretion. Patients with severe liver disease also develop platelet dysfunction due to abnormal platelet aggregation and reduced TXA_2 production.

Treatment

Direct treatment at the underlying cause. DDAVP and tranexamic acid can be useful. Seek haematological advice in complex patients.

Conclusion

The process of haemostasis is complex and platelets play a pivotal role. Understanding the physiology of platelets not only helps us in the management of perioperative haemostasis but also forms a basis for understanding the mechanism of antiplatelet agents.

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Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Platelets for anaesthetists—Part 2: pharmacology

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Key points

- Aspirin is the most widely used antiplatelet agent.
- The thienopyridine group of antiplatelet agents block platelet activation by inhibiting the adenosine diphosphate receptors.
- Good understanding of the pharmacodynamics and pharmacokinetics of antiplatelet agents provides us an insight into the perioperative management of patients with antiplatelet agents.
- Perioperative management of patients with antiplatelet agents comprises a fine balance between the risk of cardiovascular events on stopping the medication and the bleeding complications due to the continuation of the antiplatelet agent.

Platelets play a major role in the pathogenesis of atherosclerosis and thrombotic diseases. Antiplatelet agents are widely used to prevent complications of the atherosclerotic disease process. As anaesthetists, we encounter patients on antiplatelet therapy regularly and more frequently. This review describes the pharmacokinetics and pharmacodynamics of various antiplatelet agents.

Platelet activation and aggregation occurs due to the binding of various ligands and agonists to several platelet receptors. The receptors of interest in relation to antiplatelet therapy are TP (thromboxane A_2 receptor), ADP (adenosine diphosphate) receptor, PAR (protease-activated receptor), and GP IIb/IIIa receptor. TP, PAR, and ADP receptors all belong to the G-protein family of receptors. There are two types of ADP receptors, $P2Y_1$ and $P2Y_{12}$. Both $P2Y_1$ and $P2Y_{12}$ are G-protein-coupled receptors. Thrombin activates platelets via PAR receptors. There are four types of PAR, of which PAR-1 and PAR-4 are present in humans. GP IIb/IIIa receptor (αIIb/β3) is a transmembrane receptor present in the surface of platelets and belongs to the integrin group of receptors.

Aspirin

The most commonly used antiplatelet agent is aspirin, which is a cyclooxygenase (COX) enzyme inhibitor. This enzyme converts arachidonic acid to prostaglandin H2 (PGH2), which itself is a precursor for the formation of other prostaglandins, in particular thromboxane A2 (TXA2) by thromboxane synthase and Prostacyclin (PGI2) by prostacyclin synthase. TXA2 is responsible for stimulation of platelet aggregation and localized vasoconstriction, while PGI2 is responsible for inhibition of platelet aggregation and localized vasodilatation.

Cyclooxygenase enzyme exists in two isoforms, COX-1 and COX-2. COX-1 is mainly responsible for TXA2 synthesis and COX-2 is mainly responsible for PGI2 synthesis. COX-2 enzyme is abundant in endothelium and exerts its antiplatelet actions. Aspirin at low doses (75–300 mg) selectively inhibits COX-1 enzyme and is responsible for its antiplatelet actions. However, at high doses (1 g day^{-1}), it inhibits COX-2 enzyme as well. Low-dose aspirin is preferred as high doses cause increased incidence of upper gastrointestinal bleeding without an increase in efficacy (Fig. 1).[1]

Aspirin is widely used in the secondary prevention of coronary events and stroke in patients with coronary artery disease, cerebrovascular disease, and peripheral vascular disease. The important adverse event with aspirin is bleeding complications in the gastrointestinal tract. This can be reduced by co-administration of proton pump inhibitor or a H_2 blocker. Aspirin is contraindicated in children and adolescents <16 yr due to risk

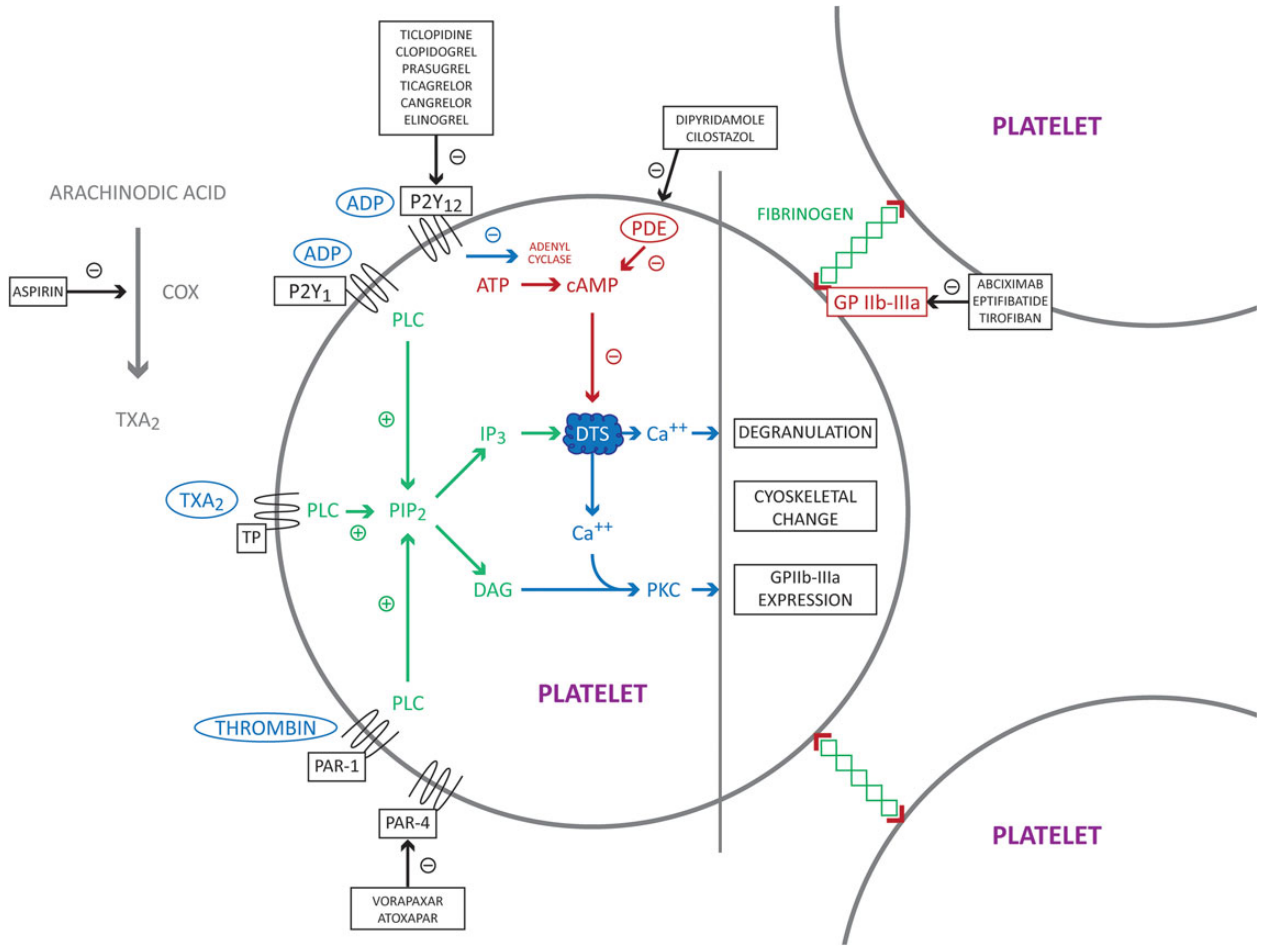

Fig 1 Mechanism of action of antiplatelet agents. ADP, adenosine diphosphate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; COX, cyclooxygenase; DAG, diacyl glycerol; DTS, dense tubular system; IP_3, inositol triphosphate; PAR, protease activated receptor; PDE, phosphodiesterase; PIP_2, phosphatidylinositol 4,5-biphosphate; PKC, protein kinase C; PLC, phospholipase C.

of developing Reye's syndrome. It should be used with caution in elderly patients and patients with asthma.

Phosphodiesterase inhibitors

Dipyridamole is pyrimidopyrimidine derivative. It prevents the degradation of cAMP by inhibiting the phosphodiesterase (PDE) enzyme. An increase in cAMP causes inhibition of platelet activation by increasing the level of calcium ions. The antiplatelet effects are also due to inhibition of adenosine uptake by platelets and other cells. Dipyridamole also inhibits PDE-5 enzyme resulting in increased levels of cGMP (cyclic guanosine monophosphate). An increased level of cGMP causes vasodilatation similar to nitric oxide.

The absorption of the oral drug is variable, but the current modified release preparations have better bioavailability. The drug undergoes extensive enterohepatic circulation with elimination half-life of 19 h.

Current indication of dipyridamole is mainly limited to the prevention of cerebral events in patients with transient ischaemic attack (TIA) and stroke. NICE (National Institute for Health and Care Excellence) recommends modified-release dipyridamole with aspirin if clopidogrel is contraindicated or not tolerated for the prevention of occlusive vascular events in patients with TIA and as second line in patients with ischaemic stroke if clopidogrel is contraindicated.

Cilostazol

Cilostazol is a PDE 3 inhibitor. Its mechanism of action is similar to dipyridamole. It is more potent than aspirin and ticlopidine. It is metabolized through a CYP3A4 enzyme system and hence prone to interaction with other drugs. Headache and hypotension due to vasodilating properties of the drug are the main side-effects, which leads to poor patient compliance with the drug. Its use is currently limited to patients with peripheral vascular disease for its vasodilating properties.

ADP receptor blocking drugs

First-generation thienopyridine: ticlopidine

Ticlopidine irreversibly binds with the $P2Y_{12}$ ADP receptor and inhibits platelet aggregation. It is very effective in reducing thrombotic events, but its use had greatly diminished because of the serious side-effects like thrombocytopenia and most importantly, neutropenia and agranulocytosis. Normally, ticlopidine is given in a twice-daily oral dose of 250 mg. It is well absorbed after an oral dose; the oral bioavailability is 80%. It is highly protein-bound. The half-life of ticlopidine is 12 h. The IPA (inhibition of platelet aggregation) is 50% in 5 days after starting the therapy. Although ticlopidine is effective in the prevention of platelet

aggregation, it is replaced by clopidogrel because of its serious side-effects. Ticlopidine is not licensed in the UK.

Second-generation thienopyridine: clopidogrel

Clopidogrel is a prodrug that requires conversion to an active metabolite by the liver for its antiplatelet effects. Clopidogrel is six times more potent than ticlopidine.[2] The active metabolite forms a disulphide bridge with the cysteine residues on the $P2Y_{12}$ ADP receptor and inhibits binding of ADP to its receptor, thereby inhibiting ADP-mediated platelet aggregation.[3] The binding of clopidogrel to the ADP receptor is irreversible and permanent for the duration of the platelets' life span (7–10 days), despite an initial drug half-life of 6–7 h. Generation of new platelets are required to restore the normal platelet physiology.

It is given as an oral loading dose of 300–600 mg followed by an oral maintenance dose of 75 mg once a day. When given a loading dose, 50–60% of IPA is achieved in 4–6 h rather than 5 days if a loading dose is not given. The bioavailability is 50% after an oral dose and is highly protein-bound. The absorbed drug is metabolized by two different pathways. In one pathway, it is degraded by esterases into an inactive metabolite. The other pathway, in the liver, it is converted to an active form in a two-step process by the hepatic cytochrome CYP450 group of enzymes, mainly the CYP2C19. This stage of metabolism accounts for considerable interpatient difference in the efficacy of clopidogrel. The drug is excreted equally through faeces and urine. Clopidogrel should be used with caution in patients with renal impairment.

Despite being the first-line agent for ADP receptor block, there is a time lag from administration of the drug to the inhibition of platelet aggregation, which may not be ideal for patients undergoing primary percutaneous coronary intervention (PCI).[4] Secondly, genetic variations in the CYP2C19 enzyme create a subset of patients who are classified as poor metabolizers (low responders). Poor metabolizers who are treated with clopidogrel for acute coronary syndrome and primary coronary intervention have higher rate of cardiovascular events. The efficacy of clopidogrel is also affected by other medications (e.g. omeprazole) that interact with CYP2C19. Omeprazole competitively inhibits CYP2C19 and hence reduces the efficacy of clopidogrel. There is also evidence that esomeprazole has similar effects on clopidogrel. Proton pump inhibitors other than omeprazole or esomeprazole are to be considered in patients taking clopidogrel.

Adverse effects include increased risk of bleeding, particularly in the perioperative period. Other side-effects include diarrhoea and rash. Thrombotic thrombocytopenic purpura is a rare complication.[3]

Third-generation thienopyridine: prasugrel

Prasugrel, a prodrug, is a thienopyridine derivative. When taken orally, 80% of the drug is absorbed into the circulation. It is rapidly hydrolysed by esterases to a thiolactone, which is then converted to the active metabolite in the liver mainly by CYP3A4 and CYP2B6 enzyme.[4] In contrast to clopidogrel, there is no reported difference in the efficacy of prasugrel due to genetic variation of CYP enzyme systems. Ninety-eight per cent of the drug is bound to protein plasma. The oral loading dose is usually 60 mg followed by a maintenance dose of 10 mg. It achieves 50% of IPA within 1 h. The active metabolite irreversibly binds to the $P2Y_{12}$ ADP receptor and causes its antiplatelet action. The active metabolite is metabolized to two inactive compounds by S-methylation or conjugation with cysteine. Approximately two-thirds of the prasugrel dose is excreted in the urine and one-third in the faeces as inactive metabolite. No dosage adjustment is necessary for patients with renal impairment. The active metabolite has an elimination half-life of 7 h. The platelet function returns to baseline levels around 7–10 days after cessation of the drug.

The risk of bleeding complications is higher with prasugrel when compared with clopidogrel.[5] It is contraindicated in patients with history of TIA and stroke.

Ticagrelor

Ticagrelor belongs to the cyclopentyltriazolopyrimidines (CPTPs) group of compounds. It is an oral reversible $P2Y_{12}$ ADP-receptor antagonist. It binds to the receptor and inhibits platelets induced by the ADP. The mechanism of action is different from the thienopyridine group of antiplatelet agents. It binds to an allosteric modulation site and creates a conformational change in the $P2Y_{12}$ receptor. In contrast to other thienopyridines, ticagrelor does not prevent binding of ADP but inhibits ADP-induced signalling.[4]

Dose: ticagrelor is taken as an oral loading dose of 180 mg followed by 90 mg twice a day for up to 12 months. Ninety per cent of patients have an IPA of more than 70% by 2 h post-loading dose. The oral bioavailability is 30–40%. It is metabolized rapidly into a circulating active metabolite by a CYP3A4 enzyme. Avoid concomitant use of CYP3A inhibitors (ketoconazole, clarithromycin) and CYP3A inducers (phenytoin, carbamazepine, rifampicin). Both ticagrelor and its metabolite are highly protein bound (>99%). The primary route of elimination is by biliary secretion. No dosage adjustment is necessary for patients with renal impairment. The terminal half-life of the drug is 7 and 9 h for the active metabolite. Apart from bleeding complication associated with all antiplatelet agents, ticagrelor is associated with transient dyspnoea.

The PLATO[6] (Platelet Inhibition and patient outcomes) trial compared ticagrelor with clopidogrel in patients with acute coronary syndrome; 18 624 patients were enrolled of which 35% had STEMI (ST Elevation Myocardial Infarction). Ticagrelor showed significant reductions in cardiovascular events when compared with clopidogrel.

Cangrelor

Cangrelor (an ATP analogue) is a short-acting i.v. $P2Y_{12}$ ADP-receptor antagonist. It has a rapid onset of action. It is given as an i.v. loading dose of 30 $\mu g\ kg^{-1}$ followed by 2–4 $\mu g\ kg^{-1}\ min^{-1}$ i.v. The maximal inhibition occurs within 15 min and a rapid reversal after discontinuation of the drug.[7]

The elimination half-time is under 9 min and platelet function tends to come to normal in 60 min. Metabolism of the drug is through dephosphorylation and is not dependent on the liver or kidneys. Cangrelor appears as an effective drug for bridge therapy during the perioperative period or even during ACS when possibility of surgery exists. Although the drug appeared promising in bridging therapy, the FDA this year refused marketing approval citing inconclusive phase III clinical trials.[8]

Glycoprotein IIb/IIIa receptor antagonists

GP IIb/IIIa receptors play a crucial role in platelet aggregation. GP IIb/IIIa receptors are present on the surface of platelets normally in an inactive form. When the platelets are activated, they undergo a conformational change resulting in binding of fibrinogen and von Willebrand factor (vWF). These molecules function as a bridge for the platelet aggregation. GP IIb/IIIa receptor blocking

drugs bind to the GP IIb/IIIa receptor and inhibit platelet aggregation by preventing the binding of vWF and fibrinogen. Abciximab is a monoclonal antibody, while the other two are synthetic derivatives.

Abciximab, the Fab fragment of chimeric murine (humanized form) monoclonal antibody, binds with the GP IIb/IIIa receptor and prevents platelet aggregation. It also binds and inhibits vitronectin receptor found in platelets and endothelial and smooth muscle cells. Abciximab is given as an i.v. loading dose of 0.25 mg kg^{-1} followed by an i.v. infusion of 0.125 μg kg^{-1} min^{-1}. After a bolus dose, the plasma levels reduce very rapidly with a half-life of 10 min due to the rapid binding of abciximab to platelets and phase II half-life of 30 min. It takes 48 h for the platelet function to recover after cessation of the medication. Abciximab can be found in the circulation even after 15 days. It is not necessary to adjust the dose of abciximab in patients with renal impairment.

Eptifibatide is a cyclic heptapeptide. It selectively binds to GP IIb/IIIa receptors and inhibits platelet aggregation. Unlike abciximab, eptifibatide does not bind to any other receptors. It is given as an i.v. bolus dose of 180 μg kg^{-1} followed by an i.v. infusion of 2 μg kg^{-1} min^{-1}.[9] It inhibits platelet aggregation in a dose-dependent and concentration-dependent manner, resulting in 80% IPA within 15 min.[9] Eptifibatide dissociates from platelets rapidly on discontinuation of infusion and is mostly excreted unchanged in urine. The plasma elimination half-life is 2.5 h. Since the drug is eliminated unchanged in urine, the dose needs to be reduced in renal impairment. If the creatinine clearance is <60 ml min^{-1}, the dose should be reduced to 1 μg kg^{-1} min^{-1}.

Tirofiban is a reversible non-peptide antagonist of the GP IIb/IIIa receptor. It is given as an i.v. loading dose of 25 μg kg^{-1} over 3 min followed by an i.v. infusion of 0.15 μg kg^{-1} min^{-1}.[9] Ninety per cent IPA is achieved within 10 min. It is excreted unchanged in urine and faeces. The half-life of tirofiban is 2 h. Similar to eptifibatide, the dose of tirofiban should be reduced to half in patients with reduced creatinine clearance (<60 ml min^{-1}).

GP IIb/IIIa receptor antagonists were associated with increasing bleeding complications when compared with other antiplatelet agents. Thrombocytopenia has been reported to occur with all three GP IIb/IIIa receptor antagonists. GP IIb/IIIa antagonists are not effective when used as the only antiplatelet agent, with the only significant benefit obtained from infusion of these drugs being during PCI. In patients undergoing PCI, GP IIb/IIIa receptor antagonists were reserved for specific patient populations as mentioned below.

PAR-1 blocking drugs

Vorapaxar, a tricyclic himbacine-derived drug, selectively inhibits thrombin-mediated platelet aggregation. FDA recently (May 2014) approved this drug for marketing purposes after phase III trials. Although it is a reversible antagonist to PAR-1 receptor, it behaves like an irreversible drug due to its long half-life. It has no effect on ADP-mediated platelet aggregation. It is given as a 2.5 mg once-daily dose. The bioavailability of this drug is almost 100%. It achieves 80% IPA within 1 week. It is metabolized by the CYP3A4 enzyme system. The main route of elimination is through the faeces. No dosage adjustment is necessary for patients with renal impairment or for mild-to-moderate hepatic impairment, but it is contraindicated in patients with severe hepatic impairment due to increased bleeding problems. The terminal half-life of vorapaxar is 8 days. Even after weeks of stopping the drug, the IPA can be as high as 50%. It is currently approved for use with either aspirin or clopidogrel for secondary prevention in patients with history of myocardial infarction (MI) or peripheral vascular disease.

Newer antiplatelet agents

There are several antiplatelet drugs currently under various stages of development.

(i) Terutuban, a thromboxane receptor antagonist.
(ii) Elinogrel, a $P2Y_{12}$ receptor blocker, it can be administered both orally and i.v.
(iii) Atoxapar, PAR-1 antagonist.

Antiplatelet therapy

There are several reasons a patient could be on antiplatelet therapy. They may be either on a platelet monotherapy or on dual antiplatelet therapy. The following list would summarize the common indications for antiplatelet therapy.

(i) Aspirin
  (a) In patients with MI (indefinitely),[10]
  (b) peripheral vascular disease (not much evidence),
  (c) primary prevention for cerebral vascular disease (not licensed),
  (d) atrial fibrillation (no longer recommended),
  (e) vascular dementia.
(ii) Dipyridamole monotherapy[10]
  (a) Ischaemic stroke if aspirin and clopidogrel is contraindicated.
  (b) TIA if aspirin is contraindicated.
(iii) Clopidogrel monotherapy[10]
  (a) All patients with MI if aspirin is contraindicated.
  (b) To prevent occlusive vascular events in patients who have had an ischaemic stroke or who have peripheral arterial disease.
  (c) Multivascular disease.
(iv) Aspirin+dipyridamole[10]
  (a) Patients with history of TIA.
  (b) Patients with history of ischaemic stroke if clopidogrel is contraindicated.
(v) Aspirin+clopidogrel[11]
  (a) At least 12 months for patients with NSTEMI (Non-ST elevation MI).
  (b) At least 12 months for patients with STEMI (ST Elevation MI) with drug-eluting stent (DES) or bare metal stent (BMS).
  (c) At least 1 month for patients with STEMI who had medical treatment with fibrinolytic agent.
(vi) Aspirin+prasugrel[12]
  (a) Patients with ACS for PCI if
  - Immediate primary percutaneous coronary intervention (PPCI) for STEMI.
  - Stent thrombosis on patients with clopidogrel therapy.
  - Patients with diabetes mellitus.
(vii) Aspirin+ticagrelor[13]
  (a) For 12 months on patients
  - STEMI if the patients have PPCI
  - NSTEMI
  - Unstable angina
(viii) I.V. eptifibatide or i.v. tirofiban[14]
  (a) Patients with unstable angina who are undergoing angiography within 96 h of admission.

Other indications

(i) Prevention of eclampsia and its complications[15,16]
(ii) Thrombocytosis (controversial and uncertain)[17]
(iii) Anticancer therapy (animal studies)

Surgery and antiplatelet therapy

Surgery on patients with dual antiplatelet therapy poses a significant challenge to anaesthetists. On the one hand, continuing dual antiplatelet therapy increases the risk of bleeding, on the

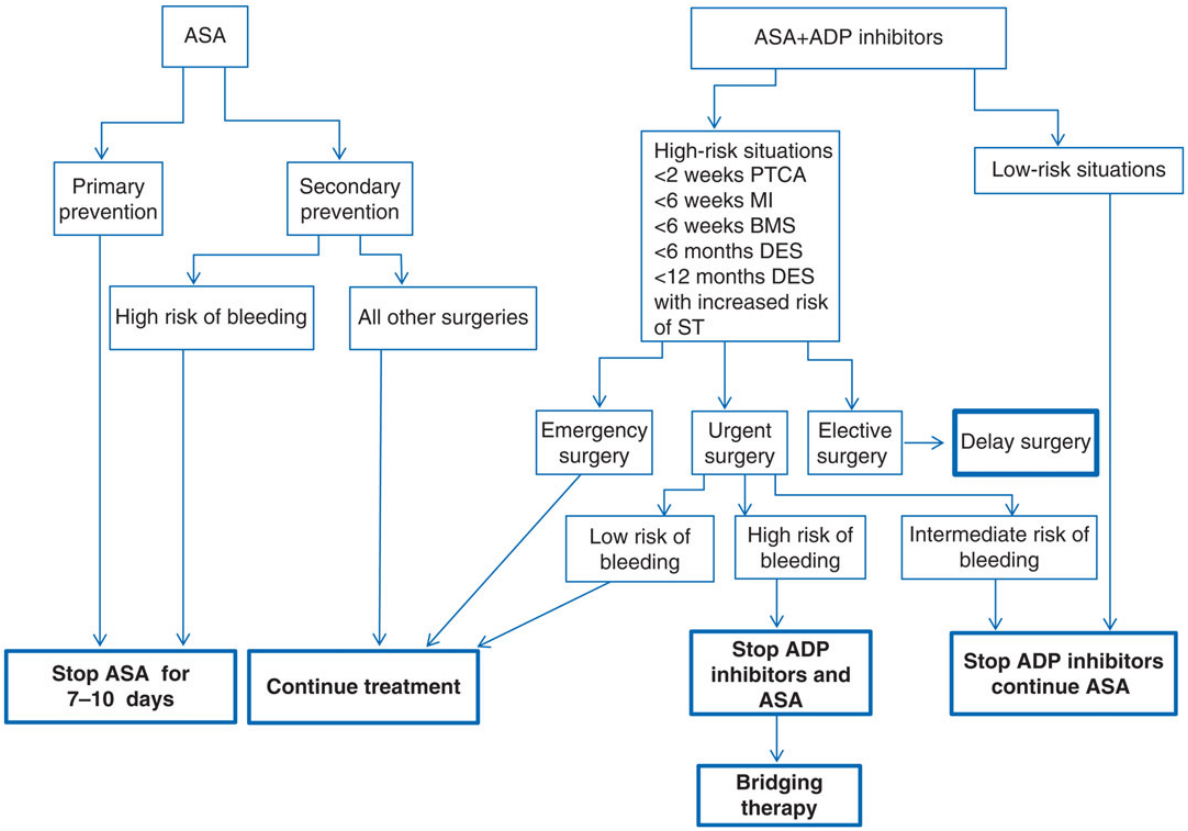

Fig 2 Antiplatelets and surgery. Reproduced with permission from Oprea and Popescu.[9]

Table 1 Antiplatelets and regional anaesthesia. Adapted (with permission) from the AAGBI guidelines on regional anaesthesia and patients with abnormalities of coagulation, 2013

Drug	Elimination half-life	Acceptable time after the drug for performing block	Administration of drug while spinal or epidural catheter in place	Acceptable time after spinal block performance or catheter removal for next drug dose
Aspirin	Not significant irreversible	No additional precautions	No additional precautions	No additional precautions
Dipyridamole	10 h	No additional precautions	No additional precautions	6 h
Ticlopidine	4–5 days	14 days	Not recommended	6 h
Clopidogrel	Not significant irreversible	7 days	Not recommended	6 h
Prasugrel	Not significant irreversible	7 days	Not recommended	6 h
Ticagrelor	8–12 h	5 days	Not recommended	6 h
Abciximab	24–48 h	48 h	Not recommended	6 h
Eptifibatide	4–8 h	8 h	Not recommended	6 h
Tirofiban	4–8 h	8 h	Not recommended	6 h
Vorapaxar	8 days	No data	Not recommended	No data

other hand, stopping the antiplatelet can lead to cardiovascular events such as stent thrombosis, MI, and death.

Each patient should be managed individually. It should be a multidisciplinary approach between surgeon, anaesthetist, cardiologist, and haematologist. The following factors should be taken into consideration.

(i) Emergency or urgent (cancer related) surgery, elective surgery.
(ii) Type of surgery: low risk, intermediate risk, or high risk for bleeding.
(iii) Time duration from the occurrence of acute coronary syndrome or PCI to the surgery and if patient had a primary PCI, type of stent, that is, DES or BMS.
(iv) Type of lesion—global coronary disease or specific coronary lesions.

Aspirin can be continued until the day of surgery in most circumstances but may need to be stopped for some specific surgeries such as intracranial surgery.

Platelet transfusions may not provide rapid reversal of the antiplatelet effects. Some antiplatelet drugs have a long half-life, so they remain in circulation for a considerable period of time. When platelets are transfused on these patients, the circulating drug will also inhibit the transfused platelets. Figure 2 illustrates the algorithm for the management of antiplatelets during surgery.

Regional anaesthesia and antiplatelet agents

There is no evidence that aspirin needs to be stopped for performing regional anaesthetic techniques. For all other antiplatelet agents, sufficient time should be allowed for the platelet function to recover. This time duration depends upon the elimination half-life and mechanism of action of the antiplatelet agents as shown in Table 1.

Conclusion

The list of antiplatelet agents in the market is growing constantly. Newer antiplatelet agents are being developed continuously to overcome the shortcomings of existing antiplatelet agents. As anaesthetists, we should continue to update ourselves with these newer antiplatelet agents to manage the patients effectively and safely during the perioperative period. A haematologist or cardiologist should be contacted in complex and difficult situations.

Declaration of interest

None declared.

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MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Anaesthesia for interventional neuroradiology

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Key points

- The spectrum of cases which are undertaken in an interventional neuroradiology suite is rapidly expanding.
- An appreciation of the underlying pathology and multisystem effects of the disease is needed.
- Cerebral protection strategies must be used.
- The hazards of remote site anaesthesia and ionizing radiation must be appreciated.
- Close monitoring in the post-procedural period is essential to identify any rapidly evolving neurological deficits, indicating potential bleeding or vessel occlusion that may necessitate emergency radiological or neurosurgical intervention.

The scope of interventional neuroradiology has expanded rapidly. Conditions which were previously untreatable or only amenable to open surgical techniques are now being considered for interventional radiological management (Table 1).

Subarachnoid haemorrhage

Subarachnoid haemorrhage (SAH) accounts for about 5% of all strokes and may be due to congenital or acquired conditions, the most common being intracranial aneurysms. Cerebral aneurysms are present in up to 6% of the population.[1] SAH requires a multi-disciplinary approach to management, at a dedicated neurosciences centre.

Patients may present with sudden-onset occipital headache ('thunder clap'). Associated features include nausea and vomiting, neck stiffness, photophobia, focal neurology, deteriorating level of consciousness, seizures, and cardiac arrest.[2] Complications after an SAH include re-bleeding (5–10% in the first 72 h), obstructive hydrocephalus (incidence of 20–30% within 3 days of ictus), and vasospasm (angiographically demonstrated arterial narrowing 3–14 days after SAH). Delayed cerebral ischaemia and vasospasm may be asymptomatic and are associated with a worse outcome after SAH. The mortality rate at 7 days post-SAH is up to 40%.

Other multisystem features include ECG changes (e.g. shortened PR interval, prolonged QTc interval, ST segment changes, and changes to T wave morphology), elevated cardiac enzymes, cardiogenic and neurogenic pulmonary oedema, and sodium disturbances. Patients with suspected diagnosis of SAH should have an urgent non-contrast computerized tomography (CT) scan (sensitivity of 95–100% on first day), and may require a lumbar puncture 12 h post-ictus if CT is negative.

Aneurysms usually develop in the Circle of Willis at sites of vessel branching. The risk of rupture is directly related to the size of the aneurysm, typically classified as small <12 mm, large 12–14 mm, and giant >24 mm.[3,4]

The gold standard for the detection of intracranial aneurysms is four-vessel digital subtraction angiography (DSA). CT angiography (CTA) is more rapid, readily accessible, and less invasive, but the sensitivity and specificity for smaller aneurysms (<5 mm) is lower.[5] Magnetic resonance angiography (MRA) can give more information regarding the cause of the intracranial bleed, but the longer scanning time is of significance in an acutely unwell patient.

Treatment of aneurysmal disease is either by endovascular coiling of the aneurysm or by open surgical clipping. The International Subarachnoid Aneurysm Trial (ISAT) was a multicentre, randomized controlled trial that compared endovascular coiling and neurosurgical clipping of ruptured intracranial aneurysms. The initial findings favoured coiling; the primary outcome (risk of death or dependence at 1 yr) occurred in 23.7% of coiled patients *vs* 30.9% of surgically clipped patients, with an absolute

Table 1 Classification of interventional neuroradiological procedures

Intracranial lesions
Diagnostic angiography
Glue embolization of cerebral arteriovenous malformation
Coil embolization of cerebral aneurysms (elective and emergency)
Embolization of carotid-cavernous fistula
Intracerebral chemotherapy for head and neck tumours
Sclerotherapy of venous angiomas
Balloon angioplasty and carotid artery stenting
Venous stenting
Therapeutic carotid occlusions for giant aneurysms and skull base tumours
Embolization of intracranial tumours
Carotid artery test and therapeutic occlusions for aneurysms and tumours
Stenting of aneurysms
Thrombolysis and thrombectomy after stroke
Treatment of cerebral vasospasm and carotid stenosis with transluminal balloon angioplasty
Extracranial lesions
Embolization of dural arteriovenous malformations, fistulae, and spinal arteriovenous malformation
Vertebral artery stenting
Vertebroplasty and kyphoplasty
CT-guided interventions
Biopsies of tumours and masses
Interventional magnetic resonance imaging
Stereotactic-guided neurosurgery—deep brain stimulation for movement disorders
Implantation of intracranial electrodes for telemetry
Temporal lobe resections for epilepsy

risk reduction of 6.9%. However, long-term follow-up of ISAT patients revealed the need for delayed re-treatment was significantly higher in coiled patients.[5–7] Coiling is the preferred treatment in the majority of aneurysms, especially posterior circulation aneurysms. Clipping may be required if the aneurysm has difficult anatomy such as a wide neck, and there is difficult angiographic arterial access, or if coiling fails.

Endovascular management of aneurysmal disease

Endovascular treatment is achieved by one of two methods—obliteration of the aneurysmal sac using coils with or without stents or on rare occasions occlusion of the proximal parent arteries feeding the aneurysm.[8] The radiologist usually uses a transfemoral arterial approach, with insertion of a femoral sheath followed by a catheter. This is then navigated into the carotid or vertebral artery. A micro-catheter is introduced through this into the cerebral circulation. Typically, detachable platinum coils are advanced into position and the coils deployed into the sac of the aneurysm until occlusion is achieved. Newer hydrocoils are available, which have a coating of synthetic polyalcohol over the platinum coil, which expands within minutes after contact with blood, resulting in good volumetric packing. Other innovations include bioactive coils, which produce an enhanced cellular response stimulating neo-intima formation across the aneurysm neck, thus preventing re-bleeding and re-growth.

Stents (metal mesh devices in the shape of a vessel) can be placed inside the parent artery at the site of the aneurysm to cover the neck of the aneurysm. This helps to keep the coils within the aneurysm in place.

Flow-diverting stents divert blood flow within an artery, thus decreasing the flow within an aneurysm. Placing high strut density stents results in spontaneous thrombosis of the aneurysm, without occluding the parent vessel. However, it must be remembered that there is a high risk of arterial thrombosis, and adequate anticoagulation should be ensured. Pre-procedural testing of platelet inhibition will shortly be expected practice for flow-diverting stents.

Balloon-expandable stents have also been introduced, and are used to assist coil embolization of difficult lesions such as dissecting, fusiform, and wide-necked aneurysms which are unfeasible for simple coiling.

Balloon trapping of an aneurysm involves balloons being placed intravascularly above and below a giant aneurysm.

Manipulation of the aneurysm sac may cause distal thromboembolism and rupture. Indications of rupture in the anaesthetized patient include sudden onset of bradycardia, or hypertension as a result of raised intracranial pressure (ICP). The radiologist may visualize contrast extravasation on screening.[6] Management includes arterial pressure control by deepening anaesthesia, or the use of antihypertensives such as i.v. labetolol. Heparin should be reversed with protamine (1 mg protamine per 100 units heparin given) if requested by the radiologist, and radiological control of the leak should be obtained. If the extravasated blood load is high, the patient may require a CT scan and the insertion of an external ventricular drain (EVD), if there is imminent danger of developing obstructive hydrocephalus. The EVD allows drainage of cerebrospinal fluid should intracranial hypertension develop. Craniotomy may be required for intracranial haematoma evacuation and surgical clipping of the aneurysm. Other complications include vascular occlusion secondary to arterial thrombus, emboli, vasospasm, or misplaced catheter or coils. Management involves increasing collateral flow by increase in arterial pressure to 30–40% above baseline, with or without direct intra-arterial thrombolysis with abciximab (a glycoprotein IIb/IIIa receptor inhibitor). I.V. aspirin is often administered, and the misplaced catheter/coils are removed,[6,8] followed by thrombectomy if indicated.

I.V. aspirin, heparin, and abciximab are administered to reduce the risk of vascular occlusion secondary to thromboembolism, pre-, intra-, and post-procedure at the request of the radiologist. In elective treatment of unruptured aneurysms, at least one dose of aspirin could be administered the day before the coiling, and if stent-assisted coiling is envisioned then aspirin and clopidogrel should be given 3–5 days before the procedure. Post-procedure, if a stent has been placed, patients may be prescribed aspirin 75 mg daily for life and clopidogrel 75 mg daily for 3 months to decrease the incidence of thromboembolic complications. Platelet function testing is also being used in some centres to identify patients who could benefit from higher dosing, balancing the risks of thrombosis and antiplatelet therapy.

Management of vasospasm has moved away from the traditional triple H therapy—hypertension, hypervolaemia, haemodilution—to hypertension and euvolaemia. Arterial pressure targets in secured aneurysms aim for a systolic arterial pressure of 160–180 and 140–160 mm Hg in unsecured aneurysms.[8] Nimodipine, a calcium channel antagonist, is given to all SAH patients for 21 days to reduce the risk of delayed cerebral ischaemia and poor outcome. If vasospasm occurs during coiling, intra-arterial nimodipine can be administered, or balloon cerebral angioplasty can be performed.[8]

Arteriovenous malformations

These are congenital abnormalities, which commonly consist of abnormally large and complex vessels, often containing fistulae

with multiple arterial and venous supplies.[9] They shunt blood from the arterial to venous system and can bleed. Patients may present with headaches, intracranial haemorrhage, and seizures. Treatment includes open surgery or embolization.

Endovascular treatment of arteriovenous malformations

Arteriovenous malformations (AVMs) are treated by glue embolization of fistulae and feeding arteries, by injecting fast setting embolic material or coils into the nidus of the AVM. Cyanoacrylate adhesives are polymerizing adhesives, which solidify when they come into contact with ionic solutions, that is, blood. Ethylene vinyl alcohol co-polymer (trade name Onyx) is a non-adhesive polymer that solidifies through the process of precipitation, allowing for controlled injection and filling of the vascular abnormality over several minutes.[4,8] The arterial pressure may need to be manipulated to facilitate deposition of embolic material within the nidus of the AVM. Complications include embolization of glue into the draining vein, resulting in venous outflow obstruction, cerebral haemorrhage, and pulmonary circulation glue embolization. Embolic material may also embolize normal brain arteries. Abrupt restoration of normal systolic pressure to a chronically hypotensive vascular bed may overwhelm the cerebral autoregulatory capacity and result in parenchymal haemorrhage or swelling, thus the mean arterial pressure should be kept to 20% below baseline.[4,8] Severe post-procedural headache may be indicative of bleeding. Steroids may be administered prophylactically post-procedure to reduce the incidence of perinidus oedema. These patients often need to have multiple procedures to achieve complete obliteration of the AVM.

Carotid artery stenosis

Patients who have symptomatic internal carotid artery stenosis (>70%) who are considered high risk for general anaesthesia and open surgery may be considered for endovascular treatment by angioplasty and stenting under local anaesthesia. This allows for constant assessment of neurology during the procedure and preservation of cerebral autoregulation. Deployment of the stent can cause parasympathetic stimulation—bradycardia and hypotension. There is also a risk of hyperperfusion syndrome and careful arterial pressure control is needed after stenting that may necessitate i.v. antihypertensive treatment. Therefore, these procedures are usually performed with anaesthetic presence to manage haemodynamic disturbances.[6,10] Other complications include vessel occlusion, thromboembolism, dissection, and perforation (Fig. 1).

Hyperacute ischaemic stroke

CT-guided i.v. recombinant tissue plasminogen activator (rtPA) administered within 4.5 h of stroke onset is currently considered the definitive treatment for hyper acute ischaemic stroke. However, in those patients in whom rtPA therapy has failed, or when the i.v. rtPA treatment window has passed, i.v. rtPA can also be given as a bridging therapy while other endovascular options are considered, such as intra-arterial rtPA. Intra-arterial therapy should be undertaken within 6 h of the onset of neurological symptoms[11] for anterior circulation strokes, and within 24 h for posterior circulation strokes.[8]

Administration of intra-arterial rtPA involves cerebral angiography to localize the occluding clot, navigation of a micro-catheter adjacent to the clot, and injection of intra-arterial rtPA. This may be combined with mechanical clot retrieval systems such as aspiration/suction systems, clot retriever devices, ultrasonography, snare, or laser devices with or without transluminal angioplasty and stenting.

A recent consensus statement has been issued by the Society of Neuroscience in Anesthesiology and Critical Care (SNACC) on the anaesthetic management of endovascular treatment of acute ischaemic stroke.[12] It recommends that preoperative assessment of patients undergoing endovascular treatment for acute ischaemic stroke should be performed as quickly as possible and should not delay treatment. Intra-arterial thrombolysis should be performed within 6 h, and thrombectomy within 8 h of symptom onset. In cooperative patients, the use of local anaesthesia with conscious sedation should be performed. However, rapid conversion to general anaesthesia may be necessary. General anaesthesia is preferred in uncooperative or confused

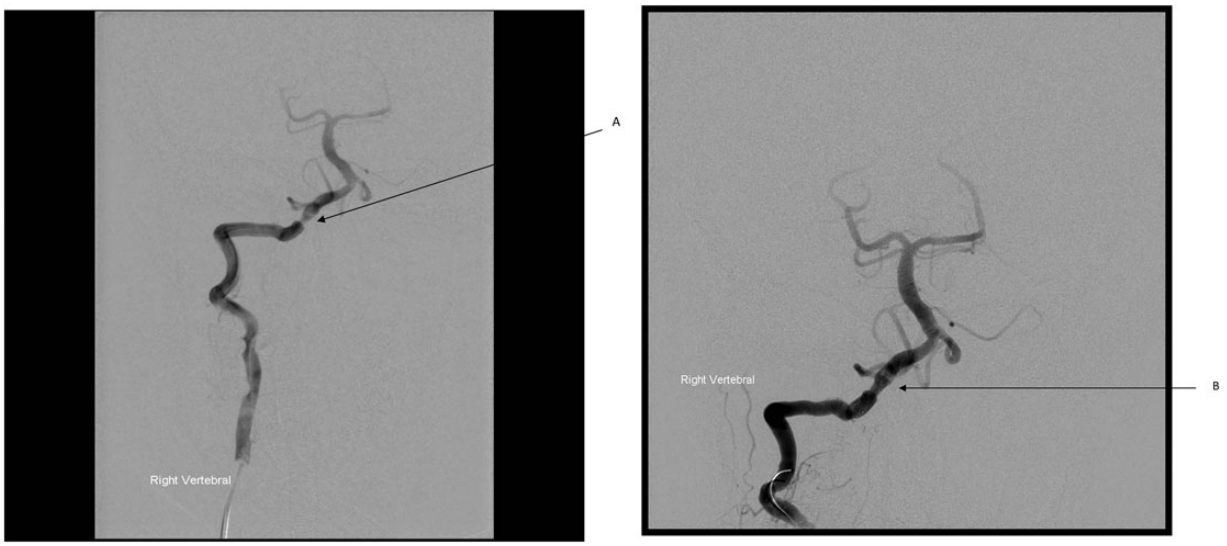

Fig 1 Vertebral artery pre-stenting: A, point of narrowing. Vertebral artery post-stenting: B, stent *in situ*.

patients. Oxygen saturation should be maintained at above 92%, with oxygen partial pressure of >8 kPa, and normocapnia. All patients should have continuous monitoring of heart rate, respiratory rate, ECG, and capnography. Arterial pressure should be measured invasively if obtainable quickly. Systolic arterial pressure should be maintained between 140 and 180 mm Hg with a diastolic arterial pressure of <105 mm Hg.[12] Patients who have undergone general anaesthesia should be extubated early, and have full neurological assessment. They should be monitored post-procedure in a high dependency unit.

The Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) trial is a randomized controlled trial to evaluate whether additional mechanical thrombectomy device treatment improves functional outcome in patients with large artery occlusion who have received i.v. thrombolytic drug treatment as standard care. The trial consists of two arms: i.v. alteplase administered within 4.5 h of onset of stroke symptoms *vs* i.v. alteplase and additional mechanical thrombectomy procedure to commence within 90 min of the start of i.v. rtPA infusion. PISTE is scheduled to complete by August 2017.

Embolization of intracranial tumours

These procedures are performed before open surgery, to reduce tumour vascularity and facilitate surgical excision. There may be significant postoperative tumour swelling and a short preoperative course of steroid may be required. Severe post-procedural pain may occur if dural vessels are embolized.[8]

Carotid artery balloon test occlusion

This aims to test the adequacy of the cerebrovascular collateral circulation before electing to occlude the carotid artery, which may be necessary for surgery for tumours involving the skull base.[9] It is performed under local anaesthetic, with continuous neurological assessment and anaesthetic presence in the case of inadequate cerebrovascular collateral circulation leading to loss of consciousness. The use of deliberate hypotension can increase the sensitivity of the test. Owing to blood flow stasis distal to the point of balloon occlusion in the artery, optimal heparinization is essential to minimize the risk of clot formation.[13]

Sclerotherapy of venous angiomas

Craniofacial venous malformations are congenital disorders, which can be disfiguring and may impinge on the airway and affect swallowing. Under fluoroscopic guidance, 95% ethanol is injected percutaneously into the lesion, causing a chemical burn and shrinking the lesion.[9] Marked swelling can occur post-procedure, and the airway must be assessed before extubation.

Methods of imaging

Computerized tomography

The CT scanner is a ring-shaped structure, which can rotate and tilt. X-ray beams are emitted from one side of the centre opening and aimed directly across to a detector on the opposite side, which measures the amount of radiation absorbed by the body part in question. The CT table moves so that the X-ray beam follows a spiral path. High-quality images can be obtained rapidly.

Dyna-CT

Dyna-CT is an X-ray technique, which allows the acquisition of a 3D image with a fixed C-arm, where the C-arm rotates around the isocentre of the body part in question and a few hundred 2D images are obtained. A cone beam reconstruction is then performed.[8]

CT angiography

CTA combines traditional CT scanning with i.v. injection of contrast allowing visualization of blood vessels and qualitative assessment of flow. It does not give any assessment of the adequacy of flow. CTA is widely used in the diagnosis of vasospasm.

CT perfusion imaging

CT perfusion imaging is an important adjunct to CT and CTA. It allows for quantification of perfusion in the brain, and thus delineates areas of the brain which may be salvageable by intervention (clot retrieval or thrombolysis).

Magnetic resonance imaging

The patient lies within a powerful magnet, and high-quality images are obtained of the area in question. Hazards of general anaesthesia in the MRI suite include those of remote site anaesthesia, and also the anaesthetist being remote to the patient in a control room during scanning. MRI compatible monitoring must be used. Other considerations include the need for long extension tubing and infusion lines.

Magnetic resonance angiography

MRA combines MRI scanning with the i.v. injection of gadolinium to allow visualization of blood vessels and flow within them.

DSA and fluoroscopy

Initially, a pre-contrast (mask) picture is taken (essentially a plain X-ray). Fluoroscopy screening is then performed and all stable structures common to both images such as bone shadows and other non-vascular structures are subtracted digitally from the mask image. Simultaneous angiography is performed by injecting contrast into the circulation. As the contrast is not on the mask image, it is not subtracted, leaving an image of the vessel (the road map). To see the radio-opaque micro-catheter tip, the real-time image of the micro-catheter is superimposed onto the road map, allowing the radiologist to follow the micro-catheter tip through the vascular circulation. Subsequently, any items introduced onto the roadmap (e.g. stents or coils) are clearly visible.[3,8] Patient movement can cause image degradation and thus decrease the quality of images obtained. Roadmap fluoroscopic imaging has allowed interventional neuroradiologists to obtain angiographic images of a blood vessel or lesion by injecting only a small amount of contrast medium; and to maintain this angiographic image while superimposing live fluoroscopic (X-ray) images on the angiographic image. In essence, giving the interventional radiologist a 'roadmap' of the blood vessel and lesion, such as a cerebral aneurysm.

Anaesthetic considerations

Patients undergoing interventional neuroradiological procedures may be elective patients in whom incidental findings of aneurysm, AVM, or other intracranial pathology have been diagnosed. These interventional neuroradiological procedures are being undertaken as primary prevention techniques to avoid disease progression. Other cases may be more urgent, for example,

those with an SAH who may need cerebral angiography and endovascular treatment within 24–48 h. Other patients may present as emergency cases, having suffered sudden and catastrophic neurological injury as a result of a thromboembolic stroke. Many of the patients who have suffered neurological injury may be confused, in pain, have involuntary movements, or are un-cooperative. Interventional neuroradiology procedures can be technically challenging and long, and it may therefore be difficult, uncomfortable, and stressful for a patient to remain still on the angiography table. A motionless and at times, apnoeic patient is needed to minimize motion artifact, and to enable high-quality images to be obtained. With advancements in interventional neuroradiology techniques, general anaesthesia is increasingly being performed in the radiology suite.

General anaesthesia also allows the provision of a physiologically stable patient where arterial pressure, ventilation, and ICP can be controlled.

Challenges of general anaesthesia in the interventional neuroradiology suite include those of remote site anaesthesia, especially dim lighting and a lack of full range of equipment and help, otherwise available in main theatres.

Preoperative

Before operation, history of current illness, pathology, multisystem effects, and review of imaging should be undertaken. The patient should be examined for Glasgow coma score, pupil size and reactivity, and focal neurological deficits elicited and documented. The history of renal impairment and use of medications such as metformin should be ascertained. Renal function (urea and creatinine) should be tested before administration of contrast. Metformin is not recommended for use in diabetics with renal impairment because it is exclusively excreted by the kidneys, and accumulation of metformin can lead to lactic acidosis. Metformin should be withheld post-contrast if eGFR is <60 ml min^{-1}. Women of child-bearing age should have a negative pregnancy test or confirm that they are not pregnant, due to high dose of ionizing radiation exposure. All patients should have preoperative blood tests—full blood count, urea and electrolytes, coagulation screen, and a valid group and save sample in the case of bleeding. Allergy history to iodine, shellfish, or contrast should specifically be ascertained. In the emergency patient who is not starved, a rapid sequence induction should be performed, with techniques used to minimize the increases in ICP.

Induction

Cerebral protection strategies (arterial pressure targets systolic 100–160 mm Hg, avoidance of hypertension which increases the risk of re-bleeding, avoidance of hypotension to ensure adequate perfusion to ischaemic areas, normocapnia 4.5–5 kPa, and avoidance of hypoxia) should be used during induction to prevent secondary damage to the brain. Vasopressors may be required during induction and maintenance. A south facing RAE or reinforced tracheal tube is used to prevent kinking or displacement by the C-arm of the image intensifier.

Standard monitoring—ECG, non-invasive arterial pressure, and pulse oximetry—should be supplemented with invasive arterial monitoring to allow for arterial pressure monitoring and sampling for monitoring of anticoagulation.

I.V. access with large-bore cannulae should be secured, due to the potential for catastrophic bleeding.

Temperature control—procedures can be long, and angiography suites typically cold. Patients should be actively warmed to maintain normothermia.

Nasogastric (NG) tube insertion—some procedures require the administration of loading doses of aspirin 300 mg and clopidogrel 300 mg to be given intraoperatively, at the radiologists' request. An NG tube may be inserted before the procedure and position confirmed by on-table scanning at the start of the procedure. In some centres, an i.v. preparation of aspirin is available.

Owing to the large volumes of endovascular catheter flush and diuretic effect of contrast, a urinary catheter is essential.

Maintenance

Interventional neuroradiological procedures are rarely painful, but they do require a motionless patient and episodes of controlled apnoea. This can be achieved by total i.v. or inhalation anaesthetic in conjunction with intermittent boluses of neuromuscular blocking agent or infusion, or remifentanil infusion. Nitrous oxide should not be used as it may cause expansion of air emboli, which may be inadvertently introduced.

Specific considerations

Radiation protection

Patients and staff are exposed to high-dose ionizing radiation. Sources of radiation include direct radiation from X-ray tube, leakage through the collimators' protective shielding, and radiation that is scattered from the patient during imaging. Staff should minimize their exposure by wearing lead aprons of at least 0.5 mm thickness, thyroid shields, and maximize their distance from the source of ionizing radiation as the dose of radiation decreases proportionally from the source, according to the inverse square law (Table 2).

Contrast and flush

Up to 2 litres of flush, and up to 300 ml of contrast are used. All patients are at risk for the development of acute contrast-induced nephropathy. Limiting the dose of contrast and good hydration lessen the risk of precipitating acute kidney injury. Patients should have their renal function monitored for 72 h post-procedure.

Anticoagulation

The anaesthetist is often required to administer heparin i.v. to minimize thromboembolic complications and prevent vessel occlusion. A baseline activated clotting time (ACT) is obtained and then a dose of 70–100 units kg^{-1} of heparin is given, followed by measurement of the ACT, aiming for a target of 2–3 times baseline.

Patient positioning

The patient's head is usually at the opposite end to the anaesthetist and anaesthetic machine. This requires extensions to anaesthetic tubing and lines which must be secured. The angiography table also moves.

Table 2 Comparison of doses of ionizing radiation

Chest X-ray	0.02 mSv	1 CXR equivalent
Abdominal X-ray	0.06 mSv	3 CXR
CT scan of head	1.4–2 mSv	100 CXR
Cerebral angiogram	5 mSv	250 CXR
CT scan of chest	6.6 mSv	300 CXR
Interventional cerebral angiogram	7–10 mSv	300–500 CXR

Extubation

Smooth emergence is important to avoid coughing and thus increases in ICP, with possible re-bleeding and rupture of unprotected or partially protected aneurysms.

Postoperative care

The patient will often require transfer through the hospital to appropriate recovery facilities or high dependency unit for close haemodynamic and neurological monitoring in anticipation of potential complications.

The future

There have been many advances in endovascular stroke devices, with increased re-canalization rates and decreased procedural time. Results of the PISTE trial in 2017 will provide invaluable data on the management of hyperacute ischaemic stroke. In patients with atherosclerosis, drug-eluting stents such as sacrolimus and paclitaxel-eluting stents are now being used for symptomatic intracranial and vertebral artery stenosis. As advances continue to be made, increasingly more complex cases will be amenable to treatment in the interventional neuroradiology suite.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Perioperative care of phaeochromocytoma

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Key points

- Initial diagnosis is achieved via analysis of metanephrine levels followed by CT or MRI.
- Half of phaeochromocytomas are diagnosed incidentally on abdominal imaging.
- A greater proportion of phaeochromocytomas are malignant, extra-adrenal, and/or familial than previously suspected.
- Associated cardiomyopathies occur relatively frequently.
- Vasopressin is effective in treating catecholamine-resistant hypotension after tumour resection.

Classification

Phaeochromocytomas are catecholamine-secreting tumours of the adrenal medulla, while paragangliomas are closely related neuroendocrine tumours arising from extra-adrenal paraganglia, some of which produce catecholamines. In this article, their perioperative management will be considered together.

Aetiology

The majority develop sporadically, although around one-third of cases have specific gene mutations which are usually inherited in an autosomal-dominant fashion. These may be associated with other tumours, for example, multiple endocrine neoplasia 2A and 2B, Von Hippel–Lindau disease, succinate dehydrogenase enzyme mutations, and neurofibromatosis.

Incidence

The annual European incidence rate of phaeochromocytomas is around 0.2 per 100 000 people.

The traditional 'Rule of 10s' states that 10% of phaeochromocytomas are 'extra-adrenal', 10% are malignant, 10% are bilateral, 10% are found in normotensive patients, and 10% are familial. However, this statement probably no longer holds true as there appears to be a significantly higher proportion of tumours that are malignant (29%),[1] extra-adrenal (24%),[2] and/or familial (32%).[3]

Symptoms

Phaeochromocytomas may present with a classic symptom triad of headache, palpitations, and sweating. Hypertension is present in around 90% of cases, although it is paroxysmal in 35–50% of these.

Other non-specific presentations include anxiety, lethargy, nausea, weight loss, hyperglycaemia, and tremor. Abdominal pain may result from bowel ischaemia due to excessive vasoconstriction. Visual disturbance may develop from papilloedema induced by malignant hypertension. Half of phaeochromocytomas are diagnosed incidentally on abdominal imaging for an unrelated indication.

Biochemical tests

Phaeochromocytomas produce a variable mixture of norepinephrine, epinephrine, or, more rarely, dopamine. Traditional biochemical diagnosis of phaeochromocytomas relied upon 24 h collections of urinary catecholamines and vanillylmandelic acid (24 h due to diurnal variation in levels), and also blood sampling for plasma catecholamines. The short half-life of plasma catecholamines makes it difficult to differentiate pathological over-production from a transient stress response to venesection.

Modern techniques measure levels of metanephrine and normetanephrine which are breakdown products of epinephrine and norepinephrine, respectively (Fig. 1). Sampling of these can be performed from either urine or plasma and there is no agreement over which is superior. Plasma tests are slightly more sensitive and more convenient to collect, while urine tests have a greater specificity. Consensus opinion from the first symposium on phaeochromocytoma recognized the superior diagnostic ability of metanephrine analysis over traditional methods, irrespective of whether the sample was derived from urine or plasma. Dopamine-secreting tumours can be identified by measuring plasma or urinary dopamine and homovanillic acid levels.

Both modern and traditional methods have numerous potential causes of false-positive results, including recent exercise, venous sampling in the sitting position, dietary factors, renal impairment, and many common medications. Examples of these medications include:

- norepinephrine re-uptake inhibitors (amitriptyline, olanzapine, venlafaxine),
- adrenergic receptor blockers (atenolol, phenoxybenzamine),
- monoamine oxidase inhibitors (moclobemide, phenelzine),
- recreational drugs (cocaine, amphetamine, caffeine),
- sympathomimetics (salbutamol, terbutaline),
- others (paracetamol).

Imaging

After positive biochemical tests, the first-line investigation for localizing the tumour is either CT or MRI of the abdomen. They have comparable sensitivities, but MRI is superior in identifying paragangliomas and its specificity is higher than that for CT.

Further functional imaging (e.g. scintigraphy) is probably not necessary in patients with a low probability of metastatic or multi-focal disease. This comprises patients aged over 40 yr, with no family history, negative genetic testing, and a small phaeochromocytoma secreting predominantly metanephrines. However, functional imaging is of crucial importance for preoperative staging in those patients with extra-adrenal paragangliomas.

Scintigraphy is an imaging technique where a radiopharmaceutical is administered to the patient and the resultant emissions are captured on a two-dimensional gamma camera to form an image. Meta-iodobenzylguanidine (MIBG-123) is a radioactive analogue of norepinephrine and is thus concentrated in adrenergic tissue after ingestion. It can be used to identify both phaeochromocytomas and paragangliomas, although it is less sensitive for dopamine-secreting tumours. Since normal adrenal glands absorb MIBG-123, the findings must be correlated with other cross-sectional imaging.

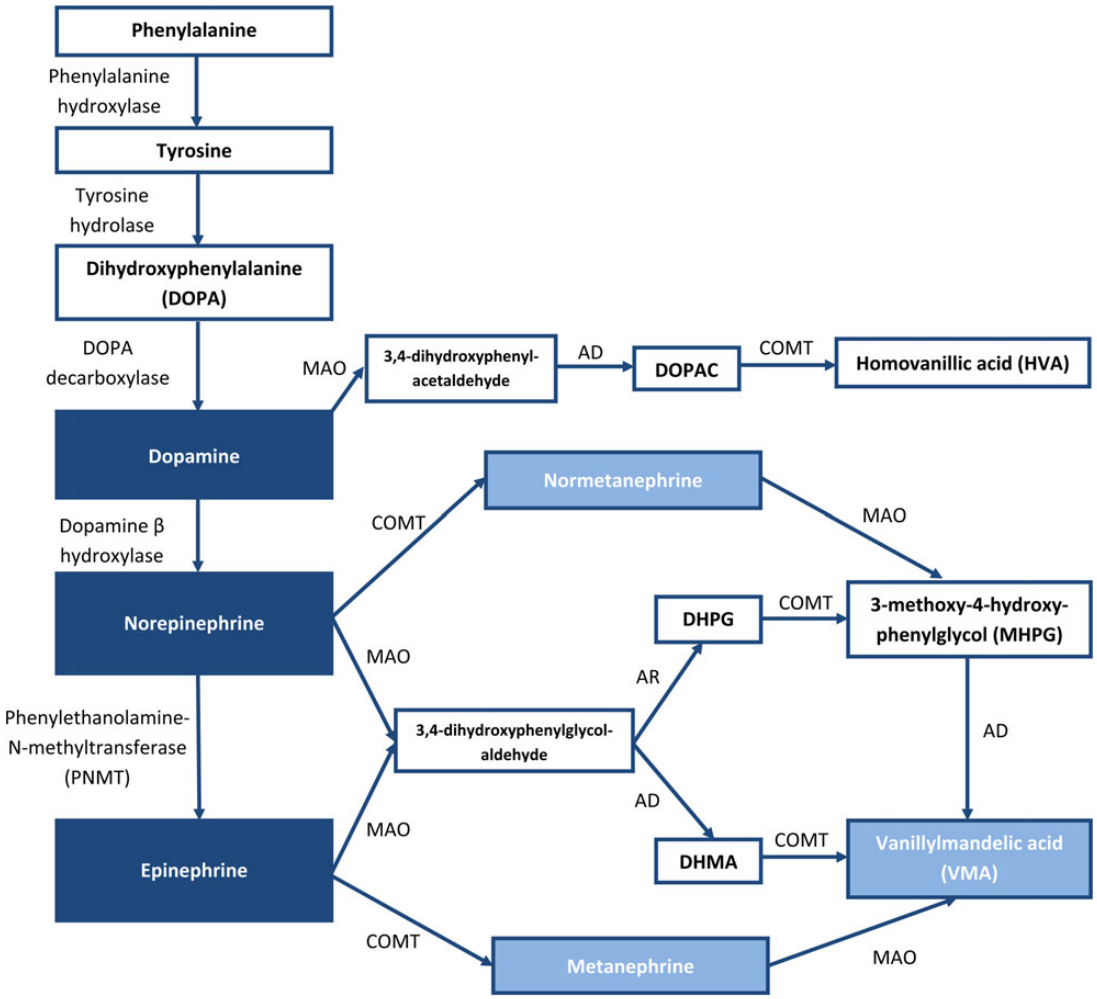

Fig 1 Catecholamine metabolism. COMT, catechol-O-methyltransferase; DOPAC, 3,4-dihydroxyphenylacetic acid; AD, aldehyde dehydrogenase; AR, aldehyde reductase; MAO, monoamine oxidase; DHPG, dihydroxyphenol-glycol; DHMA 3,4-dihydroxymandelic acid.

Preoperative preparation

The objectives of preoperative care include:

- arterial pressure control,
- reversal of chronic circulating volume depletion,
- heart rate and arrhythmia control,
- assessment and optimization of myocardial function,
- reversal of glucose and electrolyte disturbances.

Arterial pressure control and volume expansion

Early phaeochromocytoma surgery saw mortality rates of up to 45%, with severe intraoperative hypertension, strokes, arrhythmias, myocardial ischaemia, left ventricular failure, and refractory hypotension after tumour resection.

Although the evidence base has recently been questioned,[4] preoperative α-block is standard practice and aims to provide preoperative arterial pressure control with subsequent restoration of blood volume (which may be titrated using serial haematocrits). Commonly used α-blockers include phenoxybenzamine and doxazosin.

Phenoxybenzamine

Phenoxybenzamine is a non-selective, non-competitive, long-acting α-blocker. Its non-competitive antagonism may reduce the effects of catecholamine surges, but may be implicated in postoperative refractory (catecholamine-resistant) hypotension. It should therefore be stopped 24–48 h before surgery due to its long half-life. Its non-specific nature also allows pre-synaptic α_2-blockade which interferes with the norepinephrine negative feedback loop that regulates norepinephrine release. The resulting uninhibited release of norepinephrine from cardiac sympathetic neurones causes a reflex tachycardia via β_1 stimulation. Central α_2-blockade also results in somnolence, headache, and nasal congestion.

Doxazosin

Doxazosin is a competitive, selective α_1-blocker. It does not cause tachycardia or sedation and some studies suggest a reduced incidence of postoperative hypotension, making it a good alternative to phenoxybenzamine. Its efficacy is currently being investigated by the PRESCRIPT trial,[5] which randomizes patients to receive either phenoxybenzamine or doxazosin.

Calcium channel blockers

Calcium channel blockers inhibit norepinephrine-induced calcium influx and have been utilized for haemodynamic control before surgery, mainly as an additional drug class to further improve control in those already α-blocked. They are not recommended for monotherapy unless patients have very mild hypertension or develop severe orthostatic hypotension with α-blockers.[6] Sustained-release nicardipine 30 mg twice daily is a commonly used preparation.

In addition to pharmacological control, a high sodium diet and fluid intake are also recommended to help restore blood volume.

Heart rate and arrhythmia control

Tachyarrhythmias may result from epinephrine/dopamine-secreting tumours or be secondary to α-blockade. Selective β_1 antagonists (such as atenolol or metoprolol) are preferred to manage these and must be started after complete α-blockade. This avoids the unopposed α-mediated vasoconstriction that could occur after antagonism of β_2-mediated vasodilatation, which may precipitate a hypertensive crisis (while the negative inotropic effect of β-blockade further compromises myocardial function).

Assessment and optimization of myocardial function

An ECG may reveal ventricular hypertrophy, tachyarrhythmias, or myocardial ischaemia.

A degree of diastolic dysfunction appears to occur in the majority of patients, while left ventricular systolic dysfunction occurs in around 10%. Echocardiography is therefore considered mandatory.

Various forms of cardiomyopathy have been described, with hypertrophic cardiomyopathy, as a result of chronic hypertension, being the most frequent. There are also many case reports of inverted (atypical) Takotsubo cardiomyopathy.

The impaired cardiac function associated with phaeochromocytoma may improve once catecholamine levels return to normal.

Reversal of glucose and electrolyte disturbances

Hyperglycaemia can occur due to increased glycogenolysis (α_1 receptors), impaired insulin release (α_2 receptors), lipolysis (β_1 receptors), and increased glucagon release coupled with peripheral insulin resistance (β_2 receptors) and is treated with standard therapies.

Electrolyte measurements will identify catecholamine-induced renal impairment. Hypercalcaemia occurs when a neuroendocrine tumour is associated with a parathyroid adenoma (e.g. as occurs in MEN 2A).

Assessment of adequate optimization

α-Blockade is commenced at least 7–14 days before surgery, although a longer course of treatment may be required for patients with cardiomyopathy or refractory hypertension. The aim is to achieve arterial pressure control with spontaneous restoration of circulating volume. Until recently, the 1982 Roizen criteria for optimal preoperative control have been cited:

- arterial pressure readings consistently <160/90,
- the presence of orthostatic hypotension with a decrease in systolic arterial pressure of at least 15% but not <80 mm Hg,
- an ECG which is free of ST or T wave changes for 2 weeks.

These should now be questioned. Although there is no consensus, contemporary arterial pressure targets are tighter (seated arterial pressure of <130/80 mm Hg) and orthostatic hypotension is not a necessity. ST or T wave changes may reflect inverted Takotsubo cardiomyopathy rather than ischaemia.

Intraoperative management

The available data do not support one intraoperative approach over another. Surgery is increasingly laparoscopic, reducing postoperative recovery times, but not haemodynamic instability. Open surgery is likely to be required for large or invasive adrenal masses and most paragangliomas.

Laparoscopic surgery may be performed via a transabdominal or retroperitoneal approach. Both are performed in the lateral position, with the retroperitoneal approach also requiring significant table break to improve access and allow triangulation of the laparoscopic ports in a relatively confined space. The

transabdominal approach is now increasingly favoured due to more familiarity with the anatomy and quicker access to the adrenal vein. While this approach does not require the significant table break, it may still be requested (probably as a historical hangover).

Risk factors for intraoperative haemodynamic instability include high pre-induction plasma norepinephrine levels, large tumour size, profound postural drop after commencement of α-blockade, and a pre-induction mean arterial pressure (MAP) above 100 mm Hg.[7] The chosen anaesthetic technique should:

- avoid drug-induced catecholamine release,
- avoid catecholamine release induced by anaesthetic or surgical manoeuvres,
- minimize haemodynamic responses to tumour handling,
- treat episodes of hypotension, particularly after tumour devascularization.

Avoiding drug-induced catecholamine release

A number of commonly used drugs may increase catecholamine levels by promoting their pre-synaptic release, inhibiting their reuptake or via raised catecholamine levels accompanying histamine release. Drugs to consider avoiding on this basis include desflurane, ketamine, morphine, pethidine, atracurium, pancuronium, ephedrine, droperidol, metoclopramide, and cocaine. In addition to stimulating sympathetic ganglia, succinylcholine may theoretically provoke tumour catecholamine release via raised abdominal pressure from muscle fasciculation, although its use has been described without complications.

Avoiding catecholamine release induced by anaesthetic or surgical manoeuvres

Although tumour handling induces by far the most significant haemodynamic responses, catecholamine release is also provoked by tracheal intubation and the raised intra-abdominal pressure associated with capnoperitoneum or coughing. Capnoperitoneal pressures of up to 28 mm Hg have been advocated to both improve surgical access and reduce venous bleeding without any apparent increase in cardiovascular instability, although the supporting evidence is sparse.[8] The arterial pressure response to pain is also likely to be exaggerated.

Magnesium sulphate

Magnesium sulphate inhibits adrenal catecholamine release and reduces α-adrenergic receptor sensitivity to catecholamines. It also dilates predominantly arteriolar vessels, reducing left ventricular afterload while maintaining preload and exerts antiarrhythmic effects via antagonism of L-type calcium channels. In a case series by James,[9] 3–5 μg kg^{-1} fentanyl combined with 40–60 mg kg^{-1} of magnesium sulphate before intubation followed by an infusion of 1–2 g h^{-1} (with further boluses if required) provided good control of systolic arterial pressure before tumour handling.

Remifentanil

Remifentanil is a popular alternative to fentanyl as its pharmacokinetic profile facilitates rapid titration to effect. It is very effective in blunting haemodynamic responses to intubation or pain, although it is inadequate in preventing hypertension associated with tumour manipulation when used as a single agent. If remifentanil is used, alternative postoperative analgesics are required.

Dexmedetomidine

Dexmedetomidine is a centrally acting selective α_2-receptor agonist with sedative and analgesic properties. Its use as part of a general anaesthetic technique is well described outside the UK. It has a slow onset and is usually loaded at a dose of around 1 μg kg^{-1} (over 10 min) and then infused at around 0.5 μg kg^{-1} h^{-1} as an adjuvant to volatile or propofol anaesthesia. In addition to its sedative and analgesic properties, its central sympatholytic effects result in substantial reductions in plasma norepinephrine levels, making it a potentially very attractive agent for phaeochromocytoma surgery. However, the relatively few case reports describing its use in this setting have still required additional vasodilators, particularly during tumour handling.

Minimizing haemodynamic responses to tumour handling

Catecholamine surges during manipulation of the tumour can result in profound hypertension, bradycardia (with norepinephrine), and tachyarrhythmias (with epinephrine). Although early surgical ligation of the adrenal vein was traditionally recommended to attenuate intraoperative haemodynamic instability, increases in catecholamine levels may still occur and the approach carries a higher risk of damaging surrounding structures, particularly for larger tumours. A recent randomized control trial found no difference in plasma catecholamine levels or episodes of haemodynamic instability between the early or late adrenal vein ligation groups.

Hypertensive crises are generally managed with a vasodilator, while tachyarrhythmias, including the reflex tachycardia seen with the use of many vasodilators, are controlled with β-blockers. β-Blockers also minimizes the excessive inotropy seen with epinephrine-secreting tumours.

Although there is little evidence on which to base drug selection, agents that have been used successfully are described below.

Phentolamine

Phentolamine is a reversible non-selective α-receptor antagonist, which primarily results in vasodilatation and can lead to reflex tachycardia. It is usually administered as a bolus of 1–2 mg, has a short duration of action, but may demonstrate tachyphylaxis. It can be used as the sole vasodilator, but is particularly useful to control surges in arterial pressure while establishing desired infusion rates of other drugs.

Sodium nitroprusside and glyceryl trinitrate

Sodium nitroprusside (SNP) and glyceryl trinitrate (GTN) are both nitric oxide donors, which cause venular and arteriolar vasodilatation. SNP causes predominantly arteriolar dilatation while GTN is principally a venodilator. Although both have rapid onset and offset of action, the decrease in arterial pressure seen with SNP is more rapid which probably explains its preferential use as the first-line vasodilator for phaeochromocytoma surgery. GTN may have a greater role in patients with ischaemic heart disease since it increases coronary blood flow by dilating collateral vessels and suppressing coronary vasospasm; conversely, SNP may reduce coronary perfusion through its greater effect on diastolic arterial pressure and theoretical potential to induce intracoronary steal. Reports on the effect of SNP and GTN on cardiac output are contradictory—probably as a result of differences in preoperative circulatory volume. SNP infusions should be started at 0.5–1.5 μg kg^{-1} min^{-1} and increased up to 4 μg kg^{-1} min^{-1} as required. At this dose, the risk of cyanide toxicity is very low for intraoperative infusions of <12 h in patients with

normal renal and hepatic function.[10] GTN infusions are usually adjusted according to response within the range of 10–200 μg min^{-1}. Tachyphylaxis commonly becomes an issue after a continuous infusion lasting over 24 h.

Nicardipine

Nicardipine, a dihydropyridine calcium channel antagonist, is a potent arterial vasodilator and can be administered by infusion intraoperatively. It is initiated at a rate of 3–5 mg h^{-1} for 15 min and adjusted by increments of 0.5 or 1 mg h^{-1} every 15 min. Once the target pressure is achieved, the infusion should be gradually reduced to 2–4 mg h^{-1}. Hypertensive crises can be treated with boluses of 1–2 mg. Cardiac output is maintained without the tachycardia seen with SNP and GTN, making it the preferred choice of some authors. However, clinical experience is still limited and its elimination half-life of 40–60 min can result in persistent hypotension. Clevidipine is a novel alternative of the same class which achieves a shorter half-life via plasma and tissue esterase hydrolysis and has been successfully used in phaeochromocytoma surgery.[11]

Esmolol

Esmolol is a selective β_1 antagonist with a rapid action and short duration. These properties make it the ideal β-blocker for these cases. The initial loading dose is 500 μg kg^{-1} over 1 min, followed by a 4 min maintenance infusion of 50 μg kg^{-1} min^{-1}, which is subsequently titrated to clinical effect.

Treating hypotension after tumour devascularization

Periods of hypotension during surgery are relatively common and may result from anaesthetic drugs (particularly if circulating volume is reduced) or from the treatment of a hypertensive episode outlasting a transient catecholamine surge. These periods can be managed with a combination of fluid boluses, titration of vasodilators, and administration of direct α-receptor agonists.

Of more significance is the hypotension seen after devascularization of the tumour which is relatively common and may be both profound and catecholamine-resistant.

The underlying mechanisms of this hypotension are still debated. One common explanation is residual α-blockade, particularly after the preoperative use of phenoxybenzamine. Abrupt catecholamine deficiency after tumour resection in combination with catecholamine receptor down-regulation caused by chronic elevation of catecholamine levels may also be implicated.

In the first instance, hypotensive agents should be stopped and fluid balance optimized taking into account the possibility of ongoing postoperative haemorrhage, myocardial dysfunction, or both. Norepinephrine can initially be used to increase peripheral vascular resistance and vasopressin should be considered if hypotension is refractory.

Vasopressin

Vasopressin causes systemic vasoconstriction and pulmonary vasodilatation by acting on V1 receptors. It also increases circulatory volume by acting on V2 receptors in the distal convoluting tubule and collecting ducts of the kidney, thereby increasing water reabsorption.

There have been several case reports of the successful use of vasopressin after phaeochromocytoma resection, although dosing practices varied widely. Bolus doses of 0.4–20 units were administered and subsequently followed by an infusion of 1–3 mU kg^{-1} min^{-1}.

Monitoring

Invasive arterial monitoring should be obtained before induction of anaesthesia. Central venous access is necessary, if only for drug infusions, and can usually be inserted after induction.

There is no evidence base to support the use of cardiac output monitoring in phaeochromocytoma surgery. Nevertheless, assessment of circulatory volume can be particularly challenging in the context of cardiomyopathy and cardiac output monitoring may be invaluable in this subgroup.

Traditionally, pulmonary artery catheters were the preferred cardiac output monitor,[12] but there are well-documented risks of insertion. Case reports describe the use of intraoperative transoesophageal echocardiography to guide fluid management and titration of vasodilators.[13]

Oesophageal Doppler has been used in the paediatric population[14] and a prospective study investigating its efficacy in phaeochromocytoma patients is currently being undertaken in Austria (http://clinicaltrials.gov/show/NCT01425710).

Devices relying on arterial pulse contour analysis may be either calibrated by lithium or thermodilution (LiDCO and PiCCO, respectively) or by an algorithm (LiDCO Rapid & Flotrac-Vigileo). Neither have been formally evaluated in phaeochromocytoma surgery.

There has been some interest in the Δdown parameter (the difference between the minimum systolic arterial pressure during the respiratory cycle in a mechanically ventilated patient and the systolic arterial pressure during an end-expiratory pause) with a small Canadian study reporting a Δdown of <2 mm Hg as predictive of adequate intra-vascular volume during phaeochromocytoma surgery.[15] There are also several case reports describing the use of a variety of these monitors in this patient cohort, some suggesting they are beneficial while others describe them as misleading.

This is not surprising. Concerns have previously been raised that cardiac output readings from algorithm-calibrated systems in particular display poor accuracy in conditions of haemodynamic instability and significantly fluctuating vascular tone.[16] As it is precisely these conditions that are observed in phaeochromocytoma surgery, the potential benefit of such devices should be questioned. Thus, although they have obvious appeal, it is hard to recommend devices relying on pulse contour analysis for phaeochromocytoma surgery.

Postoperative care

If the procedure is surgically uncomplicated, most patients should be suitable for extubation at the end of surgery. All patients should receive invasive arterial pressure monitoring in a high dependency environment for at least 24 h after the procedure. Hypertension is most commonly the result of pain, co-existing essential hypertension, urinary retention, or fluid overload. Inadvertent ligation of the renal artery precipitates hyper-reninism, which may lead to delayed hypertension. Persistent hypertension heralds more sinister causes such as incomplete tumour resection or metastatic disease. Even in those patients without recurrence, hypertension is present in 26% at 5 yr and 55% at 10 yr after surgery. All patients should therefore receive both clinical and biochemical outpatient follow-up at 6 weeks and 6 months followed by an annual review for at least 10 yr.

The mechanisms and management of postoperative hypotension have been discussed previously.

Lifelong steroid replacement is indicated if a bilateral adrenalectomy has been performed, but steroid supplementation is rarely required otherwise. One common regimen is initiated

before operation with 100 mg of hydrocortisone administered every 8 h. In the first postoperative 72 h, the hydrocortisone dosage is weaned to 25 mg twice daily before being converted to oral prednisolone.

Hypoglycaemia due to rebound hyper-insulinism can occur when the inhibitory effect of norepinephrine on insulin producing cells is eliminated and its presentation may be masked by concurrent β-receptor blockade. Regular blood glucose monitoring and appropriate titration of dextrose infusions is therefore recommended.

Incidental presentation during surgery

Phaeochromocytoma may first present during incidental surgery. Although historically associated with mortality rates of up to 40%, a recent review of 62 cases between 1988 and 2010 showed a perioperative mortality of 8%[17] with the majority of deaths occurring after operation.

Presenting features include hypertension (by far the most common presentation during incidental surgery), tachyarrhythmias, and cardiac failure associated with hypotension and pulmonary oedema. This makes the differential diagnosis wide and in the aforementioned review, only 26% of cases were suspected as a phaeochromocytoma intraoperatively.

If phaeochromocytoma is suspected, intraoperative management follows the same principles as in elective cases. Factors triggering release of catecholamines should be eliminated, including tumour manipulation, and invasive arterial monitoring should be instigated urgently. Hypertension may be controlled by the use of an α-blocker, such as phentolamine, or nitrates. Unopposed β-blockade may precipitate myocardial dysfunction via the mechanisms previously discussed, thus any severe tachycardia would be best controlled with esmolol due to its β_1 selectivity and short duration of action.

Surgery should be terminated as soon as is feasible and thus, unlike planned phaeochromocytoma surgery, continued catecholamine surges may persist after operation. Excessive intra- and postoperative vascular spasm may result in myocardial or cerebral infarction, acute kidney injury, and/or mesenteric ischaemia.

Postoperative management should be provided on a high dependency unit until haemodynamic control is achieved with definitive surgery generally waiting until optimal adrenergic blockade. In a very small minority of cases, definitive surgery may be expedited if multi-organ failure ensues, despite maximal medical therapy.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Statistical analysis: sample size and power estimations

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Key points

- The reporting of the sample size calculation is useful to identify the main outcome and the minimum difference or effect of clinical importance.
- Sample size calculations require the minimum standardized difference, type I error rate, and power.
- *Post hoc* power estimations can help identify important 'negative' studies where no significant difference or effect is found.
- Type I errors occur when the null hypothesis is incorrectly rejected, meaning that research incorrectly identifies a difference or effect as significant where no such difference exists.
- Type II errors occur when the null hypothesis is incorrectly accepted, meaning that research fails to identify a significant difference or effect that actually exists.

Medical research sets out to form conclusions applicable to *populations* with data obtained from randomized *samples* drawn from those populations. Larger sample sizes should lead to more reliable conclusions. Sample size and power considerations should therefore be part of the routine planning and interpretation of all clinical research.[1] The purpose of this article is to outline the issues involved and to describe the rationale behind sample size and power calculations.

Research has significant costs in terms of organizational outlay and staffing, and also the potential costs to patients and subjects. Patients in clinical trials may be subjected to the risks of receiving potentially useless or harmful new treatments, or of not receiving a beneficial new treatment if they are assigned to a control arm. Consequently, there is a strong ethical justification for researchers to ensure that the data they collect are sufficient and of adequate quality such as to maximize the likelihood of the research contributing to practically useful conclusions. There are two main ways in which the conclusions from an interventional clinical trial may be incorrect when applied to the population as a whole. These are called type I and II errors (Table 1).

Type I errors and confidence levels

A type I error occurs when the effect of an intervention is deemed significant when in fact there is no real difference or effect due to the intervention. In statistical terms, this occurs when the null hypothesis is incorrectly rejected and this causes a false-positive result. Type I errors are caused by uncontrolled confounding influences, and random variation. The probability of a type I error occurring can be pre-defined and is denoted as α or the *significance level*. In most clinical research, a conventional arbitrary value of $P<0.05$ is commonly used. Thus, if the null hypothesis is rejected, there should be a 5% chance of a type I error. As the sample size of a study increases, the *P*-value will decrease. The corresponding $1-\alpha$, or 95%, represents the *specificity* of the test.

Type II errors

A type II error occurs when the effect of an intervention is deemed insignificant when in fact the intervention is effective. In statistical terms, this occurs when the null hypothesis is incorrectly accepted and this causes a false-negative result. Type II errors are more likely to occur when sample sizes are too small, the true difference or effect is small and variability is large. The probability of a type II error occurring can be calculated or pre-defined and is denoted as β.

Power

The *power* of a study is equal to $1-\beta$ and represents the *sensitivity* of a test. It is more conventional to refer to the power of a test rather than β. Power is the probability of correctly finding a

Table 1 Type I and II errors

	The null hypothesis is true: there is no true difference	The null hypothesis is false: there is a true difference
Study accepts the null hypothesis	Correct conclusion: specificity (1–α)	Type II error (β)
Study rejects the null hypothesis	Type I error (α)	Correct conclusion: power (1– β)

given, existing difference or effect as significant. This tends to be arbitrarily set at 80%, meaning that if a difference or effect exists, there will be a 20% probability of a type II error and the null hypothesis being incorrectly accepted. The convention of having a greater tolerance of type II compared with type I errors reflects the perceived greater seriousness of promoting an intervention that has no benefit compared with the risk of missing a potentially beneficial one, although the pharmaceutical industry would understandably have a different take on this. The power of a study is increased by increasing the sample size.

Procedure for estimating a sample size

There are four quantities that need to be specified to perform sample size calculations.

The minimum difference or effect that represents clinical importance

This refers to the smallest clinically relevant difference which it would be useful to find as significant in the trial and should be stated clearly by the researcher before conducting the study. Larger minimum effect sizes or differences suggest the potential for separation of the underlying populations, so it should be easier to find significance and improve the power of the study. Conversely, smaller minimum effect sizes suggest potential overlap of the underlying populations and the power to find the effect as significant will be reduced with an increased type II error.

Standard deviation

The standard deviation σ of the population from which a data set is sampled affects the probability of error for a given sample size. For tightly distributed data (with a relatively small σ), a statistical test is more likely to detect a significant difference, than for loosely distributed data with a relatively high σ and more potential for overlap of the distributions.

When undertaking research, the population σ may not be known. Estimates may be obtained from previously published data or by the conduct of a pilot study. However, as an empirical estimate, σ can be calculated using the *1/5th rule*. As 6 standard deviations represent >99% of the data or the range in a Gaussian distribution, a conservative estimate of σ (which will therefore be a slight overestimate) can be made by dividing the likely range of values for the variable by five and using this empirical estimate for the sample size calculation.

The desired type I error rate

By convention, in medical research, this is often set at $P<0.05$, but this does not have to be so. For example, there may be more than one specified outcome of interest in a study, so this increases the probability of the overall type I error or of a false-positive response. An approach to reduce this risk is to lower the significance level. A simple approach for a small number of comparisons is to use the Bonferroni correction which simply lowers the threshold for significance by dividing the desired overall type I error rate by the number of comparisons or hypotheses tested. So for two and three outcomes or comparisons, the P-value for significance would be lowered to <0.025 and <0.017, respectively, to keep the overall type I error to $P<0.05$ in the study. Conversely, one can simply multiply each P-value by the number of hypotheses and only reject those still at $P<0.05$ to keep control of the overall type I error rate at that level.

The power, based on the desired type II error rate

Again by convention, power is often set at 80% for most medical research, but this does not have to be the case. In the situations where the additional risks and inconveniences to the subjects are minimal, the costs of the study are low and the practicalities of the study are supportive, higher power at >90% may be more appropriate to further reduce the risk of a type II error and the failure to identify a true effect of the intervention or treatment.

The standardized difference

The minimum difference and the standard deviation σ can be combined as minimum difference divided by the standard deviation.

$$\text{Standardized difference} = \frac{\text{minimum difference}}{\text{standard deviation } (\sigma)}$$

This expresses the minimum difference as a multiple of the standard deviation and is termed the *standardized difference* and it is this that is essentially used for sample size calculations.

The above information can be combined in a formula to give an estimate of the required sample size:

$$n > \frac{2K\sigma^2}{d^2}$$

where n is the minimum number in each group, σ the standard deviation of the measured variable, d the minimum clinically important difference, and K a constant derived from the required power and α error.

This can be simplified, using the standardized difference, to estimate the number in each group for a two-group study with significance set a $P<0.05$ and power at 80%:

$$n > \frac{16}{(\text{standardized difference})^2}$$

So to find as significant a minimum difference equal to 1 standard deviation, n=16 patients in each of the two groups will be required.

For categorical data expressed as proportions in two groups, where p is the average of p_1 and p_2, the standardized difference is estimated by:

$$\text{Standardized difference} = \frac{p_1 - p_2}{\sqrt{p(1-p)}}$$

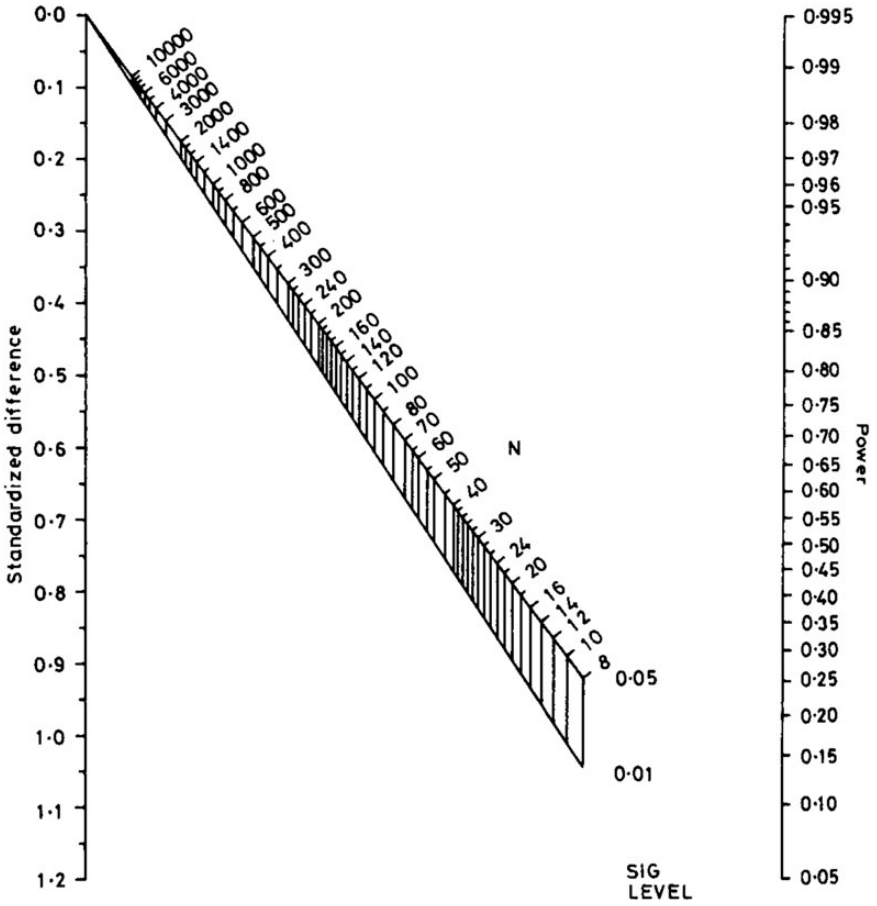

Fig 1 Altman nomogram, reproduced from Altman,[2] with permission.

So to find a difference in proportions of 0.75 and 0.25 as significant, again n=16 patients in each of the two groups will be required as the standardized difference is 1. The proportions could represent binary (yes/no) outcomes such as postoperative nausea and vomiting or mortality.

Alternatively, the *Altman nomogram* can be used to calculate sample size by drawing a straight line through the standardized difference, α level, and power to read off the sample size (Fig. 1).[2]

Retrospective power calculations

Prospective sample size calculations allow for optimal sample size planning in order to obtain adequate control over the risks of type I and II errors. However, it is possible to calculate after the study, or *post hoc*, the estimated power of a study. Although this is useful for planning future studies, it is also helpful in the interpretation of a negative trial that did not identify a significant effect for the intervention. A *post hoc* power calculation can help decide if the original study, as conducted, did have sufficient power to find the specified minimum difference or effect as significant. Hence, we can decide between 'useful' and 'not so meaningful' negative clinical trials.

Conclusion

From the foregoing, it should be clear that any meaningful clinical trials should report the sample size and power estimations for the study. Even foregoing the simple mathematics that are required, a sample size calculation should at least help identify for the reader the minimum difference or effect of importance of the intervention and of course, the primary outcome.

Declaration of interest

M.O.C. has Editorial Board roles with the British Journal of Anaesthesia, European Journal of Anaesthesiology and the International Journal of Obstetric Anesthesia.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

Podcasts

This article has an associated podcast which can be accessed at http://www.oxfordjournals.org/podcasts/ceaccp_16.05.01.mp3.

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Anaesthesia for free flap breast reconstruction

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Key points

- Deep inferior epigastric perforator free flap is considered the gold standard in free flap breast reconstruction.
- Appropriate patient selection is a predictor of good clinical outcome in microsurgery.
- Provision of a full hyperdynamic circulation and maintenance of a normal body temperature helps to optimize flap perfusion.
- Careful positioning of the patient is imperative for long procedures to prevent peripheral nerve damage and pressure sores.
- Changes to clinical free flap perfusion need to be recognized quickly and managed appropriately—early detection remains the most important factor in the salvage of free flaps.

Breast reconstruction: an overview

In the UK, all patients undergoing mastectomy should be offered breast reconstruction surgery either at the time of the mastectomy or as a delayed procedure.[1]

There are several options for breast reconstruction, which can be broadly divided into implant-based or autologous flap reconstruction using the patient's own tissue. Implant-based reconstruction often involves the use of saline tissue expanders initially which usually require replacement with a definitive silicone implant. Autologous flap surgery uses a combination of skin, fat, and sometimes part of the underlying muscle. The flap is moved from areas such as the abdomen, upper back, inner thigh, upper hip, or buttocks to the chest where it is shaped into a new breast. For implant-based reconstruction, 34% of patients suffer complications such as capsular contracture or a foreign body scarring reaction, that requires them to have further surgery within 5 yr.[2] Although autologous flap reconstruction involves a longer duration of initial surgery, when compared with implant-based reconstruction, it may be associated with a reduced number of operations, lower complication rates, and it is often easier to achieve a more natural aesthetic appearance.

Autologous flaps can be pedicled or free. The most common example of the former is the latissimus dorsi flap, where donor tissue remains connected to the original donor site via an intact vascular pedicle, and is moved into the breast defect through the axilla. In contrast, free flaps are completely detached from the body with division of the vascular pedicle, and then the blood supply is reestablished using microvascular surgery techniques. The two most common free flap procedures for breast reconstruction are the transverse rectus abdominis myocutaneous (TRAM) free flap and the deep inferior epigastric perforator (DIEP) free flap. These procedures harvest an ellipse of lower abdominal tissue and the flap is then transferred to the chest. Unlike the TRAM flap, the DIEP procedure spares the rectus abdominis muscle which helps to preserve abdominal strength, halving the likelihood of a bulge or hernia and shortens recovery time. Because of this, the DIEP flap is now considered the gold standard for free flap breast reconstruction and will be the main focus of this article.

DIEP free flap breast reconstruction

Owing to the requirement for microvascular surgery, DIEP reconstruction is carried out in specialist regional plastic surgery centres.

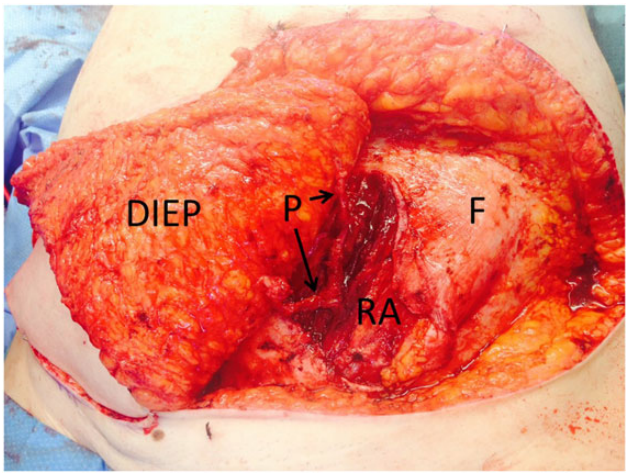

Fig 1 Intraoperative view of DIEP flap viewed from foot of the operating table. The DIEP flap has been reflected to the patient's right side with vascular perforators (P) shown as they are dissected through split in rectus abdominis (RA) muscle, seen under deep fascia (F) which has been opened for access.

DIEP flap breast reconstruction involves three main stages:

(i) Raising of the flap with dissection through the rectus abdominis muscle to meticulously separate out the small perforator vessels originating from the deep inferior epigastric artery (Fig. 1).
(ii) Microvascular anastomosis to the internal mammary artery and vein in the chest.
(iii) Insetting of the flap and shaping of the transferred tissue.

Primary ischaemia and reperfusion

These are two separate phases of surgery which can affect the viability of the free flap. Primary ischaemia of the flap occurs as blood flow ceases during flap transfer which induces anaerobic cellular metabolism. This leads to an increasing lactate, a decrease in intracellular pH with increasing calcium and pro-inflammatory mediator levels. The severity of the damage caused by primary ischaemia is proportional to the duration of ischaemia. The oxygen consumption of skin is five times lower than that of muscle at rest (0.2 and 1 ml min^{-1} per 100 g of tissue, respectively). Consequently TRAM flaps, which include skeletal muscle, are more sensitive to ischaemia than DIEP flaps.

Reperfusion is the second important phase in free flap surgery and begins with vessel declamping after completion of microvascular anastomosis. Typically, blood flow restoration reverses the physiological transient changes triggered by primary ischaemia. However, an ischaemia/reperfusion injury may occur if some factors are not favourable, such as prolonged ischaemia or inadequate perfusion pressure. In this case, reperfusion injury occurs when blood flow allows the influx of inflammatory substances that may ultimately cause flap compromise.[3]

Free flap microcirculation

Blood flow through the microcirculation is crucial to the viability of a free flap. The microcirculation is a series of successive branches of arterioles, capillaries, and venules from the central vessels. Regulation of blood flow and oxygen delivery is accomplished by these three functionally distinct portions of the microcirculation.

Dissected vascular tissue is denervated and therefore loses intrinsic sympathetic tone. However, the feeding artery and draining vein at the recipient site still respond to physical, humoral, and chemical stimuli such as cold, circulating catecholamines, and pharmacological agents. The absence of intact lymphatic drainage increases the risk of interstitial oedema.

Patient selection and anaesthetic assessment

The importance of appropriate patient selection is a well-known predictor of good outcome in microsurgery. As a result, most of the women presenting for DIEP reconstruction are fit and well apart from their breast cancer. Advanced age alone is not a contraindication to surgery as long as co-morbidities and general health allow the patient to undergo long and extensive surgery. Although smoking is not a contraindication, smokers are advised to stop smoking for at least 4 weeks before surgery. Nicotine-induced vasoconstriction, carbon monoxide-related tissue hypoxia, and blood hypercoagulability caused by increased platelet aggregation can cause problems with breast skin flap vascularity and donor site morbidity.[4] Similarly, obese patients may be advised on weight reduction methods before surgery to improve surgical outcome. Absolute contra-indications to surgery are hypercoagulable states, such as sickle cell anaemia and polycythaemia, which greatly increase the risk of anastomotic thrombosis. A thorough assessment is essential before anaesthesia, and should follow general principles, including adequate planning of anaesthesia and postoperative care.

Anaesthesia for free flap breast reconstruction

There are surprisingly few good randomized controlled trials regarding the best anaesthetic management for patients undergoing free flap surgery. However, a good understanding of the physiology of blood flow both in the systemic circulation and through the free flap will help to make sensible management decisions.

Physiological goals

Survival of the free flap depends on an adequate blood flow and although blood is not a Newtonian fluid and the vessels are not rigid, the Hagen–Pouiselle equation includes a number of parameters which are amenable to manipulation to improve flap survival.

$$\text{Blood flow} = \frac{\pi}{8}\frac{\Delta P}{\mu}\frac{r^4}{l}$$

Although the length (l) is fixed, manipulating pressure gradient (ΔP) across transplanted tissue (systemic arterial pressure minus venous pressure), vessel radius (r), and blood viscosity (μ) can all dramatically improve flow through the flap. The pressure gradient is primarily a function of the systolic arterial pressure which should be adequate to maintain perfusion. Equally important however is the calibre of the blood vessel. Ensuring that the patient is warm and normovolaemic will result in vasodilatation, a low systemic vascular resistance and good peripheral perfusion both to the free flap and the rest of the patient. Traditional teaching recommends that good flap perfusion will be assured if systolic arterial pressure remains within or above the patients' physiological range. However, for breast free flap surgery, it is noteworthy that the flap is anastomosed to the internal mammary artery, which due to its proximity to the heart will have an excellent perfusion pressure. If a low systemic vascular resistance is achieved then flow can occur through the

free flap even if the systolic arterial pressure is below normal. Furthermore, over-zealous fluid administration in an attempt to achieve a supra-normal arterial pressure target is not recommended as this will only result in interstitial oedema, compromising blood flow and gas exchange at the level of the microcirculation. Avoiding hypovolaemia, vasoconstriction, and hypothermia are vital to prevent flap compromise or failure.

Induction, monitoring, and maintenance

Owing to the long duration of surgery, patients are intubated and ventilated. Venous access should be gained with a large gauge peripheral line on the opposite side to surgery as many women will have undergone axillary lymph node sampling or clearance. In women who have undergone chemotherapy, this can be challenging and central venous access may be required. In addition, an arterial line, urinary catheter, and core temperature probe are recommended. Monitoring of fluid requirements can also be achieved using a central venous catheter, but increasingly this can be avoided by the use of some form of cardiac output monitoring and goal-directed fluid therapy, such as an oesophageal Doppler monitor (ODM).

The duration of surgery may be >8 h. Anaesthesia can be maintained using a volatile anaesthetic in oxygen-enriched air or a propofol infusion. In our centre, desflurane is used because of its quick offset; however, isoflurane and sevoflurane offer their own advantages. Isoflurane maintains microcirculatory flow and sevoflurane may attenuate ischaemic–reperfusion injury. More research is required to assess the effects of desflurane on the microcirculation. Although a total i.v. anaesthetic technique offers the advantages of reduced postoperative nausea and vomiting and a smoother recovery profile, emergence can be prolonged after a long infusion. When using a propofol infusion, an appropriate depth of anaesthesia monitor is recommended. Both techniques can be combined with either a remifentanil infusion or intermittent fentanyl boluses. Remifentanil offers excellent intraoperative analgesia, rapid control of arterial pressure, marked vasodilation, and negates the use of a neuromuscular blocking agent.

Adequate ventilation to ensure normal arterial Po_2 and Pco_2 is essential. Hypoxia will produce catecholamine release and vasoconstriction. Hypocapnia will also lead to vasoconstriction, and hypercapnia can cause sympathetic nervous system stimulation.

Patient positioning

Careful positioning of the patient is imperative to avoid the well-recognized problems of peripheral nerve damage and pressure sores. Patients lie supine with arms abducted (crucifix position) and care should be taken to ensure abduction is <90° to prevent brachial plexus injury. Forearms should be in a neutral position to prevent ulnar nerve injury and the arms fixed into position with ties to allow the patient to be sat up intraoperatively to assess for symmetry. Heel pads are used to prevent pressure sores and pillows placed under the knees to stop painful hyperextension. Surgery can last between 6 and 10 h and patients are at risk of stiff, painful joints after operation. It is advisable, if possible, to passively move joints throughout the procedure and at the end of surgery, to help reduce joint pain and stiffness.

Temperature control

Preventing hypothermia is a key component to ensuring adequate conditions for flap perfusion. Large tissue areas are exposed for prolonged periods of time. In addition, induction of anaesthesia leads to redistribution of blood and equilibration of core and peripheral temperature. This is because inhalation agents and opioids reduce the threshold for vasoconstriction by 2–3°C and promote heat loss by vasodilation. If no effort is made to maintain temperature, patients undergo a significant temperature decline over the course of a long procedure.

Forced air-warming devices should be used to maintain normothermia. A surgical access type blanket can be used, but sometimes the opening of the blanket is not large enough to allow access to both the surgical sites of the lower abdomen and the upper chest. We recommend using an underbody warming blanket which overcomes this problem and also allows active warming to begin in the anaesthetic room before induction, while monitoring is established. In addition, the operating theatre should have an adequate ambient temperature, and warm i.v. fluids and humidified gases used to prevent hypothermia.

Haematocrit

The appropriate haematocrit is an optimum balance between viscosity, blood flow, and adequate oxygen-carrying capacity and is thought to be in the region of 30–35%. Maintaining normovolaemia during haemodilution allows a decrease in viscosity, associated decrease in peripheral vascular resistance, increase in cardiac output, and improved tissue blood flow.

Transfusion is rarely required for a single delayed reconstruction but may be needed in individuals undergoing mastectomy with immediate reconstruction, particularly those undergoing bilateral reconstruction.

Fluids and goal-directed therapy

A hyperdynamic circulation with a high cardiac output, peripheral vasodilation, and a large pulse pressure is the ideal to maintain adequate microcirculatory perfusion. In microvascular surgery, a decrease in cardiac output is mainly due to a reduction in preload, either from loss of circulating volume or from pharmacological vasodilation. Any reduction in cardiac output induces vasoconstriction mediated by the sympathetic nervous system, renin–angiotensin aldosterone, and baroreceptor reflex. Therefore, maintenance of an appropriate cardiac output is important for free flap surgery. While the traditional approach was for aggressive fluid therapy, our experience in free flap breast surgery suggests this is not necessary, as fluid losses are not great and due to the proximity of the internal mammary artery to the heart, there is excellent perfusion. Our recommendation is to use goal-directed fluid therapy and our practice is to use an ODM to guide administration of crystalloid and colloid fluids, by monitoring the effect of fluid boluses on stroke volume. A recent trial compared ODM with central venous catheters in free flap perforator surgery. A total of 104 patients were randomized to one of the two groups to receive 250 ml of balanced starch solution titrated against stoke volume increase (ODM group) or sustained right atrial pressure 12–15 cm H_2O (CVP group). Additionally, they received 1–2 litres of crystalloid solution to replace fluid losses. The Doppler group showed reduced anaesthetic time, although operative time was not significantly different between the groups. There were no probe-related complications in the oesophageal Doppler group; however, in the CVP group, six patients suffered complications related to insertion of the central venous catheter. One patient suffered an iatrogenic Horners syndrome and five patients suffered symptomatic haematomas at the site of insertion. Overall fluid input was not different, but patients in the CVP group had a smaller fluid output (blood loss, urine, etc.) and were in greater positive fluid balance compared with

the oesophageal Doppler group. In addition, the patients in the Doppler group spent a mean of 1.9 days less in hospital compared with the other group. There was no difference in core temperature or flap complications between the groups.[5]

Vasoactive drugs

During the dissection stages of surgery, controlled hypotension may be requested. This is usually achieved by altering vapour ±propofol/remifentanil concentrations. Vasodilators are generally avoided as they may be harmful due to the risk of blood flow steal away from the flap. During anastomosis of the flap, normotension is usually sufficient to ensure an adequate perfusion pressure through the tissue. The use of vasoconstrictors is a contentious issue in free flap anaesthesia, largely over fears that systemic vasoconstriction leads to reduced flap perfusion. However, there are very few good quality studies that support this and only a few vasoconstrictors have been studied in this context. A recent retrospective study of over 250 microsurgical breast reconstructions examined intraoperative phenylephrine±ephedrine use and concluded that vasopressor use did not adversely affect outcome.[6] Further studies are needed to fully evaluate and compare the effect of different vasopressors on the free flap microcirculation. However, the use of phenylephrine and ephedrine to maintain normotension in adequately filled patiently appears safe.

Anticoagulation

Deep venous thrombosis is a risk in prolonged surgery. Anti-embolism stockings and cyclically inflating anti-embolism leggings are used, as is prophylactic subcutaneous heparin which also improves flap survival.

Emergence

Coughing and retching increase venous pressure and reduce flap flow; therefore, smooth emergence and extubation is desirable. Techniques to smooth extubation include the use of a low-dose remifentanil infusion to aid tube tolerance, deep extubation, or exchanging the tracheal tube for a supra-glottic airway device.

Analgesia

Patients undergoing DIEP reconstruction have two operative sites—the chest and the lower abdomen. Compared with mastectomy alone, free flap breast reconstruction is thought to be less painful as the flap is insensate and its use for wound closure avoids excess skin stretching. Therefore, the chest wound is usually less painful than the abdomen incision. While systemic analgesics are usually sufficient to treat pain, transverse abdominal plane blocks have been shown to reduce postoperative opioid requirement up to 48 h. They can be placed by the anaesthetist at induction under ultrasound guidance or by the surgeons under direct vision.[7] The latter offers the advantage of accurate placement and reduction in risk. In addition, a catheter can be placed to allow local anaesthetic to be infiltrated after operation. This is mostly placed under direct vision by the surgeon at the end of the procedure. Systemic postoperative analgesia usually consists of paracetamol, non-steroidal anti-inflammatory drugs if appropriate, and opioids which can be given using patient-controlled analgesia or orally. It is important that optimum analgesia is continued into the postoperative period to not only ensure patient comfort but also prevent surges in sympathetic activity which could compromise free flap survival.

Postoperative care

Secondary ischaemia occurs after flap transfer and reperfusion. This period is more harmful to the flap than primary ischaemia. Free flaps affected by secondary ischaemia present with massive intravascular thrombosis and significant interstitial oedema. Although the skin and fat of a DIEP free flap can tolerate up to 10–12 h of ischaemia, after only a few hours, irreversible pathological changes arise in the muscle used in a TRAM free flap. It is essential that all measures taken to ensure adequate tissue perfusion during surgery are continued after operation.

Causes of free flap failure

The overall failure of DIEP free flaps is 0.9%.[8] These are most commonly due to surgical complications and therefore poor flap perfusion should be rapidly identified with expeditious return to theatre before compromise becomes irreversible (Table 1).

Monitoring the free flap

Clinical flap observations remain the most common method of monitoring. Early detection remains the most important factor in the salvage of free flaps. Therefore, it is essential that staff caring for these patients are able to recognize an ischaemic flap.

(i) Evaluation of flap colour
(ii) Capillary refill time
(iii) Skin turgor
(iv) Skin temperature
(v) Bleeding on pinprick

An auditory assessment of blood flow using an 8 MHz transcutaneous Doppler is often used by placing the probe on the skin overlying the perforator blood vessel on the flap. This spot is usually marked by the surgeons. The Doppler signal is checked at regular intervals after operation in recovery and on the ward.

If the cause of flap ischaemia is arterial, the flap is cool, pale, with slow capillary refill time, no bleeding on pinprick, and has loss of arterial (triphasic) Doppler signal. If the cause is venous, the flap is warm, congested, bluish in colour, has brisk capillary refill time, rapid bleeding of dark blood on pinprick, and has loss of venous Doppler signal (normally a continuous sound).

Managing the ischaemic free flap

When recognized early and managed promptly (within 6 h), compromised flaps have a 75% salvage rate. The definitive management of a struggling or failing flap is usually surgical and patients require urgent re-exploration to inspect the vascular

Table 1 Causes of free flap failure

Surgical causes	Non-surgical causes
Arterial—technical problems with anastomotic site, spasm, thrombosis due to vessel trauma	Oedema due to excess fluid administration
Venous—kinking of pedicle at the anastomotic site, spasm, thrombus, compression due to haematoma or dressings	Hypercoaguable states
Reperfusion injury due to prolonged ischaemic time	

pedicle for kinks and compression, assess patency of the anastomosis, identify thrombus formation, perform embolectomy if appropriate, or administer intra-arterial thrombolysis.

The same anaesthetic principles used intraoperatively should be continued in the event of compromised flap perfusion, to provide a physiological environment that promotes optimum flap flow.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Severe community-acquired pneumonia

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Key points

- Severe community-acquired pneumonia (CAP) is associated with a high mortality rate and significant morbidity.
- Of patients presenting to hospital with CAP, up to 10% will require critical care admission.
- *Streptococcus pneumoniae* continues as the most common infective pathogen.
- *Staphylococcus aureus*, *Legionella*, and gram-negative pathogens are increasingly frequent causative pathogens.
- Combined viral and bacterial infections may induce a more severe spectrum of disease.

Severe community-acquired pneumonia (CAP) remains a frequent reason for admission to hospital. It is the most common cause of septic shock requiring escalation to treatment within an intensive care unit (ICU). Despite earlier recognition and recent advances in supportive care, severe CAP is still associated with substantial morbidity and mortality, more often seen in the elderly and those with considerable comorbidities.

Definition

CAP is defined as an acute infection of the pulmonary parenchyma, with symptom onset in the community. Diagnosis can still be made within 48 h of hospital admission to meet criteria for a community-acquired infection. Severe CAP is defined as a pneumonia requiring supportive therapy within a critical care environment, that is associated with a higher mortality rate. Severe CAP is frequently a multisystem disease and patients will often present with multiple organ failure.

Epidemiology

The annual incidence of CAP is 1.6–10.6 per 1000 adult population in Europe.[1] Between 1.2% and 10% of patients requiring hospital admission to treat CAP will require ICU admission. The incidence of CAP increases with age, and more than 90% of deaths related to severe pneumonia occur in patients over the age of 70. The 28 day mortality rate in patients admitted to critical care is ~17%, which increases to 24.4% in those requiring invasive mechanical ventilation and 28.8% in those that develop septic shock.[1] Mortality rates in younger patients are more influenced by the severity of the infection rather than the presence of comorbidities. Even in the absence of comorbidities, severe CAP is associated with excess mortality over subsequent years among survivors independent of age.

Clinical features

CAP classically presents with a triad of infective signs (fever, leucocytosis), clinical signs and symptoms (sputum production, tachypnoea, cough, pleuritic chest pain), and a new or changed infiltrate as observed on radiography, for which there is no other explanation except infection. However, these clinical signs and symptoms may not be universally seen or present typically, particularly in the elderly or immunosuppressed. Diagnosis of CAP may be clouded or complicated by underlying disease states that

Table 1 Common pathogens implicated in severe CAP

Pathogen	Risk factors	Other features
Streptococcus pnemoniae	Alcoholism, HIV, i.v. drug abuse, hyposplenism	Pleural effusion, empyema
Staphylococcus aureus	Structural lung disease, i.v. drug abuse, influenza	Pneumothoraces, cavitation
CA-MRSA	Influenza	Necrotizing pneumonia, cavitation, neutropenia, skin pustules
Legionella species	Smoking, foreign travel	Neurological symptoms, raised creatinine kinase, diarrhoea, transaminitis, relative bradycardia
Gram-negative bacilli	Structural lung disease, recent antibiotics, immunosuppression	
Klebsiella pneumoniae	Alcoholism, aspiration	Leucopenia, cavitation, empyema
Acinetobacter baumannii	Alcoholism, aspiration	
Pseudomonas aeruginosa	Smoking, aspiration, HIV, structural lung disease	
Haemophilus influenzae	Aspiration, COPD, smoking, HIV, i.v. drug abuse	
Moraxella catarrhalis	COPD, smoking	
Respiratory viruses	Viral pandemics	Interstitial infiltrates or normal chest radiography
Mycoplasma pneumoniae	Cyclical pandemics	Headache, erythema multiforme, positive cold agglutinin titres
Chlamydophilia		Interstitial infiltrates
Pneumoniae	COPD, smoking	
Psittaci	Exposure to birds	Horder spots, transaminitis
Anaerobes	Alcoholism, aspiration, i.v. drug abuse	Cavitation
Mycobacterium tuberculosis	Alcoholism, HIV, i.v. drug abuse	

affect cardiorespiratory function and by atypical or subacute presentations of infection.

Aetiology

Pneumonia develops when the defensive mechanisms within the lung become overwhelmed by a pathogen which has been either inhaled or aspirated. This is more likely to occur with more virulent pathogens and in patients with reduced host defences. Pathogens responsible for CAP are varied and wide-ranging in their capacity to cause severe disease and extra-pulmonary features (Table 1). The predominant pathogen throughout all age groups remains *Streptococcus pneumoniae*. *Legionella*, gram-negative bacilli, influenzae species, and *Staphylococcus aureus* are becoming increasingly common causes of severe CAP requiring critical care admission in comparison with CAP managed outside of critical care units. The frequency of other less prevalent causes of CAP such as *Chlamydophilia psittaci*, *Coxiella burnetii*, and *Mycoplasma pneumoniae* varies according to epidemiological setting and in part on the diagnostic techniques that are used. No causative organism is identified in up to 36% of cases of severe CAP.

Streptococcus pneumoniae

Streptococcus pneumoniae is a gram-positive α-haemolytic capsulated organism. Infective risk is highest in the immunocompromised, elderly, and hyposplenic patients, although overall frequency is reducing due to vaccination against this pathogen. The clinical response after infection is related to pneumococcal virulence factors and the genetic background of the patient. These indices are believed to alter the systemic inflammatory response that is produced through pneumococcal infection. Although the overall incidence of penicillin resistance is reducing in adults, antibiotic-resistant *S. pneumoniae* may be seen in several patient groups including: severely ill patients admitted to ICU, those at the extremes of age, patients that have recently received β-lactam therapy, immunosuppressed patients, alcoholics, and patients with medical comorbidities.

Staphylococcus aureus

Staphylococcus aureus is a gram-positive aerobic coagulase-positive diplococcus. Resistant strains such as methicillin-resistant *St. aureus* (MRSA) are increasingly isolated in patients diagnosed with severe pneumonia, although surveillance and eradication among at-risk patients has been successful in reducing incidence. MRSA is treated with antibiotics such as vancomycin, linezolid, teicoplanin, and rifampicin, although resistance to vancomycin is increasing. Community-acquired MRSA (CA-MRSA) pneumonia may occur in previously healthy patients with no prior healthcare exposure, often after influenza and can predispose to severe necrotizing pneumonia. The incidence of CA-MRSA currently remains low but needs consideration in any younger patient requiring physiological support for severe CAP.

The Panton–Valentine leukocidin (*PVL*) exotoxin (also referred to as Toxigenic *St. aureus*) is strongly associated with virulent strains of *St. aureus*. The *PVL* gene is carried by both MRSA and methicillin-sensitive *St. aureus* (MSSA). Most PVL-SA strains are currently MSSA, although there is an increasing association with CA-MRSA infection. *PVL*-SA strains are usually associated with community-acquired infections, producing a particularly severe form of haemorrhagic pneumonia that is often preceded by a 'flu-like' illness or necrotizing soft tissue infection (Table 2). Antimicrobials such as linezolid and clindamycin are thought to be effective at suppressing toxin production.

Viral pneumonias

Viral infections are an increasingly common cause of severe CAP, accounting for up to 18–30% of cases. In recent years, we have seen the appearance of several virulent respiratory strains that can cause a severe pneumonic disease, progressing to multi-organ failure. These have included avian influenza A virus (H5N1), Middle East respiratory syndrome coronavirus (MERS-CoV), influenza A virus (H1N1), and severe acute respiratory syndrome. Viral pneumonias often have seasonal predilection and may be preceded by a viral prodrome inclusive of fever, myalgia,

Table 2 Panton–Valentine leukocidin *St. aureus* pneumonia

Epidemiology	Clinical signs	Investigations
Immunocompetent adults Community-acquired MSSA strains more common Preceding 'flu-like' illness or necrotizing skin infection Household history of PVL-SA skin sepsis Rapidly progressing infection with a high mortality rate	Haemoptysis Profound hypotension Diarrhoea and vomiting Tachycardia >140 beats min^{-1} Tachypnoea Skin pustules	Chest radiography may show multi-lobar infiltrates, effusions, or cavitation Markedly elevated C-reactive protein Leucopenia Raised creatinine kinase Sputum Gram-film reveals multiple gram-positive cocci Negative pneumococcal and legionella urinary antigens

Table 3 Risk factors for healthcare-associated and MDR pneumonias

Healthcare-associated pneumonia
Chronic haemodialysis
Residence in a nursing home or extended care facility
Contact with a family member with an MDR pathogen
Hospitalization for >2 days during the previous 90 days
I.V. antibiotics, chemotherapy, or wound care within previous 30 days
Immunosuppressive disease or immunomodulating therapy
Multi-drug-resistant organisms
Previous antibiotic therapy within 3 months
Recent hospitalization
Alcoholism
Immunosuppression
Multiple medical comorbidities (particularly structural lung disease)

non-productive cough, and headache. Pregnancy, obesity, chronic disease, advanced age, and immunosuppression are risk factors for severe illness and development of complications.

Nearly 20% of patients with CAP who have proven bacterial pneumonia are co-infected with a virus. It is often unclear if the viral organism is the primary causative pathogen or has predisposed the patient to secondary bacterial infection.[2,3] Secondary bacterial infection was reported in 4–24% of patients requiring critical care admission during the H1N1 pandemic in 2009. *Streptococcus pneumoniae*, *St. aureus*, and *H. influenzae* were the more common pathogens isolated in these patients in addition to the virus. Mixed infections are thought to induce a more severe inflammatory response in comparison with an individual pathogen, with variable and overlapping signs and symptoms occurring. Although biomarkers such as C-reactive protein (CRP) are more significantly raised in bacterial disease, they are insufficiently sensitive or specific to be used as sole diagnostic indicators to aid differentiation between bacterial and viral pneumonias. Multiplex polymerase chain reaction (PCR) assays enable concurrent recognition of multiple viruses and is now the gold standard diagnostic test. Routine use of these assays has substantially progressed epidemiological knowledge of respiratory viruses. PCR may be performed on nose and throat swabs and nasopharyngeal and tracheal aspirates.

Healthcare-associated pneumonia

Infections with pathogens usually associated with hospital-acquired pneumonias (HAP) are an emerging cause of CAP. Healthcare-associated pneumonia (HCAP)—in which pneumonia develops in patients who have had recent contact with the healthcare system (Table 3)—is distinguished from CAP not just by the environment in which infections develop but also by the causative pathogens involved. HCAP is often caused by MRSA or multi-drug resistant (MDR) gram-negative pathogens such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. HCAP is associated with an increased severity of pneumonia and an excess mortality. This is due to the effects of infection with MDR pathogens and also the age, relatively poor functional status, and related treatment restrictions of those that tend to be affected.

Investigations

General investigations are performed to aid diagnosis, identify the causative pathogen, assess severity, identify complications, and to monitor response to treatment. Investigations should be guided by the severity of pneumonia, previous antibiotic therapy, comorbid illness, and epidemiological factors.

Radiology

Chest radiography (CXR) is the first-line imaging modality in severe CAP. Bacterial and viral pathogens may both induce a wide range of CXR changes. Multi-lobar consolidation is often seen in—although not restricted to—pneumonia involving *Legionella, Streptococci,* and *Staphylococci* spp. *Staphylococcus* pneumonia may present with cavitation and pneumothoraces, whereas CA-MRSA may be associated with rapidly enlarging effusions. Chest ultrasound is useful in confirming the presence of an effusion or empyema and may also assist in identifying the presence of a pneumothorax or fluid overload. Computed tomography (CT) of the thorax should be considered in severe infection or if the patient fails to improve.

Microbiology

In at least 30% of cases, no causative pathogen is isolated. Routine microbiological investigations in severe CAP should include microscopy and quantitative culture of sputum samples, blood cultures, PCR, or direct immunofluorescence of respiratory tract samples, urinary *Legionella* and pneumococcal antigen tests. Serum pneumococcal antigen may also be detected with a reported sensitivity of 70–80%. Urine antigen tests are more sensitive than blood cultures and will remain positive even after the patient has been exposed to appropriate antibiotic therapy. It is, however, of note that *Legionella* urine antigen testing will only detect serogroup 1 which is responsible for 80–95% of CAP due to *Legionella* species and therefore may provide falsely reassuring information. As a general rule, urine antigen tests are most useful for 'ruling in' rather than 'ruling out' disease, as a negative test result for a specific pathogen may only have a sensitivity of 40–86% in early infection and thus false-negative results are not uncommon. If a

Table 4 CURB-65 severity score

Prognostic features
Confusion—abbreviated Mental Test Score ≤8, or new disorientation in person, place, or time
Blood urea >7 mmol litre^{-1}
Respiratory rate ≥30 bpm
Blood pressure—diastolic ≤60 mm Hg or systolic <90 mm Hg
Age ≥65 yr
Risk stratification (each prognostic feature present scores 1 point)
0–1: Low risk (<3% mortality risk)
2: Intermediate risk (3–15% mortality risk)
3–5: High risk (>15% mortality risk)

patient is *Legionella* urine antigen-positive, sputum samples should be tested, so that the species of *Legionella* can undergo epidemiological matching. Bronchoscopy, bronchoalevolar lavage, protected specimen brushing, and thoracocentesis may aid identification of a causative agent when the diagnosis is not established or treatment is failing.

An HIV test should be considered in all patients who are positive for *Streptococcus pneumoniae*, in severe disease and when atypical features are present. Serological assays may aid in the diagnosis of less common pathogens such as *C. burnetii* and when PCR is not available. β-d-glucan forms part of the cell wall of fungi including *Aspergillus* and an assay is available as a means of diagnosing invasive fungal infection. Measurement of procalcitonin (PCT) may help to differentiate between infectious and non-infectious causes of respiratory failure, although must not be used in isolation. PCT can also be used to monitor the efficacy of antibiotic treatment.

Risk stratification

Timely recognition of high-risk patients with severe illness is essential in ensuring that appropriate antibiotic treatment is started promptly and physiological support continues within an appropriate setting. Traditionally, physicians have used clinical evaluation to define severity. Structured severity assessment tools have been developed to assist decision-making regarding critical care admission. They should be used in combination with clinical data, near-patient investigations, and biomarkers to assess severity. Risk stratification tools that are used regularly include the Pneumonia Severity Index (PSI), British Thoracic Society (BTS) CURB-65 score (Table 4), and Severe Community-Acquired Pneumonia Score (Table 5) jointly produced by the American Thoracic Society and Infectious Disease Society of America (ATS/IDSA).[2] Both PSI and CURB-65 have been more extensively validated to recognize low-risk patients and are not as good at predicting need for critical care support. Other risk stratification scores have been developed, including SMART-COP (Table 6), which was created to help identify patients who may require invasive respiratory or vasopressor support.[4] Both ATS/IDSA and SMART-COP perform well as risk stratification tools in identifying patients who require ICU admission, but further validation is required for both.

In an aim to improve simplicity through the use of a single stratification tool, NICE have recommended that CURB-65 be used in combination with clinical judgement and arterial blood gas analysis to guide need for critical care admission.[5] An approach using early warning scores, a risk stratification tool, and a resuscitation bundle could potentially reduce ICU admissions and mortality.[6,7]

Table 5 ATS/IDSA severe CAP score. A need for NIV can substitute for a respiratory rate ≥30 bpm or a Pa_{O_2}/FI_{O_2} ratio ≤250. The presence of one major, or three or more of nine minor criteria should warrant consideration for critical care admission

Minor criteria
Respiratory rate ≥30 bpm
Pa_{O_2}/FI_{O_2} ratio ≤250
Multilobar infiltrates
Confusion/disorientation
Urea ≥7.14 mmol litre^{-1} (≥20 mg dl^{-1})
Leukopenia (WBC count <4×10^9 cells litre^{-1})
Thrombocytopenia (count <100×10^9 platelets litre^{-1})
Hypothermia (core temperature <36°C)
Hypotension (SAP <90 mm Hg; requiring aggressive fluid resuscitation)
Major criteria
Invasive mechanical ventilation
Septic shock with the need for vasopressors

Table 6 SMART-COP score of 3 or more points identifies 92% of those who will require intensive respiratory support

Variable	Points
Systolic arterial pressure <90 mm Hg	2
Multi-lobar involvement on chest radiography	1
Albumin level <35 g litre^{-1}	1
Respiratory rate 50 yr and younger: ≥25 bpm Older than 50 yr: ≥30 bpm	1
Tachycardia (≥125 beats min^{-1})	1
New onset confusion	1
Oxygen level 50 yr and younger: Pa_{O_2}<70 mm Hg, oxygen saturation ≤93%, or Pa_{O_2}/FI_{O_2} ratio <333 Older than 50 yr: Pa_{O_2}<60 mm Hg, oxygen saturation ≤90%, or Pa_{O_2}/FI_{O_2} ratio <250	2
Arterial pH<7.35	2

Management

Diagnosis and aggressive interventions at a very early stage of disease presentation may prevent progression on to multi-organ involvement. Early appropriate parenteral antibiotic administration has been demonstrated to improve patient outcomes, particularly in patients at a higher risk of death.[8] The majority of patients that die with severe CAP tend to do so from complications of multi-organ failure rather than from primary respiratory failure alone and often require renal replacement therapy, invasive circulatory monitoring, and support. Adherence to protocols such as those produced by the BTS or IDSA/ATS is associated with a reduction in overall mortality.[2,9]

Respiratory

Patients with respiratory failure despite high-flow oxygen therapy can be managed with non-invasive ventilation (NIV) or invasive ventilation.[10] NIV is of particular benefit in those patients who are immunosuppressed, have underlying obstructive lung disease or *Pneumocystis jiroveci* infection. A lower Pa_{O_2}/FI_{O_2} ratio and bilateral alveolar infiltrates suggesting acute respiratory distress syndrome (ARDS) are independent predictors of NIV failure and in such patient groups, progression to invasive mechanical ventilation should be considered at an early stage. Early

- First line treatment should include a combination of a broad spectrum β-lactamase stable antibiotic such as co-amoxiclav with a macrolide such as clarithromycin
- In patients allergic to penicillin, a second-generation (e.g. cefuroxime) or third-generation (e.g. cefotaxime or ceftriaxone) cephalosporin* can be used instead of co-amoxiclav, together with clarithromycin
- Adding a fluoroquinolone* is an option for those with high severity pneumonia not responding to combination β-lactam/macrolide antibiotic regimen
- When *Pseudomonas aeruginosa* is a consideration an anti-pseudomonal beta-lactam or carbapenem should be given
- For severe legionella pneumonia, a fluoroquinolone* is recommended, in combination with either a macrolide or rifampicin#
- If necrotizing or cavitating pneumonia is suspected a combination of IV linezolid 600 mg twice daily, IV clindamycin 1.2 g four times a day and IV rifampicin 600 mg twice daily should be added to the initial empirical regimen

Fig 1 Anti-microbial recommendations, amended from BTS Guidelines 2009.[9] *Associated with hospital-acquired infections such as *Clostridium difficile*; #potential small risk of cardiac electrophysiological abnormalities with quinolone–macrolide combinations.

identification of a failed NIV trial is important as several trials have demonstrated poorer outcomes in patients requiring intubation after a prolonged unsuccessful NIV trial. Most patients with severe CAP will require intubation and mechanical ventilation, particularly in the presence of persistent hypoxaemia, severe acidosis, depressed consciousness, or progressive hypercapnia. These patients should be managed with a lung-protective ventilation strategy using low tidal volumes (6 ml kg^{-1} predicted body weight) and plateau airway pressures <30 cm H_2O. Although high PEEP levels may improve oxygenation, there is no mortality difference in comparison with ventilation using low PEEP except in ARDS with a $Pa_{O_2}/F_{I_{O_2}}$ ratio <200 mm Hg.[11]

Advanced respiratory rescue techniques including prone ventilation, extra-corporeal carbon dioxide removal ($ECCO_2R$), and extra-corporeal membranous oxygenation (ECMO) should be considered in cases of refractory hypoxaemia or symptomatic hypercarbia.[12]

Cardiovascular

Hypotension should be managed according to the *Surviving Sepsis Guidelines* of 2012.[13] Fluid resuscitation, vasopressor, and inotropic support is guided by clinical assessment in combination with dynamic flow monitoring, including pulse contour analysis devices (LiDCO™, PiCCO™, Vigileo™), transoesophageal Doppler, and transthoracic echocardiography.

Supportive treatment

Standard care for all patients should include adherence to ventilator-acquired pneumonia and catheter-related bloodstream infection bundles, nutritional support, deep venous thrombosis, and gastric ulcer prophylaxis and chest physiotherapy. Steroids are not routinely recommended as adjunctive therapy in hypoxaemic respiratory failure except in *P. jiroveci* pneumonia. There is currently insufficient evidence to support the use of either G-CSF or statins.

Antimicrobials

Antibiotic therapy is usually begun on an empirical basis based on severity of illness (often guided by severity scoring such as CURB-65), the BTS (Fig. 1) and NICE guidelines, patient risk factors, and local epidemiology of resistant organisms.[5,9] Initial treatment is broad spectrum, aiming to provide cover for *S. pneumoniae*, *St. aureus*, *Legionella*, and gram-negative bacteria. Coverage for atypical bacteria and MDR pathogens should be considered if risk factors for these pathogens are present (Table 2). Atypical and MDR pathogens are more common in patients requiring ICU care. Patients with severe CAP treated with combination antibiotic therapy including a macrolide have an improved survival rate compared with monotherapy. Empirical macrolide monotherapy should be avoided due to emerging pneumococcal resistance. Once a pathogen is identified, antibiotic coverage should be narrowed unless there are concerns about dual pathogen infection. This approach is associated with fewer complications, reduced risk of *Clostridium difficile* infection, and minimizes development of antibiotic resistance. In severe disease, septic shock or in a non-responding patient, continuous infusions of time-dependent antibiotics such as β-lactams and carbapenems may improve outcome. There is however an elevated risk of both line-related infections and thrombophlebitis, both of which are more prevalent in immunosuppressed patients.[14]

In patients admitted to ICU, the ideal duration of antibiotic therapy remains uncertain. The BTS and NICE guidelines suggest 7–10 days antibiotic treatment initially. If infection with *St. aureus* or a gram-negative bacilli is suspected or confirmed, antibiotic therapy should be continued for 14–21 days.[9] Cavitating pneumonias and lung abscesses are usually treated for several weeks. Short-course antimicrobial therapy has the potential to improve efficacy and minimize the emergence of resistant organisms. The use of biomarkers such as highly sensitive PCT or CRP may help to reduce the duration of antibiotic treatment without an increase in either mortality or treatment failure.

Treatment for most viral pneumonias is primarily supportive, apart from in patients with severe influenza and patients at high risk of complications. Depending on current local influenza rates, anti-viral therapy may be started empirically while awaiting viral PCR results. Treatment with oseltamivir or zanamivir is recommended for Influenza A infection, and if started within 48 h of symptom onset may reduce the duration of symptoms, severity of disease, and risk of complications. Aerosolized ribavirin may be of benefit in treating respiratory syncytial virus, human metapneumovirus, and parainfluenza infections in immunocompromised patients.

Complications

Patients with severe CAP often have prolonged critical care admissions and are at risk of developing severe septic shock, renal and hepatic failure, coagulopathy, and central nervous system problems including vascular events, encephalopathy, meningitis, and convulsions. Pulmonary-related complications are frequent and depend on the infecting pathogen.

(i) *Parapneumonic effusions and empyemas* are seen in up to 60% of patients with severe pneumonia. Although many pleural effusions will resolve with appropriate antimicrobial therapy, ultrasound-guided fluid aspiration and analysis should be performed if an effusion is present. Diagnostic aspiration yielding pus, pleural fluid with a pH <7.2, or a positive gram stain or culture are all indications for a tube thoracostomy and drainage of the effusion. Thoracoscopic decortication and drainage should be considered in the presence of an organized empyema or treatment failure.

(ii) *ARDS*. Treatment is primarily supportive using a lung-protective ventilatory strategy. Prone ventilation may be used in severe ARDS with a $Pa_{O_2}/F_{I_{O_2}}$ ratio <150 mm Hg and $F_{I_{O_2}}$

of at least 0.6.[12] Early use of neuromuscular blockers in patients with severe ARDS improves 90 day survival and ventilator-free days.[15]

(iii) *Lung cavitation and abscess* formation are associated with infection from *St. aureus,* gram-negative bacilli, *Aspergillus*, *Mycobacterium*, and *Nocardia* species. Failure to respond to antibiotic therapy may raise the possibility of a non-infectious underlying cause such as vasculitis, bronchial obstruction, or infection with a resistant bacteria, mycobacteria, or fungi.

(iv) Bacterial and influenza pneumonias are associated with cardiac-related complications including myocardial infarction, arrhythmias, and decompensated cardiac failure. Pulmonary inflammation is thought to trigger cytokine release that up-regulate the inflammation of atherosclerotic plaques, decreasing plaque stability and increasing the risk of rupture. Cardiac events are associated with a substantial increase in mortality.

Failure to respond to treatment

Patients who do not demonstrate improvement within 72 h of commencing antibiotics and supportive care should be considered non-responders. If a patient requires critical care admission, the risk of failure to respond to treatment may be as high as 40% with a mortality that is increased several-fold. Independent risk factors for failure to respond include multi-lobar infection, presence of cavitation or pleural effusions, liver disease, and leucopenia. The efficacy of empirical antimicrobials may be reduced through emerging resistant pathogens such as CA-MRSA, Extended Spectrum β-lactamase-producing organisms, and Carbapenemase-producing Enterobacteriaceae. Failure to respond to treatment should result in re-evaluation of initial microbiological results, supplementary diagnostic testing, and either an escalation or change in antibiotic therapy. Alternative diagnoses such as an eosinophilic or organizing pneumonia need also be considered in patients who are slow or fail to respond to conventional treatment. The possibility of undiagnosed immunosuppression should be investigated and further history explored.

Summary

Despite the advancements in supportive care, severe CAP remains a common reason for critical care admission that is associated with a high mortality. *Streptococcus pneumoniae* remains the most common pathogen. However, disease due to gram-negative organisms is more frequent in patients requiring critical care admission and are increasingly MDR, despite antibiotic stewardship and increasing surveillance. Further research is needed to elucidate the extent to which viruses are involved in the pathogenesis of severe CAP. Viral and bacterial infections may co-exist, but it is unclear to what extent these organisms are causing the disease or have predisposed the patient to secondary infection. Future developments within this field are likely to concentrate on diagnostics and the ability to identify a causative pathogen within a shorter timeframe.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Sarcoidosis and anaesthesia

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Key points

- Sarcoidosis is a multisystem inflammatory disease with variable presentation occurring with an incidence of 3000 new cases per year in the UK. The pulmonary system is involved in over 90% of cases.
- The supraglottic region is commonly the site of sarcoid infiltration, and hilar lymphadenopathy can cause vocal cord palsy. Careful airway assessment is advised.
- Hypercalcaemia is the result of activated macrophages producing excess 1,25-dihydroxyvitamin D3, and can cause nephrocalcinosis. Renal function should be checked before operation.
- There is no definitive treatment but patients will often be receiving high-dose steroids or immunosuppressant drugs with concomitant side-effects.
- Preoperative assessment should focus on the airway, pulmonary, cardiac, and renal systems.

Mr D, a 65-yr-old gentleman, presented with a hoarse voice in July 2008. Computerized tomography (CT) scan of his head, neck, and thorax confirmed right vocal cord palsy, but no cause was identified. Blood chemistry was normal. Over the next 2 yr, ENT repeatedly reviewed Mr D and found no cause for the vocal cord palsy.

In June 2010 he was booked for a right vocal cord fat augmentation and presented to the anaesthetic pre-assessment clinic. Blood tests at this appointment revealed a raised urea (12.3 mmol litre^{-1}) and a raised creatinine (170 μmol litre^{-1}). ECG showed a right bundle branch block (RBBB). No action was taken. He was admitted for surgery in October 2010 and seen before operation by a consultant anaesthetist who made no record of his blood results. Surgery was uneventful and Mr D was discharged home the same day. No GP follow-up of the abnormal renal function was arranged.

Four months later Mr D was admitted with severe malaise, complaining of itch, cramps, and dizziness. Blood chemistry was grossly abnormal (creatinine 391 μmol litre^{-1}, urea 17.3 mmol litre^{-1}, Ca^{2+} 3.48 mmol litre^{-1}). After treatment with i.v. fluids and bisphosphonates, he underwent multiple investigations to elicit the cause of his hypercalcaemic renal failure.

Renal biopsy showed severe scarring with microcalculi in the interstitium and CT scanning identified significant mediastinal and upper abdominal lymphadenopathy. These were sampled at endobronchial ultrasound and confirmed non-necrotizing granuloma consistent with a diagnosis of sarcoidosis.

Mr D was commenced on prednisolone, which normalized the calcium levels with concomitant improvement in renal function and was referred to the chest physicians for ongoing care. Pulmonary function testing elicited respiratory involvement with TLCO (transfer factor for carbon monoxide) reduced to 67% of predicted. Echocardiogram was normal.

Key learning points

- Anaesthetists have a responsibility to check and document blood results before operation
- New deterioration in renal function always warrants further investigation of the cause
- Prolonged hypercalcaemia can cause nephrocalcinosis and irreversible renal scarring
- Vocal cord palsy can be caused by mediastinal lymphadenopathy

Introduction

Sarcoidosis, a term originally coined by Boeck in 1899, is a multisystem inflammatory disease characterized by tissue infiltration with T lymphocytes, mononuclear phagocytes, and non-caseating granulomas. Pulmonary involvement is almost universal. Sarcoid is subject to ethnic, geographic, seasonal, and immunogenetic variability, which confers a variable prevalence of 4.7–64/100 000.[1] The highest incidence is seen in northern European and African-American individuals.[1] In the UK, each year there are about 3000 new diagnoses of sarcoid. Despite extensive research, the exact cause of sarcoidosis remains unknown but the generally accepted view is that it results from the exposure of a genetically susceptible individual to an environmental trigger that produces a Th1-type inflammatory response. A variety of triggering agents have been suggested including inorganic dusts and infectious agents such as mycobacterium.

An interesting case is the higher incidence of sarcoidosis observed in New York firefighters after the World Trade Centre was destroyed in 2001,[2] supporting the suggestion that dust exposure may be a factor.[1]

Patients with sarcoidosis may require anaesthesia for diagnostic procedures (e.g. mediastinoscopy or lung biopsy), for treatment of airway complications of the disease, such as bronchial stenosis, or, as the disease course is long, they may require incidental surgery.

The aim of this article was to outline the pathophysiological and clinical features of sarcoid and highlight the implications for the anaesthetic management of these patients.

Pathogenesis

The key immunopathogenic process in sarcoid is an excessive host immune response to an antigen with the subsequent formation of non-caseating granulomas. The antigen may be microbial or an organic or inorganic substance. Granulomas contain a central core composed of epithelioid cells, macrophages and multinucleated giant cells, surrounded by fibroblasts, B-cells and CD8 T-cells.[3] $CD4^+$ T-cells and epithelioid cells subsequently interact and drive the formation and maintenance of granulomas through secretion of interleukin-2, interferon-γ and TNF-α, which all serve to amplify the local immune response. Granulomas may persist, resolve without sequelae or lead to irreversible fibrosis.

Genetics

Major histocompatibility class II alleles affect the course of the disease. HLA DR3 carries a better prognosis with spontaneous resolution, whereas HLA DR14 and HLA DR15 carry a worse prognosis. Genome-wide association studies have shown other loci that are associated with increased risk, for example, butyrophyllin-like 2 (BTNL2) and ANXA11[1] genes. Thus genetic susceptibility to sarcoidosis depends on multiple genes, the presence of which in combination can substantially enhance risk.

Clinical presentation and diagnosis

The presentation of sarcoidosis is very variable and dependent on the pattern of organ involvement. A significant proportion of patients are asymptomatic and sarcoidosis is detected as an incidental finding, often when a chest radiograph is performed for other reasons. Constitutional symptoms such as malaise, fever, and weight loss are common. When symptomatic, pulmonary involvement usually causes cough and dyspnoea. There are a number of 'classic' presentations such as Löfgren's syndrome (hilar lymphadenopathy, erythema nodosum, fever and arthralgias), and Heerfordt's syndrome (parotits, uveitis, fever and facial palsy). Organ specific features will be reviewed below. Initial investigation will include a full blood screen, urinalysis, ECG, lung function tests and CT scanning.

Three quarters of patients have an elevated serum angiotensin-converting enzyme concentration.[4] This is neither specific nor sensitive and therefore of little value in diagnosis or disease severity marking. Chitotriosidase is a more useful marker. It is an enzyme produced by activated macrophages, which degrades chitin and is elevated in sarcoidosis.[5]

Where the clinical and radiographic features are characteristic further investigation may not be pursued, but otherwise a biopsy from the relevant site is obtained to look for evidence of non-caseating granuloma, and to exclude other conditions such as tuberculosis or lymphoma. Endobronchial ultrasound-guided mediastinal lymph node biopsy is widely used for diagnosis and has a diagnostic yield of 85%.[3]

Further imaging such as nuclear medicine gallium scanning, positron emission tomography (PET) scanning, and contrast-enhanced magnetic resonance imaging (MRI) may be required occasionally, the latter particularly where neurosarcoid is considered.

The prognosis of sarcoidosis is very variable. The condition will resolve spontaneously in many patients, but in up to one-third of patients a more protracted course may occur and require specific treatment. Lofgren's syndrome often remits rapidly and spontaneously but more chronic presentations are more likely to require treatment and longer term monitoring. If the disease persists beyond 5 yr, remission is unlikely. Disability and death are most likely to result from pulmonary, cardiac, or neurological disease.

Systems involvement

Upper respiratory tract

Mucosal infiltration of the nose, nasopharynx, tonsils, or larynx occurs in ~5% of cases.[6] The epiglottis and ary-epiglottic folds are the most common site of infiltration. Interestingly the cords are often spared. Patients may present with dyspnoea, stridor, dysphagia, or with obstructive sleep apnoea (OSA).[7] Occasionally laryngeal involvement may be severe enough to necessitate emergency tracheostomy.[8]

The incidence of bronchospasm is increased and 38% of those with sarcoid granulomata in the bronchial tree demonstrate airway hyper-reactivity to methacholine.[9]

Pulmonary

Pulmonary involvement is seen in over 90% of cases.[3] The radiographic pattern is often used to stage the disease although this staging does not describe the course of disease in any individual patient: Stage I disease describes isolated hilar and mediastinal adenopathy, stage II adenopathy and parenchymal involvement, stage III parenchymal involvement without adenopathy, and stage IV lung fibrosis. The parenchymal changes are distributed in a peribronchovascular and perilymphatic pattern and include reticulonodular and nodular opacities, ground glass opacities, and sometimes larger nodules. Typically they show a mid- and upper zone predominance. These changes may resolve or progress to irreversible scarring. Pleural inflammation may occur but complications such as effusion are uncommon.

Lung function tests may show a restrictive or an obstructive pattern and often correlate poorly with radiological evidence of disease. There is a reduced diffusing capacity and a reduction in

lung compliance which progresses with the time course of the disease.

Pulmonary hypertension is not uncommon in advanced sarcoidosis and is largely the result of fibrosis of the distal capillary bed, chronic hypoxaemia, or both. Compression of the pulmonary arteries by adenopathy and left ventricular diastolic dysfunction also contribute to the development of pulmonary hypertension. Its presence significantly worsens prognosis (Figs 1 and 2).

Cardiac

Cardiac sarcoidosis is related to granulomatous infiltration of the myocardium and conducting tissue, and is much more common than clinically appreciated. In Japan, it is found in 50% of cases of sarcoidosis at post-mortem examination.[3] Clinical presentation varies from asymptomatic to palpitations to sudden death. Supraventricular arrhythmias occur in about a third of patients[10] with atrial fibrillation being the commonest rhythm disturbance. The QT interval is prolonged[11] and may cause ventricular arrhythmias, particularly premature ventricular contractions (PVCs). Degrees of atrioventricular block are also common and implantable pacemakers or an internal cardioverter defibrillator may be required. Cardiomyopathy may lead to congestive cardiac failure and be life-threatening.

Renal

Renal sarcoid takes two main forms. The first is an acute granulomatous interstitial nephritis. The second, seen in 10% of patients with sarcoid[12] is nephrolithiasis and nephrocalcinosis caused by abnormal calcium metabolism. Activated macrophages within the granulomas produce large amounts of 1,25-dihydroxyvitamin D3. The excess 1,25-dihydroxyvitamin D3 increases absorption of dietary calcium, which is then partially excreted in the urine. The hypercalciuria and hypercalcaemia eventually cause nephrolithiasis and nephrocalcinosis. If untreated, renal calcium deposition may lead to chronic renal failure.

Liver and spleen

Liver involvement is often asymptomatic but occasionally presents as cholestasis, hepatic failure or portal hypertension. Fifteen per cent of patients have splenic lesions on CT.[13]

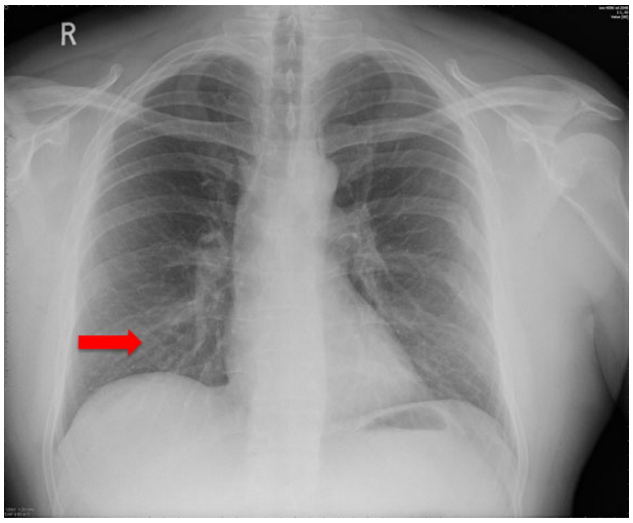

Fig 1 Plain AP chest radiograph showing typical reticulonodular shadowing.

Haematological

Forty per cent of patients have anaemia, leukopenia, or both, and lymphopenia. Thrombocytopenia is rare unless there is gross splenic involvement.

Ocular

Twenty-five to 80% of patients with sarcoid have eye involvement[13] often preceding the diagnosis of sarcoidosis by many years. Chronic anterior uveitis is more common than its more painful acute counterpart.

Neurosarcoidosis

Neurosarcoidosis is often asymptomatic but is detected in a quarter of post-mortem cases and can affect any part of the nervous system.[3] Cranial nerve involvement is the commonest presentation with the optic and facial nerves most affected. Pituitary sarcoid can lead to decreased antidiuretic hormone production and disordered thirst. Small fibre neuropathy can affect all nerves including the autonomic system.

Treatment

There is no cure for sarcoidosis; treatment modifies only the course of the granulomatous process. Patients who are asymptomatic can be monitored in the hope of spontaneous remission; otherwise, steroids remain the first-line treatment option. Moderate doses are used in most cases (20–40 mg day^{-1} for an adult), but high doses are given when there is life-threatening disease such as acute respiratory failure, neurological deficit, or cardiac disease. The dose is maintained until disease activity is controlled, and then reduced. Maintenance treatment is often continued for 12 months in the first instance. Patients may experience side-effects such as weight gain, diabetes, osteoporosis and increased susceptibility to infection.

Where there is evidence of disease progression despite glucocorticoid therapy, or where the dose cannot be weaned to a low

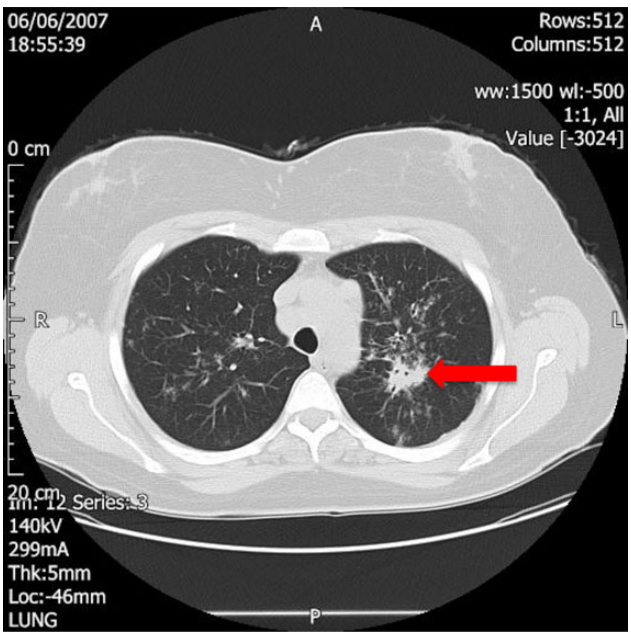

Fig 2 CT thorax showing the 'galaxy sign' particularly evident in the left lung.

Table 1 Common Drug Therapy for sarcoidosis. CXR, chest X-Ray; LFT, liver function test; LMWH, low molecular weight heparin; NDMRs, non depolarising muscle relaxants; PFTs, pulmonary function tests; RSI, rapid sequence induction; U&E, urea & electrolytes

Drug	Side-effects	Anaesthetic considerations
Prednisolone	Weight gain Hypertension Osteoporosis Fragile skin Impaired glucose tolerance Immunosuppression Electrolyte abnormalities Reflux	Preoperative electrolyte correction Impaired stress response-steroid replacement required Sliding scale if diabeticRSI if significant reflux Careful intra operative positioning
Methotrexate	Liver and renal toxicity Interstitial pneumonitis Myelosuppression Immunosuppression	Preoperative assessment of respiratory function including PFTs and CXR Preoperative FBC/U &E, LFT Avoid nephrotoxic drugs Low threshold for prophylactic antibiotics
Leflunomide	GI side-effects Liver toxicity Neutropenia Hypertension Neuropathy	Preoperative FBC, U&E, LFTs Avoid hepatotoxic drugs Baseline BP before operation Preoperative documentation of any neurological deficit
Azathioprine	GI side-effects Liver toxicity Myelosuppression	Preoperative FBC, U&E, LFTs Avoid hepatotoxic drugs Antagonists of NDMRs may require higher doses Low threshold for prophylactic antibiotics
Thalidomide	Teratogenicity Venous thrombosis Neuropathy Drowsiness Bradycardias Hypotension	Use of LMWH Cautious use of anaesthetic anti-thromboembolism stockings agents as may have an increased tendency to bradycardias, hypotension, and a slower recovery from anaesthesia.
Infliximab	Myelosuppression Increased risk of malignancy and serious infections	Preoperative FBC, U&E, LFTs Low threshold for prophylactic antibiotics

level, alternative immunosuppressant agents are considered. The evidence base for many of these is poor with the literature mainly being case series. Methotrexate is the most commonly prescribed second-line therapy. It can cause interstitial pneumonitis compounding sarcoid lung disease. Other cytotoxic agents are sometimes used: azathioprine, leflunomide, cyclophosphamide, and mycophenolate, for example. These agents cause neutropenia, liver toxicity, renal toxicity, and GI side-effects. The concomitant use of NSAIDs requires caution.

If these fail to control the disease, then cytokine modulators can be added. Pentoxyphyllin is a phosphodiesterase type 4 inhibitor used as an anti-inflammatory and T-cell inhibitor. Its use is steroid sparing. Thalidomide is used for severe skin sarcoidosis, and infliximab for central nervous system, skin, and eye lesions. Occasionally, anti-malarials are prescribed for mild hypercalcaemia or skin involvement in preference to corticosteroids (Table 1).

Perioperative management

Preoperative assessment

Given the multisystem nature of sarcoidosis, a meticulous work up is essential and this is best done at a scheduled visit to an anaesthetic pre-assessment clinic. Thorough history, examination, and notes review will elucidate the main systems involved.

History taking should follow a systems approach. Dysphagia, dysphonia, stridor, and noisy breathing may suggest airway involvement and the Stop-Bang scoring system can provide a useful measure of severity of OSA.[14] Symptoms of exertional dyspnoea, chest pain, or palpitations should be sought and investigated. An assessment of functional status is vital and is very representative of respiratory and cardiovascular functioning.

A detailed drug history is important. Steroids can suppress the hypothalamic–pituitary–axis, and many patients with active sarcoidosis will be taking moderate to high doses of glucocorticoids. An early morning cortisol assay or ACTH stimulation test can be useful in determining the extent of suppression.

Routine examination should include the respiratory and cardiovascular systems but if regional anaesthesia is planned pre-existing neurological deficit should be sought and carefully mapped.

Simple investigations can be very informative. Routine blood tests should include FBC, urea & electrolytes (U&E), liver function test (LFT), and serum calcium. Particular attention should be paid to the kidney in order to avoid postoperative renal complications. The serum calcium should be brought into the normal range before anaesthesia. Methods available to achieve this are ketoconazole, bisphosphonates, and calcitonin infusion. LFTs are important because many of the drug treatments cause hepatic inflammation or toxicity.

An ECG will act both as a baseline and serve to highlight any conduction disturbance. If suspected, a period of Holter monitoring can be used before elective surgery. Frequent PVCs are associated with a prolonged QT_c interval. ECG changes of right ventricular hypertrophy with strain should alert the anaesthetist to the possibility of pulmonary hypertension and an

echocardiogram is mandatory if any degree of pulmonary hypertension or cardiomyopathy is suspected. Specialist review by a cardiologist may be sought with a view to MRI, PET scan, or angiography. Higher degrees of heart block may require pacing before operation.

Symptomatic pulmonary involvement is best assessed formally with pulmonary function tests rather than chest X-Ray alone as radiological signs and functional status may be disparate. Cardio-pulmonary exercise testing may be useful in this group, especially if there is cardiac involvement, to assess perioperative risk and plan postoperative care.

For patients presenting with laryngeal involvement preoperative flexible nasendoscopy and CT of the neck and thorax will help delineate the level of involvement and guide airway planning.

Intraoperative

Conduct of anaesthesia

Routine use of AAGBI monitoring is recommended. The need for additional invasive monitoring will depend on the patient and the operation, and the usual considerations apply. If cardiac sarcoid is suspected or diagnosed, then the CM5 ECG configuration (right arm lead on manubrium, left arm lead on V5, and indifferent lead on left shoulder) can aid the identification of ischaemia intraoperatively. Arrhythmias need to be recognized promptly and treated according to ALS guidelines. If severe pulmonary hypertension is present, right heart catheterization can be useful to guide specific treatment especially if the use of specific pulmonary artery vasodilators is planned.

For patients with laryngeal involvement, a strategy for airway management should be decided in conjunction with the ENT surgeons based on the results of preoperative investigations. A selection of airway equipment should be available. Microlaryngoscopy tubes and jet ventilation catheters may be particularly helpful. A short course of dexamethasone can help minimize postoperative oedema and postoperative observation in a high dependency area may be indicated.

Choice of anaesthetic agent is wide but should take into consideration the multisystem nature of the disease. For example patients with cardiac sarcoid may be sensitive to the negatively inotropic effect of induction agents and their dose should be tempered. Patients with pulmonary involvement may have reactive airways and benefit from avoidance of thiopental- and histamine-releasing agents such as morphine and atracurium. Drug dosing and choice may need to be altered if there is renal or liver involvement. Antibiotics should be given according to local guidelines especially as many patients will be taking steroids and other immunosuppressants. For patients on long-term steroids, hydrocortisone cover will need to be considered and dosed according to the grade of surgery.

Cutaneous sarcoid and the prolonged use of steroids accentuate the need for skin protection. Careful positioning is required too, partly owing to steroid thinned skin and partly owing to the potential presence of distal neuropathy.

Local, regional, or axial anaesthesia should be considered in those patients in whom general anaesthesia may exacerbate poor lung or cardiac function.

Postoperative

Postoperative care depends upon the nature and site of the surgery and the disease pattern of the sarcoidosis. Potential difficulties include respiratory difficulty, arrhythmias, and renal impairment. High dependency or intensive care may be required.

For those with significant pulmonary disease, early involvement of the respiratory team and chest physiotherapy is advisable and postoperative oxygen therapy should be prescribed. Multi-disciplinary care is appropriate and desirable.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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The place of goal-directed haemodynamic therapy in the 21st century

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Key points

- Goal-directed haemodynamic therapy (GDT) describes a complex bundle of care used perioperatively in high-risk adult surgical patients and for adults with sepsis.
- Through various combinations of fluids, oxygen, and vasoactive drugs, total blood flow and calculated tissue oxygen delivery are augmented with the aim of improving patient outcome.
- Haemodynamic monitoring (either invasive or minimally invasive) is required.
- GDT significantly reduces the duration of hospital stay and overall postoperative complication rate, specifically postoperative kidney injury, respiratory failure, and wound infection.
- The impact of GDT on mortality remains uncertain. Adequately powered pragmatic multicentre trials into GDT are therefore justified.

This article will discuss the history and subsequent development of goal-directed haemodynamic therapy (GDT), reviewing briefly the significant clinical trials of GDT, and finally suggest a practical clinical guide to GDT based on the most up-to-date evidence synthesis. The future role for GDT will also be discussed.

The high-risk surgical patient

The 'high-risk' surgical patient may be classified in a variety of ways. One suggested threshold includes those patients who have an individual postoperative mortality risk exceeding 5%, incorporating surgical factors such as complexity and urgency (often emergency), and patient factors such as comorbidities and (increasing) age.[1] 'Extremely high-risk' patients are those whose postoperative mortality risk is >20%.[2] Another classification describes those patients undergoing procedures that carry an inherent mortality rate exceeding 5%. Twenty-five per cent of the surgical population undergoing vascular, upper gastrointestinal, lower gastrointestinal, and hepatobiliary surgery fall into this latter category.[3]

Measures of cardiovascular fitness can also be used to stratify patient risk. Patients unable to achieve four metabolic equivalents (METS) (such as climbing a flight of stairs or gardening) are designated high risk, as are those with an anaerobic threshold (AT) of <11 ml of oxygen per kilogram per minute (ml O_2 kg^{-1} min^{-1}) on preoperative cardiopulmonary exercise testing (CPET). High-risk surgical patients account for 12.5% of surgical activity and yet this group accounts for 80% of postoperative deaths. However, <15% of high-risk surgical patients are electively admitted to critical care in the UK.[1]

Goal-directed haemodynamic therapy

GDT describes a complex bundle of care used perioperatively in high-risk adult surgical patients, and for adults with acute severe sepsis or septic shock. Total blood flow and tissue oxygen delivery are augmented through the use of various combinations of supplemental fluids, vasoactive drugs (inotropes, vasopressors, and vasodilators), and oxygen, with the aim of improving patient outcome. Although initially developed in critical care for use in high-risk surgical patients with shock, GDT is also now used in general surgical, orthopaedic, cardiothoracic, and vascular surgery.

Historically, empirical perioperative haemodynamic goals have been set and the effects of specific interventions assessed using information on blood flow gained from a cardiac output (CO) monitor. Originally, a pulmonary artery (right heart) catheter was required to measure haemodynamic variables using thermodilution techniques. Now different measurement modalities exist which have been well validated. The most widely used technologies include oesophageal Doppler monitoring (CardioQ-ODM™, Deltex Medical Ltd, UK) and arterial pulse contour analysis devices such as LiDCO™ (LiDCO Ltd, UK), PiCCO (PULSION Medical Systems SE, Germany), and the FloTrac Sensor/Vigileo monitor system (Edwards Lifesciences Corporation, USA).

A number of approaches have been suggested for the optimization of haemodynamic variables in the perioperative period and in patients with critical illness. Monitoring of pulse pressure or systolic pressure variation in the arterial pressure trace has been used as a means of predicting fluid responsiveness.[4] Stroke volume (SV) variation derived from a CO monitor has also been used in this way. The 'holy grail' of using tissue perfusion monitoring as a means of guiding haemodynamic management is often suggested, and was partially evaluated in studies of gastrointestinal tonometry,[5–7] but as yet no perfusion monitor has been effectively used in this way. The properties of the 'ideal' haemodynamic monitor are shown in Table 1. An in-depth review of all the available technologies is beyond the scope of this article.

The most frequently targeted haemodynamic variables include CO, SV [from which oxygen delivery (DO_2) and oxygen consumption (VO_2) can be calculated], and systemic vascular resistance. These variables may then be indexed to body surface area (average values being 1.9 m^2 for men and 1.6 m^2 for women) to enable comparison of the individual's measured values against a specified haemodynamic goal. Related target variables that are measures of the balance between oxygen delivery and oxygen utilization have also been studied and include mixed venous oxygen saturation SVO_2, oxygen extraction ratio (O_2ER), and blood lactate.

GDT has had a controversial history, some of which is due to the fact that it is a 'complex intervention' with multiple interacting components and also that the early studies of GDT required placement of a pulmonary artery catheter (PAC) in a critical care environment. More recent studies however have used less invasive devices and not mandated critical care admission as part of the intervention.

Table 1 Properties of an 'ideal' haemodynamic monitoring system (adapted from Vincent and colleagues[8])

Accurate and reproducible measurement of relevant haemodynamic variables
Rapid response time
Operator-independent equipment
Derived information can readily be used to guide therapies
Easy to use
Causes no harm to patients
Cost-effective

The theory

It is well established that oxygen consumption increases perioperatively. The magnitude of this change varies, but one study of 100 elderly patients undergoing elective major abdominal surgery reported an average increase of 44%, and others have reported increases of more than 50% in some instances.[9] This increased metabolic demand requires an increase in oxygen delivery that the patient may not be able to achieve through a spontaneous increase in CO.[10,11] The increased metabolic demand caused by major surgical trauma, when coupled with inadequate resuscitation and organ hypoperfusion, is strongly implicated in the development of postoperative multiple organ failure (MOF).

Tissue hypoxia is central to the development of postoperative MOF,[11] and its incidence is increased in high-risk patients with limited cardiovascular reserve. The hypothesis behind GDT is that augmentation of CO and oxygen delivery leads to improved tissue perfusion and oxygenation, thereby preventing the development of MOF. This in turn should confer a survival benefit resulting in high-risk patients undergoing major surgery experiencing fewer postoperative complications. Through optimization of SV and low-dose inotropy (dopexamine), Jhanji and colleagues[12] demonstrated that sublingual and cutaneous microvascular flow and cutaneous tissue oxygen partial pressure can be significantly increased after major gastrointestinal surgery.

Background

Interest and research into GDT followed the publication of the first use of the 'flow-directed balloon-tipped pulmonary artery (right heart) catheter' in humans by Swan and colleagues in 1970.[13] Before this, the use of the Fick principle to determine CO had been possible in the laboratory setting but was not routinely performed at the bedside in critically unwell patients.

The pulmonary artery catheter

The first description of right heart catheterization to aid diagnosis in critically unwell patients was by Bradley[14] in 1964 at St Thomas' Hospital, London. Until that time, right heart catheterization had only been used in patients with cardiac valvular disease and congenital heart disease. Using the Seldinger technique,[15] Bradley advanced miniature cardiac catheters from the basilic vein (or a branch thereof) in the antecubital fossa, subsequently taking pressure recordings in the right atrium, right ventricle, and pulmonary artery using a manometer. Four years later, Branthwaite and Bradley[16] (again at St Thomas') published the first paper describing right heart catheterization in humans using thermodilution to measure CO. The technique involved the use of a thermistor mounted in the tip of the catheter to detect the change in temperature of blood in a pulmonary artery after the injection of 10 ml of room temperature 5% dextrose or 0.9% saline into the right atrium (injected via a second catheter placed in the internal jugular vein). The CO measurements obtained were validated against the direct Fick technique, the method used previously to determine CO.

Swan and colleagues[13] added an inflatable latex balloon just proximal to the tip of a dual-lumen catheter in 1970 (major and minor lumens with the minor lumen being connected to the balloon). Inflation of the balloon allowed for the consistent (and safer) progression of the catheter through the heart and the

great vessels and also afforded the measurement of pulmonary artery wedge pressure (an indirect measure of left atrial pressure). Again this catheter was inserted via a vein in the antecubital fossa and did not require fluoroscopy to guide placement, so could be positioned at the bedside in critically unwell patients. Early modifications included positioning a thermistor at the tip (akin to Branthwaite and Bradley), thereby allowing measurement of CO by thermodilution.

The controversy of the PAC

In its initial stages, GDT required a PAC to calculate the haemodynamic data. Unfortunately, concerns about PAC safety followed and the publication of a large cohort study suggested that PAC use was associated with increased mortality and increased use of critical care resources.[17] Naturally, this attracted substantial interest and as a result PACs, and with them GDT, fell out of favour. More recent randomized controlled trials (RCTs)[18–20] have failed to demonstrate significant evidence for either benefit or harm when using a PAC to guide therapies perioperatively or in critical care. Interest in GDT has been re-invigorated however with the advent of newer minimally invasive devices that provide haemodynamic monitoring without the risks inherent with the PAC. An obituary for the PAC was written in 2013,[21] but it is still commonly used in some clinical environments including cardiac surgery and cardiac intensive care.

William Shoemaker

Using the PAC to measure haemodynamic variables, Shoemaker and colleagues[22,23] (Los Angeles, USA) were the first to describe the physiological patterns in surviving and non-surviving postoperative patients with shock secondary to surgical and accidental trauma. They found that patients who survived maintained higher physiological indices after operation [such as cardiac index (CI) and oxygen consumption (VO_2)] than those who died, and that this was associated with shorter periods of circulatory shock. Shoemaker and colleagues went on to suggest that therapy in this high-risk population should be aimed not at restoring normal physiological variables as had been previously thought, but at achieving higher than normal, 'supranormal', haemodynamic indices postulating that this would serve to meet the higher postoperative metabolic demands.

Goal-directed therapy literature

The first prospective trial evaluating GDT in high-risk surgical patients was by Shoemaker and colleagues in 1988.[24] The investigators, guided by measurements taken using a PAC, used fluids (crystalloids, synthetic colloids, and packed red cells), vasoactive drugs, and supplemental oxygen to achieve their GDT aims (although oxygen was not explicitly described as being part of the therapeutic intervention). The GDT goals sought in the protocol group are listed in Table 2.

The GDT group, in whom therapies were initiated before operation, achieved an average DO_2I>600 ml min^{-1} m^{-2} in the postoperative period and had significantly reduced: number of days on intensive care, number of ventilator days, number of postoperative complications, and number of postoperative deaths. Although this was an enthusiast-led, single-centre trial, and therefore had a high risk of bias, the evidence was compelling enough that subsequent trials have sought to build on these findings.

Table 2 Shoemaker and colleagues[24] GDT targets

Haemodynamic goal	Comparison with normal
CI>4.5 litre min^{-1} m^{-2}	50% greater
DO_2I>600 ml min^{-1} m^{-2}	At least 10% greater
VO_2I 170 ml min^{-1} m^{-2}	30% greater

PAC literature

In the UK, papers by Boyd and colleagues[25] and Wilson and colleagues[26] both reported significant reductions in morbidity and mortality in high-risk surgical patients where CI and oxygen delivery were augmented perioperatively using fluids, oxygen, and dopexamine, guided by a PAC. Wilson[26] also demonstrated significant reductions in length of stay (Boyd and colleagues[25] also showed that the GDT group tended to spend less time in intensive care and had a shorter hospital stay, although this was not statistically significant). But whereas Boyd and colleagues[25] admitted all patients to intensive care postoperatively, Wilson and colleagues[26] have been criticized because although patients in their intervention group routinely went to critical care, many patients in their control group were cared for postoperatively on the ward.

Not every trial into PAC-guided GDT has demonstrated its benefit. Studies into patients with established critical illness have demonstrated that such an intervention is associated with either no difference between groups or in some cases harm in the intervention group, suggesting that the timing of GDT during the clinical course is important.

In a prospective RCT of mixed critical care patients, and again using dobutamine, Hayes and colleagues[27] found that despite achieving significantly higher CI and DO_2I (but surprisingly lower oxygen extraction) in the protocol group, in-hospital mortality was in fact significantly lower in the control group. The authors suggested that good physiological reserve (and perhaps a less severe illness) conferred a survival benefit, as patients in the control group were able to achieve the GDT indices with fluids alone. However, whereas Shoemaker and others have instituted therapy before operation, this study included mainly postoperative surgical patients and those with established critical care illnesses such as acute respiratory failure and septic shock.

In the largest negative PAC GDT trial to date, Gattinoni and colleagues[28] were unable to demonstrate a significant difference in mortality, organ dysfunction, or length of stay on intensive care between the protocol and control groups. In this trial, SVO_2 was also evaluated as a target for GDT (and also CI), as it represents the balance between oxygen consumption and oxygen delivery. Interestingly, significantly fewer patients in the CI group were able to achieve their targets compared with the control group and significantly fewer of the older and sicker patients were able to meet their respective goals, suggesting again the influence of premorbid cardiovascular function on the effectiveness of GDT.

Non-PAC literature

Although originally closely associated with the PAC, a distinct parallel GDT literature derives from the use of less invasive monitors such as lithium indicator dilution and arterial pulse contour analysis (LiDCO™) and oesophageal Doppler monitoring.

Using oesophageal Doppler monitoring-guided GDT and gastric tonometry to assess gastric mucosal pH (pHi—used as a marker of gut and therefore global hypoperfusion/hypovolaemia), Mythen and Webb[5] demonstrated a significantly lower incidence of gut mucosal hypoperfusion in the GDT group, which in turn was associated with significantly reduced postoperative major complication rate, average number of intensive

care days, and average number of hospital days. This association between pHi and outcome echoed previous work.[29]

Pearse and colleagues[30] published the first RCT looking specifically at *postoperative* GDT. Using LiDCO™ to guide therapies (including dopexamine) aimed at increasing oxygen delivery, the researchers demonstrated significant reductions in the number of complications per patient, the total number of complications, and the length of hospital stay in the protocol patients. There was also a 41% cost reduction in overall hospital stay associated with the GDT patients.

Again not every non-PAC GDT study has demonstrated benefit. Challand and colleagues[31] used the oesophageal Doppler to guide intraoperative GDT with colloid in patients undergoing colorectal surgery, stratified into being either aerobically 'fitter' (AT>11.0 ml O_2 kg^{-1} min^{-1}) or 'less fit' (AT 8.0–10.9 ml O_2 kg^{-1} min^{-1}) on the basis of preoperative CPET. Each group was then randomized into receiving standard therapy or GDT. Results showed that GDT did not improve time to readiness for discharge, nor overall length of hospital stay. And in a subgroup analysis, the 'fitter' GDT subgroup had a significantly increased median time until they were ready for discharge and a significantly prolonged length of stay. Interestingly, the GDT group also had significantly more intraoperative blood loss.

Finally, the largest UK multicentre RCT into haemodynamic optimization by Pearse and colleagues[32] has recently been published. 'OPTIMISE' (ISRCTN04386758) compared usual therapy *vs* minimally invasive CO monitor-guided GDT using a LiDCOrapid™ (LiDCO Ltd, UK) in high-risk patients undergoing major gastrointestinal surgery. The intervention period extended from the induction of anaesthesia until 6 h after operation. The haemodynamic therapy algorithm group received 250 ml colloid boluses to achieve a sustained increase in cardiac SV plus a fixed-dose infusion of dopexamine in order to optimize oxygen delivery (this GDT algorithm having previously been evaluated).[12]

On its own, the study failed to demonstrate a significant difference between the treatment and protocol groups in either primary (moderate and major complications and 30 day mortality) or secondary [POMS (Postoperative Morbidity Survey)-defined morbidity on day 7, infectious complications, critical care-free days, and all-cause mortality at 30 days after surgery] outcome measures. However, when the results are included in an updated systematic review and meta-analysis, they suggest that GDT significantly reduces the number of postoperative infections and length of hospital stay, which is consistent with the evidence summary reported in the Cochrane review by Grocott and colleagues[33] in 2012 (discussed below).

Sepsis

The first RCT looking specifically at GDT in early sepsis was by Rivers and colleagues[34] in 2001. Patients with severe sepsis or septic shock were randomized to receive either standard therapy or early goal-directed therapy (EGDT) in the emergency department of an inner city tertiary-level hospital for at least 6 h after presentation (and before admission to critical care).

In keeping with previous studies into GDT, synthetic fluids, packed red cells, and vasoactive drugs were used to attain haemodynamic targets (antimicrobial therapy was given to both groups at the discretion of the treating clinicians). Although only a single-centre trial and only partially blinded (therefore open to bias), the EGDT group had significantly lower in-hospital mortality, 28 and 60 day mortality. The duration of hospital stay was also significantly longer in patients receiving standard therapy who survived to discharge.

These results echoed previous studies in that GDT appeared to be of benefit if it is instigated early in the development of a critical illness, and the Rivers EGDT protocol subsequently formed the basis of the Surviving Sepsis Campaign initial resuscitation recommendations when managing severe sepsis and septic shock.[35]

More than a decade after the Rivers trial, however, three further multicentre trials have now recently been published investigating the validity of EGDT in the management of early sepsis. Their results differ from the Rivers trial in that neither the North American Protocol-Based Care for Early Septic Shock (ProCESS) trial,[36] the UK Protocolised Management in Sepsis (ProMISe) trial,[37] nor the Australasian Resuscitation in Sepsis Evaluation (ARISE) trial[38] were able to demonstrate a significant survival benefit for protocol-based EGDT over usual care at 90 days. All three studies concluded that EGDT did not confer a survival benefit in the management of patients admitted to the emergency department with early septic shock. As the ProMISe authors comment though, it may be that usual resuscitation techniques have evolved sufficiently since the Rivers trial that the extra benefit shown by EGDT previously would now not be seen.

Systematic reviews and meta-analyses

Studies into GDT have provided evidence both for and against its use and there have been a number of systematic reviews and meta-analyses performed to determine whether GDT is beneficial.[39–42] There is significant heterogeneity in the trials themselves, for example, in the population studied, the haemodynamic goals targeted, and the techniques used to achieve those goals, and in the approaches to meta-analysis used in the reviews.

A recent Cochrane review by Grocott and colleagues[33] explicitly reviewing the effects of perioperative GDT on postoperative outcome is the most rigorous to date. From an original electronic search yielding 10 462 studies, a total of 31 RCTs met the inclusion criteria (containing a total of 5292 patients). Based on their analyses, GDT did not significantly improve either overall mortality (at longest follow-up—the primary outcome) or hospital/28 day mortality (a secondary outcome) when compared with control (targeting explicit goals that were less than the intervention, as opposed to 'usual care'). This is contrary to previous meta-analyses that had shown mortality benefit with GDT.[39–42] However, the Cochrane mortality results were sensitive to methods of analysis, with several approaches resulting in a statistically significant improvement in mortality, suggesting uncertainty about the no-difference conclusion. Notwithstanding this, GDT was shown to reduce the postoperative incidence of kidney injury, respiratory failure, and wound infections, as well as the overall postoperative complication rate. For every 100 patients treated with GDT, an extra 13 will avoid a complication, two will avoid renal impairment, five will avoid respiratory failure, and four will avoid a postoperative wound infection when compared with control. GDT was also shown to significantly reduce the postoperative length of stay in hospital, though not the postoperative length of stay in critical care. Importantly, there was no evidence of harm associated with GDT.

GDT was shown to significantly reduce the mortality in elective surgery, however, when compared with urgent or emergency surgery, although there was no correlation with type of surgery, be it general, vascular, or cardiac. There was very limited data relating to patients undergoing emergency surgery. Interestingly, postoperative mortality was also not significantly affected by:

(i) the timing of GDT (be it preoperatively, intraoperatively, or postoperatively),
(ii) the type of therapy used (fluids alone or in combination with vasoactive drugs),
(iii) the haemodynamic goal targeted (be it CO and oxygen transport, SVO_2, or O_2ER and lactate).

Long-term outcome

Although shown to significantly reduce postoperative complications (and short-term mortality in elective surgery), the question remains: is there a signal that GDT can affect long-term outcome or is overall survival purely down to the original disease process? In the only long-term study of its type, Rhodes and colleagues[43] have attempted to answer this question by following-up patients from a study by Boyd and colleagues[25] in 1993 (described above) in which the patients in the protocol group received GDT targeting a DO_2I of 600 ml min^{-1} m^{-2}. At the time of randomization, both the control and protocol groups had been well balanced in terms of patient characteristics, type (and urgency) of surgery, and comorbidities. Outcome data were available in all but one of the original 107 patients.

Fifteen years post-randomization patients in the protocol group showed significantly improved survival with the median survival increased by over 3 yr and more than twice as many survivors in the protocol group than the control group (11 *vs* 4 patients). The avoidance of a postoperative complication had also conferred a significant survival advantage. And even in those patients who did develop a postoperative complication, GDT appeared to improve long-term survival. Development of cardiovascular or renal complications had the greatest (negative) impact on long-term survival.

Economic impact

Intensive Care National Audit and Research Centre (ICNARC, UK) data demonstrate that even though mortality from critical illness is decreasing, the number of adults requiring admission to critical care is increasing. So even though GDT has been shown to reduce postoperative complication rates and increase long-term survival in high-risk surgical patients, is it cost-effective in terms of additional resources (especially critical care resources), training, and maintenance of the new devices required for its implementation?

Ebm and colleagues[44] have recently undertaken a cost-effectiveness analysis of GDT to determine the implications of using GDT after operation for all high-risk surgical patients as opposed to providing usual care. The authors constructed two decision tree models: one analysing the costs and benefits in the short term (those relating to the hospital in the first 28 postoperative days), the other for the long term (those relating to society). The short-term model was developed based on the results of a previous study by Pearse and colleagues[30] (albeit only a single-centre study) and the long-term model simulated a hypothetical 67-yr-old patient using follow-up data from a separate publication by Rhodes and colleagues[43] (the only long-term GDT follow-up study, as described above).

Ebm and colleagues[44] found that GDT increased quality-adjusted life expectancy and provided healthcare savings to both the hospital and society. Specifically, in the short term, GDT was found to be more efficient and cost less than usual care, with a cost-reduction of £2631.77 per patient (£2134.86 per hospital survivor). Even accounting for maximum prolonged hospitalization and complications, GDT provided a cost saving of £471.65 per patient. An initial investment for two GDT monitors and training of staff cost £40 386.75, which would be offset after treating only 16 patients. This equates to GDT making savings after only 1.8 months (based on an average of 100 patients utilizing GDT over the course of the year).

In the long term, GDT was associated with an increased quality-adjusted life expectancy of 0.82 yr, lifetime cost savings of £1542.16 per patient (a 10% cost reduction compared with usual care, due to reduced hospital length of stay and decreased likelihood of developing complications), and a 99% probability for healthcare providers that GDT was cost-effective and thus the optimal choice for high-risk surgical patients.

A perioperative GDT algorithm for patients undergoing major non-cardiac surgery

It is unclear whether the original Shoemaker GDT values as described above are still appropriate today. Modern GDT management is concentrated on correcting hypovolaemia, using a haemodynamic monitor to target changes in SV. Once the patient is deemed 'volume replete', attention can then be turned to augmenting CO and with it maximizing oxygen delivery, with or without the use of vasoactive drugs.

Optimizing SV

Using information gleaned from a haemodynamic monitor, increases in SV, and therefore CO, are achieved initially through fluid challenges, typically consisting of 250 ml of either crystalloid or colloid. By convention, in GDT, an SV increase of ≥10% after a fluid challenge indicates that the patient is 'volume dependent' or 'volume deplete' and further fluid boluses are required to optimize ventricular performance. This is seen at point A in Figure 1 where an increase in end-diastolic volume (ΔV) after a fluid challenge results in an increased SV. This is because on the ascending portion of the Frank–Starling curve, an increased end-diastolic volume causes increased ventricular wall stretch and thus an increased force of cardiac contraction is developed[45] (positive inotropy).

If the SV increases by <10% after a fluid challenge then the patient is termed 'volume independent' or 'volume replete' and further fluid challenges (at that clinical time point) are not required

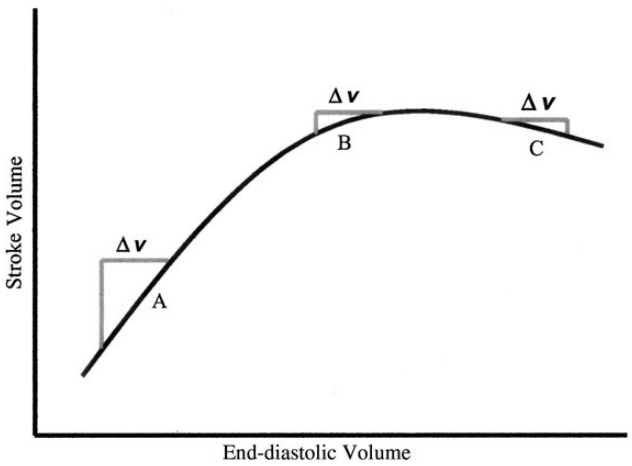

Fig 1 Adapted from the Frank–Starling law of the heart and depicts the relationship between SV and end-diastolic volume (or intravascular volume) for the human cardiac ventricle. (Taken from Grocott and colleagues[46] with kind permission from Lippincott Williams and Wilkins/Wolters Kluwer Health.)

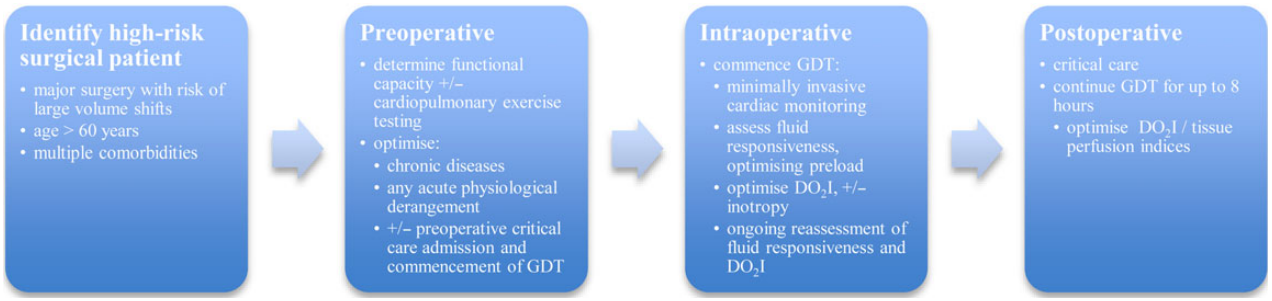

Fig 2 Suggested algorithm for the perioperative management of high-risk surgical patients (adapted from Lobo and de Oliveira[48] and Lees and colleagues[49]).

to improve ventricular performance. This is demonstrated by point B. Finally, if the SV decreases after a fluid bolus, then this is indicative of a decrease in ventricular performance due to ventricular overdistension. This is seen at point C and the patient may be at risk of ventricular failure and pulmonary oedema. It is important to remember that the Frank–Starling curve is in fact a family of curves, the position of which on each axis is dependent on the afterload and state of inotropy. Decreased afterload and increased inotropy shift the curve up and left (increasing SV), the opposite occurring with increased afterload and decreased inotropy.

Augmenting CO and oxygen delivery

Once SV has been optimized, CO (and with it systemic oxygen delivery) can be increased through the use of blood transfusions, oxygen, and vasoactive drugs (typically inotropes). The most frequently studied inotrope in GDT literature is the dopamine analogue dopexamine, a β-adrenergic (β_2) and dopaminergic (DA1 and DA2) agonist. The perioperative use of low-dose dopexamine ($\leq 1\ \mu g\ kg^{-1}\ min^{-1}$) in high-risk surgical patients undergoing major surgery has been associated with decreased length of stay and a reduced 28 day mortality.[47] Dopexamine doses $\geq 1\ \mu g\ kg^{-1}\ min^{-1}$ have failed to show any survival benefit however and are associated with detrimental side-effects such as tachycardia.

Although early studies into GDT have advocated achieving a $DO_2I > 600\ ml\ min^{-1}\ m^{-2}$ for any surgical patient deemed high risk, as discussed by Lobo and de Oliveira,[48] DO_2I should perhaps be augmented on an individualized basis depending on the patient's preoperative values, the nature of surgery, and predicated VO_2I increase. Regardless, the aim of any DO_2I increase should be to keep DO_2 above baseline to reduce the likelihood of perioperative tissue hypoxia.[48] A suggested algorithm for perioperative GDT is shown in Figure 2.

Conclusion

The available evidence suggests that GDT has a role in the perioperative outcome of the high-risk surgical patient, by reducing the postoperative complication rate and the length of stay in hospital. However, the absolute mechanism for the benefit of GDT remains unclear.

A number of questions remain:

(i) When should GDT be commenced during the perioperative period? GDT was traditionally commenced in the preoperative period, but intra- and postoperative GDT has also shown benefit.
(ii) Which GDT technique should be used?
(iii) What types and quantities of fluids should be used?
(iv) Which haemodynamic monitoring device should be used? The PAC was previously the 'gold standard', but its use is controversial and has been superseded by newer technologies such as those described briefly above.
(v) Which vasoactive drug is preferential?
(vi) Is critical care admission an important component of the package?

Despite these questions, recent NICE guidance[50] stating that CardioQ-ODM™ oesophageal Doppler monitoring can be considered to guide intraoperative fluid therapy in higher risk patients where invasive cardiac monitoring was planned highlights the perceived benefits that optimizing CO and oxygen delivery has on patient outcome. Patient selection is clearly important, with 'fitter' patients and those with established disease less likely to benefit. Larger, adequately powered, pragmatic multicentre trials are justified to evaluate the effectiveness of perioperative GDT in routine clinical practice.

Supplementary material

Supplementary material is available at *BJA Education* online.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

Podcasts

This article has an associated podcast which can be accessed at http://www.oxfordjournals.org/podcasts/ceaccp_16.06.01.mp3.

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A complete list of references is available as Supplementary material.

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Civilian aeromedical retrievals (the Australian experience)

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Key points

- Various forms of retrieval and retrieval services exist.
- Capability of the referral service needs to be identified early.
- Unwell patients are at increased risk of physiological derangement during aeromedical transfer.
- Management of certain conditions require specific treatment plans to account for the pathophysiology and aviation changes.
- Logistics, communication, and follow-up are vital to successful retrievals.

Retrieval medicine is the process by which suitably qualified and trained personnel utilize appropriate equipment and transport platforms to clinically manage and safely transport a patient from one location to another.[1]

Retrievals can be subclassified into primary, secondary, and tertiary. Primary retrieval is the transport of patients to their initial hospital reception. This may be their nearest hospital, or directly to a larger and more distant centre such as a designated trauma centre.[2,3] Secondary retrievals move patients from a non-specialized hospital to a higher level of clinical care such as for neurosurgery, interventional cardiology, complex obstetrics, or paediatrics. Tertiary retrievals transport patients between two similarly specialized hospitals.

In 'modified primary retrievals', an injured or unwell patient has already been taken to an initial health facility that has minimal capacity to increase the level of care to that provided in the prehospital environment. In these circumstances, the retrieval team apply similar practices to a true primary retrieval, albeit in a more controlled clinical environment.[3]

In Australia, owing to the large land mass and relatively low population density, specialized medical services are clustered mostly in coastal urban centres. Therefore, many referrals are from rural and remote areas where access to specialist medical services is limited.[2]

Journeys range from a few kilometres and a few minutes in major capital cities to several thousand kilometres over many hours from isolated rural communities. While distance might not be limiting, other access issues such as terrain and weather extremes play roles in the structure of services.

Most retrieval occurs within state health system jurisdictions or within state boundaries. If there is need to transfer patients interstate or internationally, pre-existing agreements between the relevant authorities are important to safely facilitate transfer. These patients have often received initial medical care at the place of presentation. With the increased ease and popularity of travel, particularly to developing nations with limited healthcare capacity, international retrievals/repatriations are becoming common. They bring with them unique logistic and cultural issues for the retrieval team, in addition to the challenges of medical retrieval.

Retrieval services are structured using a combination of doctors, nurses, paramedics, drivers, aircrew, and administrative staff. There are varying levels of interaction between the different disciplines, depending on the structure and culture of the organization. Retrieval services can be hospital-based, independent, military, private, public, or not for profit. Increasingly, *ad hoc* retrieval services are being replaced in favour of more structured permanent services. Depending upon jurisdiction, retrieval teams may need to satisfy civilian aviation rules, including health, security, drug, and alcohol checks before working as aircrew in the aeromedical setting.

Aviation and altitude

Air travel comes with inherent physiological changes and health risks, even for healthy people. These changes are less well tolerated by unwell patients and the health risks associated are magnified.[1,2,4]

Helicopters used for aeromedical retrieval, in general, do not have pressurized cabins and therefore operate below 10 000 feet above sea level (FASL). Fixed-wing aircraft pressurize cabins to between 7000 and 8000 FASL (similar to commercial airliners). At sea level, the partial pressure of inspired oxygen is 149 mm Hg, while at 8000 FASL, this decreases to 108 mm Hg.[4] This is the equivalent of breathing 15% inspired oxygen at sea level. Therefore, relative hypoxia (either due to altitude or inadequate pressurization of the aircraft) is common. Potential effects include myocardial ischaemia, syncope, impaired mental performance, and loss of consciousness. Supplementary oxygen may be required in flight if the aircraft is not pressurized to sea level cabin altitude.[4]

Immobility during long transport increases the risk of thromboembolic events. Noise, temperature, and vibration stress can all have a deleterious effect on patient stability and create a demanding work environment for medical crew. Motion sickness can be a serious complication for the obtunded or unwell patient as well as for the retrieval team, and routine prophylaxis should be considered.[4] Fear of flying and of heights are both factors that may need to be dealt with before loading a patient for their flight.

In addition to changes in the partial pressure of gases with increasing altitude, specific knowledge of and compensation for the changes in atmospheric pressure is required. The physical effects on the body of decreasing barometric pressure include the expansion of gas-filled cavities such as the middle ear, lungs, sinuses, gastrointestinal tract, and potential spaces such as the pleural space. If the patient's clinical condition requires, the cabin may be pressurized at or near sea level or the flight level reduced to increase the barometric pressure. Conditions necessitating this include severe hypoxia, undifferentiated major trauma, bowel pathology, and diving-related illnesses. When pressurized to sea level cabin altitude, aircraft cannot reach their normal cruising altitudes. They carry higher fuel loads, fly lower and slower, which will reduce their flying range and may expose them to increased turbulence and adverse weather conditions.

Referral

The determination process for prioritizing and appropriately allocating retrieval assets is multifactorial. These are summarized in Table 1. Communication with the receiving team (where known) is mandatory, to agree on a clear management plan. When determining the mode of transfer, several considerations are important. Helicopters are able to access more referral sites than fixed-wing aircraft, but have a shorter range, a more confined work area, louder noise, and more vibration stressors. Transfer by road usually allows easy access to referral sites and allows easier stopping with less ambient noise, but at the expense of a much slower transfer time.

Table 1. Factors affecting the decision to retrieve

Referral factors
• Referrer's skills in diagnosis and resuscitation
• Resources available
• Contingency plan/nearest available support services
Patient factors
• Natural history of disease
• Response to initial treatment
• Urgency of transfer
• Complications
• Social factors (including willingness to fly)
• Size, weight, mobility of patient
Retrieval team
• Capacity
• Equipment
• Personnel
• Skills
Receiving hospital
• Accepts referral
• Bed availability, availability of intensive care bed, etc.
• Ability to manage referral, i.e. interventional capacity
Aviation factors
• Distance (including need for refuelling)
• Time
• Weather
• Terrain (including availability of landing strip, helipad, road access)
• Destination
Logistical factors
• Safe working hours
• Skill set of team
• Other demand on resources
• Cost

Preflight

Assessment and stabilization

The structured assessment of airway, breathing, circulation, neurology, and other major factors is conducted before patient movement. Preferably, this is conducted at the referral healthcare facility, although this may contribute to significant delays while the retrieval team are transported between the retrieval aircraft and the referral hospital or patient location. Alternatively, the patient may be brought to the departure point/airstrip by the referral team. Pragmatism will occasionally necessitate a focused primary survey before initial movement and a more detailed assessment at either the receiving hospital or before a longer flight.

'Scoop and Run' *vs* 'Stay and Play' has long been a point of divergence across many retrieval medicine experts and retrieval services around the world.[3] In essence, there are patients who will benefit *most* from a rapid assessment, minimal stabilization, and prompt transfer to definitive care. Others will deteriorate significantly *en route* without the initiation of further stabilization by

the retrieval team before transfer. The decision regarding which of these principles may be most appropriate in a given circumstance is complicated, varying not just with patient and pathology factors, but also with local skill, transport team skill, logistics, and time to definitive care.[1,3]

Initiation of reliable monitoring is important during this assessment and stabilization phase. This may range from an oxygen saturation probe to invasive monitoring with insertion of central venous and arterial access. With the confounding risks of air travel, clinicians must be mindful of both the potential for deterioration in the air, the limited ability to escalate treatment in flight and balance this with the need for timely transportation. Intubating a patient at an airstrip may not be optimal, but is likely to be more successful than attempting the same on a rapidly deteriorating patient wearing seatbelts, in turbulence, at altitude.

One of the most hazardous times for a patient is the time of transfer from the hospital to the aircraft. This is more difficult when extra transfers are necessary; for example, when the patient needs ambulance transfers to and from the aircraft. Risk increases with increasing number of individual patient movements.[3] Apart from the potential disconnection and dislodgement of tubes and monitoring, there are hazards to staff. Obese or intoxicated patients, exposure to extremes of weathers, limited visibility, and hazardous environments all challenge effective prehospital care delivery.[2]

Preparation for inflight management and monitoring

Equipment and monitoring used inflight should be light, portable, robust, and familiar. Monitors need to utilize both visual and auditory modalities due to the presence of bright ambient light and noise pollution. Monitors and equipment have limited battery life and not all aircraft have the facility to charge equipment in flight. The more parameters used on a monitor, the higher the power consumption. Back-up power supply is necessary for vital pieces of equipment. Specialized equipment such as point-of-care pathology devices and ultrasounds may be considered where necessary. A number of professional bodies have guidelines about the minimum requirements for transportation.

Apart from initial resuscitation and monitoring, a number of critical care and comfort matters are necessary to facilitate transportation. The extent to which these are managed depends upon the time and distances involved in transit.

While pain relief is often an acceptable minimum during short primary transfers, the use of complex techniques such as regional and neuraxial block requires expertise, equipment, and time to establish and manage. Nevertheless, these techniques should be considered, particularly for longer transfers. Attention to pressure care areas is also important, especially in the muscle-relaxed and ventilated patient.

All patients should have i.v. access, although the use of i.v. fluids may be limited to longer flights or where there are clinically significant changes to the blood volume or electrolyte status of the patients. A urinary catheter should be considered, for comfort or for monitoring of urine output. Glycaemic control and nutrition both need attention during long flights. Insulin requiring diabetic patients are a group in which it is necessary to maintain ongoing administration of exogenous insulin, albeit with a goal of a relatively higher blood glucose level than the usual targets (4–10 mmol litre^{-1}). As in intensive care, tight glycaemic control during transport may lead to complications of hypoglycaemia.[5] Enteric feeds are normally ceased and disconnected, although supplemental fluid may be required. Gastric tubes should ideally be aspirated periodically to ensure decompression of the stomach. In ventilated patients, free draining gastric tubes are recommended to prevent dilatation and improve ventilation dynamics.

Inflight

Reassessment and management in the case of deterioration

The ongoing assessment of the patient during transportation is different from that in hospital. During flight, continuous direct observation of the patient supplemented by monitored data is essential. Strategies used on the ground to ameliorate deterioration (including positioning, institution of drugs and infusions, suction, or escalation of respiratory support) are difficult or impossible to adopt during transport. In flight, access to the patient is limited due to cabin size and patient position. All personnel need to be restrained and equipment securely stowed during key phases of flight, due to potential turbulence at lower altitudes, thus limiting rapid access. Communication with the patient, fellow crewmembers, and ground teams are limited due to aircraft noise and isolation. Performing procedures of any kind in the air is difficult, even for the most experienced aeromedical practitioner. Commencing and maintaining cardiopulmonary resuscitation in flight remains very challenging. Therefore, pre-emptive performance of procedures for expected deteriorations such as intubation, central venous access, and a plan for deterioration is vital before departure.

Post-flight

Transfer to the destination medical facility

A plan for offloading the patient and transfer to the definite facility must be confirmed. The patient may need a further road transfer, which may require continued medical escort. Adequate equipment, drugs, and monitoring will be required for the road transfer.

Handover

At the destination, after introductions and identification, the patient is handed over to the receiving team. Various methods exist for handover. Whichever method is used, it should be structured and locally agreed upon to ensure the transfer of relevant verbal and written information. The patient is normally under the care of the retrieval team until formal handover has been completed.

The retrieval team plays only a transient role in the care of a critically unwell patient. However, it is often at a time of high stress and emotions, particularly for families. Clear communication and regular clinical updates to coordinating agencies therefore remains essential.

Disease-specific management

The ventilated patient

Positive pressure ventilation is instituted in many patients to manage obstructing airways, ventilatory failure, circulatory collapse, and neurological defects and derangements. Transport ventilators should comply with the national standards, including all alarm warnings. As audible alarms may not be heard in aircraft, visual alarms should be activated concurrently. Electrically powered turbine ventilators will reduce oxygen use and are preferred for longer distance transfers. Ventilators vary in their capability to compensate for altitude and monitoring expired tidal

volumes. Measurement and display of minute volumes is required, particularly after ascent and descent. Tracheal tube cuff pressure should also be monitored and adjusted to avoid tracheal mucosal injury from excess pressure after climb. Pneumothoraces need to be drained before departure as they will expand during ascent, causing circulatory compromise.

Non-invasive ventilation

The use of non-invasive ventilation (NIV) has a controversial role in transportation.[6] Some patients with less severe hypoxia or other respiratory failure may be safely transported with NIV, negating the need for intubation in already compromised patients. The deterioration of the patient, failure of NIV, and the need to intubate inflight are major hazards. A risk assessment must be carried out before transfer, and if the risk of deterioration, failure, or intubation is deemed to be a real possibility, NIV may not be the most appropriate choice.

When electing to transfer using NIV, several considerations should be made. Rapidly progressing pneumonia is unlikely to benefit from NIV, while pulmonary oedema from congestive cardiac failure might be well managed with NIV. A trial on the ground to ensure the patient tolerates and responds to the technique is necessary, with escalation to invasive ventilation if unsuccessful. Equipment challenges may also arise; not every transport ventilator can provide NIV, and those which do may require very high flow rates (up to 30 litre min^{-1}) and hence have unachievable compressed gas requirements. Turbine ventilators are better suited for transport NIV due to their reduced compressed gas requirements.

Cardiac disease

The transfer of a patient for interventional cardiology services is one of the most common reasons for aeromedical retrieval.[2] Monitoring for arrhythmias and the ability to defibrillate/pace is necessary. Managing cardiogenic shock may include the use of inotropes, vasodilators, and ventilatory support. In cases where there will be a time delay to percutaneous coronary interventions, advice about thrombolysis should be sought. Patients who have experienced cardiac arrest may be receiving therapeutic cooling. This may be continued in flight with appropriate protocols, cooling interventions, and monitoring.

Non-cardiogenic shock

Invasive monitoring such as central venous pressures and ultrasound-guided intravascular volume assessment to guide vasopressor and inotropic therapy may be necessary. The time required, equipment, and sterile set up available need to be considered in conjunction with the patient stability and likely transfer time. In longer transfers, apart from initial resuscitation, these patients may need intubation, ventilation, and attempts to correct the underlying process before transfer to an aircraft.

Trauma and surgery

The issues related to trauma in the military prehospital setting are covered well in a previous article.[7] These principles apply in the civilian setting. If available, blood products should be taken on all major trauma retrievals. Approved temperature-controlled blood shippers are available. If used and monitored appropriately, unused products may be returned for future use. When there is a need for urgent surgical care such as with testicular torsions, incarcerated hernias, or ongoing haemorrhage, expediting transfer is vital. The use of tranexamic acid, maintenance of temperature, permissive hypotension, and damage control resuscitation are all current concepts in the acute management by the retrieval team. In cases of acute abdomen or obstruction, the use of gastric decompression should be considered.

Paediatrics

The management of the deteriorating child requires appropriately skilled personnel and equipment. Issues of consent both at origin and destination and also to aid in assessment, comfort, and management of the child lend weight to the transfer of a parental figure. Neonatal transportation should ideally be performed by specialized services.[8] Transfer of the mother may be as either a passenger or an extra patient depending upon her clinical status.

Obstetric pathology

Transfer of the obstetric patient is due to either complex obstetric pathology or need for neonatal input. The management of preterm labour including tocolysis should be undertaken in conjunction with the receiving obstetric unit.[9] Initiating treatment of preeclampsia including the use of magnesium infusions will decrease the risk of seizures in a hostile environment. Team members should be able to manage the safe delivery of a baby, provide neonatal resuscitation, and manage a post-partum haemorrhage; however, all reasonable attempts must be made to avoid delivery in transit.

Psychiatric transfers

The transfer of patients with altered mental state poses a risk of harm to the crew and aircraft. Techniques for safe sedation may be necessary for the transfer. Intubation is very rarely needed and exposes the patient to risks and delays transport to the necessary psychiatric services. I.V. sedation is often very effective.

Table 2. Organizational considerations in aeromedicine

Error and incidents
- Orientation programme
- Ongoing information updates
- Risk identification systems
- Incident reporting systems
- Follow-up systems

Crew
- Selection of crew
- Ongoing maintenance of professional standards
- Personal health management
- Fatigue management and shift work
- Substance use and misuse

Aviation safety
- Regulations of the civilian aviation authority
- Air traffic control
- Weather, landing strip information
- Logistical management systems

Aircraft safety
- Approval for modification of aircraft for medical purposes
- Approval of equipment for aviation use
- Ongoing aircraft maintenance
- Servicing and updates of equipment and systems (e.g. oxygen delivery)
- Cleaning of aircraft and infection control
- Warning systems for airline safety

Ketamine-based sedation has been used effectively in this patient group.[10] Security personnel may need to be present on the flight.

Follow-up and audit

Because of the transient role of the retrieval service in the care of the patient, ongoing feedback from the receiving hospitals is necessary to ensure quality of care is maintained. A system needs to be in place to ensure that patient outcomes and discharge information is disseminated to pertinent individuals. This is particularly important in cases where there have been poor outcomes or errors.

A number of organizational factors are necessary for the accreditation of the retrieval service.[2] In additional to those of a normal healthcare provider, these include aviation and transportation factors. See Table 2. Systems including occupational health and incident management need to be in place at an organizational level. As with any healthcare organization, the retrieval service needs to undergo an accreditation process to ensure the quality of service provided to patients meets the standards set by the overseeing body and ensuring the personnel and systems are appropriate for the services rendered. Retrieval organizations may also utilize checklists, manuals, and guidelines in order to facilitate the safe practice of medicine in hostile and challenging conditions.[2]

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Human factors in complex airway management

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Key points

- Human factors are vital to the successful management of an anticipated difficult airway.
- Careful planning and preparation are key to success, with a logical strategy being selected and the airway management being undertaken by a competent anaesthetist.
- Careful consideration of the risks of each technique will assist a thorough preoperative assessment to be undertaken, and the logical plan and equipment selected.
- A detailed pre-anaesthetic briefing of the multidisciplinary team is required to ensure that all personnel are aware of the plan and their role in the anaesthetic room.
- Situational awareness is vital to ensure that fixation errors are avoided. Disciplined communication and thoughtful followership ensure good team dynamics.

Human factors have been defined as 'the environmental, organisational and job factors, and human and individual characteristics which influence behaviour at work in a way which can affect health and safety'[1] and have been described with particular relevance to anaesthesia in the Anaesthetists Non-Technical Skills Framework.[2] When dealing with a patient with a complex airway, exceptional attention to human factors is vital to success. This has been noted extensively in the literature after two high profile cases.[3,4] Recently, there has been adoption of human factors in healthcare at the highest level with the signing of a Concordat from the National Quality Board by organizations such as the General Medical Council, The Care Quality Commission, and Health Education England.[5]

The Fourth National Audit Project of the Royal College of Anaesthetists (NAP4) examined major complications in airway management and concluded that poor human factors could have contributed to 40% of the cases reported. In 25% of these cases, inadequate human factors were felt to be a major contributor to a poor outcome.[6] Further analysis specifically looking at human factors in cases reported to NAP4 reported that there were potentially an average of four human factors issues per reported case.[7] This article sets out to describe our experience of the importance of human factors when dealing with patients with an 'anticipated difficult airway' and describes our strategy, particularly in planning, preparing, briefing the team, and conducting the airway management with an illustrated example.

Our hospital experience

Aintree University Hospital NHS Foundation Trust is a large teaching hospital situated in North Liverpool. It is a tertiary referral centre for head and neck surgery providing specialist services to around 1.5 million residents in Merseyside, Cheshire, South Lancashire, and North Wales. The population served by Aintree includes some of the most socially deprived communities in the country, with high levels of illness. The Head and Neck Unit is the largest in the UK, carrying out ~800 cases per year. This provides our anaesthetists and surgeons with a wealth of experience in dealing with patients with abnormal airway anatomy and frequently, difficult airways. Our department is the home to the nationally recognized Aintree Difficult Airway Management (ADAM) course.[8]

Specific human factors in complex airway management

Leadership

It is important that the team is aware as to who is in charge of the case. The leader will usually (although not always) be the most experienced anaesthetist and their role is to:

- Formulate the airway management plan(s) and communicate this to the team, so they are all 'on the same page'.
- Allocate roles with the team and identify any limitations in skill mix.
- Maintain situation awareness and not become task fixated while the airway is being secured.
- Define the trigger points for moving from Plan A to B (and subsequent plans) if required.

Teamwork

Good teamwork is integral to success in all airway management. This is particularly important in the anticipated difficult airway. Salas and colleagues[9] described a team as 'a distinguishable set of two or more people who interact dynamically, interdependently, and adaptively towards a common and valued goal, who have each been assigned specific roles or functions to perform, and who have a limited life-span membership'. It is therefore very important that the team is aware of the plan(s) for airway management, their role in the process, and anything else that is expected of them. A team brief will ensure that this is achieved with an opportunity to ask questions and clarify any differences in opinion.

Situation awareness

Situation awareness itself has been described as 'the perception of the elements in the environment within a volume of time and space, the comprehension of their meaning and the projection of their status in the near future'.[10] Loss of situation awareness is one of the most common recurring features in adverse incidents involving airway management.[7] The three stages of situational awareness include:

- Gathering information. This will start with taking a history and examining the patient and will be supplemented by other investigations such as nasendoscopy, CT scan, and discussion with surgical colleagues. Once airway management occurs then further information is gathered from monitors, images on fibreoptic cameras, and tactile feedback. Mistakes may occur if the individual misinterprets task-relevant information.
- Interpreting the information. Mistakes may occur if an individual wrongly perceives specific information.
- Anticipating future states. Mistakes may occur if future status is wrongly predicted, either from a poor initial mental model or personal memory failure. (A mental model is an explanation of a person's thought process, or what they expect to happen.)

Good situation awareness when performing a complex task can be maintained in different ways. In the trauma team scenario, the trauma team leader (TTL) maintains a 'hands off' approach and stands at the foot of the bed so they maintain an all round view and are effectively 'driving the bus'.[11] In this way, the TTL is not directly involved in any practical tasks themselves and so are able to observe the patients management in 'real time'.

Decision-making

After assessment of the patient before operation, the clinician should identify the potential difficulties and problem areas for that individual. The risks and benefits of each potential airway management method need to be weighed up. These may vary from case to case. The location of the planned intubation, experience level of staff available, and clinical urgency of the case are all factors that may deem a normally suitable technique, unsuitable. Once a decision has been made and 'Plan A' formulated, it is important to continue to re-evaluate the clinical situation taking into account any significant changes and ensuring that 'Plan A' remains the best plan.

Although the Plan A, B, and C approach is favoured, it is important to recognize that some airway cases are such that there may only be one plan. In such circumstances, the most senior anaesthetist will manage the airway and if this is devolved to a senior trainee, it must be done under close and direct supervision with a clear plan for stepping in.

Followership

Although good leadership is crucial to good teamwork, so too is good followership. A follower is defined as anyone not acting in the position of leader and responding to organizational actions; a person who is active rather than passive.[12] In terms of difficult airway management, this encompasses actions such as anticipation, support of the team leader, and good communication using feedback loops. A feedback loop is where the sender (e.g. the team leader) transmits an instruction to another member of the team who receives it and then feeds back they have understood the instruction (or decoded the message correctly).

Communication

Good communication is paramount to the successful execution of securing the patient's airway and simple steps can ensure that communication flows from the team leader to the other members of the team. Previous work by Gawande and colleagues[13] cited communication failures as being responsible for 43% of errors in three large teaching hospitals in the USA. We have found a team brief to facilitate good communication among the multi-disciplinary team

The team brief allows:

- introduction of team members,
- the team to be reminded of individual levels of training and competencies,
- allocation of tasks,
- discussion of potential problems and highlighting solutions,
- clarification of the team leader's mental model and the airway plan(s).

There are several aspects of communication skills that should be highlighted, particularly in the management of the patient with an anticipated difficult airway.

- 'Sterile Cockpit': During the intubation attempt, the team should aim for what is described in the airline industry as a 'sterile cockpit'. This infers that the noise level is kept to an absolute minimum by having only the required team members present. This enables all monitors, comments, and instructions to be heard clearly ensuring vital information is not lost.

Case history

The importance of human factors in the management of an anticipated difficult airway will be illustrated by the case described in Table 1.

Fascial space infections (dental abscesses) can be considered the archetypal anticipated difficult airway;[14] they can be life-

Table 1 Case history

A 62-yr-old male presented to The Accident and Emergency Department with acute dysphagia for liquids arising on a background of a 3 week history of worsening toothache and facial swelling
On examination, he was pyrexial (39°C), dysarthric, and was drooling as he could not swallow his saliva. He also could not assume the supine position
He had trismus with 1 cm of mouth opening, swelling and erythema over his left cheek, and mandible spreading to the left anterolateral aspect of his neck. He had an old fracture of his nose
He was tachycardic (110 beats min^{-1}) but not hypotensive. His Sa_{O_2} was 92% on room air. Nasendoscopy revealed only the left nares to be patent. The anatomy of the oropharynx at nasendoscopy was found to be severely distorted, full of secretions and with a mucosa prone to contact haemorrhage. The glottis could not be visualized. A full blood count revealed a leucocytosis, and clotting abnormalities

threatening and cause serious postoperative problems. They are heterogenous in their presentation, and can involve the whole upper airway and all the access routes into the airway.

The anticipated difficult airway is different from the management of the unanticipated difficult airway. The anaesthetist knows there are going to be problems in advance and consequently has time to select the best intubation plan to deal with their patient's particular constellation of problems. It is crucial that the plan is enacted precisely, necessitating attention to detail at every step of the intubation plan from positioning and oxygenation through to confirmation of tube placement in the trachea.

The anaesthetist must have a pragmatic approach to assessment, planning, and execution of the intubation plus the human factors involved at each stage. To this end, we advocate a six-step method used by the ADAM website[8] if time allows.

Aintree six-step approach to difficult airway management

Q1: How much time do I have?
Q2: What access to the airway is available (nose, mouth, trachea)?
Q3: How compromised is the airway?
Q4: Which fascial spaces are involved?
Q5: Which management plan(s) best fits the circumstances?
Q6: Could I make the situation worse? If so, how?

Question 1

Difficult airways are time critical emergencies and can be classified as follows:

(i) No time for assessment and planning: Need to act immediately to avoid hypoxic brain injury/death. Correct use of the DAS algorithms[15] is crucial to outcome.
(ii) Some time for assessment and planning: The six-step approach is used remembering that actions can gain or lose time; airway management is a fluid situation with often incomplete information and so it is necessary to take stock repeatedly and avoid being too rigid in one's approach.
(iii) Adequate time for assessment and planning. A structured approach is required to assess options, evaluate risk, and maximize success. We use the ADAM website[8] and methodology and it is used for illustration here, although of course other methods may be used.

Questions 2–4

The available access routes are first considered. Airway compromise is multi-factorial and for this patient, sepsis indicates urgency, influences management, and is associated with more complications. Trismus is not always due to pain: the joint may be compromised. Pharyngeal involvement causes stridor, drooling, dysphagia, and tongue immobility. Nasendoscopy is the most important investigation. It is simple to perform, confirms nasal patency, and indicates the location of airway distortion and the degree of oedema. Imaging is useful if the patient can lie flat as it accurately defines the fascial spaces involved, differentiates between cellulitis and abscess, reveals vascular sheath involvement, and confirms the diagnosis of mediastinitis if suspected clinically.

Question 5

Once assessment and investigation are completed, the clinician uses the information to decide which airway management plan best fits the patients' circumstances. Airway management should not follow a 'one size fits all' approach. The breadth of techniques means a 'bespoke' plan should be sought that is best suited to deal with the problems at hand. A good way to do this is by considering the limitations of each plan in the context of the patient's problems. When using the ADAM website, each choice of technique is evaluated against the clinical scenario and an analysis of limitations, potential complications, and likely success is used to identify the technique that is most likely to succeed without complications

Question 6

The last step considers how one's actions can make the situation worse. This is done by constructing an intubation plan detailing potential pitfalls and to discuss it with the whole team in advance. The ADAM website generates a printable 'contingency plan' (Table 2) splitting the intubation into its constituent steps and listing the anticipated problems for each step. The left-hand column lists generic potential problems likely to be encountered whenever the equipment is used, in this case awake fibreoptic intubation. The right-hand column highlights how the patient's problems are likely to cause difficulty and at which stage in the intubation this may arise. Used at the team brief, it enables everyone to effectively be on the 'same page'; when to expect specific problems, how they will manifest themselves. Table 2 does not provide solutions but rather highlights potential pitfalls leaving it to the user to formulate a response. It also determines in advance when it would be appropriate to abandon the procedure and consider other options (if any).

How the patient was managed

Assessment and planning

The severe trismus and indurated anterior neck meant that there was only one viable route into the airway: the

Table 2 Contingency table for the patient described in Table 1

Generic problems	Patient-specific problems
1. Check equipment/position patient	
Adverse patient position	
Inadequate nasal patency	
Illumination not satisfactory	
Monitor image not optimized	
Wrong size tube	
Wrong type of tube	
2. Prepare nares, oxygenate, start sedation	
Omit supplemental oxygen	
Increasing airway obstruction (LA effect)	
Apneoa (excess sedation)	
Respiratory depression (excess sedation)	
3. Mount tracheal tube on fibrescope	
Tube not loaded	
Tube loaded via Murphy's eye	
Tube/fibrescope interface not lubricated	
Omit anti-fog solution	
4. Negotiate fibrescope through the nose	Operator traumatizes nasal mucosa causing bleeding: coagulopathy
Fogging of lens	
Secretions obscure view	
Inadequate nasal patency	
Traumatic bleeding obscures view	
Friable tissue obscures view (e.g. polyp)	
Disorientation	
Failure to traverse nose	
Nasal congestion/hyperaemia	
Naso-pharyngeal obstruction (e.g. adenoids)	
5. Explore pharynx, larynx, and trachea	Contaminant obstruction:
Epiglottis obscures glottis	spontaneous or iatrogenic abscess rupture
View becomes 'red out' (blood) or 'white out' (secretions)	iatrogenic bleeding
Prolapsing pharyngeal wall obscures view	Airway distortion (cellulitis)
Excessive vocal cord movement	
Excessive reflex glottic closure	
Unexpected gastric reflux	
Accumulating pharyngeal secretions	
6. Position fibrescope in trachea	
Carina not realized	
7. Railroad tracheal tube over fibrescope into trachea	Tube advancement problem: nares, epiglottis, arytenoid, subglottic
Tube not loaded/loaded incorrectly	Bleeding: trauma, abscess rupture
Tube diameter too large to enter nostril	
Tube/fibrescope step problem	
Tube hold up: nostril, epiglottis, arytenoids, or subglottically	
Inadvertant removal of fibrescope from trachea	
8. Confirm tube position relative to carina	
Cannot identify carina	
Patient distress due to iatrogenic total airway obstruction	
9. Remove fibrescope leaving tracheal tube	
Difficult fibrescope removal (no lubrication)	
10. Re-confirm tube position with CO_2/bag movement	
No capnograph trace	
No ventilation	
Difficult ventilation	
11. Induce anaesthesia and inflate cuff	
Inadvertent loss of i.v. access	
12. Confirm bilateral lung ventilation	
Ruptured tube cuff	
Endobronchial intubation	
Difficult ventilation	

left nostril. Awake fibreoptic intubation was considered the only option (awake tracheostomy would have been very difficult).

Preparation

All equipment was prepared and checked in advance. The patient was told why an awake intubation was necessary so that they

Table 3 Airway team

Name	Role
Consultant anaesthetist	Airway team leader Responsible for final plan based on all the available information Ultimately responsible Conducts team brief Supervises advanced trainee
Advanced trainee (ST6–7) in Anaesthesia	Perform the airway management within their competency under the supervision of the consultant anaesthetist Helps formulate the airway management plan
Intermediate trainee anaesthetist (ST3) in anaesthesia	Perform sedation using TCI remifenanil Induces patient once position of the tracheal tube has been confirmed
Operator department practitioner	Prepare the airway equipment Assist the anaesthetist undertaking the airway management
Support worker	Act as a 'runner' should an emergency arise or additional equipment is or help is needed
Consultant ENT surgeon	Contributes to the airway management plan Undertake an emergency surgical airway if indicated Perform a rigid laryngoscopy if indicated Support the anaesthetic team
ENT speciality trainee (ST4)	Work under the supervision of the ENT Consultant and perform the roles of the ENT consultant under their supervision
Theatre nurse	Has available equipment ready to allow an immediate surgical airway or rigid bronchoscopy. Needs to be ready in the operating theatre

understood the reasoning behind the decision and what the procedure actually involved. We also explained that the nature of his infection would mean he would be kept sedated and ventilated on ITU for between 12 and 48 h to allow his airway to improve before extubation.

We do not premedicate with benzodiazepines nor do we administer anti-sialogues; in a case such as this, they will be ineffectual. We do prepare the nares with a topical vasoconstrictor to minimize bleeding from the turbinate's vessel-rich mucosal bed and avoid any concomitant topical local anaesthetic. We believe that the use of local anaesthetic in this instance could worsen the airway.[16] Our technique for AFOI has previously been described using single-agent sedation with target-controlled infusion (TCI) remifentanil to facilitate awake fibreoptic intubation,[17] but this may be considered controversial by other anaesthetists in the UK and is just one technique. It provides analgesia and sedation and we believe it is more likely to preserve upper airway reflexes than topicalization with local anaesthetics. This advanced airway technique should not be used for the first time on a complex case without first gaining experience in lower risk cases.

It is advisable to anaesthetize such patients on the operating table rather than a trolley. The former allows better patient positioning, better access to the patient for the anaesthetist (and surgeon should a surgical airway be necessary), and reducing the chance of an accidental extubation when transferring the anaesthetized patient. A decision was also made as to where to manage the airway: in the anaesthetic room or in the theatre itself? The advantage of the anaesthetic room is privacy while the advantage of theatre is its space and lighting should a surgical airway be needed. We elected to anaesthetize the patient in theatre.

All cases of anticipated difficulty should have their neck surface anatomy assessed beforehand. In this case, the thyroid and cricoid cartilages were impalpable because of overlying induration and swelling. The neck itself felt 'woody' in terms of its poor tissue compliance and immobility. This alerted us to the fact that a surgical airway would be a difficult undertaking.

Team briefing

The introduction and implementation of the WHO Surgical Checklist has been reported to reduce in-hospital 30 day mortality.[18] We implemented a team brief at the start of each operating list led by the consultant anaesthetist. In this instance, he clearly stated that this was a 'high stakes' airway with only one clear route of access (LEFT nostril) and that an awake fibreoptic intubation would be performed. Using the ADAM contingency plan (Table 2), it was made clear that bleeding was a real threat and that should the AFOI be abandoned, it would be due to bleeding or the inability to railroad the tracheal tube. In such circumstances, it was extremely unlikely that the sedation could be aborted and the patient returned to full consciousness with a clear airway. In which case, a surgical airway would be needed and that this would be difficult to perform. The composition of the 'airway team' is described in Table 3.

Managing the airway

The patient was arranged in an upright sitting position on the operating table as the patient did not tolerate lying down. Nasal spectacles were fitted and oxygen commenced at 15 litre min^{-1}. I.V. access was obtained and an infusion of Hartmann's solution commenced. The sedationist titrated the TCI remifentanil while maintaining constant verbal communication; the endpoint being a drowsy but cooperative patient. The sedationist was then tasked with monitoring the patient and not the image of the patient's airway on the monitor. Remifentanil has a profound effect on respiration; the patient can be awake but apneoic. The sedationist placed a hand on the patient's chest to assist respiratory monitoring and if movement stopped, he prompted the patient to breathe.

Once the patient had achieved an appropriate level of sedation, the airway operator instructed the ODP to load a warmed 6.0 nasal RAE tube onto a lubricated fibrescope. We ensured the scope had not traversed the Murphy's eye and taped the pilot

balloon tubing to the tube adjacent to the connector so it could not dangle across the patient's face and eyes. Anti-fog solution was carefully applied to the lens of the scope, then the position of the prong of the nasal spec in the left nostril adjusted to allow the scope to enter the nose and the procedure began.

The nostril was easily traversed without traumatizing to the mucosa, but once the oropharynx was entered, no anatomical landmarks could be identified due to tissue oedema and collections of secretions. However, by only advancing the scope into black airspace, the operator soon found himself in the trachea, despite the lack of any recognizable intervening anatomy. The scope was then held in the mid-trachea, avoiding contact with the carina (which could trigger coughing) while preparations were made to deliver the tracheal tube.

The scope was handed to the ODP, who was then instructed to hold its position in the trachea. The airway operator lubricated the tip and cuff of the tube before using two hands to gently advance the tube into the nostril ensuring the bevel faced laterally and so was less likely to traumatize the turbinates. Once through the nostril, the tube was rotated 90° clockwise so the bevel faced the epiglottis (minimizing hold up). Should hold up be experienced the tube would have been rotated 180° anti-clockwise so the bevel now faced the arytenoids: the next point of hold up. Once the tube had entered the trachea, we confirmed its position visually before smartly removing the scope, allowing the patient to breathe easily again as the oedematous airway had been completely occluded by the scope and tube. The anaesthetic circuit with 100% oxygen at 15 litre min^{-1} was attached, bag movement and most importantly CO_2 trace observed before anaesthesia was induced with propofol, and surgery commenced. The lowest recorded Sa_{O_2} during the procedure was 93%. I.V. dexamethesone was administered.

Intraoperative management

The surgeons incised and drained the collections. The erythema and induration on the anterior neck extended towards the sternoclavicular joints, its extent outlined with a marker pen. As airway oedema is expected to worsen in the first 12–48 h after operation, we elected to keep him intubated and sedated. However, before transferring him to the critical care unit, we performed a CT scan to exclude the diagnosis of mediastinitis (suspected in view of the extensive cellulitis and the degree of sepsis). No collection was seen.

Postoperative care

After operation, we closely monitored the airway by nasendoscopy and had a low threshold for re-imaging if considered necessary. Regular reviews were made of microbiology, surgical drains, and whether all sources of infection had been removed. The decision to extubate was taken after 36 h once the airway oedema had resolved. During the interim, great care was taken by nursing staff to avoid accidental extubation.

Extubation strategy

Extubation can be considered as, if not more, challenging than intubation.[19] Consideration was given as to where the extubation should take place: critical care or the operating theatre? In our institution, critical care has the equipment and the personnel with the experience to deal with a patient such as this. A Cook Staged Extubation kit was utilized to facilitate blind reintubation as this was an 'at risk' extubation according to the DAS guidelines.[19] After siting the kit's guide wire under direct vision with a fibrescope and preoxygenation, the patient was sat up and extubated easily under remifentanil sedation (so that the patient was awake and tolerating the tube with appropriate reflex suppression), leaving the guide wire in place. The extubation was successful, and the patient remained on the critical care unit for another 12 h with the staged extubation guide wire *in situ* before it was removed and the patient discharged to the ward. Should the patient have required re-intubation, the Cook re-intubation catheter would have been advanced over the guide wire into the trachea and used as a bougie to facilitate rapid blind reintubation.

Summary

Human factors are vital in the safe and successful management of a patient presenting with an anticipated difficult airway for a surgical procedure. Careful planning and preparation are essential and rely on an accurate history and examination supplemented by specialist imaging such as nasendoscopy. It is important to determine the 'best plan' as sometimes there is only one plan. A team brief allows all members to be aware of their roles and responsibilities and to be on the 'same page' and this must be multi-disciplinary. Clear communication is vital not only with initial intubation but throughout the whole case with an airway team leader coordinating activities and facilitating decision-making.

Declaration of interest

S.M. and P.G. are both faculty members of the Aintree Difficult Airway Management Course. Neither have any financial gain from this course.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Ventilator-associated pneumonia

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Key points

- Ventilator-associated pneumonia (VAP) is the most common healthcare-associated infection in adult critical care units.
- VAP is associated with increased intensive care unit stay, patient ventilator days, and mortality.
- There is no agreed definition of VAP.
- The main pathogenic factor in the development of VAP is biofilm formation within the tracheal tube (TT) and microaspiration of secretions.
- The incidence of VAP can be reduced by many means including the use of care bundles and modified TTs.

Ventilator-associated pneumonia (VAP) is the most common healthcare-associated infection (HAI) in adult critical care units.[1] It is associated with increased intensive care unit (ICU) stay, patient ventilator days, and mortality.[2] VAP is thought to increase the mortality of the underlying disease by ~30%.[3] At present, there is no consensus definition for VAP, although many have been proposed. VAP is complicated by the lack of a consensus 'gold standard' definition to test the accuracy of potential diagnostic criteria. This article reviews the currently used diagnostic criteria, the role of care bundles and other novel techniques in VAP prevention, and recent advances in surveillance systems to overcome the diagnostic difficulties.

Diagnosis

Currently, the diagnosis of VAP is based on a combination of clinical, radiological, and microbiological criteria. There are a wide range of clinical conditions that mimic VAP in ventilated patients, including acute respiratory distress syndrome (ARDS), pulmonary oedema, pulmonary contusion, tracheobronchitis, and thromboembolic disease. Some of the clinical features used to define a VAP (e.g. change in tracheal secretions) are subjective and are subject to inter- and intra-observer variation. The diagnostic value of these clinical criteria in isolation, and in combination, has been reviewed recently by Klompas.[4] While individual clinical criteria appear to lack clinical sensitivity, combination of clinical criteria with laboratory criteria and radiological features improves the accuracy of a clinical diagnosis.[4] Fabregas and colleagues[5] found radiological infiltrates plus two from three of fever, leucocytosis, and purulent secretions, to have a sensitivity of 69% and specificity of 75% for diagnosing VAP.

There are no radiological criteria pathognomonic of VAP and the interpretation of chest radiographs in ventilated patients is very difficult. Single air bronchograms and fissure abutment are highly specific, but they lack sensitivity.[4]

Invasive and non-invasive sampling techniques are used to obtain microbiological specimens to diagnose VAP. Invasive techniques include bronchoscopic alveolar lavage (BAL) and protected specimen brushings (PSB), while less invasive techniques include mini BALs. Tracheal aspirates are the least invasive to obtain but the most likely to be contaminated with oro-pharyngeal colonizing bacteria. Quantitative cultures are often used to differentiate between colonization and infection. The diagnostic threshold for BALs is 10^4 colony forming units per millilitre (CFU ml^{-1}) and this is often the gold standard against which other diagnostic

criteria are compared. However, as bronchoscopic sampling cannot guarantee sampling from the area of the lung most affected, the sensitivity of this test is low, although the specificity is quite high (significant false-negative rate). Several studies have compared the value of quantitative invasive *vs* non-quantitative, non-invasive cultures. Meta-analyses comparing these have come to the conclusion that neither method confers any advantage on survival, length of ICU stay, or duration of mechanical ventilation.[6]

Current definitions

The Clinical Pulmonary Infection Score (CPIS) was developed by Pugin and colleagues[7] to facilitate the diagnosis of VAP using clinical variables. It gives a score of 0–3 for temperature, leucocytosis, $Pa_{O_2}/F_{I_{O_2}}$ ratio, chest radiography, tracheal secretions, and culture of tracheal aspirate. The maximum score that can be obtained is 12 and a score >6 is diagnostic of VAP. The assessment of the CPIS score is prone to considerable inter-observer variability, particularly with regard to interpretation of the tracheal secretions and the chest X-ray (CXR).

The United States Centre for Disease Control (CDC) definition[8] was designed as a surveillance tool for HAI but has been used in the diagnosis of VAP. It was not meant for the diagnosis of pneumonia, neither is it specific for VAP. However, it has been shown to have good sensitivity and positive predictive value, but its low specificity limits its value when compared with bronchoscopic cultures.

The Johannson criteria diagnosed a VAP based on the presence of new or progressive infiltrates on the CXR associated with at least two of three clinical features—leucocytosis, purulent secretions, temperature >38°C. Diagnosis by these criteria was compared with immediate post-mortem lung biopsies; the sensitivity was only 69%, while the maximum specificity was 75%.[5]

The HELICS[6] criteria are used for VAP surveillance in Europe. These again rely on a combination of clinical, radiological, and microbiological criteria and classify the pneumonia from PN1 to PN5 based on the microbiological method used. PN1 refers to diagnosis by minimally contaminated lower respiratory tract (LRT) specimens (BAL, PBS, distal protected aspirates), while PN4 refers to positive sputum culture or to non-quantitative LRT aspirates such as tracheal aspirates. Therefore, a unit's VAP rate can vary significantly depending on the microbiological method used.

VAP pathogenesis

The main pathogenic factor in the development of VAP is biofilm formation within the tracheal tube (TT) and microaspiration of secretions. The presence of a TT interferes with the normal protective upper airway reflexes and prevents effective coughing. The oropharynx becomes rapidly colonized by aerobic gram-negative bacteria after illness, antibiotic administration, and hospital admission. These contaminated secretions pool above the TT cuff and slowly gain access to the lower airway through a fold in the wall of the cuff. A bacterial biofilm, which is impervious to antibiotics, gradually forms on the inner surface of the tube and serves as a nidus for infection. This pathogen-rich biofilm is pushed into the distal airways by ventilator cycling and in the setting of immunosuppression associated with critical illness causes pneumonia. The longer the duration of ventilation, the greater the risk of developing VAP. Nursing patients in a supine position increases the risk of microaspiration and enteral feeding via a nasogastric tube increases the risk of aspiration of gastric contents. It follows that attempts to prevent VAP would focus on measures to reduce biofilm formation and microaspiration.

VAP prevention

The role of care bundles

A care bundle refers to a group of evidence-based interventions related to a particular condition which when applied together significantly improves patient outcome. In 2007, the Department of Health launched 'Saving Lives; reducing infection, delivering clean and safe care', a campaign to prevent and control hospital-acquired infection. This included 'High Impact Intervention No 5—Care bundle for ventilated patients', the aim of which was to reduce VAP. The original document consisted of daily sedation holds, bed head elevation, gastric ulcer prophylaxis, and oral care. It was updated in 2010 to include oral hygiene with adequate strength anti-septics, subglottic aspiration, and TT cuff pressure monitoring in addition to the initial four care interventions. A before and after study based in a large Scottish ICU studied the effectiveness of the original four high impact interventions (HII). They were able to demonstrate over 95% adherence with the bed end elevation and chlorhexidine elements and 70% compliance with the wake and wean elements (overall bundle compliance 70%). There was a significant reduction in their VAP rates (from 32 cases per 1000 ventilator days pre-intervention to 12 cases post-intervention), methicillin-resistant *Staphylococcus aureus* rates, and antibiotic use. However, they were unable to demonstrate a reduction in the duration of mechanical ventilation and overall ICU admission duration.[9] A similar study based in Spain used intra-cuff pressure control in addition to the other four methods. Although overall compliance was <30%, they were able to demonstrate reduction in VAP rates, ICU length of stay (LOS), and duration of mechanical ventilation.[10] However, a systematic literature review of four studies concluded that the lack of methodological rigor precluded any conclusive statements regarding the bundles' effectiveness or cost-effectiveness.[11]

TT modification

As it is the TT that provides the continuous path between the oral cavity and the distal airways, VAP prevention strategies have focused on TT cuff design to prevent microaspiration.

Cuff pressure control

An inflating cuff pressure <20 cm H_2O favours increased passage of secretions between the cuff and the wall of the trachea, while >30 cm H_2O may cause tracheal mucosal damage. Despite routine cuff pressure controls, variations in TT cuff pressure frequently occur, exposing patients to increased risk of VAP. Several devices have been developed to constantly monitor and adjust the TT cuff inflation pressure. Randomized controlled trials have shown a reduced rate of VAP in the treatment arm of a study testing the Nosten device (Nosten; Leved, St Maur, France).[12]

Subglottic secretion drainage

Subglottic secretion drainage systems usually consist of an accessory aspiration conduit opening above the TT cuff and a vacuum source. Secretions may be continuously or intermittently removed from the subglottic space. A meta-analysis of 13 randomized controlled trials showed that subglottic secretion drainage was effective at reducing VAP rates, also reducing the

time to onset of first VAP, reduced duration of mechanical ventilation, and reduced ICU LOS.[13]

TT cuff design

Most common TT cuffs have a high volume–low pressure cuff made of poly vinyl chloride. The surface of a traditional TT cuff folds when inflated in the trachea, creating potential channels through which secretions can drain. A tapered cuff shape made of ultra thin polyurethane seems to offer the most protection against secretion channelling leading to VAP.[14]

TT coating

Bacterial colonization and biofilm formation on the inner surface of the TT can be prevented by coating it with a thin layer of antimicrobial agents. Among many agents, silver appears to have been the most widely studied. NASCENT was a multicentre study that recruited more than 2000 patients to be randomized to either a silver-coated TT or a standard TT. They reported a significant reduction in VAP rates in the treatment arm and delayed time to onset of VAP. However, they were unable to show a reduction in ICU LOS or duration of ventilation.[15] Other agents used for coating include chlorhexidine and titanium dioxide.

Nebulized gentamicin

This has been investigated as a means of prevention of biofilm formation. Compared with systemic cephalosporins, nebulized gentamicin attained a higher concentration within the TT and there was a lower incidence of biofilm formation. Interestingly, none of these biofilms was from organisms that commonly cause VAP. However, more work needs to be done before this method can be recommended.[16]

Kinetic therapy

Mucociliary clearance is inhibited by immobility. Mechanical rotation of patients with 40° turns achieves more significant clearance of secretions than current standard therapy of 2 hourly turns. It has been shown to lower the incidence of VAP, but have no effect on duration of ventilation, LOS, or mortality. However, kinetic therapy requires specialist equipment and has been associated with significant complications such as intolerance to rotation, unplanned extubations, loss of vascular access, and arrhythmias.[17]

Care of airway equipment

Studies have shown that TT colonization and biofilm formation begins within 24 h of intubation. Strict attention to hand hygiene when handling the TT, closed-circuit suction systems, use of heat and moisture exchangers, and limiting ventilator tube changes to whenever they are soiled, all contribute towards reducing biofilm formation.

Feeding

Although the early establishment of enteral feeding is of benefit to critical care patients, reflux and aspiration of gastric contents is the main cause of VAP. It has been suggested that post-pyloric feeding may reduce the incidence of VAP. Several studies so far have shown a non-significant trend towards a reduction in VAP, but more conclusive evidence is needed before a definite recommendation is made.

Probiotics

Probiotics compete with VAP-producing organisms in the oropharynx and stomach. The improved microbial balance has been shown to reduce the incidence of VAP but does not improve ICU or hospital mortality or duration of ventilation.[18] This meta-analysis was based on several small studies of varying heterogeneity and its methodology has been questioned.

Intubation-related events

Reducing the duration of intubation with the use of sedation holds and weaning protocols and reducing unplanned extubations and minimizing re-intubation have also been shown to reduce VAP incidence.[14]

The 2013 CDC VAE/VAC definitions

Most preventive strategies have shown a reduction in the incidence of VAP, but this has not translated to a definite outcome benefit such as a reduction in duration of ventilation, LOS, or mortality. As ICU patients are a heterogeneous group of patients with multiple factors affecting their individual outcome, it is often difficult to show an outcome benefit from a single intervention. Another complicating factor is that the criteria used for diagnosis of VAP vary from study to study. Often, they are based on clinical criteria only. This cannot solely be blamed on study design as critical care societies and other governing bodies have so far not been able to agree upon common diagnostic criteria. As VAP rates are related to surveillance and carry monetary fines, it has become imperative that a common overarching definition is agreed upon. It was with this intention that a new official multisociety definition was created last year (Table 1).

The new surveillance definition has broadened the focus beyond pneumonia to encompass other common complications of ventilation and making surveillance as objective as possible. The new definition identifies a hierarchy of surveillance targets. The first tier of ventilator-associated condition (VAC) identifies patients whose respiratory status has deteriorated after a period of stability or improvement. This is designed to capture all pulmonary and non-pulmonary complications serious enough to lead to persistently higher F_{IO_2}, PEEP, or both settings. Subsequent tiers are designed to identify the subset of VACs that are infection-related. An infection-related ventilator-associated complication (IVAC) occurs in a patient who has concurrent systemic features requiring antibiotic treatment and a possible pneumonia occurs in a patient with an IVAC and positive qualitative cultures, while a probable VAP occurs in a patient with positive quantitative cultures. The probable VAP criteria can also be met by positive pleural fluid culture, lung tissue with histological evidence of infection, positive diagnostic tests for Legionella, or selected respiratory viruses. Of note, compared with previous definitions of VAP, radiographic evidence of pneumonia is not included in any part of the new algorithm.

Currently, it is unknown how well an IVAC will correlate with a prior definition of VAP. Preliminary data suggest that ~40% of VACs meet the criteria for IVAC. In a retrospective analysis of a prospective multicentre study that measured the implementation of VAP prevention guidelines over 24 months, there was poor agreement between VAC, IVAC, and VAP (based on Johannson criteria) definitions.[19] In theory, all VAP patients should form a subset of the VAC patients, but only a minority of the VAP patients met the diagnosis for VAC. This may have been because some of the VAP cases may not have caused sufficient

Table 1 2013 CDC VAE/VAC definitions

New respiratory deterioration: ventilator-associated condition (VAC)	≥2 days of stable respiratory function [stable or reducing PEEP or daily minimum fraction of inspired oxygen (F_{IO_2})] followed by an increase in daily minimum PEEP ≥3 cm H_2O or a daily increase in F_{IO_2} by >20 points sustained for ≥2 days
New respiratory deterioration associated with infection: infection-related ventilator-associated condition (IVAC)	On or after third day of mechanical ventilation patient has VAC+ Temperature >38°C or <36°C or White cell count >12 000 mm^{-3} or ≤4000 mm^{-3} and One or more antibiotics started within 2 days before or after onset of VAC and continued for at least 4 days
New respiratory deterioration with possible evidence of pulmonary infection: possible pneumonia	IVAC+ Purulent respiratory secretions (secretions from lungs, bronchi, or trachea that contain ≥neutrophils and ≤epithelial cells per low power field Or Positive cultures of a potentially pathogenic organisms (qualitative, semi-quantitative or quantitative)
New respiratory deterioration with probable evidence of pulmonary infection: probable pneumonia	IVAC+ Purulent respiratory secretions And Positive culture of potentially pathogenic organisms (tracheal aspirates ≥10^5 CFU mm^{-3}, or bronchoalveolar lavage culture ≥10^4 CFU mm^{-3} or semi-quantitative equivalent Or IVAC+ Positive pleural fluid culture (specimen from thoracocentesis and not from indwelling chest drain) or Positive diagnostic test for Leigionella species or Positive diagnostic tests on respiratory secretions for respiratory viruses or Positive lung histopathology

deterioration in ventilation parameters or may not fit the stringent time criteria to fit the VAC definition. Both VAPs and IVACs may be caused by a non-infectious pulmonary process and an infectious non-pneumonic process, for example, ventilator-associated tracheobronchitis and a urinary tract infection.

Although VAC and IVAC may be non-specific, their higher correlation with worse outcomes, ease of data collection, and objective definitions make them promising options to replace VAP as a quality indicator. Over the last decade, a large body of knowledge has been collected regarding reduction in VAP incidence and its associated costs. It is possible that these interventions may have little impact on reducing VAC and IVAC as they have been designed solely for prevention of pulmonary infection.

Other problems with the new definition that will require modification include adjustments in the level of PEEP due to non-respiratory conditions, use of antibiotics for non-respiratory conditions, excluding manoeuvres used to provide comfort care in terminally ill patients from constituting a VAC.

While the new definitions have been designed to introduce clarity and objective criteria to the diagnosis of ventilator-related problems, further studies are required to authenticate the definition of IVAC and reimbursement should not be tied to the prevention of VAC until we know if it is a preventable and what steps need to be taken to prevent it.

It has long been recognized that respiratory tract infection is a complication of mechanical ventilation and we have developed successful strategies to minimize the risk. However, without agreement upon what defines a VAP, we will never be able to quantify the success of these strategies. Perhaps our focus should shift towards preventing all ventilator-associated events as defined by the new surveillance criteria. While VAP prevention methods would possibly work in the proportion of ventilator-associated events caused by IVACs, we would have to develop further strategies such as strict fluid balance and adherence to low tidal volume ventilation to mitigate non-infection-related ventilator-associated events.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Medical leadership in perioperative practice: I

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Key points

- Developing clinical leadership is increasingly important as management structures change to encourage greater clinical participation.
- There are many different models to describe leadership, used interchangeably to explain the skills required from a leader and the team.
- Modern leadership theories concentrate on teamworking and communication rather than the character traits of those in charge.
- Teams work together to achieve shared objectives. Members have different roles and skills; their interaction determines the success of the team.
- There are many resources in the NHS for leadership development, many of which are free and easily accessible.

In the last 10 yr of UK healthcare planning, there has been a growing body of policy, strategy, and guidance that have raised the profile of clinical leadership. Alongside this progressive integration of clinicians into leadership and management structures, there are many new formal education programmes such as the NHS Leadership Academy programmes and associations dedicated to developing this area of interest, such as the Faculty of Medical Leadership and Management.

The consultation paper 'High Quality Care for All', commissioned by the Prime Minister and written by Lord Darzi in 2003, drew a line under the 'managers as leaders' mindset that has directed NHS management structures since the Griffiths Report introduced the general manager role in 1983. The case presented for clinical leadership of healthcare services was compelling: stronger focus on quality care, ability to partner with patients and other professionals at the point of care, and the use of existing clinical team leadership skills within a management role.

In subsequent years, the Francis report, Berwick report, and other key publications have highlighted the need for strong clinical leadership in ensuring that future care is of an appropriately high level of quality and safety. The Health and Social Care Act, introduced by Andrew Lansely in 2012, laid the ground-works for the large structural changes that we have seen in UK healthcare over the last 18 months. One of its principal aims was a move towards clinically led commissioning, putting clinicians 'in charge of shaping services, enabling NHS funding to be spent more effectively'. This vision of involving clinical leaders in planning healthcare models and pathways to improve efficiency and clinical effectiveness has been echoed in subsequent key reports, most recently by the current Chief Executive of NHS England in his 'Five year forward view'.

This article will explore the principals and models behind clinical leadership, critically analyse whether medical leadership improves healthcare delivery, and evaluate the educational and support resources available.

Leadership *vs* management

Both leadership and management are needed to administer and develop health services. Leadership roles that have a significant administrative burden can distract from important leadership functions and make leadership roles unappealing. The terms are often used interchangeably, but require different skills and focus as seen in Table 1.

Models and theories behind clinical leadership

The term leadership has proved difficult to define, with a myriad of definitions and theories being born over the last six decades. A useful definition by Stodgill in the 1950s states that 'leadership may be considered as the process of influencing the activities of an organized group in its efforts towards goal setting and goal achievement'. This describes the process between a leader, and those being influenced, it does not, however, describe the individual behind the leadership. Peter Drucker, who researched and published widely on the subject of leadership for more than 50 yr, describes it more succinctly as 'the only definition of a leader is someone who has followers'.

In 2010, Hartley and Benington[1] described three perspectives on leadership. Each perspective placing an emphasis upon a different leadership variable:

(i) the personal qualities of the leader,
(ii) the leadership position in the organization,
(iii) the social processes of leadership.

Personal qualities

There has been much written regarding the personal characteristics of those who lead. The Great Man theory as populated by Thomas Carlyle in the 1940s was based upon the assessment of military men, and it assumed that great leaders are born, and not made. The following two decades expanded on this theory by attempting to describe the attributes and behaviours that led a person to successful leadership; namely exhibiting qualities such as self-confidence, self-awareness, and resilience.[2] This model is conceptually easy, and has been studied for the longest time of any leadership model. However, despite many attempts, it has not been possible to isolate a defined list of leadership traits related to outcomes. A fixed set of traits does not take into account different requirements depending on the situation, and furthermore is incorrect in the implication that leadership training will be of no benefit.

Research by the consulting firm Hay, sampling 3871 executives worldwide, found that leaders can exhibit up to six distinct leadership styles, seen in Table 2. Goleman[3] describes these styles in more detail and explains that although each leader will have their own innate style, in order to be effective, one must also be flexible in using their less dominant styles.

The skills involved in leading a team may exhibit 'role diversity' depending on whether the leader is 'near' or 'far' from the team (Fig. 1). For example, a clinical director may need to be approachable, show empathy, and engage with teams, while a CEO of a large organization needs to be charismatic and visionary. This has implications for an individual's progression, where a skillset may flourish in one role but be inadequate for higher roles.

Leadership position

Leadership can be described as having a position or role that commands authority. For example, a clinical consultant or chief executive has formal authority and therefore the legitimacy to lead others. However, exerting authority is not the same as leadership. There are many examples of ineffective leadership by those in authority, just as there are many examples of leadership that take place outside of formal roles.

Authors have described the differences in leadership between those with and without authority. Mountford and Webb[4] argue that although the most obvious leaders within an organization may be those that hold formal positions of authority, those without formal authority are just as able to take ownership of a problem and drive through change.

In the NHS, clinical staff are in a unique position to take on an informal leadership role as their close proximity to patients

Table 1 Summary of differences between management and leadership

Management	Leadership
Managing processes or stable tasks, e.g. writing the rota	Managing people through changes, e.g. providing a safe service with reduced resources and increased demand
Short-term focus	Long-term focus
Target setting	Vision setting
'Tame' problems (problems with solutions readily apparent)	'Wicked' problems (problems that have complex solutions or perhaps no solution at all)
Doing things right	Doing the right thing

Table 2 Summary of key characteristics of different leadership styles. Adapted from Goleman[3]

Leadership style	Ambition	Example phrase
Directive	Immediate compliance	'Do it the way I tell you'
Pacesetting	Accomplishing tasks to high standards	'This is the way to do it'
Visionary	Providing direction and vision	'This is where we are going, and why'
Coaching	Professional development of employees	'Here is an opportunity to practice'
Participative	Building commitment and generating new ideas	'What do you think'
Affiliative	Creating harmony	'It's important we all get on'

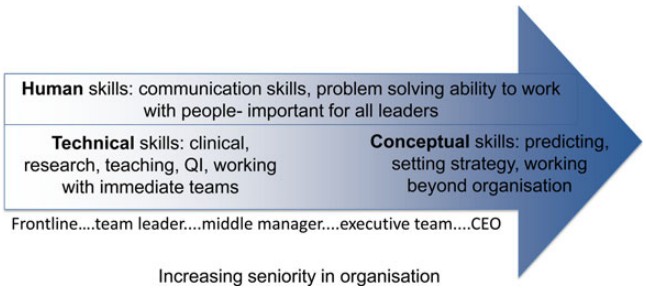

Fig 1 Importance of skill diversity in leadership roles depending on position. Adapted from Mumford (2000).

allows them to understand frontline realities and opportunities for improvement. However, their lack of formal role can often prevent them from being able to tackle the problems they face. Those without authority can exert leadership, but they need to tackle issues through influencing others, rather than direct control.

Leadership as a social process

A popular perspective of leadership in healthcare is as a complex and adaptable relationship between people in a group, where leadership by one person is not permanently possessed and where there is the potential for a shift of leadership, governed by both formal and informal influences. This view considers the relationship between 'leaders' and 'followers' and highlights how 'followers' may shape the kind of approaches that leaders use.

Viewing leadership as a 'social process' allows a better understanding of the importance of democratic or distributed leadership in healthcare. 'Distributed leadership' is described by Grint,[5] as being the collective responsibility of lots of individuals, each with their own unique skills. For distributed leadership to work, there is also a requirement for 'collective flexibility' where individuals undertake leadership, but only as, and when, necessary, that is, they must know when to lead, and when to follow. This description is familiar to all working in theatre, trauma, or resuscitation teams, where leadership of the group may change hands depending on the skills available and the evolving situation.

Organizations that develop collective leadership and capability are more successful than those who focus on developing individual capability. This includes evidence of better financial outcomes in commercial organizations, and clinical and financial outcomes in healthcare for organizations that utilize distributed leadership models. Leadership should be distributed to 'wherever expertise, capability and motivation sit within an organisation and that all staff must take responsibility for striving for excellence in providing safe, compassionate care'.[6]

Leadership as a social process in the NHS

The national improvement body 'NHS Improving Quality' has built on 'social movement' theory, in improvement projects like NHS Change Day (http://www.changeday.nhs.uk) and Sign up to Safety (http://www.england.nhs.uk/signuptosafety). Social movement theories developed from the observations of large-scale changes seen in mass action like the American civil rights movement. These involve collective action by individuals, in groups that may have shifting and ill-defined leadership, but result in sustained change on a scale that is difficult to achieve with traditional 'top down' change projects. The leadership required to direct such a movement is distributed among the group, and is a 'shared social process'. Leaders must be connected to many people, able to communicate well across traditional boundaries, and be able to take information and share it with many.[7] In the case of NHS Change Day, social media communication encouraged more than 280 000 pledges of improvement actions.

The evidence for clinical leadership

As the UK healthcare model becomes more complex, good patient outcomes are no longer just dependent upon excellent clinical management at the individual clinician–patient level. There are now tiers of supporting processes, microsystems, and organizations that can determine the provision of good quality care, and clinicians can provide leadership throughout these tiers.

Permeating these different levels affords clinicians multiple benefits. At the strategic level, they can keep the focus on funding and delivering strategies that are responsive to the patients' needs. At the service level, clinicians can influence and design processes to provide better organizational performance. Where clinicians and patients interact, clinical leaders play a role as role models in providing good quality care.

There are ample case studies of successful organizations using strong clinical leadership to improve the quality of care. Kaiser Permanente, Virginia Mason, and Intermountain Healthcare in the USA, Jönköping County in Sweden, Canterbury District in New Zealand, and Salford Royal Hospital in the UK have all instigated clinical leadership and improvement training, and clinically lead management and leadership infrastructures to successfully improve care, often on a large scale and with impressive and sustained results.[8]

In a McKinsey consulting survey of 1200 hospitals in 2011, those with a higher proportion of clinically trained managers had better management practices, and these better practices correlated to a number of clinical outcomes, including mortality, readmission, and infection rates. In 2011, a cross-sectional study in America showed a positive association between having a medically trained chief executive and top ranking quality scores in a number of specialities. This association was replicated in the UK, where a study in 2012 examined hospital performance data and showed that higher clinical representation on the hospital board correlated with better performance, patient satisfaction, and mortality.

The motivation of clinical leaders

Max Weber described four main 'motivations' that drive social change; a recent health-worker-oriented adaption of these original motivations[9] describes the motivation of medical leaders.

(i) 'Shared purpose': This may act as an extrinsic motivator, inspiring clinicians to take up leadership roles to help further an aim they strongly believe in.
(ii) 'Self-interest': Career progression and job security may act as both intrinsic and extrinsic motivators to encourage clinicians to assume leadership roles.
(iii) 'Respect': The desire to seek professional creditability or personal approval may act as an intrinsic motivator, encouraging clinicians to pursue leadership positions.
(iv) 'Tradition': Pressures to uphold appropriately professional practice (e.g. membership of professional bodies) may be a powerful extrinsic and intrinsic motivator for clinicians to take leadership roles to ensure appropriate standards are being met.

Barriers to clinical leadership

Despite the wealth of evidence suggesting that clinical leadership is important for the provision of safe, clinically effective care, many clinicians are ambivalent about taking on a formal leadership role.

These barriers are particularly important when considering the failing or struggling organization, where the inverse leadership law dictates that those organizations in most need, will find it even harder to recruit attractive candidates (Table 3).

The importance of teamwork

Leadership can only exist in combination with followership, and so it is important to outline some of the theories behind what constitutes a successful team.

Table 3 Barriers to leadership. Adapted from leadership vacancies in the NHS (The Kings Fund)[10]

Barrier	Explanation
Professional risk	Clinical leaders can feel more exposed as they hold clinical accountabilities, e.g. Caldicott Guardian and responsibility for care provided by the whole clinical workforce. Clinical leaders can lose their clinical registration if serious failings occur and the job security of leadership roles is significantly less than clinical roles—the average trust CEO tenure is 700 days
Lack of training	The lack of formal training in unfamiliar subjects such as finance, lack of mentorship, and talent management stops talented leaders from applying for senior clinical positions
Clinical conflict	Clinical leaders face dilemmas regarding committing themselves to more non-clinical work, deskilling, and 'losing face' among their clinical counterparts
Personal and financial disincentives	Clinical leaders can find themselves juggling both clinical and non-clinical duties with worsening work-life balance and less financial incentives compared with their clinical colleagues

Effective teams are generally made up of groups of individuals with differing skills that come together for a period of time to work towards a common goal or goals. Within the team, individuals will have defined roles and will share accountability for the collective work of the team and its respective outcomes.

This is an idealized model, and does not represent many of the teams seen in clinical practice. It is commonly understood that most teams will not work effectively from the start and that they need to grow, evolve, and learn together. The move from a working group to a real team[11] constitutes evolving from a state in which decisions are made solely by the team leader without discussion, to a more democratic position whereby the leader guides discussion and the team feel empowered and consequently able to accept accountability for outcomes.

Roles within teams

Belbin[12] characterizes nine roles that individuals within teams can play (Table 4). These roles are linked to 'individuals behavioural strengths and weaknesses in the workplace' (www.belbin.com). Determining what role you would innately tend towards can be useful in understanding how you may behave within

Table 4 Summary of Belbin team roles. Adapted from the Belbin website, www.belbin.com

Role	Description of role
Shaper	*Pushes the team to focus and improve*
Implementer	*Plans practical, workable strategies to achieve goals*
Completer finisher	*Finishes, scrutinizes, and quality controls team's work*
Co-ordinator	*Focuses the team's work around their objectives*
Team worker	*Helps the team to get together*
Resource investigator	*Considers external application of team's ideas and work*
Plant	*The creative problem solver in the team*
Monitor-evaluator	*Helps weigh up team's options*
Specialist	*Team's specialized knowledge input*

Table 5 The five dysfunctions of a team. Adapted from Lencioni (2003)

Dysfunction	Leaders role in diminishing the dysfunction
1. Absence of trust	Building an environment that does not punish vulnerability while also demonstrating their own vulnerability to promote trust
2. Fear of conflict	Recognizing conflict can be productive and exercising restraint in monitoring conflict, ultimately allowing it to resolve naturally
3. Lack of commitment	Pushing the team for closure and adherence to schedules but also displaying confidence in making decisions that may ultimately be wrong
4. Avoidance of accountability	Creating a culture of accountability but being willing to enforce discipline if necessary
5. Inattention to results	Demonstrating and maintaining a commitment to results

teams. In particular, Belbin highlights the importance of a balance or spread of roles within teams.

Dysfunctional teams

In 'The trouble with Teamwork',[13] Lencioni explores some of the common problems encountered by teams. He focuses on what he sees as the five dysfunctions of teams and what the role of the leader should be in helping to diminish these dysfunctions (Table 5).

Developing clinical leadership

A variety of leadership frameworks exist to support leadership development in the NHS. In 2008, the NHS Institute of Innovation and the Academy of Medical Royal Colleges produced the Medical Leadership Competency Framework, intended to define which aspects of leadership should be covered in medical learning and curricula. It describes competencies that can be achieved in undergraduate and postgraduate training, and during continuing practice, focusing on 'delivering the service' as the key goal of medical leadership (Fig. 2).

The NHS Leadership Academy has updated this work with their Healthcare Leadership Model published in 2013 (Fig. 3). Rather than competencies, this focuses on leadership behaviours and their impact on others, and so more accurately reflects current thinking about leadership focusing on interpersonal skills. It is aimed at all healthcare workers and for those in any position, not only formal leadership roles.

Both the framework and model were based on a review of existing healthcare leadership research, consultations with key organizations, and focus groups and structured interviews within the NHS.

There is a range of resources available from newly formed and existing bodies to those who wish to learn more about leadership in theoretical and practical roles (Table 6).

In summary, leadership can be examined from a number of perspectives to provide some insight into what the requirements are for good leadership. In healthcare, we work in changing multidisciplinary teams, and so the social aspects of leadership—for example communication, teamwork, and collaboration—are most important. These skills and behaviours are emphasized on all the available leadership frameworks. There are many

Fig 2 The Medical Leadership Competency Framework—©NHS Leadership Academy and Academy of Medical Royal Colleges, 2010. All rights reserved.

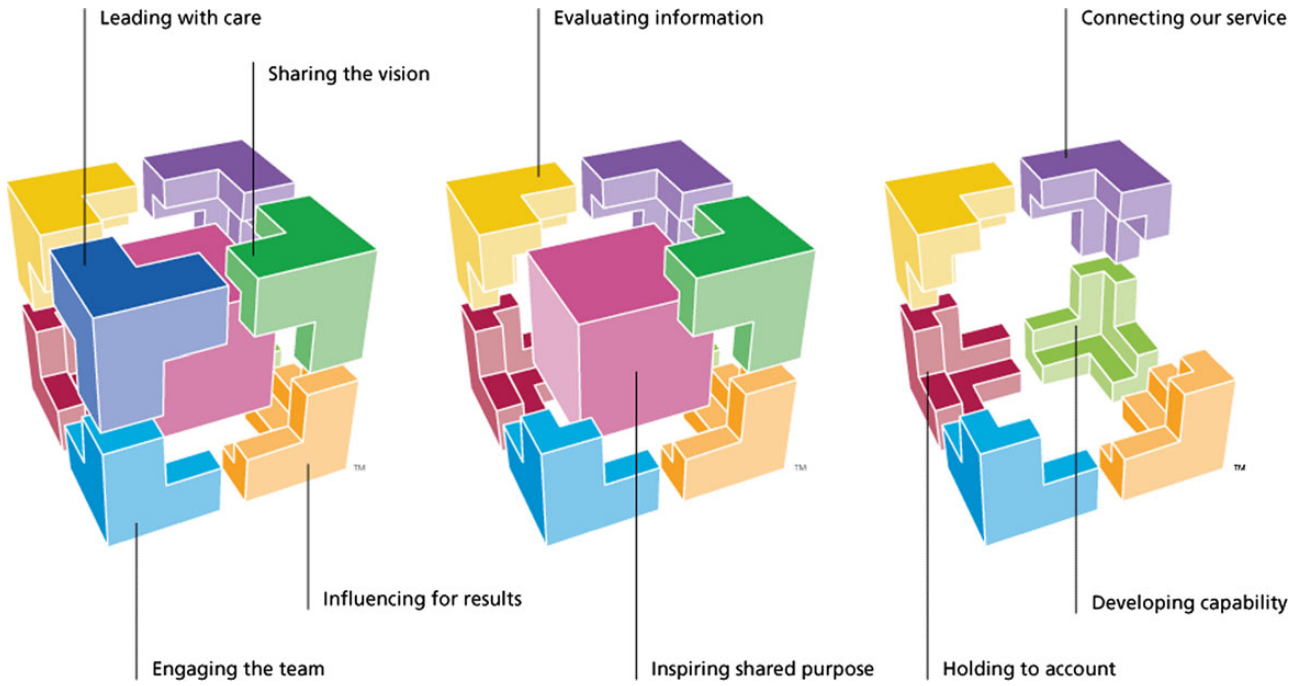

Fig 3 The NHS Leadership Academy Healthcare leadership model. ©NHS Leadership Academy, 2014. All rights reserved.

Table 6 Sources of information or training on medical leadership

The Institute for Healthcare Improvement: www.ihi.org	An independent not-for-profit organization in the US that works to improve quality care for patients using a variety of improvement tools. The IHI Open School has open access, free improvement, and leadership online teaching courses
NHS Leadership Academy: www.leadershipacademy.nhs.uk	Hosted by NHS England, NHS LA runs tiered leadership training and online resources that are free to NHS staff, alongside local delivery partners that promote leadership training in regions
NHS Improving Quality: www.nhsiq.nhs.uk	NHS England's national improvement body created from the NHS Institute of Innovation. Their remit is to provide improvement and change expertise
Academi Wales: http://www.academiwales.org.uk	All public sector leadership and resources in Wales are held under the umbrella of Academi Wales, run by the Welsh Government. They provide online and face-to-face courses and learning resources
NHS Scotland National Leadership Unit: http://www.nes.scot.nhs.uk/education-and-training/by-theme-initiative/leadership-and-management	Leadership resources for clinicians and managers in Scotland. Running development programmes, encouraging network formation and cross-sector working
The Health Foundation: www.health.org.uk	An independent charity promoting safety and quality improvement work. It runs several fellowship schemes and provides funding for safety research and improvement projects
The Kings Fund: www.kingsfund.org.uk	An independent charity and think tank which runs leadership development courses and producing commentaries and policy guidance based on healthcare research
The Faculty of Medical Leadership and Management (FMLM): www.fmlm.ac.uk	Constituted by the AoMRC, this is a membership organization requiring a subscription that allows access to conferences, coaching, and networking. Membership spans a diverse cohort, from medical students to chief executives of hospital trusts. It also administers the national clinical advisors scheme for trainee doctors

opportunities in local and national programmes to develop these skills, and there is ample evidence for an improved quality of care in organizations which encourage training and development of clinical leaders.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Revalidation FOR ANAESTHETISTS RCA Revalidation matrix Matrix reference I LO2, I LO5

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Medical leadership in perioperative practice: II

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Key points

- The role of a successful leader requires defining, understanding, and co-ordination of the vision, purpose, and roles of those around them and requires the management of change.
- Change does not happen by itself. It requires individuals to use opportunities that arise as a springboard for action.
- Managing change requires an understanding of the viewpoints of all potential stakeholders and is a key aspect of leadership.
- Resistance to change is in many cases not resistance to the proposed change, but a reflection of the psychological process involved in letting go of the past ways of working.
- Individuals within organizations occupy a complicated space that is a function of their relationships, occupation, and political allegiance that successful leadership needs to navigate.

Clinicians are well used to making decisions about treatment based on best available evidence. However, changing the processes within healthcare organizations to allow delivery of the best available, evidence-based treatment can be slow.[1] The scope of change required to allow such implementation may be very small, requiring only minor modifications to a single step of existing practice or it may result in the development of new patient pathways that require significant investment or involve major system changes across multiple organizations and people. For the vast majority of cases, achieving significant change is not something that a single individual can manage. They will require the support from colleagues, possibly from multiple professions, across multiple specialities, and investment be that solely time, or more importantly resources, including finances. The return on this investment, that is, the Value of the change, should be always borne in mind.

This article will identify some of the issues that arise when trying to implement change. It will examine the challenges at the organizational, professional, and individual level. Understanding the issues at these various levels can help individuals who wish to drive change, be that changes to a clinical pathway, or changes to structure or function within an organization or even beyond.

Organizational development and leadership

The basic model for organizational development is similar to the model used in patient diagnosis and treatment. There needs to be an understanding of the problem (diagnosis), with perhaps some particular areas for deeper investigation, and an intervention (treatment) that should be evidence-based leading to a desired outcome. The role of the leader in this context is to scope the vision, encourage, and hold to account the achievement of the desired outcomes and facilitate the overall co-ordination of the above-described efforts. The information gathering that is used to support any diagnosis differs from our traditional methodology in that much of it may be qualitative. Semi-structured interviews, questionnaires, and focus groups are examples of qualitative methodologies that may be used.[2] A root cause analysis is a type of qualitative investigation that many will be familiar with.[3]

A concise model for organizational development is the Weisboard 6-box model (Fig. 1). This model has leadership at the centre, with the role of the leader defined as keeping the other boxes aligned. Weisboard makes reference to the informal and the formal issues within each box, recognizing that within each box, there is the way things are supposed to be done, and the way things actually are done. Attempts to change structures, relationships, or rewards will not be successful if a leader does not take

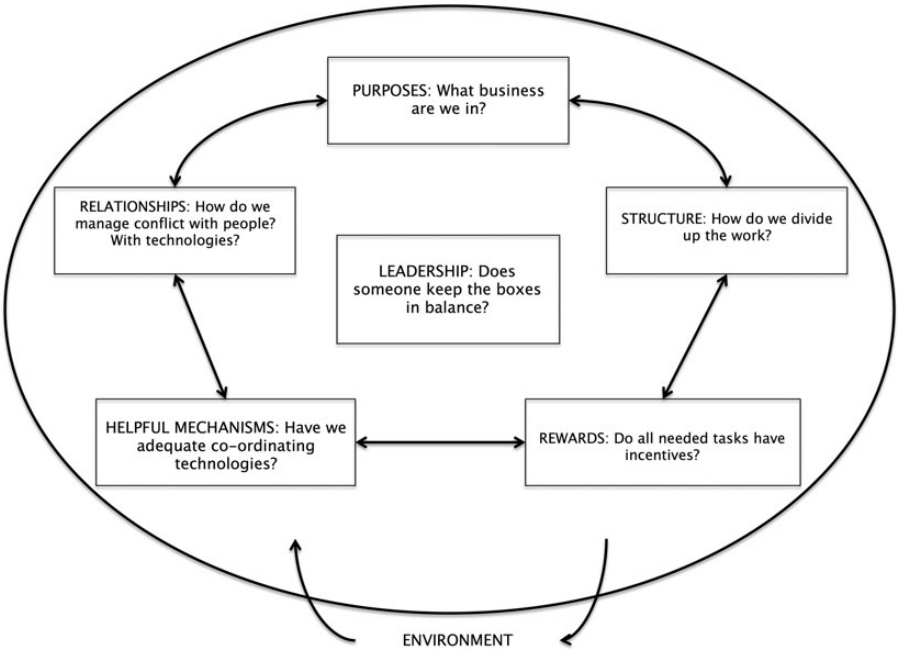

Fig 1 The 6-box organizational model (taken from Weisboard MR. Organizational diagnosis: six places to look for trouble with or without a theory. *Group Organ Manage* 1976; 1: 430–47).

account of both formal and informal issues and leaders need to maintain balance across all of the boxes (domains) if they, and their organizations, are to be successful.

Models such as the Weisboard 6-box model are equally applicable to small-scale leadership of change as they are to organizations as a whole. An example for anaesthetics might be the development of a system to improve the booking system for an emergency theatre. Such a project will require that the lead takes into account and aligns the overall purpose of the project, the relationships of those involved in the booking system to each other, the incentives of all involved, and potentially a disincentive to gaming the booking system.

At an organizational level, a hospital can also identify issues within each of those domains, although at organizational level, the descriptions will be more general, but maintaining the balance between the various domains remains the fundamental requirement.

The clinical leader

The Weisboard model is not specific to healthcare but provides a useful reference point and highlights the leadership role as one of vision and co-ordination. The role of clinical leaders is emerging and further discussion about the role, qualities required, and perception of clinical leaders can be found in the recent article by Nicol and colleagues.[4] The issue highlighted by Nicol and colleagues about negative perception is discussed in greater depth later in the section related to resistance to change.

The organizational perspective

The vast majority of Anaesthetists in training or permanent roles in the UK will work predominantly within NHS Hospitals. These large organizations have many competing priorities. Organizations face financial/economic, regulatory, societal, technological, and political pressures, and have to manage areas that go well beyond the day-to-day clinical experience we have, into areas such as finance, estates, and workforce management. The formal primary purpose of the organization will be providing safe, high quality healthcare, but there has to be a secondary purpose of providing this healthcare within a financial envelope. Work by Porter[5] has brought these two purposes together in the concept of 'Value' where Value is the product of patient outcomes (including experience) for the cost of delivering those outcomes.

Any proposal to change practice that requires organizational support, such as pathway redesign or new equipment purchases, will need to show that such investment is in line with both the primary and secondary purpose and thus deliver improved value. It must also align with the strategic plan of the organization and current organizational objectives. This is the underlying purpose of a business case that sets out the clinical and financial implications of any proposed development. This logical approach to change and focus on the endpoint of an improved service is what we as doctors are familiar and comfortable with and relates to our quantitative, rational backgrounds and is often the perspective taken by the organization. However, it must be borne in mind that even an entity such as 'management' or 'the organization' is made up of a complex network of formal and informal relationships that must be carefully negotiated to garner support. The role of 'the playmaker' is further discussed below.

The change may pass the first hurdle of organizational support, but if the issues considered in the rest of the article are not considered, there is little likelihood of success. The possibility of taking what is by definition a suboptimal situation that required change, and disenfranchising stakeholders, creates a situation where the change will not occur, and the required change will become even harder to implement.

The stakeholder perspective

Stakeholders have been defined as any individual or group that can affect or is affected by organizational performance.[6] Within

any organization, each stakeholder simultaneously occupies a rational and occupational role.[7] Within healthcare, the occupational role is a function of the professional background and the training. Regulation and purpose of other healthcare professionals may be strikingly different from the medical perspective. This could broadly be termed their purpose if they are to be related to the Weisboard model. The political role may also be different from the medical perspective.

If change is to be successful, the purpose, formal and informal relationships between each stakeholder and the organization, and the relationships of the stakeholders to each other, and incentives of all involved should be understood and every effort made to align the purpose and incentives of the change with those who will undergo the change.

Playmakers and opportunity for change

The role of 'playmaker' has been described by Pitt and colleagues[8] as individuals that 'display a variety of skills that include: imagination, judgement, tolerance of ambiguity and change, articulacy, persuasiveness and determination'. These playmakers possess the qualities needed to identify with the structures, relationships, and purpose of both the organization and internal and external stakeholders. These are the individuals that drive change and also those that allow change to occur.

The opportunity for change may present in many ways. The model that underlies many of the traditional views of organizational development is that of formal enquiry and subsequent intervention. Pitt and colleagues suggest the reality may be more episodic and opportunistic with the seizing of opportunities or management of threats as they develop as a consequence of change in the internal or external environment. Preparation and a clear understanding of the wider organizational and political landscape are key to being able to enter the arena as a playmaker at a time, and with a proposal, that is likely to have maximal impact.

Change and transition

In 1962, Rogers described the adoption of innovation and illustrated the point with the curve shown in Figure 2. The adoption and spread of innovation will never be instantaneous, despite the best efforts of anyone involved. Any change that requires a change in position or behaviour of a member of staff will require that individual to undergo a transition.

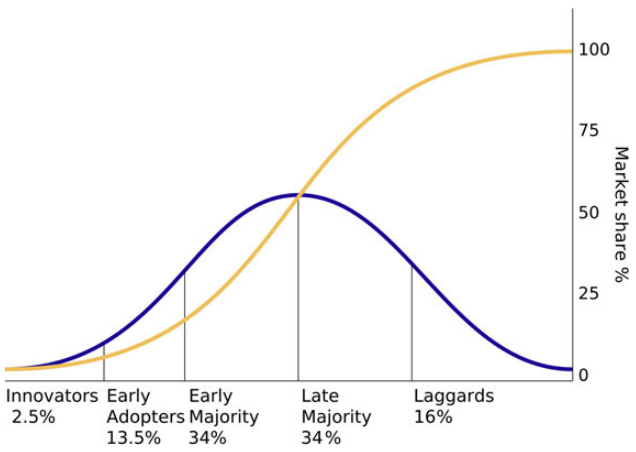

Fig 2 Diffusion on innovation based on Rogers (1962). Image is copyright free and taken from http://en.wikipedia.org/wiki/Diffusion_of_innovations.

The emotions associated with personal change are strikingly familiar to those seen in a grief reaction. Adams and colleagues[9] have laid these out as a timeline with fluctuating emotion as the person affected moves towards acceptance. Starting with immobilization at the beginning of transition, self-esteem increases during 'minimization', and decreases during depression to its lowest level when acceptance of reality and letting go allow self-esteem to increase once again. Through a phase of testing and search for meaning; finally, internalization enabling self-esteem to increase again. The time frame is varying according to individuals and circumstances.

A similar model by Bridges highlights the requirement for a period of neutrality before acceptance and a 'new beginning'. Bridges three phases of transition are:[10]

(i) Letting go of the old ways and the old identity people had. This first phase is an ending, and the time when you need to help people with their losses.
(ii) Going through an in-between time when all the old is gone, but the new is not fully operational. This is called the neutral zone and it is when the critical psychological realignments and repatternings take place.
(iii) Coming out of the transition and making a new beginning. This is when people develop new identities, experience new energy, and discover a new sense of purpose that make the change begin to work.

The transition is the time during which the change agent (often the leader), with their clear view of the future once the change has been completed, needs to provide support to those undergoing the change, for whom time and emotional energy needs to be spent letting go:

> Situational change hinges on the new thing, but the psychological transition depends on letting go of the old reality and the old identity you had before the change took place.[7]

Within the context of this article, it is assumed that the change agent is attempting to mitigate the negative effects of change and transition on those undergoing change, but the issues associated with transition are equally applicable to any person who changes role, even in terms of a positive change such as a promotion. The change does not have to be an externally imposed organizational change and would be equally applicable to new consultants.

Resistance to change

Analysis of resistance to implementation of 'The Productive Operating Theatre' (TPOT) by Waring and Bishop[11] identified three main themes for resistance to change:

(i) Questioning the motives of the leaders
(ii) Questioning the expertise of leaders
(iii) Perceived negative consequences for clinical practice

Similar themes emerge from the attempted reorganization of an emergency department in the 1990s where role change across boundaries (in one case between doctors and nurses and in another between different specialities) resulted in questions of legitimacy and failure of the project. The 'solutions' were highly contested, sometimes with hostility, and a key block was perceived legitimacy when crossing boundaries which was perceived as a threat.[12]

These examples of resistance to change from within the NHS are practical examples of well-described reasons for resistance.

Questioning the motives of the leaders for the TPOT project is a form of resistance related to lack of trust. This arises out of concerns that the project is being used a cover for financial gain at a cost of high quality care, or that it is being used as a tool to exert control.

> Over the course of our observations clinicians increasingly vocalised the view that the working group had become dominated by managerial interests to 'cut costs'.
>
> Surgeons often remarked that the departmental manager had 'no business in telling me when I should arrive in theatre'.

This lack of trust is often not anticipated by managers, even clinical managers and leaders, who underestimate the significance of mistrust, especially when they perceive there to be a benefit for those undergoing the change.[13]

Perceived negative consequences for clinical care result from the project managers and the (theatre) staff coming to different conclusions about the costs and benefits of the project. This results from different value sets, or more likely different information being held by the various stakeholders, with the inevitable outcome of different conclusions. The importance of anticipating such conflict is a core theme that is reiterated in many of the papers cited in this article.

The perceived negative consequences can also relate to a fear of change from the status quo. It has been argued that much fear and negative emotion associated with change is not to the change itself but is related to the loss and destabilization of current positions. The management of such loss and transition has been covered in the previous section.

Kotter and Schlesinger describe different forms of resistance and how they can be approached. The importance of relationships and the need to appreciate more than a utilitarian view of any change is again highlighted in this paper where an example of 'tearing apart' a section of bank is used and the resultant loss of morale and staff.[14] The '8 step Kotter model'[15] of change is a commonly used and referenced model of change that is a useful 'aide memoire' to review and check before and during any change process.

The leaders perspective

The article has mainly focused on the issues from the perspective of those being changed, but a change agent will themselves require change and adaptation, even if it is to the reality that they helped to create. They themselves will have undertaken a journey, and adaptation to their new role will also require a period of transition. Understanding the effect that such transitions may have on their ability to lead, which we have defined according to the Weisboard model as one of intricate co-ordination, is critical to them emerging from the transition with the reality of the new world reflecting their initial vision. This can be particularly difficult when the transition has involved the mutation or termination of supportive relationships.

Conclusions

The NHS, and healthcare in general, is undergoing continual change. Health leaders have an important role in understanding and putting into context necessary change for those they lead and themselves. This article aims to bring out some of the important aspects of change and how this can aid better leadership and improvement ultimately bringing improved care for patients and better working environment for staff.

Declaration of interest

J.F.: Board Director UCLH; Board Director HealthServices Laboratories LLP; Board Trustee The Nuffield Trust; Governing Body Member Aylesbury Vale Clinical Commissioning Group; Mentor HealthBox Europe.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Ultrasound-guided lumbar central neuraxial block

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Key points

- Ultrasound-assisted neuraxial block is an advanced technique for use in patients with difficult spinal anatomy.
- The use of a pre-procedural scan improves the technical efficiency of central neuraxial block (CNB) by facilitating precise identification of underlying anatomical structures.
- The risk of traumatic or failed lumbar CNB may be reduced by the use of neuraxial ultrasound.
- Detailed knowledge of lumbar spinal anatomy and sonoanatomy is essential for interpretation of neuraxial ultrasound images.
- Practitioners should familiarize themselves with ultrasound-assisted neuraxial block in normal individuals before attempting it in patients with difficult anatomy.

The practice of central neuraxial block (CNB) has traditionally relied on the palpation of bony anatomical landmarks, namely the iliac crests and spinous processes, together with tactile feedback during needle insertion. However, these landmarks may be difficult to identify accurately—a problem exacerbated by altered patient anatomy, including obesity, age-related changes, and previous spinal surgery.

A 2008 guideline by the National Institute for Health and Care Excellence (NICE) recommended the routine use of neuraxial ultrasound for epidural catheterization, concluding that ultrasound might help achieve correct catheter placement.[1] This ultrasound-assisted approach to CNB involves performing a pre-procedural scan which helps to identify relevant landmarks and thus guide subsequent needle insertion. Over the last decade, a large body of evidence has accumulated to support the benefit of this approach. Real-time ultrasound-guided CNB (where the needle is inserted under direct and continuous ultrasound visualization), on the other hand, remains an experimental and highly complex technique which will not be discussed further.

This article describes the relevant anatomy of the adult lumbar spine, the key ultrasonographic views, and a systematic approach to neuraxial ultrasound to facilitate the performance of CNB. An overview of the current evidence is also presented.

Gross anatomy of the lumbar spine

The lumbar spine comprises five vertebrae (L1–L5). Each vertebra has two functional parts: a vertebral body and a vertebral arch. Each vertebral arch is composed of a spinous process, pedicles, laminae, transverse processes, and superior and inferior articular processes. The lumbar spinous processes are broad (in the superior–inferior dimension), flat, oblong-shaped structures that project posteriorly from the union of the laminae. The superior and inferior articular processes extend posteriorly in a cranial and caudad direction, respectively, from the point at which the pedicles and laminae fuse. Long, slim transverse processes protrude laterally from the vertebral arch at the junction of the laminae and pedicles. The laminae slope from posterior to anterior in a caudad-to-cephalad direction. In contrast to the thoracic spine, the laminae and spinous processes of adjacent lumbar vertebrae do not overlap. This gives rise to distinct gaps—the interlaminar and interspinous spaces—through which the vertebral canal can be accessed. These spaces can be enlarged by forward flexion of the lumbar spine. The anterior wall of the vertebral canal is formed by the posterior longitudinal ligament and the posterior

surface of the vertebral bodies and intervertebral discs. The posterior wall of the vertebral canal comprises the laminae and the ligamentum flavum, which forms a thick, fibrous bridge over the interlaminar spaces (Fig. 1).

General preparation for scanning

The patient is placed in a sitting or lateral decubitus position for the block, with forward flexion at the lumbar spine. This eliminates lumbar lordosis, opens up the lumbar interspinous spaces, and generally improves the acoustic window. The use of a curved, low-frequency (2–5 MHz) probe is recommended to provide enhanced beam penetration, and wide field of view, both of which improve identification of anatomy.

Sonoanatomy of the spine and ultrasonographic views for neuraxial block

Bone is not penetrated by ultrasound and casts a dense acoustic shadow. The contours of the posterior bony surfaces of the lumbar vertebra thus have characteristic patterns of acoustic shadowing that are key to interpretation of the sonoanatomy of the lumbar spine. Visualization of the vertebral canal is only possible through the soft-tissue acoustic windows of the interlaminar and interspinous spaces.

There are five basic ultrasonographic views of the spine that can be systematically obtained:

(i) parasagittal transverse process view,
(ii) parasagittal articular process view,
(iii) parasagittal oblique (interlaminar) view,
(iv) transverse spinous process view,
(v) transverse interlaminar (interspinous) view.

The parasagittal oblique (interlaminar) view (PSO view) and the transverse interlaminar/interspinous view (TI view) are the most important views in clinical practice since they provide a view of the neuraxial structures through acoustic windows. These structures include: ligamentum flavum, posterior dura, spinal canal, anterior dura, and posterior longitudinal ligament.

Parasagittal transverse process view

The ultrasound probe is placed over the lower lumbar spine in a parasagittal orientation, a few centimetres lateral to the midline. The transverse processes appear as finger-like acoustic shadows, separated by the striated psoas major muscle, which lies deep to the transverse processes. The erector spinae muscle lies superficial (posterior) to the transverse processes (Fig. 2 top).

Parasagittal articular process view

Maintaining a strictly sagittal orientation, the ultrasound probe is now moved medially until the acoustic shadows of the transverse processes give way to a pattern of continuous hump-like shadows, formed by the overlapping superior and inferior articular processes. The articular process view is also distinguished from the transverse process view by the more superficial depth of the acoustic shadows (Fig. 2 bottom).

Parasagittal oblique (interlaminar) view (PSO view)

Starting from the parasagittal articular process view, the ultrasound probe is now slowly tilted to direct the beam in a lateral-to-medial direction until the humped pattern of the articular processes changes into a 'sawtooth' pattern of acoustic shadows. The 'teeth' correspond to the downsloping laminae and the gaps between represent the interlaminar spaces. The PSO view therefore gives us an acoustic window into the vertebral canal.

Structures that are penetrated by the ultrasound beam are (from posterior to anterior): ligamentum flavum, epidural space, dura (posterior), intrathecal space, dura (anterior), and posterior longitudinal ligament. The ligamentum flavum, epidural space, and posterior dura appear as a hyperechoic linear structure and are collectively referred to as the *posterior complex*; while the anterior dura, posterior longitudinal ligament, and posterior border of the vertebral body and discs constitute a deeper hyperechoic linear structure called the *anterior complex*. In practice, the individual elements of these complexes are usually not distinguishable (Fig. 3).

Transverse spinous process view

In order to obtain a transverse spinous process view, the ultrasound probe is placed in a horizontal orientation with the centre of the probe placed over the midline. If the ultrasound beam is placed over a spinous process, the tip of the spinous process appears as a superficial hyperechoic 'cap' surmounting a tall dense acoustic shadow. Lateral to the spinous process, the erector

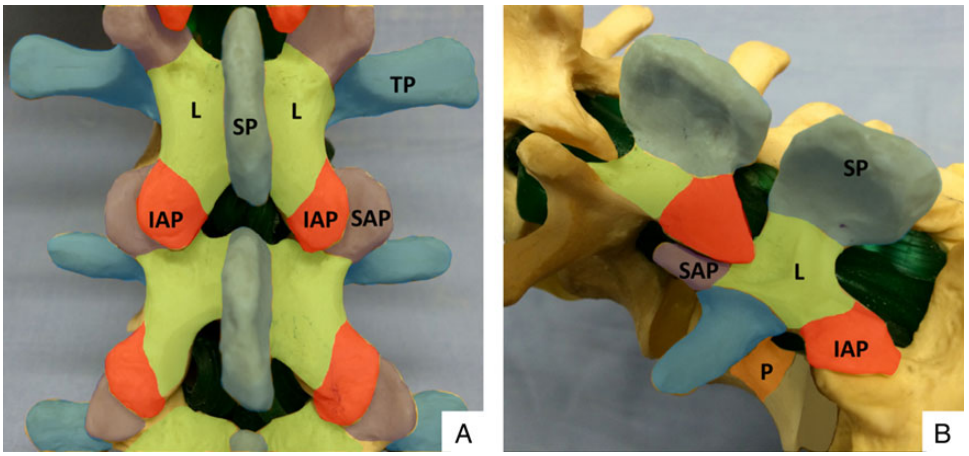

Fig 1 Bony anatomy of the lumbar spine, posterior view (A) and oblique view (B). SP, spinous process; IAP, inferior articular process; SAP, superior articular process; L, lamina; TP, transverse process; P, pedicle. (Image courtesy of www.usra.ca.)

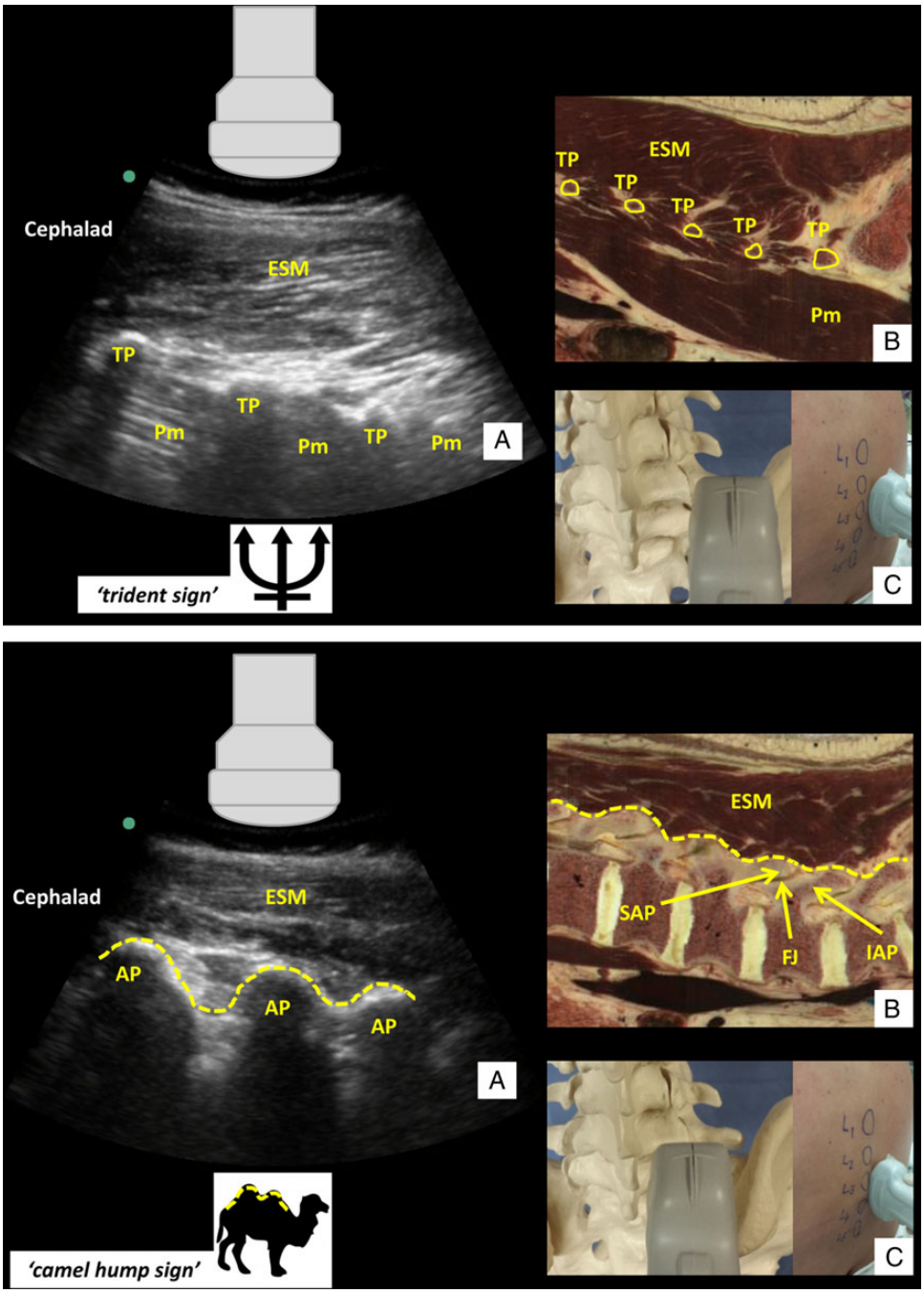

Fig 2 (Top) Parasagittal transverse process view of the lumbar spine (A) with corresponding anatomical section (B) (virtual slice extraction from *visiblehuman.epfl.ch*) and ultrasound probe orientation (C). ESM, erector spinae muscle; TP, transverse process; Pm, psoas muscle. The appearance of the finger-like acoustic shadows produced by the transverse processes is also called the 'trident sign'. (Bottom) Parasagittal articular process view of the lumbar spine (A) with corresponding anatomical section (B) and ultrasound probe orientation (C). ESM, erector spinae muscle; AP, articular process; SAP, superior articular process; IAP, inferior articular process; FJ, facet joint. Dotted lines in (A) and (B) highlight the contour of the articular processes, resembling a series of camel humps ('camel hump sign'). (Image courtesy of www.usra.ca.) [Anatomical section images courtesy Prof. R.D. Hersch, Ecole Polytechnique Fédérale de Lausanne (EPFL), site: http://visiblehuman.epfl.ch, with original 3D data from the Visible Human Project, US National Library of Medicine, Bethesda.]

spinae muscle can be visualized, with the lamina of the vertebral body casting its own dense acoustic shadow at the level of the anterior border of the erector spinae muscle (Fig. 4).

Transverse interlaminar/interspinous view (TI view)

Starting from the transverse spinous process view, the TI view is obtained by sliding the probe in a cephalad or caudad direction as needed until the beam enters the acoustic window between the spinous processes. A slight cephalad tilt in the horizontal plane may have to be applied to compensate for the angulation of the spinous processes. The interspinous ligament appears as a hypoechoic midline stripe. The hypoechoic intrathecal space is bounded anteriorly and posteriorly by the parallel hyperechoic lines of the anterior and posterior complexes, respectively (Fig. 5).

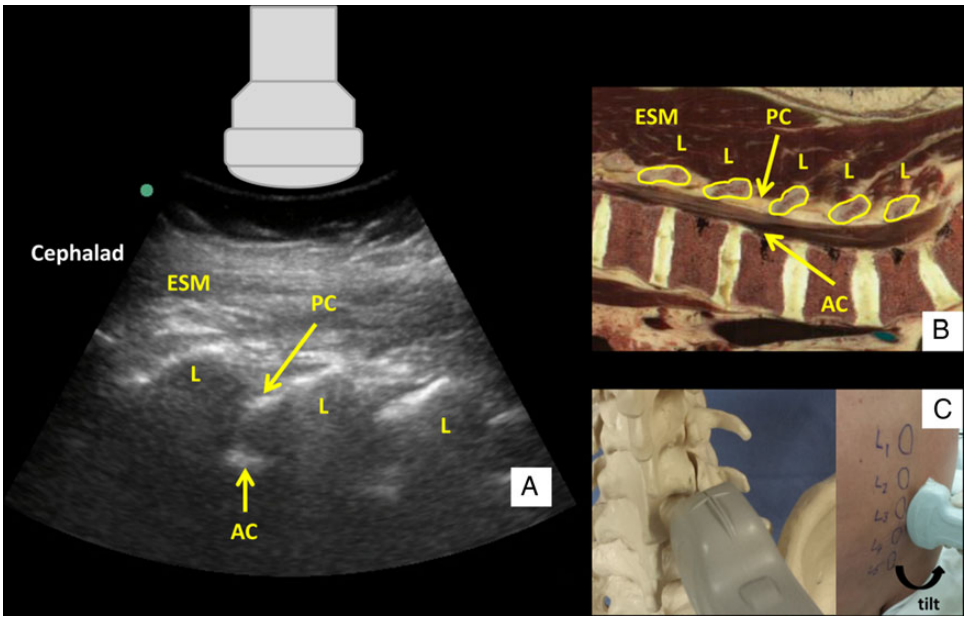

Fig 3 Parasagittal oblique view of the lumbar spine (A) with corresponding anatomical section (B) and ultrasound probe orientation (C). ESM, erector spinae muscle; L, lamina; PC, posterior complex; AC, anterior complex. (Image courtesy of www.usra.ca.) [Anatomical section image courtesy of Prof. R.D. Hersch, Ecole Polytechnique Fédérale de Lausanne (EPFL), site: http://visiblehuman.epfl.ch, with original 3D data from the Visible Human Project, US National Library of Medicine, Bethesda.]

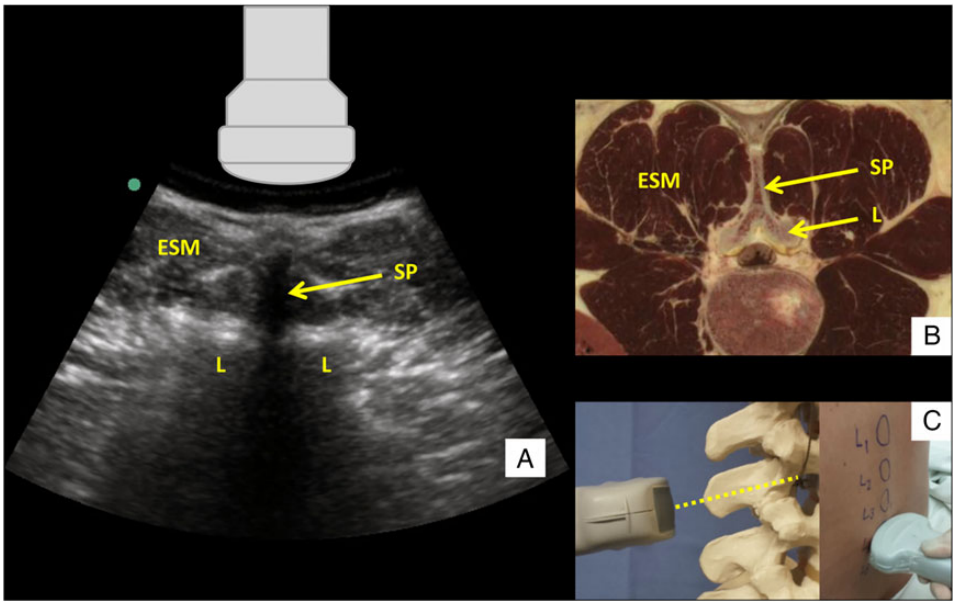

Fig 4 Transverse spinous process view of the lumbar spine (A) with corresponding anatomical section (B) and ultrasound probe orientation (C). ESM, erector spinae muscle; L, lamina; SP, spinous process. Dotted line in (C) represents the direction of the ultrasound beam. (Image courtesy of www.usra.ca.) [Anatomical section image courtesy of Prof. R.D. Hersch, Ecole Polytechnique Fédérale de Lausanne (EPFL), site: http://visiblehuman.epfl.ch, with original 3D data from the Visible Human Project, US National Library of Medicine, Bethesda.]

Systematic approach to ultrasound-guided neuraxial block by a midline approach

1. Patient position and equipment
   - Place patient in the position in which neuraxial block will be performed: sitting or lateral, with forward flexion of the lumbar spine.
   - Attempt to identify midline and lumbar spine by palpation of standard anatomical landmarks.
   - Use a low-frequency (2–5 MHz), curved-array probe.
2. Parasagittal transverse process view
   - Place probe in a sagittal orientation ~3–4 cm lateral from midline on lumbar spine, slightly cephalad to the sacrum

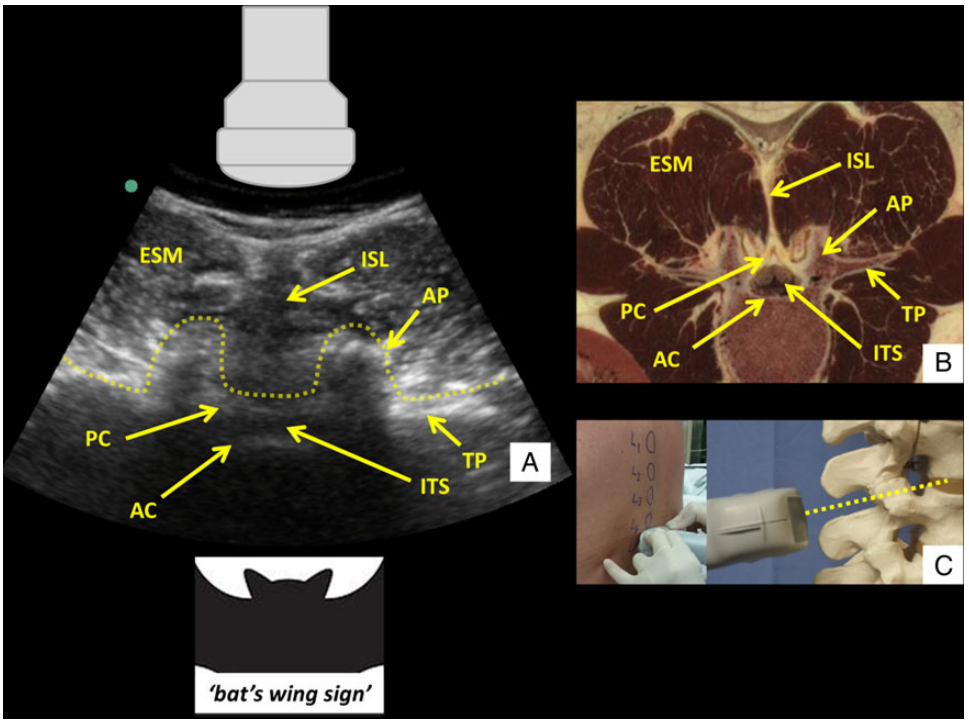

Fig 5 Transverse interlaminar view of the lumbar spine (A) with corresponding anatomical section (B) and ultrasound probe orientation (C). ESM, erector spinae muscle; PC, posterior complex; AC, anterior complex; ITS, intrathecal space; ISL, interspinous ligament; AP, articular process; TP, transverse process. Dotted line in (A) outlines the contour of the ultrasonographic structures giving rise to the 'bat's wing sign'. Dotted line in (C) represents the direction of the ultrasound beam. (Image courtesy of www.usra.ca.) [Anatomical section image courtesy of Prof. R.D. Hersch, Ecole Polytechnique Fédérale de Lausanne (EPFL), site: http://visiblehuman.epfl.ch, with original 3D data from the Visible Human Project, US National Library of Medicine, Bethesda.]

to identify the finger-like acoustic shadows of the transverse processes.

Key ultrasonographic structures: erector spinae muscle, psoas muscle, transverse processes

3. Parasagittal articular process view
   - Slide probe medially while maintaining a strictly parasagittal orientation.
   - Observe the transition from the discontinuous pattern of the transverse process view to the continuous, hyperechoic line formed by the articular processes.

   Key ultrasonographic structures: erector spinae muscle, articular processes
4. Parasagittal oblique (interlaminar) view (PSO view)
   - From the parasagittal articular process view, tilt the probe obliquely to direct the ultrasound beam more medially into the vertebral canal.
   - Observe the transition from the rounded 'humps' of the articular processes to the sawtooth-like acoustic shadows of the laminae, with the hyperechoic posterior and anterior complexes visible in between.

   Key ultrasonographic structures: laminae, posterior complex, intrathecal space, anterior complex
5. Identify and mark appropriate intervertebral spaces, using the PSO view
   - In the PSO view, slide the probe caudad until the sacrum is identified as a long horizontal hyperechoic line. This is an important and easily recognizable ultrasonographic landmark. The gap between the hyperechoic line of the sacrum and the 'sawtooth' of the adjacent L5 lamina represents the L5–S1 interspace. Starting at this point, each interspace is centred on the ultrasound screen and a corresponding skin mark made at the midpoint of the long edge of the probe to indicate its location.
6. Transverse interlaminar/interspinous view (TI view)
   - Turn the probe 90° into a transverse orientation and slide cephalad or caudad to obtain the TI view into a chosen lumbar interspace.
   - The anterior complex is the most important ultrasonographic landmark; the posterior complex is often only faintly visible.
   - Cephalad tilt of the probe and beam may improve the quality of the view, especially where spaces are narrow.

   Key ultrasonographic structures: anterior complex, posterior complex, midline interspinous ligament, articular processes, transverse processes
7. Identify and mark needle insertion for a midline approach, using the TI view
   - Centre the neuraxial midline on the screen.
   - Make skin marks at the: (i) midpoint of the probe's long edge (corresponding to the neuraxial midline); (ii) midpoint of the probe's short edge (corresponding to the interspinous/interlaminar space). The intersection of these two marks gives the needle insertion point for a midline approach.
   - Estimate needle insertion depth by measuring the distance from skin to the deep aspect of the posterior complex.
   - If a satisfactory TI view (i.e. one in which the posterior complex is visible) cannot be obtained, the location of the interlaminar space may be instead determined from the PSO view, which usually offers a larger and better window into

the vertebral canal. This is the same skin marking used to indicate the identity of the intervertebral levels (see point 5). The intersection of this mark with the skin mark of the neuraxial midline obtained in the TI view is a suitable alternative needle insertion point for a midline approach.

8. Needle insertion
   - Insert the needle at the marked site in the midline (Fig. 6).[2]
   - Maintain the same cephalad angle with respect to the horizontal plane that was applied to the probe to obtain the optimal TI view.
   - Needle insertion and re-direction should be guided by tactile feedback (contact with bone, 'feel' of the ligamentum flavum, loss of resistance, etc.) in a similar manner to the conventional landmark-based technique of neuraxial block.
   - Ensure that needle redirections are not inappropriately large, and that there is no deflection from its intended trajectory, particularly when using smaller-gauge spinal needles.

Alternative skin marking and needle insertion for a paramedian approach

In patients with narrowed interspinous spaces, a paramedian needle approach may be required for successful entry into the epidural/intrathecal space. The use of ultrasound to facilitate a paramedian (paraspinous) approach has recently been described,[3] and this technique may also be used where a satisfactory TI view cannot be obtained.

Here the transverse spinous process view is used to identify the neuraxial midline and the spinous processes bordering the targeted intervertebral space. The spinous process shadow is centred in the middle of the ultrasound screen, and skin marks are made at: (i) the midpoint of the long edge of the probe (corresponding to the neuraxial midline); (ii) the midpoint of the short edge (corresponding to the spinous process in the transverse plane). This is repeated for at least two adjacent spinous processes. The initial needle insertion point is marked 1 cm lateral to the midline and 1 cm superior to the line indicating the lower spinous process. The needle is inserted with a slight medial and cephalad angulation (5°–10°) alongside the spinous process (Fig. 7).[4] Tactile feedback (e.g. contact with the bony lamina) will indicate the need for incremental needle redirection, usually in a cephalad direction. Once again this is done in a similar manner to the conventional landmark-based technique of neuraxial block, and is based on a sound understanding of vertebral anatomy.

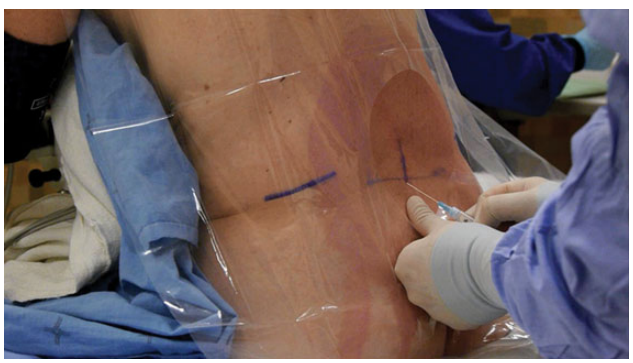

Fig 6 Needle insertion for a midline needle approach at the intersection point between the skin markings of the neuraxial midline and the interspinous/interlaminar space. This image is extracted from an instructional video available online at http://youtu.be/vgitdMn8RnI.[2]

Ultrasound for lumbar spinal and epidural anaesthesia: current evidence

Accurate identification of specific intervertebral levels

There is consistent evidence to suggest that neuraxial ultrasound can be used to identify vertebral levels more accurately than palpation of surface anatomical landmarks. A recent systematic review highlighted the poor correlation between vertebral levels determined by ultrasound and palpation, with rates of agreement varying from 14% to 64%.[5] In the majority of cases, the levels determined by palpation were higher, and often by more than one interspace, than when determined using ultrasound. Other studies have used additional imaging techniques such as plain radiographs, computed tomography,[6] and magnetic resonance imaging to further verify the accuracy of vertebral level identification. Once again, ultrasound proved both more accurate and more precise than palpation, since any discrepancy was only one space above or below the true level, when compared with two or three levels with palpation. Ultrasound correctly identified the vertebral level 68–76% of the time; underscoring the fact that it is not infallible. However, these were older studies and operator experience may be a factor, as shown by a more recent study indicating that accuracy rates of >90% can be achieved with adequate repetition.[6]

Measurement of depth to the intrathecal or epidural space

There is excellent correlation between ultrasound-measured depth and actual needle insertion depth using either transverse, sagittal, or PSO views.[5] The difference between the actual and measured distance in most studies was small, ~5 mm. Ultrasound measurement tends to underestimate actual needle insertion depth, probably due to compression of tissues by the ultrasound probe. Other sources of error include the accuracy of the placement of the electronic calipers, minor inaccuracies inherent in the technology, and differences in beam and needle trajectory.

Improvement in clinical efficacy of neuraxial block

Data from randomized, controlled trials (RCTs) suggest an improvement in the clinical efficacy of obstetric epidural analgesia when using ultrasound compared with surface-landmark guided techniques.[5,7] Significantly, lower rates of incomplete analgesia (2% *vs* 8%) and post-block pain scores were reported in the largest of these studies involving 300 obstetric patients.[8] In this instance, the pre-procedural scan, block, and outcome assessment were carried out by a single, experienced operator.

Vallejo and colleagues[9] studied 370 labour epidurals performed by a cohort of first-year anaesthesia trainees, with or without guidance from a pre-procedural ultrasound scan performed by a single experienced operator. The failure rate (defined by the need for epidural replacement secondary to inadequate analgesia) in the ultrasound-assisted patient group was significantly lower (1.6% *vs* 5.5%, $P<0.02$).

Shaikh and colleagues[7] published a systematic review and meta-analysis comparing ultrasound-guided and non-ultrasound-guided neuraxial techniques. This encompassed

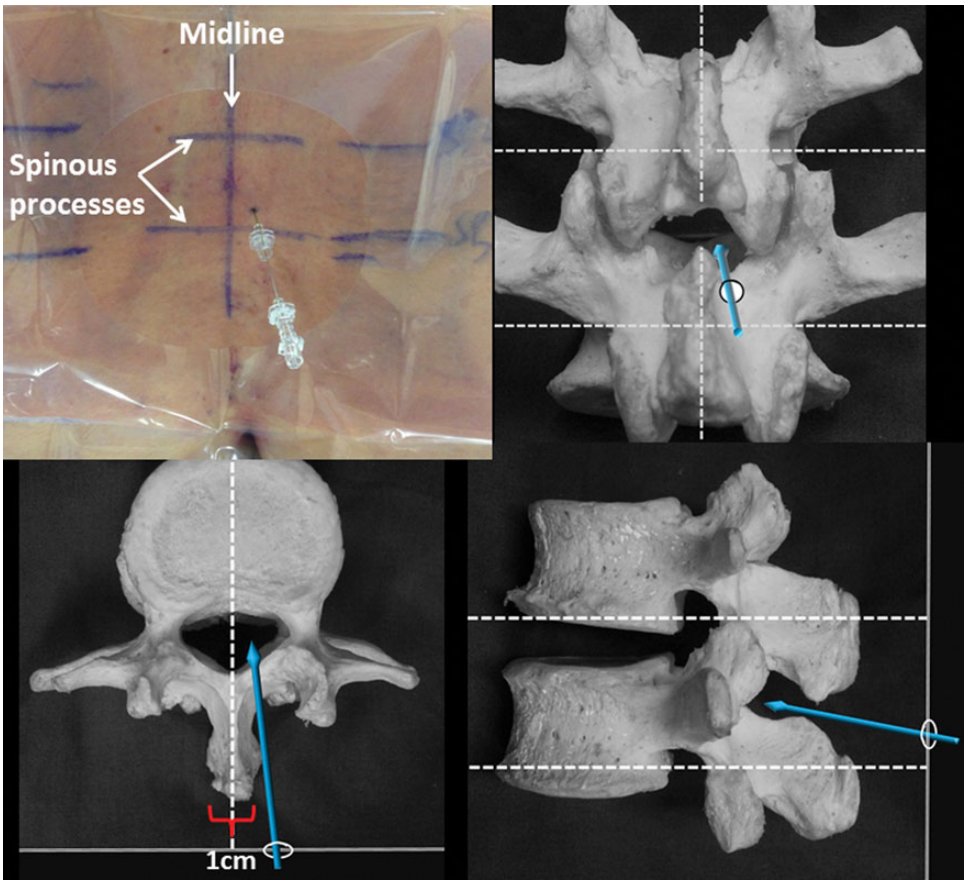

Fig 7 Needle insertion for a paraspinous (paramedian) needle approach using surface markings of the neuraxial midline and the spinous processes. The needle is inserted 1 cm lateral to the midline and 1 cm superior to the line of the lower spinous process. This image is extracted from an instructional video available online at http://youtu.be/-lE6xMUXMuQ.[4]

epidural, spinal, and lumbar puncture procedures, and included both adult and paediatric populations, and both pre-procedural and real-time ultrasound scans. A 79% reduction in the overall procedure failure rate was observed when ultrasound guidance was used. A significant (49%) reduction in procedural failure has also been confirmed in a more recent meta-analysis by Perlas and colleagues.[5] They identified six additional studies published between 2012 and 2014 and evaluated efficacy data from a total of 14 RCTs involving 1768 patients, including those with obscured surface anatomical landmarks secondary to obesity, scoliosis, or previous spinal surgery: eight RCTs studied obstetric epidural anaesthesia, three studied spinal anaesthesia in orthopaedic patients, and three evaluated diagnostic lumbar puncture within the emergency department setting.

Improvement in technical performance of neuraxial block

Both meta-analyses show that neuraxial ultrasound can improve the technical performance of CNB. This is clinically relevant as multiple needle passes cause tissue trauma and may increase the risk of complications. Shaikh and colleagues[7] found a significant reduction in both skin punctures and needle redirection attempts with the use of ultrasound, while Perlas and colleagues[5] noted a reduction in overall needle passes (mean difference 0.75).

CNB may be especially challenging in instances where anatomical landmarks are abnormal or poorly palpable, and here ultrasound is of particular benefit. In their study of 120 orthopaedic patients with obesity (BMI >35 kg m^{-2}), lumbar scoliosis, or previous lumbar spinal surgery, randomized to receive spinal anaesthesia by the conventional landmark-guided technique or by an ultrasound-assisted approach, Chin and colleagues[10] reported that pre-procedural ultrasound significantly increased first-attempt success rates, and reduced both the median number of needle insertions and additional needle passes. Subgroup analyses in obese patients with BMI>35 kg m^{-2} or poorly palpable landmarks demonstrated that the ultrasound-guided approach reduced the number of needle insertion attempts and needle passes by >50%. In their meta-analysis, Shaikh and colleagues[7] similarly found that the use of ultrasound produced a more marked decrease in needle redirections in the subgroup of patients with predicted technical difficulty compared with those without (mean difference 3.65 *vs* 0.99 passes).

Acquiring competency in ultrasound-assisted CNB

As with any advanced skillset, ultrasound-assisted CNB requires study and practice if competence is to be attained. Learning studies are limited to date but suggest that case experience of at least 30–40 procedures may be required for competency.[6,11]

Recommended learning strategies include the following:

- familiarization with the gross anatomy and sonoanatomy of the spine,
- repetitive scanning on human volunteers and patients,
- the use of spine phantom models for scanning and needle insertion,[12]
- hands-on instruction at expert-led workshops,
- self-directed learning using reference articles,[13]
- online interactive scanning models (e.g. http://www.usra.ca/vspine.php) and instructional videos.[2,4]

Summary

The current evidence supports the use of neuraxial ultrasound as a useful adjunct to conventional CNB techniques: it can be used to accurately identify lumbar intervertebral levels and allows precise measurement of depth to the epidural space. Neuraxial ultrasound may also improve the efficacy and safety of CNB by facilitating more accurate needle placement and decreasing the number of needle redirections and skin punctures.

Ultrasound-assisted CNB is not designed to replace the conventional surface landmark-guided technique, which is simple and effective in the majority of patients. Rather, it is an advanced tool to be used when technical difficulty is anticipated or when increased precision is desired. Having said that, the acquisition and maintenance of competency in neuraxial ultrasound requires practice. We therefore recommend that anaesthetists should incorporate neuraxial ultrasound into their clinical practice whenever possible until they attain the desired level of comfort with the ultrasound-assisted approach to CNB.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Ventricular arrhythmias and sudden cardiac death

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Key points

- Arrhythmias of ventricular origin carry the greatest risk of sudden death.
- The presence of structural heart disease is the most important risk factor in the development of malignant ventricular arrhythmias.
- Ventricular arrhythmias causing cardiac arrest within 48 hours of myocardial infarction carry the same prognosis as that of a similar sized infarct without cardiac arrest.
- Acute management focuses on resuscitation, chemical or electrical cardioversion, electrolyte restoration, and overdrive pacing.
- Implantable cardioverter defibrillators and electrophysiology catheter-based ablations now offer improved survival and quality of life, respectively.

There are 50–100 unexpected, sudden cardiac deaths (SCDs) per 100 000 population per year in Europe and USA, categorized by symptom onset to cardiac arrest time of <1 h.[1] Despite the decline in coronary artery disease mortality and advancements in resuscitation services, survival from these events remains low. Unfortunately, they often occur outside the hospital environment and are associated with a survival rate of <10%. The majority occur in adults over 35 yr of age and at least half of these events can be attributed to ventricular arrhythmias, although the true incidence is unknown due to inevitable degeneration to asystole if unwitnessed.

These arrhythmias may be the presenting complaint in the emergency department and may feature throughout the perioperative period, including at preoperative assessment, during surgery and in the recovery phase, for example in intensive care. They may also be the direct target of therapy in the case of electrophysiological catheter ablation and implantable cardioverter defibrillators (ICDs). They are more frequent and carry greater risks in patients with structural heart disease, but younger patients with ion-channel abnormalities can also be susceptible.[2] This review classifies the causes and significance of ventricular arrhythmias based on the presence or absence of structural heart disease and provides a simple system to aid confident distinction from supraventricular arrhythmias. Treatment goals focus on acute management, including pharmacological agents and electrical cardioversion and also the long-term role of ICDs and ablation therapies.

Pathophysiology of ventricular arrhythmias

Arrhythmia morphology

Ventricular ectopic beats

Ventricular ectopic beats increase in incidence and frequency with age, with <1% incidence in children under 11 yr to over 60% in subjects over 75 yr. While often benign in nature, hypertension with left ventricular (LV) hypertrophy risks morbidity and sudden death. The mortality risk varies with the extent of underlying disease. However, contrary to previous preoperative risk scores, in the absence of structural heart disease, even frequent and complex ectopics may be completely benign.

Ventricular tachycardia

Ventricular tachycardia (VT)[3] is defined as a heart rate >100 beats min^{-1} with three or more consecutive beats originating from the ventricles, independent of atrial or atrioventricular (AV) nodal conduction. QRS is >120 ms on ECG. They may be non-sustained (<30 s) or sustained (>30 s). Classification can be via clinical presentation, ECG, or disease entity, the latter of which is demonstrated in Table 1. Monomorphic VT has a single QRS

Table 1 Classification of ventricular arrhythmias by disease entity

Monomorphic
1. Structural heart disease
   (a) Coronary artery disease
   (b) Dilated cardiomyopathy
   (c) Hypertrophic cardiomyopathy
   (d) Valvular heart disease
   (e) Congenital heart disease
   (f) Infiltrative heart disease (e.g. sarcoidosis, amyloidosis, haemochromatosis)
2. No structural heart disease
   (a) RV outflow tract VT (fibro-fatty replacement of muscle)
   (b) LV outflow tract VT
   (c) Idiopathic LV septal VT (fascicular VT)

Polymorphic
1. Normal corrected QT interval
   (a) Acute ischaemia or scar
   (b) Catecholaminergic polymorphic (CPVT)
   (c) Brugada syndrome
2. Long corrected QT interval (>440 ms men, >460 ms women)
   (a) Congenital
   (b) Acquired
      (i) Drugs
      (ii) Electrolyte abnormalities
      (iii) Neurological injury
      (iv) Starvation
3. Short corrected QT interval

morphology, suggesting a stable structural focus, for example, scar. Polymorphic VT presents with continuously changing QRS configuration from a more global activation sequence such as hypoxaemia, metabolic abnormalities, catecholamines, and acute myocardial ischaemia. Torsades de pointes is a rare, polymorphic VT, associated with congenital or drug-induced long QT syndrome. It is covered at length in a previous *CEACCP* article and is not discussed further.[4]

Ventricular fibrillation

Ventricular fibrillation (VF) is a life-threatening, chaotic rhythm, with marked variability in cycle length and morphology up to 300 beats min^{-1}, with loss of cardiac output. The underlying mechanism for the origins of VF is poorly understood, but prolonged monomorphic VT is a known risk factor, contributed by ischaemia, free radical production, and intracellular calcium release. It can also be precipitated by iatrogenic pacing of the myocardium during the refractory period of cardiomyocytes, which corresponds to the upstroke of the T wave on ECG.

Arrhythmogenic substrate

Coronary artery disease

Two arrhythmogenic mechanisms are described in patients with coronary disease:

(i) acute myocardial ischaemia, resulting in polymorphic VT, which degenerates to VF;
(ii) myocardial scarring due to ischaemic cardiomyopathy where the main arrhythmogenic events is a re-entry monomorphic VT.

Scarring increases the proportion of non-conducting tissue, for example, fibroblasts, to conducting myocytes. This changes the velocity and uniformity of action potentials passing through the scarred muscle. Slow conduction and fibrous anatomical barriers generate multiple circuits, risking re-entry of action potentials into repolarizing muscle.

Despite acute coronary artery occlusion being the main trigger for arrhythmogenic events, family history plays an important role in outcome independent of traditional risk factors, with polymorphisms discovered in multiple stages of the atheroma to plaque cascade. Importantly, in survivors of cardiac arrest due to VF with associated acute ST segment elevation myocardial infarction (STEMI), acute prognosis is not significantly different from that associated with an infarct of similar size without arrest and constitutes part of the MI process. However, the formation of scar after 48 h becomes an arrhythmogenic substrate and risks clinically significant, secondary VT or VF.

Cardiac risk factors for SCD

Hypertension and the consequence of LV hypertrophy are recognized arrhythmogenic substrates, as is left bundle branch block. The Framingham Study, which began in 1948, has looked into risk factors for cardiovascular disease over a long period of time and has shown that cigarette smoking, obesity, and diabetes also increase the risk of SCD. While modest exercise is protective, vigorous exercise in unfit individuals carries a burden of risk as do the social and economic stresses that influence acute coronary events.[1]

Cardiomyopathy

In 15–20% of patients with structural heart disease, cardiomyopathies are responsible for arrhythmogenic SCD, especially when associated with LV systolic dysfunction. More importantly, however, severe ventricular impairment is also associated with a higher percentage of non-arrhythmogenic sudden death, due to pump failure.

Absence of structural heart disease

This arrhythmia group commonly carries a benign prognosis. The majority originate from the RV or LV outflow tracts and anterior/posterior fascicles (fascicular VT). The incidence of tachycardia-related cardiomyopathy and SCD is extremely low. However, there are a rare heterogeneous group of arrhythmogenic syndromes, which are strongly related to life-threatening ventricular arrhythmias and SCD, especially in the young population. Inherited gene mutations are responsible for primary electrophysiological abnormalities and disruption of cardiac cell ion channel function (channelopathies).[5] Examples include:

(i) Long QT (>440 ms in men, >460 ms in women) is a heterogeneous group of at least 13 forms, where the prolonged repolarization period risks Torsades de pointes VT. It is predominantly a potassium-channel abnormality.
(ii) Brugada syndrome is a sodium-channel gene abnormality, with normal QT interval.
(iii) Catecholaminergic polymorphic VT, which occurs during exertion or emotional trauma, is a ryanodine receptor gene abnormality.
(iv) Short QT, a rarer, heterogeneous group, where the QT is typically <300 ms is typically a calcium-channel abnormality, with abnormally short repolarization.

Brugada syndrome warrants further explanation as it has a particularly high risk of SCD with a structurally normal heart. The loss of sodium channel function during phase 1 causes an imbalance between sodium and calcium influx, and different stages of repolarization between endocardium and epicardium. This generates a vulnerable period for an extrasystole during the phase 2

plateau, which can trigger a re-entry tachycardia. Diagnosis depends upon both characteristic coved ST elevation in V1–V3 leads, followed by a negative T wave and clinical criteria (any one):

(i) documented VF or polymorphic VT,
(ii) family history of SCD at <45 yr old,
(iii) coved-type ECG in family members,
(iv) syncope,
(v) nocturnal, agonal respiration.

The ECG signs in isolation are of questionable significance. There are three ECG subtypes for the one condition. Type 1 is the classic shape and is shown in Figure 1. Type 2 has a more saddle-shaped ST elevation and type 3 can be either shape but <2 mm ST elevation.

Diagnosis of VT

Eighty per cent of broad complex tachycardias are ventricular. The positive predictive value in patients with coronary artery disease, heart failure, angina, and age >35 yr is over 95%. However, supraventricular tachycardia (SVT) can be responsible. The distinction between ventricular and supraventricular is important as misdiagnosis risks inaccurate therapeutic decisions, which could be potentially fatal. However, this distinction can be difficult and the debate should not impinge on delivering safe and effective therapy. If there is doubt, one should assume the rhythm is VT.

Broad complex SVT can arise from:

(i) aberrancy (bundle branch block),
(ii) antegrade conduction through an accessory pathway (pre-excitation).

With aberrancy, conduction is still via the His–Purkinje system but with a fascicular abnormality, that is, left or right bundle branch block. The right bundle normally repolarizes more slowly than the left, thus even in health, the timing of a supraventricular beat may depolarize one bundle, while the other is still refractory. An example of pre-excitation would be that seen in Wolf–Parkinson–White syndrome.

Clinical information

Stable VT may be asymptomatic or present with palpitations only. Faster rhythms impact more negatively on cardiac output, producing presyncopal symptoms like dizziness and light headedness, syncope (loss of consciousness with spontaneous recovery) to sudden cardiac arrest, or SCD if not resuscitated.

Physical examination may demonstrate signs of AV dissociation, specific to VT. These signs include varying pulse volume with beat-to-beat variability of systolic arterial pressure, alternating intensity of the first heart sound and irregular cannon A waves. These large pressure waves are transmitted up the internal jugular veins when the right atrium contracts against a closed AV valve. Tachycardia termination by vagal stimulation, for example, Valsalva manoeuvre, suggests supraventricular origin but may occasionally influence VT.

Electrocardiography

With VT, there is often positive or negative concordance in the chest leads, with entirely positive (R) or entirely negative (QS) waves in leads V1–V6, thus concordance has no RS complexes. Criteria favouring VT can also be found in SVT with aberrancy. The supraventricular impulse is transmitted to the ventricle via an abnormal connection but with discordance in the chest leads and RS complexes present. Very broad complexes (>160 ms) increase the likelihood of VT.

The Brugada diagram is an algorithm that aids VT diagnosis from ECG (Fig. 2):

(i) The absence of an RS wave in all of V_1–V_6 precordial leads diagnoses VT immediately and is nearly 100% specific. An example would be VT arising from the ventricular apex as

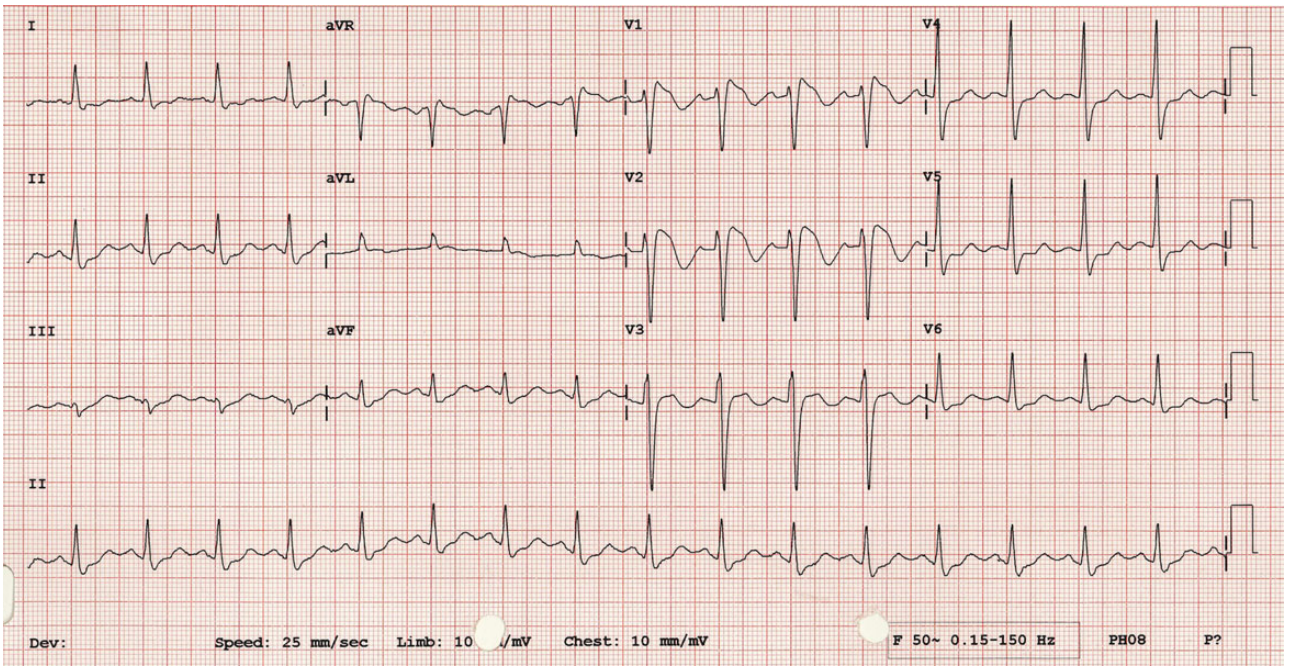


Fig 1 Twelve-lead ECG type 1 pattern in Brugada syndrome (images via http://lifeinthefastlane.com/ecg-library/ventricular-tachycardia/).

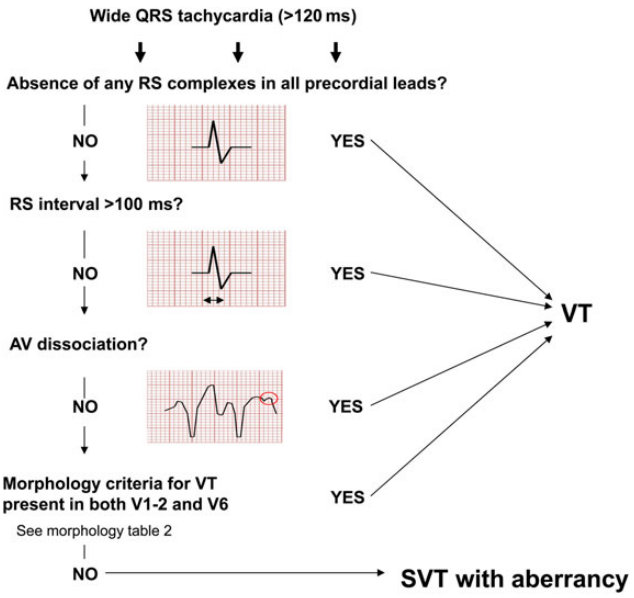


Fig 2 Brugada diagram to distinguish supraventricular from ventricular tachycardia.

the wave propagates in the opposite direction to normal depolarization. A positive R wave in aVR is seen.

(ii) If any RS wave is present, and over 100 ms (interval from start of R to nadir of S), VT is diagnosed.

(iii) If the RS wave is shorter than 100 ms, but there is clear evidence of AV dissociation (slower p waves, not linked to QRS), then VT is diagnosed. AV dissociation is difficult to see when the heart rate exceeds 150 beats min^{-1}.

(iv) Finally, if an RS is present in any precordial lead, <100 ms, with no obvious AV dissociation, then morphology criteria using only $V_{1–2}$ and V_6 are used for final clarification. QRS morphology criteria are summarized in Table 2.[6,7] They separate the rhythm based on right or left bundle branch type appearance.

Suggesting VT, capture beats occur when an occasional, normal sino-atrial node impulse is conducted through to the ventricle. Fusion beats occur when ventricular muscle is depolarized simultaneously by both a normal, supraventricular and abnormal, ventricular beat, which produces a QRS duration length between the two (Fig. 3). They are the collision of wave fronts from two different directions, forming a hybrid beat. Capture and fusion beats are often absent with higher rate VT.

Consider the ECG in Figure 4. There is a wide complex, monomorphic tachycardia (135 beats min^{-1}), with QRS of 185 ms. Concordance is not present in all leads as there appear to be both positive (e.g. V1–2) and negative (e.g. V5–6) complexes. Using the Brugada algorithm, RS complexes appear in V1–4, but not all precordial leads, thus the origin of the arrhythmia could still be supraventricular. However, aVR is positive and RS complexes are >100 ms, thus the diagnosis of VT can be made with confidence. Negative complexes in V6 and positive in V1 suggests an origin from the lateral LV, because of the direction of impulse travel. For completeness, there may well be p waves (e.g. V1 nadir), but they are not obvious, thus no AV dissociation is reliably seen. The pattern is an RBBB-type because of positivity in V1–2, and there is a QS wave in V6. All of these tests add weight to the diagnosis of VT. V1 has an R wave notch, which does not feature in any classification; this demonstrates the limitations of any template system of discrimination.

Investigations

In the preoperative patient with ventricular ectopics or in VT, excluding structural heart disease is the primary focus.[8] History of syncope, heart failure, or arrhythmias up to 2 months after myocardial infarction are all high-risk characteristics. Electrolyte abnormalities and use of illicit drugs should be identified and addressed.

Important investigations include:

Twelve-lead ECG: looking for underlying disease like Q waves, bundle branch block, and ventricular hypertrophy and also signs of arrhythmogenic syndromes. Long-term ECG monitoring via implantable loop recorder is useful in monitoring symptoms and correlating them to arrhythmias, but as they provide no therapies, patients with structural heart disease are better protected and monitored by insertion of an ICD instead.

Exercise testing: identifies silent ischaemia in coronary artery disease but also exercise-induced arrhythmias like catecholaminergic polymorphic VT. Frequent ventricular ectopic beats during exercise risk serious cardiovascular events in patients with structural heart disease, although not specifically SCD.[1] They are difficult to treat, with β-blockers being the only class of drug proven to be efficacious.

Echocardiography: first-line investigation for evaluation of LV and RV function and wall thickness, regional wall motion abnormalities, valvular disease and congenital abnormalities.

Cardiac magnetic resonance imaging:[9] shows higher diagnostic accuracy than echocardiography in identifying and quantifying myocardial scar burden which has been directly linked to SCD; demonstrates accurate and reproducible measurements of LV ejection fraction and volumes; offers qualitative assessment of RV structure and function.

Coronary angiography: should be performed in all individuals with risk factors for coronary artery disease and inducible ischaemia on non-invasive testing.

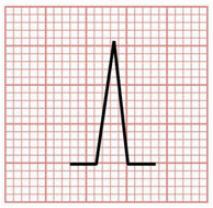
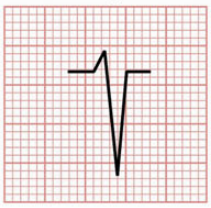
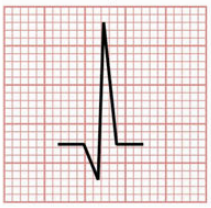
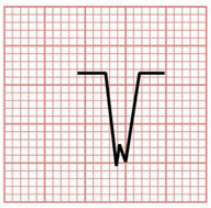
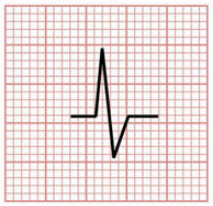
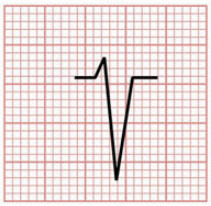
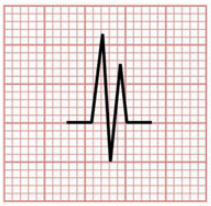
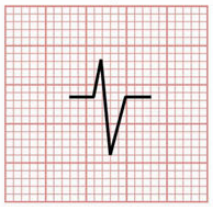
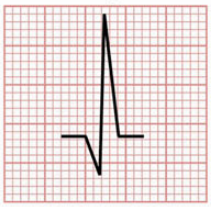
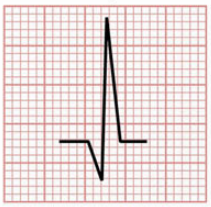
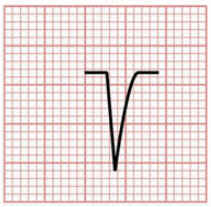
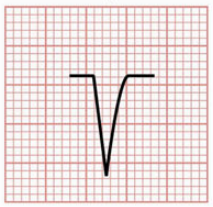
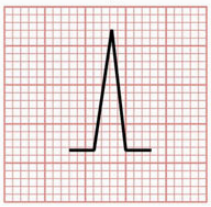
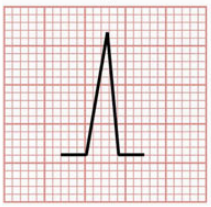
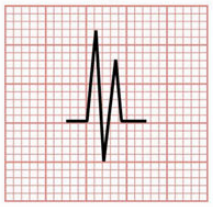
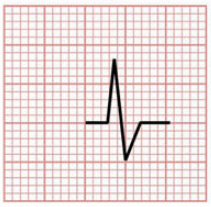
Cardiac CT scanning: non-invasive imaging of congenital coronary malformations or those in whom MRI is contraindicated. Calcification of normal vessels can also be quantified as a 'coronary artery calcium score'.

Electrophysiological studies: to induce VT are useful in patients with coronary artery disease to guide diagnostic evaluation and after VT ablation to assess its efficacy. They are also useful as an accessory tool in patients with syncope of unknown cause and structural heart disease to document or exclude ventricular arrhythmias.

Electrophysiological studies

In the laboratory, electrophysiological mapping may be able to detect the source of the ventricular arrhythmia, which can be subsequently ablated using radiofrequency. Mapping, via femoral access, often under local anaesthesia, can provide anatomical reconstruction, which is then correlated to the arrhythmia. Stimulation of the ventricle can evaluate inducibility of VT in at-risk patients, characterize VT pattern and assist treatment choices. Mapping catheter electrodes are usually positioned in the high right atrium, ventricle, coronary sinus (alongside mitral annulus), and His bundles (alongside tricuspid annulus). ECG, echocardiography, and MRI (if no ICD) are vital to predict region of interrogation and avoid unnecessary procedure length. Thus, a lateral infarct suggests circumflex territory and lateral LV source. The RV can be accessed via the femoral vein, the LV either across the interatrial septum or retrograde passage via the aorta,

Table 2 Morphology criteria for VT *vs* SVT

Tachycardia with RBBB-like QRS	Tachycardia with LBBB-like QRS
Lead VI	*Lead VI-2*
Monophasic R = **VT** (V1) 	R > 30 ms = **VT** (V1) 
QR = **VT** (V1) 	Notched S = **VT** (V1) 
RS = **VT** (V1) 	> 60 ms to nadir of S = **VT** (V1) 
Triphasic = **SVT** (V1) 	
Lead V6	*Lead V6*
R to S ratio <1 = **VT** (V6) 	QR = **VT** (V6) 
QR = **VT** (V6) 	QS = **VT** (V6) 
QS = **VT** (V6) 	Monophasic R = **SVT** (V6) 
Monophasic R = **VT** (V6) 	
Triphasic = **SVT** (V6) 	
R ro S ratio >1 = **SVT** (V6) 	

RBBB = Right Bundle Branch Block, LBBB = Left Bundle Branch Block

through the aortic valve. The VT QRS morphology will determine the origin of the arrhythmia, thus RBBB pattern suggests the LV as source and vice versa. The His bundle interrogation should exclude the impulses arising from a supraventricular source. Occasionally, especially with structurally normal heart VT, increased automaticity with sympathomimetic drugs, for example, isoprenaline, may be required to generate the arrhythmia.

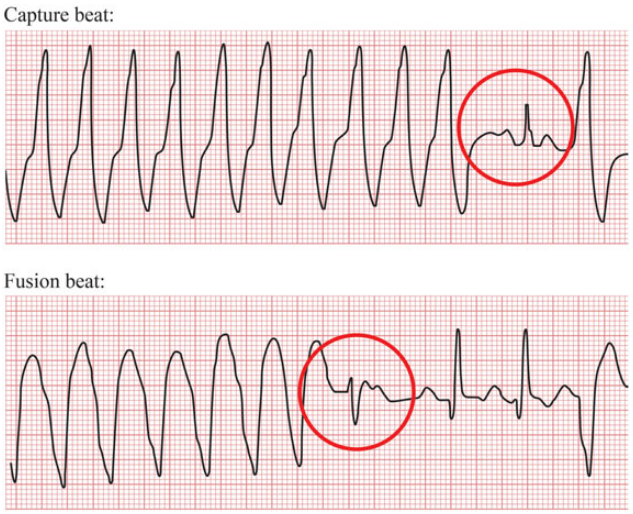


Fig 3 Capture and fusion beats.

Management of VT and prevention of sudden death

Resuscitation

In the case of a cardiac arrest, the algorithm of advanced life support is applied. The latest resuscitation algorithm for tachycardia in adults is shown in Figure 5. Haemodynamically unstable VT presents with syncope, hypotension (typically systolic pressure below 90 mm Hg), pulmonary oedema, angina, confusion, and cardiac arrest. End-organ hypoperfusion mandates prompt termination of the arrhythmia, by synchronized DC cardioversion, which is both quicker and more effective than by chemical means. Under general anaesthesia or conscious sedation, a 120–150J synchronized biphasic shock is used, which is increased in increments to a maximum of three attempts. Reversible causes like hypoxaemia, electrolyte abnormalities (in particular hypokalaemia <4 mmol litre^{-1}, hypomagnesaemia, hypocalcaemia), and drug toxicity should be corrected. The Resuscitation Council advise senior help early, rather than the use of multiple pharmacological agents. In the context of acute ischaemia and primarily STEMI, immediate revascularization is indicated.

Pharmacological therapy

Historically, the main treatment of acute ventricular arrhythmias has been pharmacological, but questions exist regarding safety and efficacy of drugs. The Vaughan–Williams classification is a useful template, although many drugs have actions across classes and others do not fit into the classification at all.

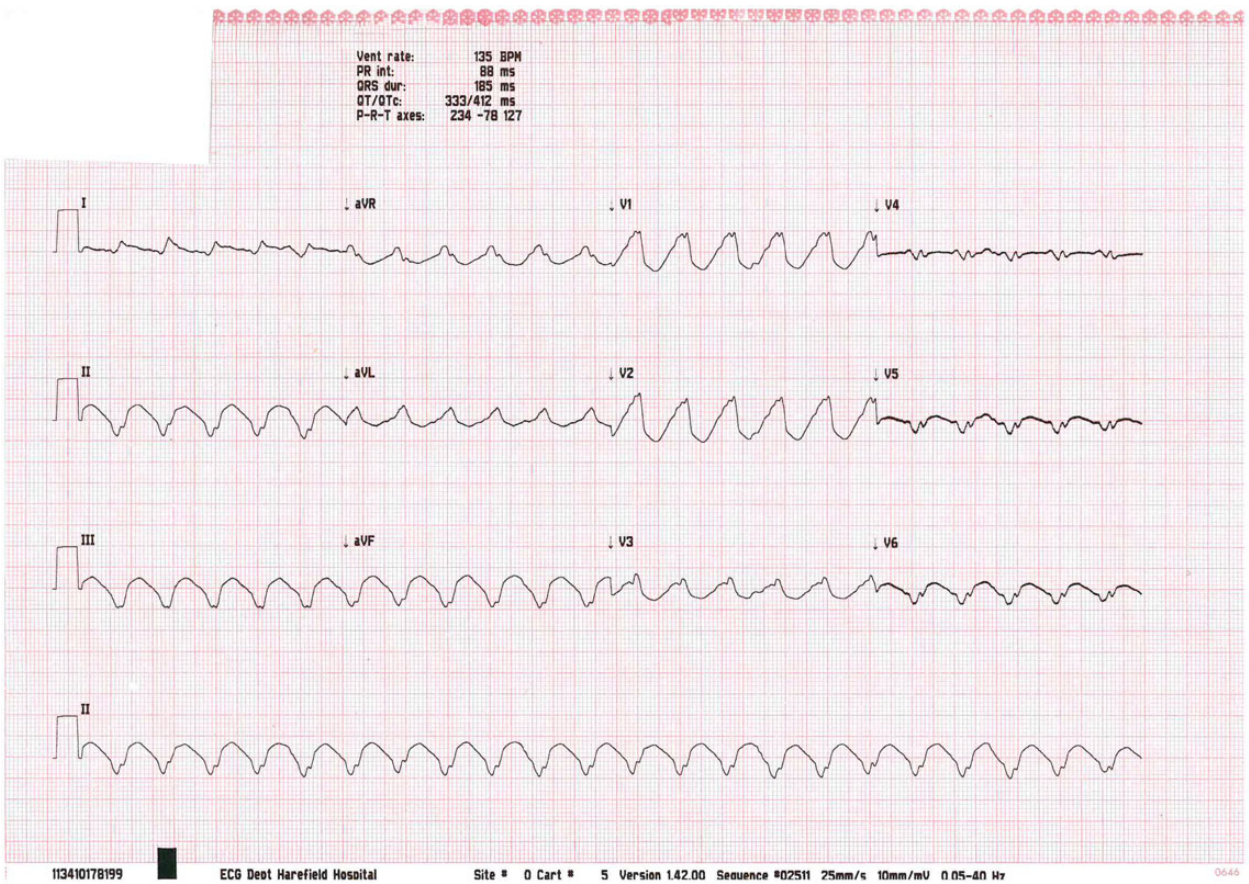


Fig 4 ECG of a broad complex tachycardia.

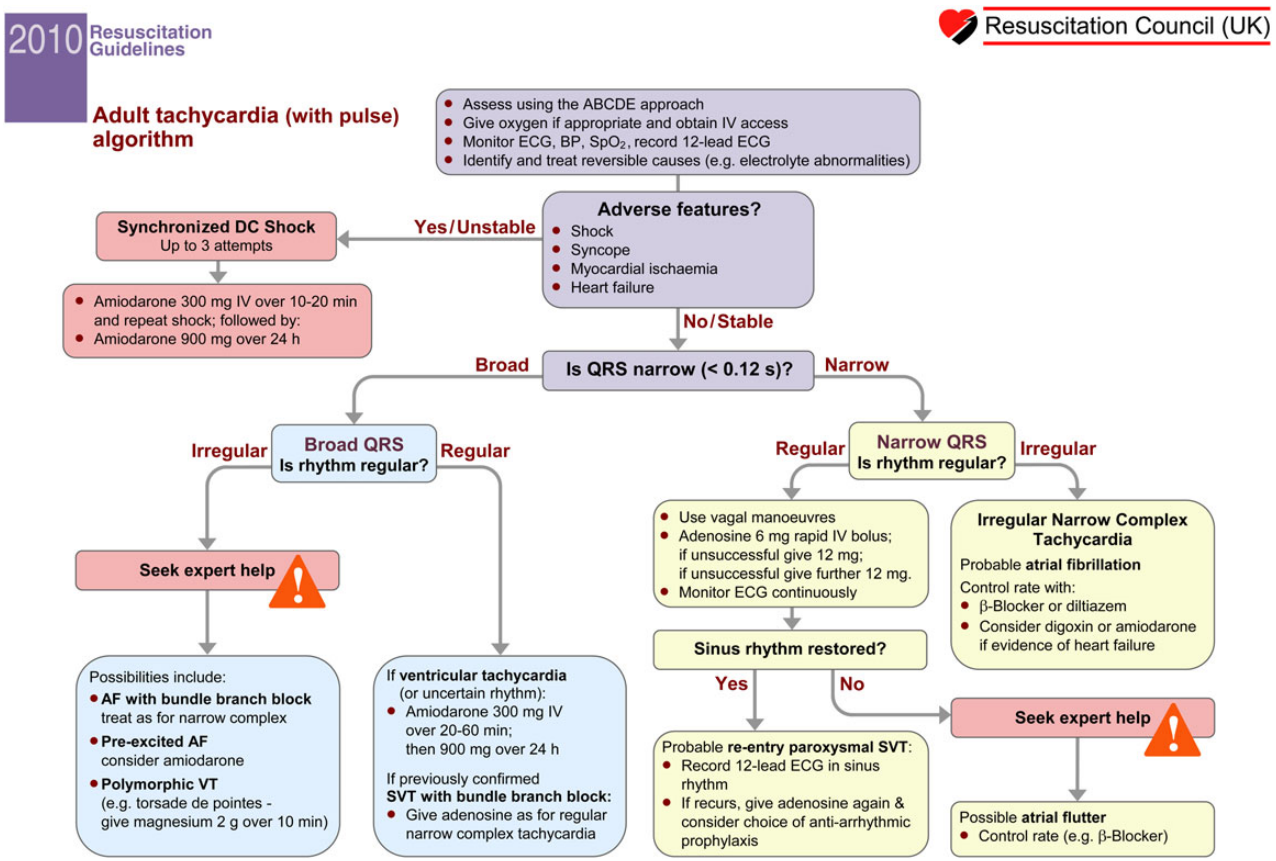


Fig 5 Resuscitation Council Algorithm for adult tachycardia (with pulse). Reproduced with the kind permission of the Resuscitation Council (UK).

Magnesium (1–2 g slow i.v.) and potassium (aim K^+ >4 mmol $litre^{-1}$) are the safest first-line therapy in all cases and can favourably influence the electrophysiological substrate in the onset of arrhythmias. The Resuscitation Council guidelines recommend expert advice for all irregular rhythms, where the arrhythmia origin may be unclear.

Class I sodium-channel antagonists

Pure class I drugs have a limited role to play in VT and are useful only in structurally normal hearts for symptomatic improvement. Flecainide has been shown to increase mortality post-MI. It has a limited role, as does propafenone in idiopathic VT only. Lidocaine may be used in stable, sustained, monomorphic VT in acute MI but increases mortality if used for prophylaxis against VF. It has a rapid onset of action but is more likely to cause hypotension than amiodarone, where the onset of action is slower.

Class II β-blockers

In the context of STEMI, β-blockers are first-line therapy.[1] They are the most successful agents in prevention of ventricular arrhythmias and arrhythmic SCD in a wide spectrum of cardiac diseases with or without underlying structural heart disease. The anti-arrhythmic efficacy stems from competitive adrenergic receptor blockade, which reduces sympathetic triggers, slows the sinus rate, and may inhibit calcium release from the ryanodine receptor. Importantly, however, they are contraindicated in Brugada syndrome as they aggravate ion current imbalances that occur during the early part of the action potential, creating a vulnerable period for an extra-systole. Unopposed vagal tone is the biggest risk factor for arrhythmias (most occur at night), thus sympatholytics and bradycardia are dangerous. In fact, pure β-agonists, for example, isoprenaline, are used for resistant VT in this group of patients.

Class III potassium-channel antagonists

Amiodarone and sotalol have been shown to reduce arrhythmogenic SCD but not all-cause mortality. Class III drugs block potassium repolarization currents and thus increase the threshold for re-entry. In haemodynamically stable patients, with low troponin–myocardial infarction or non-ischaemic VT, there is Class C evidence for the use of either procainamide or amiodarone to terminate confirmed or suspected VT. Procainamide has both class I and III actions and has a favourable side-effect profile but is no longer regularly available in the UK.

Class IV calcium channel blockers

Class IV calcium channel blockers, for example, verapamil, should never be used to terminate broad complex tachycardia of unknown origin as they may precipitate VF. They have a select role to play in confirmed fascicular VT.

Other agents

The role of adenosine continues to remain controversial. The 2010 ILCOR guidelines state that adenosine may aid in diagnosing VT but will not terminate it. Adenosine is considered safe only if an SVT can be confidently excluded using tools discussed, or if

SVT with bundle branch block has been previously confirmed. Otherwise, it too may precipitate VF. Amiodarone and adenosine are the only drugs recommended to be used without expert consultation in all broad complex tachycardia groups.

It is important to recognize that ventricular arrhythmias are often the final common pathway in the unstable heart. Drugs with most success long term are not those above, which act directly on conducting muscle. Instead, it is drugs like ACE inhibitors, lipid-lowering agents, and aldosterone antagonists, for example, spironolactone, that influence the course of ischaemia, fibrosis, and biochemical derangement before the arrhythmogenic substrate is set.

Implantable cardioverter defibrillator

The ICD is a battery-powered invasive device with four functions:

(i) Sensing: the device compares atrial and ventricular rates to assign arrhythmia causation.
(ii) Pacing: anti-bradycardia and overdrive anti-tachycardia pacing (ATP).
(iii) Cardioversion: synchronized electrical current to terminate cardiac output-compatible arrhythmias.
(iv) Defibrillation: to terminate VF.

While implanted in much the same way as a permanent pacemaker, general anaesthesia is usually recommended as VF is induced at the end of the procedure to test function and response time.

There is compelling evidence to support their use in the presence of ischaemic heart disease, with impaired LV ejection fraction, supported by NICE guidelines, updated in 2014.

ICDs are also recommended as options for treating people with previous serious ventricular arrhythmia, that is, people who, without a treatable cause:

- have survived a cardiac arrest caused by either VT or VF, or
- have spontaneous sustained VT causing syncope or significant haemodynamic compromise, or
- have sustained VT without syncope or cardiac arrest, and also have an associated reduction in LV ejection fraction of 35% or less but their symptoms are no worse than class III of the New York Heart Association (NYHA) functional classification of heart failure.

They are also recommended for treating people who:

- have a familial cardiac condition with a high risk of sudden death, such as long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, or arrhythmogenic right ventricular dysplasia, or
- have undergone surgical repair of congenital heart disease (http://www.nice.org.uk/guidance/ta314/resources/guidance-implantable-cardioverter-defibrillators-and-cardiac-resynchronisation-therapy-for-arrhythmias-and-heart-failure-review-of-ta95-and-ta120-pdf).

Direct comparison of ICDs with anti-arrhythmic drugs has shown a clear reduction in SCD in carefully selected patients with a high-risk profile.[10] Importantly, anti-arrhythmic drugs such as β-blockers, amiodarone, sotalol, and mexiletine still have a role in primary and secondary prevention. They reduce the arrhythmogenic burden and consequently the number of ICD shocks delivered.

Anti-tachycardia pacing

ATP through a temporary pacing wire can overdrive and terminate arrhythmias successfully and more importantly is the first technique an implanted ICD is programmed to perform in the presence of wide complex tachycardia. A slow, monomorphic VT can be detected then accelerated by the device to a short-lived burst of faster ventricular pacing, which on cessation terminates the VT, without the need for general anaesthesia. If unsuccessful, a subsequent burst of fast pacing followed by a low-voltage shock may also work. High energy shocks are very effective but are both painful and are a considerable drain to the ICD battery. ATP is unlikely to work during fast, haemodynamically unstable VT and risks degeneration to VF.

ICDs and surgery

As the indications for ICDs increase, so does the number encountered in patients presenting for surgery. While a detailed management plan for patients with implanted electronic cardiac devices[11] is outside the scope of this review, some important principles apply:

(i) Electromagnetic interference may inappropriately trigger the device. This includes electrocautery (monopolar much greater than bipolar), nerve stimulators, evoked potential monitors, electroconvulsive therapy, radiofrequency ablation, and MRI. Succinylcholine fasciculations, shivering, and large tidal volumes should not interfere with ICD sensing.
(ii) All ICDs can be deactivated with a magnet. This turns off the shock therapy and anti-tachycardia modes but has no effect on pacing and anti-bradycardia modes. Removal of the magnet should restore full device function. However, reactivation to pre-magnet settings is not guaranteed, thus a full ICD check should be completed after operation.
(iii) Formal ICD deactivation by a cardiac technician may be required if surgery is near the box site (e.g. cardiothoracics), remembering that deactivation of the device leaves patients vulnerable to malignant arrhythmias. It is helpful to know the model type, as the interrogation consoles are manufacturer-specific.
(iv) External defibrillator pads are recommended in all ICD patients and the device must be reactivated at the end of surgery.
(v) Anaesthetic management should focus on reducing arrhythmias. Cardiostable, non-histamine-releasing drugs are recommended. Electrolyte disturbances, particularly potassium and magnesium, should be corrected and meticulous attention should be applied to Seldinger-type insertion of intra-vascular lines.

Ablation of ventricular arrhythmias

Evidence for catheter ablation of VT is mostly from patients with ischaemic heart disease. It is not a simple procedure and few patients are able to tolerate VT for sufficient time to allow all the necessary mapping required to identify all possible re-entry sites. Ablation energies can be applied using radiofrequency, cryotherapy, low energy direct current, or laser.

Success rate varies between 50% and 80% with reported complication rate up to 10% depending on the urgency of the procedure. Evidence exists for both prior and post-ICD implantation with successful reduction in arrhythmic burden and ICD therapies. No direct comparison between ablation and anti-arrhythmic drugs has been performed to date. Despite successful arrhythmia treatment, it is unclear if VT catheter ablation has an effect in SCD and mortality.

A small proportion of patients with RV and LV outflow tract VT have otherwise structurally normal hearts and this procedure importantly may offer a permanent cure.

The success of ablation procedures is expanding into more experimental techniques, including transthoracic pericardial access, transcoronary chemical ablation, and also spinal cord modulation to suppress VT.

Anaesthesia for ablation procedures is covered in a previous *CEACCP* article.[12]

Conclusion

The most important determinant in assessing the clinical significance of ventricular ectopic beats or tachycardia is the presence or absence of structural heart disease. Benign arrhythmias are more likely in patients under 35 yr old, except in those with hereditary channelopathies. Confidence in excluding the diagnosis of SVT with aberrancy is complex and may require expert help. Treatment of acute VT is via resuscitation, electrical or chemical cardioversion, and then assessing the need for further preventive therapy. ICDs and electrophysiology catheter-based ablations now offer improved survival and quality of life, respectively. Deactivating the defibrillation and anti-tachycardia function of an ICD can be achieved with a magnet. This leaves the patient vulnerable to arrhythmias; thus, the use of external defibrillation pads is mandatory.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Anaesthetic considerations for patients with neurosurgical implants

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Key points

- Survival rates for patients with neurosurgical pathology are improving, resulting in more of these patients presenting for incidental surgery. The non-specialist can safely anaesthetize neurosurgical patients by adhering to general neurophysiological principles.
- Cerebrospinal fluid diversion devices (shunts) used to treat hydrocephalus are not only ventriculoperitoneal, the distal end may be placed into the intrapleural space or the right atrium. The proximal end can also arise from the lumbar spine.
- Neurosurgical pathology is not necessarily a contraindication to regional anaesthetic techniques, nor to laparoscopic surgery.
- The duration of dual anti-platelet therapy for patients with intracranial stents depends on the site and nature of the stent. In the emergency setting, advice from the specialist centre should be sought.
- An understanding of the indication for long-term neurosurgical or neuroradiological implants is useful when planning anaesthesia and postoperative care.

Innovations in neurosurgical technology, neurosurgical techniques, approaches to surgical access, and interventional neuroradiology have revolutionized the treatment of many neurosurgical and neurological conditions, with many pathologies now amenable to surgical intervention; aggressive tumour resection in eloquent areas and on/adjacent to the motor strip, Parkinson's disease, epilepsy, benign intracranial hypertension, pituitary tumour, intracranial aneurysm surgery, and radiological intervention to name a few. Survival rates over 5 and 10 yr have improved and it follows that patients with residual tumour, cerebrospinal diversion devices (shunts), indwelling therapeutic implants (devices) and stents, and spinal metal work are more likely to present to their local hospital for non-neurosurgical procedures.

Broadly speaking, patients with neurosurgical pathology requiring non-neurosurgical procedures can be considered in four main groups:

- Incidental surgery in a patient with an intracranial mass lesion.
- Trauma patients requiring emergency life-saving surgery that also have acute traumatic brain or spine injury.
- Obstetric interventions in patients with intra-cranial or spinal pathology.
- Interventions in patients with neurosurgical or neuroradiological implants.

An understanding and application of basic neurophysiological principles[1] underpins successful anaesthesia in all of the mentioned groups and this has been comprehensively addressed in papers focusing on the management of patients requiring surgery with combined neurological pathology and trauma,[2–4] or obstetric problems.[5,6]

This article will focus on anaesthetic considerations for the individual with a shunt to divert cerebrospinal fluid (CSF), those taking anti-platelet therapy for intracranial vascular stents/coils, and those with neurosurgical implants.

General anaesthetic considerations

Preoperative assessment

The baseline neurological status, with documentation of the Glasgow coma score (GCS) and pre-existing focal deficits, is important to ascertain before embarking on general anaesthesia. In addition, features suggesting elevated intracranial pressure (ICP) (Fig. 1) should be sought as they may alert the anaesthetist to a malfunctioning shunt or device.

A new or worsening headache, new neurological deficits, or increasing frequency or new onset of seizures are suggestive of raised ICP. The headache occurs as a result of traction on, or distortion of the cerebral blood vessels and dura mater. It is classically postural, worse when recumbent or upon straining and may be associated with nausea and vomiting caused by irritation of the vomiting centre.

A focused physical examination that identifies either papilloedema or decreased consciousness is also suggestive of high ICP. The predominant concern is the possibility of subsequent brain herniation with further elevations or peaks in ICP. The herniation can be transtentorial (cephalad) causing ipsilateral midriasis and contralateral hemiplegia, or tonsillar (caudad) through the foramen magnum leading to respiratory or cardiac arrest as the brainstem is compressed. The classical, although late, clinical features of brainstem compression are either Cushing's triad—hypertension, bradycardia, and widened pulse pressure, or abnormal respiratory patterns caused by pressure on the respiratory centres, for example, Cheyne–Stokes or apnoeas.

In the face of new signs or symptoms, the specialist centre should be contacted for advice/review and elective procedures postponed.

A thorough drug history will enable planning of postoperative analgesic regimes, the key drugs to consider are (i) anti-platelets in those with intracranial stents, (ii) anti-epileptics, especially in patients likely to benefit from multi-modal postoperative analgesia including pregabalin or gabapentin, to prevent drug interactions or over dosage, and (iii) anti-parkinsonian drugs to prevent drug interactions.

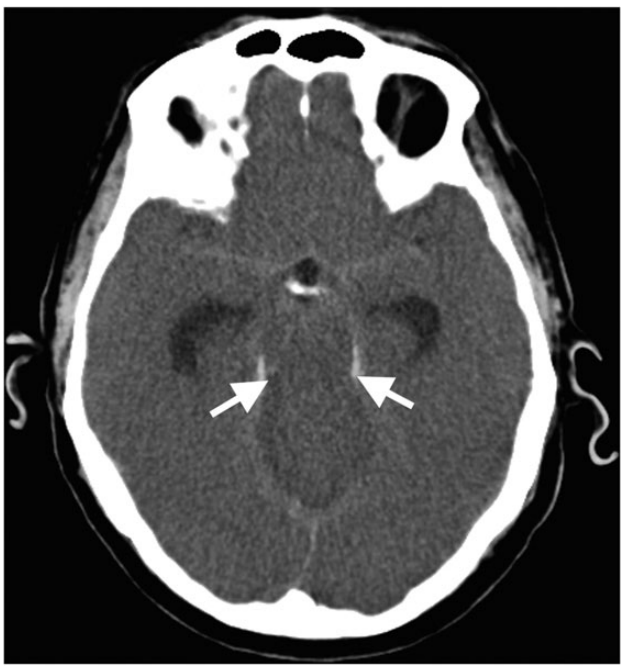

Fig 1 Radiological features of intracranial hypertension. Axial CT shows widespread loss of grey–white matter differentiation, sulcal effacement, and effacement of the basal cisterns (arrows). The temporal horns of the lateral ventricles are dilated indicating acute hydrocephalus.

Intraoperative management

For patients with raised ICP, the anaesthetic technique should maintain normal physiology, prevent further elevations in ICP, and enable rapid emergence to permit assessment of postoperative neurological function.[4] Total i.v. anaesthesia using propofol and remifentanil target-controlled infusions has several benefits, including rapid onset and offset, maintenance of cerebral flow-metabolism coupling, and reduction in cerebral metabolic rate ($CMRO_2$). Alternatively, volatile anaesthesia is perfectly acceptable, provided MAC is limited to ≤1 (up to 1.5 MAC sevoflurane) to avoid excessive cerebral vasodilatation. Nitrous oxide increases $CMRO_2$, worsens the cerebral vasodilatation caused by inhalation agents, and is not recommended for use in patients with raised ICP.

For patients undergoing short procedures with normal ICP and a functioning shunt, a secured intracranial aneurysm or an implantable stimulator device, a supraglottic airway device, and spontaneous ventilation is well tolerated.

Postoperative care

Assuming uneventful surgery and anaesthesia, standard recovery procedures and postoperative care, with the addition of neurological observations, are sufficient until the patient is considered safe to transfer from the recovery/post-anaesthetic care unit to the ward.

High dependency or intensive care admission should be guided by the surgical insult [e.g. oesophagectomy in a patient with a deep brain stimulator (DBS)] or by any neurological deterioration or unexpected new symptoms or signs. Admission to either area due to a neurological cause warrants urgent investigation, often imaging based, and referral to the neurosurgical centre for advice that should not be delayed while waiting for a bed.

When prescribing postoperative analgesia, the anaesthetist should consider how best to reduce the need for high-dose opiates that could sedate the patient and mask neurological deterioration, or suppress ventilatory drive and cough. Regional anaesthetic techniques, including neuraxial blocks, are not necessarily contraindicated in those with neurosurgical pathology and practical guidance is available.[2] As with any regional technique, local guidance relating to anti-platelet therapy should be followed.

Anti-neuropathic adjuvant analgesics may also be considered (while remaining aware of their sedative side-effects), including pregabalin, gabapentin, clonidine, and ketamine. Neuroanaesthetists are increasingly administering ketamine, despite the historical contraindication to its use in the neurosurgical population. Its use remains controversial, but there is emerging evidence that it may be neuroprotective[7] and it can be used safely in adults.

Specific anaesthetic considerations

Cerebrospinal fluid diversion devices (shunts) and incidental surgery

Congenital hydrocephalus, acquired hydrocephalus, non-communicating hydrocephalus, and chronic raised ICP may be managed long term by placement of a shunt to divert CSF from

the third ventricle via a one-way valve into the patient's peritoneum (ventriculoperitoneal, VP, shunt), right atrium (ventriculoatrial, VA, shunt), or pleura. Occasionally, a patient may present with a lumboperitoneal shunt. When patients with shunts present for incidental surgery, concerns include the risks of:

- Laparoscopic surgery and intracranial transmission of CO_2.
- Shunt infection with potential retrograde infective meningioencephalitis or ventriculitis.
- Shunt failure with recurrent hydrocephalus.

Despite these concerns, a well-functioning shunt does not contraindicate pneumoperitoneum or dictate open surgery.

It has been suggested that the intra-abdominal component of a VP shunt be clamped before carbon dioxide insufflation in laparoscopic surgery, and displaced away from the surgical field to prevent pneumocephalus and iatrogenic shunt damage, respectively.[8] The one-way valve, however, is designed to withstand pressures below 300 mm Hg and clamping is not required.[9]

It has been reported that while pneumoperitoneum >15 mm Hg may cause a slight transient increase in ICP, the increase is of little clinical significance, whereas clamping the shunt may be more detrimental in terms of ICP increase and has the potential to cause damage to the device.[10]

We advocate avoiding shunt manipulation unless experienced at doing so.

For elective cases, prophylactic antibiotics should be according to local hospital policy. Uncomplicated emergency cases with localized infection from appendicitis can sometimes be managed in the district general hospital after discussion with the neurosurgical centre, but the patient should be observed after operation and shunt contamination or occlusion considered early in the differential diagnosis in the face of neurological deterioration. Emergency cases with presumed widespread intra-abdominal infection should be discussed with and (most often) transferred to the neurosurgical centre to allow externalization of the shunt and treatment of the abdominal pathology.

There remain, however, a number of issues the anaesthetist should be aware of listed in Table 1.

While rare, specific complications have been reported.

- The presence of a ventriculo-peritoneal shunt increased conversion from laparoscopic to open surgery due to intra-abdominal adhesions, but shunt infection rate appeared unaltered by intra-abdominal surgery.[11]
- Positive pressure ventilation was observed to cause ventriculo-pleural shunt obstruction.[12]
- Shunt placement affected premorbid functional status, for example, onset of pulmonary hypertension after VA shunt insertion.[13]

Intracranial vascular stents and anti-platelet therapy

Interventional neuroradiology is a rapidly expanding field that offers complex combined treatments to patients with neurovascular pathology. Patients who have undergone intervention

Table 1 Preoperative considerations for the anaesthetist according to the type of shunt present

Type of shunt	Considerations in preoperative assessment
All	1. Preoperative GCS and documentation of any focal neurological deficit, including pupil size/reactivity, to allow postoperative comparison 2. Careful consideration of access point for invasive lines, most shunts are tunnelled behind an ear and along the posterior border of the sternocleidomastoid muscle. Both sides of the neck should be assessed, as remnants of previous shunts may remain *in situ*
Ventriculo-peritoneal	1. Signs of intra-abdominal infection should trigger a discussion with the neurosurgical team about the management of potential shunt infection 2. Multiple shunt revisions may result in intra-abdominal adhesions, and resultant prolonged/difficult surgery 3. Close neurological observation after operation is essential
Ventriculo-atrial (distal catheter tip placed in the mid to lower right atrium via the internal jugular vein)	1. May drain high volumes of CSF, so a blocked shunt may cause a more rapid hydrocephalus than that seen with other shunts—this is less of a problem with new-generation shunts 2. Look for signs of pulmonary hypertension 3. Internal jugular and subclavian lines are inadvisable—consider alternatives, the shunt enters the right atrium
Ventriculo-pleural (distal catheter tip placed in the third/fourth intercostal space via a mini thoracotomy or mini thoracostomy)	1. Look for pleural effusion on the side of the shunt that may be large—seek advice before draining the effusion, and consider transferring to the neurosurgical centre as the shunt may need to be externalized 2. IPPV may cause shunt blockage, a slow to rouse patient should alert the anaesthetist to this possibility 3. Lung atelectasis and postoperative lower respiratory tract infection should be avoided. The patient will need excellent respiratory excursion, and may benefit from postoperative physiotherapy
Lumbar-peritoneal	1. Risk of lumbar meningitis 2. An acute increase in lumbar spinal canal pressure may compromise spinal cord perfusion pressure, hypotension must be avoided 3. Consider patient position to avoid excessive kinking or pressure on the tunnelled portion of the shunt. It is situated between the skin and transversus abdominus muscle, and is often palpable below the skin. Particular care should be taken when using lateral supporting bolsters to ensure they do not cause pressure on the tunnelled portion of the shunt

Table 2 Intracranial stent location, and the consequences and management of stent occlusion

Type of stent	Consequence of occlusion	Likely neurology when occluded	Emergency management
Venous stent	Raised intracranial pressure due to reduced venous drainage	Postural headache (worse lying down), nausea and vomiting, visual disturbance, decreased LOC, coma	Refer for consideration of thrombectomy or intrastent thrombolysis; consider glycoprotein IIb/IIIa Ensure free drainage of the contralateral side to the stent
Carotid stent	Ischaemic stroke	Ipsilateral hemisphere CVA, with contralateral hemiplegia	Raise AP to allow perfusion via circle of Willis Refer for consideration of thrombectomy or thrombolysis
Posterior cerebral artery stent		Posterior cerebral artery syndrome: contralateral hemianopia; cortical blindness; chorea; hemiballismus; contralateral hemiplegia; thalamic pain; occulomotor nerve palsy	Refer for consideration of thrombectomy or thrombolysis
Middle cerebral artery stent		Middle cerebral artery syndrome: contralateral hemiparesis or hemiplegia; contralateral ataxia; aphasia (if dominant hemisphere); contralateral hemianopia	
Anterior cerebral artery stent		Anterior cerebral artery syndrome: contralateral pelvic or lower limb hemiplegia or hemiparesis; apraxia; anosmia	

without stent insertion can be anaesthetized without further concern.

For patients with intracranial stents, it is important to determine why and when it was inserted, anatomical location, and the potential consequences of stent occlusion (Table 2). Stents in vessels forming part of the circle of Willis will often have been placed to facilitate coiling of a wide-necked aneurysm (Fig. 2); the consequences of stent occlusion will depend upon overall patency of the circle of Willis.

Patients with intracranial stents will be commenced on anti-platelet therapy to prevent intra-stent thrombosis, the duration of which is variable, and should be checked with the interventional radiologist responsible. As with coronary artery bare metal stents, the risk of thrombosis decreases over time, as the lumen becomes endothelialized. Most of the ischaemic events, associated with interruption of anti-platelet therapy, occur within 6 months of the endovascular treatment.[14]

Typically, dual-agent therapy (aspirin+clopidogrel) is continued for 6 weeks, after which clopidogrel is stopped. Patients with jugular venous stents will continue on life-long aspirin therapy. If emergency surgery is deemed necessary, yet the patient presents in the first 6 weeks, bridging of anti-platelet therapy with perioperative infusion of the glycoprotein IIb/IIIa inhibitor, eptifibatide, is an option.[15]

The newer direct factor Xa inhibitors such as rivaroxiban are not currently used, and evidence is lacking on their duration of anti-coagulant effect when stopped; the general consensus is that they should be regarded as presenting a similar bleeding risk as clopidogrel, and need to be bridged if discontinued. In the event of a patient requiring emergency surgery while taking rivaroxiban for prevention of intra-cranial stent thrombosis, expert haematological advice should be sought.

Long-term dual anti-platelet therapy is unlikely to be necessary, as drug-eluting stents are not used.

Anaesthetic implications of neurostimulator devices

A multitude of non-cardiac implantable electrical devices (IEDs) are now available and the odds of patients with such devices presenting for surgery are increasing. Specific to the neurosurgical patient, devices include:

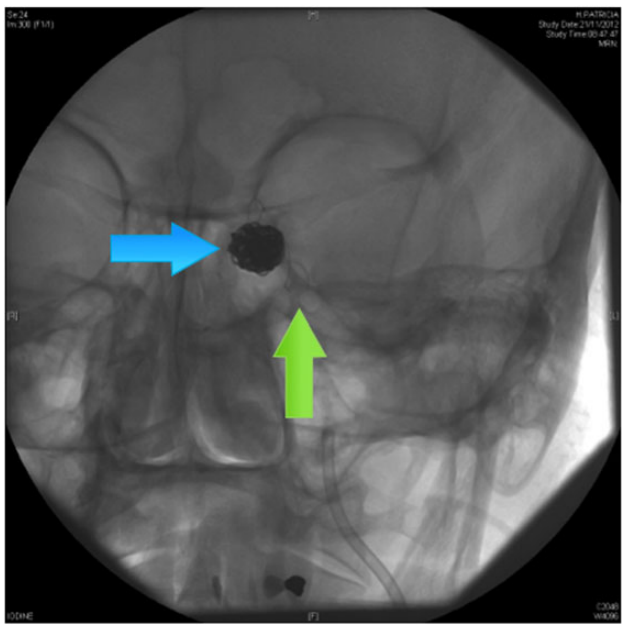

Fig 2 Radiological image taken after successful coiling and stenting of an arterial intracranial aneurysm. The blue arrow points to the coils; the green arrow points to the intracranial arterial stent.

- Vagal nerve stimulators: inserted to control refractory epilepsy. The mechanism of action is poorly understood, but stimulation of the cervical vagus nerve is believed to modulate cerebral neuronal excitability via the limbic system, noradrenergic neurotransmitter systems, or generalized brainstem arousal systems.[16] Similar to a cardiac pacemaker, the device consists of a stimulation generator placed subcutaneously below the left clavicle and connected to a left vagal nerve electrode implanted in the neck.

- Deep brain stimulators: an implanted pacemaker sited to stimulate deep brain structures such as the thalamus, globus pallidus, and subthalamic nuclei. They are used to manage Parkinson's disease and other movement disorders, depression, obsessive–compulsive disorder, chronic pain, and epilepsy. The device sits in the same position as a cardiac pacemaker (Fig. 3); there may be a second device on the right. The leads exit the chest towards the neck.
- Spinal cord stimulators: indicated for failed back surgery syndrome, complex regional pain syndromes, peripheral vascular disease, and refractory angina. Electrodes are placed percutaneously or via surgical laminectomy to stimulate the spinal cord at levels appropriate for the targeted pain (C4–T1 for upper limb pain; C6–T2 for angina; T9–L1 for lower limb pain). Temporary electrodes are usually placed first and stimulated externally. Patients may, therefore, present for incidental surgery with external or internal stimulator wires. Neuraxial anaesthesia is not contraindicated, provided the site for spinal/epidural needle insertion is remote from the spinal cord stimulator. Any epidural catheter should be inserted with caution to ensure it is not within the vicinity of the stimulator electrode. An operative note or radiological confirmation of the site of the spinal cord stimulator should, therefore, be obtained before proceeding with epidural catheter placement (Fig. 4).
- Intrathecal baclofen pump devices: have a box sited in the subcutaneous tissue of the abdominal wall allowing easy access for drug delivery and programming. A catheter connecting the device to the lumbar intrathecal sac is tunnelled under the skin, in much the same way as a lumbar peritoneal shunt. Sudden malfunction can result in acute baclofen withdrawal, a medical emergency.

Clear guidelines exist for the perioperative management of patients with implanted cardiac devices, whereas no such guidance is currently available for neurosurgical stimulators. Safety concerns focus on the potential interaction with or damage to the devices by electrocautery, external cardiac defibrillation, peripheral nerve stimulation, magnetic resonance imaging (MRI), and neuraxial anaesthesia. Perioperative management should be guided by an understanding of the anaesthetic implications of the underlying disease for which the electrical device has been placed. Preoperative assessment of the following will enable the anaesthetist to plan for device problems or failure:[17]

- type and location of non-cardiac IED,
- date of implantation and last check,
- current status of IED in terms of symptom control,
- programmability of the device,
- severity of symptoms when the device is turned off,
- current medications.

The WHO preoperative checklist should include discussion regarding the nature, implications, and potential complications of the IED and how to proceed in the event of emergency cardiac defibrillation.

Diathermy and implanted electronic devices

Manufacturer's guidelines should be followed regarding the intraoperative use of diathermy (e.g. http://professional.medtronic.com/pt/neuro/dbs-md/ind/product-advisories/WCM_PROD083579#.Ul0sCRajPdk). Electrocautery is not absolutely contraindicated, although there are risks of nerve, tissue, or device damage if used. Case reports of thermal lesioning of brain tissue and death linked to the use of diathermy have been published.[18] Electrocautery should be avoided or limited to bipolar. If monopolar diathermy is required, the earth plate should be placed as far from the IED and the stimulator leads as possible. Wherever possible, consult with the device technician before and after surgery.

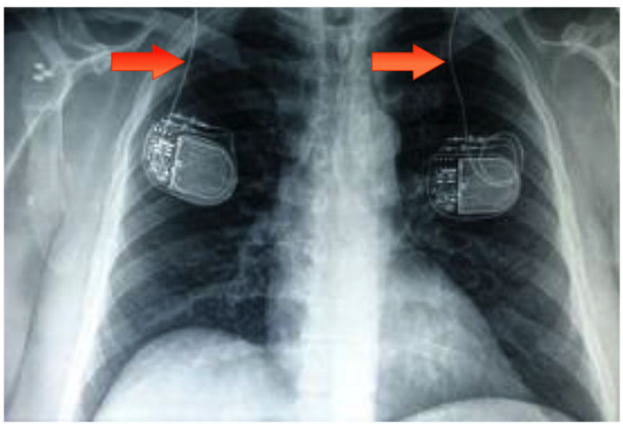

Fig 3 CXR showing bilateral implanted electrical devices, note the cephalad lead direction. The combination of this type of picture on CXR and an absence of pacing spikes on an ECG can help the anaesthetist determine the nature of the implantable electronic device.

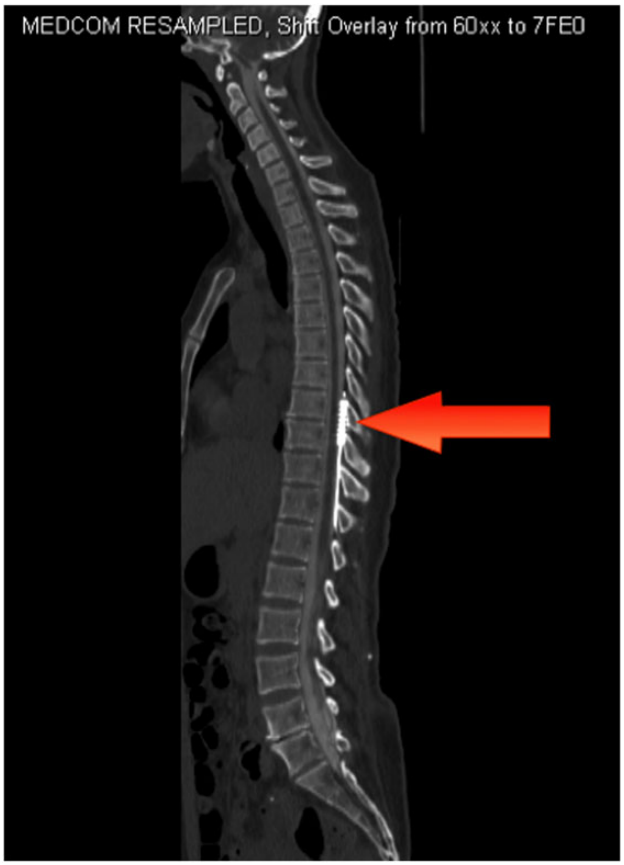

Fig 4 Sagittal reconstruction of the thoracic spine showing the thoracic spinal cord stimulator (T8/9 red arrow) and its leads extending to the inferior border of T11.

Nerve stimulators and implanted electronic devices

Nerve localization using peripheral nerve stimulators may interfere with IEDs. Insufficient case reports exist to quantify the risks, although they are likely to be low, especially if stimulation currents, pulse duration, and frequency are minimized. This complication is avoided entirely when ultrasound-guided block techniques are used.

Cardiac arrest, defibrillation, and implanted electronic devices

Literature to guide the use of external cardioversion with non-cardiac IEDs is absent. In the event of cardiorespiratory arrest or life-threatening dysrhythmia necessitating DC cardioversion, one must proceed with the expectation that the quantity of electrical energy discharged will damage the IED. The defibrillator electrodes should be positioned perpendicular to and as far away as possible from the device; use the lowest electrical energy possible (preferably delivered by a biphasic defibrillator) for the clinical scenario and subsequently reassess the patient and IED function if a shock is delivered, and there is return of spontaneous circulation.

MRI and implanted electronic devices

Theoretically, MRI may induce electrical currents and tissue heating or disrupt IED function. There have been case reports of functional impairment of deep brain stimulators after MRI and it is suggested that individual cases are discussed with the treating clinician, the MRI radiologist, and the device technician.[17]

Of note, electroconvulsive therapy (ECT) is considered safe, but the recommendation is to place the ECT electrodes as far away from the DBS wires as possible to reduce electrical current induction, and to turn the device off before ECT. Phaecoemulsification is considered safe, with no interference with the device reported.[19]

Summary

Neurosurgical patients may be encountered outside of a specialist neurosurgical centre in a wide range of scenarios. With an absence of well-established guidelines for the management of these patients, the general anaesthetist might face uncertainty. These patients may be managed safely in the non-specialist centre by the application of basic principles combined with knowledge of neurosurgical interventions outlined in this article.

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Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Substance abuse in anaesthetists

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Key points

- Raising awareness and improving education about addiction have not resulted in a decrease in mortality or relapse rates.
- The literature tends to highlight the opioid-dependent trainee, but all grades of anaesthetists abuse these drugs.
- Substance dependence is recognized as a disease not a crime and should be treated as such.
- Postponing intervention until evidence of substance abuse is obtained 'beyond reasonable doubt' increases the risk of a tragic outcome.
- Each anaesthetic department should nominate a consultant responsible for member's welfare.

Approximately 10–14% of all doctors will become substance-dependent over their lifetime; the incidence in anaesthetists being 2.7 times greater than other physician groups.[1,2] Including alcohol, studies describe 0.86–2% of anaesthetic trainees and 1.3% of consultants being addicted; if alcohol is excluded, drug addiction occurs in 1.6% of trainees and 1% of non-training grades.[1,3,4] Sixty-two per cent of residency programme directors in the USA reported at least one trainee with a substance abuse problem and a worrying progressive increase in incidence was noted, being highest over the 10 yr since 2003.[3,4]

Anaesthetists are over-represented at treatment centres in the USA with 2.5 times greater attendances compared with other physician groups.[2] Conversely at the Practitioners Health Programme (PHP) in London, anaesthetists appear to be under-represented, possibly meaning anaesthetists are either not coming forward for help or they are being managed elsewhere, as it is unlikely that the incidence is appreciably lower in the UK (C. Gerada, Medical Director, The Practitioner Health Programme, London, personal communications and unpublished data).

Definitions

Substance abuse has been defined as 'the repeated, excessive or inappropriate use of a mood altering substance resulting in negative consequences[†] in one or more life areas, and where addiction cannot be diagnosed' (M. Kaufmann, Medical Director, Ontario Medical Association Physician Health Programme, Toronto, Canada, personal communications and unpublished data).

Addiction is defined by the American Society of Addiction Medicine (ASAM) as 'a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviours. Addiction is characterized by inability to consistently abstain, impairment in behavioural control, craving, diminished recognition of significant problems with one's behaviours and inter-personal relationships and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. . .' (ASAM, 2011 reproduced with permission).

Risk factors

Whether there is such an entity as an addictive personality is debateable, but the single biggest risk factor is a family history of drug or alcohol dependence. Onset involves the interaction of developmental and environmental factors in addition to inherited and other genetic factors, which determine the severity of substance abuse and its subsequent course—a mixture of nature and nurture (Table 1).

[†]Negative consequences include domestic, social, financial, and legal problems.

A common misconception is that anxiety, depression, or both are the cause of substance use. They may well be a contributory factor, as is job-related stress, but more often than not they are the result of chronic substance abuse, especially where alcohol is involved. In the majority of cases, mood problems resolve with abstinence and so tend not to be treated immediately. Those who do have a co-morbid diagnosis need close psychiatric support.

It is possible to become physically dependent on a drug and suffer withdrawal if it is stopped abruptly, but not be addicted by definition, unless the hallmark signs of craving, loss of control, and compulsion are present.

Patterns of substance abuse

Among trainees, the main drugs abused are:[3,4]

(i) i.v. opioids (fentanyl in 64%),
(ii) alcohol (35%),
(iii) marijuana (14%),
(iv) cocaine (12%),
(v) hypnotics (midazolam in 12%),
(vi) oral opioids (10–14%),
(vii) anaesthetic agents [propofol 5–8%; inhalation agents (including nitrous oxide) 2–3%].

Fifteen per cent used drugs before commencing anaesthetic training, 22% abused more than one drug,[4] and 18% died or nearly died without family or work colleagues being aware of there being a substance abuse problem.[1]

Fentanyl and its derivatives are responsible for up to 20% of admissions to specialist physician treatment programmes in the USA (P. Earley, Earley Consultancy, Georgia Professionals Health Program, Atlanta, GA, USA, personal communications and unpublished data). The onset of tolerance and addiction are rapid, as more risks are taken to divert increasing amounts for personal use, so raising the likelihood of being discovered. Fentanyl abuse appears to occur in a younger age group than alcohol problems, as it is usually detected much earlier in the course of events (the median time to abuse being discovered is 4 months),[4] compared with alcohol abuse which may take many years before detection (Fig. 1). Doses of up to 500 μg (10 ml) of fentanyl per day are common, but over 50 ml has been reported. Despite various methods to tighten control over opioids,[1,4] the incidence would not appear to be decreasing,[4] as addicts become very resourceful—fentanyl can even be extracted from transdermal patches using a microwave oven. Many substance abusers report prior use of minor opioids, in particular codeine, but on trying fentanyl, never turn back. After long-term intake, opioid tablets can exhibit the same classic opioid withdrawal seen with fentanyl, so should not be dismissed as 'milder cases' of addiction.

Propofol—first use to detection is also usually within 4 months. Craving and compulsion can be particularly intense, resulting in some users inserting an indwelling i.v. cannula for increasingly frequent top-ups. Intoxication commonly results in minor trauma and road accidents; withdrawal signs include anxiety and diaphoresis. Propofol users are often 'polyaddicts', predominantly female, and have frequently have a history of early life trauma, depression (in the family and self), and a high frequency of relatives with substance dependence.[6] Propofol abuse is associated with a high mortality (28–45%).[5,7] Acquisition for personal use is relatively easy, since unlike major opioids, the use of propofol is not tightly monitored in the UK or in Australia.

Inhalation agents when abused are also associated with a high mortality (26%), with 22% of anaesthetic departments surveyed in the USA identifying at least one case.[8]

Whereas alcohol remains the first choice of drug when all doctors are considered, 2015 figures from Australia[7] represent a considerable change from previous patterns seen among anaesthetists. Propofol was implicated in a remarkable 41% of substance abuse cases, with 32% using major opioids and 27% alcohol.[7]

Table 1 Risk factors for the development of substance abuse disorders

Risk factors for developing substance dependence
In general
1. Parental history of alcohol or drug abuse (even when adopted at birth)
2. Childhood abuse—physical, emotional, or sexual
3. Dysfunctional family/lack warmth and support
4. Having another mental health disorder
5. Being male[4]
6. Experimenting with drugs/alcohol at young age
7. Peers who use drugs
8. Tendency for doctors to self-medicate
9. Sense of professional immunity from addiction
Additional risk factors specific to anaesthetists
1. Direct contact with drugs (we are the only doctors to give drugs directly, rather than by proxy via a prescription)[5]
2. Daily exposure to highly potent and addictive opiates and sedatives—drugs most other doctors do not encounter[5]
3. Drugs are immediately available
4. Only a small volumes are required, so easy to remove (divert)
5. Drug abuse as a student may encourage trainees to enter the speciality hoping for easy drug access
6. Sensitization to fentanyl and propofol by aerosol contamination in the theatre atmosphere have been proposed and discussed[5,6] (but in the author's opinion also, is unlikely at the nanomolar concentrations described)

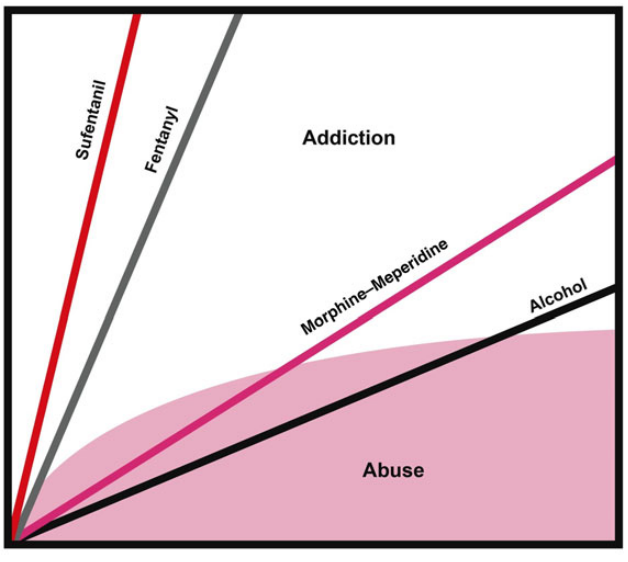

Fig 1 The relative addictive potential of several drugs. The intent is to display the concept visually; therefore, no numerical values are given. Alcohol dependence typically requires years to become apparent, whereas addiction to sufentanil occurs almost instantaneously. The rate of onset of addiction is directly related to the potency of the drug abused. Reproduced and Adapted with permission from WP Arnold III, Millers Anesthesia 6th Edn. 2005; 3167.

Interestingly, intoxication and witnessed use were more common modes of presentation than the usual behavioural signs. This could be demonstrative of the profound craving and compulsion described with propofol and fentanyl driving the addict to be less risk averse and use the drugs in situations where they are more likely to be caught out. Over half these cases were consultants; Skipper and colleagues'[2] study of consultants found opioids to be the drug of choice in 55%—both reminders that opioid abuse is not a problem exclusive to trainees.

Signs of substance use

Although behavioural changes are the most frequent indicator addicts usually continue to maintain a professional demeanour and function at a surprisingly high level[9] but when physical and behavioural changes do become noticeable, the disease process is often well advanced. Any suspicions must therefore be treated seriously and acted upon at the earliest opportunity. When the substances abused are anaesthetic drugs, an addict will ensure they are always at work in the theatre environment to maintain their supply. Conversely, an alcoholic will try to stay away from work as much as possible.

Signs and symptoms of substance abuse may include:

1. Decreased performance, unreliability, disorganization, unexplained absenteeism.
2. Lateness (although will often arrive in the workplace very early, to draw up drugs for cases unsupervised).
3. Requesting extra shifts (especially weekends), working late, favouring long lists to maximize drug access.
4. Preference for working alone.
5. Offering to prepare drugs for day lists before going home after a night shift.
6. Offering to draw up drugs for cases in other areas of the hospital.
7. Willingness to attend calls (often fictitious) out of main theatre environment (excuse to prepare drugs).
8. Offering to cover colleagues for breaks.
9. Frequent requests for toilet or refreshment breaks (with a change in mood or pin-point pupils on return).
10. Nasal rubbing/itching or drowsiness after drug 'top ups'
11. Nasal discharge, yawning, tears, pallor, sweating, piloerection, feeling cold if withdrawing from drugs.
12. Suspicious or protective behaviour around locker or briefcase.
13. Dropping or breaking an already empty drug ampoule to get a full replacement.
14. Poor anaesthetic record keeping—particularly altered or (deliberately) illegible entries.
15. Using anaesthetic techniques without narcotics, falsifying charts, and diverting drugs for own use.
16. Recurrent minor physical and facial injuries (commonly associated with propofol abuse).[6]
17. Difficulty finding the person when on call.
18. Frequent appearances in the hospital when not on call or on leave.
19. Patients regularly in pain postoperatively (out of proportion to documented doses of opioids allegedly administered).
20. Insistence on administering analgesia personally in the recovery room.
21. Incidences of questionable judgement, frequent clinical mistakes, and serious incidents.
22. Not joining in departmental activities or social events with colleagues.
23. Frequent gastrointestinal complaints (commonly associated with opioid withdrawal).
24. Weight loss, pallor.
25. Poor sleep, anxiety, depression.
26. Frequent vague, unexplained, or complex illnesses.
27. Chaotic career path often with many locum posts and working below qualification level as the addict will move on when suspicions are aroused.
28. Favouring covered arms and feet to conceal injection sites.

The family and relationships suffer too, and outside work there may be:

(i) sexual, marital, and financial problems,
(ii) drink-driving convictions,
(iii) decreased involvement in family activities and commitments,
(iv) dependent children developing behavioural problems,
(v) frequent arguments—life revolves around the partner's addiction; family walk round 'on egg-shells' due to unpredictable moods,
(vi) social isolation and loss of friends,
(vii) cessation of hobbies and other interests.

Intervention

This is the process of explaining to a doctor that concerns have been raised about their behaviour, presenting them with any evidence of substance abuse and formulating a plan of action. Usually, by this time, a doctor no longer feels good after taking the drug—rather it has become necessary to maintain their usage just to be able to function and prevent unpleasant withdrawal symptoms. The inevitable lying, stealing, and violation of their normal moral code cause considerable shame and guilt. You will usually have in front of you a fearful colleague whose home and social life have already disintegrated. Being a doctor is often the glue that still holds these individuals together and now that their professional status is also at risk, not admitting to a problem is quite common initially on a purely protective basis, even if they are well aware of their difficulties. Alternatively, they may of course be in complete denial as part of their addiction and be incapable of perceiving their predicament. Often the doctor's repeated absences and strange behaviour may make it difficult to appear sympathetic, but a non-judgemental approach can result in a more productive intervention.

Sometimes, the doctor is actually relieved to have their addiction exposed. This group is usually compliant with suggestions for treatment options and tend to have a better outcome. Inpatient management at a treatment centre is advisable for i.v. opioid addiction. The best approach are those based on the 12-step recovery method, the foundation of the Alcoholics Anonymous (AA) recovery programme, and endorsed by the specialist physician addiction treatment centres in the USA and by the London PHP.

An angry response is more difficult and often happens with those in denial. These doctors should be offered the option of an assessment either with the employer's occupational health service or a substance abuse treatment centre (usually free of charge in the UK), and the opportunity to 'prove' they do not have a problem by consenting to hair or urine testing. If there is considerable evidence of drug abuse but non-compliance with suggestions, in the interest of patient safety, the regulatory authorities (the GMC in the UK) must be contacted and the doctor may be suspended from working. Sometimes, it is helpful to

stress that addiction is recognized as a disease for which there is treatment.

These meetings should not be conducted on a 1:1 basis, and never be 'corridor conversations'. Trainees should report suspicions to their College Tutor, Educational Supervisor, or other designated consultant mentor. Consultants and other non-training grades should speak to the Clinical Director, who should arrange to meet with the doctor equipped with names and phone numbers (see details below) of suitable contacts and have already been in touch with the occupational health department and/or a psychiatrist with expertise in addiction problems, who should also attend. The Australia and New Zealand College of Anaesthetists has recently recommended that there should be a consultant who is nominated as the Welfare Officer in each department, who may also be pivotal in the management of these cases.[10]

Always be aware that the sick doctor's memory and comprehension of what has been said may not be 100% and it is important to end the meeting with a recap of what has been discussed. Finally, there is a real risk of self-harm after intervention and no doctors should be allowed to go 'home alone' after this initial meeting exposing the addict's problems. Before the meeting, in the UK, a member of the British Doctors and Dentists Group (BDDG) or Sick Doctors Trust (SDT) may be contacted for support. The doctor should see their GP or go into treatment as soon as possible, especially if drug or alcohol withdrawal is a risk.

The role of medical regulators

The following comments regarding the role of regulators in dealing with doctors with substance abuse issues relate to the situation in the UK where the General Medical Council is the statutory body who regulate the medical profession.

If patient harm has occurred, the GMC must be contacted and the doctor excluded from the workplace. If there is evidence of drug abuse but non-compliance by the doctor during the intervention, GMC referral is also advised. Even if no patient harm has occurred, in the interests of patient safety, employers will usually exclude the doctor from the workplace until investigations are complete and a diagnosis confirmed. Some employers then make a decision about referral to the GMC at a later date or advise the doctor to self-refer. As a reminder, the GMC's publication *Good Medical Practice* (2013) states that 'If you have concerns that a colleague may not be fit to practise and may be putting patients at risk, you must ask for advice from a colleague, your defence body or us. If you are still concerned you must report this, in line with our guidance and your workplace policy, and make a record of the steps you have taken'.[11]

Sometimes, when contacted for advice, or after self-referral, if all the conditions usually imposed on the registration of addicted doctors (e.g. attendance at peer support groups below) are being addressed, the GMC may suggest continuing to manage the problem at a local level with the support of the occupational health service and an addiction psychiatrist. Suspension of registration is not necessarily the rule, although it is often the case with all but the occasional relatively straightforward alcohol problem.

The GMC is particularly interested that the doctor displays insight into their problems and is willing to participate in remedial action. After referral or the first statutory hearing, if these prerequisites can be demonstrated, the GMC's sanctions may be a little more benevolent. The sanctions for doctors with substance abuse problems would appear to be rather varied. Suspension of registration for opioid addiction can be for 2 yr (but recently, the author has seen two cases back at work within a year). Some opioid-addicted doctors find the regular hair testing (paid for by the GMC) is a helpful deterrent.

The doctor is allocated two, sometimes three, psychiatrists (who may or may not be addiction specialists) and a case supervisor, all of whom submit reports before review GMC hearings. A doctor is permitted to take someone along as moral support to hearings (the BMA Doctors for Doctors Unit has recently been providing this at no cost to members). When suspended from clinical practice, most doctors cease their defence body subscriptions, but membership at the time of onset of the investigative process enables provision of legal representation at the GMC hearings.

Worthy of mention here is that the GMC regard the theft of drugs as a concomitant of addiction and when in recovery, the doctor is deemed to be honest again. This was highlighted at the Shipman Inquiry.[12] If no patient harm has occurred, addiction is investigated as a health rather than conduct issue, even if a doctor has taken drugs from the workplace. Unfortunately, many employers still insist on reporting the doctor to the police for theft, and pursue the disciplinary route, which causes much added distress with court appearances and future difficulties with visa applications and working overseas.

Doctors who are recreational drug users and have been prosecuted by the police for possession are automatically reported to the GMC.

Relapse

A relapse is the return to substance use after a period of abstinence. It signifies that the individual still has a need for something to alleviate distress, usually because some important personal issues have not yet been addressed. For an opioid addict, abstinence must mean no alcohol either, which can be a pit-fall for many. The median time to relapse is 2.6 yr with a mortality of 13%,[4] 85% using the original drug of choice.[13] There is no place for minimizing the importance of a relapse by calling it 'a bit of a slip' and caution should be exercised in cases of poly-addiction that a doctor is using substances not included in their hair testing or not their main original drug of abuse. Examples of these 'cross-addictions' and behaviours are gambling, sex, excessive spending, and food. Compulsive behaviour around these activities can cause as much damage for the doctor's domestic and professional life as the original substance abuse.

Hair testing is preferable for opioid and propofol detection to verify the addict remains abstinent. It is more difficult to falsify than urine (which can be bought 'clean' or as reconstitutable powder on the Internet).

Reports of sustained abstinence by doctors in general are good—between 74% and 90%.[9] In a literature review, Earley[14] discusses some rather dismal earlier figures for anaesthetists. Skipper and colleagues'[2] study, however, which excluded trainees, found anaesthetists had fewer positive chemical tests, no more relapses, and stayed in employment to the same degree as other doctors—76% remained working in anaesthesia. These good outcomes were attributed to them being in a nationally recognized recovery programme and being rigorously monitored.

In Bryson's[3] study, 73.3% of trainees remained in anaesthesia, with a 29% relapse rate and 3% mortality. Warner and colleagues[4] also reported a 29% relapse rate, but higher mortality of 13%. Domino's study of all medical specialities found a slightly higher relapse rate in those returning to anaesthesia.[13]

The predictors for a relapse/negative outcome are:[13,14]

- positive family history,
- co-morbid psychiatric disorder,
- i.v. opioid use,
- history of previous relapse.

Back to work?

Addicts do not 'grow out of' drug dependence neither is the time spent in treatment a cure. Recovery is an ongoing process and not a nicely compartmentalized event and often requires major life changes. Whether substance abusing anaesthetists should continue in anaesthesia has provoked several recent articles which give an excellent overview of the debate.[3,5,9,14]

At the Talbott Recovery Campus in Atlanta (which has extensive experience treating anaesthetists), several consultants formed an anaesthesia study group, publishing the Medical Personnel Addiction Recovery Inventory (MPARI) tool,[14] and building on the Angres Criteria (1998), which are used by many State Health Programmes in the USA to stratify the likelihood of returning to anaesthetic practice (D. Angres, Medical Director, Positive Sobriety Institute, Chicago, IL, USA, personal communication).

Angres criteria

Category I—Certain return to anaesthesia immediately after treatment:

- Tremendous love for/commitment to anaesthesia
- Accepts and understands the disease
- Bonding with AA (or narcotics anonymous) and has a sponsor
- Strong family support
- Committed to recovery
- Balanced lifestyle
- No evidence of dual diagnosis, for example, bipolar disorder
- Treatment team, anaesthetic department, and employer support return

Category II—Possible return to anaesthesia (after some time away):

- Relapsed with recovery underway
- Dysfunctional but improving family situation
- Involved, but not bonded with AA/NA
- Improving recovery skills
- Some denial remains
- Mood swings without other psychiatric diagnosis

Category III—Redirect into another speciality:

- Prolonged i.v. use
- Prior treatment failure and relapses
- Disease clearly remains active
- Went into anaesthesia for drug access
- Dysfunctional family
- Non-compliant with regulatory bodies
- Poor recovery skills and no bonding with AA/NA, no sponsor
- Severe co-morbid psychiatric diagnosis

(Reproduced and adapted with permission, D. Angres).

These criteria are a guide only as there is no 'one size fits all' and each case should be judged individually. Simulation sessions as a prelude to recommencing clinical practice have been found to be very useful. Return to work should be gradual, with time allowed for GMC and other appointments; finishing work in time to attend AA if required is helpful. One difficulty has been finding departments willing to offer placements for trainees who have been dismissed from their original Deanery.

The high mortality from both drug use and suicide remains a difficult problem. Hopefully, as awareness, education, and case management improve, those in the throes of addiction who so often see no future ahead may begin to see some hope and ultimately more anaesthetists can return to work and lead productive and contented lives once again.

Contact details of UK drug dependency support organizations for doctors

Practitioner health programme (PHP)

http://www.php.nhs.uk/
A confidential NHS funded service open to doctors and dentists living in the London area (although the service does provide telephone advice only for those outside of London).

Sick Doctors Trust (SDT)

www.sick-doctors-trust.co.uk
An independent charity, providing a 24 h helpline manned by doctors who are in recovery from addiction themselves. It provides support to doctors who think they may have a problem with their use of alcohol or other drugs. The helpline also accepts calls from family and colleagues.

The British Doctors and Dentists Group (BDDG)

www.bddg.org; http://www.bddg-london.org/
A UK-wide network of 18 groups of doctors and dentists in recovery from addiction. Callers can be put in touch with another doctor near to their home (in some cases, an anaesthetist) who may then introduce them to their local group. Doctors under GMC sanctions are often required to attend these groups as conditions of their continued registration.

Declaration of interest

The author is a Trustee with the charity, the Sick Doctors Trust.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Dexmedetomidine: its use in intensive care medicine and anaesthesia

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Key points

- Dexmedetomidine provides a unique quality of conscious sedation which resembles natural sleep.
- Its administration does not result in respiratory depression.
- It is licensed for intensive care sedation in the UK.
- Its use as a perioperative sedative is growing.
- The use of dexmedetomidine as a sole agent for general anaesthesia in specific circumstances has been reported.

Dexmedetomidine is a relatively new drug to the UK having been launched in October 2011 with marketing authorization for sedation of adult intensive care unit (ICU) patients only. Despite this, its unique pharmacological profile has led to its unlicensed use in a number of areas of anaesthetic and critical care practice where evidence for its efficacy is mounting.

Drug actions

Dexmedetomidine is the S-enantiomer of the veterinary sedative medetomidine. It is a highly selective α_2-adrenoceptor agonist demonstrating an α_2:α_1 selectivity ratio of 1620:1. This makes it eight times more selective for the α_2-adrenoceptor than clonidine.

Sedation and anxiolysis

These properties are mediated via agonism of α_2-adrenoceptors primarily in the locus coeruleus of the pons where it results in dose-dependent inhibition of norepinephrine release. It is postulated that this results in disinhibition of the ventrolateral preoptic nucleus which then releases inhibitory neurotransmitters. This pathway is part of the complex circuitry governing natural sleep, resulting in a quality of sedation with dexmedetomidine which more closely resembles normal physiological sleep than the more familiar GABA-ergic sedatives (propofol and the benzodiazepines). This sedation is characterized by preserved muscle tone and ventilation, by spontaneous and evoked movements, and by awakening by external stimuli. Once roused, patients are cooperative and can typically obey simple instructions. Once the external stimulus is discontinued, patients resume the previous level of sedation. Electroencephalogram studies have further confirmed that the sedative effects of dexmedetomidine mimic stage 2 non-rapid eye movement sleep.[1]

Analgesia

It is likely that dexmedetomidine exerts effects at various sites in the pain pathway, but its main site of action is at the level of the spinal cord where stimulation of α_2-receptors in the substantia gelatinosa of the dorsal horn reduces the release of nociceptive neurotransmitters such as substance P.

Effects on organ systems

The cardiovascular effects of the drug are biphasic (Fig. 1). At higher rates of infusion, such as during administration of a loading dose, the predominant effect is hypertension due to activation of α_{2B} receptors on vascular smooth muscle. This is superseded by hypotension and bradycardia as a result of the centrally mediated inhibition of sympathetic outflow. Case reports of bradycardia leading to asystole after loading dose administration of the drug in conjunction with multiple other

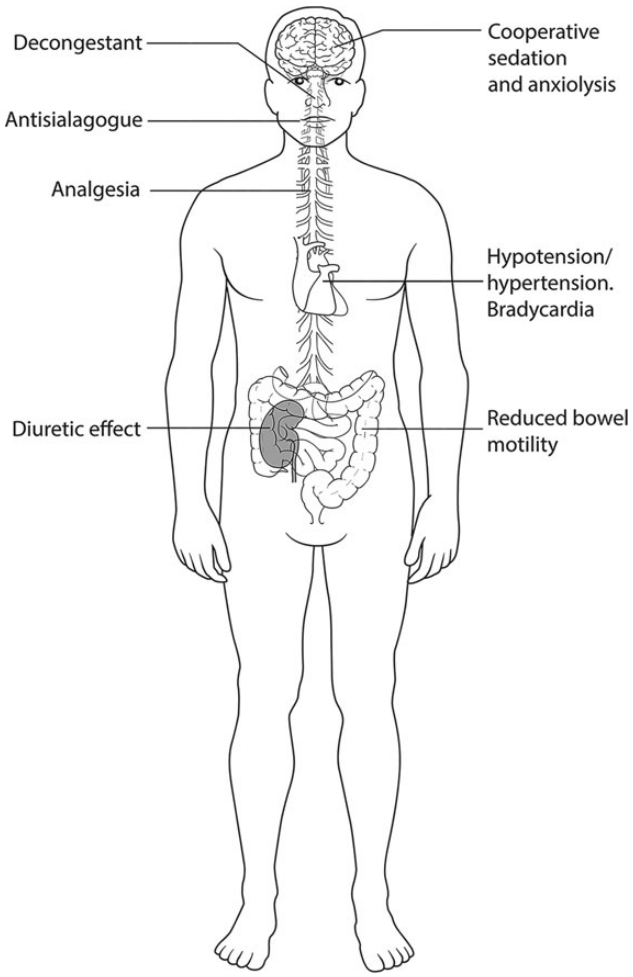

Fig 1 Effects of dexmedetomidine on organ systems.

anaesthetic agents can be found in the literature.[2] Cardiovascular adverse effects associated with dexmedetomidine may be expected to be more pronounced in hypovolaemic patients, in those with diabetes mellitus or chronic hypertension, in the elderly and in those with high vagal tone.

A defining feature of the sedative action of dexmedetomidine is its minimal effect on ventilation, even when given in doses 10 times the maximum recommended.[3] In addition, MRI studies have shown that the airway remains patent during dexmedetomidine sedation.

Owing to actions on peripheral α_2-adrenoecptors, dexmedetomidine also has decongestant and antisialagogue effects. It may theoretically reduce bowel motility, although to our knowledge, there have been no reports of associated complications. Dexmedetomidine suppresses shivering, possibly due to agonism of α_{2B}-receptors in the hypothalamus. It exerts a diuretic effect by inhibiting the action of ADH at the collecting duct.

Despite its imidazole structure, dexmedetomidine has not been found to cause any clinically significant adrenal suppression.

Pharmacokinetics

Administration is possible via multiple routes, with a bioavailability of 16% when given orally, 65% nasally, and 82% buccally. It is 94% protein bound with the unbound drug freely crossing the blood–brain barrier to exert its central effects, with a distribution half-life of 6 min. It undergoes glucuronidation, hydroxylation, and N-methylation in the liver to inactive metabolites which are then renally excreted. Hepatic impairment therefore should prompt a dose reduction due to decreased protein binding and metabolism, while renal impairment and renal replacement therapy requires no dose adjustment. It has a terminal elimination half-life of ~2 h with clearance estimated at 39 litre h^{-1}. Its steady-state volume of distribution (118 litres) is increased in patients with low plasma albumin concentration, prolonging the terminal half-life and context-sensitive half-time in such patients.[4]

Pharmaceutical information

Dexdor®, the formulation of dexmedetomidine marketed in the UK by Orion Pharma (UK) Limited, is presented as a clear, colourless solution containing 100 μg ml^{-1} concentrate. It is available in ampoules of 2 ml and vials of 2, 4, and 10 ml. It is diluted before administration to a concentration of 4 μg ml^{-1} using glucose 5% or sodium chloride 0.9% and can be administered centrally or peripherally.

Contraindications

Uncontrolled hypotension and second- or third-degree heart block (unless a pacemaker is fitted) may potentially be worsened by administration of dexmedetomidine. The presence of 'acute cerebrovascular conditions' is also considered a contraindication as research in animals has shown a decrease in cerebral blood flow with dexmedetomidine. However, human studies have demonstrated a maintenance of flow-metabolism coupling with decreased rate of metabolic consumption in the brain matching the decreased cerebral blood flow.[5]

Sedation in the ICU

Dexmedetomidine is indicated for patients requiring a sedation level not deeper than arousal in response to verbal stimulation [corresponding to Richmond Agitation-Sedation Scale[6] (RASS) 0 to −3; Table 1]. It is not suitable for patients requiring deep sedation.

Two phase III multicentre, randomized, double-blind trials[7] compared dexmedetomidine for the sedation of intubated patients with the established sedatives, propofol (PRODEX) and midazolam (MIDEX). Dexmedetomidine was found to be as effective as propofol and midazolam in maintaining the target level of light to moderate sedation. The median duration of mechanical ventilation was significantly shorter with dexmedetomidine than with midazolam, but not when compared with propofol. No difference in ICU length of stay, hospital length of stay, or mortality was seen with 45 day follow-up.

In keeping with its unique mechanism of action, patients receiving dexmedetomidine were found to be more rousable, more cooperative, and better able to communicate their pain than those receiving the other sedatives. There was, however, more hypotension and bradycardia with dexmedetomidine when compared with midazolam, although with no increase in the rate of drug discontinuation due to adverse effects. The rates of hypotension and bradycardia with dexmedetomidine and propofol were comparable. Drug discontinuation due to lack of efficacy was higher with dexmedetomidine and the authors state that with the current maximum dose, lack of efficacy can be expected in ~1 in every 8 to 10 patients.[7]

Table 1 The Richmond Agitation-Sedation Scale.[6] Dexmedetomidine is indicated for patients requiring sedation levels corresponding to levels 0 to −3 as shaded

Points	Classification	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behaviour towards staff
+2	Agitated	Frequent non-purposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained (>10 s) awakening, with eye contact, to voice
−2	Light sedation	Briefly (<10 s) awakens with eye contact to voice
−3	Moderate sedation	Any movement (but no eye contact) to voice
−4	Deep sedation	No response to voice, but any movement to physical stimulation
−5	Unrousable	No response to voice or physical stimulation

A recent Cochrane review[8] supported the finding of reduced duration of mechanical ventilation with dexmedetomidine sedation, and also found a reduced ICU length of stay.

Potential indications

While non-inferiority to established sedatives for the licensed indication is proven, most UK ICUs currently reserve this drug for clinical situations in which they feel dexmedetomidine will provide additional benefits. This is in-keeping with the Intensive Care Society's position that 'the [sedative] agents chosen should be individualized to the patient's requirements, characteristics and the clinical situation'.[9] While robust large trial evidence for these indications is not available, clinical experience of the use of dexmedetomidine with an application of its specific pharmacological properties suggest the following indications.

As a bridge to extubation

Dexmedetomidine does not cause respiratory depression or airway compromise. Patients sedated with it are more cooperative, communicative, and better able to follow commands than with other agents. It also depresses the gag reflex and improves tracheal tolerance when compared with other sedatives.[9] This therapeutic profile makes it suitable for continuing infusion through the period of extubation in patients who deteriorate once sedatives are discontinued (e.g. the agitated patient), allowing for a smooth and non-combative extubation. Conversion of failed to successful extubation with the introduction of dexmedetomidine has been demonstrated in small trials.

While remifentanil, as an ultra-short-acting opioid, is also sometimes used as a bridge to extubation, dexmedetomidine sedation can be continued post-extubation with less potential for respiratory depression or airway obstruction.

As an alternative sedative

Where propofol sedation is contraindicated (e.g. due to hypertriglyceridaemia) but in whom the delayed extubation associated with midazolam would be potentially detrimental.

Where the clinician feels an α_2-agonist would be beneficial

Where the clinician feels an α_2-agonist would be beneficial (e.g. sedation or drug withdrawal) but in whom clonidine is not efficacious. The improved specificity of dexmedetomidine for the α_2-receptor makes it a more effective sedative than clonidine.

Patients at particular risk of critical care delirium

SEDCOM,[10] a phase IV trial comparing dexmedetomidine and midazolam for light sedation, found a reduction in the prevalence and duration of delirium in the dexmedetomidine group (and again found a significantly shorter time to extubation in this group). This reduction in delirium confirms findings from previous trials (although not a universal finding)[8] and has led to guidance from the Society of Critical Care Medicine[11] recommending dexmedetomine be used for sedation of patients with delirium not related to benzodiazepine or alcohol withdrawal in preference to benzodiazepines.

Where sedation is required to tolerate non-invasive ventilation in the ICU

Lack of respiratory depression and provision of 'rousable sedation' might make it particularly suitable for such patients. Small trial evidence of its efficacy in this situation is available.

There is early interest in a possible benefit of dexmedetomidine sedation in patients with sepsis via attenuation of immunosuppression.

Barriers to use on ICU, including pharmacoeconomic analysis

The frequency of the use of dexmedetomidine is anecdotally much lower than the other sedatives, with many units reserving it for the above clinical situations where it may be specifically indicated. This is likely to be due to a combination of factors. First, dexmedetomidine provides a novel, 'conscious sedation', unlike that of the other sedatives, with which critical care staff may be less familiar. In addition, the acquisition costs of the drug are higher than other agents—dexmedetomidine sedation of a 70 kg patient at the dose range of 0.2–1.4 μg kg^{-1} h^{-1} for 24 h would cost £26–184. This compares with sedation of a 70 kg patient with propofol at the dose range of 0.3–4 mg kg^{-1} h^{-1}, which would have an up-front drug cost of £10–130 (costs and dose ranges as listed in the British National Formulary, March 2015). However, on the basis of the marketing company's cost-minimization analysis exploring costs associated with drug preparation, management of adverse events, co-prescribed medicines, and reduced costs associated with earlier extubation, the Scottish Medicines Consortium considers the economic case for the use of dexmedetomidine to be demonstrated.[12]

Drug administration

The dexmedetomidine infusion is begun at an infusion rate of 0.7 μg kg^{-1} h^{-1} and is then adjusted according to response within the dose range 0.2–1.4 μg kg^{-1} h^{-1}. In contrast to its use in anaesthesia, it is recommended that no loading dose is given when used for sedation in the ICU. After dose adjustment, a new steady-

state sedation level may not be reached for up to 1 h. Many ICUs have protocols in place to allow nurses to bolus sedation when indicated, but it is important to note that dexmedetomidine should not be administered in this way. There is no published experience with infusions lasting >14 days.

A discontinuation syndrome manifest as rebound agitation, hypertension, and tachycardia is recognized after prolonged clonidine infusion and has occasionally been reported with dexmedetomidine.[5] When stopping the drug, patients should be monitored for symptoms and if apparent should prompt a more gradual dose reduction.

Dexmedetomidine in anaesthetic practice

Although unlicensed for use other than for intensive care sedation in the UK, in the USA, dexmedetomidine is approved for sedation of non-intubated patients before and/or during surgical and other procedures.

The recommended dosing regimens when using dexmedetomidine for periprocedural sedation in the USA are described below.

A loading infusion of 1 μg kg^{-1} over 10 min

A reduced loading infusion of 0.5 μg kg^{-1} over 10 min is recommended for patients over 65 years of age and when less invasive procedures are to be undertaken (e.g. ophthalmic).

A maintenance infusion

This is generally initiated at 0.6 μg kg^{-1} h^{-1} and titrated to the desired clinical effect between doses of 0.2 and 1.0 μg kg^{-1} h^{-1}. Maintenance infusion at 0.7 μg kg^{-1} h^{-1} is advised when performing awake fibreoptic intubation until the tracheal tube is secured.

A reduction in the loading and maintenance dose are recommended when administering the drug to patients with hepatic impairment. Dexmedetomidine enhances the pharmacodynamic effects of other sedatives, anaesthetics, hypnotics, and opioids and concomitant use therefore should also prompt a dose reduction. Similarly, if a patient is being converted to dexmedetomidine from another sedative, a loading dose may not be necessary.

Perioperative use

Sedative premedication

Its anxiolytic, sedative, sympatholytic, and antisialagogue properties, along with a lack of respiratory depression make dexmedetomidine suitable for premedication. The drug also acts as an anaesthetic-sparing agent and obtunds the pressor response to intubation. Its versatility in route of administration is an advantage in paediatric premedication where intranasal administration of 1 μg kg^{-1} dexmedetomidine was shown to be as effective a sedative as midazolam 0.5 mg kg^{-1} orally, with modest haemodynamic effects.[13]

Anaesthetic and opioid-sparing agent

Dexmedetomidine decreases anaesthetic requirements and is opioid sparing. These properties are particularly useful in certain patient populations where the respiratory-depressant properties of opioids may be particularly detrimental, such as in bariatric surgery.

Sympatholysis

A Cochrane review in 2009[14] examined the theoretical benefits of α-agonists in obtunding the perioperative stress-induced increase in sympathetic activity, and thereby reducing cardiac complications of surgery. The authors found that perioperative α_2-agonists reduced mortality and myocardial ischaemia, with the greatest benefit seen in patients undergoing vascular surgery. There was, however, an increase in perioperative hypotension and bradycardia with drug administration. Overall, the data available to the authors were insufficient to make firm conclusions about the safety and efficacy of perioperative α_2-agonists and further studies were called for.

Continuous infusion of dexmedetomidine throughout the extubation period has been used for emergence smoothing. The drug also offers effective prevention and treatment of emergence phenomena.

Postoperative analgesia

Postoperative dexmedetomidine infusions have been used to supplement other forms of analgesia in patients in whom opioid-induced respiratory depression would be potentially deleterious. A small randomized controlled trial of thoracic surgical patients found less supplemental epidural opioid was needed in the group who also received an i.v. dexmedetomidine infusion.

Neuroanaesthesia

Dexmedetomidine is routinely used in our centre for neurosurgical procedures requiring intraoperative patient cooperation, that is, awake craniotomy for supratentorial tumour resection or deep brain stimulator implantation. It does not suppress epileptiform activity in patients undergoing electrocorticography and so is useful in epilepsy surgery.

Dexmedetomidine administration has no effect on intracranial pressure. Although there were initial concerns that it may reduce cerebral blood flow leading to ischaemia, multiple studies have demonstrated a matched reduction in cerebral blood flow and cerebral metabolic rate.[5] It does not affect somatosensory-evoked potentials or motor-evoked potentials and so may be a useful anaesthetic-sparing agent and analgesic supplement in scoliosis surgery.

Experimental studies show dexmedetomidine has neuroprotective effects in hypoxic–ischaemic and traumatic brain injury models. This neuroprotection appears to be afforded by the action of the drug on α_{2A}-receptors and at imidazoline receptors. The clinical relevance of these findings is yet to be fully evaluated.

Sedation for invasive procedures

Awake fibreoptic intubation

A recently published Cochrane review[15] examined the use of dexmedetomidine for awake fibreoptic intubation. Owing to the heterogeneity of the available studies, they were unable to conduct a full meta-analysis. The review considered four randomized controlled trials examining dexmedetomidine given by bolus followed by infusion with controls of midazolam, fentanyl, propofol, and normal saline. They concluded that dexmedetomidine significantly reduced the participants discomfort with awake fibreoptic intubation compared with control groups. No significant differences were seen between the treatment and control groups in terms of airway obstruction, hypoxia, or cardiovascular adverse events. However, the authors note that these conclusions are based on weak evidence and they await the report of ongoing trials.

Many small randomized controlled trials have reported benefits when using dexmedetomidine for sedation for invasive procedures compared with standard techniques. Procedures investigated include radiological and gastrointestinal endoscopic procedures, awake carotid endarterectomy, shockwave lithotripsy, and dental procedures.

Sedation for non-invasive procedures in challenging patients

The pharmacotherapeutic properties of dexmedetomidine have led to its use for paediatric and adult sedation for radiological investigations. It is of particular use in patients in whom the respiratory-depressant effects of other sedatives should be minimized, for example, those with obstructive sleep apnoea or an anterior mediastinal mass.

Regional anaesthesia adjuncts

A limited number of studies have shown a prolongation of regional nerve block when dexmedetomidine was added to the local anaesthetic. Clonidine remains popular as an adjunct to local anaesthetic for caudal epidural in children. The use of dexmedetomidine has been described as efficacious in providing prolonged neuraxial analgesia, although its superiority to clonidine for this indication has not been proven.

General anaesthesia single-agent case reports

There have been case reports of the use of dexmedetomidine as a sole agent for general anaesthesia. These patients required doses of 5–10 μg kg^{-1} h^{-1} (5 to 10 times the maximum recommended for procedural sedation) to be adequately anaesthetized. The authors chose this technique in two of the cases due to the nature of the surgery; laser ablation of a tracheal stenosis, and a tracheal debridement with stenting and bronchopulmonary lavage. Dexmedetomidine allowed preservation of respiratory drive with easy maintenance of a patent airway (one patient required a chin lift). There was no haemodynamic compromise in this small group of patients.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

Podcasts

This article has an associated podcast which can be accessed at http://www.oxfordjournals.org/podcasts/ceaccp_16.07.01.mp3.

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Anaesthetic implications of performance-enhancing drugs

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Key points

- Performance-enhancing drug use has hidden problems beyond the visible enhancements.
- Always ask about associated drug and supplement use, and needle sharing.
- Clearly document discussion of risks associated with performance-enhancing drug use and anaesthesia.
- Be non-judgemental when conducting your thorough history.
- Caution must also be exercised when prescribing drugs for athletes with regard to banned substances. A list of banned and accepted substances can be found at the World Anti-doping Agency website www.usada.org/substances/prohibited-list.

Society is changing. In parallel to a worryingly obese population is a contra population increasingly pre-occupied with obtaining the perfect physique.

Performance-enhancing drug (PED) use is classically associated with elite performance level athletes. However, PED use is increasingly crossing over into the amateur arena (Fig. 1).

'Goldman's dilemma' was posed to elite athletes by physician and author of 'Death in the Locker Room', Robert Goldman. He asked athletes whether they would take a drug that would guarantee them overwhelming success in sport but would cause them to die after five years. He found that approximately half of the athletes stated that they would take the drug.

It is estimated that up to 40% of regular gym goers abuse anabolic steroids. In the USA, there are an estimated 3 million anabolic-androgenic users of whom 60% are non-competitive recreational bodybuilders or non-athletes, who primarily use these drugs for cosmetic purposes.[1] These figures are likely to be a gross underestimation. In our own anaesthetic practice, we have noticed a significant increase in the number of patients admitting to the use of these drugs. These patients are generally considered fit ASA I and II patients. However, the effect of using PEDs may run more than skin deep. PED misuse is not unique to adults and steroid abuse prevalence has also been reported in teenagers. The aim of this article is to provide an overview of common PEDs and potential implications of their use in anaesthesia.

Building mass, strength of muscle and/or bones

Steroids, peptide and protein hormones, β-agonists

Anabolic steroids

Anabolic steroids are derived from cholesterol and are available commercially in i.v. and oral preparations. They are popular with sprinters, weight lifters, and body builders. They are similar in structure to the male sex hormone testosterone, and therefore, they enhance male reproductive and secondary sex characteristics. As a result, patients may develop acne, feminization, virilisation, and in men normal sex function is altered, resulting in impotence, infertility, and gynaecomastia. In women, they may cause male characteristics to develop. Anabolic steroids increase muscle mass and strength by encouraging new muscle and cell growth, allowing athletes to train harder and longer. However, anabolic steroids also adversely affect the cardiovascular system

Fig 1 Why athletes take performance-enhancing drugs.

and liver. Relevant cardiovascular changes include secondary polycythaemia, hypertension, cardiomyopathy, left ventricular hypertrophy, and cardiac muscle fibrosis. There is an increased risk of myocardial infarction and cerebrovascular events. Patients may be prone to dependence and behavioural outbursts, known as 'roid rage'.[2]

Anaesthetic considerations. Preoperative assessment should start with identification of potential anabolic steroid abusers, such as those with excessive muscle mass or a thick neck. Patients may not volunteer the information freely. Ask about cycling of steroids and associated drug use, either recreational or to counteract some of the side-effects caused by steroid use (Table 1). Steroids may be injected and a history of needle sharing should alert you to the possibility of blood-borne viral infections. Special attention should be paid to the airway, neck thickness, and the size of the tongue. Patients need to be informed of the risks associated with PED use and anaesthesia. This discussion should be clearly documented in the notes.

Investigations should include routine blood tests, in particular looking for electrolyte imbalances, abnormal liver function, and polycythaemia from steroid and associated drug use. Symptomatic side-effects of steroid misuse will also need to be actively sought such as obstructive sleep apnoea by using the STOP-bang questionnaire and patients will need an ECG (±echocardiogram) to look for left ventricular hypertrophy and hypertensive disease, arrhythmias, or previous cardiac damage.

Induction: Steroid users often have over-developed deltoids and neck muscles, which may impinge neck movement and lead to difficulties during bag-mask ventilation and intubation. Extra muscle mass will lead to a high rate of oxygen consumption and patients may desaturate much quicker than expected. The shear weight of their muscle may reduce thoracic compliance and therefore make ventilation difficult. Have a low threshold for intubating these patients.

Maintenance: These patients may have increased oxygen and anaesthetic agent requirements. Some patients may also be resistant to non-depolarizing neuromuscular blocking agents thought to be due to an increase in nicotinic receptors. There may be a physiological bradycardia and a prophylactic anticholinergic, such as glycopyrrolate, may be useful to keep at hand. Renal clearance may also be affected by excessive muscle mass, hence affecting drug metabolism.

Extubation: These patients are physically strong and at risk of psychotic episodes, especially on emergence. A bite block is advised and if these patients go into laryngospasm negative pressure pulmonary oedema is a potential risk. It is important to wake them gently and slowly. Clonidine may be used to 'take the edge off' emergence.[3]

Postoperative: There is a case report of a patient who had become so dependent on anabolic steroid use that after major surgery for an aortic valve repair, he was un-extubatable and remained intubated for 21 days until anabolic steroid supplementation was restarted.[4] Analgesic requirements can be variable in

Table 1 Anabolic steroid cycling regimes.[2,3] Artificial LH analogues (LHA), for example, tamoxifen, antagonize oestrogen receptors and increase testosterone levels. During a steroid cycle, LHA reduce water retention in muscle and prevent gynaecomastia. In between cycles, LHA encourage testosterone levels to increase to their baseline quicker. Preservation of baseline testosterone is important in maintaining muscle mass, as steroid cessation can inhibit testosterone production by 50%

Steroid dosing regimes			
Cycling	4–12 weeks	Complete abstinence from steroid use between cycles	Minimizes side-effects
Stacking	4–12 weeks	Use of more than one steroid per cycle (with complete abstinence between cycles)	Avoids tolerance
Pyramiding	4–12 weeks escalating dose	Cycling starts with normal therapeutic dose and increase in increments 100 up to 1000 times	The dose is slowly reduced towards the end of a cycle to avoid withdrawal

these patients. Theories suggest that either training can increase the threshold to pain, hence low analgesic requirements, or alternatively the high levels of circulating endorphins released during exercise increase tolerance to painkillers, resulting in high analgesic requirements. These patients are prone to polycythaemia and its associated risks and will need to be prescribed appropriate venous thromboembolism (VTE) prophylaxis.

Practicalities: Choose an appropriately sized arterial pressure cuff. Consider extra protection of pressure points, deep venous thrombosis prophylaxis, and the implications of manual handling of these patients. Be aware that patients with significant muscle mass may have a large potassium release after deflation of limb tourniquets and may require treatment with insulin dextrose, calcium, and fluids. If tourniquet times are >2 h, monitor for ECG changes and perform an arterial blood gas to look for hyperkalaemia.

Peptide hormones: human chorionic gonadatrophin and luteinizing hormone

These are often used in conjunction with anabolic steroids to either enhance the muscle building properties or to counteract the side-effects caused by high levels of oestrogen. Human chorionic gonadatrophin is a naturally occurring hormone produced by the fetus stimulating the development of both male and female sex steroids. When used in combination with anabolic steroids, it increases testosterone and hence muscle growth in men. It also prevents loss of testicular volume seen with solitary steroid use. It does not enhance muscle development and is not a banned substance in women, especially as they may have naturally high levels when competing while pregnant. Luteinizing hormone (LH) is a peptide hormone secreted by the pituitary gland. It is important in maintaining normal levels of testosterone in men and oestrogen in women. It is used by weight lifters as an anti-aromatization therapy. Artificial LH analogues such as tamoxifen antagonize oestrogen receptors and increase testosterone levels. They are generally well tolerated by users with few implications for anaesthesia.

Protein hormones: human growth hormone, insulin-like growth factor, and insulin

Human growth hormone (HGH) is naturally produced by the pituitary and is important for growth and development in adolescence. It stimulates protein synthesis (increased muscle mass), bone growth (increased bone strength), and reduces body fat by activating adipose tissue breakdown. HGH is a popular PED as it is difficult to detect. Insulin-like growth factor (IGF-1) (somatomedin-C) also stimulates protein and bone synthesis. Insulin is important in the metabolism of carbohydrates, fat, and protein and can be used in combination with anabolic steroids or HGH to promote muscle mass by further stimulating protein synthesis. Artificially elevated levels of all of these hormones are detrimental to health. HGH is associated with acromegaly, enlargement of the kidneys, liver, and tongue, myopathies, hypothyroidism, cardiac disease, arthritis, diabetes mellitus, impotence, and osteoporosis. IGF-1 has a similar side-effect profile to HGH, with the additional risk of high-dose insulin causing hypoglycaemia, which may even progress to coma and death.[5]

Anaesthetic considerations. In addition to those for anabolic steroids, these patients may have the added complications associated with acromegaly. Thyroid function tests and blood glucose should be checked preoperatively and blood glucose be monitored intraoperatively.

β_2-Agonists: terbutaline, salbutamol, and clenbuterol

β_2-Agonists are well-known therapeutic agents used primarily for their bronchodilating effect. Some β_2-agonists such as clenbuterol and fenoterol have additional anabolic effects thought to be mediated via β_2-receptors, although the exact mechanism is unclear. There is some evidence that long-term high-dose oral salbutamol can also improve muscle strength and endurance performance.[6] Owing to these perceived benefits, abuse is common and all β_2-agonists are banned by the World Anti-Doping Agency with the exception of inhaled salbutamol and salmeterol when used for therapeutic purposes.

Anaesthetic considerations. Side-effects of β_2-agonists are well documented and include tachyarrhythmias, prolonged QT, hypokalaemia, and lactic acidosis. Toxicity is usually associated with acute ingestion and should be treated with appropriate i.v. fluids, β-blockers, potassium supplementation, and bicarbonate before induction of anaesthesia.[7] The long-term consequences of abuse are unknown.

Stimulants

Amphetamines, caffeine, and cocaine

Amphetamines

Amphetamines are sympathomimetic amines. They were first synthesized in 1887, but become popular in WWII when they were used to delay fatigue and increase alertness in troops. They are used by many athletes in competition and also by gymnasts, wrestlers, and ballet dancers to suppress appetite and reduce weight gain. Amphetamines cause the release of excitatory neurotransmitters such as dopamine, resulting in central nervous system (CNS) stimulation, resistance of fatigue, increased

alertness, enhanced speed, power and aggression, reaction times, endurance, and concentration. They are also associated with a sense of euphoria. Short-term use can be associated with hypertension, vomiting, abdominal pain, angina, cerebral haemorrhage and death, distorted perception of pain and fatigue, and can lead to injury. Long-term use is associated with facial dyskinesias, confusion, paranoia, insomnia, dependence, and cross-tolerance.

Anaesthetic considerations. Preoperative: Chronic and acute users need to be considered separately and a detailed history must therefore be sought.

Intraoperative: Acute use is associated with increased anaesthetic requirements and has been implicated in intraoperative intracranial hypertension. In contrast, chronic users require significantly less anaesthetic, thought to be due to CNS catecholamine depletion. A case of cardiac arrest has been reported in literature believed to be due to the inability of the patient to mount a pressor response after an increase in venous capacitance on induction. Long-term amphetamine abuse will also lead to cross-tolerance of other sympathomimetic agents resulting in refractory hypotension while under general anaesthesia. Therefore, consider a titrated induction, arterial line, and directing acting vasopressors, such as phenylephrine and epinephrine. Patients are at risk of developing serotonin syndrome (SS) which may be precipitated by the administration of additional drugs that increase serotonin levels. For this reason, droperidol, ondansetron, and tramadol should be avoided, and care taken with other opioids. Diagnosis of SS is clinical and includes the triad of autonomic hyperactivity, abnormalities of neuromuscular tone leading to hyperthermia and rhabdomyolysis, and in the awake patient, alteration of mental status. Treatment is largely supportive.[8]

Postoperative: There is the potential for unexpected/refractory hypotension and the delayed development of SS.

Caffeine

Caffeine is popular in endurance events, such as cycling and can shave 90 s off a 1 h time trial.[9] Caffeine helps to shorten reaction time and improve concentration. It enhances muscle contraction and increases the time to exhaustion via glycogen sparing. It causes a diuresis which may assist in masking other PED use. The doses used in sport greatly exceed routine coffee use with 12 μg ml^{-1} of caffeine taken as a positive urine sample. This is equivalent to 6–8 cups of coffee (600–800 mg). Excessive amounts of caffeine intake can cause indigestion, diarrhoea, cardiac arrhythmias, and hypertension. In combination with other stimulants, such as ephedrine, it may be fatal.

Cocaine

Cocaine is a popular recreational drug in PED using athletes. It gives a sense of euphoria and increases alertness of the user. Repeated use leads to tachyphylaxis requiring more potent fixes. As the drug wears off, depression may ensue. It can also affect coordination and cause anxiety, irritability and restlessness, cardiac arrhythmias/infarction, seizures, and cerebral haemorrhage. These patients are also at risk of developing SS.

Anaesthetic considerations. Intraoperatively, patients may become hypertensive, tachycardic, and develop arrhythmias. Management guidelines can be found at http://www.toxbase.org/Poisons-Index-A-Z/C-Products/Cocaine/.

Increased delivery of oxygen to exercising tissues

EPO, blood doping, artificial O_2 carriers

Recombinant human erythropoietin (rHuEPO)

Recombinant human erythropoietin (rHuEPO) is popular with endurance athletes, cyclists, marathon runners, and cross-country skiers. Erythropoietin (EPO) stimulates erythropoiesis in bone marrow and increases red blood cell (RBC) density, thereby augmenting oxygen-carrying capacity and increasing it by as much as 7–10%. It can be detected in the blood and urine, but is removed from the body within a short time making detection difficult. Officials can infer use by testing athletes haematocrit and by comparing it to previous results create a biological passport.

There are a number of different forms of rHuEPO: EPO-α, β, δ, ω, and ζ are the most common in clinical use. EPO Z (Zeta, Z Retacrit) was patented in Italy by the Italian Medicines Agency in September 2010. It is currently undetectable in urine. It is believed that the Chinese have also manufactured an undetectable form of erythropoietin.

Significant side-effects are the consequence of an increase in RBCs resulting in an increased Hct and blood viscosity, causing the heart to work harder and increasing the risk of a myocardial event. In the brain, hyperviscosity reduces cerebral blood flow resulting in hypoxia and potentiating the risk of a cerebrovascular event. These detrimental sequeale may be further compounded by prolonged exercise and dehydration. rHuEPO is also associated with hypertension and hyperkalaemia. Users may develop antibodies to rHuEPO and it has been associated with sudden death during sleep in a number of pro cyclists.

Anaesthetic considerations. A detailed history should identify the possible complications of use. Investigations should include a full blood count, electrolytes, and ECG. Ensure the patient remains well hydrated and has appropriate VTE prophylaxis after operation.

Blood doping

This is the practice of infusing whole blood into an athlete to increase their oxygen-carrying capacity. It has a similar affect to training at high altitude and is popular with long distance event athletes, cyclists, and marathon runners. Allogenic transfusions carry the same risks as for non-athletic patients, in particular the risk of acquired viral infections, and volume and iron overload.

Artificial O_2 carriers

These are man-made substances which aim to mimic the oxygen carrying capabilities of haemoglobin, such as perfluorocarbons (PFCs).

Relaxants

β-Blockers, cannabinoids, alcohol

Relaxants are popular with athletes who require a steady hand for competing in sports.

β-Blockers

β-blockers are popular with shooters, ski jumpers, archers, and orchestral musicians, as they act as an anti-tremor agent and anxiolytic. Side-effects are well established and include depression, bronchospasm, and sleep disturbance.

Anaesthetic considerations are the same as for prescription drugs.

Cannabinoids

Cannabinoids are compounds contained within the Marijuana plant containing tetrahydrocannabinol (THC), which has psychoactive properties. This undergoes slow elimination and may stay in tissues for weeks. Cannabinoids enhance the sedative/hypnotic effects of other CNS depressants and may result in cross-tolerance with barbiturates, opioids, benzodiazipines, and phenothiazines. Patients may have impaired lung function because of associated tobacco use. Acute use is associated with a tachycardia, vasodilatation, and postural hypotension. THC increases cardiac output by 30% and hence cardiac work and oxygen demand. There is also a theoretical risk of psychiatric and autonomic interaction with anaesthetic agents.[10]

Mask drug use

Diuretics, epitestosterone, secretion inhibitors

Diuretics

Diuretics are popular in judo, boxing and wrestling, horse racing, and rowing, as they encourage diuresis to assist with PED excretion and can also be used to assist with rapid weight loss. Significant side-effects include dehydration, hypotension, muscle cramps, and electrolyte imbalance.

Anaesthetic considerations are the same as for prescription drugs.

Epitestosterone

Epitestosterone is a naturally occurring form of testosterone that does not enhance performance. However, drug tests for testosterone measure the testosterone to epitestosterone ratio (T/E ratio). By injecting epitestosterone, an athlete can lower their T/E ratio and mask the use of testosterone. Epitestosterone alone has no significant side-effects.

Secretion inhibitors

Secretion inhibitors are clinically used to treat gout. They have a similar structure to organic acids, which are removed by transport proteins in the kidney. They block these transport proteins and prevent the appearance of drugs (PEDs) in the urine. Possible side-effects include nausea, vomiting, allergic reactions, and kidney problems.

Nutrition, supplements, protein shakes

Food supplements are viewed as legal and are used by 76–100% of athletes compared with 50% of the normal population. It is unknown whether they enhance performance. The adverse effects are also unknown. ProProtein shakes are associated with a high nitrogen load and clearance may be put under strain in patients with impaired renal function. PED use is also associated with laxative abuse, bulimia nervosa, and anorexia nervosa and their associated problems.

Up and coming stars on the sports scene

Xenon, Aicar, and GW1516, and gene doping

Xenon

This is a noble gas currently under investigation for use as a widespread anaesthetic agent. It first came to light in the 2014 Winter Olympics when it was revealed that Russian skiers were using it to increase the O_2-carrying capacity of their blood. Xenon increases the expression of transcription factor HIF1a. This, in conjunction with HIF2, regulates the cellular responses to hypoxia including increased expression of erythropoietin.[11]

Aicar and GW1516

Aicar and GW1516 both have an action via the nuclear receptor PPAR-δ which is intrinsically involved in energy uncoupling in adipose tissue and skeletal muscle. Aicar (aminoimidazole carboxamide riboside) is an agonist of the PPAR-δ-AMPkinase pathway, while GW1516 is a direct PPAR-δ agonist. GW1516 was originally developed by GlaxoSmithKline, but production was stopped in 2006, because of an increased risk of cancer in patients who were taking high doses. However, production was continued by other agencies and has been found in samples from professional cyclists in 2013. Despite being detectable in urine, it is the third highest selling product on one Internet site.

Gene doping

Gene doping utilizes gene therapy technology to manipulate DNA for the purpose of performance enhancement. Specific targets include the genes for erythropoietin, IGF-1, and vascular endothelial growth factor.[12]

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Referral and transfer of the critically ill child

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Key points

- Centralization of paediatric intensive care has led to an increase in the numbers of critically ill children being transferred between hospitals.
- Most children are transferred by a specialist transport team.
- Time-critical cases may still need to be transferred by the referring hospital and it is important that skills and equipment are maintained.
- Working with shared mental models can promote safe practice.
- Anaesthetists are an essential part of the team that stabilizes and transfers critically ill children.

Centralization of paediatric intensive care over the last 20 yr, to lead centres serving a network of referring hospitals, has led to an increase in the numbers of critically ill children being transferred between healthcare institutions in the UK. The majority of these transfers are undertaken by specialist teams, with only 7% conducted by an *ad hoc* non-specialist team.[1] Evidence of fewer critical incidents and improved outcomes after specialist transfer supports this balance of provision.[2] However, current capacity and the need for time-critical transfer mean that non-specialists should be prepared to resuscitate, stabilize, refer, and, on occasions, transfer the critically ill child.

National structure

In recent years, there have been significant changes to the systems in place to refer, transfer, and care for critically ill children. This evolution of paediatric intensive care units (PICU) in the UK dates back to 1996 when the Department of Health, in the face of evidence that centralization of services at larger centres improves patient outcome, set up a national coordinating group. The aim was to outline a strategy to develop and unify the services caring for critically ill children. They initially found an *ad hoc* service with a lack of structure, training, and staff. There were few specialist transport services and those that did exist were unit-based, bed-dependent, and often not staffed 24/7.

Paediatric intensive care services in the UK have now been centralized to 29 PICU.[1] This concentration of facilities and skills, with lead centres serving a network of referring hospitals, increases the need to transfer critically ill children between hospitals. In 2013, there were 10 726 unplanned admissions to PICU not after surgery, with 5382 admitted via another hospital and so necessitating a transfer.[1] Ninety-two per cent of transfers to a PICU were performed by a specialist transport team.[1] Meanwhile, changes to the structure of medical training and an increased role for consultant-delivered care have led to the development of regional transport teams (www.picsociety.uk). Different models have been adopted, with some PICU-based teams and some standalone off site services. There are also examples of combined teams with neonates and adults. Increasingly, however, the defining features of a regional service are the provision of a single point of telephone contact to access immediate clinical advice, call conferencing between clinicians with digital recording, and 'go at all times' transport, which is independent of PICU bed availability.

This drive towards specialist transport provision is supported by evidence that it enhances safety and quality, with reduced rates of critical incidents and a lower risk-adjusted mortality rate in PICU.[3] It has been suggested that the use of specialist transport teams might extend the reach of PIC and initiate high-quality care at the remote hospital, ameliorating the effect of any delay in reaching the tertiary centre.[3] In this way, the transport team and resources can be conceptualized as a mobile intensive care unit (ICU).

Specialist paediatric transport teams now operate to national standards, as set out by the Paediatric Intensive Care Society (PICS).[4] These state that the service should have a consultant available 24 h a day, who is not providing cover for the PICU, to advise and join the transport team if necessary. Other healthcare professionals on the team are also required to be appropriately trained in transferring critically ill children. PICS also describe standards for equipment, audit, care of parents, and outreach education.

Internationally available standards include those of the Commission on Accreditation of Medical Transport Systems (www.camts.org). Their accreditation process consists of evaluating criteria to demonstrate the quality of a transport team and the safety of the transport environment.

Despite the availability of specialist transport services, there are still times when a local hospital will need to transfer a patient using their own resources. This may be because the child has a time-critical condition and it would take longer for the transport team to get to the local hospital and transfer the patient to a PICU. The referring hospital may also be required to use their own team to transfer if the specialist service is unavailable for operational reasons. The transport team and PICU can offer help and advice, but the team and equipment will need to be provided by the referring hospital. This presents major challenges to maintain skills, equipment, and policies, particularly when these are only used occasionally.

Referring a patient

Early referral, with discussion and provision of clinical advice, is an essential component of a hub and spoke model of care. This capability has been strengthened by the regional transport service development with a single point of contact to a transport consultant providing 'medical control' and call conferencing facilities, allowing discussions with appropriate specialists in a 'virtual room'.

After early discussion and agreement of a clinical plan, the patient's critical care can often be continued in the referring hospital close to home. Thirty per cent of all calls to transport teams are for advice[5] and this is an increasingly important function of regional teams. Calls that result in activation of a transport team need to be triaged to an appropriate level of care and speed of response. For this process to be efficient and accurate, the information provided needs to be of a high quality. The use of structured referral forms by the caller and receiver is beneficial and clear guidance on the process, with supporting information and standard operating procedures, should be available online.

Stabilization and transport

Children in a referring hospital should be resuscitated and stabilized before they are transferred to a PICU. This should be started before the arrival of a specialist transport team.

The stabilization of a critically ill child may take place in a number of areas in the hospital. They may have presented to the emergency department (ED), in which case a resuscitation room with specific paediatric equipment may be available. Children may also deteriorate during their hospital admission. A ward environment provides additional challenges to acquire appropriate staff or equipment. It may be advantageous to move some of these children to the operating theatre or the general ICU for stabilization before transfer. The Advanced Life Support Group (ALSG) lists the essential equipment,[6] and it is vital that this equipment is checked and maintained appropriately.

Senior input is required during paediatric stabilization. Until the patient is handed over to the transport team, the paediatric consultant will usually lead their care. They should involve, as appropriate, the anaesthetic consultant, ED consultant, and the multi-professional team. Many anaesthetists find themselves in less familiar territory when faced with a critically ill child. Sometimes, they will not have regular children's anaesthesia lists, with only a responsibility for emergency care. In the field of anaesthetics, this has been exacerbated by a reduction in paediatric practice in district general hospitals and a concentration of this workload on colleagues with a critical mass of activity. However, the Royal College of Anaesthetists (RCoA) curriculum stipulates that as part of the award of a CCT, they should be able to 'manage the airway in children and babies' and to 'provide safe transport of critically ill children and babies'.[7] PICS states that 'all anaesthetists and intensivists with emergency or elective paediatric responsibility should have up to date knowledge of advanced paediatric life support/resuscitation and stabilisation of critically ill children'.[4]

RCoA guidance on the provision of paediatric services (2015) recommends that all anaesthetists who work with children should maintain appropriate skills.[8] This should be a matter considered in annual appraisal. This can be through local courses and attachments to tertiary centres. Managing Emergencies in Paediatric Anaesthesia for Consultants (MEPA-FC) is a national course using simulated scenarios to cover all aspects of recommended paediatric CPD for anaesthetists.

Transport-specific courses provided by the ALSG (www.alsg.org) promote the ACCEPT approach to transfers.

A—Assessment
C—Control
C—Communication
E—Evaluation
P—Preparation, packaging, and pre-departure checks
T—Transport

Having a standardized model ensures 'the right patient is taken at the right time, by the right people, to the right place by the right form of transport and receives the right care throughout'.

A 4-yr-old girl presents to a district general hospital with irritability and vomiting. Her mother tells the ED staff that she has a ventriculo-peritoneal shunt. Ten minutes after her admission to ED, her conscious level decreases from A to P on the AVPU scale. The on-call anaesthetic specialist trainee registrar is called to assess and she intubates and ventilates the child. A CT scan shows hydrocephalus and a blocked shunt is suspected. After discussion with the neurosurgical team and the regional PICU consultant, facilitated by the regional transport service, there is agreement that this a time-critical case as the girl needs emergency neurosurgery.

Assessment

The standardized approach to the assessment of a critically ill child is well documented by the ALSG and is taught as part of the APLS course.[6] The structured ABCD approach helps to minimize errors and prevent missed diagnoses.

Airway—She is intubated with a 5.0 mm oral tracheal tube which is taped securely 14 cm at the lips. A chest X-ray shows the tip of this to be at T2.
Breathing—She is ventilated with a transport ventilator, with end-tidal CO_2 monitoring currently 4.5 kPa.
Circulation—Arterial pressure 90/50 (60). Two points of peripheral IV access are secured.
Disability—She is sedated with morphine and midazolam infusions. An atracurium infusion is started. Pupils recorded pre-intubation were equal and reactive.

Assessment also includes decisions about who will be transferring the patient. Transfers of patients requiring emergency neurosurgery should usually be undertaken by the referring hospital, as this is likely to be time-efficient.

Because of the time-critical nature of the case, it is agreed that the referring hospital will undertake the transfer. This is discussed with the parents. The anaesthetic trainee has achieved higher paediatric competencies but has never transferred a child before. The anaesthetic consultant decides that they should personally accompany the patient, with the trainee attending for experience. An ED nurse with paediatric experience also joins the team. Senior cover for the hospital is maintained by calling the second on-call consultant.

Control

Leadership during the stabilization and transfer is vital to ensure safety and efficiency. Overall control may change a number of times throughout the transport process. This may initially be held by the ED consultant who may hand over care to the paediatric consultant for stabilization and then to the anaesthetic or transport consultant for the transfer. There will always be times when the care is shared, but formal handovers can reduce errors.

The paediatric and anaesthetic consultants are present in the ED. The paediatric and ED consultants have taken a shared lead in the care at this point but will formally hand over to the anaesthetic consultant before transfer.

Communication

The stabilization and transport of children involves multiple individuals working in teams across hospital sites. Poor communication is a frequent reason for systems to fail and errors to occur. Structured communication, for example, Situation, Background, Assessment, Recommendation (SBAR), is becoming commonplace and may reduce these failures.

The CT images are sent to the tertiary neurosurgical team electronically. All discussions with the specialist teams are via recorded conference calls led by the transport consultant. Handovers and details of discussions are documented in the patient's notes.

Evaluation

A final decision about the appropriateness of the transfer needs to be made by the senior team members in charge of the patient. Practical decisions must be made about how the transfer will take place, including the mode of transport. Nearly, all time-critical transfers by the referring hospital team in the UK will be by road ambulance.

All team members agree the transfer is time-critical and the referring anaesthetic consultant should lead a transfer by road ambulance.

Preparation, packaging, and pre-departure checks

Acute hospitals admitting children should ensure that they have appropriate equipment for stabilizing and transferring patients when required. Transport trolleys designed for adults are ideal when utilized with weight-specific harnesses for children. Transport devices such as the BabyPod II can be used to safely transport small babies. Vacuum mattresses can provide enhanced safety when weight-specific harnesses are not available. Collaboration on standard procedures with the paediatric team regarding babies at the interface between neonatal and paediatric care is important, as some patients may best be packaged in a transport incubator. If a specialist transport team is conducting the transfer, they will bring the necessary equipment with them and liaise with the referring team regarding stabilization procedures that can be started or completed before their arrival. Preparing infusions to an agreed protocol can save significant time, but the referring team must ensure they are accurately prescribed and labelled.

The time spent resuscitating and stabilizing the child before transfer should be balanced against the need for avoiding delay in time-critical cases.

The senior ED nurse contacts the ambulance service and requests a 'category 1' emergency transfer. The transport trolley is obtained from the general ICU. No specific paediatric restraint is available, but there is a vacuum mattress. While waiting for the ambulance to arrive, the patient is transferred to the trolley and packaged using the vacuum mattress. The ventilator, monitor, and infusion pumps are attached. Time is taken to ensure that the equipment is secured safely, has adequate battery supply, and sufficient oxygen is available. The patient is continuously reassessed during this process and she remains stable.
A hospital mobile phone is collected and it is confirmed that everyone has appropriate insurance cover for the transfer. Inter-hospital transfer documentation is started by the anaesthetic trainee.
Before leaving on the transfer, pre-departure checks are carried out. This can be compared in importance with the pre-anaesthetic brief and serves to reinforce a shared mental model, reducing the risk of critical incidents.

Transport

The transfer can be conceptualized as a period of mobile intensive care. Acceleration, deceleration, and cornering forces can have significant physiological effects on children, particularly small babies or those who are under-resuscitated. Transport

should be as smooth as possible with speed moderated appropriately. The use of lights and sirens has reduced because of the increased accident risk and the harmful physiological stress to the patient. A risk assessment should be conducted before using them, involving discussions between the driver or paramedic and the transport team as to whether their use would provide a smoother transfer. If a parent is travelling with their child, they should be briefed about the transfer process and any safety procedures.

The tertiary centre should be contacted before the patient is transferred, with a clinical update and an estimated time of arrival. This may involve calling PICU or the receiving anaesthetic consultant if the patient is going straight to theatre.

It is agreed with the paramedics that a blue-light transfer is appropriate, but a steady speed with controlled acceleration and deceleration would be preferred. The mother of the girl says she would like to travel in the ambulance, and this is agreed to. The girl is loaded into the ambulance with the anaesthetic consultant taking full control of the transfer. Documentation is completed during the transfer. The patient is handed over to the neurosurgeons and anaesthetists in the tertiary hospital.

Working with the transport team

When a specialist transport service is providing the transfer, it is important that the working interface between the referring hospital team and the transferring team is effective.

Key to the success of the process is a handover of leadership without loss of vital information and resources. Senior members of the paediatric and anaesthetic team at the referring hospital, who are responsible for the patient while in their institution, will be key in ensuring that the transport team are provided with the best possible environment to complete the stabilization and package the patient for transfer.

The connection between accurate assessment of the problems and evaluation of the transport priorities are control and communication. Providing support and expertise to the transport team while allowing them space to do their job efficiently and safely requires a good understanding of human factors. Clarification of control and leadership is particularly important if a crisis occurs and transport teams are increasingly providing crew resource management (CRM) training to assist with this.

Efficient use of resources in the context of the local and regional infrastructure is particularly important and utilizing key individuals from the referring team with appropriate knowledge and skills is vital. Early preparation of photocopied notes, drug prescription charts, and investigation results will speed up the process and will often form part of checklists on the arrival and departure of the team. Radiology images will need to be transferred electronically.

Legal framework

The transfer of patients necessitates that the care is handed over from the referring hospital team to the transport team and then from the transport team to the receiving hospital team. Recognizing that there is not a sudden change in responsibility for the patient's care, but that this shifts and is dynamic during stabilization and preparation for transfer, is central to understanding that a patient's best interests remain paramount throughout the process.

From referral to handover, the patient remains the sole responsibility of the referring hospital team (and consultant) until an adequate handover of the patient to the transport team has been completed. This should be a verbal handover and can only take place once the transport team has arrived at the patient's bedside. The referring hospital team is responsible for the ongoing care of the patient and should continue to provide the highest available levels of care and support until the transport team has arrived and taken a handover. While awaiting the arrival of the transport team, the referring hospital team may be given advice from the transport service or a third party (such as the receiving unit/other specialist clinician). However, they are responsible for providing adequate information upon which that advice is obtained and for deciding whether or not to act in accordance with that advice.

On handover at the referring hospital, the transport team will assume joint responsibility for the management of the patient with the referring hospital team consultant. The transport consultant on duty will assume ultimate responsibility for the patient when the transport team departs the referring hospital with the patient. The referring hospital consultant(s) and team cannot abdicate responsibility for the patient to the transport team at handover and the consultant(s), and other responsible staff within the referring hospital, should render to the transport team any assistance necessary to enable the safe preparation of the patient for transfer.

Legally, individuals are protected by case law relating to the Bolam test. This states that 'If a doctor reaches the standard of a responsible body of medical opinion, he is not negligent'. Therefore, as long as an anaesthetist is maintaining their CPD in line with current standards and is acting in the best interests of the child, even if that is in difficult circumstances, they will be supported.

Risk assessment

Risk assessment in transport is a dynamic process and should be focused on two key areas. First, an assessment of the patient determines their level of dependency, the risks to them associated with transport, and the mitigation including identification of accompanying staff. Secondly, there is identification of risks associated with the team and logistics including safety, health, and wellbeing.

Increasingly, patient early warning scores (EWS) are embedded in hospital practice and offer an ideal validated tool for identifying and tracking physiological challenges. The likelihood of deterioration during transfer should be assessed together with the potential for requiring additional interventions. The mode of transport will create specific risks associated with access to the patient and equipment, team familiarity with the environment, and complexity of the logistics.

Mode of transport

The majority of secondary inter-hospital transfers in the UK are undertaken by road ambulance, with data from 2008 indicating that only 2% involved air transport.[9] Until recently, the logistical challenges of organizing an air transfer, outside of Scotland where a national service exists, have been considerable. Provision of aircraft was dependent on commercial, Search and Rescue or Helicopter Emergency Medical Service aircraft availability. This situation is changing, and since 2013 The Children's Air Ambulance (www.theairambulanceservice.org.uk) has been operating with a number of specialist NHS paediatric transport teams in an attempt to improve equitable access to air transport when required.

The mode of transport choice is dependent on many factors, including:

- clinical condition,
- time,
- distance,
- weather,
- traffic,
- landing sites,
- cost.

The advantages and disadvantages of different forms of transport[10] should be carefully assessed.

The future

Given the anecdotal and research evidence[3] in support of regionalization and the potential economies of scale offered by combined or co-located services, it is likely that further change will occur. The model currently being developed in Scotland with co-located neonatal, paediatric, and adult services and integration of primary and secondary transport by ground and air is perhaps where the future lies. This is likely to be supported by the increasing prevalence of Pre-Hospital Emergency Medicine posts with a structured training programme. The drive to supra-regionalization of services in managed clinical networks with ambulance bypass protocols, as seen in cardiac and trauma, will blur the boundaries even more. Maximizing the use of expensive resources, such as HEMS, will require collaboration across specialities and healthcare boundaries.

Change to systems will occur, but anaesthetists will continue to be an essential part of the multi-professional team caring for critically ill children who require stabilizing and transferring. Focusing on the core skills required, and understanding the systems in place, is central to ensuring that care is both safe and of high quality.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Spinal cord stimulation

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Key points

- Spinal cord stimulation (SCS) is a cost-effective treatment of some common neuropathic and ischaemic pain syndromes.
- Failed back surgery syndrome is the most common indication for SCS.
- Appropriate patient selection and education is key to successful SCS.
- Different stimulation regimens (frequency, pulse width, amplitude) are used to target the relevant dorsal column fibres.
- Significant technological advances in SCS (rechargeable batteries, accelerometer technology, new lead design) may improve effectiveness.

Chronic pain conditions that fail to improve with conventional medical management (CMM) are a significant burden for the individual and society. While the initial cost of spinal cord stimulation (SCS) is considered high, both its clinical and cost-effectiveness are now well established. The position of SCS in the treatment algorithm has progressed, and for specific neuropathic and ischaemic pain conditions, there is moderate to strong evidence supporting its use.

Melzack and Wall presented the Gate Control Theory of Pain in 1965. They proposed that transmission of pain signals could be regulated at the level of the dorsal horn by inhibitory interneurones activated by A-fibres. In 1967, Shealy and colleagues[1] proposed that electrical stimulation of these A-fibres in the dorsal columns (DCs) could activate the inhibitory interneurones in the dorsal horn and influence pain transmission. A bipolar plate was placed directly over the spinal cord in cancer patients. They called it 'Dorsal Column Stimulation'. In more recent years, it has been called SCS. The early interventions were effective, but were associated with multiple complications.

The techniques have evolved to less invasive percutaneous lead insertion with multiple electrodes in the epidural space. More advanced implantable pulse generators (IPGs) and programmable systems have led to improved effectiveness and versatility. This is reflected by a steady increase in the implantation rates over the last decade in Europe and the USA.

Neuromodulation techniques are also indicated in non-painful conditions. Sacral stimulation of the S3 nerve is used to manage urinary urge incontinence and faecal incontinence. Deep brain stimulation is used for a multitude of movement and psychiatric disorders. Vagal nerve stimulation may have a role in refractory epilepsy. However, this article will address the role of SCS in the management of chronic pain conditions.

Anatomy

The DC of the spinal cord is a layered structure with the more distal, sacral fibres located more medially, and the more rostral fibres in the lateral part of the DC.[2] It transmits ascending proprioceptive and light touch sensations via the A-β fibres. These are large myelinated fibres which include the dorsal roots, dorsal root entry zone, dorsal horn, and DC.[3] An active electrode placed in the posterior epidural space preferentially depolarizes these large myelinated fibres. Knowledge of the spinal cord anatomy explains why stimulation of more rostral lateral fibres (as in axial back pain) is more challenging than stimulating caudal medial fibres (radicular leg pain). As the electrical field moves laterally, there is an increased risk of stimulating unwanted areas, like the dorsal or ventral roots, leading to adverse effects (painful sensations or muscle contractions). The target level for stimulation in failed back surgery syndrome (FBSS) after adequate lumbar surgery is generally the lower thoracic spine (T8–9). This is because the low lumbar nerve fibres enter the cord at T12 and become established in the DC at the level of T9. In the case of post-cervical surgery, the target is generally the mid-cervical (C4–5) level.

Mechanism of action

An SCS consists of a power source (IPG) connected to a lead with a cathode (negative electrode) and an anode (positive electrode). The cathode and anode create an electrical field within the biological tissue that can depolarize the target nerves. Stimulation of the DC fibres effectively reduces pain in many neuropathic and ischaemic pain syndromes. The following mechanisms of action are proposed:

(i) Inhibition of action of wide dynamic range (WDR) neurones: WDR neurones are important 'gate-keepers' in the dorsal horn during pain transmission. They may be switched off when stimulated by A-fibres in the DC.[4]
(ii) Activation of GABAergic inhibitory interneurones in the dorsal horn.
(iii) Activation of supraspinal mechanisms: Descending serotonergic neurones and locus coeruleus neurones.
(iv) Suppression of the neuroimmune response: Markers of glial and immune cell activity, up-regulated in neuropathic pain states, are down-regulated in SCS patients.[5]
(v) Suppression of efferent sympathetic fibres.
(vi) Stimulates peripheral release of vasodilatory proteins.

Stimulation patterns

The stimulation parameters are adjusted to achieve the best results. The standard variables in SCS are the frequency, pulse width, and amplitude. The pulse width is generally between 100 and 500 μs. The amplitude is usually 2–8 V. The frequency can vary depending on the stimulation regimen. The stimulation patterns vary between the different diagnostic groups with FBSS requiring higher voltages generally in the 3.0–8.0 V range while other groups would require lower amplitudes, generally in the 2.5–4.0 V range. The same applies to pulse width and frequency selection with FBSS requiring larger pulse width settings. The stimulation patterns are individualized.

Power output or amplitude from the IPG may be in the form of a constant current (CC) or constant voltage (CV). With CC, the voltage is automatically adjusted with changes in the resistance (impedance) to maintain a CC. The amplitude is given in volts (V). With CV, the voltage remains constant and as the impedance varies, the current will change. The amplitude is given in milliamps (mA).

Shorter pulse widths preferentially recruit dorsal roots, and target specific dermatomes. As the pulse width increases, the medial DC fibres are recruited preferentially, and a greater area of the DC is stimulated.

The frequency can vary depending on the stimulation regimen.

(i) Conventional or tonic stimulation: Uses frequencies of 60–100 Hz. This produces paraesthesia in the target area. This is the most common mode of stimulation, but in the last few years, two more modes have gained in popularity.
(ii) Burst stimulation: Involves five pulses in a burst (500 Hz pulse frequency in each burst) with a burst frequency of 40 Hz. Burst stimulation produces little or no paraesthesia.
(iii) High-frequency stimulation: Uses frequencies of 5–10 kHz. This pattern does not generate paraesthesia, but may produce effective pain relief.

Indications for SCS

The management of chronic neuropathic and ischaemic pain conditions is challenging. Often, these patients have attended multiple clinicians, tried a variety of pharmacological and interventional therapies with limited success, and are struggling with psychological, occupational, and social stressors. The indications for SCS are as follows.

Failed back surgery syndrome

The majority of SCSs are implanted for FBSS. This is a syndrome that is often characterized by disabling back and/or radicular limb pain after adequate spinal surgery, with nociceptive and neuropathic components, which often responds poorly to analgesic agents or reoperation. Two randomized control trials (RCTs) compared conventional SCS with either CMM or reoperation in FBSS. The primary outcome in both studies was significant pain relief defined as more than 50% reduction in reported pain scores.

The PROCESS study randomized 100 FBSS patients to either SCS+CMM or CMM alone.[6] The patients were followed up at 6, 12, and 24 months. The SCS group reported improved pain relief, quality of life, and functional outcomes when compared with the CMM group. North and colleagues[7] randomized 50 FBSS patients to either reoperation or SCS and followed them over an average of 3 yr. The patients could cross-over to the other treatment if the initial intervention failed to adequately relieve their pain. SCS was more effective than reoperation regarding pain relief, patient satisfaction, and opiate requirements. Patients in the reoperation group were more likely to cross-over to the SCS group. SCS may be an alternative to reoperation or opioid therapy in FBSS patients. It is deemed to be a cost-effective treatment option when compared with CMM (£10 480 per QALY gained) or reoperation (£9219 per QALY gained).[8]

The above trials focused on patients with predominantly radicular lower limb pain. Patients with axial back pain are a more difficult group of patients to treat with conventional SCS. Recent data suggest that high-frequency SCS, burst stimulation, or combined SCS+peripheral nerve field stimulation (PNfS) may increase the efficacy of neurostimulation in this challenging group.[9–13]

HF-SCS may be particularly effective for the management of patients who have failed conventional SCS or patients with axial back pain.[9] However, the findings of Al-Kaisy and colleagues contrast with the first double-blind placebo-controlled RCT in SCS. Perruchoud and colleagues[10] compared HF-SCS with sham in a group of patients established on conventional SCS. HF-SCS at a frequency of 5 kHz was not significantly better than sham stimulation in terms of difference to conventional stimulation, pain control, and quality of life. While these results are equivocal, preliminary reports from the SENZA-RCT US Pivotal Study (unpublished data at present) would suggest that HF-SCS has a role in the management of back and leg pain in FBSS.

Burst stimulation may be more effective than tonic stimulation in some chronic radicular pain syndromes.[11] Schu and colleagues[12] randomized patients already receiving conventional SCS to tonic 500 Hz stimulation, burst stimulation, or a sham treatment. Burst stimulation does not produce paraesthesia, and this fact facilitates a double-blind, placebo-controlled study design. Burst stimulation was significantly better than the other two treatment arms. RCTs comparing conventional and burst stimulation directly in FBSS, and in various neuropathic pain syndromes, are required.

PNfS is achieved with a subcutaneous lead placed directly into the painful area. The logic behind this is to target the traditionally difficult to treat areas such as the lumbar spine which often respond poorly to SCS or other simulation regimens. PNfS systems

are sometimes combined with a conventional SCS to create hybrid systems. Observational studies of hybrid systems indicate an additional benefit with PNfS+SCS, in particular in patients with nociceptive axial back pain refractory to SCS alone.[13] We did not identify an RCT to support the routine use of hybrid systems in FBSS.

Complex regional pain syndrome type 1

One RCT investigated the use of SCS in combination with physical therapy (SCS+PT) (n=36) *vs* physical therapy only (PT) (n=18) for the management of complex regional pain syndrome (CRPS).[14] Of the 36 patients, trial stimulation was successful in 24. After 6 months, there was a significant decrease in pain in the SCS+PT group. The pain relief was sustained at 2 yr. A 5 yr follow-up suggested that there was no sustained benefit at this point. However, this may be due to methodological problems in the follow-up study, and a long-term retrospective analysis supports the effectiveness of SCS for CRPS type 1 over a 5 yr period.[15]

Taylor and colleagues[16] performed a systematic review of SCS in CRPS in 2006. They identified level A evidence for SCS in CRPS type 1, and level D evidence in type 2 CRPS. A 12 yr prospective cohort study supported SCS as an effective pain treatment in 63% of CRPS type 1 patients implanted with an SCS.[17] A predictor of long-term success in this study was a reduction of more than 50% in the pain score after a 1 week stimulation trial.

SCS is also a cost-effective option in CRPS. When compared with CMM, SCS cost £16 596 per QALY gained.

Chronic leg ischaemia

Pain associated with chronic leg ischaemia (CLI) is difficult to manage. Surgical restoration of adequate blood flow to the leg is desirable, but it is often impossible to achieve. These patients are referred to as non-reconstructable chronic critical leg ischaemia, and their pain is often inadequately controlled with oral analgesics. Lower limb amputation is sometimes indicated.

In 2013, Ubbink and Vermeulen[18] reviewed six controlled trials comparing the use of SCS+CMM with CMM. The primary outcome in most of the studies was limb salvage. The review demonstrated a significantly higher limb salvage rate in the SCS group. Also, patients managed with SCS had a significant reduction in pain score, analgesic use, and Fontaine stage (III to II). The cost associated with SCS at 2 yr in one study was higher than the conservative management group (€36 500 *vs* €28 600). The mechanism of action of SCS in CLI may be modulation of nitric oxide or prostaglandin production, or modulation of the sympathetic nervous system.[19]

Chronic angina refractory to treatment

Several small RCTs have investigated the role of SCS in chronic angina refractory to treatment (CART). It compares favourably with coronary artery bypass grafting (CABG). A systematic review of these studies suggested that SCS was an effective and safe treatment option for CART.[20] It produced similar symptom control when compared with CABG, but in some cases, SCS was associated with lower morbidity and mortality. Implantation of an SCS is also a more cost-effective therapy than revascularization in CART.

Other indications

Multiple case reports and small case series exist describing the use of SCS in other neuropathic conditions including diabetic neuropathy, post-herpetic neuralgia, and post-amputation pain syndromes. However, these indications currently lack evidence and implantation should only be considered on a case-by-case basis after a successful trial period.

Insertion of an SCS

Patient selection

The success of SCS is heavily dependent on appropriate patient selection. To date, RCTs in SCS involved patients with persistent pain (neuropathic or ischaemic) resistant to CMM for more than 6 months. They should have a definite diagnosis or an identifiable pain generator, and a positive trial of stimulation. Patients with major psychiatric disorders, psychological distress, or unreasonable expectations are not suitable. For these reasons, a preoperative psychological assessment is advised. The patient must have the cognitive capacity to give informed consent, demonstrate an ability to understand and use the device properly, and commit to weaning off inappropriate and/or ineffective medication.

Pre-implantation considerations

(i) Stimulation trial: Before inserting the full system, the implanter can site a temporary percutaneous lead under local anaesthetic and connect it to an external pulse generator. The patient may report where they feel paraesthesia, and whether it is covering the painful area. This allows the implanter to position the electrodes over the appropriate area. The temporary lead may be left *in situ* for a few days. This allows the patient to experience SCS. There is no consensus on the adequate length of stimulation trial to accurately predict success of implantation. There is significant inter-institutional variation. There may also be complications during the trial phase such as disconnection and infection which can distort the patient's experience. After a successful trial, the temporary lead is removed and a permanent lead placed. Occasionally, the coverage may not be as good with the permanent lead resulting in disappointment. The accuracy of the trial in predicting successful implantation has never been fully established. Recently, there has been a trend towards on-table trial with implantation on the same visit to theatre in selected patients with strong indications for SCS such as FBSS and CRPS.[21] A failed trial is declared if it is not possible to stimulate the painful area, or the patient finds the paraesthesia is ineffective or unpleasant. If this occurs, the trial lead is removed and an alternative management plan is discussed with the patient.

(ii) IPG type: Determine if a rechargeable device (RIPG) or a primary cell (IPG) is most appropriate. If the patient has a busy life with limited time for recharging and uses basic programs with low energy requirements, then a primary cell is probably more appropriate. Conversely, a patient with less time constraints who uses complex programs (i.e. high-energy requirements) should consider a rechargeable system. RIPGs are growing in popularity.

(iii) Site of the IPG: It is important for the comfort of the patient to determine the best location for the IPG. Avoid placing under the belt line, or in areas of allodynia. The most common sites for IPG implantation are the gluteal region or anterior abdominal wall.

(iv) Lead type: Two main types of lead exist. A cylindrical lead can be placed percutaneously via an epidural needle system. Alternatively, a paddle lead can be placed in the epidural space via a laminectomy and sutured to the dura.

The majority of SCS leads are placed percutaneously. There is also a hybrid percutaneous paddle lead now available.

(v) Psychological evaluation by a mental health professional: Significant psychiatric disorders or psychological distress are contraindications to implantation. A mental health professional should screen all potential SCS recipients, identify and treat any mental health issues, and make a recommendation to the pain physician on the suitability of implantation.

(vi) Optimization of co-morbidities: Diabetes mellitus, systemic infection, coagulopathies, or low platelets (<100 000 mm^{-3}).

(vii) Screen for methicillin-resistant *Staphylococcus aureus*: If positive, the patient should undergo eradication therapy (follow local policy guidelines).

Factors that are contraindications to implantation or raise concern for the implanter are listed in Table 1. Most factors are relative contraindications, and the ultimate decision to proceed should be made by an informed patient and their consultant.

SCS implantation

The procedure should be undertaken in a standard operating theatre environment with appropriate monitoring, X-ray screening, and trained personnel. The patient should receive prophylactic antibiotics within the hour pre-procedure, and staff should pay meticulous attention to sterility. The procedure may be performed under local, spinal, or general anaesthesia (GA). If GA is used, somatosensory-evoked potentials may be required to confirm that the correct level of paraesthesia is achieved. Alternatively, the implanter can use X-ray images to match the trial leads position. Figure 1 shows two eight-electrode percutaneous leads in the posterior epidural space.

IPG programming

After implantation, a number of programs can be uploaded to the IPG. The frequency, amplitude, and pulse width can be varied to optimize the SCS efficacy. The patient can then use a hand-held telemetry programmer at home to switch the IPG on and off, and to switch between programs.

Postoperative management

The patient is assessed to ensure that appropriate paraesthesia or pain relief is achieved and they can use the system effectively. If no complications are identified after operation, they may be discharged home. Any signs of neurological deterioration post-implant should prompt an urgent CT scan to rule out epidural haematomas or spinal cord injury from the SCS lead. Other complications occur over the medium to long term. Lead migration and fracture have been significant problems in the past. However, the incidence of these complications is falling with the introduction of new anchoring techniques and more resilient leads. Table 2 lists the more common SCS complications.

Special considerations

(i) MRI compatibility: The use of MRI in patients with a SCS *in situ* is controversial. It may lead to unintended stimulation, lead heating which could cause tissue damage, movement of the system with loss of pain relief, and/or damage to the system. If imaging is required in these patients, the medical team should consider another modality (CT scan). If MRI is indicated, it may be possible to keep the leads out of the magnetic field. Newer SCS systems are MRI compatible with lead shielding that resists significant heating and tissue damage.

(ii) Diathermy: This should be avoided in patients with an SCS. If necessary, bipolar diathermy should be used. If unipolar diathermy is warranted, the reference plate should be positioned as far away from the SCS system as possible.

(iii) Cardiac pacemakers and defibrillators: Pacemakers may perceive SCS signals as cardiac activity and may not pace in demand mode. The implanter should communicate with the patients' cardiology team if a pacemaker is *in situ*. The pacemaker may be re-programmed to reduce its sensitivity to extra-cardiac electrical activity.

(iv) Pregnancy: A growing number of females of child-bearing age are having spinal surgery with resulting FBSS in this age group. The safety profile and management of SCS in pregnancy is a relatively new clinical concern, and several case reports and case series detailing the management of these women have been published.[23] We are not aware of data to suggest any adverse obstetric outcomes in women with an active SCS. Conversely, there are no prospective data at present to support safety in the obstetric population.

(v) Neuraxial analgesia/anaesthesia: There is a risk of damage or infection of the SCS leads when performing a neuraxial technique. It is possible to perform a neuraxial technique, after discussion with the pain team, under strict sterile conditions and with radiological guidance. However, other anaesthetic and analgesic options should be considered first.

Table 1 Contraindications or cautions to SCS

No definite diagnoses or pain generator
Spinal stenosis (with effacement of CSF, cord compression, or both) at the site of lead placement
Significant psychological or psychiatric disorder
Evidence of substance abuse
Pacemakers or defibrillators (consult with cardiology team)
Require frequent MRIs in the future (e.g. active malignancy)
Anticoagulation therapy or coagulopathy
Significant cognitive impairment (unable to appreciate the goals and limitations of SCS)
Concerns of secondary gain (e.g. ongoing litigation, compensation, etc.)
Driving with a conventional SCS switched on is not recommended (especially in operators of heavy goods vehicles—this should be discussed in the pre-trial counselling)—an HF-SCS system (HF10) is approved for driving in Europe
Pregnancy (some patients continue stimulation, but it is not licensed in pregnancy)
Failed trial in conventional SCS

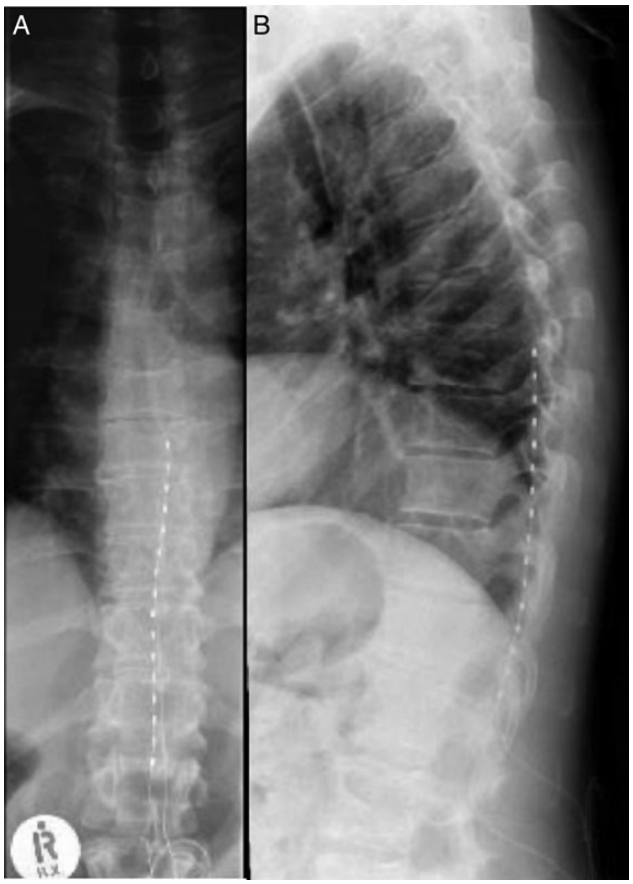

Fig 1 Two percutaneous leads are positioned in the posterior thoracic epidural space [anteroposterior view (A) and lateral view (B)]. They are positioned at the level of T8–12 in a patient with FBSS.

Table 2 Common SCS complications[22]

Hardware-related (27–30%)
Lead migration (13%)
Lead fracture (9%)
Hardware malfunction (3%)
Biologic (3–5%)
Infection (3–5%)
CSF leak (0.3%)
Symptomatic hematoma (0.3%)
Other (3–4%)
Procedural pain
Device-pocket pain

Optimizing outcomes

The Neuromodulation Appropriateness Consensus Committee (NACC) in 2014 identified a number of measures that may improve patient outcomes.[24] SCS is a cost-effective therapy if complications are minimized, and outcomes are optimized. The NACC recommended proper patient selection and standardized physician training and credentialing. Also, improved equipment, evolving knowledge, and evidence-based guidelines will optimize patient outcomes.

Future directions

Advances in device technology will improve future outcomes. Lead design is one of the major areas of development in SCS. Early systems supported a single four-contact lead. Now, multilead systems with up to 32-contacts are available. Surgically placed paddle-leads with up to five electrode columns are also available. Postural changes can pose significant problems for patients with an SCS. They may report more intense stimulation when lying supine and inadequate stimulation when mobilizing. This is related to the mobility of the spinal cord within the cerebrospinal fluid. Some manufacturers are incorporating accelerometer technology to adapt the systems output for different postures. New wireless devices remove the need to implant large IPGs, and reduce the risks associated with the conventional implantation techniques.

There is a growing interest in paraesthesia-free stimulation with burst and high-frequency regimens. These are more acceptable to patients, and may provide equal, if not better, symptom control. However, there is a need for adequately powered RCTs to support their use.

While not strictly SCS, stimulation of the dorsal root ganglion (DRG) is a promising new neuromodulation technique. The DRG plays a central role in neuropathic pain syndromes, and has become a target in the management of dermatomal neuropathic pain. Early reports from observational studies are promising, with good pain relief reported in leg and foot regions in patients with dermatomal neuropathic pain.[25] RCTs are awaited to confirm these results.

Conclusion

There has been an explosion in the variety of SCS devices, stimulation regimens, and clinical applications. However, the evidence-base is lagging behind. Further RCTs are required to stratify the use of this technique and identify the best patient populations. Currently, the evidence base supports conventional SCS in patients with FBSS, CRPS, CLI, and CART. Further evidence is required to definitively establish the role of HF-SCS and/or burst stimulation in FBSS patients refractory to conventional stimulation. The roles of hybrid systems and DRG stimulation remain to be established. Appropriate patient selection and education with specialist physician training are crucial for best outcomes.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Spinal cord injury and chronic pain

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Key points

- Chronic pain is common in spinal cord injury (SCI) patients.
- An assessment of whether this pain is unrelated or related directly to the spinal injury or the compensatory mechanisms is important.
- A multidisciplinary approach to the management is recommended.
- Principles of treatment for neuropathic pain in SCI patients are similar to those in non-SCI patients.
- Treatment of pain and its impact on life should focus on improving the biological, cognitive, and social impacts of pain.

Pain is defined by the International Association for the Study of Pain (IASP) as 'an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage'. Pain is classified as acute if it is <12 weeks, and chronic if it is >12 weeks and persists despite an apparent lack of ongoing injury.

In spinal cord injury (SCI) patients, chronic pain is common. It impacts about 70% of patients with one-third of these experiencing severely intense pain impacting on mood, functioning, and quality of life.[1] The pain can be nociceptive, neuropathic, or visceral. Nociceptive is the most common and can be due to the initial trauma, muscle and joint overuse, for example, upper limbs and wheelchair use, and injury-related muscle weakness, spasm, and contractures. Neuropathic pain can develop acutely or after 1 yr post-injury and can present at or below the level of injury. Visceral pain is thought to originate from the abdomen or thorax and may be related mainly to constipation.

We review here the classification, mechanisms, clinical diagnosis, and management of pain in SCI patients.

Definitions and classifications

Classification of the neurological deficits in SCI patients

The American Spinal Injury Association (ASIA) classifies SCI on the degree of sensory and motor loss. The level of injury is defined as the lowest spinal segment with intact sensation and antigravity muscle strength (MRC power >3) where there is normal sensorimotor function above. The type of injury is classified from complete injury (A), sensory incomplete (B), motor incomplete with more than half of the muscle groups below the injury involved (C), motor incomplete with less than half the muscle groups below the injury involved (D), and normal (E). The difference between complete and incomplete loss is sparing of sacral function. Understanding the sensory motor deficits of SCI patients is crucial to the examination of the nervous system when assessing neuropathic and nociceptive pain.

Classification of pain in SCI patients

Classification of chronic pain in SCI has three tiers[2] (Fig. 1) as defined by the 'International Spinal Cord Injury Pain' (ISCIP) group. Tier 1 describes pain by its pathological origin: nociceptive, neuropathic, other, and unknown. In tier 2, nociceptive pain is subcategorized into musculoskeletal, visceral, and other pain types, while neuropathic pain is classified into pain at the injury level or below and other pain type. Tier 3 describes the source of

TIER 1	TIER 2	TIER 3
Nociceptive pain	• Musculoskeletal pain • Visceral pain • Other nociceptive pain	-Shoulder osteoarthritis -Constipation -Autonomic dysreflexia headache
Neuropathic pain	• At level pain • Below level pain • Other neuropathic pain	-Spinal cord compression -Spinal cord ischaemia -Carpal tunnel syndrome
Other pain		-Fibromyalgia -Irritable bowel syndrome
Unknown pain		

Fig 1 Classification of pain after SCI. Adapted from Bryce and colleagues.[2]

the pain, for example, osteoarthritis of the shoulder, bladder spasm.

Pathophysiology of chronic pain in SCI

We know far more about nociceptive pain mechanisms than neuropathic pain mechanisms. For this reason and because nociceptive pain transmission is the same in SCI and non-SCI patients, we focus on understanding how the injured spinal cord goes on to develop chronic neuropathic pain.

Our understanding of SCI neuropathic pain comes predominantly from animal research.[3] After SCI, structural neuroplasticity and sprouting of new dendritic fibres is critical for recovery and it is these changes that may add to neuropathic pain, muscle spasticity, and autonomic dysreflexia.

At the level of injury, neuropathic pain is thought to result from hyper-excitable neurones which have exaggerated responses to stimuli at or below the normal activation threshold. Hyper-excitability results from altered expression of *N*-methyl-d-aspartate and glutamate receptors, sodium and calcium channels, increased glial activation, and/or hypofunction of endogenous inhibitory neurones. The success of sodium and calcium channel blocking analgesics in providing neuropathic pain relief supports this hypothesis.

Below the level of injury, the mechanisms of perceived pain are less clear. In complete spinal cord transection, the origins theoretically must be in the intact portion of the central nervous system above the level of injury. In these patients, the source of the 'pain generator' is unknown and could arise from spontaneous activity in disinhibited polysynaptic pathways, a sensitized spinothalamic tract, or from a more central origin such as the thalamus or cortex.

An alternative explanation is that below level, pain could be produced by a dysfunctional relationship between the fast lateral spinothalamic tract and the slow medially located polysynaptic pathway. It is possible that post-injury, the polysynaptic tract may dominate over the spinothalamic tract which explains the late onset and diffuse nature of pain with its associated after-sensations after a stimulus. Crucially, the polysynaptic pathway is also capable of transmitting to de-afferented pathways giving the sensation of pain below the level of injury.

Clinical assessment

A careful pain history and a neurological and clinical examination are needed to make a diagnosis and guide treatment. Patients might have a range of symptoms including allodynia, hyperaesthesia, dysesthesia, and paraesthesia and asking only for pain descriptors in the history might not reveal the problem. Patients often describe their symptoms as 'I don't have sensation below my level of injury, but I do get pain'.

The approach to assessing pain requires an appreciation of biological, psychological, and social elements. Information about the site, onset, character, radiation, alleviating factors, temporal pain profile, exacerbating factors, and severity of pain is a reasonable start. Diagrams of the body where people can shade in areas of felt pain are useful where the pain location is not discrete. Understanding the characteristics of the pain is important to differentiate nociceptive from neuropathic pain. Nociceptive pain is dull, aching, stabbing, heavy, movement sensitive, and non-spontaneous. Neuropathic pain can be spontaneous or stimulus-provoked. Its characteristics are burning, shooting, electric shock, loss or gain of odd somatosensations, allodynia, and hyperalgesia. Criteria used for diagnosis of SCI-related neuropathic pain would include:

(i) A history of a relevant lesion or disease affecting the spinal cord, cauda equine, or both.
(ii) The pain is located at or below the neurological level of the SCI and there is either:
  (a) at least one diagnostic test confirming a lesion or disease of the spinal cord, cauda equine, or both and/or;
  (b) a negative or positive sensory signs in the area of pain compatible with the spinal cord or root lesion.
(iii) Other causes of pain, such as nociceptive or peripheral neuropathic pain, are excluded or considered highly unlikely.[3]

Without meeting these criteria, the pain may otherwise be regarded as nociceptive with either a sensory, mechanical, or visceral origin.

When taking a pain history, it is also important to elicit factors the patient has recognized may predispose to pain, why they think they are in pain, and what has caused them to address their pain now. This information addresses the patient's ideas, concerns, and expectations of how their pain can be managed and allows the clinician to start understanding what may be done to help.

A drug history will reveal what medications they may have tried and failed to control the pain, along with their other medications which could contribute to pain or mood. A previous medical history may reveal medical conditions that are the cause of the patient's pain which have been missed because of the focus on the SCI itself. A family, social, psychological, and smoking/alcohol history may reveal elements of how the psychology and social elements are influencing pain perception. One of the many anxiety and depression scales may be used to this end. Psychosocial factors have been found to strongly influence perceived pain severity and coping mechanisms.[4,5]

The examination for pain involves assessing the various areas where the pain is reported. This includes a neurological examination of the area and testing the different sensory modalities looking for normal or abnormal sensory or motor conduction. Joint, skin, and other examinations where indicated should also be undertaken when required.

When the above information has been collated, formulation of a diagnosis, required investigations, and management plan will follow and should be done in conjunction with the patient. The management plan will usually have three aspects: pain control, treat psychological factors, and aid the return of function. The success of the plan depends heavily on patient involvement in the management of their pain, as it is a pain they will likely have for life.

Managing pain in SCI

General approach

The general approach to managing pain acute or chronic is the multidisciplinary team. This team involves pain specialists, clinical psychologists, psychiatrists, physiotherapists, a spinal cord injury specialist / rehabilitation specialist, and social and occupational therapy services. The entire team is necessary to treat the biology of pain, address psychological factors, and reduce obstacles to a normal life.

The psychosocial impact of the injury on the patient is huge and is a variable factor in successful management. Depression is common and patients might benefit from a multidisciplinary CBT-based approach to managing their pain.[6] This may involve referral to a clinical psychologist, psychiatrist, or both. CBT in non-SCI chronic pain has been shown to significantly change pain experience, cognitive coping, and positive coping measures and reduce behavioural expression of pain.[7] The psychological therapy may also be delivered as formal pain management programmes, psychological counselling, physiotherapy, occupational therapy, and self-help strategies. A psychiatrist may be needed if depression, anxiety, or another new or pre-existing psychiatric condition is affecting their pain or vice versa. A close working relationship is essential in these cases to manage the psychiatric components of the pain management, and ensure that pain medications do not upset any psychiatric disease.

When social factors play a large role, referral to the social services may be needed. The SCI population receive heavy social and occupational therapy input to help them return to work and life after their injury. Involving these teams in pain management may be required to aid this process and manage pain, particularly when concerns over housing, finances, having the correct wheelchair, etc. are causing them to focus negatively on their pain.

Medical management (drugs, psychology, and physiotherapy)

Treatment of chronic non-neuropathic/nociceptive pain should follow an escalation ladder. Initially, regular simple analgesics such as paracetamol used in conjunction with non-steroidal anti-inflammatory drugs are appropriate, but must be used with caution due to the risk of stress ulcers and impairing kidney function. Escalating to tramadol or mild opioids such as codeine and then stronger opioids such as morphine may be justified. Treatment of pain contributors such as muscular spasm is equally important as treating the pain. Muscular spasm is treated with spasmolytics, such as baclofen or methocarbamol.

Treatment of neuropathic pain is similar to that of non-SCI patients. In our unit at Stoke Mandeville Hospital, we provide treatment in accordance with the NICE guidelines. First-line drugs are the tricyclic antidepressants. Second-line drugs are the anti-convulsants. Treating neuropathic pain with medication requires starting a medication, and observing for a benefit after 6 weeks. If there is no benefit at 6 weeks, the dose may be increased or the drug can be stopped. Neuropathic analgesics should not be stopped suddenly but reduced gradually as they affect multiple organ systems.

First-line drugs commonly used are amitriptyline and dosulepin. Starting doses of amitriptyline 10–25 mg at night increased to a maximum of 75 mg daily are used. Higher doses require specialist supervision. Increases should be made in 10–25 mg increments per week. Amitriptyline should be avoided in severe liver disease, recent myocardial infarction, and cardiac arrhythmias. Tricyclic agent side-effects include dry mouth, blurred vision, constipation, difficulty with micturition, and cardiovascular side-effects. Dosulepin should be started at 25 mg at night for 3 days and then escalated at 25 mg increments 3 daily to 75 mg. A dose of 150 mg may be required. Its contraindications are identical to amitriptyline. If the sedation produced by amitriptyline and dosulepin is not tolerated, alternative non-sedating tricyclic antidepressants such as nortriptyline, imipramine, or lofepramine may be better alternatives.

The second-line anticonvulsant neuromodulatory analgesics are the gabapentinoids. Pregabalin is effective and well tolerated by patients with neuropathic pain after SCI.[8] The use of gabapentin and its effectiveness has been debated.[9–11] Gabapentin should be started at 300 mg on day 1, 300 mg twice a day on day 2, and 300 mg three times a day on day 3. Based on individual patient response and tolerance of side-effects, the dose can be escalated to a maximum of 1200 mg three times a day in increments of 300 mg day^{-1} every 2–3 days. Slower increments may be required where side-effects are an issue, but a faster titration is strongly advised against. Withdrawing gabapentin likewise requires a slow decrement of the dose as abrupt cessation can cause anxiety, insomnia, nausea, pain, and sweating. Common gabapentin side-effects include dizziness, diarrhoea, dry mouth, dyspepsia, nausea and vomiting, abdominal pain, weight gain, and memory loss. Rarely, gabapentin may be the cause of acute pancreatitis.

Tramadol has shown to be effective, as a third-line treatment after gabapentinoids[12] in some studies. Duloxetine may have some beneficial effect in central pain,[13] and in those who have neuropathic pain and diabetes. It seems to work by preventing the re-uptake of norepinephrine, serotonin, and dopamine. Lamotrigine reduces spontaneous pain in patients with incomplete SCI.[14] Sodium channel blockers such as lidocaine can produce analgesia both by a central and peripheral action. An i.v. lidocaine test is occasionally used in patients with a view to trying oral mexiletene. In refractory pain and spasm, intrathecal morphine, alone or in combination with baclofen and clonidine, has been used. Visceral pain requires regular gastroenterology and urology reviews for treatment of underlying causes such as constipation and urinary tract problems.

Specialist physiotherapy for preventing and treating overuse of muscles and joints is as important as is treating the pain itself. For individuals with SCI and neuropathic pain, regular exercise training leads to significant improvements in pain, stress, and reduces depression. The mechanism by which exercise does this is poorly understood, but it does change perceived pain and therefore reduces stress related to pain. Moreover, exercise exerts its influence on depression through reducing stress. Furthermore, exercise may help to improve chronic musculoskeletal pain and may indirectly influence neuropathic SCI pain. Abnormal posture, gait, and overuse all contribute to pain and may be addressed by physiotherapy, exercise, retraining, and environmental modifications. One of the most disabling and frequent causes of mechanical pain in the SCI population is shoulder pain. Shoulder range of motion exercise started as early as possible after injury is important to minimize shoulder pain. The overall aim of a rehabilitative physiotherapy programme is

to increase self-efficacy and promote greater activity and normal participation.

Surgical pain interventions

Surgical interventions can be classified by what they are intending to treat: nociceptive pain, neuropathic pain, visceral pain, or other pain. Typically, surgical intervention for pain is used in compression neuropathies, syringomyelia drainage, and treatment of segmental pain at the level of injury with dorsal root entry zone (DREZ) lesioning.

Chronic wheelchair use can cause carpal tunnel syndrome, ulnar nerve entrapment, thoracic outlet syndrome, and pudendal neuropathy. Carpal tunnel syndrome is treated with surgical decompression or injections, and ulnar entrapment with nerve trunk transposition surgery. Thoracic outlet syndrome is treated by minimizing physical activities that potentiate nerve irritation. Surgical decompression is a last resort and involves nerve decompression by removal of the first rib, release of the scalenes, or both. Thoracic outlet syndrome must not be confused with syringomyelia whose presentation is similar but whose treatment is very different. Pudendal neuropathy occurs when the pudendal nerve is compressed by thickened sacrotuberous, sacrospinous ligaments, or both from prolonged sitting. It can be the cause of perineal pain when lying down. Its treatment includes alterations to wheelchair ergonomics, physical therapy, analgesia, steroid injections around the ligaments and nerve canal, pulsed radiofrequency ablation of pudendal nerve, and surgical decompression as a last resort.

Early-onset radicular pain after any spine surgery may result from malposition of the implanted screws or clips. For late onset radicular pain, dislocated material, worsening kyphosis, or both can be the cause. Correction of any of these causes requires further surgery.

Syringomyelia may present initially with pain at the level of injury and new neurological deficit. Diagnosed with MRI, it results from blockage of cerebrospinal fluid (CSF) flow at the level of the injury caused by vertebral disc compression, arachnoiditis, or both. The treatment includes CSF bypass shunting, arachnoid grafting, and duraplasty. However, pain is rarely the indication for surgery as it remains unclear whether the pain originates at or above the level of the injury.

DREZ ablation is effective on segmental pain at the level of injury. The DREZ is the section of small pain fibres that enter the spinal cord at the dorsal horn tip.[14] It is mainly used for pain at lower injury levels, incomplete SCI, and for unilateral pain.

Specialist therapies for pain in SCI: neurostimulation

A large portion of patients' SCI pain is refractory to pharmacological treatment and so alternative interventions are being explored.[15] Categorized as non-invasive and invasive, they are all essentially a form of neurostimulation. Non-invasive neurostimulation techniques are transcutaneous electrical nerve stimulation, repetitive transcranial magnetic stimulation, and transcranial direct current stimulation. Invasive neurostimulation techniques are peripheral nerve stimulation, nerve root stimulation, spinal cord stimulation (SCS), deep brain stimulation (DBS), and motor cortex stimulation (MCS).

Invasive neurostimulation of the spinal cord or brain should only be considered when there is severe debilitating chronic pain and all other therapies have failed. SCS possibly works by: decreasing spinothalamic tract activity, reestablishing sensory afferents, interrupting pain processing due to maladaptive plasticity,[16] and stimulating spinal cord–brainstem loops.[17] DBS is more effective on nociceptive pain than deafferentation pain. MCS-induced pain relief may relate to activation of descending pain control systems. MCS has a better clinical potential as it has fewer complications than DBS, and is better supported by evidence for its use in central pain in SCI patients.[18]

Summary

Pain in SCI patients is complex. The mechanism is poorly understood and it is further complicated by the psychosocial impact of the nature of injury. Treatment and management modalities do not work in isolation and need to be combined with pharmacological methods, physical therapy, and psychological input in specialist centres. More research needs to be conducted in novel experimental therapies with emphasis on improving patients' quality of life after SCI.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Paediatric massive transfusion

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Key points

- Defined by red blood cell transfusion of 50% of total blood volume (TBV) in 3 h, 100% in 24 h, or >10% of TBV per minute.
- Massive blood loss in the paediatric patient, often from blunt trauma, can be difficult to assess. Surgical bleeding is often anticipated and usually occurs in a monitored environment where blood loss can be assessed as it occurs.
- The underlying cause of haemorrhage and subsequent management has a profound effect on the body's ability to maintain haemostasis.
- Management requires assessment of the degree of blood loss and replacement of blood products to maintain volume and haemostasis. This may be assisted by the application of a 'massive transfusion protocol'.
- Point-of-care testing (thromboelastography, ROTEM) and the use of individual clotting factors may offer more timely and direct means of correcting coagulopathy from massive blood loss.

Defining paediatric massive transfusion

Diab and colleagues[1] suggested the following:

(i) Packed red blood cell (PRBC) transfusion of 50% of total blood volume (TBV) in 3 h,
(ii) PRBC transfusion of 100% TBV in 3 h,
(iii) PRBC transfusion of >10% of TBV min^{-1}.

Pathophysiology of massive blood loss and transfusion

Figure 1, adapted from Diab and colleagues,[1] identifies pathophysiological factors contributing to coagulopathy during massive transfusion. It identifies the changes that occur during trauma and surgery as a consequence of tissue injury, blood loss, and therapeutic interventions.

Trauma-induced coagulopathy is a multi-factorial process. Tissue damage results in the release of tissue factor and subsequent activation of the coagulation cascade. Hypoperfusion that occurs after massive blood loss causes increased expression of thrombomodulin in turn binding to thrombin and activating protein C. Activated protein C inhibits cofactors V and VIII and in excess also depletes plasminogen activator inhibitor-1 (PAI-1), reducing tissue plasminogen activator inhibition and accelerating the formation of plasmin and fibrinolysis. Similar pathophysiological changes can occur during major surgery with massive blood loss.[1]

Coagulopathy may also develop during massive transfusion. This occurs as a result of haemodilution from volume replacement and can be exacerbated by hypothermia and acidosis. The storage temperature of blood products at 1–6°C can contribute to hypothermia in patients requiring massive transfusion. For each 1°C decrease in temperature, coagulation factor activity decreases by 10%. Below 34°C, clotting times prolong, platelets pool within the spleen, and there is impaired adherence and aggregation. Significant hypocalcaemia (ionized calcium <0.6 mmol $litre^{-1}$), induced by blood product citrate binding to circulating serum calcium and acidosis (pH<7.3), reduces the activation of coagulation on platelet cell surfaces and disrupts haemostasis.[2]

Certain patient groups are more prone to massive blood loss. Neonates comprise a special at-risk group. The haemostatic system is incompletely developed at birth and matures throughout infancy. The concentration of procoagulant and anticoagulant

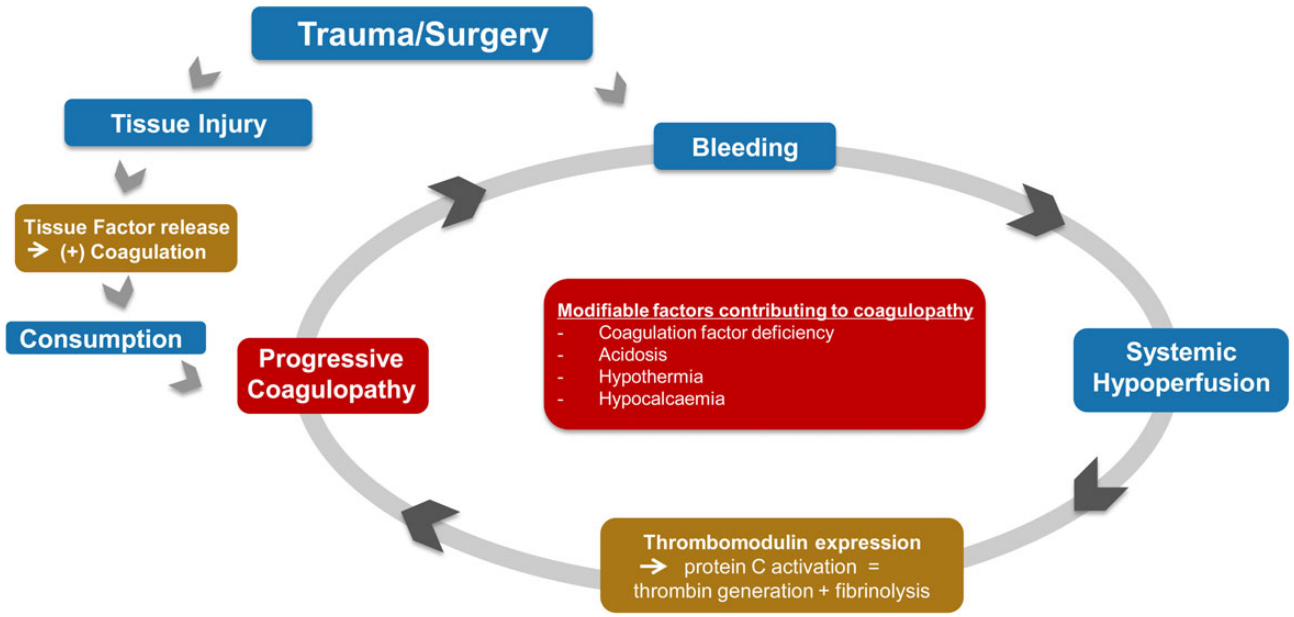

Fig 1 Pathophysiological factors contributing to coagulopathy during massive transfusion. (Modified from Fig. 1 of Diab and colleagues, with permission from *British Journal of Haematology*, John Wiley and Sons.)[1]

proteins is low and remains so until 6 months of age. Fibrinogen is qualitatively dysfunctional, existing in fetal form for 6–12 months after birth.[1] Consequently, the haemostatic changes during massive transfusion in this population are profound, often resulting in an increased bleeding risk. In addition, burns patients may have a consumptive coagulopathy with microangiopathic haemolysis, cardiac patients undergo the haematological insult induced by bypass, and patients in liver failure may have reduced levels of clotting factors and thrombocytopaenia.[1]

Management of massive transfusion

Assessment of blood loss

The principles of assessing paediatric massive blood loss are similar to adults. They rely on clinical signs, symptoms, monitoring, and investigations. As with adults, dyspnoea, altered mentation, hypotension, and reduced capillary refill can be used to assess haemodynamic state. However, paediatric patients have good physiological reserve, maintaining arterial pressure even after a loss of 25–40% of blood volume. Consequently, the clinical signs and symptoms of hypovolaemia may not be good predictors of early haemorrhage. A narrow pulse pressure may be a more sensitive sign of hypovolaemia than tachycardia or systolic hypotension. Lactic acidosis secondary to hypoperfusion and decreased urine output are additional indicators of hypovolaemia. Invasive monitoring in the form of intra-arterial and central venous pressure monitoring may be indicated if blood loss is assessed to be greater than one blood volume, further losses are expected, there is serious head injury, or there is major trauma of unknown severity. It may also assist the assessment of peripheral oxygenation via measurement of lactate and mixed venous oxygen saturation.

Assessment of blood loss in theatre can be difficult. Clinical signs are affected by anaesthesia and blood loss calculated by direct observation, collection in suction bottles, and weighing of swabs are inaccurate and impractical, often underestimating volume lost.[1] Despite difficulty in using clinical signs and symptoms to determine paediatric blood loss, transfusion requirements using volumes of crystalloid and blood products given to maintain vital parameters (including heart rate, arterial pressure, central venous pressure) can be used to help determine the degree of blood loss. Blood loss being approximated as one-third of crystalloid or an equivalent volume of colloid replacement required to maintain haemodynamic stability.[3] Of note, the estimated blood volume of a preterm infant is 90–100 ml kg^{-1}, a term infant <3 months 80–90 ml kg^{-1}, and a child >3 months 70 ml kg^{-1}.[1]

Blood volume replacement strategies

The management of massive transfusion requires that circulating blood volume is restored and blood components are given such that haemostasis is maintained or returned to normal. In uncontrolled haemorrhage, damage control or haemostatic resuscitation aims to minimize iatrogenic resuscitation injury, prevent worsening of shock and coagulopathy, and obtain definitive haemostasis, usually via surgical control. It differs from the traditional management of haemorrhagic shock by limiting crystalloid fluid resuscitation and by transfusing blood products empirically before coagulopathy is identified by testing. In the paediatric trauma setting, increased crystalloid volume replacement has been associated with increased transfusion requirements, coagulopathy (prolonged prothrombin times), and a tendency towards increased mortality and multi-organ failure rates.[4]

Permissive hypotension is a fluid management strategy, often used in adult trauma settings, that targets a suboptimal arterial pressure until definitive management of bleeding can be obtained. It aims to maintain end-organ perfusion while limiting crystalloid resuscitation, thereby limiting dilutional coagulopathy, clot disruption, and cellular dysfunction. Evidence for use in both the adult and paediatric population is limited. Given that children have a large physiological reserve and compensate for blood loss with minimal change in vital signs, it may not be an appropriate strategy in the paediatric population.

An important concept of haemostatic resuscitation is construction of a balanced transfusion strategy delivering red blood cells, fresh-frozen plasma (FFP), platelets, coagulation factors, and anti-fibrinolytics. Early administration of predefined balanced ratios of PRBC, FFP, and platelets has been associated with improvements in patient outcomes in adult trauma and non-trauma patients. Particularly those receiving higher ratios of FFP and platelets to PRBC than have been used in the past.[4] Evidence for the optimal product ratio, in both adult and paediatric patients, is yet to be determined. Despite this, many adult massive transfusion protocols suggest a PRBC:FFP:platelets ratio of 1:1:1 to best represent whole blood loss, with early consideration of fibrinogen replacement and use of tranexamic acid (TXA) in specific circumstances. Of note, research into lower PRBC:FFP ratios during massive transfusion in children is yet to indicate significant improvements in morbidity and mortality.[5] For this reason, and possibly due to difficulty in providing FFP quickly, most guidelines advocate replacement in a PRBC:FFP:platelet ratio of 2:1:1.

The composition of volume replacement during massive blood loss can vary depending on the clinical circumstance. In the trauma setting, patients can sustain coagulopathy from tissue factor released from damaged tissues and hypoperfusion, often requiring early replacement of fibrinogen and coagulation factors. In the surgical setting, preoperative tissue injury and volume depletion is less likely and patients often have invasive monitoring in a regulated theatre environment. Blood loss can often be assessed by monitored vital parameters, laboratory testing, and required fluid replacement. Red blood cell replacement is guided by transfusion thresholds and estimated blood loss. If bleeding is controlled, the introduction of PRBC can be guided by the use of a maximal allowable blood loss equation and clinical response to fluid therapy. An equation in common use is as follows:

$$\text{Maximal allowable blood loss} = \left(\frac{\text{Hb initial} - \text{Hb low}}{\text{Hb initial}}\right) \times \text{EBV}$$

where Hb initial is starting Hb and Hb low is acceptable threshold Hb below which red cell replacement should begin. Hb low should be determined with consideration of patient condition and clinical situation EBV is estimated blood volume.

For example, a 10-yr-old child that weighs 30 kg is undergoing surgery where significant blood loss is expected. Starting Hb is 13 g dl^{-1} and acceptable low Hb is deemed to be 7 g dl^{-1}. Estimated blood volume is 70 ml kg^{-1}×30 kg or 2100 ml.

$$\text{Allowable blood loss} = \frac{13 - 7}{13} \times 2100 \text{ or } 970 \text{ ml}$$

PRBC transfusion should therefore be considered after assessed loss of ~1 litre of blood.

Further administration of other blood products including platelets and cryoprecipitate can be guided by standard laboratory or point-of-care testing. If speed of blood loss precludes this, introduction of platelet therapy after one or two blood volumes loss and cryoprecipitate after three blood volumes loss has been described.[3]

Once bleeding has been controlled, volume restored and blood products administered, appropriate therapeutic targets after massive transfusion could include the following: Hb 80 g $litre^{-1}$, fibrinogen >1.0 g $litre^{-1}$, PT ratio <1.5, platelet count >75×10^9 $litre^{-1}$ (excluding traumatic head injury 100×10^9).

Table 1 Flow rates of i.v., intraosseous cannulas[6]

I.V. catheter	Maximum rate of flow with gravity (ml min^{-1})	Maximum rate of flow with pressure (ml min^{-1})
14 G 50 mm cannula	236.1	384.2
16 G 50 mm cannula	154.7	334.4
18 G 45 mm cannula	98.1	153.1
20 G 33 mm cannula	64.4	105.1
22 G 25 mm cannula	35.7	71.4
15 G 25 mm intraosseous needle (tibial)	68.2	204.6

Equipment during a massive transfusion

Administration of large volumes of blood products requires adequate vascular access. During paediatric trauma where massive haemorrhage is suspected, if no access is established after 90 s or two attempts, intraosseous access is appropriate. Table 1 indicates flow rates of i.v. and intraosseous cannulas of differing gauge and length.[6]

Products need to be warmed and the rate of transfusion will indicate which method of warming will be most suitable. Devices using countercurrent exchange (Level 1 fast flow H-1200; Smiths Medical, London, UK) and magnetic induction (FMS 2000; Belmont Instrument Corp., Billerica, MA, USA) should be used for patients requiring increased transfusion volumes (>100 ml min^{-1}). At moderate flow rates (<100 ml min^{-1}), there is significant heat loss after i.v. tubing leaves the warmer. If small volumes of transfusion are required directly warming blood via insulating i.v. tubing can be effective or utilizing an in-line warmer close to the infusion site (Buddy, Belmont Instrument Corp.).[7]

Blood salvage is used in the paediatric setting. Initially, when cell salvage was introduced into paediatric practice 'fixed volume bowls' of >300 ml volume were used, so that blood loss required needed to be >500 ml. However, advances in technology have allowed for the use of smaller bowls (down to 50 ml) and more recently 'continuous disc or centrifugal processing' allowing smaller volumes of blood to be processed faster.[7] Its use in elective or emergency procedures should be considered when anticipated blood loss is >20% of the patients estimated blood volume. Allogenic blood transfusion was significantly reduced in volume and frequency when used in craniofacial, major orthopaedic (acetabuloplasty and scoliosis correction), and complex cardiac surgery.[8] Cell savers have an additional use as they can wash PRBC before transfusion in cases where significant blood loss is expected. High levels of potassium and hydrogen ions after storage are washed out and the resulting hyperkalaemia and acidosis from rapid transfusion, particularly in smaller children, can be mitigated.

Complications of massive transfusions

Table 2 indicates complications and management suggestions after massive transfusions. Complications can be divided into transfusion reactions, immunological, metabolic, and miscellaneous. Along with the risks associated with single unit blood transfusions, patients receiving greater volumes of transfusion are more prone to complications, particularly those contributing to coagulopathy—hypocalcaemia, acidosis, and hypothermia.

Table 2 Complications and management suggestions after massive transfusions (modified from Table 1 in Diab and colleagues, with permission from *British Journal of Haematology*, John Wiley and Sons)[1]

Complication	Comments and management suggestions
Transfusion reactions	
Allergic	Range from urticarial to anaphylaxis. Consider steroids or diphenhydramine
Haemolytic transfusion reaction (acute, and delayed)	Consider giving O RBCs and AB plasma for emergency released blood products
Febrile non-haemolytic transfusion reaction	
Immununological complications	
Transfusion-related acute lung injury (TRALI)	
Transfusion-related immunomodulation (TRIM)	May be responsible for increased risk of bacterial infection
Transfusion-associated graft *vs* host disease (Ta-GVHD)	Irradiation of cellular blood products for patients at risk (neonates, immunosuppressed)
Metabolic complications	
Hypocalcaemia	Citrate overload from rapid transfusion, neonates and patients with liver disease are at higher risk
Hypomagnesaemia	Transfusion of large volumes of magnesium poor fluid and citrate overload
Hyperkalaemia	From haemolysis of RBC from storage, irradiation. Fresh RBCs (<5–10 days old, irradiated <24 h before transfusion or washing may decrease risk
Hypokalaemia	Owing to re-entry into transfused blood cells, stress hormones, metabolic alkalosis
Metabolic alkalosis	Citrate overload
Acidosis	Owing to hypoperfusion, citrate overload, liver dysfunction
Hypothermia	
Miscellaneous	
Coagulopathy	Refer to pathophysiology section
Transfusion-associated circulatory overload (TACO)	Differs from TRALI. May require oxygen and diuretics
Air embolism	Potentially fatal complication. Careful use of rapid infuser

Massive transfusion protocols

Owing to the multi-factorial nature of coagulopathy during trauma and surgery, massive transfusion protocols have been developed to guide resuscitation, facilitate communication and logistical support, and prevent coagulopathy before it occurs. By standardizing the empirical use of blood products, they facilitate appropriate blood product replacement during critical haemorrhage. In the adult population, the use of massive transfusion protocols has resulted in faster delivery of blood products, decreased rates of multi-organ failure, and improved 30 day survival.[9] The early initiation of multi-component therapy, facilitated by reduced delays in ordering and delivery, has the potential to prevent excessive use of crystalloid, correct and prevent coagulopathy, and minimize the complications of massive transfusion.[4] Massive transfusion protocols, particularly in paediatric trauma settings, are yet to identify a reduction in mortality and morbidity, but have been shown to reduce time to transfusion.[5]

Predicting who will require a massive transfusion and triggering a massive transfusion protocol can be difficult. In the adult population, several scoring systems exist to predict likelihood of requiring a massive transfusion. Variables, including INR (>1.5), systolic arterial pressure (<90 mm Hg), haemoglobin (<11 g dl^{-1}), base deficit (>6), FAST scan positive, heart rate (120 beats min^{-1}), temperature (<35.5°C), penetrating trauma, and or pelvic/long bone fractures, have been used to predict the need for massive transfusion.[10] No similar scoring systems exist in the paediatric population.

Triggering a massive transfusion protocol

- Clinical identification of patient at risk. Determined by mechanism of injury (trauma, head injury, pelvic/long bone fractures), surgery, vital parameters [reduced systolic pressure, hypothermia (35°C)].
- Transfusion requirements. As per previous definition of massive transfusion.
- Biochemical analysis. Evidence of acidosis (base deficit >6), coagulopathy (INR>1.5), reduced haemoglobin (Hb<7 g dl^{-1}).

It is important to note that a massive transfusion protocol is not a blood product prescription. It is a pathway used to define when to initiate the protocol, what blood products to immediately release, which tests to utilize, and to activate arrangements for getting the blood products to the patient quickly. While packs are supplied containing designated units of blood products, administration remains as directed by the treating clinician in accordance with patient weight and clinical response. Logistical considerations during massive transfusion include early notification of blood bank and consultation with haematology. Theatre staff should be delegated responsibility for blood product collection, storage, and documentation of usage. Products should not be exposed to room temperature for longer than 20 min and unused products should be returned when appropriate. Blood bank should be notified of deactivation of the MTP.

An example of a paediatric massive transfusion protocol is displayed in Figure 2.[11]

Recent developments

Point-of-care testing

Laboratory evaluation of the massively bleeding paediatric patient is challenging and conventional coagulation assays including prothrombin time (PT), partial thromboplastin time (PTT), platelet count, and fibrinogen levels are time-consuming. Specific information on clot formation and haemostatic abnormalities such as platelet dysfunction, hyperfibrinolysis, and factor XIII deficiency are not provided. The use of thromboelastometry (TEG) and rotational thromboelastometry (ROTEM) measures coagulation in real time at the patients' current temperature and observes the viscoelastic properties of whole blood from initiation of coagulation to fibrinolysis. Despite no evidence that TEG and ROTEM reduce the morbidity and mortality in massively transfused patients, they do reduce time for availability of test results. This may better direct the early use of individual blood products and reduce transfusion requirements.[1 12] Such point-of-care testing may be a useful adjunct to conventional testing for paediatric patients requiring massive transfusion.

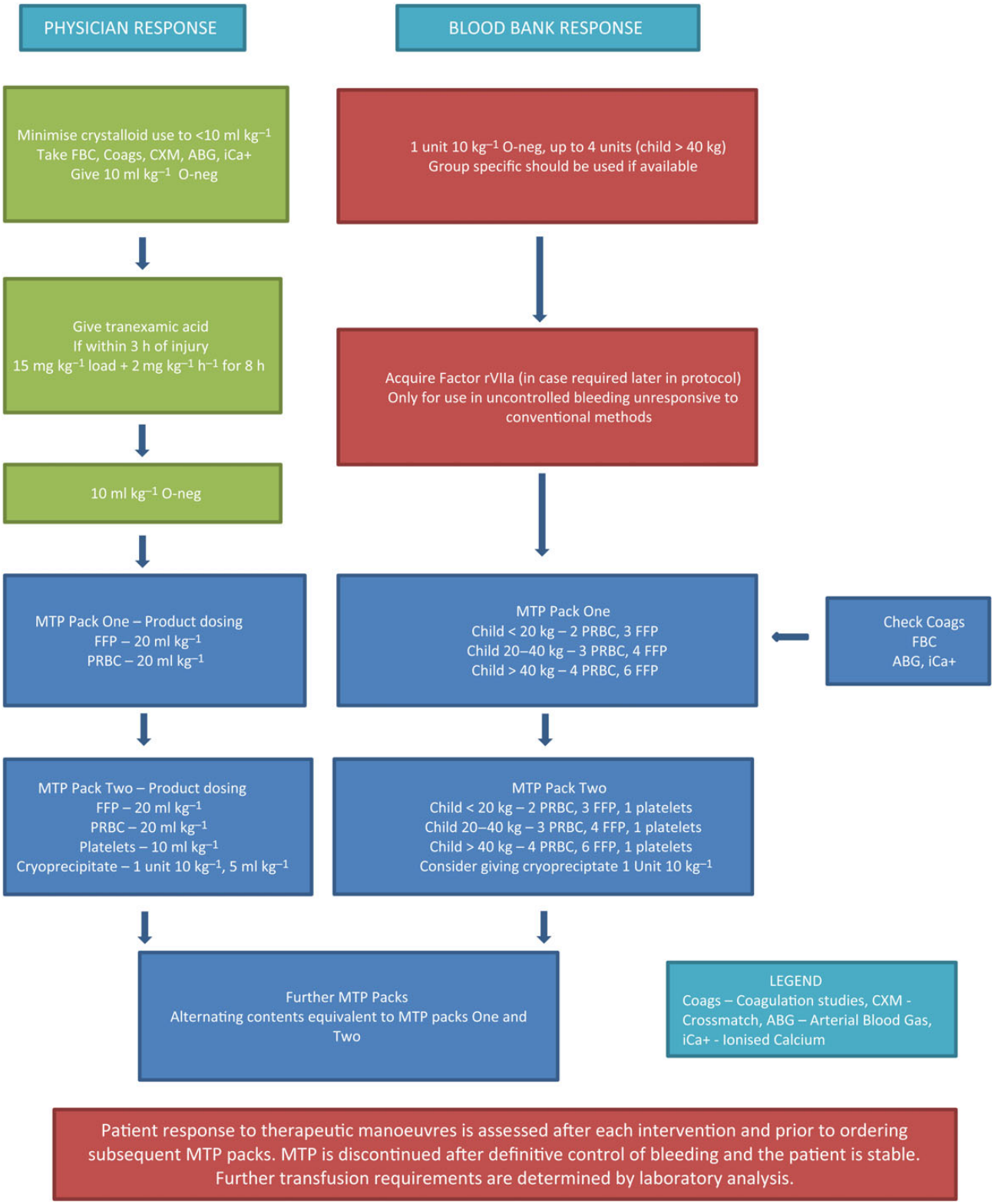

Fig 2 A sample paediatric MTP.[11]

Factor concentrates

The advent of individual factor concentrates and products containing specific factor combinations have raised the question of where they fit in the management of bleeding disorders, particularly during massive transfusion. The advantage of these preparations is that they exist in small volumes and may be useful for treatment of coagulopathy with avoidance of problems related to volume overload. This is likely to be of use in

correcting abnormalities in patients who are not actively bleeding and do not require concurrent volume resuscitation.

Fibrinogen is the precursor to fibrin and is cleaved by thrombin after the initiation, amplification, and propagation phases of the coagulation cascade. Fibrin is crucial in mediating Von Willebrand factor and platelet interactions, subsequently providing a catalytic surface for thrombin generation and clot formation after endothelial injury. If consumed or diluted as a result of trauma, during massive blood loss or transfusion, coagulation is impaired. It has been suggested that in the paediatric population, fibrinogen deficiency may develop more quickly than other factor deficiencies and that during massive blood loss and subsequent transfusion, it should be replaced early.[1] Obtaining laboratory fibrinogen levels is time-consuming and transfusion thresholds and dosing guidelines are not well established. During massive bleeding, a target level of >1.5–2 g litre^{-1} is suggested. One gram of fibrinogen administration increases plasma fibrinogen by ~0.25–0.28 g litre^{-1} in adult patients and each unit of FFP, cryoprecipitate, and fibrinogen concentrate contains 0.5, 0.3, and 0.9–1.3 g, respectively, of fibrinogen.[13] Studies have shown reduced transfusion requirements and mortality after its use in adult trauma patients. There may be benefit for its use in paediatric patients for the treatment of acquired hypofibrinogenaemia [loss or dilution coagulopathy, trauma, cardiac and thoracic surgery, liver failure, disseminated intravascular coagulation (DIC)]. The suggested fibrinogen concentrate dose is 70 mg kg^{-1}. Of note, the haemostatic efficiency of fibrinogen requires intact platelet activation, thrombin generation, and activated factor XIII-mediated polymerization. Consequently, the use of fibrinogen replacement during hyperfibrinolysis and DIC may be ineffective and require the use of anti-fibrinolytics such as TXA.[13]

The use of factor VIIa has been shown to improve the coagulopathy in adult patients with post-traumatic haemorrhage and decrease blood transfusion requirements. However, there is no evidence that it improves mortality and may increase the risk of thromboembolic complications.[1] Administration of factor VIIa is often included in massive transfusion protocols as a last resort to improve haemostasis. The recommended dose is 90 μg kg^{-1} for an adult patient, and varying studies looking at off-label dosing in paediatric patients after massive transfusion vary from 20 to 180 μg kg^{-1}.[1]

Prothrombin complex concentrate (PCC) is a preparation containing human plasma-derived vitamin K-dependent clotting factors II (prothrombin), VII, IX, and X. It has been used in the treatment of bleeding in congenital or acquired vitamin K-dependent coagulation deficiency and reversal of warfarin. There is little evidence in the literature on the use of PCC in the treatment of coagulopathy from uncontrolled bleeding in children, but it may offer an alternative to FFP if volume overload is of concern. If fibrinolysis or disseminated intravascular coagulation is present, the use of PCC is contraindicated. Owing to the prolonged half-lives of prothrombin and factor X (40–72 h), patients can become hypercoagulable and are at increased risk of thromboembolism.[13]

Tranexamic acid

TXA is a lysine analogue which inhibits fibrinolysis by binding to both plasminogen and plasmin, thereby reducing the breakdown of fibrin. The CRASH 2 trial in adult trauma patients demonstrated a reduction in mortality and bleeding, particularly if given early in the resuscitation process (<3 h from injury to treatment, preferably within 1 h from injury).[14] In paediatric patients, TXA is used to reduce the amount of bleeding in at-risk surgeries, including cardiac, craniofacial, and spinal. Dosing ranges vary, but it is suggested that timely administration of TXA within the first 3 h of trauma for children is beneficial. A loading dose of 15 mg kg^{-1} is given over 10 min and a maintenance infusion of 2 mg kg^{-1} h^{-1} for at least 8 h or until bleeding stops.[15] Similar dosing regimens have been used prophylactically for surgeries at high risk of bleeding.

Table 3 provides suggestions for dosing blood products, clotting factors, and TXA.

Table 3 Suggestions for dosing blood products, clotting factors, and TXA

Drug	Dosing
Cryoprecipitate	5–10 ml kg^{-1}
Fibrinogen concentrate	70 mg kg^{-1}
Prothrombin concentrate	25–50 IU kg^{-1}
Factor VII	90 μg kg^{-1}
Tranexamic acid	Loading dose 15 mg kg^{-1}, maintenance 2 mg kg^{-1} h^{-1} for 8 h (or bleeding cessation)

Conclusion

Massive haemorrhage in paediatric patients is a stressful and hazardous situation for all concerned. Management requires assessment of initial and ongoing blood loss with frequent evaluation of response to therapy. The aim is for resuscitation using adequate volume and composition of blood products to treat and prevent anticipated changes in coagulation. Massive transfusion protocols have been designed to ensure these requirements are met and have been shown to be feasible in paediatric practice. Point-of-care testing, using TEG and ROTEM, may provide a useful adjunct to laboratory testing to more quickly and accurately guide blood product use. TXA and single and multi-factor concentrates may be useful in the management of massive bleeding and therefore may warrant consideration in the development of future paediatric massive transfusion protocols.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Principles of total intravenous anaesthesia: practical aspects of using total intravenous anaesthesia

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Key points

- Co-administration of propofol and remifentanil by target-controlled infusion (TCI) is highly effective for obtunding response to noxious stimuli and constitutes 'ideal' total i.v. anaesthesia (TIVA).
- Currently, no evidence supports the use of one propofol TCI model over another and all have proved reliable in clinical practice.
- Titration of effect-site concentration to patient response is vital throughout induction and maintenance phases of TIVA.
- TIVA typically achieves a deep plane of anaesthesia—a processed EEG device is indicated principally for the prevention of excessive hypnosis.
- Awareness occurs with TIVA when technical failure prevents the administration of appropriate drugs—vigilance for such errors is essential.

Advanced pharmacokinetic models for target-controlled infusion (TCI) have facilitated an increasing use of total i.v. anaesthesia (TIVA) in various clinical settings. The technical complexity and labour-intensive methodology of TIVA can deter clinicians and lead to default use of a volatile agent.

Pharmacological agents used for TIVA

In theory, any combination of i.v. hypnotic(s) and opioid(s) can be used and opioid-free techniques are described. In practice, the synergy between TCI infusions of propofol and remifentanil proves highly effective at obtunding response to noxious stimuli[1] and for this article constitutes 'ideal' TIVA. This drug combination achieves equilibrium between adequate depth of anaesthesia and rapid recovery. Intermittent boluses of agents or manually controlled infusions may produce an inadequate effect.[2]

Types of surgery

The specific indications for TIVA are given in Table 1. TIVA is applicable to nearly all types of surgery but has particular value in clinical scenarios where a stress-free awake extubation free of laryngospasm is required. TIVA confers many advantages over a conventional volatile technique, particularly a better recovery profile with reduced risk of postoperative nausea and vomiting, and can facilitate intraoperative wake-up while retaining amnesia. The use of TIVA for cases requiring a rapid intubation sequence is controversial but is safely practiced.

Choice of propofol TCI model

Choice of propofol TCI model is determined principally by the programming available in commercial infusion devices, and whether the patient's age is ≥16 yr. Currently, there is no evidence to support the use of one model in preference to another and all have proved reliable in clinical practice. All models have similar limitations in terms of the accuracy and stability of predicted plasma and effect-site concentrations. Most anaesthetists have experience of using Marsh plasma-targeted infusions for sedation and are re-assured when embarking on TIVA that this model administers a larger mass of drug for any given numeric

target (Table 2). Migration to the Schnider or modified Marsh effect-targeted models occurs as confidence and experience accrue.

Starting the infusions

The TIVA novice typically asks '*are propofol and remifentanil infusions started simultaneously?*' Experienced TIVA practitioners have their preferred recipe for induction and the answer may vary.

- When both agents are to be given by effect-site targeting, the answer is undoubtedly yes.
- The situation is less clear when an effect-targeting propofol model is used with remifentanil in plasma-targeted mode. If the drugs are started simultaneously, the propofol effect-site concentration will increase much more rapidly than remifentanil and useful synergy of action is difficult to obtain early on. An alternative approach is to start the remifentanil first and allow equilibration at the effect-site before commencing propofol. This speeds subsequent induction as anaesthesia is achieved at lower propofol effect-site concentrations. Apnoea is a significant risk and effective pre-oxygenation must be accompanied by reminders to the patient to breathe deeply.
- When plasma-targeted infusions of both agents are started simultaneously, remifentanil equilibrates at the effect-site long before propofol. This can result in an apnoeic but potentially aware patient unless the propofol target is significantly 'over-pressured'. This latter approach is akin to a large manual bolus with the likelihood of adverse cardiovascular effects. Allowing remifentanil to equilibrate at the effect-site before starting the propofol is a useful technique with risks and benefits as described in the previous section.

Selecting TCI targets

Highly effective drug synergy allows the choice of high propofol/low remifentanil effect-site concentrations or the converse to achieve a desired clinical effect.[1] The use of a low propofol/high remifentanil combination allows more rapid recovery but is associated with apnoea and the need for assisted ventilation. Many clinicians use such a combination for short cases instead of allowing the patient to breathe a volatile agent spontaneously. Remifentanil has little hypnotic action and it is recommended that for the majority of patients, a minimum effect-site propofol concentration of 2 μg ml^{-1} (for patients >50 yr of age) or 3 μg ml^{-1} (<50 yr) is maintained. Individual clinical response to propofol and remifentanil TCI is highly variable and although effect-site concentrations may be suggested (Table 3), these cannot be guaranteed as invariably efficacious (see example in Fig. 1).

Table 1 Specific indications for TIVA

Malignant hyperthermia risk
Long QT syndrome (QTc ≥ 500 ms)
History of severe PONV
'Tubeless' ENT and thoracic surgery
Patients with anticipated difficult intubation/extubation
Neurosurgery—to limit intracranial volume
Surgery requiring neurophysiological monitoring
Myasthenia gravis/neuromuscular disorders, and situations where NMBs are of disadvantage
Anaesthesia in non-theatre environments
Transfer of an anaesthetised patient between environments
Daycase surgery
Trainee teaching
Patient choice

Monitoring TIVA

At present, propofol plasma concentrations cannot be measured minute-to-minute in a practicable manner. Clinical calibration of the individual patient before 'knife-to-skin' can be achieved by noting the increments in effect-site concentrations which show:

- loss of response to shaking and shouting;
- loss of haemodynamic response or limb movement with vigorous jaw thrusting;[3]
- absence of tachycardia or even bradycardia with laryngoscopy and intubation.

This methodology provides three calibration points to guide the minimum and maximum targets to be used. If neuromuscular paralysis is required, it should not be given until a lack of response to jaw thrusting has been achieved. Titration of effect-site concentration to patient response during surgery is vital, particularly as excessive hypnosis is a more common problem than inadequate depth. It is possible to use Tivatrainer pharmacokinetic software (www.eurosiva.eu) to predict the necessary effect-site concentrations in real time during drug administration. This program graphically plots the 50 and 95% probabilities of lack of response to a noxious event (akin to 1 and 2 MAC for volatiles) when propofol and remifentanil TCIs are used simultaneously (Fig. 1). Clinical judgement and software predictions can be supplemented by the use of processed EEG data which

Table 3 Suggested minimum effect-site concentrations for TIVA in adult patients. These targets must be increased or decreased depending on individual patient response and/or processed EEG data

Suggested effect-site concentrations for TIVA				
Age (yr)	Spontaneous breathing		IPPV	
	Propofol (μg ml^{-1})	Remifentanil (ng ml^{-1})	Propofol (μg ml^{-1})	Remifentanil (ng ml^{-1})
<50	4–6	1–3	3–4	5–8
>50	2–4	1-2	2–3	3–6

Table 2 Comparison of the bolus dose of propofol and subsequent infusion rate administered to a male patient, 177 cm and 85 kg by three TCI models when the target is set at 3.5 μg ml^{-1}. Data derived from Tivatrainer 9 software (www.eurosiva.eu)

Patient age (yr)	Effect-targeted Schnider		Effect-targeted modified Marsh		Plasma-targeted Marsh	
	Bolus dose (mg)	Subsequent infusion rate (mg h^{-1})	Bolus dose (mg)	Subsequent infusion rate (mg h^{-1})	Bolus dose (mg)	Subsequent infusion rate (mg h^{-1})
40	63	830	100	1040	71	1100
80	53	670	100	1040	71	1110

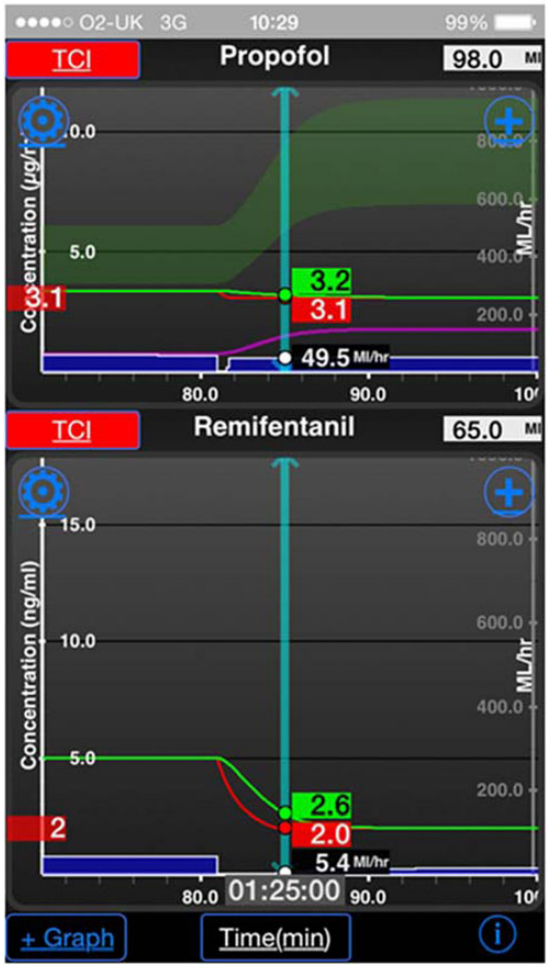

Fig 1 Screenshot from an Apple iPhone showing the perioperative use of Tivatrainer 10 software (www.eurosiva.eu). In this example, the drugs were administered using plasma-targeted models. The software is used to predict the outcome of a planned reduction in remifentanil target from 5 to 2 ng ml^{-1} when the propofol effect-site concentration is 3.2 µg ml^{-1}. The planned decrease in opioid concentration would increase the likelihood of response to noxious stimulus and could increase the chance of awareness. An increase in propofol target to 5–6 µg ml^{-1} would be needed to minimize such risk at the lower remifentanil concentration. Key: Red line/numerals, plasma target concentration; green line/numerals, effect-site concentration; blue line, pump infusion rate; green shading, range of propofol effect-site concentrations consistent with 50% (lower line) and 95% (upper line) probability of lack of response to noxious stimulus at the simultaneous remifentanil effect-site concentration. *X*-axis, time (min).

will detect excessive hypnosis but does not reliably predict response to noxious stimulus.[4]

ASA status and advanced age

TIVA is highly effective at achieving a deep plane of anaesthesia. Consequently, this technique must be used cautiously in patients compromised by advanced age or poor ASA status but still confers advantage in terms of recovery profile. The Schnider effect-model administers a lower dose of propofol (Table 2) for any given numeric target compared with the Marsh kinetics (despite the prediction of higher peak plasma concentration). Some clinicians consider this to be of advantage in the frail adult as haemodynamic side-effects are lessened. The Schnider model does include age as a modulating factor on bolus dose and infusion rate. However, this imposes only a small difference on the mass of drug administered between ages (Table 2) and should not be relied upon to prevent an exaggerated cardiovascular response. When the Minto model is used in effect-targeting mode, the bolus dose is three to four times greater than with plasma-targeting. This higher plasma concentration increases the likelihood of chest wall rigidity or severe bradycardia via non-vagal mechanisms. Consequently, Minto effect-targeting is best reserved for younger robust patients. In practice, a slowly incremented approach to the final effect-site concentration of both drugs is advocated in frail subjects irrespective of the models chosen. The clinician must assess the patient's level of consciousness and cardiovascular status before every increment in target.

Table 4 Checklist for setting up TCI systems

1. Use only dedicated pharmacokinetic TCI pumps
2. Ensure that you are trained in use of the chosen pump and pharmacokinetic model
3. Ensure the pumps have been serviced in the past 12 months
4. Ensure the pumps are plugged into the mains
5. Ensure the batteries are charged
6. Ensure that the drug dilutions are correct and are entered correctly into the pump
7. Ensure that the correct syringe type and size data are entered and that the syringes are mounted correctly
8. Ensure that the pump is programmed for the drug actually attached to it
9. Ensure that the low and high infusion pressure alarms are set (to warn of disconnection and a 'tissued' cannula, respectively)
10. Ensure that the correct patient data are entered
11. Consider if the targets set are appropriate to the patient's age and ASA status
12. What is plan B if the pump(s) fail?

Table 5 Recommendations for preventing technical problems with TIVA

1. Complete the TCI system checklist
2. Affix the i.v. cannula firmly to the patient's skin
3. Keep the site of TIVA infusion visible so that disconnection, leakage, or a 'tissued' cannula are readily detected
4. Use only a dedicated two- or three-way TIVA set which incorporates
   - anti-siphon valves on the drug administration lines
   - non-return valve on any i.v. fluid line
   - minimal dead space distal to the point of agent and/or i.v. fluid mixing
5. Use only Luer lock syringes for administering drugs
6. Do not label the remifentanil syringe until the drug has been added to the diluent
7. Always check the infusion site if a pump alarms (except 'syringe empty', 'infusion paused', or 'mains failure')
8. Flush TIVA drugs from the dead space of a three-way administration set before connection to the patient cannula, and out of the cannula at the end of the case

Setting up and using TIVA equipment

The RCoA's Safe Anaesthesia Liaison Group and the NAP5 investigators reported that technical failure accounts for most cases of anaesthetic awareness using TIVA. The recommendations in Tables 4 and 5 incorporate and extend the lessons from their publications. It is vital that TCI infusion devices are checked as thoroughly as the anaesthetic machine.

Failure of pump programming

Most commercial TCI devices 'forget' their programming with complete failure of both mains and battery power. In this situation, the clinician has three options with similar disadvantages;

- Default to a volatile-based technique with the likelihood of an exaggerated haemodynamic response due to synergism between propofol, remifentanil, and volatile molecules at the effect-site.
- Re-start the pump in manual mode using the millilitres per hour rates exhibited on the device display just before power failure. If a rapid increase in target is subsequently required, the clinician must calculate an additional bolus before increasing the infusion rate or an inadequate effect-site concentration would result.
- Re-start the pump in TCI mode. The device will be naïve to the drug already present at the effect-site and an exaggerated haemodynamic response is highly likely to occur unless the chosen target is titrated upwards incrementally.

Terminating the infusions

It is reasonable to decrease TCI targets near the end of surgery, but closure of some wounds produces intense noxious stimulation in the absence of locoregional techniques. Targets should not be reduced inappropriately just to promote a more rapid recovery (Fig. 1). Generally, the infusions are more safely stopped once the final sutures are applied. The remifentanil infusion can be continued at a target of 1–2 ng ml^{-1} to smooth extubation if desired. Delayed recovery after TIVA may be seen in patients who have received morphine at the higher end of the dose range or when the Marsh model is used in obese subjects. Patients are often content to receive assisted ventilation at subanaesthetic concentrations of TIVA drugs and may need active encouragement to open their eyes and take spontaneous breaths. Post-extubation apnoea remains a risk until remifentanil is completely cleared from the effect-site.

Potential problems with TIVA

Awareness

Clinicians often quote awareness as the reason for avoiding TIVA, although evidence to support this view is very limited. Interpretation of outcome data from some large studies[5 6] is confounded by heterogeneity in drug combinations and techniques included as 'TIVA' (Errando and Zhang, personal communications). By analogy, an 'oxygen/nitrous oxide/no volatile' technique would not reasonably be included in studies of awareness with inhalation anaesthesia. Highly controlled studies on awareness during TIVA are few in number but have failed to demonstrate an increased incidence.[7–9] Studies using an isolated forearm technique have shown equivalent rates of responsiveness in subjects receiving TIVA or volatile anaesthesia titrated to bispectral index.[10 11] Technical errors and poor application of knowledge were highlighted in the NAP5 report as the major cause of awareness during TIVA, and 75% of these cases would have been prevented by suitable education and training. Conversely, interruption in delivery of volatile anaesthesia was highlighted in NAP5 as the key factor in generating accidental awareness. The use of 'ideal' TIVA free from technical errors would have prevented nearly all of these cases by avoiding the 'gap' phenomenon which occurs with volatile agent administration. NICE has recommended deployment of a processed EEG device when administering TIVA and NAP5 emphasized that this is particularly necessary in patients who require neuromuscular paralysis. However, prevention of excessive hypnosis is probably the most beneficial outcome of using such devices during TIVA.[12]

Morbid obesity

TIVA for the morbidly obese is challenging but regularly practiced, although the current TCI models are not formally validated for use in such patients. Pump manufacturers limit the input weight to the Marsh model at 150 kg, although this can usually be increased with their proprietary software. However, a bolus dose calculated on actual body weight is likely to represent a significant overdose and attract unwanted cardiovascular side-effects at induction.

A different problem arises in the Schnider and Minto kinetics because these models use the 'James equation' to derive lean body mass (LBM). This equation generates a paradoxically diminishing value of LBM as BMI exceeds 42 in men and 35 in women. Manufacturers prevent input of anthropomorphic data exceeding these sex-specific BMI values as the derived LBM is important in the pharmacokinetic calculations.

For the Schnider model, the rate constant for drug elimination from the central compartment (K_{10}) is corrected for LBM and this limits the infusion rate applied as actual body weight increases. If BMI exceeded the critical value, the infusion rate would be insufficiently corrected and the high rate of drug administration might generate exaggerated haemodynamic effects. The converse is true of the Minto model where the central and rapidly equilibrating compartment volumes and the K_{10} rate constant increase proportionately with LBM. At BMIs above the critical value, the pump would progressively reduce bolus dose and infusion rate and an inadequate analgesic effect would be provided.

The 'correct' body mass to use with TIVA has been investigated and currently Servin's formula for calculating an input mass for TCI infusions seems most useful.

$$\text{Input mass} = (\text{ideal body weight}) + 0.4 \times (\text{actual} - \text{ideal})$$

where

$$\text{ideal body weight} = \text{ideal BMI}\ (\text{male } 22,\ \text{female } 26) \times \text{height}^2\ (\text{m})$$

However, propofol is highly lipid-soluble and excess fat in the morbidly obese provides a sink into which the agent diffuses from the plasma. Theoretically, the patient's actual body weight is required for calculation of an infusion rate which maintains the targeted plasma or effect-site concentration; under-prediction has been demonstrated in some studies using 'ideal mass' derivatives.[13] Recently, an allometric propofol TCI model for patients with actual body weights of 5–160 kg has been described and may allow uneventful TIVA for the morbidly obese in the future.

At present, caution must be exercised when providing TIVA to the morbidly obese who appear to be particularly at risk of accidental awareness when neuromuscular blocking drugs are used. Continuous clinical assessment of the obese patient is particularly important, and use of processed EEG monitoring in the morbidly obese is recommended by both NAP5 and NICE.

Analgesia and hyperalgesia

Several studies have emphasised that morphine must be administered at least 30–40 min before stopping a remifentanil infusion, and the need for doses between 0.15 and 0.3 mg kg^{-1}. The

phenomenon of acute opioid tolerance after remifentanil has been addressed in a recent meta-analysis which concluded that the use of high intraoperative concentrations is associated with small but significant increases in acute pain after surgery.[14] The use of adjunctive non-opioid analgesics and locoregional techniques are of particular benefit with TIVA, as is fentanyl 'rescue' in the immediate postoperative period.

Propofol-related infusion syndrome

Propofol-related infusion syndrome (PRIS) presents as acute metabolic acidosis and cardiac dysfunction in combination with one or more of the following features: rhabdomyolysis, hypertriglyceridaemia, or renal failure. Currently, there are no published case reports of PRIS occurring in association with TIVA. There are three cases reports where clinicians abandoned an adult TIVA technique due to discovery of an unexplained metabolic acidosis. However, these patients subsequently failed to exhibit other features of PRIS. The use of TIVA in paediatric practice is considered safe and possibly an ideal technique,[15] even though PRIS is more likely to occur when this age group is exposed to propofol sedation in a critical care setting.

Conclusion

TIVA is the default solution for a patient with malignant hyperthermia risk who requires general anaesthesia. Poor education and training in the use of this technique is likely to result in a significant risk of awareness. The use of propofol and remifentanil by TCI and adherence to simple recommendations will obviate most of this risk.

Declaration of interest

D.M. is a member of the Committee of SIVA, the UK Society for Intravenous Anaesthesia (www.siva.ac.uk).

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

Podcasts

This article has an associated podcast which can be accessed at http://www.oxfordjournals.org/podcasts/bjaed_total_intravenous_anaesthesia_vol_16_issue_8.mp3.

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Does near-infrared spectroscopy play a role in paediatric intensive care?

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Key points

- Near-infrared spectroscopy (NIRS) has played a role for many years in the operating theatre, but its role in the intensive care unit is gaining importance.
- NIRS has a role to play in the identification of low cardiac output together with serial lactate and mixed venous samples.
- The role for NIRS in critically unwell patients is increasing, especially those with sepsis and poor perfusion.
- NIRS may also play a role in the prediction of long-term neurological outcome related to low cerebral oximetry intraoperatively and after operation in the intensive care unit.
- NIRS is likely to play an increasingly important role in the coming years in paediatric intensive care.

Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS) is a non-invasive, portable technology which monitors oxygenation in the brain, muscle, and other organs. It detects subtle changes in tissue oxygenation in real time by measuring the capillary–venous oxygen saturation in the tissue directly beneath the sensor. It has been used over the past decade by anaesthetists in operating theatres, but is gaining support in the intensive care setting, especially in the paediatric congenital cardiac disease population.

History

Red-light radiation was discovered by accident in 1800 by Sir Fredrick William Herschel. It was only in the 1950s that NIRS was developed further in the manufacturing industry. The first medical publication regarding NIRS was in 1977. Throughout the 1980–1990s, there was extensive development of the equipment, especially with the development of light-fibreoptics and monochromatic detectors. The first publication of cerebral NIRS in humans was published by Ferrari in 1985,[1] but it was only in 1993 that the US Federal Drug Administration (FDA) finally approved NIRS for medical and commercial use. The first commercially available NIRS, the INVOS 3100®, was marketed in 1993 (Somanetics Corporation, Troy, MI, USA).

Technical aspects of NIRS

NIRS uses infrared light (700–900 nm) to monitor the tissue bed beneath the sensor containing small gas-exchanging vessels (arterioles, capillaries, and venules). In contrast to pulse oximetry which measures just the pulsatile arterial saturation, NIRS measures the mixed vascular oxygen saturation and is thought to roughly reflect 16% arterial and 84% venous saturation. In the optical window of 700–900 nm, light can pass easily through skin and bone, and most photon absorption is from haemoglobin.

NIRS uses the Beer–Lambert law of tissue absorption. As light passes through the tissue, a certain amount of light is absorbed and scattered. Oxyhaemoglobin and deoxyhaemoglobin mainly absorb the light, while the other components (such as adipose tissue and fat) absorb to a lesser extent. Light is scattered by tissue interfaces and cellular particles that vary with age and brain

tissue maturation. To accurately measure oxyhaemoglobin and deoxyhaemoglobin to calculate rSO_2 (tissue oxygen saturation), it is necessary to account for absorption and light scattering by other compounds, which requires a device construct utilizing at least three wavelengths and two source–detector separations. Accuracy is improved by using more wavelengths, more source–detector separations, or both.

From the differential absorption of the two wavelengths of light by oxygenated and deoxygenated haemoglobin, NIRS devices provide an estimate of oxyhaemoglobin saturation in a volume of tissue beneath the probe.

As most of the measured blood in tissues is venous, NIRS should reflect a value similar to but slightly higher than Sv_{O_2}. This is the crux in understanding the NIRS machine and the role that it plays both in the operating theatre and in intensive care.

NIRS and its role in the operating theatre

NIRS was originally developed as a device in the operating theatre which allowed real-time measurements of cerebral oximetry during deep hypothermic circulatory arrests (DHCA) and during cardiopulmonary bypass (CPB). There has been concern for many years regarding neurological outcomes post-cardiac surgery, especially in paediatric congenital cardiac surgery and this device has been used as a surrogate in the operating theatre for Sv_{O_2} (mixed venous saturations) and allows direct cerebral oximetry readings.

The optimal time for the application of the cerebral monitor is before induction of anaesthesia to allow a baseline cerebral oximetry reading to be measured.

Trends in the NIRS readings are thought to hold more value than the absolute reading. It is hoped that the ability of the NIRS machine to immediately detect changes in cerebral oxygen saturation during CPB provides an early opportunity to act, which might eventually lead to improved neurological outcome. The types of problems which could be detected by NIRS leading to altered cerebral oxygenation in an operating theatre include (but are not limited to) CPB cannulation problems, effects of deep hypothermia and low flow CPB, effects of antegrade cerebral perfusion, and effects of ventilation or anaesthetic strategies affecting cerebral blood flow. A recent study has also demonstrated normal cognitive outcomes at 12 months of age in a group of infants who underwent neonatal aortic arch repair with the use of NIRS to monitor regional cerebral perfusion.[2] NIRS may play a role in centres who perform DHCA during cardiac surgery, allowing continuous monitoring of cerebral perfusion, despite changes in pH and temperature.

The clinical applications of NIRS in the operating theatre are increasing and include cardiovascular surgery, carotid endarterectomies, neurosurgery, and in the role of tissue perfusion to name but a few.

NIRS and its role in paediatric intensive care

Low cardiac output syndrome

Inadequate oxygen delivery after congenital cardiac surgery, low cardiac output syndrome, is associated with increased morbidity and mortality in the postoperative period. The reasons for low cardiac output are multifactorial and include an inflammatory response post-CPB, the effects of a cross-clamp and myocardial ischaemia, reperfusion injury, the effects of hypothermia, inadequate cardiac protection, and finally the effects of ventriculotomy. Low cardiac output syndrome is common in a proportion of infants after cardiac surgery and can lead to late neurological impairment among survivors.

The measurement of low cardiac output has been something that intensivists have strived to measure in a non-invasive and simple way. Boyd and colleagues[3] in 1959 published a paper where catheters were placed in the left atrium and pulmonary artery to measure cardiac output by the Fick principle and mixed venous oxygen saturation (Sv_{O_2}) in 34 children after open heart surgery. They found that two-thirds of patients with a cardiac index of <2 litre min^{-1} m^{-2} and an Sv_{O_2} <50% died. In 1975, Kirklan and colleagues published the relationship between cardiac output and outcome in infants after open heart surgery. They found that a cardiac index of <2 litre min^{-1} m^{-2}, measured by dye dilution, was associated with an increase in mortality.[4] These studies highlighted the association between low cardiac output and death, therefore meaning that another monitor to allow the earlier detection of this condition has an important role to play in the postoperative period.

Markers of cardiac output and tissue perfusion are used on a daily basis in intensive care, such as serum lactate and mixed venous saturation, pH and base excess, and clinical indicators such as colour of the skin, presence of mottling, urine output, core–peripheral temperature difference, capillary refill time, hypotension, tachycardia, and poor pulses. Objective cardiac output measurements include indicator dilution (dye, temperature, lithium), oxygen consumption (Fick), bioimpedence, and Doppler.[5] These are generally too cumbersome and technologically challenging to be used on a daily basis in intensive care and this is one of the reasons that NIRS may play a vital role as a non-invasive tool to detect early low cardiac output by looking at decreases in cerebral oximetry due to increased cerebral oxygen consumption. This allows early intervention resulting in improved patient outcome.

NIRS is used as a proxy for Sv_{O_2}. Several studies have looked at the correlation between cerebral oximetry and Sv_{O_2}, jugular venous saturation, or mixed venous saturation in neonates and infants after cardiac surgery. In a prospective, observational study, Ranucci and colleagues[6] found that cerebral Sv_{O_2} correlated with SVC saturation (Sv_{O_2}) in paediatric cardiac surgical patients, although the venous saturation tended to be higher than the cerebral Sv_{O_2}. The correlation was better in cyanotic patients. NIRS was found to be a reliable trend detector and changes in cerebral Sv_{O_2} correlated with changes to Sv_{O_2}. In a prospective, observational study of 52 neonates and infants after cardiac surgery, Kaufmann and colleagues[7] showed a significant correlation between Sv_{O_2} measured from either the flank or abdomen and venous saturation.

NIRS can be used either together with or instead of other devices for measuring tissue oxygenation such as LiDCO (lithium dilution cardiac output) or PiCCO (pulse contour cardiac output monitoring).

What NIRS reading should you start treating?

In healthy neonates, infants, children, adults, and even animals, Sv_{O_2} ranges from 60 to 80%. Normothermic cerebral desaturation to the 30–45% range is associated with biochemical and histological evidence of injury in a wide variety of animal models, and time dependency has been demonstrated. Brain injury increases hourly at Sv_{O_2} <40%.[8] Thus, there is a buffer between normal and cerebral hypoxia–ischaemia.

In the case of trending devices, it is indicated to restore rSO_2 values in the normal range when the rSO_2 values decrease below 20% of normal.

See Table 1 for treatment of desaturation.

Table 1 Treatment of desaturation

- Check the sensors and ensure that they are properly applied to the skin surface
- Check the cerebral oxygen return: this is especially applicable when the child has either ECMO or bypass cannulas in place. The head position needs verification and the cannula flow and positions need to be checked and corrected
- Arterial pressure needs to be adequate to ensure that you have adequate cerebral perfusion. Vasopressors or an increase in the pump flow may be needed to improve perfusion
- Systemic oxygenation may be inadequate. This can easily be checked with blood gas analysis and easily rectified with increasing the inspired oxygen concentration
- pH needs to optimized and >7.2. Hypercarbia needs to be avoided, as does a metabolic acidosis
- Haemoglobin needs to be checked and optimized

Evidence for NIRS in paediatric intensive care

One of the most compelling pieces of research is from Phelps and colleagues. This research showed that low regional cerebral oxygen saturation as displayed by NIRS in the first 48 h after the Norwood procedure has a strong association with subsequent adverse outcome.[9] Similarly, an rSO_2 of <45% for >180 min in the perioperative period among infants undergoing Norwood procedure is associated with MRI findings of brain injury.[10] These studies have led to a surge in the use of NIRS in the univentricular population. Johnson and colleagues retrospectively looked at a group of neonates pre-Norwood procedure comparing those who had NIRS with those who did not before operation. It was noted that those with NIRS had fewer incidences of intubation and mechanical ventilation pre-Norwood compared with those who did not have NIRS. The NIRS group had a higher Sa_{O_2} (92% *vs* 88%, *P*=0.001) and this higher Sa_{O_2} was not associated with impaired systemic oxygen delivery and did not lead to earlier palliation or surgery.[11] More recently, a pilot study was published in *Cardiology in the Young* which showed in a small group of 10 patients an inverse relationship between cerebral NIRS reading and serum lactate level. This was especially true when the cerebral NIRS reading was <60% and in the biventricular population.[12]

NIRS sites other than the brain

Originally, NIRS was used to measure cerebral oxygenation, but now its use has evolved to evaluate oxygenation of tissues other than the brain. These other somatic sites include over the liver, abdomen, kidney, or muscle such as the thigh. The sensor can simply be placed on the body part of interest, for example, the flank in the case of a child where you are interested in renal perfusion.

Mesenteric rSO_2 in infants shows a close relationship to Sv_{O_2} and lactate in the early postoperative period after CPB.[13] Mesenteric desaturation by NIRS was related to the development of necrotizing enterocolitis in medical neonates.[14]

Renal NIRS (T12–L1) in the first 24 h after CPB predicts the extent of creatinine elevation at 48–72 h, suggesting the relationship of this regional measure to ischaemic organ injury.[15]

It has been found that two-site NIRS monitoring provides better estimate of Sv_{O_2} than monitoring in either the cerebral or somatic sites alone. Chakravarti and colleagues published the usefulness of two-site NIRS measurements in 2009. They showed a strong correlation between the averaged cerebral Sv_{O_2} and the development of lactic acidosis in children after cardiac surgery. An averaged cerebral and renal Sv_{O_2} reading <65% predicted a lactate level >3.0 mmol litre^{-1}, with a sensitivity of 95% and a specificity of 83% (*P*=0.0001).[16]

The two-site approach can be applied clinically when assessing volume of distribution such as in shock states, during CPB, and with vasoactive drug treatment. There is growing evidence of the use of NIRS for head-injured patients, dehydrated patients, and volume resuscitation in hypovolaemic shock, where multisite NIRS plays a role.

However, a recent paper disputes the use of multi-site somatic NIRS and its usefulness in predicting low cardiac output states in the paediatric population. Bhalala and colleagues[17] showed that in a population of 20 paediatric patients undergoing congenital cardiac surgery, the use of splanchnic and renal NIRS did not predict low CO.

See Table 2 for an explanation of all recent evidence for NIRS in paediatric intensive care.

NIRS and its association with long-term outcomes

NIRS with its ability to recognize and allowing us to treat cerebral deoxygenation in a timely manner should be associated with improved long-term outcomes. As discussed earlier, Andropoulos and colleagues[2] published MRI findings and neurodevelopmental outcomes in children at 12 months of age when regional cerebral perfusion was utilized during aortic arch reconstructions. The children in whom a neuromonitoring technique was used had similar neurodevelopmental outcomes to the reference population norms. Kussmann and colleagues[24] also recently looked at NIRS and long-term outcome and examined over 100 children undergoing biventricular repair with NIRS monitoring. Perioperative periods of diminished cerebral oxygen delivery, as indicated by rSO_2, were associated with 1 yr PDI (Psychomotor and Developmental Indexes of the Bayley Scales) and brain MRI abnormalities among infants undergoing cardiac surgery. These studies support the use of NIRS for long-term cognitive sparing in this population.

Advantages to the NIRS monitor

NIRS possesses some unique characteristics such as being non-invasive, real time, and a continuous measurement of regional tissue oxygen saturation. It allows assessment of trends and interventions to occur in a timely manner. There is a strong belief that NIRS monitoring may improve outcome after paediatric cardiac surgery, but we are aware that NIRS, like most other monitors in the operating theatre and in the intensive care unit, is not validated for its use. A recent review article supports NIRS as a haemodynamic monitor in the critically unwell patient identified Class II level B evidence.[25]

Limitations to NIRS

Caution must be exercised in extrapolating regional measurements to global findings. Changes in regional oxygen saturation may reflect local changes and not necessarily indicate global hypoperfusion.

As mentioned above, no study has validated the correlation of low NIRS reading with other measurements of low cardiac output. Low regional cerebral oxygenation measurements do not necessarily indicate a low cardiac output state or global altered cerebral perfusion.

Table 2 Studies supporting NIRS in PICU

Study	Study population	Conclusion
De Oliveira and colleagues[18]	SVC Sv_{O_2} in the outcome of septic shock in paediatric patients	It was found that the addition of venous saturation monitoring improved survival, with the greatest impact in patients with initially low Sv_{O_2}
Hoffmann and colleagues[19]	Sv_{O_2} post-Norwood procedure	An early postop detection in low Sv_{O_2} and early treatment of same improves survival
Chakravarti and colleagues[16]	Cerebral and renal NIRS compared with serum lactate in children after cardiac surgery	A strong correlation was found between the averaged renal and cerebral rSO_2 and the development of lactic acidosis. An average cerebral and renal Sv_{O_2} <65% predicted a lactate level >3.0 mmol litre^{-1}
Hoffman and colleagues[20]	Cerebral *vs* renal-somatic NIRS in postop cardiac neonates	NIRS can identify altered perfusion observed in shocked states. NIRS can be used to assess the global O_2 economy after complex cardiac surgery
Fortune and colleagues[14]	Cerebral and mesenteric NIRS probes to evaluate the risk of developing necrotizing enterocolitis	As the somatic/cerebral rSO_2 ratio decrease to <75%, the risk of developing necrotizing enterocolitis was eight times greater
Hoffmann and colleagues[21]	Renal rSO_2 measurements post-Norwood procedure and the prediction of developing renal failure day 3 postop	rSO_2 measured in the renal region in the first 24 h predicted the development of renal failure on day 3 postop
Abdul-Khaliq and colleagues[22]	Congenital heart disease children, comparing cranial NIRS with jugular venous bulb saturation	NIRS measured from the side of the head correlated closely to jugular bulb saturation
Hoffmann and colleagues[23]	Neonatal single ventricle population postop, their Sv_{O_2}, and neurodevelopment	An average 48 h postop cerebral rSO_2 <55% was associated with impaired neurodevelopmental outcome, assessed at school age

There can be interference related to extra-cerebral tissue such as scalp, skull, dura, skin, and so on. Hyperbilirubinaemia and excess melanin will cause a reduction in the rSO_2 relative to the regional venous measure.

There is concern regarding the cerebral arterial/venous blood partitioning: there is considerable individual variation of arterial/venous ratios. There is also considerable variation in the haemoglobin content of the blood. Non-metabolizing cerebral tissue can lead to a discrepancy in the reading of the NIRS monitor.

NIRS is quite a new technology and continuing to develop. There is no gold standard to compare it to and it will take time for the technology to evolve and mature.

Evidence-based medicine is needed to distinguish myths and habits from what is effectual and what actually produces a result. Therapeutic interventions for critically ill children are often performed with imperfect evidentiary data, commonly extrapolated from adult studies, or absent entirely.[26] However, if strict evidence is needed for every aspect of care of the critically ill child, physicians will have no room to develop care effectively. None of the monitors currently being used in the operating theatre have been shown to improve long-term outcome, and it can be difficult to challenge the cerebral oximeter.

Conclusion

NIRS is a non-invasive oximetry which allows real-time monitoring of tissue oxygenation and is increasingly being used in the operating theatre to see trends in cerebral oxygenation for children undergoing cardiac surgery. It has the ability to quickly identify desaturation events in the operating theatre which provides an opportunity to correct a situation. Its role in the postoperative cardiac patient in paediatric intensive care is not fully established yet, but evidence suggests it has an important role in this area too.

Any new monitoring device needs to be validated. There is no gold standard of tissue oxyhaemoglobin content, so validation of NIRS can be difficult to do.

Lactate and mixed venous have proven their roles in the identification of poor oxygen delivery, especially in the intensive care setting. NIRS may be a valuable adjuvant tool in identifying this condition early, but more research is needed to define its exact role.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Corrigendum

The place of goal-directed haemodynamic therapy in the 21st century

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In the originally published version, the Declaration of interest section was incomplete. It should have read:

Declaration of interest

M.P.G. has received unrestricted grant funding from Deltex Medical Ltd paid to his institution (UoS/UHS/UCL/UCLH) and fees for lecturing from Fresenius Kabi (2008) and Edwards Lifesciences (2009 and 2016).

M.G.M. is Smiths Medical Professor of Anaesthesia and Critical Care UCL and a Consultant at UCLH. He is Director of the UCL Centre for Anaesthesia and The UCL Discovery Lab and a resident PI at the Institute of Spots Exercise and Health. He is a paid Consultant for Edwards Lifesciences (via UCL Consulting and independently) and Deltex in the USA. He was a National Clinical Advisor for the Department of Health Enhanced Recovery Partnership until May 2013; Stock holder and advisory board for Medical Defence Technologies LLC (^{3}Gastrostim^{2} patented); Director Bloomsbury Innovation Group a community interest company owned by UCLH Charity; Co-Inventor of ^{3}QUENCH^{2} (fluid management system) IP being exploited by UCL Business. His institution has also received charitable donations and grants from Smiths Medical Endowment, Deltex Medical and Fresenius-kabi. He was also co-author of the GIFTASUP guidelines on peri-operative fluid management; Editor in Chief of Peri-operative Medicine; on the Editorial Board of the *BJA* and Critical Care; a member of the Improving Surgical Outcomes Group; Expert advisor to the NICE IV fluids guideline development group; Chairman of the Board of The National Institute of Academic Anaesthesia; Co-Director Xtreme Everest; Co-Chair Evidence Based Perioperative Medicine (EBPOM). In the past 20 years he has also received honoraria and travel expenses from Fresenius-kabi, BBraun, Baxter, Cheetah, LidCo, AQIX, Hospira and Massimo. He does a small amount of Private Medical Practice.

J.-O.C.D. has no conflicts of interest to declare.

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Diastolic dysfunction in anaesthesia and critical care

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Key points

- Diastolic dysfunction (DD) is associated with common comorbidities such as systemic hypertension, atrial fibrillation, and diabetes.
- "Heart failure with preserved ejection fraction" is destined to become the most prevalent cause of heart failure in the UK and extubation can provoke acute heart failure in these patients.
- DD predicts weaning failure in critical care and increased perioperative risk over a wide range of non-cardiac specialities and in previously asymptomatic patients.
- Perioperative diagnosis of DD has been facilitated by the increasing use of tissue Doppler imaging echocardiography.
- New treatment options are becoming available.

Ventricular function defined by systolic ejection is well recognized by clinicians due to its readily quantifiable and interpretable echocardiographic parameters. In contrast, ventricular function defined by its diastolic capacity to fill is less widely appreciated, perhaps because abnormal relaxation and reduced compliance are more challenging properties to demonstrate and correlate clinically. Both ventricles share these properties, but left ventricular (LV) dysfunction causes the greatest morbidity. Systolic and diastolic LV dysfunction may exist together or in isolation and any combination can lead to critically raised left atrial (LA) pressure, given the physiological challenges that anaesthesia, mechanical ventilation, and critical illness can bring.

This article will describe relevant pathophysiology of LV diastolic dysfunction (DD) and its relationship with perioperative risk and demonstrate why early recognition in perioperative and critical care medicine is important. It will also discuss diagnostic methods, current and emerging treatment options, and how the perioperative pathway can be optimized in this patient group.

Pathophysiology of DD

The ventricle's ability to fill depends on its fixed viscoelastic stiffness and its variable capacity to relax. Diastole is classically divided into four stages—isovolumetric relaxation, early rapid filling, late slow filling, and atrial contraction. Isovolumetric relaxation refers to the rapid decrease in LV pressure with little or no change in volume and ends with the opening of the mitral valve and early LV filling. These early phases, sometimes referred to as LV suction, are characterized by a rapid decline in LV intracavity pressure and require energy in the form of ATP as substrate for sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase to pump cytosolic calcium back into the sarcoplasmic reticulum and enable uncoupling of actin and myosin. This mechanism helps to explain why myocardial ischaemia can raise LV filling pressure so precipitously.

Filling later in diastole is more dependent on ventricular compliance and is affected by numerous factors, including the accumulation of cytoskeletal collagen, which increases with age, longstanding wall stress, and various neuro-humoral factors. Less common causes of impaired ventricular compliance are infiltrative diseases, pericardial constriction, and collection.

Any combination of the factors above can raise left ventricular end-diastolic pressure (LVEDP) with compensatory increases in LA pressure. Consequently, as pulmonary venous hydrostatic pressure increases, so does the potential for dyspnoea and pulmonary oedema.

DD is usually asymptomatic at rest, but as it progresses, it can become unmasked by exercise or when the cardiovascular system is stressed beyond its physiological reserve, for example, during episodes of uncontrolled systemic hypertension, fluid overload, or atrial fibrillation (AF).

Tachycardia

Tachycardia shortens time for LV filling, so diastolic relaxation must occur more rapidly if stroke volume is to be maintained or increased. This is normally accomplished without an increase in LA pressure, demonstrating the normal ventricle's capacity to increase its diastolic properties under stress. However, in patients with DD, this capacity is markedly diminished and even a modest tachycardia can lead to overt heart failure.

Atrial fibrillation

The relationship between AF and heart failure with preserved ejection fraction (HFpEF) is strong, but causality is not easy to establish as the two pathologies can be interdependent. Structural remodelling and LA dilatation resulting from DD and LA pressure overload is a common cause of AF, while longstanding AF can cause a tachycardia-induced myopathy, raised LV filling pressure, and LA dilatation. In patients with DD, new-onset AF causes loss of late LV filling with an immediate reduction in preload, systolic ejection, and cardiac output.

Ventricular loading conditions

Loading conditions refer to the combination of preload and afterload acting on the ventricle at any one time. General anaesthesia, mechanical ventilation, and the surgical stress response affect LV loading conditions variably but in patients with DD, tracheal extubation carries greatest risk. The combination of tachycardia, increased ventricular preload (antecedent intravascular volume expansion, coughing with deep spontaneous inspiratory effort), and increased LV afterload (circulating catecholamines, systemic hypertension, zero PEEP) can combine to raise LA pressure high enough to precipitate acute pulmonary oedema.

Heart failure with preserved ejection fraction

Between one-quarter and a half of all patients presenting with classical symptoms of heart failure have a syndrome known as 'HFpEF' in which symptomatic pulmonary congestion is associated with a systolic ejection fraction in excess of 50%. Its prevalence is increasing due to our ageing and increasingly comorbid population and in a decade, HFpEF is destined to become the most prevalent form of heart failure.[1]

Several large, community, and inpatient-based observational studies from Europe and North America have demonstrated that, when compared with patients with heart failure with reduced ejection fraction (HFrEF), patients with HFpEF tend to be older, female, have less ischaemic heart disease (IHD) but more AF and more non-cardiac comorbidities, including diabetes, obesity, peptic ulcer disease, cancer, chronic obstructive pulmonary disease, and anaemia.[1] While HFpEF is thought to include heterogenous aetiologies such as ventricular dyssynchrony, LA dysfunction, and abnormalities of global and longitudinal strain, DD can be found in at least 70% of cases.[2] Furthermore, this value is likely to be an underestimate as most HFpEF patients are diagnosed using resting echocardiography and some may develop detectable DD only when stressed or exerted.

Surgical patients with HFpEF should be identifiable by their preoperative history and clinical signs. However, those with subclinical DD can pass easily through preoperative assessment with the potential to decompensate in the operating theatre in the presence of unfavourable LV loading conditions.

Increased perioperative risk

The association between DD and perioperative complications is increasingly apparent and identification of DD appears to be important in pre-assessment for a wide range of surgical specialities.

In cardiac surgical patients, evidence of DD has been shown to predict difficulty in weaning from cardiopulmonary bypass and other postoperative complications.[3–5]

In high-risk vascular patients, the presence of DD (with or without preserved ejection fraction) was independently associated with postoperative adverse events (P=0.002) and increased hospital length of stay [7 days (range 5–10) *vs* 5 days (range 4–6), $P \leq 0.001$].[6]

In patients undergoing low- and intermediate-risk surgery, a preoperative diagnosis of DD (with or without preserved ejection fraction) was independently predictive of postoperative pulmonary oedema [odds ratio (OR) 4.6, 95% confidence interval (CI) 2.9–7.2, $P \leq 0.001$] and major cardiac events (OR 4.0, 95% CI 2–7.9, $P \leq 0.001$).[7]

In patients undergoing vascular surgery, even the presence of asymptomatic DD has been shown to be independently associated with postoperative 30 day cardiovascular events (OR 1.8, 95% CI 1.1–2.9) and long-term cardiovascular mortality (OR 3.0, 95% CI 1.5–6).[8]

Failure to wean from mechanical ventilation

Weaning from mechanical ventilation coupled with discontinuing sedation can lead to adrenergic stimulation, hypertension, and tachycardia, which may provoke overt heart failure in at-risk patients.

The periodic withdrawal of ventilatory support to assess an intensive care unit (ICU) patient's potential for successful extubation is known as a 'spontaneous breathing trial' (SBT). In an observational study of patients being weaned from mechanical ventilation, including a variety of physiological and comorbidity-related variables, echocardiographic evidence of DD was found to be the most powerful independent predictor of failed SBT (OR 6.6, 95% CI 1.2–27, P=0.03).[9] These findings were supported by another study which demonstrated that LV DD was predictive of weaning failure, whereas LV systolic dysfunction was not.[10]

Sepsis

A recent meta-analysis of patients with sepsis, severe sepsis, and septic shock found that DD was present in 48% and was significantly associated with mortality (RR 1.82, 95% CI 1.12–2.97, P=0.02).[11] Interestingly and in contrast, systolic dysfunction was present in only 30% and this was not associated with mortality. Future treatments for septic shock may be directed towards potential DD and the β-blocker esmolol is currently under evaluation in this patient group [ESMOSEPSIS trial (ClinicalTrials.gov identifier: NCT02068287)].

Diagnosis of DD

Specific echo measurements are necessary to make a formal diagnosis of DD. However, there are simpler, more accessible ways to recognize when patients either have the condition or may be at-risk of it.

History taking, clinical examination, bloods, ECG, and basic two-dimensional (2D) echo information at the preoperative visit can help detect the structural abnormalities associated with either its cause (left ventricular hypertrophy, LVH) or effect [atrial enlargement, pulmonary hypertension (PH) and RV dysfunction].

History

Early in the disease, recognition of DD can be difficult, especially at the preoperative visit. However, clinical suspicion of DD should be heightened by a history of several cardiac and non-cardiac risk factors.

Cardiac risk factors include LVH, systemic hypertension, and coronary artery disease. Non-cardiac risk factors include increasing age, female sex, diabetes, and renal impairment.

As the disease progresses, breathlessness, reduced exercise tolerance, and orthopnoea ensue, even in the presence of a normal LV ejection fraction.

Associated structural abnormalities

Left ventricular hypertrophy

All patients with LVH, regardless of its cause, will have some degree of DD. Voltage criteria for LVH are satisfied when the combined ECG voltages of the V2 S wave and V5 R wave exceed 35 mm, but LVH is then quantified in the TTE parasternal long axis (PLAX) view.

LA enlargement

LA enlargement indicates remodelling due to chronic atrial pressure/volume overload and in the absence of significant structural heart disease, this is likely to be caused by DD. A broad (>120 ms) and sometimes notched (or 'bifid') P-wave in lead II with deepening (>1 mm) of the negative P-wave segment in V1 is known as 'P mitrale'. LA diameter can be measured in the TTE PLAX view or 'eyeballed' in relation to the size of its neighbouring aortic root. LA area can be measured in the apical four-chamber (A4C) view.

Pulmonary hypertension

In the absence of obvious structural heart or chronic lung disease, PH should invite suspicion of DD. A formal diagnosis of PH requires Doppler interrogation, but associated RV dilatation and/or systolic impairment seen in the 2D TTE A4C view can provide supportive evidence.

Right atrial enlargement

Right atrial (RA) enlargement indicates chronic RV pressure or volume overload and in a patient without significant valvular or chronic lung disease, this is also likely to be the result of DD of either or both ventricles. An abnormally tall P-wave in lead II (>2.5 mm) and positive segment of the P-wave in V1 (>1.5 mm) is known as a 'P pulmonale'. RA size is best eyeballed or measured in the 2D TTE A4C view.

Biomarkers

Brain natriuretic peptide (BNP) and its inactive N-terminal fragment pro-BNP (NTproBNP) are released by the ventricles during periods of excessive myofibrillar stretch associated with high filling pressure. Their half-lives are 20 min and 1–2 h, respectively, so both can be used to screen for heart failure in symptomatic patients with strong negative predictive value at thresholds of 35 pg ml^{-1} for BNP and 125 pg ml^{-1} for NTproBNP.[12] Elevated levels can be found in other conditions such as renal disease.

Doppler assessment

In patients with sinus rhythm, conventional pulsed wave (PW) Doppler of trans-mitral bloodflow reveals a biphasic waveform. The initial (E) wave represents early, passive LV filling and the following (A) wave results from active atrial contraction (Fig. 1A and B). The relationship of these peak velocities is known as the E/A ratio and, varies according to LV diastolic properties and the pressure gradient between the LA and LV.

Previous American Society of Echocardiography (ASE) guidelines for the evaluation of LV diastolic function recommended a variety of PW measurements to grade severity of DD including E/A ratio, E wave deceleration time, and pulmonary venous flow analysis.[13] However, these measurements are challenging for the non-cardiologist to interpret, poorly validated, and often difficult to obtain in critically ill patients. Furthermore, all conventional Doppler measurements are strongly influenced by loading conditions that, as described previously, are highly variable in this patient group. In addition, pathology that alters normal trans-mitral flow, such as mitral valve disease or AF, will render interpretation of diastolic function inaccurate or impossible from these measurements. In April 2016, the ASE published updated, and considerably simplified, guidelines that recommend the use of just four variables: E/A ratio, LA volume index, tricuspid regurgitation velocity (a surrogate measure of PA pressure), and data derived from Tissue Doppler at the mitral annulus.[14]

Tissue Doppler imaging assessment

Tissue Doppler imaging (TDI) uses a low-pass filter to exclude blood flow and measure tissue velocity, and it can be used to measure the velocity of longitudinal displacement of the LV basal wall as it relaxes and fills in diastole.

TDI at of the mitral annulus reveals a waveform that is similar in shape to the PW trans-mitral (inflow) E and A waves but, only in the opposite direction, and the corresponding peak velocities are known as e prime (e′) and a prime (a′) (Fig. 1C and D). Measurements should ideally be taken from both the septal and lateral annulus, and then averaged (Fig. 1).

If E is conceptualized as LA/LV driving pressure and e′ is the increase in LV volume, then E/e′ represents the relationship between LV pressure and volume change—or, known as elastance, with its reciprocal being compliance. Therefore, the higher E/e′ are the more likely there is to be higher the likelihood of DD. E/e′ has been shown to reflect LV filling pressure in patients with both preserved and reduced ejection fraction HFpEF and HFrEF.

TDI data are important because they are independent of loading conditions and are easy to obtain so they have considerable utility in critically ill patients. Furthermore, e′ can be measured in AF, when there is no A wave, and also in sinus tachycardia, when E and A waves are often fused, precluding conventional Doppler assessment. Importantly, accuracy of TDI can be affected by abnormalities of basal LV motion, for example, such as mitral annular disease or basal regional wall motion abnormalities.

The updated ASE guidelines have a greater emphasis on TDI to confirm or refute the presence of DD, particularly for patients with normal ejection fraction (Fig. 2), and this makes them much more applicable to patients in the perioperative and critical care setting.

Management strategies

Chronic heart failure

Disease-specific therapies aimed at the underlying pathogenic mechanisms of HFpEF have been largely unsuccessful so far.

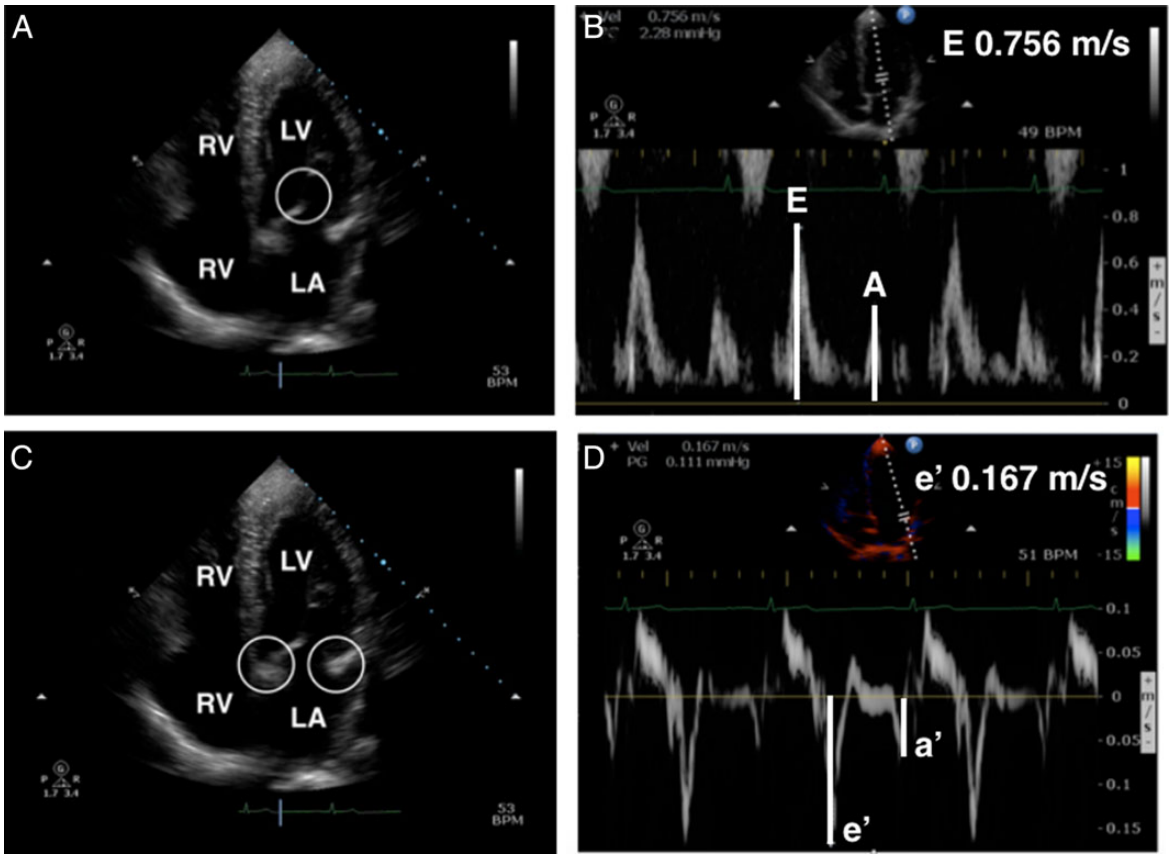

Fig 1 A4C and Doppler images required for measurement of E and e′. (A and B) The circle represents the required position for mitral inflow Doppler sampling (E) at the tip of the MV leaflets. (C and D) The circles represent the required position for TDI sampling (e′) at the medial and/or lateral MV annulus.

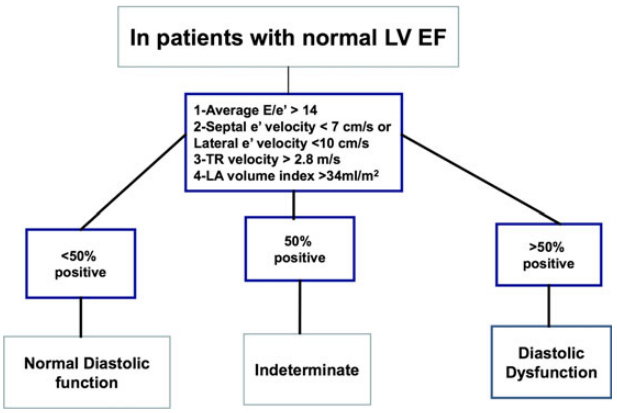

Fig 2 Algorithm for the diagnosis of LV diastolic dysfunction in subjects with normal left ventricular ejection fraction (reproduced with permission from Nagueh *et al* 2016[14]).

However, some pharmacological interventions are supported by smaller studies. Calcium channel blockers can improve exercise capacity and morbidity and spironolactone has been shown to reduce mortality but only in those with elevated serum natriuretic peptides.[15]

Recent clinical HFpEF guidelines have concentrated on pharmacological management of associated comorbidities, including systemic hypertension, fluid overload, AF, and tachycardia.[16]

In HRrEF, heart rate control is clearly important. Patients with EF<35% are currently established on maximal β-blockade and increasingly also the non-β-mediated, sino-atrial node-slowing drug ivabradine if their heart rate remains over 75 after maximal medical therapy, as advocated by NICE TA 267.

Perioperative care

Preoperative cardiology consultation and optimization is recommended in the presence of uncontrolled heart failure, IHD, hypertension, or AF.

The extent and invasiveness of intraoperative cardiac monitoring should be decided on a case-by-case basis according to the severity of DD and surgical procedure. The therapeutic window for fluid management is notoriously small in DD patients and intraoperative fluid management should focus on minimizing LV filling pressure while avoiding inadequate preload and its associated low-output state. Goal-directed fluid restriction using cardiac output monitoring may be useful, but further studies are needed to evaluate this approach in patients with known DD.

Owing to the potential problems with extubation in patients with DD, a more gradual approach may be beneficial and, in severe cases, postoperative critical care admission should be considered.

Acute heart failure

In acute heart failure (AHF), heart rate lowering should be done with caution, balanced against the risk of bradycardia and cardiogenic shock, as patients with DD are less able to increase their stroke volume and are more reliant on heart rate for modulation of their cardiac output. Rate control is the clinical priority in all patients with AF, but in those with severe DD, acute AF, and shock, return of sinus rhythm should be a key consideration.

Ventricular inotropy (contractility) and lusitropy (relaxability) are physiologically coupled. Both are affected by catecholamine-induced calcium transit out of and back into the sarcoplasmic reticulum. Also, any increase in inotropy will cause a reciprocal increase in lusitropy via increased elastic recoil. Inotropic drugs tend to improve lusitropy via these mechanisms, but this is not guaranteed.

The β-agonist dobutamine $\leq 5\ \mu g\ kg^{-1}\ min^{-1}$ has demonstrable lusitropic effect in normal hearts, but in heart failure patients, this is blunted and above this dose, lusitropy is non-existent.[17] Tachycardia and arrhythmias are common side-effects.

The β-independent phosphodiesterase inhibitor milrinone[18] and, more recently, the calcium-sensitizer levosimendan[19] have both demonstrated short-term improvement of diastolic parameters in patients with decompensated heart failure, but definite improvements in mortality have been harder to establish. These drugs may benefit DD patients in combination with established β-blockade.

Few studies have evaluated outcomes in treatments for AHF, a recent exception being the RELAX-AHF randomized, placebo-controlled trial, which evaluated a 48 h infusion of serelaxin, the recombinant form of human relaxin-2. Treatment was well tolerated and significantly improved dyspnoea, early AHF worsening, length of hospital stay, and 180 day cardiovascular and all-cause mortality equally in both HFpEF and HFrEF patients.[20] Where so many others have failed, serelaxin may succeed to become a DD treatment option of the future.

Summary

DD is a common and frequently overlooked clinical entity in surgical and critical care patients. It has been associated with increased perioperative risk over a broad range of surgical specialities, so early recognition, and management of this condition are important if complications are to be avoided. New treatments are emerging for both chronic and AHF and the expansion of echocardiography with TDI into perioperative medicine and critical care has made recognition of DD much easier.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Intravenous lidocaine for acute pain: an evidence-based clinical update

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Key points

- I.V. lidocaine is a potent anti-inflammatory, anti-hyperalgesic, and gastrointestinal pro-peristaltic drug.
- Level 1 evidence from gastrointestinal surgery demonstrates decreased pain scores, opioid analgesic consumption, and side-effects.
- I.V. lidocaine is a useful acute pain adjunct to achieve enhanced recovery after surgery outcomes.
- Patients may show particular benefit when they have acute hyperalgesia, when opioids are not effective in treating acute pain, or both.
- Our acute pain service experience confirms that with careful patient selection, appropriate monitoring, and nursing policies, lidocaine infusions may be safely continued for several days after operation.

Poorly controlled acute pain remains one of the most undesirable consequences after surgery. Despite increased awareness and widespread efforts to address this, reports continue to estimate that a significant number of patients undergoing surgery experience moderate to severe pain, with a majority of them expressing dissatisfaction with their pain management.[1] Advances in multimodal analgesia have largely replaced conventional opioid mono-therapy, but continued reliance on opioids to manage postoperative pain may at least partly explain the inadequacy of conventional acute pain management.

Almost 30 yr ago, the well-known 'WHO Step Ladder' was introduced and has since become a widely accepted concept for rational pain management. This concept has had a major impact on developing the current rationale for the management of acute pain by introducing the concept of multimodal analgesia, highlighting the importance of determining pain severity, encouraging step-wise pain management, and suggesting a wider role for adjuvant agents. Even the origins of the more current concept of opioid-sparing analgesia can probably be traced back to this WHO Step Ladder.

The role of analgesic adjuvants in perioperative pain management, notably ketamine, lidocaine, and the gabapentinoids, continues to be explored. In most situations, the use of these drugs allows for further significant decrease in the requirement or reliance on opioids for adequate pain management. While clinical research in the past two decades has supported the use of these adjuvant drugs in the management of postoperative pain, their exact positioning within the original WHO Step Ladder paradigm continues to evolve. We believe that the use of some of these adjuvants should be based on the identification of pronociception which often presents as hyperalgesia.[2] This understanding of the role of pronociception, often independent of severity and coexisting with surgical postoperative pain is, in our opinion, a very important addition to the concept of the original WHO step ladder.

In our experience, adoption of this modification improves the safety and outcomes of acute pain management. Anti-hyperalgesia therapies (e.g. ketamine, lidocaine, clonidine, and pregabalin) have demonstrated decreases in pain scores, opioid analgesic consumption, and opioid side-effects. Within this group of analgesic adjuvants, lidocaine is unique in that it has been shown to improve important enhanced recovery after surgery (ERAS) outcomes—early ambulation and feeding, early fitness for discharge, and increased patient satisfaction.[3]

Lidocaine is a widely available and commonly used local anaesthetic. When administered i.v., it demonstrates anti-hyperalgesic properties that improve acute postoperative pain

management. In this review, we will briefly discuss the pharmacology of i.v. lidocaine, explore the evidence for its use, and share our experience with its use for acute pain management.

Understanding the pharmacology

Lidocaine is an amide-type local anaesthetic that exerts its pharmacological action through the block of sodium channels in neural tissues, thereby interrupting neuronal transmission. This action is best demonstrated when the drug comes directly in contact or in the vicinity of neural tissues. The systemic effects of lidocaine are also probably or at least partially, related to this mechanism.[4] The exact mechanism by which i.v. lidocaine provides systemic analgesia remains largely unknown. Published and ongoing research is continuing to support the use of i.v. lidocaine in acute pain management and is also offering some further insights into its mechanisms of action.[5–12]

An excellent review of the pharmacology of lidocaine has been published elsewhere.[4] In summary, the early clinical evidence for the analgesic effects of i.v. lidocaine came from its use in chronic neuropathic pain where the clinical benefit has been established. Basic science studies and further work in animal models suggest that the systemic effect of lidocaine occurs predominantly in damaged and dysfunctional nerves, where it prevents depolarization of the neuronal membranes. There is also some suggestion that systemic lidocaine may also reduce and/or prevent the neo-proliferation of active sodium channels and block their spontaneous firing, especially in traumatized and scarred tissues. In acute pain, i.v. lidocaine demonstrates significant analgesic, anti-hyperalgesic, and anti-inflammatory properties. It also reduces sensitivity and activity of spinal cord neurones (central sensitization) and decreases *N*-methyl-D-aspartate receptor-mediated post-synaptic depolarization. Other studies have additionally demonstrated a clinically relevant decrease in systemic inflammatory markers in patients receiving lidocaine perioperatively.[6–9]

The dose of i.v. lidocaine necessary for analgesia in the perioperative period is 1–2 mg kg^{-1} as an initial bolus followed by a continuous infusion of 0.5–3 mg kg^{-1} h^{-1}. The most widely reported and clinically effective dose range appears to be from 1 to 2 mg kg^{-1} h^{-1}. Lidocaine has a high hepatic extraction ratio and its metabolism depends not only on hepatic metabolic capacity, but also on hepatic blood flow. A continuous infusion (without a bolus) will take 4–8 h to achieve a steady-state plasma concentration (Fig. 1). On discontinuation after prolonged infusion, the plasma levels decrease rapidly (Fig. 2). The context-sensitive half-time after a 3 day infusion of lidocaine is ~20–40 min, and there is no accumulation over time in healthy individuals. Monoethylglycinexylidide (MEGX) and glycinexylidide (GX) are the two major metabolites of lidocaine. MEGX has similar convulsant and anti-arrhythmic potency as lidocaine. However, MEGX is rapidly metabolized by the liver to GX. MEGX has also been shown to decrease the clearance of lidocaine. GX has significantly less activity than lidocaine and is both metabolized and excreted by the kidney. MEGX has been known to cause toxicity in patients with cardiac failure and GX known to accumulate in patients with renal failure.

Despite the well-described safety profile in numerous clinical trials, it must be reiterated that systemic lidocaine has a very narrow therapeutic index; central nervous system (CNS) toxicity occurs (>5 μg ml^{-1}) slightly above the therapeutic plasma level (2.5–3.5 μg ml^{-1}). The factors that influence the plasma concentration of free lidocaine include the dose and rate of injection, acid–base status, hypercapnia and hypoxia, low plasma protein levels, and

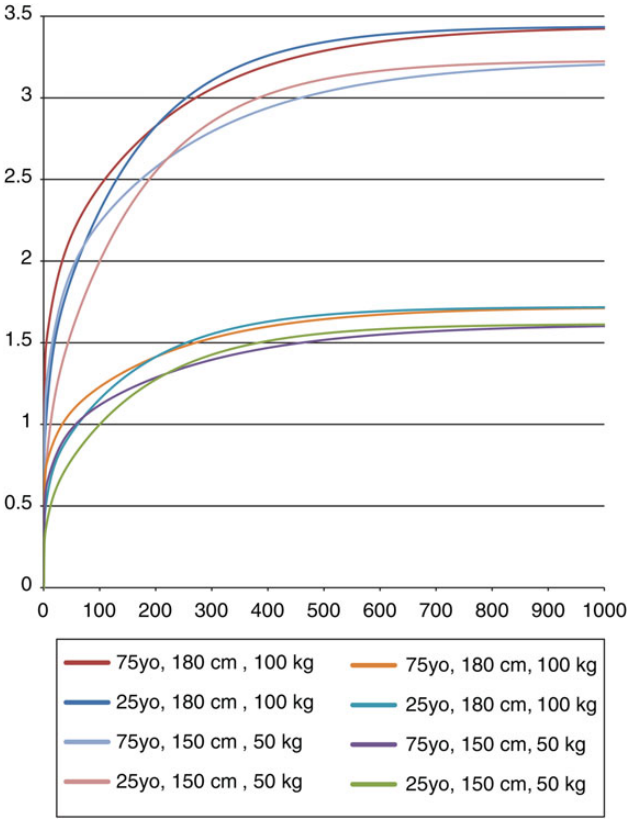

Fig 1 Pharmacokinetic simulation for i.v. lidocaine infusion (*without bolus*) with plasma concentration in microgram per millilitre is represented on the Y-axis and time in minutes on the X-axis.

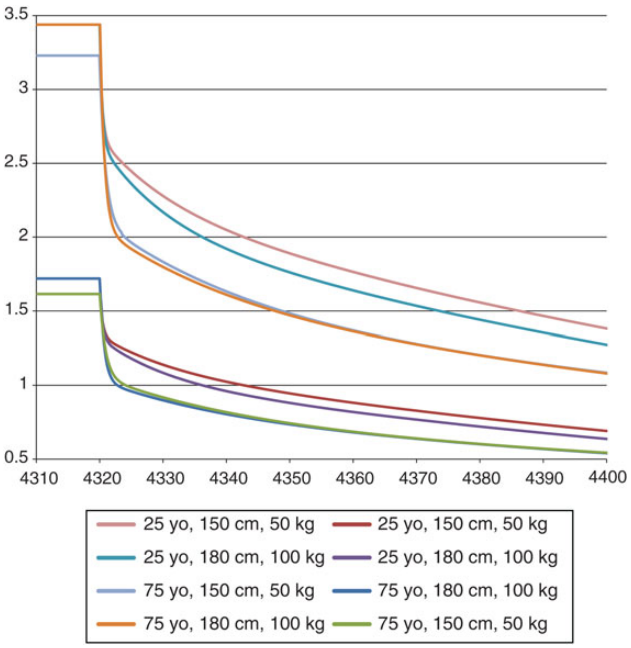

Fig 2 Pharmacokinetic simulation for i.v. lidocaine on discontinuation of infusion —plasma concentration in microgram per millilitre is represented on the Y-axis and time (*since initiation*) in minutes on the X-axis.

diminished hepatic or renal function. Very rarely do patients actually have a hypersensitivity, idiosyncrasy, or diminished tolerance to systemic lidocaine that is independent of the above-

mentioned factors. In our experience, lidocaine toxicity is almost always a result of an iatrogenic error in dose, delivery, or infusion pump programming.

The progression of clinical presentation in lidocaine toxicity often follows a well-described course and closely mirrors the increasing plasma concentration. When the plasma concentration of lidocaine exceeds 5 μg ml^{-1}, patients will first exhibit CNS symptoms of toxicity. This begins ~6 μg ml^{-1} and is quite definite at 10 μg ml^{-1}. In awake patients, these CNS symptoms follow an almost predictable progression. It begins with numbness of the tongue, metallic taste, a feeling of light headedness, and then complaint of tinnitus. Visual disturbances then progress to muscle twitching, unconsciousness, and seizure development. If undetected or untreated, this will proceed into coma, and the patient will probably suffer a respiratory arrest, cardiovascular collapse, or both. In clinical practice, the more common complaints as systemic lidocaine approaches toxic levels are sedation, sleepiness, light-headedness, relaxation, euphoria, unreality, and 'flying and drunkenness'. Toxicity with lidocaine results in cardiovascular system (CVS) signs in awake patients far less frequently than CNS symptoms for two reasons. First, lidocaine itself is less cardiotoxic than the lipophilic bupivacaine. Secondly, and probably more importantly, these CVS events occur when the serum levels exceed 10 μg ml^{-1}, which is well above that necessary to exhibit CNS toxicity (5–6 μg ml^{-1}). These CVS signs include negative inotropy (greater in patients with conduction problems or after myocardial infarction), effects on conduction (prolonged PR interval and QRS duration, sinus tachycardia, sinus arrest, and partial or complete atrio-ventricular dissociation), and effects on vascular tone (where hypertension often precedes hypotension). Once again, these effects are potentiated by acidosis, hypercapnia, and hypoxia which in turn worsen myocardial depression; increase arrhythmias; and can prove to be fatal.

An important clinical *correlate* of the i.v. lidocaine toxicology—as long as the patients are awake (or are easily aroused from sleep) and remain communicative, it is the subtle CNS symptoms and signs that precede major complications and they should therefore be carefully sought after by the nursing staff (Table 1). A *corollary* to this concept—cardiac signs will be the primary presentation if the CNS symptoms have been missed. And a *caveat* to the safety of i.v. lidocaine—decreased dosing and continuous cardiac monitoring is required in patients with cardiac, hepatic, or renal dysfunction and in those who are deeply sedated or anaesthetized—usually in the operating theatres, recovery units, or in the intensive care unit (ICU).

Evaluating the evidence

Perioperatively, when i.v. lidocaine is administered as a continuous infusion at clinically relevant doses (1–2 mg kg^{-1} h^{-1}), it usually results in plasma concentrations that remain below 5 μg ml^{-1}. Lidocaine at this plasma level is adequate to attenuate sympathetic responses, decrease pain, and demonstrate a significant volatile anaesthetic and opioid-sparing effect. This use of lidocaine for up to 24 h has been widely reported to show a significant decrease in pain, reduce analgesic requirements along with a faster return of intestinal function, and overall reduction in side-effects.

Rimbäck and colleagues[5] published one of the earliest clinical trials with i.v. lidocaine. They had previously observed that intraperitoneal lidocaine reduced the incidence of postoperative ileus and wanted to determine if this was a local or systemic effect of the drug. They enrolled 30 patients undergoing open cholecystectomy who were given radio-opaque markers to swallow before their surgery. They observed that the patients randomized to i.v. lidocaine treatment (100 mg bolus followed by 3 mg min^{-1} for 24 h) showed significant recovery in bowel motility that was confirmed by serial radiographs. These patients also had less pain, opioid requirements, and recovered faster. The investigators suggested that i.v. lidocaine reduced ileus and/or enhanced gut function recovery through one or more of five mechanisms—excitatory effect on gut smooth muscle (direct), reduced pain and opioid requirements (indirect), block of sympathetic reflexes, reduced catecholamine production, and an anti-inflammatory effect.

Groudine and colleagues[6] randomized patients undergoing open radical prostatectomy to receive placebo or lidocaine (bolus 1.5 mg kg^{-1} followed by 3 mg min^{-1} continued until 60 min after skin closure). They confirmed the safety of this regimen by estimating the plasma concentrations to remain within the therapeutic range (1.3–3.7 μg ml^{-1}). They reported a significant reduction in opioid analgesic requirements, decreased pain scores with greater satisfaction, and earlier return of bowel activity in the patients receiving lidocaine. They also noted that on the third postoperative day, when the surgical drains were being removed, most patients receiving lidocaine had either passed flatus or had a bowel movement, were ambulant, and had progressed to a full diet. These patient outcomes mentioned above are exactly those sought by many ERAS protocols and this study highlighted the possible important role played by i.v. lidocaine in achieving clinically relevant ERAS outcomes.

The effect of intraoperative lidocaine administration is sustained beyond its infusion period and continues into the postoperative period.[7] This study confirmed that patients receiving lidocaine had decreased analgesic requirements and pain scores that became more prominent 36 h after the lidocaine infusion had been terminated.

As other ERAS protocols become more widely adopted and meticulously implemented, the impact of single modalities or interventions become more difficult to define, demonstrate, or prove. Kaba and colleagues' study[8] showed that i.v. lidocaine can play an important role even in a standardized colorectal ERAS protocol. They randomized 45 patients undergoing laparoscopic colon resections to receive placebo or i.v. lidocaine (bolus of 1.5 mg kg^{-1} followed by 2 mg kg^{-1} h^{-1} for 24 h). Other than decreasing pain scores, analgesic consumption, and side-effects well beyond the duration of lidocaine infusion, they observed two other important findings. When titrated with a depth of anaesthesia monitor, patients receiving lidocaine required a significantly lower MAC of volatile anaesthetic agent. More importantly, these patients had a significant improvement in their dynamic pain scores. In other words, while the pain scores at rest were no different, on mobilization, deep breathing, and coughing, the patients receiving lidocaine were able to perform better than those receiving a standard opioid-based analgesic protocol.

At least two studies have compared i.v. lidocaine with thoracic epidural analgesia. Kuo and colleagues[9] studied patients undergoing open colonic resections and randomized them into three groups—epidural, i.v. lidocaine, and placebo. While patients with epidurals had better pain relief, lower opioid consumption, earlier return of bowel function, and lesser production of cytokines than i.v. lidocaine during the 72 h after colonic surgery, the i.v. lidocaine group was better in all respects than the control group. This study, while confirming thoracic epidural analgesia as the 'gold standard' for open surgery, suggested that i.v. lidocaine may offer a useful alternative, especially when epidurals are contraindicated, refused, or fail. In 2011, Wongyingsinn and colleagues[10] compared i.v. lidocaine with epidural analgesia for

Table 1 Summary of the Ottawa Hospital Policy for i.v. lidocaine

Stage	Treatment	Monitoring	Comments
Preparation	The initial dose is administered in a clinical area where continuous cardiac monitoring, non-invasive AP, pulse oximetry, and resuscitative equipment/cardiac arrest cart is available	• Assess clinical status, vital signs, and pain scores at rest and with activity • The patient or healthcare professional may also complete a Brief Pain Inventory (BPI) and/or DN4 questionnaire • Weight—If patient's BMI is more than 30, use ideal body weight (IBW)	The physician must be available to remain in attendance with the patient for at least 15 min after administration of the lidocaine bolus
Initiation	Bolus dose i.v. lidocaine = 1.5 mg kg^{-1} given slow i.v. push over 2–4 min followed by infusion (see below)	• Assess pain q 15 min until pain is stable, or as determined by the physician • Continuous visual patient monitoring during first 20 min after initiation of infusion, and then as per physician's orders • Oxygen saturation, AP, and heart rate: q5 min for first 20 min, then q30 min for 1 h, then as per physician's orders • Side-effects—sedation score: *None*—fully awake, alert. *Mild*—occasionally drowsy, easily aroused. *Moderate*—frequently drowsy; easily roused, drifts off to sleep during conversation. *Severe*—somnolent; difficult to arouse, minimal or no response to stimuli Sleep—normal sleep; easily aroused, RR> 10 and even, not shallow • ECG monitoring may be carried out at the discretion of the attending physician • Administer midazolam 1–2 mg i.v. p.r.n. if patient develops twitching, or tremors	• In patients with co-morbidities or at the discretion of the physician, the bolus dose can be reduced or infusion duration may be increased (given over 1 h) • If the patient develops symptoms or signs of toxicity, further treatment can be adjusted or avoided
Infusion	• Usual range for a lidocaine infusion is 0.5–2 mg kg^{-1} h^{-1} • The usual starting dose is 1 mg kg^{-1} h^{-1} • This infusion can be increased or decreased by 0.25–0.5 mg kg^{-1} h^{-1} based on clinical response (pain scores) or signs of toxicity • Allow 8 h for steady-state serum levels to be achieved before making dosage adjustments	• Observe for signs of toxicity including twitching, tremors, or seizures Hypertension may be an early warning sign of toxicity • The most common symptoms of toxicity include sedation, tinnitus, metallic taste, and perioral numbness • These symptoms usually disappear with cessation of the infusion for 1–2 h and resumption of the infusion at a decreased rate • Other signs of toxicity include respiratory depression, dizziness, confusion, blurred vision, double vision, visual hallucinations, bradycardia, hypotension, and agitation • Page/call APS stat if patient develops any signs or symptoms of toxicity and/or if there is no change in pain scores and analgesic consumption	• On the APS, routine serum lidocaine level testing is not necessary • However, in the event of life-threatening symptoms that may be attributed to lidocaine toxicity, serum lidocaine levels should be drawn and sent for analysis • These symptoms may include: hypotension, abrupt/severe change in the level of consciousness, bradycardia • In all these cases, the lidocaine infusion must be stopped immediately Note: Serum lidocaine levels take several days or weeks to be reported and are therefore of limited usefulness for APS patients • Mild sedation or other mild symptoms of lidocaine toxicity (peri-oral numbness, heavy tongue, tinnitus) should not require lidocaine blood level testing • Mild to moderate sedation can be secondary to lidocaine or opioids • Typical duration of infusion is 12–72 h, but may be extended at the discretion of APS physician to achieve bowel recovery and opioid-sparing pain control
Infusion titration and termination	• Lidocaine infusion for APS patients may be discontinued at the discretion of attending anaesthesiologist once bowel recovery is underway and oral analgesics are both tolerated and sufficient for pain control	• Patients may experience a sudden reduction in their pain scores and opioid analgesic requirements in the first 24 h after starting lidocaine • Continue to optimize multimodal analgesia • Anti-hyperalgesic medications (e.g. pregabalin) may be required to replace or supplement i.v. lidocaine	

laparoscopic colonic resections in a standardized ERAS protocol. They reported no difference in postoperative pain intensity, early mobilization, dietary intake, duration of hospital stay, and postoperative complications between groups. This study confirms that even in well-established protocols, for laparoscopic colorectal surgery, i.v. lidocaine can ensure the same ERAS outcomes as continuous epidural infusions.

Lidocaine may also be useful as an adjunct to treat postoperative ileus. Many of the above-mentioned clinical trials have suggested that lidocaine may have an indirect effect on gut motility by decreasing pain, opioid analgesic requirements, and sympathetic block.[5–10] A remarkable case series reports the use of i.v. lidocaine in the management of ileus secondary to spinal cord injury.[11] These authors report that in patients with ileus (duration 4–10 days), after a serious spinal cord injury refractory to conventional medical management, five out of seven of these patients experienced resolution of their ileus with a lidocaine infusion of 10–20 h duration. This finding suggests that lidocaine may have a more direct effect on the gut than previously considered. It is our opinion that i.v. lidocaine may prove to be the drug of choice in the management of postoperative ileus, although further controlled studies are necessary to confirm this.

Beyond the colorectal and abdominal surgery literature, the role of i.v. lidocaine has been evaluated in other surgical models with mixed results. Farag and colleagues[12] published a clinical trial that evaluated the contribution of i.v. lidocaine in 116 patients undergoing complex spinal surgery. They reported that patients receiving i.v. lidocaine (2 mg kg^{-1} h^{-1} from induction to 8 h after operation) had a significant (10–20%) reduction in pain scores and a 25% reduction in opioid consumption at 48 h. This intervention also led to a significant improvement in overall recovery for these patients. I.V. lidocaine has also been described to be beneficial in patients with chronic pain after spinal cord injury, a well-known pain model with notoriously few effective treatment options.

The use of i.v. lidocaine in other models of acute pain has produced less consistent results—for example, patients undergoing hip arthroplasty, hysterectomy, and some other procedures did not demonstrate a clinical or statistically significant analgesic benefit from this drug.[13,14] Despite these results, studies examining i.v. lidocaine in experimental ischaemic pain in volunteers, post-amputation stump pain, and in the prevention of persistent pain after breast surgery continue to provide encouraging results.[15–17] We expect more trials in a wide variety of surgical models to be performed and reported in due course.

Until this date, there have been at least six published systematic reviews with meta-analyses (Level 1 evidence) for the perioperative use of i.v. lidocaine. Sun and colleagues[3] published a systematic review which confirms that for abdominal surgery, i.v. lidocaine consistently reduces analgesic consumption, pain scores, and side-effects. When subgroup analysis compared laparoscopic procedures with open surgery, systemic lidocaine significantly improved return of bowel function and shortened hospital stay in the open surgery group.

The Ottawa experience

It has been well described that postoperative pain remains incompletely controlled in some settings and increased understanding of its mechanisms is required. It is well known that opioids are effective in treating acute pain when it is predominantly nociceptive in nature. More recently, it has been appreciated that opioids themselves can cause hyperalgesia—opioid-induced hyperalgesia. It is also known that patients undergoing certain procedures develop acute neuropathic pain and opioids are not effective in blunting this 'pronociception'.[2] Acceptance of this concept is vital to the understanding of the role of i.v. lidocaine in the management of acute pain. This concept is based on the well-known fact that opioids and anti-hyperalgesics (ketamine, lidocaine, and pregabalin) act on opposing sides of the nociception–pronociception paradigm.

When a patient is identified as having or being at risk of developing acute hyperalgesia, we recommend the use of anti-hyperalgesic medication such as i.v. lidocaine, ketamine, or gabapentinoids. The objective diagnosis of acute neuropathic pain can be made using Bouhassira's widely accepted DN4 questionnaire.[18]

We strongly believe that i.v. lidocaine plays an important role as an analgesic adjunct when used to block or treat acute hyperalgesia. We have additionally taken advantage of its versatility, easy availability, low cost, and wide familiarity of use and have observed significant clinical benefit that outweighs the potential risks from its use that encouraged us to standardize this protocol and widen its availability.

In 2009, the acute pain service (APS) of our tertiary level university hospital implemented a protocol for the use of lidocaine infusions for perioperative pain management (summarized in Table 1). This protocol allowed for the continuous infusion of i.v. lidocaine in the surgical wards without continuous ECG monitoring. We audited the first 3 yr of this protocol implementation and after research and ethics board approval, completed a retrospective quality assurance study in 2013. Patients receiving i.v. lidocaine for pain management by APS physicians were identified from the pharmacy database for the 3 yr period between September 2009 and August 2012. During this period, 169 patients received lidocaine; of which, 102 patients were analysed with complete data. The patients were 52% male with mean age 53 yr (range 18–89 yr). The indications for i.v. lidocaine are divided between laparotomy and other gastrointestinal surgeries (49%), spinal surgery (16.7%), trauma (12.7%), amputations (6.9%), hysterectomies (5.9%), other orthopaedic surgeries (3.9%), and others (4.9%). The duration of lidocaine infusion was 2–3 days for ~75% of the patients. Preoperative chronic pain and chronic opioid use were present in 50 and 35.3% of all patients, respectively. A bolus dose (mean dose of 1.34 mg kg^{-1} and range 0.75–2.5 mg kg^{-1}) was used in 95% of our patients. The lidocaine infusion dose ranged between 0.5 and 2 mg kg^{-1} h^{-1}. Eleven per cent of patients received i.v. lidocaine after failure of epidural analgesia in bowel surgeries. Mild side-effects and/or signs of toxicity were reported in six patients—the infusion was stopped for four and reduced for two patients. For ~40% of patients, lidocaine was started as an adjuvant after failure of the initial plan in controlling pain. In these patients, there was a significant (20–25%) reduction in opioid consumption within 24 h. When comparing the decrease in pain scores, patients receiving i.v. lidocaine showed a clinically relevant improvement in dynamic pain when compared with rest pain, which has been reported elsewhere by studies done by Koppert and colleagues[7] and Kaba and colleagues.[8]

Almost half of our patients underwent intra-abdominal surgical procedures. Spine and trauma surgery accounted for another 27.4% of our i.v. lidocaine usage. In the spinal surgery population, there is a higher incidence of chronic pain, neuropathic symptoms, and chronic opioid usage that make lidocaine an ideal parenteral analgesic adjunct. Our trauma population often have multiple injuries that preclude the use of regional anaesthesia techniques. Patients with rib fractures have also shown significant benefit from lidocaine infusions.

To study the safety of these prolonged infusions, we have used a three-compartment model with age, height, and weight

as covariates (Kuipers and colleagues) to simulate the pharmacokinetics of a prolonged infusion.[19] This was done for two doses of infusions—1 and 2 mg kg^{-1} h^{-1}. We have found that without an initial bolus, the levels of lidocaine increase gradually over 4 h and then stabilize at ~8 h (Fig. 1). They remain stable over the next few days in the models and then rapidly decline upon discontinuation of the infusion (Fig. 2). We find this pharmacokinetic model reassuring and in keeping with our current clinical practice. Other investigators have reported up to 14 days of continuous infusion without toxicity.[20]

Practical application

Valid and continued training of the nursing staff is of vital importance to the safe and successful implementation of this protocol. On the surgical wards, i.v. lidocaine may be used, but standard resuscitative equipment should be available for immediate use. The immediate in-house availability of the APS team during the daytime and on-call anaesthesia team after hours ensures round the clock support of the nursing staff.

An important caveat remains; that the initiation of this therapy is clearly defined as requiring the anaesthetist in attendance and to be commenced in a monitored setting. Most of our patients receiving i.v. lidocaine after operation have received a bolus (1–2 mg kg^{-1} to maximum of 100 mg over 1 min) as part of their anaesthetic induction. The remaining patients have the lidocaine commenced while they are awake in the postoperative period in the post-anaesthetic care unit or PACU, with a similar bolus dose given over 2–4 min. The infusion is started immediately after the bolus, both during the anaesthetic and in PACU at a rate of 1 mg kg^{-1} h^{-1}. In the awake patient, this rate can be adjusted upwards to 1.5 or 2 mg kg^{-1} h^{-1}. The lidocaine infusions are run for 2–3 days and can be reduced again to 1.5 or 1 mg kg^{-1} h^{-1} depending on the benefit. All patients will also receive our standardized multimodal analgesia APS protocols. When the patient leaves the PACU to the surgical ward, a protocol is printed and attached to the patient chart. For patients on i.v. lidocaine, we ensure careful bedside monitoring (Table 1) by the nursing staff, meticulous and regular follow-up by the APS team along with proper handover and communication between them and the surgical teams.

In 2009, the Ottawa Hospital implemented a formal protocol (Nursing Policy #2-397/2009) to guide the administration of i.v. lidocaine for acute pain management on the standard surgical wards (Table 1). We summarize our experience with i.v. lidocaine and focus on patient safety factors:

(i) *Patient selection*: Patients who may benefit from i.v. lidocaine are summarized in Table 2. I.V. lidocaine may have adverse effects on cardiac conductivity, myocardial contractility, and precipitate partial or grand mal seizures. Hence, caution is warranted in patients with history of any degree of heart block, heart failure, or seizure disorder. Impaired liver and renal function or drug interactions may also impair lidocaine clearance; hence, this needs to be carefully considered. A thorough list of potential drug interactions and medical conditions that place patients at increased risk was listed in the formal policy.

(ii) *Regional anaesthesia techniques*: I.V. lidocaine is contraindicated when other regional anaesthesia techniques are concurrently used, especially where bolus or large doses of any local anaesthetic are administered. Examples include epidural, plexus blocks, and TAP blocks. I.V. lidocaine infusion can be initiated 4–8 h after the last epidural or regional catheter bolus, TAP block, and is best initiated in these situations without a bolus dose. In the case of a failed epidural, as long as the epidural infusion was stopped without an epidural bolus (test dose), i.v. lidocaine can be initiated immediately—again without a bolus dose. Individual patient factors may also need consideration in all these situations and extended monitoring may be justified.

(iii) *Physician and nursing factors*: I.V. lidocaine may only be ordered by anaesthetists—all nurses on the wards where this treatment modality is to be implemented should be educated regarding the policy and procedures associated with i.v. lidocaine for acute pain management.

(iv) *Maintenance of i.v. lidocaine on the standard ward*: when i.v. lidocaine therapy is started in theatre, a critical care area such as PACU or ICU, therapeutic levels (2.5–3.5 μg ml^{-1}) may be maintained on the standard ward with no need for continuous ECG monitoring. Assessments of level of sedation, and so on are done as per i.v. PCA standards—however, ECG monitoring, Sa_{O_2}, and arterial pressure (AP) measurement device should all be immediately available.

(v) *Dose*: The usual rate of i.v. lidocaine therapy is 1 mg kg^{-1} h^{-1}. Acceptable range is 0.5–2 mg kg^{-1} h^{-1}. Need for continuation of therapy to be assessed on a daily basis.

(vi) *Initiation of i.v. lidocaine therapy*: Patients with ASA status I or II with no concern for adverse effect or drug interactions with i.v. lidocaine may be considered for initiating therapy on the standard wards. Consider portable continuous ECG, Sa_{O_2}, and AP monitors during loading dose and for 15 min after. The anaesthetist may administer 1.5 mg kg^{-1} (total max. of 100 mg) i.v. by intermittent bolus over 4 min. The anaesthetist should stay in attendance for 15 min after loading dose completed.

(vii) *High-risk patients*: Less healthy patients (especially elderly, obese, and those with hepatic and renal dysfunction) are at risk for respiratory depression in the first few hours after initiation of lidocaine treatment, secondary to the

Table 2 Summary of indications for i.v. lidocaine

	Alternative to regional anaesthesia	Acute pain with pronociception (hyperalgesia)
Intraoperative	1. Epidural—contraindicated or failed 2. Laparoscopic surgery 3. Enhanced recovery protocols 4. Trauma—multiple, significant injuries	1. Opioid dependence or tolerance 2. Surgery at a site of chronic pain 3. Previous experience of poorly controlled pain 4. Substance abuse
Postoperative	1. Epidural—inadequate or failed 2. Laparoscopic converted to open 3. Trauma—burns, degloving, crush injury 4. Rib, clavicle, or sternal fractures 5. Prevention or treatment of ileus	1. Acute neuropathic pain—DN4+ 2. Opioid-sparing technique—obese, OSA, elderly, and those with opioid side-effects 3. Difficult to treat patients—chronic pain/opioid tolerance/substance abuse 4. Neuropathic pain models—spine surgery and limb amputations

opioids administered before initiation of lidocaine therapy. It may be reasonable to initiate and continue the i.v. lidocaine therapy in a higher dependency monitored area like PACU, step-down unit, or ICU. Once the dose of lidocaine has been titrated, they should remain closely monitored for 4–8 h for the plasma concentrations to stabilize. The titration of therapy and level of care needs to be individualized to the patient needs.

(viii) *Equipment and drug administration concerns (bags, pumps, and connectors)*: Use 250 ml commercially supplied bags of a standard 0.4% lidocaine solution. Ensure the bags are well labelled in their stock area and must avoid mistaking for 500 ml i.v. bags. It is preferable to use an i.v. administration pump with preprogrammed settings (0.4% and 250 ml) from a drug library for i.v. lidocaine—once i.v. lidocaine is chosen, only the patient's weight and dose (in mg kg^{-1} h^{-1}) need to be inputed. Programming of the pump is performed by the primary bedside nurse and cross-checked by another nurse before initiation. There must be protection against the possibility for gravity free-flow of the i.v. lidocaine. This is easily achieved by only administering the i.v. lidocaine via the side-port of a PCA Y-connector that has an anti-free-flow valve (often referred to as an anti-siphon valve) built into the Y-connector.

Conclusion

The concepts of multimodal analgesia and its therapeutic options in the management of acute postoperative pain are still evolving. Identification of acute hyperalgesia is an important concept that improves the safety and efficacy of acute pain management. I.V. lidocaine is a useful option in the prevention and/or treatment of acute hyperalgesia. The benefits of perioperative i.v. lidocaine infusions have been confirmed with good quality evidence; these include decreases in pain scores, analgesic consumption, and side-effects with improvements in ERAS outcomes. We are also able to attest to the safety of i.v. lidocaine infusions for postoperative pain on standard surgical wards, provided a well-established APS protocol is followed.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

Podcasts

This article has an associated podcast which can be accessed at http://www.oxfordjournals.org/podcasts/bjaed_intravenous_lidocaine_vol_16_issue_9.mp3.

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Non-invasive ventilation in the perioperative period

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Key points

- Perioperative non-invasive ventilation (NIV) may reduce the incidence of postoperative complications in high-risk surgery or patients with significant respiratory disease.
- NIV has been shown to reduce postoperative morbidity and length of stay in critical care units.
- Clear mortality benefits from perioperative NIV are difficult to demonstrate but may be present in selected patient groups.
- Appropriate staff training and monitoring environment, ideally in a critical care area, are required to facilitate safe delivery of NIV.
- The optimal settings and duration of therapy remain unclear and need to be individualized for each patient, aided by institutional guidelines.

Background

Maintenance of adequate perioperative respiratory function is of paramount importance for the safe delivery of anaesthesia and surgery and an uneventful recovery thereafter. Optimized tissue oxygenation plays a pivotal role in the preservation of organ function and is vital for wound healing and the protection of surgical anastomoses.

Physiological changes in the perioperative period

Surgical patients often experience profound physiological changes to their respiratory system. General anaesthesia reduces oropharyngeal tone and airway reflexes. A decrease in respiratory rate and tidal volumes from opioid and anaesthetic agents leads to reduced minute ventilation, hypercarbia, and displacement of alveolar oxygen. This may be compounded by a blunted central ventilatory drive. Furthermore, functional residual capacity (FRC) declines, reducing the effective oxygen reservoir. Closing capacity approaches FRC during general anaesthesia, causing small airway closure and atelectasis and ventilation–perfusion mismatch is exacerbated, leading to increased physiological deadspace and shunt. There is also increasing recognition of ventilator-induced lung injury as a contributory factor to postoperative pulmonary dysfunction.

Patient factors such as advanced age, premorbid cardiorespiratory disease, smoking, obesity, and anaemia may all increase the likelihood of developing postoperative pulmonary complications (PPC). Surgical factors include positional changes, diaphragmatic splinting, and direct surgical injury to the lungs, pleura, diaphragm, chest wall, abdominal wall, or to the nerves supplying the respiratory muscles. Impaired immune function, postoperative pain, reduced clearance of secretions, and medication side-effects may all also compound respiratory dysfunction.

Postoperative pulmonary complications

While often used interchangeably in clinical practice, the terms postoperative respiratory dysfunction (PRD), PPC, and postoperative respiratory failure (PRF) should be distinguished for an accurate consideration of the topic. PRD refers to the expected

alterations in postoperative pulmonary function as described above. In contrast, PPC can be defined as any postoperative abnormality of the respiratory system that produces an identifiable disease or dysfunction, is clinically significant, and adversely affects the clinical course. PRF has been defined as mechanical ventilation (MV) for more than 48 h after surgery or the need for reintubation and MV after postoperative extubation.[1]

The overall incidence of PPC is quoted as 5–10% among all surgical patients but as high as 40% after abdominal surgery.[1] PPC may adversely affect surgical morbidity and mortality and lead to an increased economic burden on healthcare systems.[2]

Non-invasive ventilation (NIV) has an important role in the prevention and treatment of PPC as it may prevent patient deterioration, reduce the incidence of hospital-acquired pneumonia, length of stay (LOS) in critical care and hospital, and need for MV and also confer mortality benefits in selected patient groups.[3,4] This review aims to summarize the biological rationale and current evidence behind NIV use in the perioperative period, reflecting its application across a very heterogenous patient population.

Principles of non-invasive respiratory support

NIV is a form of mechanical ventilatory support that does not require an artificial airway (tracheal tube or tracheostomy). It may be thought of as an umbrella term comprising both continuous positive airway pressure (CPAP) and non-invasive positive pressure ventilation (NPPV). Compared with invasive MV, NIV is associated with improved patient comfort, reduced need for sedation, improved neurocognitive function, and a lower rate of nosocomial infections.[4] The physiological benefits of NIV are summarized in Table 1.

NIV modalities

The immediate objectives of NIV are optimization of oxygenation and carbon dioxide clearance, relief of dyspnoea, reduction in the work of breathing, and prevention of respiratory muscle fatigue. CPAP provides a constant positive pressure throughout the respiratory cycle. This prevents airway obstruction, alveolar collapse, and atelectasis and maintains FRC while reducing left ventricular afterload. In contrast, NPPV augments the patient's inspiratory effort with a set level of positive pressure support when inspiratory flow is detected by the ventilator. Once the patient's inspiratory flow decreases below a certain threshold, pressure support reverts back to a predetermined level of PEEP, allowing spontaneous exhalation. In addition to the benefits from CPAP, NPPV augments the patient's tidal volume, reduces the work of breathing by decreasing respiratory muscle load, and promotes recruitment of collapsed lung units. Theoretically, CPAP is preferred in hypoxaemic respiratory failure, while NPPV may be utilized in hypercapnoeic patients; however, in practice, a combination of modes is often used.

Table 1 Physiological benefits of NIV

Improved oxygenation and CO_2 clearance
Alveolar recruitment
Reduction in atelectasis
Preservation of lung volumes (FRC, tidal volume, vital capacity)
Reduced work of breathing
Maintenance of airway patency (including splinting partially obstructed airway)
Reduced extravascular lung water/pulmonary oedema
Reduced left ventricular afterload
Enhanced left ventricular performance
Avoidance of complications of invasive mechanical ventilation

Interfaces

Tight-fitting masks

These include nasal masks, devices covering both the nose and mouth or full facemasks which rest on the forehead and cover the eyes. Their advantages include a small dead space, ability to deliver inspiratory pressure support, and applicability in patients with limited neck access (e.g. cervical surgery or collar). However, they are associated with increased patient discomfort, claustrophobia, pressure damage to skin and soft tissues, and risk of airway compromise in vomiting patients.

CPAP hoods

These devices encompass the entire head with a pneumatic seal at the neck. They may be better tolerated by some patients and generally achieve a good seal without major pressure points. They may be preferable to masks in bearded and edentulous patients or after facial trauma, and also allow the patient to talk and interact more easily compared with other devices. Hoods are generally limited to delivery of CPAP, and issues with noise and inability to humidify inspired gases are particular problems associated with their use.

High-flow nasal cannulae

High-flow nasal cannulae (HFNC) deliver warmed, humidified oxygen with flow rates of up to 60 litre min^{-1}, allowing delivery of higher inspired oxygen fractions to patients in respiratory distress. They also confer several advantageous physiological effects including low-level PEEP generation, washout of nasopharyngeal deadspace, preserved mucociliary function, and improved patient comfort that may improve respiratory parameters after surgery.[5]

Practical considerations

No clear guidance exists regarding optimal timing of use and pressure settings utilized in perioperative NIV. Gradual increases in PEEP and inspiratory pressure support improve patient tolerance and the lowest effective ventilator settings required to achieve predefined therapeutic targets (improved dyspnoea, respiratory rate, or Pa_{O_2} and Pa_{CO_2} values) should be used. Clear explanation to the patient, ideally in the preoperative setting, can significantly enhance postoperative NIV success. Nasogastric tubes can be used for gastric decompression but are not mandatory in all clinical settings. Provision of enteral nutrition is not contraindicated but should be balanced against the risk of potential pulmonary aspiration. Either intermittent or continuous NIV may be utilized depending on the clinical context. The former is generally better tolerated by the patient and allows breaks for oral intake and communication.

A clear strategy outlining periods on NIV, rest intervals, and overall daily NIV duration should be agreed and communicated to both patients and care providers. As the patient's clinical condition improves, the duration or frequency of NIV cycles may be reduced. However, the optimal overall duration of NIV therapy for individual conditions has not yet been established and should be a focus for further research. The use of NIV should be one part of an overall perioperative strategy including adequate

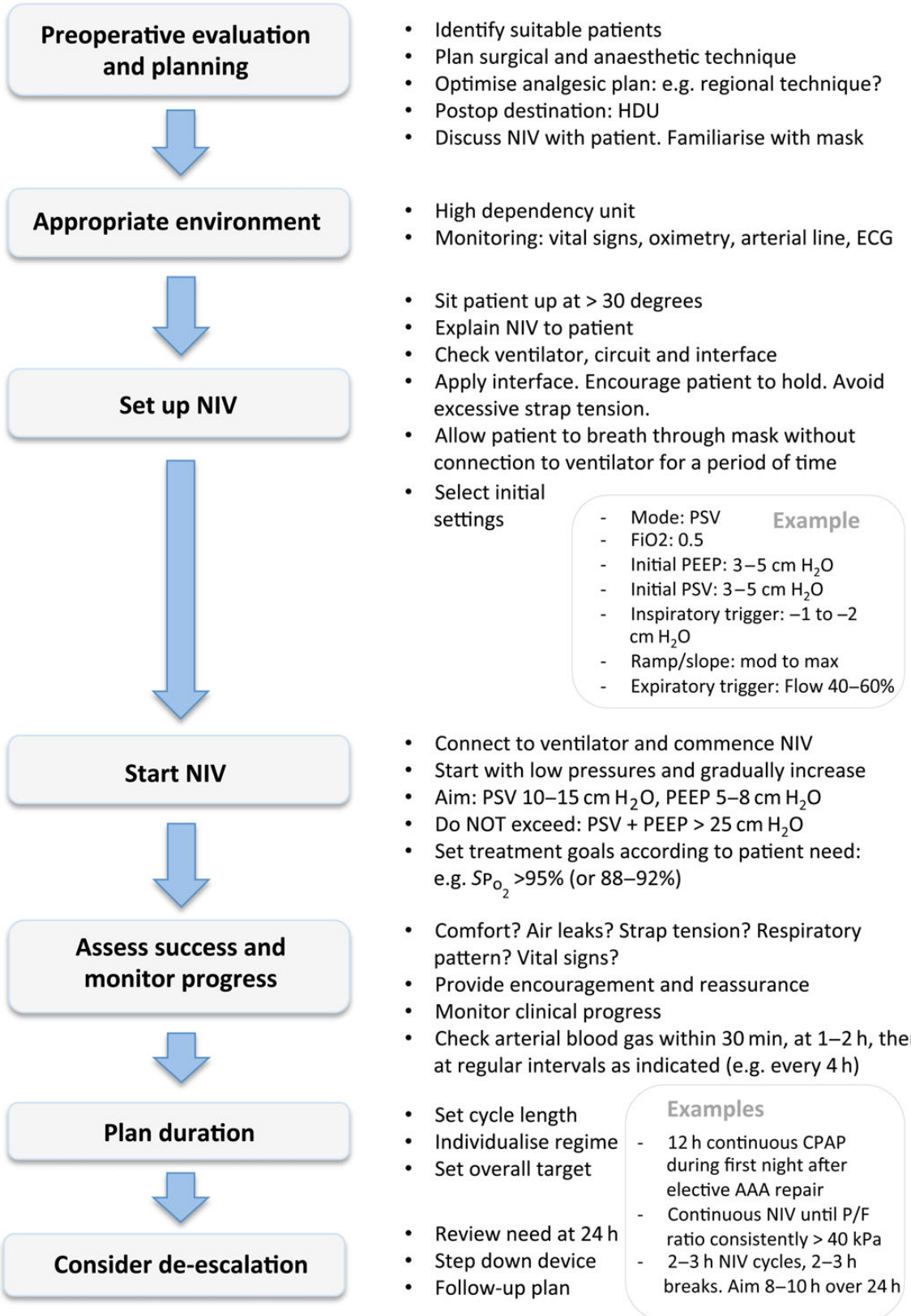

Fig 1 A practical guide to perioperative NIV use.

analgesia and antiemesis, early mobilization, physiotherapy, and breathing exercises and should be supported by an organizational framework facilitating preoperative patient selection, staff training, robust clinical governance, and patient follow-up. An example of a practical approach to perioperative NIV is given in Figure 1.

Where to manage NIV after surgery

In general, patients requiring postoperative NIV should be managed in a critical care area to allow close monitoring, frequent sampling of arterial blood gases, and rapid escalation to invasive ventilatory support if required. Furthermore, critical care units are familiar with the provision of NIV, the management of the surgical condition, and common postoperative problems. The main exception to this is patients with sleep-disordered breathing on long-term domiciliary CPAP who may, depending on the nature of their surgery and type of anaesthetic received, be suitable for surgical ward-based care. Local practice and protocols will vary, but patients with their own CPAP machine who are able to put on a mask and operate the device themselves and who have received either regional anaesthesia or a general anaesthetic of short duration with minimal opiate requirements may be managed on general wards with their own machine. Patients on home CPAP who have undergone prolonged, major surgery with significant postoperative analgesic requirements should be managed in a critical care area in the initial postoperative period. Any patient on domiciliary NPPV is likely to have either a degree of chronic ventilatory failure or a significant central component to sleep-disordered breathing and should be managed in a critical care area.

Limitations of NIV

NIV has several limitations, contraindications, and complications (Table 2). Circuit leaks, poor mask fit, inadequate trigger levels, and pressure settings are potentially modifiable factors that may improve treatment success. It is vital to identify treatment failure promptly, as a delay in intubation and MV is associated with worse outcomes and higher mortality in this patient group.[1,4,6] Additionally, it is crucial to be alert to respiratory compromise representing an early but non-specific sign of an underlying surgical complication. Improvement of ventilatory parameters by NIV usage should therefore not lead to a delay in appropriate investigations and treatment.

Table 2 NIV—contraindications and complications

Contraindications to NIV	Complications of NIV
Absolute	Treatment failure
Patient refusal	Delayed intubation (with increased morbidity and mortality)
Cardiac or respiratory arrest	Barotrauma
Immediate need for tracheal intubation	Pneumonia
Relative	Haemodynamic compromise
Reduced conscious level	Pulmonary aspiration
Severe agitation and poor cooperation	Gastric insufflation
Haemodynamic instability/shock	Claustrophobia
Multiple organ failure	Discomfort
Active cardiac ischaemia or arrythmias	Facial skin lesions
Upper airway obstruction (may be helped by NIV in OSA)	Ocular damage
Uncontrolled upper GI bleed	Noise exposure (helmets)
Uncontrolled vomiting	Arm oedema and deep vein thrombosis
Excessive respiratory secretions	Patient–ventilator dyssynchrony
Facial trauma	Air leaks
Rapidly worsening respiratory failure	Mucosal dryness/nasal congestion
	Exacerbation of delirium
	Carbon dioxide rebreathing
	Mechanical failure

Role of NIV in the perioperative period

Indications for NIV in the perioperative period can be broadly divided into two categories: prophylactic NIV, which aims to prevent the development of PPC; and therapeutic NIV, which is used in established respiratory compromise to prevent progression on to MV and the associated detrimental sequelae. A brief review of current evidence for perioperative NIV is presented below.

Timing

The use of NIV may be considered at various stages of the patient's perioperative journey. Preoperative CPAP may have beneficial effects on symptom severity and PPC in patients with obstructive sleep apnoea (OSA).[7] However, the minimum duration of therapy in order to achieve a clinically significant benefit is unknown. In addition, NIV may have a role as an adjunct during preoxygenation on induction of anaesthesia, for example, in bariatric patients or as part of a 'delayed sequence induction' strategy in emergency anaesthesia for critically ill patients.[4] Intraoperative use of NIV has been described for procedures such as endovascular repair of abdominal aortic aneurysms (AAA) or during coronary angiography in patients with severe respiratory disease. However, NIV is most commonly used in the postoperative period, either due to the patient's comorbid disease or after surgery carrying a high risk of PPC.

Major abdominal surgery

Up to 50% of patients will experience hypoxaemia after abdominal surgery and 8–10% will ultimately require tracheal intubation.[1] Current evidence suggests that both prophylactic and therapeutic use of CPAP may improve postoperative oxygenation, reduce atelectasis, decrease the incidence of pneumonia and rates of re-intubation, and reduce the length of intensive care stay after major abdominal surgery. However, a mortality benefit from NIV has thus far not been convincingly demonstrated by either well-designed studies or meta-analyses.[1,3,8]

Thoracic surgery

PPC pose a particular problem in thoracic surgery and represent the most frequent cause of death in patients after lung resection, where the requirement for re-intubation carries a mortality of up to 60–80%. NIV use after thoracic surgery has been demonstrated to be safe without an increase in bronchial stump disruption and persistent air leaks. NIV also improves gas exchange, reduces the need for MV, and lowers mortality in patients with respiratory failure after lung resection. Of note, initial failure to respond to NIV appears to predict overall treatment failure.[1,9]

Thoracoabdominal surgery

Evidence for thoracoabdominal aortic aneurysm repair suggests that prophylactic nasal CPAP reduces the incidence of pulmonary complications and leads to a shortened hospital LOS. Patients with respiratory compromise after thoracoabdominal oesophagogastrectomy have been shown benefit from therapeutic NPPV, with reductions in reintubation, septic shock, and critical

care LOS. Interestingly, there seems to be no increase in the incidence of gastric over-distension or anastomotic leakage. Nonetheless, a mortality benefit has not been demonstrated thus far.[1,10]

Vascular surgery

In addition to the use of CPAP prophylactically after thoracoabdominal surgery described above, CPAP has been studied as a prophylactic measure in patients who have undergone elective AAA repair.[11] Application of nasal CPAP for 12 h after AAA repair was found to result in significantly improved oxygenation and fewer episodes of severe hypoxia, without impacting on rates of mortality, cardiac and respiratory complications, mortality, and LOS.

Cardiac surgery

Between 40% and 90% of patients undergoing open cardiac surgery develop PPC. A series of small- to medium-sized randomized controlled trials (RCTs) support the use of prophylactic nasal CPAP and have shown a reduction in PPC (including pneumonia and reintubation rates) and need for critical care admission. Benefit from therapeutic NIV use has so far not been demonstrated, possibly reflecting additional aetiological factors in the development of respiratory failure in cardiac surgical patients.[4]

Solid organ transplant

Respiratory failure is the leading cause of short-term mortality after solid organ transplant. One small RCT in 40 patients receiving kidney, liver, and lung transplants demonstrated that NPPV significantly improved oxygenation and reduced septic complications, the need for invasive ventilation, and intensive care mortality. However, overall hospital mortality was unaffected. A further observational study reported a high rate of NIV treatment success, preventing intubation in 85% of patients after lung transplantation.[1]

Sleep-disordered breathing

Sleep-disordered breathing (upper airway obstruction during sleep) occurs in around 20% of the adult population. It ranges from snoring to obstructive sleep apnoea (OSA), the latter being characterized by cessation of breathing for at least 10 s in the presence of inspiratory effort. The incidence of clinically relevant OSA has been estimated to be around 22% in the general surgical population, with 70% of patients being undiagnosed at preoperative evaluation. Patients with OSA are at increased risk of perioperative complications including hypoxaemia, hypercapnoea, arrhythmias, myocardial ischaemia, delirium, and unplanned intensive care unit admissions.

Robust evidence for perioperative NIV use in this patient group is scarce. Preoperative CPAP may control disease severity, reduce PPC, and increase patient familiarity with the therapy. Postoperative *de novo* use of CPAP may lead to a reduction in respiratory complications.[7] The merits of sleep studies as a screening tool for undiagnosed OSA remain unclear, although the ASA has recently recommended perioperative evaluation in patients at risk of OSA and advocates consideration of preoperative CPAP in severe disease.[12] NIV should be used as part of a clear perioperative strategy including identification of patients with OSA, targeted intraoperative management, cautious use of opioids and sedatives, and careful postoperative monitoring in an appropriate environment.[12]

Bariatric patients

Morbidly obese patients have a high risk of PPC, and restrictive ventilatory pathology from increased abdominal and chest wall load will often co-exist with comorbid disease such as OSA and obesity hypoventilation syndrome. NIV may be used before operation to assist preoxygenation on induction of anaesthesia and after operation to improve oxygenation and reduce critical care admission and LOS in this group. A mortality benefit with NIV may be evident in obese patients whom become hypercapnoeic after operation. Concerns over increased risks of anastomotic disruption in gastric bypass surgery have been allayed by a recent dedicated RCT.[1,13]

Chest trauma

There is a growing body of evidence that NIV may alleviate acute respiratory failure secondary to blunt chest injuries. A recent meta-analysis suggested that NIV may lead to improved oxygenation, a reduction in pulmonary complications, a lower rate of intubation, and improved overall mortality. However, NIV use in the perioperative period for a multi-trauma patient should also be guided by concomitant injuries and the timing of further operative interventions.[14]

Future trends

The application of perioperative NIV is expanding with increasing recognition of its potential role in preoperative physiological optimization and preoxygenation. Intraoperative NIV may be used in selected patients with severe cardiorespiratory disease who cannot lie flat due to orthopnoea and are not suitable for general anaesthesia. There are emerging data to support HFNC use in cardiac surgical patients[15] and a large European study is currently evaluating their use after abdominal surgery.[16] It is hoped that future studies will help to define their precise role in the prevention and management of PPC in high-risk populations.

Conclusion

It is difficult to demonstrate a mortality benefit with NIV usage in elective surgical populations due to a relatively low baseline risk, although there may be an underlying survival signal in selected high-risk patient groups.[1,3] However, NIV use has been shown to have other important patient-centred benefits, including prevention of PPC and reductions in critical care and hospital LOS. Perioperative NIV should be delivered in an appropriate environment, with trained staff and close monitoring. Surgical complications, often signified by respiratory failure, must be identified before NIV is commenced and invasive ventilation should not be delayed if NIV fails. With a heterogenous patient population, having greatly differing risk profiles for respiratory compromise and presenting for a large variety of surgical procedures, an individualized approach to respiratory management is warranted.

Declaration of interest

A.G. has received honoraria and speaker's fees from Armstrong Medical UK Ltd beween 2014 and 2016.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

Podcasts

This article has an associated podcast which can be accessed at http://www.oxfordjournals.org/podcasts/bjaed_NIV_perioperative period_vol_16_issue_9.mp3.

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Phosphate homeostasis in critical care

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Key points

- Serum phosphate is under tight physiological control.
- Hypophosphataemia is common in hospitalized patients, particularly in the critically ill.
- Hypophosphataemia causes multisystem effects if left untreated.
- Phosphate disturbances are often multifactorial.
- Treatment of hyperphosphataemia secondary to rhabdomyolysis or tumour lysis syndrome should be instituted promptly.

Phosphorus plays a critical role in many biological processes, including energy metabolism, cellular signalling, nucleic acid metabolism, membrane integrity, and bone mineralization.[1] Phosphate is an inorganic molecule containing four oxygen atoms and a central phosphorus atom. In its ionic form, phosphate (PO_4^{3-}) is negatively charged, leading it to be an ideal buffer and easily combining with positively charged calcium ions to contribute to hydroxyapatite, the main mineral component of bone, where up to 85% of the body's phosphate stores exist.

Physiology

Phosphorus in the diet is present in inorganic and organic forms. Organic phosphorus is absorbed less freely than inorganic phosphate. Phosphate absorption is highly efficient, with 60–70% of an intestinal load absorbed from a typical diet,[2] occurring mostly in the duodenum and jejunum.

Intestinal absorption occurs both by non-regulated passive transport through the paracellular pathway and regulated active mechanisms[3] via type IIb sodium phosphate co-transporters on the mucosal surfaces. Intracellular transport and export via the basolateral membrane is likely related to movement down the concentration gradient to the relatively low serum concentration.

Three families of sodium/phosphorus (Na/Pi) co-transporters exist. Type I is present in the kidneys and liver, type II in the kidney, small intestine and lung, and type III in most areas of the body.

Plasma phosphorus consists of phospholipids, ester phosphates, and inorganic phosphates. Inorganic phosphates are completely ionized, circulating primarily as hydrogen phosphate $H(PO_4)^{2-}$ or dihydrogen phosphate $H_2(PO_4)^-$ in a ratio of 4:1 at a plasma pH of 7.40.[4]

Phosphate and calcium share an intimate relationship, not least due to the high mineral content of the bone comprising combinations of these molecules. Hydroxyapatite has the formula $Ca_{10}(PO_4)_6(OH)_2$ and provides bone with its compressional strength. Also hydroxyapatite, calcium, and phosphate co-exist in the bone as exchangeable forms of salts, such as $CaHPO_4$ and other amorphous calcium salts. These are in equilibrium with the calcium ions in the extracellular fluids, importantly providing a rapid buffering mechanism to prevent the calcium ion concentration from altering. The calcium ion concentration is therefore under tight control of within a few per cent of the normal level of 1.2 mmol litre^{-1}.

The plasma concentrations of phosphate and calcium are small in proportion to the total body content, but it is these parameters that are under hormonal control (Fig. 1).

Vitamin D3 (cholecalciferol) is a fat-soluble steroid synthesized in the skin, as a result of irradiation of 7-dehydroxycholesterol by ultraviolet rays. It is also present in a similar form in the diet. It is activated by a hepatic enzyme, 25-hydroxylase, placing a hydroxyl group in the 25 position of the vitamin D molecule, resulting in the formation of 25-hydroxycholecalciferol (calcidiol). Further,

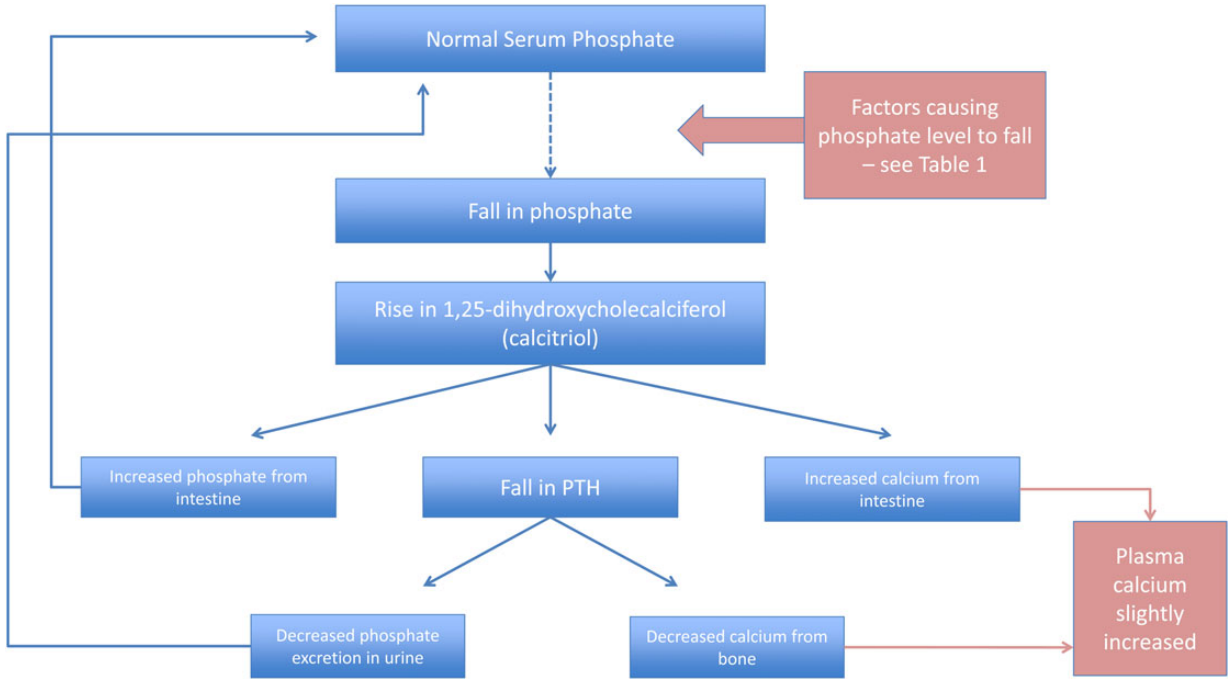

Fig 1 Hormonal control of phosphate. PTH, parathyroid hormone.

conversion to its most active form, 1,25-dihydroxycholecalciferol (calcitriol), occurs in the proximal tubules of the kidneys with negative feedback at each stage by 25-hydroxycholecalciferol, and parathyroid hormone, respectively. Hypophosphataemia also encourages the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol.

1,25-Dihydroxycholecalciferol raises calcium and phosphate levels by increasing gut absorption. Here, the type IIb sodium phosphate co-transporter appears to be regulated at the membrane level by 1,25-dihydroxcholecalciferol, but not at a transcriptional level. 1,25-Dihydroxycholecalciferol also increases activity of the osteoblasts, laying down calcium into the bone matrix and increases calcium and phosphate reabsorption by the epithelial cells of the renal tubules.

Parathyroid hormone is released in response to changes in calcium concentration but also acts on phosphate. As parathyroid levels increase, the bone releases calcium and phosphate-containing minerals into the circulation. Parathyroid hormone also has a direct effect on the kidney to increase tubular reabsorption of calcium, but also to decrease the phosphate reabsorption by acting on the proximal tubules. The net effect is that phosphate levels decrease in response to parathyroid hormone. Parathyroid hormone also promotes formation in the kidneys of 1,25-dihydroxycholecalciferol, therefore enhancing the absorption of calcium and phosphate from the gastrointestinal (GI) tract.

Phosphate is completely reabsorbed by the kidney when the plasma concentration is below 1 mmol litre^{-1} with none lost to the urine. Above this critical concentration, phosphate loss is proportional to the concentration present.

Hypophosphataemia

Up to 5% of hospitalized patients may have low serum phosphate concentrations <0.8 mmol litre^{-1}, but this is more common in critically ill patients.[5] One study of 2730 critically ill patients in Australia reported an incidence as high as 26%.[6] Profound hypophosphataemia (<0.32 mmol litre^{-1}), which can lead to physiological disturbances, is much less common however.

There are four mechanisms by which hypophosphataemia can occur:

(i) redistribution,
(ii) decreased absorption,
(iii) increased renal loss,
(iv) renal replacement therapies.

Critical care patients and those undergoing surgery commonly have multiple risk factors that may lower phosphate levels. This is particularly true for major surgery, such as cardiac surgery and abdominal aortic surgery.[7] After major hepatic surgery, hypophosphataemia is extremely frequent.[7] Internal redistribution is the most common cause in these physiologically stressed patients. Glycolysis causes an increase in the phosphorylated compounds in the liver and skeletal muscle, the source of which is the inorganic phosphate in extracellular fluid. The use of insulin, or stimulation of increased endogenous insulin secretion, will cause a decrease in serum phosphate levels by moving phosphate intracellularly along with glucose. Epinephrine, glucagon, and other hormones also produce this effect by a similar mechanism (Table 1). This can become more problematic in patients with underlying phosphate depletion—such as those who are fasted for prolonged periods, malnourished due to chronic alcohol intake, or anorexia nervosa. During the anabolic period, after re-feeding, there is an influx of phosphate into the cells which can lead to a severe hypophosphataemia. This is the primary manifestation of the 're-feeding syndrome'.

Patients with hyperglycaemia, and subsequent osmotic diuresis (and therefore loss of phosphate in the urine) who are treated with insulin, are at risk of hypophosphataemia, and this should be monitored closely and corrected as necessary.

Another redistributive cause of hypophosphataemia is respiratory alkalosis.[8] Extracellular decreases in carbon dioxide will result

Table 1 Causes of hypophosphataemia

Internal redistribution	
Hormonal triggers	Insulin, glucagon, epinephrine, dopamine
Drugs	Carbohydrate infusions, β-2 agonists, steroids, xanthine derivatives
Respiratory alkalosis	Mechanical ventilation, sepsis, alcohol withdrawal, hepatic coma, anxiety, salicylate overdose
Glucose shifts	Treatment of DKA, re-feeding after malnutrition
Rapid cell uptake/proliferation	Hungry bone syndrome (post-parathyroidectomy), acute leukaemia
Renal losses	
Drugs	Diuretics including acetazolomide and metolazone
	Tenofovir
	Imatinib
	Glucocorticoid/mineralocorticoid therapy
Acute volume expansion	
Hyperparathyroidism—primary and secondary	
Renal transplantation	
Fanconi syndrome	
Primary renal phosphate wasting	X-linked hypophosphataemic rickets
	Autosomal-dominant hypophosphataemic rickets
	Tumour-induced osteomalacia
Decreased intestinal absorption	
Poor phosphate diet and/or malabsorption	
Phosphate binding antacids	
Steatorrhoea or chronic diarrhoea	
Vitamin D deficiency or resistance	
Renal replacement therapy	

in a similar change within the cell. Elevated pH stimulates glycolysis leading to hypophosphataemia. Respiratory alkalosis may be the precipitating factor in the hypophosphataemia-induced acute rhabdomyolysis that can occur in alcoholic patients; however, the underlying hypophosphataemia may initially be masked by the release of phosphate from injured muscle cells.

Post-parathyroidectomy and sometimes with thyroidectomy, there can be a rapid deposit of calcium and phosphate into the bone, the 'hungry bone syndrome' in those previously osteopenic, which can be symptomatic.

Poor oral intake alone is rarely a sole cause for hypophosphataemia due to the high efficiency of the gut to absorb dietary phosphate and up to 100% renal reabsorption. It can become more of a problem in conditions associated with GI phosphate loss however, such as chronic diarrhoea, vomiting, or the use of aluminium or magnesium containing antacids or other phosphate binding drugs. GI effects are worsened in those with concomitant vitamin D deficiency.

Renal loss of phosphate has a number of causes, most commonly due to the use of diuretic therapy (Table 1). Acute volume expansion can also cause phosphate to decrease due to diminished proximal sodium reabsorption on which phosphate transport closely depends.

Renal replacement therapy is a common cause of hypophosphataemia in the critically ill patient due to loss with effluent waste. Replacement in this situation is important to prevent physiological consequences of hypophosphataemia due to rapid changes in serum concentrations.

Hyperphosphataemia

Hyperphosphataemia can also be attributed to four different mechanisms:

(i) acute phosphate load,
(ii) cellular shift,
(iii) decreased renal clearance,
(iv) pseudohyperphosphataemia.

Acute phosphate load can be divided into exogenous and endogenous. Exogenous load is uncommon, but has been seen in patients using phosphate-containing laxatives,[9] which can lead to acute phosphate nephropathy, and those taking high-dose fosphenytoin for the treatment of seizures. These are usually in association with volume contraction (diarrhoea), renal impairment, or both.

Endogenous load is seen more frequently, in tumour lysis syndrome and rhabdomyolysis. Tumour lysis syndrome is commonly caused by chemotherapeutic agents in patients with large tumour burden and rapid cell turnover, such as non-Hodgkins or Burkitt's lymphoma, but can also occur spontaneously in the course of these disease processes. Cell turnover releases potassium, phosphate, purines, and proteins, the latter two of which can be converted to uric acid and urea, respectively, and cause hyperuricaemia. The need for urgent renal replacement therapy may be required as the kidney is overwhelmed with cell components. In rhabdomyolysis, the severity of hyperphosphataemia and hypocalcaemia may be increased if haem pigment-induced acute kidney injury ensues.[10]

Acute cellular shifts of phosphate are far less common but can be seen in diabetic ketoacidosis, with severe hyperglycaemia alone, and in lactic acidosis. All types of metabolic acidosis reduce the glycolysis rate and therefore the phosphate taken up into cells. Lactic acidosis is associated with cell death and subsequent release of intracellular phosphate. Consequently, hypophosphataemia can then be seen when these conditions are treated.

Patients with acute or chronic kidney disease develop hyperphosphataemia primarily due to a decrease in glomerular filtration rate. To some extent, this can initially be maintained by suppression of the sodium–phosphate co-transporters in the luminal membrane of the proximal tubules, but below filtration rates of 20–25ml min^{-1}, phosphate reabsorption is thought to be maximally suppressed, and inevitably leads to an increase

Table 2 Causes of hyperphosphataemia

Acute phosphate load	Tumour lysis syndrome Rhabdomyolysis Exogenous phosphate, for example, sodium phosphate laxative, fosphenytoin
Cellular shift	Metabolic acidosis
Decreased renal clearance	Acute or chronic kidney disease Increased tubular reabsorption • Hypoparathyroidism or pseudohypoparathyroidism • Bisphosphonates • Vitamin D toxicity • Acromegaly • Familial tumoural calcinosis
Pseudophyperphosphataemia	Endogenous • Hyperglobulinaemia • Hyperlipidiaemia • Haemolysis • Hyperbilirubinaemia Exogenous • Amphotericin B • Heparin • Tissue plasminogen activator

Table 3 Adverse clinical effects of severe hypophosphataemia

Respiratory
Acute respiratory failure
Impaired diaphragmatic contractility
Failure to wean from mechanical ventilation
Cardiovascular
Decreased myocardial contractility, decreased stroke volume
Increased inotropic requirement
Arrhythmias
Metabolic
Insulin resistance
Depletion of 2,3 DPG–oxygen dissociation curve shifts to left
Neurological
Delirium
Seizures
Coma
Gastrointestinal
Dysphagia
Ileus
Haematological
Haemolysis
Leucocyte dysfunction—impaired phagocytosis and granulocyte chemotaxis
Musculoskeletal
Weakness
Myalgia

in plasma levels due to ongoing absorption via the gut. Dysfunctional kidneys are unable to efficiently form 1,25-dihydroxycholecalciferol, leading to a secondary hyperparathyroidism. Additionally, hyperphosphataemia can independently contribute to cardiac causes of death through increased myocardial and vascular calcification, and microcirculatory complications[11] in patients with chronic renal failure.

Other causes of decreased renal clearance of phosphate secondary to increased proximal tubular reabsorption can be seen in Table 2.

A pseudohyperphosphataemia can occur due to interference with laboratory analysis in conditions such as hyperglobulinaemia, hyperlipidaemia, hyperbilirubinaemia, and haemolysis. Some drugs can also cause this falsely raised laboratory result, such as amphotericin B and heparin. Values for phosphate should be determined using alternative techniques in these cases.

Consequences of disordered phosphate

As previously discussed, the causes of hypophosphataemia in the critically ill are multifactorial. A combination of sepsis, trauma (in particular, burns and head trauma), acid–base disorders, glucose/insulin therapy, catecholamines, and diuretic use mean that patients in critical care are at much higher risk of hypophosphataemia with higher associated mortality. It is unclear however whether hypophosphataemia contributes directly to this mortality increase, or is a marker of illness severity (Table 3).[7]

Symptomatic hypophosphataemia usually occurs when the phosphate level is lower than 0.32 mmol litre^{-1}.[8]

Symptoms can often be explained due to complications of impaired metabolism—in particular, muscle dysfunction, presenting with acute respiratory failure, failure to wean from ventilation, decreased myocardial contractility with increased inotropic requirement, or with skeletal muscle weakness and rhabdomyolysis. Rhabdomyolysis is more common in those with pre-existing myopathy, e.g. chronic alcoholism, where subsequent hypophosphataemia may precipitate rhabdomyolysis.

Another major cause of symptomatic hypophosphataemia is depletion of 2,3 diphosphoglycerate.[8] This causes a shift of the oxygen dissociation curve to the left, affecting oxygen delivery to tissues, and in those with chronic lung disease, this effect may be even more marked. Cardiac arrhythmias, both supraventricular and ventricular in origin, can occur alongside this.

Haematological effects of hypophosphataemia seen in the critically ill are those of haemolysis and leucocyte dysfunction—impaired phagocytosis and granulocte chemotaxis. Dysfunction in leucocytes explains the higher incidence of Gram-negative sepsis in hypophosphataemic patients.[8]

Insulin resistance and ileus are common features seen in the critically ill and postoperative patient group, and can be caused by or contributed to by hypophosphataemia. Altered mental status, delirium, seizures, and coma, have most often been described in the course of refeeding. Hypophosphataemia can also lead to both peripheral and central neuropathies.[8]

Hypocalcaemia and tetany may occur with rapid increases in plasma phosphate due to deposition of calcium into soft tissues. Severe hyperphosphataemia with symptomatic hypocalcaemia can be life threatening, not least because of the negative inotropic effects on the myocardium. Therefore, haemodialysis is often indicated in these patients, particularly in those with pre-existing impaired renal function.

Treatment

Hypophosphataemia does not always necessitate replacement therapy,[8] as this depends on the body's overall phosphate status. Degrees of severity of hypophosphataemia may lead to either enteral or parenteral replacement.

A serum phosphate level below 0.64 mmol litre^{-1} (2 mg dl^{-1}) in asymptomatic patients warrants enteral replacement, in patients who are reliably absorbing feed and have adequate vitamin D stores. Enteral phosphate replacement is given in the form of Phosphate Sandoz® effervescent tablets. Each tablet contains

PO_4^{3-} 16.1 mmol, Na^+ 20.4 mmol, and K^+ 3.1 mmol. The usual adult dose is up to 6 tablets daily (dissolved in water) in divided doses, to produce a solution that can be given safely via feeding tubes. Tablets should not be taken with aluminium, calcium, or magnesium salts as these will bind phosphate and reduce absorption.

Parenteral phosphate replacement is indicated if the patient has severe hypophosphataemia (<0.32 mmol litre^{-1}) or is symptomatic. It may also be considered for patients unlikely to absorb oral agents. A commonly used treatment is the Phosphate Polyfusor®, a solution containing 50 mmol PO_4^{3-}, 9.5 mmol K^+, and 81 mmol Na^+ in 500 ml, given over 24 h via a central venous catheter. This preparation should be infused alone, via a dedicated port of a central line, and if given peripherally should have a dedicated cannula. Peripherally, the ideal is to reduce the rate of infusion due to risk of pain and phlebitis at the injection site, but with close monitoring could be given at the same rate as the central dose.

Caution should be taken in those with renal impairment, as in this particular group, the risk of iatrogenic hyperphosphataemia is significant. Phosphate replacement may exacerbate hypocalcaemia and can cause metastatic soft tissue calcification. At least, daily monitoring is necessary for those having treatment to reduce the risk of hyperphosphataemia. Calcium should be corrected before administration of phosphate replacement.

Phosphate Sandoz® and Phosphate Polyfusor® contain a relatively high dose of sodium which may be unsuitable for some patients requiring phosphate replacement.

Another common replacement regimen includes that of i.v. potassium phosphates. Products can be a combination of monobasic potassium phosphate and dibasic potassium phosphate. They must be diluted before use in either 0.9% sodium chloride or 5% glucose to a minimum volume of 100 ml, and given at a rate of no greater than 20 mmol of phosphate per hour preferably via a central line. This avoids administrations of high-sodium content fluid, and in patients requiring potassium replacement and phosphate, can be very useful. Dose should be titrated against plasma phosphate and potassium levels regularly to avoid hyperphosphataemia and hyperkalaemia.

Alternatively, potassium acid phosphate (potassium dihydrogen phosphate) with a neat concentration of 1 mmol ml^{-1} each of potassium and phosphate can be used. Other alternatives such as Glycophos® (20 mmol phosphate, 40 mmol sodium in 20 ml solution) or Addiphos® (40 mmol phosphate, 30 mmol potassium, and 30 mmol sodium in 20 ml solution) can be added to i.v. fluids including TPN.

Hyperphosphataemia should be treated by correction of the underlying cause. In the case of rapid cell turnover or rhabdomyolysis, renal replacement therapy may be indicated and should be instituted promptly.

Summary

Phosphate disturbances in critically ill patients are relatively common, often multifactorial, and can occasionally have catastrophic consequences if not monitored and treated appropriately. Transient changes may be left without intervention due to rapid movement between intracellular and extracellular spaces if the patient remains asymptomatic. Correction of phosphate disturbances should be done carefully with close monitoring, regular review, and a thorough knowledge of the pharmacology and physiology and an understanding of the potential pitfalls of standard laboratory monitoring.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Measurement in pain medicine

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Key points

- Structured pain assessment using a variety of validated measures can be an important aid to assist diagnosis of pain, direct treatment, and evaluate it.
- Assessment of acute pain severity is crucial for effective perioperative management and to reduce risk of chronicity.
- The multidimensional character of chronic pain requires specialized assessment tools for elucidation of sensory components and also cognitive and psychological dimensions.
- Specialized scales can be used in many settings as screening tools to support diagnosis of neuropathic pain, the essential first step in its treatment, and for assessment of pain in very young and elderly patients.

The often complex, multidimensional, and subjective nature of pain makes it very challenging to assess both in terms of intensity and in terms of relief as a response to treatment. It is important for pain assessment in any setting to have scientifically valid tools to determine quality and intensity of pain, aid diagnosis, direct treatment, and evaluate effectiveness after discrete interventions. Valid, reliable, and sensitive tools are required to direct treatment for patient care, and for service provision to evaluate the success of therapy. Pain measurement tools also aid research on mechanisms of pain and outcomes of treatment. A wide variety of validated measures have been conceived and developed over the last 40 yr, and have been instrumental in highlighting the multifaceted complexity of the human pain experience. It is of utmost importance to note that they do not supplant the need to clinically assess pain, but add to the quality of that assessment.

Measurement validity, reliability, sensitivity, and specificity

Validity is the degree to which a test measures either a quantity or hypothetical construct which it is intended to assess. This includes:

- Face validity—what does it appear to measure?
- Content validity—does it cover all relevant items (e.g. symptoms) in a given condition (e.g. depression)?
- Criterion-related validity—predictive of future state, and ability to diagnose existing state.
- Construct validity—degree to which a test measures hypothetical constructs or traits.

Reliability is based on the consistency of a measure across different conditions and time points:

- test–retest reliability (coefficient of stability)—assesses stability of results over time,
- internal consistency—assesses if scale items are measuring the same thing (e.g. anxiety, not unintended measurement of depression) (Cronbach's α),
- interrater reliability (Cohen's κ value).

The sensitivity of a measure is its ability to correctly identify the presence of the condition where it exists. For example, a measure with 80% sensitivity detects the condition in 80% of a population with that condition (true positives), but 20% with the condition are undetected (false negatives).

The specificity of a measure is its ability to correctly identify the absence of the condition where it does not exist. For example,

a measure with 80% specificity detects the absence of the condition in 80% of a population (true negatives), but 20% without the condition are ascribed it (false positives).

Sensitivity to change is indicated by a change in response to an intervention in direction and proportion with good correlation with other measures.

Measurements in acute pain

Assessment of acute pain is crucial to ensure safe and effective management of patients with an acute surgical or medical illness, and as part of routine perioperative care. Most of the scales used in acute pain settings are one-dimensional and designed for the assessment of intensity of pain, degree of pain relief, or other aspects of pain. The visual analogue scale (VAS) and numeric rating scale (NRS) are most commonly used to assess the present intensity of acute pain. They are reliable, valid, sensitive to change, and easy to administer for measurement of severity of pain. The NRS, using an 11-point scale (0—'no pain' to 10—'worst pain', or 'pain as bad as it could be'), is often preferred due to its administration simplicity and reliability.[1] VAS is considered the 'gold standard' technique and is used particularly in pain-related research. It consists of a 100 mm unmarked line with standardized wording: 'no pain' on the left of the line, and 'worst pain imaginable' on the right—the patient then places a mark on the line corresponding to their level of pain. A disadvantage of this scale is that it does not give instant rating as measurement is needed and application of the scale requires explanation to the patient when the level of understanding may be decreased in the early post-anaesthetic period. Categorical verbal rating scale (VRS) uses words to describe the magnitude of pain, for example, none, mild, moderate, severe. VRS is a quick, simple tool with a high validity as an indicator of pain intensity; however, it may be less precise and sensitive than VAS.[2] Language can be a barrier to effective administration.

Although neuropathic pain is commonly related to chronic conditions, it is present in about 3% of all patients with acute pain.[3] The prevalence depends on the type of performed surgery—for example, almost all patients post-inguinal herniotomy describe features of neuropathic pain in the early postoperative period. An awareness of this and early assessment of neuropathic component of acute pain is crucial for appropriate management. One-dimensional scales are inadequate for neuropathic pain assessment which requires specialized scales.[4] There is no consensus which scale [e.g. Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale, Douleur Neuropathique en 4 questions (DN4), PainDETECT] is best for the assessment of acute post-surgical neuropathic pain. In the acute setting, in a study by Sadler and colleagues,[5] LANSS identified five of 165 patients (3%) as experiencing acute neuropathic pain, whereas DN4 identified seven patients in the same group of 165 individuals (4.2%). Another study by Hayes and colleagues[6] showed that patients with acute neuropathic pain represented only 1.04% of studied group, showing 78% of them had pain at 6 months, and 55% at 12 months.

Measurements in chronic pain

Multidimensional scales

Melzack and Casey suggested that pain has three major dimensions: sensory–discriminative, motivational–affective, and cognitive–evaluative. This led to development of one of the most evaluated multidimensional self-rating scales—the McGill Pain Questionnaire (MPQ) and its Short Form. MPQ consists of 20 subgroups of words describing sensory (subgroup 1–10), affective (11–15), evaluative (16), and miscellaneous components of pain (17–20). Each subgroup has a list of words with a given ranking—the word chosen by the patient with highest ranking is used for scoring. For example, in the assessment of 'Thermal' properties of perceived pain, the word 'searing' has a higher score than 'hot'. The total score—the pain rating index (PRI)—is a sum of ranked scores. In addition, present pain intensity (PPI) is assessed on a six-point scale (i.e. pain from 0 to 5). MPQ has been used in the research of acute and chronic pain due to its high reliability and validity. This questionnaire has been translated into a number of languages without affecting its utility. Outcomes of MPQ can be easily analysed statistically to compare efficacy of treatment methods.

The Brief Pain Inventory (BPI) is another multidimensional tool. Initially developed for cancer pain measurement, it has been validated for assessment of pain in a wide range of chronic syndromes. The BPI is a 17-item self-rating scale. It requests the patient to indicate the site(s) of pain by shading a body diagram. It also uses an 11-point NRS to assess the pain intensity in the preceding 24 h—'most', 'least', 'average', and 'right now', and degree of pain relief from current treatment. In addition, it uses an 11-point NRS of interference in seven domains of usual activities/functions and mood (e.g. work, sleep, mood, relations with other people). It has been validated in 12 languages to date (Fig. 1).

Neuropathic pain scales

Neuropathic pain is typically more distressing and more difficult to control than other forms of pain and is associated with greater health-seeking behaviour. It requires specialized diagnostic skills and specific treatment methods.

Discriminative tools to aid in the diagnosis of neuropathic pain have been developed to support diagnosis and differentiate between types of pain. They can be especially useful in primary care settings—however, they are not designed to replace clinical examination and specialized tests.

Generic tools like the McGill Pain Questionnaire have some discriminative properties but specific scales based on neuropathic descriptors and simple examination findings are preferred to distinguish between nociceptive and neuropathic pain. LANSS pain scale, DN4, PainDETECT, and Neuropathic Pain Score (NPS) are used as screening tools for neuropathic pain—however, there is no conclusion which is best for clinical practice.

The LANSS was the first such scale, which over the years has had validity confirmed in multiple studies.[7] The LANSS consists of seven weighted items: five sensory items and two clinical examination findings (allodynia and pinprick test). More than 12 points out of a maximum of 24 suggest that a neuropathic mechanism is likely to be contributory. It has 80% sensitivity and more than 90% specificity in comparison with expert clinical assessment. Although designed as a screening tool, it has shown sensitivity to treatment effect (reduction in LANSS after treatment) but not to placebo. LANSS takes about 5 min to complete, but it involves a physician's input. Patient self-reported S-LANSS has been developed recently and identifies patients with pain of predominantly neuropathic origin and is particularly useful in prevalence studies[8] (Fig. 2).

The DN4 scale which consists of six items related to symptoms and three physical examination findings identifies neuropathic components of pain with similar sensitivity and specificity to LANSS.[9]

The PainDETECT scale is a self-reported tool originally designed to distinguish neuropathic lower back pain from mechanical back pain.[10]

NPS was the first scale designed to measure severity of neuropathic pain based on intensity of 11 descriptors. NPS shows sensitivity to treatment effect.[11]

Mood and affect

The correlation between pain and psychological factors is well documented. They can influence pain perception, effectiveness of treatment, or even increased risk of chronicity of acute pain after surgery or trauma.[12–15]

Anxiety and depression measurements

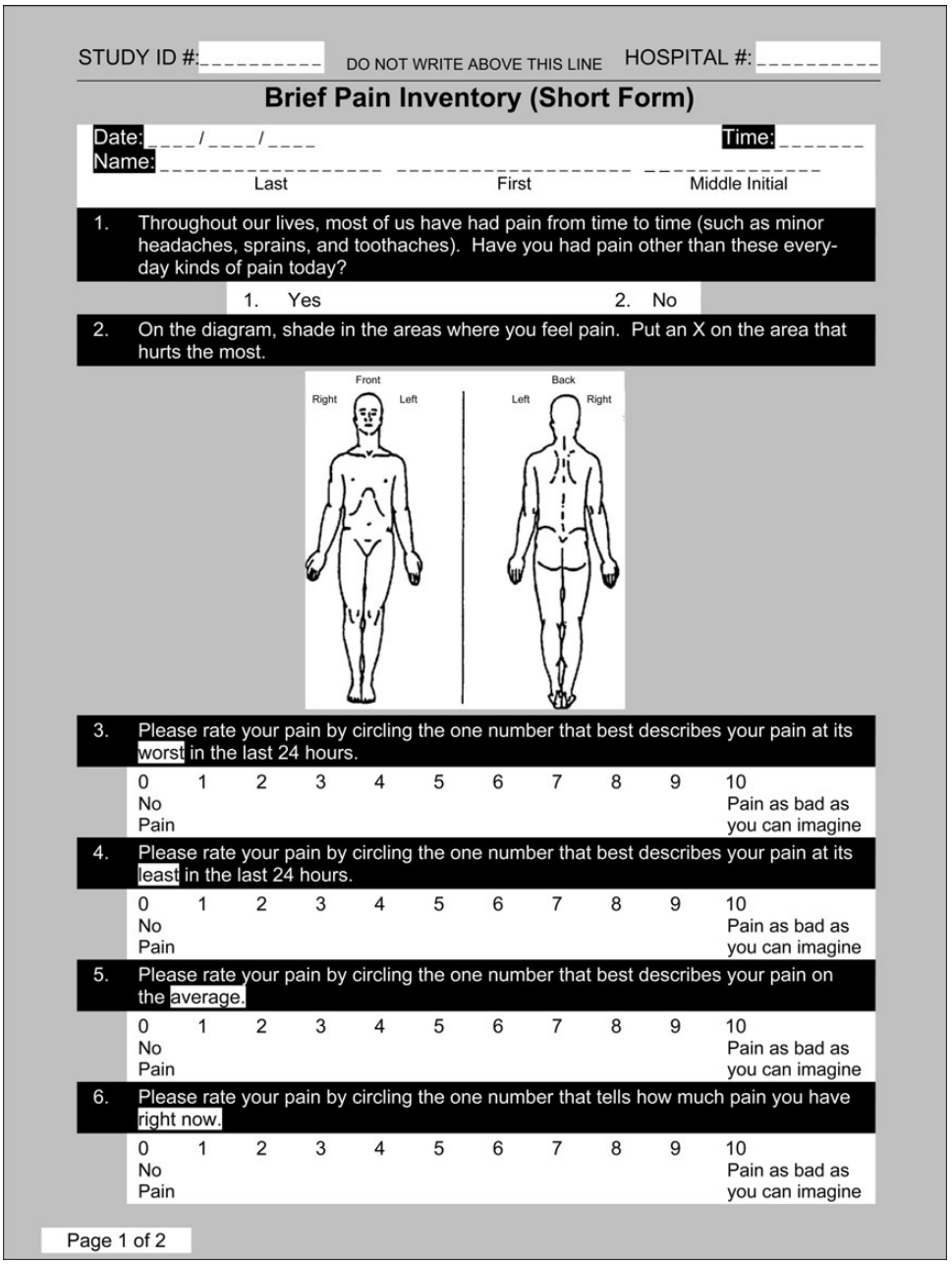
The Hospital Anxiety and Depression (HAD) scale is a highly validated scale across a number of healthcare settings, which assess risk of anxiety and depression in hospital or community. The HAD scale consists of 14 items—seven for anxiety and seven for depression. Each item scores from 0 to 3 points. The item scores are summed—scores of more than eight out of 21 for anxiety and/or depression represent clinically significant risk of these entities, with score-related ranking of severity as mild (8–10), moderate (11–15), and severe (16–21). It has higher sensitivity than specificity.

More recently developed scales, for example, Patient Health Questionnaire (PHQ-9) (for depression) and Generalized Anxiety Disorder 7 (GAD-7), are used increasingly.

Pain beliefs and coping assessment

Pain coping measurements: catastrophizing

Catastrophizing is a negative emotional–cognitive–attitudinal pain perception and leads to over-predictions of pain, increased use of healthcare, and longer hospital stays.[16] High scores are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Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: _____

Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.

Front Back

Right Left Left Right

3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 No Pain 1 2 3 4 5 6 7 8 9 10 Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 No Pain 1 2 3 4 5 6 7 8 9 10 Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

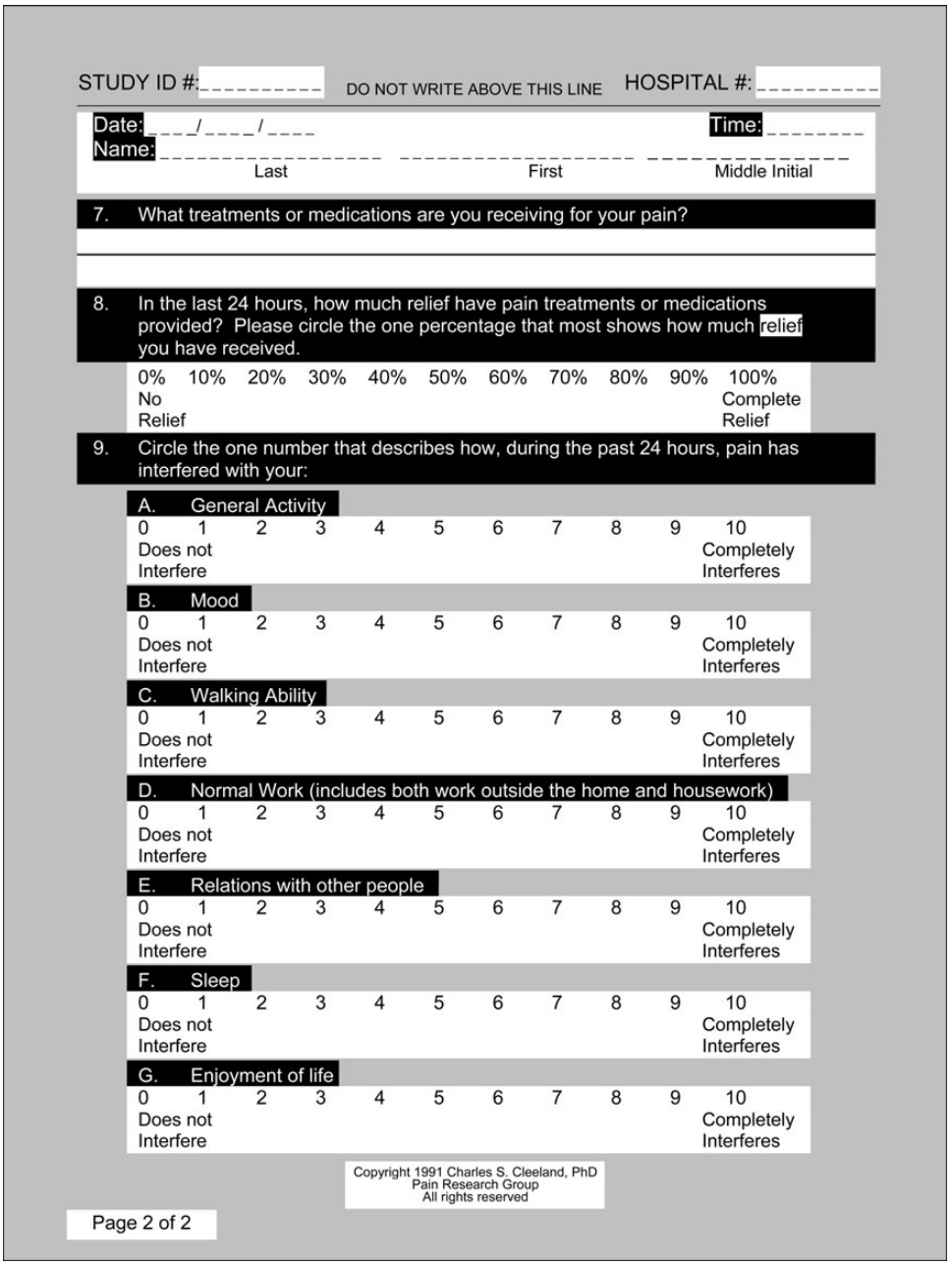
0 No Pain 1 2 3 4 5 6 7 8 9 10 Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 No Pain 1 2 3 4 5 6 7 8 9 10 Pain as bad as you can imagine

Page 1 of 2

Fig 1 BPI scale. Reproduced with the permission of Charles S. Cleeland, PhD, Pain Research Group.



STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date: ____/____/____ Time: _____

Name: _____ _____ _____

Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% No Relief 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

C. Walking Ability

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

Page 2 of 2

Fig 1 Continued

associated with poorer function. The 13-item Pain Catastrophizing Scale lists statements which describe different thoughts or feelings associated with pain, for example, 'I worry all the time about whether the pain will end' or 'I become afraid that the pain would get any worse'.[17] Patients indicate the degree of frequency of those thoughts on a five-point scale. Total score of more than 30 out of 52 indicates clinically significant catastrophizing. Recent research also shows that catastrophizing is a risk factor for severe acute postoperative pain, and development of chronicity.

Measures of pain beliefs and attitudes

A patient's pain beliefs are central to their reporting of their pain experience, and are informed by their understanding of the nature and cause of pain, and the complex interaction of pain on their function and mood. Confidence in the patient's own ability to cope with pain and its impact on daily life is one of the strongest predictors of treatment outcome.[18] The Pain Self-Efficacy Questionnaire assesses patients' confidence in performing daily activity—10 statements related to daily life e.g. 'I can enjoy things or I can do some form of work despite pain'—on a seven-point scale. A total score of more than 40/60 predicts good response to self-management and return to work.

Health-related quality-of-life assessment

Quality-of-life measurement is important in chronic disease states including pain, as it is of paramount importance to the

The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale

Explain: This pain scale can help to determine whether the nerves that are carrying your pain signals are working normally or not. It is important to find this out in case different treatments are needed to control your pain.

A. PAIN QUESTIONNAIRE

Think about how your pain has felt over the last week. Please say whether any of the descriptions match your pain exactly.

1. Does your pain feel like strange, unpleasant sensations in your skin? Words like pricking, tingling, pins and needles might describe these sensations.

a) NO – My pain doesn't really feel like this..... (0)
b) YES – I get these sensations quite often.....(5)

2. Does your pain make the skin in the painful area look different from normal? Words like mottled or looking more red or pink might describe the appearance.

a) NO – My pain doesn't affect the colour of my skin..... (0)
b) YES – The pain does make my skin look different from normal ..... (5)

3. Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations when lightly stroking the skin, or getting pain when wearing tight clothes might describe the abnormal sensitivity.

a) NO – My pain doesn't make my skin abnormally sensitive in that area (0)
b) YES – My skin seems abnormally sensitive to touch in that area.....(3)

4. Does your pain come on suddenly and in bursts for no apparent reason when you're still? Words like electric shocks, jumping and bursting describe these sensations.

a) NO – My pain doesn't really feel like this..... (0)
b) YES – I get these sensations quite often ..... (2)

5. Does your pain feel as if the skin temperature in the painful area has changed abnormally? Words like hot and burning describe these sensations.

a) NO – I don't really get these sensations..... (0)
b) YES – I get these sensations quite often..... (1)

B. SENSORY TESTING
Skin sensitivity can be examined by comparing the painful area with a contralateral or adjacent non-painful area for the presence of allodynia and an altered pinprick threshold (PPT).

1. Allodynia
Examine the response to lightly stroking cotton wool across the non-painful area and then the painful area. If normal sensations are experienced in the non-painful site, but pain or unpleasant sensations (tingling, nausea) are experienced in the painful area when stroking, allodynia is present.

a) NO – Normal sensations in both areas ..... (0)
b) YES – Allodynia in painful area only ..... (5)

2. Altered pinprick threshold
Determine the pinprick threshold by comparing the response to a 23-gauge (blue) needle mounted inside a 2 ml syringe barrel placed gently onto the skin in non-painful and then painful areas.

If a sharp pinprick is felt in the non-painful area, but a different sensation is experienced in the painful area, eg. none/blunt only (raised PPT) or a very painful sensation (lowered PPT), an altered PPT is present.

If a pinprick is not felt in either area, mount the syringe onto the needle to increase the weight and repeat.
a) NO – Equal sensation in both areas ..... (0)
b) YES – Altered PPT in painful area..... (3)

SCORING:
Add values in parentheses for sensory description and examination findings to obtain overall score.

TOTAL SCORE: _____ (maximum 24)

If score <12, neuropathic mechanisms are unlikely ***to be contributing to the patient's pain.***
If score ≥12, neuropathic mechanisms are likely ***to be contributing to the patient's pain.***

Fig 2 LANSS scale. Reproduced with permission of M. Bennett. Source: Bennett M, The LANSS Pain Scale: The Leeds assessment of neuropathic symptoms and sign. Pain 2001;92: 147–157.

patient, and can demonstrate the global impact of a condition on the patient's life, and the effect of treatment. The European Quality of Life Instrument (EQ 5D) measures five domains (mobility, self-care, usual activity, pain, and mood) against a five-point descriptor scale of symptom/impact intensity. It also has a measure of overall health with a vertical VAS from 0 to 100—from 'worst health you can imagine' to 'best health you can imagine'. The test is easy to use with wide applicability but may not be sensitive enough to capture subtle changes in response to treatment (especially if QOL is scored low). The scores can be affected by comorbidities, and the scoring system is complex.

Pain-related functional assessment

Pain-related function scales measure disability level and pain interference with daily activity. It is a very important outcome in pain medicine along with pain severity with which it strongly correlates. Most measurement tools assess multiple domains of function like daily activity, work, socializing, but also mood or sleep. Pain Disability Index (PDI) was created for the brief self-assessment of function in a wide range of painful conditions. It consists of seven domains (family/home responsibilities, recreation, social activity, occupation, sexual behaviour, self-care, and life support activity) which are assessed on an 11-point NRS. The PDI has been used to evaluate effectiveness of treatment methods. It is quick to administer and correlates well with other more complex tests like the Multidimensional Pain Inventory, but may have only modest reliability. The Oswestry Disability Index (ODI) is the most commonly used test internationally to measure the degree of disability and to estimate quality of life in low back pain. The current version of the form was described in the *Spine* journal in 2000.[19] The self-completed questionnaire contains 10 topics: intensity of pain, lifting, ability to care for oneself, ability to walk, ability to sit, sexual function, ability to stand, social life, sleep quality, and ability to travel. Each is tested by six statements weighted from 0 to 5 points (0—lack of disability, 5—severe disability). The final percentage of disability is calculated based on a simple formula.

There are many other tools assessing function specific to disease states such as the Oxford Knee Score, and the Roland Morris, but these are beyond the scope of this review.

Clinical trials

The existence of so many measurement scales used in clinical practice makes the evaluation of treatment between centres very difficult. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommended six core outcome domains:

- pain intensity—assessed by NRS: a 50% reduction is accepted as a substantial improvement,
- physical functioning—assessed by the Multidimensional Pain Inventory or BPI,
- emotional functioning—assessed by the Beck Depression Inventory and Profile of Mood States,
- patient ratings of improvement and satisfaction with treatment—assessed by the seven-point Patient Global Impression of Change scale.

The aim is to achieve consensus as to what domains to measure, and which tools to use, to improve clinical trial methodology. IMMPACT also recommended that two or more different methods should be used to evaluate the clinical importance of improvement or deterioration in participants in chronic pain clinical trials.

Cancer pain

Pain is one of a number of symptoms measured in palliative medicine. Many of the scales above have validation for use in this area. However, there are specific instruments validated for assessing pain, other common symptoms, and functional disabilities in palliative care e.g. the Memorial Symptom Assessment Scale (MSAS) and its Short Form (MSAS-SF).

Pain in extreme of ages

Pain in an ageing population is very common: 40% of those living independently, and 80% of elderly persons living in care homes report pain. Numerical ratings scale and facial pain scales have comparable sensitivity and are associated with a high completion rate, good concurrence, and acceptable reliability. Patients with dementia may lack the capacity to self-report, and the recognition of pain depends on observation of their pain behaviour or facial expression—e.g. the MOBID-2.

Paediatric pain assessment has its own challenges, as neonates, preverbal children, or those with significant handicap may not self-report their pain experience, and behavioural or biological measurements may be used. The PedIMMPACT consensus group recommended the following:

- self-report scales: the Piece of Hurt Scale for children 3–4 yr old; the Faces pain scale for 4–12 yr old; and VAS for older than 8.
- behavioural scales: FLACC (face, leg, activity, cry, and consolability) for postoperative pain and COMFORT scale in critical care settings.

Conclusion

There is a large body of literature concerning validity, sensitivity, and reliability of many scales designed to measure different aspects of the pain experience in every clinical setting. Many have also been validated in different cultures/languages, underscoring their robust utility and applicability. Although context can limit their validity and care should be taken to avoid overinterpretation, correctly used, validated scales are very useful for the measurement of multidimensional facets of pain to support diagnosis e.g. in neuropathic pain, to set a baseline against which to measure treatment success or failure, to guide clinical endeavour at the patient level, and in pain research, where standardization is necessary to allow meaningful comparison between different pain management strategies. Such scales may have further important implications for service improvement, and in health economics.

Declaration of interest

N.P. is the FPM question writer/examiner.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Heritable connective tissue diseases, vasculitides, and the anaesthetist

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Key points

- Connective tissue disorders (CTD) are rare conditions and often underdiagnosed.
- There are two main groups of CT disease: heritable disorders and auto-immune conditions.
- Vasculitides are often associated with CTD and are characterized by inflammation of blood vessels which can lead to organ dysfunction.
- It is important to recognize their multi-organ system nature, such that patients can be adequately pre-assessed and optimized before surgery.
- Their symptomatology can result in a number of challenges in the perioperative period and recognition of this can prevent unnecessary complications and cancellations.

Background

Connective tissues (CTs) serve to support, separate, or connect various tissues in the body. They are composed of collagen, elastin, proteoglycans, and glycoproteins. Genetic defects in a single component of CTs may manifest in more than one organ and as such CT disorders (CTD) have overlapping features, making diagnosis challenging.

CTD can be divided into two main groups:

- heritable disorders of CT (HDCT), for example, Marfan's, Ehlers–Danlos, osteogenesis imperfecta.
- auto-immune conditions, for example, rheumatoid arthritis.

HDCT are a group of genetic conditions commonly caused by single-gene mutations with a variable inheritance pattern. They vary in reported incidence but are generally described as being rare. A review of the most common HDCT is presented below.

Heritable disorders of connective tissue

Marfan's syndrome

Originally described in 1896, the incidence is ~2–3 per 10 000 individuals, making it the most common autosomal dominant (AD) disorder of the HDCT.[1] Life expectancy has improved to ~72 yr due to improved management.

The genetic mutation responsible is defective fibrillin-1 (FBN1) gene on chromosome 15. Fibrillin-1 forms the main component of microfibrils which form the elastic tissue of aortic media. Mutations increase the susceptibility of elastic fibres to proteolysis leading to stiff aortic walls.

Diagnosis is based on the revised Ghent consensus criteria. Table 1 outlines the major clinical manifestations and highlights features pertinent to anaesthetists.

Aortic root dilatation of the ascending aorta is found in 50% of adults with Marfan's syndrome (MFS).[1] Patients presenting for surgery should be managed in conjunction with cardiologists in order to allow estimation of risk, timely surgical intervention, and careful planning of the perioperative period. Current

Table 1 Clinical manifestations and anaesthetic implications of MFS. *Particularly relevant to the anaesthetist

Organ system	Clinical features	Anaesthetic implications	Management
Ocular	Ectopia lentis (lens dislocation)*	Increased risk of ocular injury	Careful ocular protection and padding
	Retinal detachment*		
	Myopia		
	Glaucoma		
Musculoskeletal	Tall stature		
	Increased arm span to height ratio		
	Arachnodactyly		
	Scoliosis*	May result in ventilatory complications. Challenging RA	
	Pectus deformity*		
	Elongated face	Difficult airway management	Careful airway assessment and planning
	High arched palate*		
	Joint hypermobility*	Joint subluxation and dislocation	Ensure careful handling and positioning
	Protrusio acetabula (reduced movement in hip joint)*		
	Pes planus		
	Dural ectasia (widening of the dural sac surrounding the spinal cord)*	Can restrict spread of local anaesthetic resulting in spinal failure	Consider MRI for identification and delineation
		Increased risk of accidental dural puncture	
Cardiovascular	Aortic root dilatation*	Increased risk of aortic dissection	Thorough multi-disciplinary preoperative assessment and investigation, e.g. ECHO
	Aortic dissection*	Increased morbidity and mortality	
	Mitral valve prolapse*		
	Aortic valve regurgitation*		Continue β-blockers
	Tricuspid valve prolapse*		Obtund pressor response on intubation and extubation
	Dilatation of the main pulmonary artery*		
	Congestive heart failure*		
	Pulmonary hypertension*		
Pulmonary	Spontaneous pneumothorax*		Lung-protective ventilation strategies
	Emphysema*		
Other	Recurrent hernias		
	Striae atrophicae		

recommendations include yearly echocardiography if the aortic root diameter (ARD) is <4.5 cm and twice per year when >4.5 cm.[1]

Risk factors for dissection include an ARD >5 cm, progressive aortic dilation beyond the sinuses of valsalva, rapid rate of aortic dilation (>2 mm yr^{-1}), and a family history of aortic dissection. An ARD of >4.25 cm m^{-2} is considered to be high risk for dissection.[1]

Patients are often commenced on a β-blocker (calcium-channel blocker if intolerant) which serves to reduce aortic wall stress due to the negatively inotropic and chronotropic effects. These should be continued in the perioperative period.

Anaesthetic considerations

No anaesthetic technique has been shown to be superior; however, the primary aim should be to minimize haemodynamic stress.[2]

Examination of the airway will allow identification of a high arched palate and prognathism which can predispose to a difficult intubation. Excessive traction on the temperomandibular joint (TMJ) should be avoided to prevent dislocation.

Invasive monitoring in terms of an arterial cannula should be considered, especially in those at increased risk of aortic dissection. Obtunding the pressor response to intubation is important for the reasons outlined above.

Careful attention to patient positioning will minimize the risk of joint subluxation and/or dislocation secondary to joint laxity.

Ventilatory problems may also be encountered. Pectus excavatum, kyphoscoliosis, and intrinsic pulmonary involvement, for example, emphysema, can increase the risk of respiratory complications. They are also at a higher risk of pneumothorax and therefore inspiratory peak pressures should be monitored closely and minimized whenever possible.

Marfan's and the pregnant patient

Concerns include the increased cardiovascular risk due to a hyperdynamic circulation and the maternal hormonal influences on elastin and collagen fibres in the aorta. The risk of aortic dissection during pregnancy is estimated to be 10% when the ARD is >4 cm.[3]

Careful planning will ensure regular follow-up, medication review (labetalol is the β-blocker of choice), genetic counselling, regular echocardiography, and a considered delivery plan to ensure delivery in a centre where the necessary multi-disciplinary skills are available.

There is no consensus about the preferred mode of delivery. The European Society of Cardiology advises Caesarean delivery in patients with an ARD >4.5 cm. Assisted vaginal delivery can

be considered when ARD is <4 cm and there is no further aortic root dilation during pregnancy.[3]

Equally, there is no consensus on best anaesthetic practice for delivery. General anaesthesia (GA) may expose the patient to haemodynamic changes that could predispose to aortic dissection. Neuraxial techniques, especially combined–spinal epidural (CSE), have several potential advantages in terms of reducing the haemodynamic stresses of delivery. However, spinal deformities and dural ectasia not only make these techniques challenging but increase the risk of dural puncture and failure.

Dural ectasia, diagnosed on MRI, is a dilatation of the dural sac, primarily in the lumbo-sacral area and is present in 63–92% of patients with MFS. Patients are often asymptomatic but can complain of lower back pain, headache, weakness and numbness above and below the knee, and genital/rectal pain. The increased volume of cerebrospinal fluid (CSF) within the theca restricts the spread of local anaesthetic (LA) and is thought to be one of main reasons for spinal failure. It is not an absolute contraindication for epidurals; however, in severe cases as delineated on MRI, caution is advised because of the risk of accidental dural puncture. We advise antenatal lumbar MRI if no previous imaging has been undertaken. If no imaging is available at delivery, we suggest consideration of a CSE as intrathecal techniques have an appreciable failure rate in this patient group. To minimize the risk of dural puncture, ultrasound can be used to locate the target interspace and determine the depth to the epidural space.

Postoperative monitoring in a high-dependency area is recommended as aortic dissection can occur in the post-partum period even in the absence of pre-existing aortic enlargement.[3]

Ehlers–Danlos syndrome

Ehlers–Danlos syndrome (EDS) represents a spectrum of phenotypically and genetically diverse conditions. Recognized features include joint hypermobility, skin hyperextensibility, delayed wound healing with atrophic scarring, bleeding tendency, and tissue fragility (Table 2). The overall incidence is 1:10 000 to 1:25 000.[4]

The Villefranche classification of EDS recognizes six major subtypes based on clinical and genetic findings. These include classic (type I and II), hypermobile (III), vascular (IV), kyphoscoliotic (VIA), arthrochalasia (VIIA and VIIB), and dermatosparaxis (VIIC). The classic, hypermobility, and vascular type are more common.

The underlying pathophysiology involves alterations in genes involved in the synthesis or post-translational modification of various collagen types.[4] Inheritance is AD in the classic, vascular, and arthrochalasia types and autosomal recessive (AR) in other forms (e.g. kyphoscoliotic).

Table 2 Clinical manifestations and anaesthetic implications of EDS

Ehlers–Danlos type	Major clinical manifestations	Anaesthetic implications	Management
Classic	Marked joint hypermobility Skin hyperextensibility Atrophic scarring	Joint subluxation and dislocation	Ensure careful handling and positioning
Hypermobile	Marked joint hypermobility Minor skin findings		
Vascular	Thin, translucent skin		Avoid adhesive tapes and dressings
	Arterial/intestinal/uterine fragility or rupture	Caution with invasive monitoring—increased risk of dissection	NIM preferred. Use of ultrasound to establish invasive monitoring
		Increased bleeding risk	Consider use of cell saver, tranexamic acid
	Hypermobility of small joints Extensive bruising Tendon and muscle rupture Characteristic facial appearance		Avoid i.m. injections and tourniquets
Kyphoscoliotic	Generalized joint hypermobility Congenital hypotonia		Consider neuromuscular monitoring
	Congenital and progressive scoliosis	May result in ventilator complications Challenging RA	
	Scleral fragility and rupture of the ocular globe	Increased risk of ocular injury	Careful ocular protection and padding
Arthrochalasia	Generalized joint hypermobility with recurrent subluxations Congenital bilateral hip dislocation		
Dermatosparaxis	Severe skin fragility Sagging, redundant skin	Difficult i.v. access	
Other features	Recurrent TMJ dislocations, occipito-atlantoaxial instability	Difficult airway management	Careful airway assessment and planning
	Increased risk of pneumothorax		Lung-protective ventilation strategies
	Valvular abnormalities (typically in EDS types III, IV, VI)		
	Reduced effect of local anaesthesia	Reduced effect of topical and RA	
	Tarlov cysts (typically present in EDS type I, II, III, VIA)	Increased risk of dural puncture	

Before operation, a thorough history and examination is essential with the aim of identifying the subtype if not known. One should enquire about bleeding history (easy bruising, bleeding gums, prolonged bleeding after procedures, and prolonged or heavy menses).

Investigations

Blood tests including coagulation assays are often normal; however, platelet aggregation abnormalities can be expected in 26% of patients.[4] The Rumpel–Leede test may be positive, indicating capillary fragility. Different forms of EDS have been also associated with deficiency of factors VIII, IX, XI, XII, and XIII. Cross-matching is advised in patients at risk of bleeding (EDS subtype IV and patients with a positive bleeding history).

An echocardiogram should be considered in EDS types III, IV, and VI as they are associated with structural cardiac complications, for example, mitral valve prolapse.

Patient monitoring

Non-invasive monitoring (NIM) is recommended unless clinically indicated as invasive monitoring predisposes to vascular wall dissection (mainly vascular subtypes).[4] NIM poses its own risks however as patients are prone to bruising and haematoma formation. The subclavian vein should be avoided as haemorrhagic control is difficult to achieve in this area. The propensity for haemorrhage and haematoma formation means that the number of needle sticks should be minimized, so ultrasound is recommended for vascular access to reduce the number of unsuccessful attempts.

Anaesthesia

There is no current recommendation over whether GA or regional anaesthesia (RA) is better. Scoliosis and spinal pathology may make neuraxial anaesthesia challenging. The guideline for vascular EDS by Orphanet UK[5] recommends avoiding neuraxial block in this subtype due to the potentially increased risk of complications, particularly spinal haematoma.

There are reports regarding ineffectiveness of LA, including the use of EMLA and peripheral nerve blocks. This may be due to tissue scarring, scoliosis, and kyphosis resulting in reduced spread of LA.

Another consideration is Tarlov cysts, which are CSF-filled cysts reported in the classic, hypermobility, and kyphoscoliotic subtypes. Since they are mainly found in the sacral area, they are only a relative contraindication for spinal or thoraco-lumbar epidural anaesthesia,[4] but care should be taken to avoid dural puncture.

Airway management

Risks predisposing to difficult airway include TMJ dislocations, premature spondylosis, or occipito-atlantoaxial instability. Repeated attempts at intubation can cause mucosal trauma which this patient group is more susceptible to in view of friable tissues and mucosa. The use of laryngeal mask airways is recommended when possible. Fibreoptic intubation should be considered to avoid mucosal injury and bleeding which can result in an obstructed view. Smaller sized tracheal tubes and regular monitoring of cuff pressures can reduce the risk of tracheal mucosal damage. High airway pressures can predispose to pneumothorax which these patients are more susceptible to (reduction in collagen types I and III in the lung).

Circulatory issues

Hypertensive episodes in the perioperative period should be avoided to minimize the risk of arterial dissection. Point-of-care testing, for example, thromboelastography, provides rapid diagnosis of coagulation abnormalities and reduces inappropriate blood transfusions. Cell salvage and tranexamic acid use should be considered. Desmopressin (DDAVP) has been shown to reduce transfusion requirements.[4]

One condition associated with EDS is postural orthostatic tachycardia syndrome (POTS). POTS is a type of dysautonomia defined as a sustained increase in heart rate of 30 beats min^{-1} or more within 10 min of standing or head-up tilt in the absence of orthostatic hypotension. This may be accompanied by symptoms of autonomic hyper-activity that are relieved by recumbency. There are few publications in the anaesthesia literature on the perioperative management of POTS. Preoperative i.v. fluids and the early use of vasopressors have been recommended.

Patient positioning

Optimal padding of pressure points should aim to reduce external tissue pressure. Careful attention should be applied to the eyes as there is a higher risk of retinal detachment and globe perforation. Adhesive tapes and dressing should be avoided due to the increased skin fragility.

I.M. injection and tourniquets are contra-indicated due to the risk of haematoma formation.

Neuromuscular symptoms can include muscle weakness, and impaired vibration sense and proprioception. This can be secondary to an axonal sensorimotor polyneuropathy. Mixed myopathic–neurogenic or myopathic features can be seen on electromyography. To ensure appropriate dosing, neuromuscular blocking agents should be titrated against neuromuscular monitoring.

After operation, vigilance for the development of haematomas and bleeding is important. Caution should be exercised with drugs that interfere with the haemostatic process including non-steroidal anti-inflammatory drugs, especially in the vascular subtype. Other postoperative complications include pneumothorax, vascular dissection, compartment syndrome, and oesophageal rupture due to vomiting.

EDS and the pregnant patient

There is no consensus on optimal delivery method as uterine rupture, prolapse, and delayed wound healing may complicate both vaginal and Caesarean delivery. Episiotomy is associated with pelvic prolapse and should be avoided.[4] The benefits of neuraxial block should be balanced against the increased risks in specific EDS subtypes as discussed above.

Stickler's syndrome

Stickler's syndrome, an AD condition, is associated with progressive craniofacial, skeletal (joint hypermobility, premature osteoarthritis, scoliosis), ocular (cataracts, glaucoma, retinal detachment, blindness), and auditory abnormalities. The incidence is estimated at around 1:10 000.[6]

Craniofacial anomalies include shallow supraorbital ridges, prominent eyes, midface hypoplasia, hypoplastic nose with anteverted nares, long philtrum, retromicrognathia, and cleft palate.[7] Twenty-five per cent of patients have a cleft abnormality which ranges from the extreme of the Pierre-Robin sequence to the mildest form of bifid uvula.[7] These abnormalities may result in difficult mask ventilation and tracheal intubation.

Vasculitis

Systemic vasculitis is characterized by inflammation of blood vessels leading to multi-organ dysfunction. They can be associated with auto-immune CTDs, infections, and drugs (secondary

vasculitides), but usually occur independently as primary vasculitides. Primary systemic vasculitis has an annual incidence of 40–54 cases per 1 000 000 people.[8]

Pathogenesis is poorly understood and thought to be related to immune complex deposition, anti-neutrophil cytoplasm antibodies, and T and B lymphocytic responses secondary to an unknown aetiological trigger.[8]

The Chapel Hill Consensus Conference proposed a nomenclature based on vessel size and histopathological features (Table 3) which was revised in 2012 to include updated nomenclature and a new category—variable vessel vasculitis.

Clinical features depend on the vessel(s) affected. Patients often describe non-specific symptoms, including pyrexia, malaise, weight loss, rash, and arthralgia. The multi-system organ involvement of such conditions will be exemplified by two conditions: Takayasu's arteritis (TAK) and granulomatosis with polyangiitis (GPA).

Takayasu's arteritis

TAK is a rare large vessel vasculitis most commonly seen in young Asian woman, resulting in granulomatous inflammation of the aorta and its large branches. This classically results in

Table 3 The Chapel Hill Consensus Conference nomenclature for vasculitis

Vasculitis	Vessel type	Vasculitis	Major clinical features
Primary systemic vasculitis	Small vessel vasculitis (SVV)	Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss)	Allergic rhinitis, asthma, peripheral eosinophilia, neuropathy, myocarditis
	Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)	Microscopic polyangiitis (MPA)	Purpura, arthritis, pulmonary haemorrhage, glomerulonephritis
		GPA (Wegener's)	Granulomatous inflammation of upper and lower respiratory tract. Lung nodules and haemorrhage, nasal crusting, deafness, sinusitis, glomerulonephritis
	Immune complex SVV	IgA vasculitis (Henoch–Schönlein)	Purpura, arthritis, abdominal pain, gastrointestinal bleeding, glomerulonephritis
		Anti-glomerular basement membrane (anti-GBM) disease	Affects glomerular (glomerulonephritis) and/or pulmonary (pulmonary haemorrhage) capillaries
		Cryoglobulinaemic vasculitis	Purpura, glomerulonephritis, neuropathy
		Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)	Urticaria, arthralgia, glomerulonephritis
	Medium vessel	Kawasaki disease	Fever, conjunctivitis, desquamating skin rash, coronary arteritis. More common in children
		Polyarteritis nodosa	Fever, weight loss, hypertension, abdominal pain, melaena, peripheral neuritis, renal ischaemia
	Large vessel	Giant cell (temporal) arteritis	Fever, visual disturbances, facial pain, and headache. Usually in >50 yr olds
		Takayasu arteritis	Decreased or absent pulses, hypertension, discrepant pressure readings between limbs and claudication. Usually in patients <50 yr
Variable vessel vasculitis (VVV)		Behçet's disease (BD)	Vasculitis occurring in patients with BD which is characterized by recurrent oral and/or genital aphthous ulcers
		Cogan's syndrome (CS)	Vasculitis occurring in patients with CS, which is characterized by ocular lesions, including interstitial keratitis, uveitis, and episcleritis, and inner ear disease, including sensorineural hearing loss and vestibular dysfunction
Single-organ vasculitis (SOV)		Cutaneous vasculitis	SOV is vasculitis in arteries or veins of any size in a single organ
		Primary central nervous system vasculitis	
		Isolated aortitis	
Vasculitis associated with systemic disease		Lupus vasculitis	Vasculitis can be associated with and may be caused by a systemic disease. Often considered to be secondary vasculitides
		Rheumatoid vasculitis	
		Sarcoid vasculitis	
Vasculitis associated with probable aetiology		Hepatitis B or C virus-associated vasculitis	Often considered to be secondary vasculitides
		Drug-induced vasculitis	
		Cancer-associated vasculitis	

stenosis and occlusion, but can also lead to dilation and/or aneurysm formation in the affected vessel. Non-specific systemic symptoms as described above are common; however, patients can present with decreased or absent pulses, hypertension, discrepant pressure readings between arms and/or lower limbs, and claudication. Complications include aortic regurgitation (AR), pulmonary thrombosis and hypertension, cerebral infarction, blindness, and limb ischaemia.

Imaging of arteries is important to aid diagnosis and monitor disease activity. Angiography remains the gold standard; however, CT modalities (CT angiography, CT PET) and MRI are more commonly used. Echocardiography is used as a non-invasive assessment of aortic root dilatation, pulmonary hypertension, and central hypertension.

Treatment includes high-dose glucocorticoids with immunosuppressive therapies for remission induction and biological agents. Endovascular procedures or bypass surgery are reserved for the treatment of critical arterial stenoses; ideally performed when inflammation is controlled.

Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)

GPA is an ANCA-associated vasculitis (peak age 55–70 yr) causing arteritis of small to medium-sized vessels and granulomatous inflammation of the upper airways and lungs. GPA also often presents with non-specific symptoms. In about 90% of patients, granulomatous involvement of upper airways occurs which presents with epistaxis, sinusitis, otitis media, deafness, hoarseness, and stridor. This can lead to nasal septal collapse or perforation and tracheal stenosis. Oropharnygeal ulcers may be present and caution should be exercised on intubation to avoid bleeding and dislodgement.

Lung involvement includes pulmonary nodules, infiltrates, fibrosis, and alveolar haemorrhage. Renal manifestations include necrotizing glomerulonephritis. Renal replacement therapy is required at presentation in 20–30% of patients. Pulmonary–renal syndrome presenting with acute renal dysfunction and pulmonary haemorrhage is frequent and when severe is associated with a high mortality (50%). Neurological manifestations include meningeal inflammation, peripheral neuropathy, and mononeuritis multiplex.

Subglottic or tracheal stenosis occurs in 9–16% of patients. These patients often complain of shortness of breath, with stridor being less common often leading to misdiagnosis.

Treatments include high-dose glucocorticoids and immunosuppression, with plasma exchange for severe renal disease and pulmonary haemorrhage as remission induction strategies. These treatments have transformed the 1 yr mortality of GPA from 80 to 10%. Relapse rates are high (50% at 5 yr) and frequently involve the upper respiratory tract, causing significant morbidity due to active inflammation and disease or treatment-related damage. With regard to subglottic stenosis, treatment options for stable disease include endoscopic techniques such as dilatation, topical mitomycin, or steroid injections.[10] Laser treatment or surgery, including segmental resection or expansion of the stenosed area, are also used. In active disease, dilatation is often required and avoidance of tracheostomy is preferable. Standard anaesthetic techniques for rigid bronchoscopy (jet ventilation and total i.v. anaesthesia for maintenance) are used.

The multi-organ nature of these conditions presents a challenge to anaesthetists. Preoperative assessment should aim to establish the extent of arteritis and end-organ involvement.

Investigations to consider include the following described below.

Full blood count: patients with active vasculitis often have leukocytosis, anaemia, and thrombocytopenia. Bone marrow suppression may be present secondary to concurrent treatment.

Renal function: it is important to establish a baseline to allow identification of worsening renal function. End-stage renal disease patients will need to have arrangements for dialysis.

Liver function tests can identify hepatic involvement and are important in monitoring patients treated with hepatotoxic drugs, for example, methotrexate.

ANCA, ESR, CRP: levels may reflect the degree of inflammation and can be used to monitor response to treatment.

ECG, ECHO: cardiac complications include heart failure, pericarditis, myocarditis, and valvular heart disease. Pulmonary hypertension can also occur.

Fibreoptic laryngoscopy and bronchoscopy in GPA can provide valuable information regarding vocal cord mobility, the extent of stenoses, and the distance from the vocal cords.

Intraoperative considerations:

- The extent of surgery and severity of the disease will determine the degree of monitoring required. In TAK, arterial cannulation may be difficult if pulses are impalpable and therefore ultrasound is recommended. Meikle and Milne[9] have suggested that due to differences in arterial pressure (AP) and therefore regional blood flow, monitoring of both upper and lower extremity AP should be considered.
- Avoidance of hypertensive episodes that can result in aortic dissection or cerebral haemorrhage in TAK. Anti-hypertensive medication should be continued before operation. Premedication and use of agents to obtund the pressor response to intubation should be considered.
- Avoidance of hyperextension, tight tracheal tube neck ties, and maintaining cerebral perfusion pressure in patients with carotid stenosis can prevent ischaemic events.
- RA in TAK aids AP control in the perioperative period and permit neurological assessment in the awake patient. The use of RA in GPA avoids airway manipulation. However, one should be aware that sympathetic blockade may worsen regional blood flow in an unpredictable 'steal' type manner.[9]
- Steroid supplementation should be used in the perioperative period for patients on long-term glucocorticoid treatment and for patients with active vasculitis.
- Thromboembolic disease is an increasingly recognized feature of several forms of systemic vasculitis and is thought to be due to the inflammatory state seen in these conditions. Currently, standard deep venous thrombosis prophylaxis regimes are recommended.

Conclusion

Patients with HDCT and vasculitides often require surgery both in elective and in emergency settings. Although rare, a working knowledge of these conditions is important to avoid perioperative complications and cancellations.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Prehospital organization and management of a mass casualty incident

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Key points

- A major incident is an incident where the location, number, severity, or type of live casualties requires extraordinary resources.
- The declaration of a major incident results in the implementation of a multi-service structured response based on key principles: command and control, safety, communications.
- Three tiers of command are recognized: operational (previously known as bronze) and tactical (silver) are located at the scene. Strategic (previously called gold) support is provided distant to the scene often at regional police headquarters.
- Healthcare support at a major incident involves the hierarchy of triage, treatment, and transportation.
- Problems commonly encountered at a major incident in the prehospital setting include issues with communication and over-triage.

The last two decades have seen healthcare systems increasingly involved in the management of mass casualties with an incidence of 3–4 major incidents per year previously cited as the UK mean and including transportation incidents, terrorism, infectious diseases, and natural disasters.[1] Increasing media coverage and the prevalence of terrorist activity and infectious disease (e.g. Ebola) has also resulted in raised general awareness. Additionally, the recent Hillsborough Inquest (relating to a sports stadium disaster in Sheffield, UK, in 1989) demonstrates how emergency services and others can be placed under significant scrutiny years after the event.

Timelines for major incidents are frequently divided into four distinct stages: initial response, consolidation phase, recovery phase, and restoration of normality, with the duration of individual components being largely determined by the nature of the incident. These are then followed by the process of Coroners' Inquests, civil/criminal trials, and public enquiries. Acute hospitals in the UK are legally bound under the Civil Contingencies Act 2004 to have a level of preparedness for major incidents, but knowledge of responsibilities and roles is often limited.[2] This article therefore deals with an overview of what constitutes a major incident and how the initial prehospital response is (in general terms) organized in a civilian setting outside the environment of significant chemical, biological, radiological, or nuclear contamination. Its intention is to provide hospital staff in anaesthesia and intensive care medicine (often the forefront of a hospital response) with a working knowledge of how emergency services work on-scene.

Major incidents

A mass casualty major incident is defined as any incident where the location, number, severity, or type of live casualties requires extraordinary resources. They tend to be classified in three ways:

1. natural or man-made,
2. simple or compound,
3. compensated or uncompensated.

Natural major incidents result from severe natural events, e.g. floods, fires, tsunamis, earthquakes, or volcanic eruptions and in addition to illness and injury frequently have the added complication of homelessness, limited food and water, and

vulnerability to infectious diseases. Man-made incidents occur whenever large groups of people are in close proximity (e.g. work, travel, leisure) and cover incidents involving transport (most common), industry, mass gatherings (defined by convention as a crowd in excess of 1000), and terrorism.

The complexity of incidents is described using the terms simple, compound, compensated, and uncompensated. A simple incident describes a major incident where infrastructure remains intact; a compound incident involves damage to infrastructure, e.g. transportation, lines/methods of communication, health services, etc. Compensated major incidents include those where 'the load is less than the extraordinary capacity', i.e. live casualties can be dealt with by mobilizing additional resources. In uncompensated incidents (frequently associated with natural disasters), the load placed on services exceeds even an 'extraordinary' capacity whereby the additional mobilization of medical resources through major incident plans are unable to cope with the number of casualties. Within high-income/high-resource countries, the majority of major incidents encountered by health services are simple, man-made, and compensated. Recent exceptions include Hurricane Katrina in New Orleans, the Chilean Earthquake, and the Japanese Tsunami.

Declaration of a major incident

Any member of the emergency services can declare a major incident using the METHANE mnemonic (Fig. 1) if they consider criteria within the above definition have been met, noting that a major incident for one emergency service does not automatically constitute a collective major incident. If doubt exists, personnel (and hospitals) can be placed on stand-by.

Response to a major incident

When a major incident is declared, emergency services and other providers have a designated set of priorities that are intended to be life-saving and enable a rapid restoration of normality in the aftermath of the event. Interventions are applied at the scene (operational and tactical) and beyond (strategic) at a designated location distant to the event (gold command). In summary, initial priorities are to save life, relieve suffering, and prevent escalation of the incident followed by protection of the environment, preservation of infrastructure, and property with a subsequent restoration of normality and facilitation of enquiries.

The process has previously been summarized in the MIMMS (Major Incident Medical Management and Support) system and in the UK is now described via JESIP (Joint Emergency Services Intra-operability Programme) via the acronym CSCATTT (Fig. 2)

Command and control

Initial emergency vehicles leave their blue lights on as the focus for an incident control point and personnel begin an initial assessment. Subsequent vehicles extinguish their lights and a predetermined command structure is then established within each emergency service: operational (bronze), tactical (silver), and strategic (gold). Commanders at the scene are described as operational commanders and the healthcare response is led by a medical and ambulance commander. One service (usually the police in the UK) assumes overall responsibility.

Two main cordons are established to ensure safety and security at the scene and support movement to and from the incident. An inner cordon covers the incident site, enclosing the operational zone and has restricted access under fire/police control. An outer cordon is physically established by the police to prevent unauthorized access to areas used by the emergency services.

With respect to zones of command, operational commanders work at the site of the incident and support personnel within that area. Depending on the nature of the incident, there may be multiple operational areas each requiring its own commander, e.g. multiple train carriages. Tactical command is usually enclosed by the outer cordon and under the responsibility of the service commanders. They co-locate at the command vehicle (JESCC or Joint Emergency Services Control Centre) where they plan and co-ordinate the response to the incident for each service and direct resource to the bronze zone as information

M: My call-sign/ Major Incident Declared

E: Exact location of the incident

T: Type of incident with brief details re vehicles, buildings etc.

H: Hazards present and potential

A: Access routes to the incident and potential rendezvous points (RVPs)

N: Approximate Number and nature of casualties

E: Emergency services: present and those required including specialist input e.g. Air Ambulance, MERIT teams

Fig 1 The METHANE mnemonic.

(e.g. number of casualties) is brought to them. Strategic command exists distant to the scene and supports tactical commanders. It also liaises with other organizations whose resources may be required, e.g. local NHS Trusts, Public Health, and Local and National Government.

Within the outer cordon and in addition to the JESCC, commanders must establish a casualty clearing station (CCS), suitable access and exit points from the site for ambulances, and a safe route of evacuation for non-injured survivors. Designated non-command personnel are required to log communications received including those made between commanders and those containing information relayed from the scene of the incident.

Safety: self, scene, survivors

Safety at the scene has individual and collective aspects. Each rescuer is required to have appropriate personal protective equipment in order to enable access to the incident site. Collectively (applying principles of distributive justice), the scene should also be secured and made safe in order to prevent rescuers becoming casualties. This principle was outlined during the London 7/7 inquest where rescue personnel had to ensure that there were no secondary devices.[3] The command and control overlay continues and at this juncture is the responsibility of fire and rescue services, although if the incident is a major crime or security alert, the police may assume command.

Communication

Poor communications are repeatedly identified as problematic. They include lack of information, failure to confirm information, and lack of coordination of information and resources between individuals and emergency services. With respect to devices, radios (with specified, secure talk-groups with recording) are the mainstay of communication within and across services. Telephone networks can rapidly become overloaded (in the 7/7 bombings: 42 000 calls inside 1 h) necessitating more basic methods of communication, for example, runners with written instructions, loud-hailers, hand signals.[4] For public information, radio and television networks can be utilized.

C: Command and Control

S: Safety of self (rescuers), the scene and survivors

C: Communications

A: Assessment of the scene

T: Triage

T: Treatment

T: Transport

Fig 2 Management process for a major incident (MIMMS and JESIP).

Medical support (triage, treatment, and transport)

Primary triage or triage sieve

The aim is to deliver the 'right patient to the right place at the right time' which, in the first instance (Fig. 3), is a very basic process based again on distributive justice. It is a continuous process repeated at multiple stages to varying levels of complexity between primary triage and arrival at hospital. Primary triage is usually performed by trained ambulance crew and has four levels of priority: P1–3 reflect reducing severity of injury (immediate, urgent, delayed), the fourth category (P4) is dead. Labels are colour-coded: red, yellow, and green for P1–3, respectively, and black or white for P4.

The process is basic with limited immediately life-saving interventions based on C-ABC approach, i.e. the triage teams will attempt to stop catastrophic haemorrhage (tourniquets, dressings, etc.) and maintain airways with basic adjuncts, an addition highlighted after 7/7. Its purpose is to move the uninjured and minor injuries to a place of safety for further assessment, while the more severely injured can be triaged and evacuated for treatment at the CCS. Personnel are provided with guidance in the form of body-length tape for paediatric cases and have colour-coded cards to record the number and type of casualty for subsequent relay to bronze commanders.

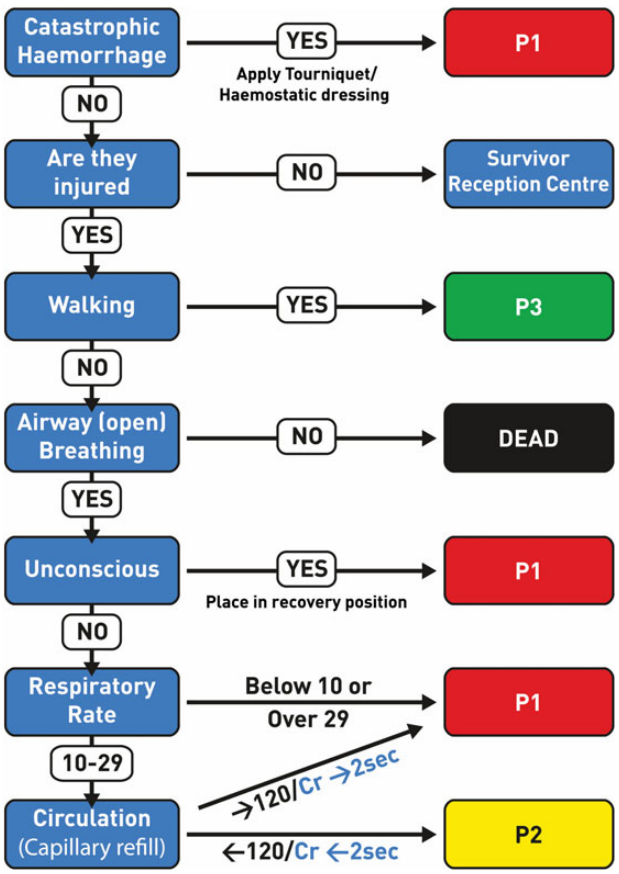

Fig 3 Triage sieve algorithm (National Ambulance Resilience Unit).

Secondary triage or triage sort

At the CCS, further triage occurs via the Triage Revised Trauma Score (TRTS) which grades severity via respiratory rate, systolic arterial pressure, and Glasgow coma scale (GCS) and assigns a maximum score of 12. Similar priorities (P1–4) and colour coding are applied, with P1 having a score of 1–10, P2 a score of 11, and P3 of 12 (Figs 4 and 5). Dead patients score 0. This once again allows rapid assessment and prioritization but should be supplemented with as much anatomical information as possible.

Over-triage

Over-triage occurs when casualties' conditions are unintentionally overestimated, i.e. non-critically ill casualties are assigned P1 or P2 categories and treatments are prioritized over casualties with more urgent needs. Typically, trauma centres will allow a triage rate (number of P1 and P2 casualties) of up to 50% under 'normal circumstances' to allow the capture of all patients with severe injury, that is, prevent undertriage.[5] However, in a mass casualty disaster, the allowable over-triage rate remains controversial as there is an association with increased mortality rates through a potential to overwhelm hospital resources diverting attention from actual critically injured patients.[6] Prevention can occur via trained personnel performing triage sieve in the first instance and by the subsequent use of physiological and anatomical data, e.g. the injury severity score.[7–9]

Treatment and transport

The organization and provision of equipment for the treatment of casualties is the responsibility of the ambulance service supported by prehospital medical staff. Some treatments may occur within the inner cordon (usually first aid: bystanders and emergency services). There may also be the facility to provide advanced treatment (such as surgery) within the CCS. Practically,

STEP 1: Calculate the **GLASGOW COMA SCORE** (GCS)

A: Eye opening:		B: Verbal response:		C: Motor response:	
Spontaneous	4	Orientated	5	Follows command	6
To Voice	3	Confused	4	Localise Pain	5
To Pain	2	Inappropriate	3	Withdrawal to pain	4
None	1	Incomprehensible	2	Flexion to pain	3
		No Response	1	Extension to pain	2
				No Response	1

Glasgow Coma Score (GCS) = A + B + C

STEP 2: Calculate the **TRIAGE SORT SCORE**

X: Convert Glasgow Coma Scale		Y: Respiratory Rate		Z: Systolic Blood Pressure	
13 – 15	4	10 – 29	4	≥ 90	4
9 – 12	3	> 29	3	76 – 89	3
6 – 8	2	6 – 9	2	50 – 75	2
4 – 5	1	1 – 5	1	1 – 49	1
3	0	0	0	0	0

Triage Sort Score = X + Y + Z

STEP 3: Assign a triage **PRIORITY**

12	=	Priority 3
11	=	Priority 2
≤ 10	=	Priority 1
0	=	Dead

STEP 4: Upgrade PRIORITY, dependent on the injury/ diagnosis

Fig 4 Triage sort and the TRTS (National Ambulance Resilience Unit).

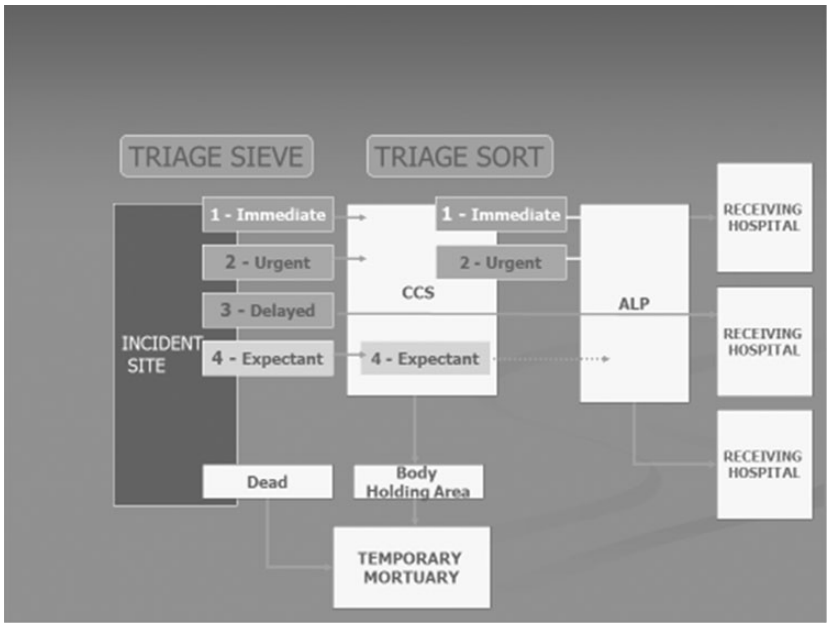

Fig 5 Basic layout of the rescue scene. CCS, casualty clearing station; ALP, ambulance loading point. Text adapted from Advanced Life Support Group.[11]

many treatments can be provided in the prehospital setting, but care is directed towards the management of airway, breathing, and circulatory problems due to time constraints and potential numbers requiring definitive treatment. The main aim of any treatment provided is to ensure patients are stable for safe transfer to an appropriate hospital facility.

With respect to transport, three key principles are required: priority (triage sort), amount of stabilization treatment priorities before transfer, and patients' destinations. In most circumstances, the priority of evacuation will match the triage priority; however, capacity, availability, and suitability of transport has to be considered when determining the order of evacuation, e.g. air evacuation for severely injured casualties. Failure to use such a process can result in multiple un-triaged patients arriving at and overwhelming hospitals' emergency departments. Such an event occurred during the Ramstein Airshow in 1988 where no form of triage was formally instituted after an airplane crashed into the spectator enclosure resulting in ambulances instantly evacuating people to hospital.[10] Similarly, during the aftermath of the 7/7 bombs, the commandeering of buses for transporting P3 casualties to hospital had the potential to overwhelm emergency departments. The input of experienced health service commanders is therefore vital at this juncture and only through working closely within the JESCC can they ensure that transport vehicles are deployed and despatched to and from the scene appropriately. Working closely with police and fire and rescue ensures safe access and egress into and from the outer cordon via an access point, ambulance parking point, ambulance loading point, and exit site. Constant logging of casualty numbers and conveying the information to local hospitals via gold command can enhance the delivery of care.

Transportation of the dead

The scene of a major incident is also a potential crime scene and therefore, the dead should not be moved without appropriate documentation and police authorization. This is with the exception of either aiding rescue of the living or preventing destruction from fire or chemicals. While the evacuation of live casualties takes priority, the command and control structure has to factor in the requirement for a temporary mortuary, respect for the dead, and their eventual transport and identification.

Summary

Major incidents are rare but have potentially devastating short- and long-term consequences on health and infrastructure. Understanding of their nature and the management systems used in the initial prehospital setting can enable hospital staff to comprehend the problems faced by emergency services and develop their own plans to deal with casualties.

Declaration of interest

In 2015 Dr Cosgrove received a grant of £5000 from the Hillsborough Family Support Group to develop guidance pertaining to the provision of Events Medicine Services. This includes major incident contingency planning.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

Podcasts

This article has an associated podcast which can be accessed at http://www.oxfordjournals.org/podcasts/bjaed_Prehospital and Hospital Major Incident Management_Dr Cosgrove_BJAEducation_Oct2016.mp3

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Hospital response to a major incident: initial considerations and longer term effects

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Key points

- Read your institution's major incident plan.
- Practice the major incident plan—clinical and non-clinical staff.
- Command, control, and communication are essential components of management.
- Consider how your department would manage ongoing care of mass casualties.
- Staff will require physical, social, and psychological support during and after a major incident.

All NHS providers in the UK are required by law to prepare for large-scale emergencies and major incidents.[1] A health-related major incident is described as *any occurrence presenting a serious threat to the health of the community*. It is likely to involve disruption of services and require the implementation of special arrangements by hospitals, ambulance, and primary care trusts.[2] For hospitals, this manifests itself as the *major incident plan* which focuses on a specific trigger e.g. the London bombings in 2005 were external major incidents that immediately created more than 700 casualties.[3] Communications from ambulance control generally activate hospitals' major incident responses. Prehospital response subsequently directs casualties to local emergency departments, although more recently NHS trusts have activated *internal major incidents* because of overwhelming service pressures e.g. in January 2015, a demand for in-patient beds out stripped availability at Peterborough Hospital.[4] By declaring a major incident, the trust was able to cancel non-urgent elective operations and emphasize the need for local primary care trusts, social services, etc. to expedite the discharge of medically fit patients requiring non-clinical support.

With respect to (the more usual) external major incidents, the majority of hospitals have plans based on prehospital incidents that tend to deal with events in the emergency department and immediate care of severely ill or injured patients. This may only be for a 6–8 h period; however, there are the so-called *consolidation* and *recovery phases* of a major incident (Fig. 1) that can impact upon the NHS trust for days, weeks, and months afterwards. These phases are inconsistently dealt with and historically NHS trusts have put little resource into such longer term effects; however, recent experiences such as the London 7/7 Bombings have brought experience and data to strategic planning.[5,6]

The hospital major incident plan

Each institution is likely to have a variation on a standard major incident plan and it is important that staff likely to be engaged by a major incident have read it and where possible participated in simulation training: it is too late to do so once a major incident has been declared. It is impossible to make detailed plans for every eventuality, so a flexible framework can enable responses to multiple forms of major incident. This begins with an understanding of the four basic major incident alerts (Table 1) and the generic outline of a major incident plan which involves *preparation for arrival*, *freeing of resources*, and *deployment of staff*. Subsequent organization and management involves the *arrival of casualties*, *assessment of injuries*, and *initial treatment*.

Preparations for arrival

This relates primarily to understanding the categorization of major incident alerts: *major incident stand-by*, *major incident declared*, *major incident cancelled*, *major incident stand-down* (Table 1).

Freeing resources

Many acute NHS trusts may be functioning at ~90% capacity across all services and with a recent decline in the number of inpatient beds, issues such as dischargeable patients requiring social care may be significant. Within the hospital specialist services e.g. intensive care units, operating theatres are often running at near maximum capacity. Creating space to receive severely injured casualties can therefore be challenging and in addition to physical space, there will be a need to increase staffing levels for the initial surge period and (importantly) for the consolidation and recovery phases, which could be a period of weeks.[7]

Part of the major incident response is the expedited discharge of ward patients and the cancelling of most elective surgery (ongoing surgical emergencies and transplant surgery are usually exempt, but this will depend upon required theatre capacity). This process creates space for patient movement within the hospital including internal 'step-down' transfers from level-3 (invasive ventilation/multi-organ support) to level-2 care (single organ support/non-invasive respiratory support) or level-2 to level-1 care (ward-based support), etc. Alternatively (or simultaneously), critical care capacity (level-3 and level-2 beds) can be expanded by utilizing space in theatre recovery areas and anaesthetic rooms where there is a familiarity with caring for ventilated patients.

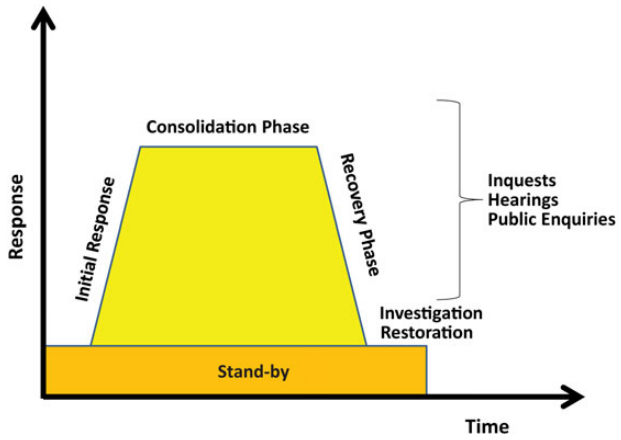

Fig 1 The stages of a major incident. London Emergency Services Liaison Panel.

Inter-hospital transfer of patients across a critical care network may be possible/necessary. This will inevitably depend upon bed availability elsewhere with the major incident and casualties potentially impacting on more than one acute NHS trust. Other compounding factors that planners need to consider are transfer teams and availability of transfer vehicles. The former usually requires experienced anaesthetic/intensive care doctors and nurses being taken away from patient care and the latter will be dependent upon how the local NHS Ambulance service is coping with the incident. Charitable and private companies can be utilized for this, as can neighbouring NHS Ambulance Trusts. Significant communications are therefore necessary in both contingency planning and the aftermath of incidents.

Deployment of staff

The time of day that a major incident is declared dictates the number of immediately available staff. The person in charge of each clinical area should ensure that staff are allocated according to need and skill set. The ideal situation for all severely injured (P1) casualties is that they are received by a trauma team whereby emergency department staff and surgeons triage and initially manage individual injuries. Within the team, it is essential that there is a constant presence of an anaesthetist and trained assistant who will follow the patient through the resuscitation room, imaging areas, operating theatres, and on to intensive care. This improves continuity of care and information transfer minimizing the likelihood of errors in treatment, particularly the administration of drugs, blood, and blood products.

Arrival of casualties

There is a high chance that the arrival of casualties will not be as controlled and co-ordinated as is intended. Many 'walking wounded' where treatment can be delayed (P3) and uninjured may self-present or be transported by bystanders. While many do not require immediate treatment, they pose significant organizational issues through weight of numbers and the fact that one or two may be delayed presentations of serious injury. Additionally, while the priority is to transfer the seriously injured, first their rescue may be hampered by access to the scene and consequently

Table 1 Major incident alerts

Major incident terms	Definition	Actions
Major incident standby	An incident has occurred but is within its early stages. It has the potential to escalate and demand the extraordinary response of the receiving trust	Confirm that standby action ONLY is required. Initial key personnel on major incident call out list are contacted
Major incident cancelled	This cancels a major incident standby call	The key personnel are again contacted and stood down
Major incident declared	This can be declared either with or without a preceding standby status. An event has occurred which mandates that a trusts major incident plan is activated	All personnel on the major incident call out list are notified. They should retrieve their major incident action cards and proceed to their designated location. As further information is obtained, actions to create extra space and prepare to receive casualties are undertaken
Major incident stand down	The major incident is perceived to be over and a plan to revert the trust to normal operation will be made	Personnel on the call out list are informed that the major incident plan is being stood down. This may be in conjunction with a recovery plan to transition the trust back to normal operational service

their arrival in the emergency department may follow the earlier arrival of P3 casualities, despite the best efforts of organization at casualty clearing stations.

To minimize delays and further prioritize treatments and care, an in-hospital triage area should be established within the emergency department. This is usually close to the ambulance bay but should also take into consideration landing areas of air ambulances. A senior clinician (ideally an Emergency Medicine Consultant) should be the designated triage officer making further rapid assessments of injury severity and allocating a triage priority: P1 (immediate life-saving interventions), P2 (interventions within 2–4 h), or P3 (less serious: treatment can be delayed beyond 4 h). Patients are moved to appropriate treatment areas within the emergency department. Constant review is necessary as P1/P2 casualties can improve and P2/P3 deteriorate. It is therefore important to be receptive to changes in triage category with time.[8]

P3 casualties usually make up the largest number of people requiring treatment. Many do not require admission but may require follow-up and contingencies for this will therefore be necessary. Planning should therefore consider an area outside the main emergency department where such patients can be triaged, assessed, and treated. If this can be done, distraction from the care of the severely injured is minimized.

Nature of injuries

Injury patterns are determined by the nature of the major incident, although the majority within the developed world involve trauma from explosions, collisions, and building collapses. Table 2 summarizes the nature of injuries suffered during the Madrid and London bombings.[8,9] Those close to the bomb are usually killed outright, meaning the injuries are often a consequence of the blast wave and flying debris.

In summary, it is important to obtain as much information as possible from the scene before patients arrive at hospital in order to direct specific treatment priorities (e.g. burns) and to protect hospital staff and infrastructure e.g. after CBRN (Chemical, Biological, Radiological, Nuclear) incidents where specialist services, training, and equipment are required.

Initial treatment: damage control

Standard management of seriously injured casualties from a major incident now involves *damage-control surgery* and *damage-control resuscitation*.[10] Of note, only 51 of 270 P1 and P2 casualties required surgery in the first 24 h after the Madrid and London bombs.[8,9] Damage-control principles aim to prevent hypothermia, acidosis, and coagulopathy, all of which are associated with increased mortality. Methods used include:

- early haemorrhage control of visible bleeding,
- limited crystalloid resuscitation with permissive hypotension,
- blood product resuscitation aimed at the clinical condition rather than laboratory values (ideally guided in part by point-of-care coagulation testing e.g. TEG or ROTEM),
- active warming of fluids and (where necessary) patients,
- surgery with an endpoint of haemostatic control only,
- stabilization in critical care to normalize temperature, clotting, and pH,
- return to theatre for definitive surgery once physiologically stable.

Radiological imaging is a valuable tool for assessing trauma patients and identifying internal injuries; however, damage-control surgery should not be delayed by a wait for imaging.

Table 2 Combined summary of injuries, Madrid and London bombings

Type of injury	Critically injured population (*n*=35)	Non-critically injured population (*n*=235)
Tympanic perforation	26 (74%)	118 (50%)
Chest injuries	27 (77%)	96 (41%)
Shrapnel wounds	28 (80%)	99 (42%)
Long bone fractures	13 (37%)	16 (7%)
Burns (superficial and partial thickness)	18 (51%)	47 (20%)
Eye injuries	7 (20%)	42 (18%)
Traumatic brain injury	17 (49%)	33 (14%)
Abdominal injury	10 (29%)	12 (5%)
Traumatic amputations (limbs, digits, ears)	12 (34%)	14 (6%)

Command and control

Within the UK, local NHS headquarters provide a command and control framework for major incidents. It follows a similar format to the prehospital structure.[2]

Strategic (gold) command

Normally chaired by the trust's chief executive or nominated deputy. It is responsible for acting upon the longer term consequences of a major incident e.g. the financial impact, planning the recovery phase, and return to normal operations. They also have a role in media liaison and tend to delegate the direct incident management to tactical command (see below).

Tactical (silver) command

Directed from a designated operating theatre. It determines the impact of the incident on the trust and makes decisions about staff deployment and the use of resources. It delegates the responsibility of running individual departments to multiple bronze commanders. Depending on the organization structure within the hospital, there may be direct communication with tactical command at the scene of the incident or the local ambulance NHS trust may provide an Ambulance Liaison Officer (ALO) to the hospital's operational command with the emergency department (see below).

Operational (bronze) command

Usually organized on a departmental basis, with commanders being senior doctors and nurses. Their role is to co-ordinate patient flow, ensuring tactical command receives timely updates about patient numbers and resources in use. This is of particular importance in operating theatres and critical care areas. These people tend not to be directly involved in clinical care but receive information from clinical teams that is used to prioritize care.

Communication

Clear communication is essential. In a major incident, traditional methods of communication (telephones, bleeps, etc.) may fail either from internal overuse or saturation of the hospital switchboard from outside calls as people attempt to gather information e.g. relatives of casualties, staff not yet at work, media organizations. Communications' contingencies therefore have to enable the transfer of information between staff for the purpose of clinical care and also provide information to relatives and media.

Fall-back plans for internal communications include the use of handheld radios in key areas by key personnel and the use of runners. This can be the most reliable way of transferring information in a chaotic environment. Written messages are carried by runners and retained as part of the records of the major incident.

From a clinical perspective, the most reliable way of accurate information transfer in a major incident is to have the same clinical team looking after the most severely injured patients from the emergency department through imaging and surgery (see the Deployment of staff section). This maintains continuity and minimizes the loss of vital information. Assigning one person to record keeping on wards and intensive care units can also assist the flow of information. During the 7/7 bombings, the Royal London intensive care unit assigned one doctor to create a database of patients being admitted to intensive care. This included listing injuries, investigations outstanding, and procedures performed. The after-action review held this document to be extremely useful in organizing subsequent care.[5]

With respect to relatives, the media, and the general public: ambulance services assign liaison officers to the NHS trust; they will be party to all communications about casualties and their management. Similarly, the police designate a liaison officer who works with a hospital representative in disseminating information in a consistent, co-ordinated manner to the media, etc. Advising people to use dedicated help-lines or specific links to social media can also ease telecommunications overload on the hospital switchboard. A dedicated police team will also reunite casualties with friends and family.

Aftermath

As stated, a hospital's main focus in a major incident is the receipt and resuscitation of large numbers of seriously injured casualties with a concurrent increase in capacity. After the 7/7 bombings, the Royal London Hospital stood down from a major incident 5 h post-event with the emergency department re-opening to trauma.[5] At this point, the operating theatres were working at full capacity and the critical care unit had not received its full complement of patients from the incident.[5,8] Such actions have the potential to further overload pressured systems. Thus, the ongoing care of the patients admitted from the incident should form part of a major incident plan as the impact of their admission and treatment is beyond a period of a few hours (see below).

Ongoing care

After the initial period of damage control resuscitation and surgery, the majority of the critically injured will be further stabilized in critical care. To identify missed injuries, they should undergo secondary and tertiary trauma surveys and more in-depth and specific investigations (laboratory, radiological, etc.). They are likely to require multiple transfers to radiology and operating theatres with an associated prolonged intensive care length of stay. After 7/7, the intensive care at the Royal London had a 12 day median length of stay (maximum 22 days), comparable with the median of 10 days after the Madrid bombings.[8,9] Furthermore, the Royal London Hospital required an additional 180 h of operating theatre time beyond elective and other emergency work. There were inevitable disruptions and cancellations to accommodate the increased need with subsequent knock-on effects for elective surgical waiting lists. Planners must therefore be aware of this impact and be able to review figures of elective and usual emergency work to assist in contingency planning related to the aftermath of a major incident.

Visiting dignitaries

Within 24–48 h of a major incident, it is inevitable that dignitaries will visit the affected area and the injured in hospital. In the UK, such people will almost certainly be Members of Parliament including Cabinet Members (UK and or devolved nations) and may include members of the Royal Family. There are inevitable security issues (especially in the wake of a terrorist incident). Advice from the Police will be provided under such circumstances and consideration should also be given to any potential disruption to patient care during an incident's recovery phase.

Staff working patterns and welfare

Critical care staff will play a significant role in dealing with ongoing care. Rotas may have to be organized and split i.e. casualties and usual workload. The requirement for extra staff may result in significant change to shifts for weeks afterwards.

The psychological wellbeing of all the staff involved in the initial response and the aftermath of a major incident is paramount. This is particularly relevant to intensive care staff as they will have to interact regularly with the sickest survivors and their families. All staff should therefore be encouraged to participate in de-briefing exercises and be offered counselling and support as required.

De-brief and future preparedness

This is arguably the most time-consuming part of a major incident. It will include action reports, follow-up, debrief, and even preparation for inquests, etc. (Fig. 1). The process may take months to years and lessons learned in individual cases should be disseminated throughout the medical community to improve on responses when other major incidents inevitably occur.

Summary

Providing clinical care to casualties is the comparatively 'easy' part of in-hospital major incident management. The organizational response required is wide reaching and the impact of receiving even a relatively small number of critically injured casualties has implications for an Acute NHS Trust lasting for weeks/months after the incident.

The key is to plan, be flexible within the plan, and to train staff in advance so that if and when a major incident occurs, the institution can respond to provide both effective care and organization in the incident's aftermath.

Declaration of interest

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Common functional pain syndromes

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Key points

- Functional pain syndromes (FPS) affect more than 15% of the population worldwide.
- Polymorphisms in the catechol-O-transferase gene are associated with FPS.
- Central sensitivity syndrome (CSS) may play a central role in FPS.
- CSS results from a complex interplay of genetic susceptibility and environmental influences.
- Future clinical trials based on pain phenotypes will allow targeted analgesic regimes.

When a patient presents with pain of no obvious organic origin, they are often labelled as having 'functional' pain. The exact diagnosis is derived from the organ system displaying the predominant symptoms e.g. musculoskeletal pain in fibromyalgia (FM) or visceral pain in irritable bowel syndrome (IBS).

The worldwide prevalence of all functional pain syndromes (FPS) is 15–20%. World Health Organization (WHO) surveys reveal that ~10% of primary care patients develop a chronic pain condition within 12 months of initial registration. Of these, at least 50% continue to have symptoms beyond 1 yr. FPS cause enormous economic burden on society with concurrent ramifications for the individual's family in particular and society in general. FM alone has been estimated to cost around £4000 per patient per year.

There has been a paradigm shift in the understanding of FPS. The old model of multiple discrete chronic pain conditions is being replaced by a more overarching, although no less complex, state of central sensitivity syndrome (CSS). Evidence is being accrued that FPS represent the phenotypic output of a complex interplay between genetic susceptibility, gene–environment interactions, and environmental triggers.

Four common FPS will be reviewed in this article: FM, IBS, temporomandibular dysfunction (TMD), and chronic cardiac chest pain (CCCP). The pathophysiology and management of each will be examined and the case presented for a shared underlying mechanism called CSS. Once this new mechanism is adopted more widely, it will allow for future novel management options to be developed in a coherent and systematic manner.

Fibromyalgia

Introduction

FM is a common, debilitating somatic functional pain syndrome. FM is a misnomer as it is not due to connective tissue, or of pure muscular, pathology. Incidence remains high in the developed nations and it represents a significant financial burden. Advances are being made in our understanding of the genetic factors and resultant functional changes associated with FM. Currently, management options are still centred on symptom control.

Definition

As of 2010, the American College of Rheumatology updated its diagnostic criteria for FM (Table 1). The use of trigger points has been replaced by a scoring system totalling the number of reported areas of pain and their severity.[1] It is predicted that these new criteria could result in a marked increase in the diagnosis of FM. Some scholars see the new criteria as a self-scoring system rather than a clinical tool.

Epidemiology

In the developed world, FM is estimated to have an incidence of between 2% and 7%. It affects both sexes but women more than

Table 1 American College of Rheumatology 2010 diagnostic criteria for FM

2010 fibromyalgia diagnostic criteria
A patient satisfies diagnostic criteria for FM if the following three conditions are met:
1 Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 or WPI 3–6 and SS scale score ≥9
2 Symptoms have been present at a similar level for at least 3 months
3 The patient does not have a disorder that would otherwise explain the pain
Ascertainment
WPI: note the number areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19
Shoulder girdle, left/right
Upper/lower arm, left/right
Hip (buttock, trochanter), left/right
Upper/lower leg, left/right
Jaw, left/right
Chest
Abdomen
Upper/lower back
Neck
SS scale score
Fatigue
Waking unrefreshed
Cognitive symptoms
For the each of the three symptoms above, indicate the level of severity over the past week using the following scale
0 = no problem
1 = slight or mild problems, generally mild, or intermittent
2 = moderate, considerable problems, often present and/or at a moderate level
3 = severe: pervasive, continuous, life-disturbing problems
Considering somatic symptoms in general, indicate whether the patient has
0 = no symptoms
1 = few symptoms
2 = a moderate number of symptoms
3 = a great deal of symptoms
The SS scale score is the sum of the severity of the three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12

men by a ratio of 9 to 1. FM has a significant financial impact. European estimates have calculated FM patients cost €5000 per patient per year more when compared with a healthy reference group. With an incidence of 2% in the UK, that represents an annual financial burden of more than 6 million pounds through medical access and extensive comorbid overlap.

Clinical presentation

Patients with FM are likely to suffer from other concurrent conditions like headaches, dysmenorrhoea, temporomandibular joint disorder, chronic fatigue, IBS and other functional gastrointestinal disorders, interstitial cystitis, endometriosis, and regional pain including back and neck pain.[2] It is important for a clinician to distinguish between a new-onset pain from an unrelated aetiology, and pain from FM presenting at a new site. What is perceived as touch in an individual from the general population is perceived as pain in individuals suffering from FM. This is probably due to their central sensitization. The term *central sensitization* implies that mechanisms in the central nervous system amplify the input from peripheral nociceptors, probably due to a complex interplay between neurotransmitters that facilitate pain transmission and those that inhibit transmission of pain signals. This interplay would also explain other symptoms commonly present in those with FM like fatigue, memory problems, and sleep and mood disturbances.[3]

Pathogenesis

There is no single 'cause' of FM. Best current evidence suggests an interplay of genetic and environmental risk factors leading to altered central pain perception. A number of consistent findings highlight the physiological and anatomical changes occurring. The pathophysiology of FM has been extensively covered in a previous article in this journal.[4] New developments are mentioned below.

Genetic factors

FM has some genetic basis. First-degree relatives are 8.5 times more likely to have FM than relatives of patients with rheumatoid arthritis. Polymorphisms in catechol-O-methyltransferase (COMT) genes are associated with FM and there is correlation between the polymorphism and the number of tender pressure points that can be elicited clinically in these patients.[5] A large study among twins demonstrated the concurrence of widespread pain among twins.[6]

Functional neuroimaging

Functional magnetic resonance imaging (fMRI) has consistently demonstrated an increased response to stimuli in the insula and anterior cingulate cortex (ACC) in patients with FM. These areas are involved in the processing and perception of unpleasant pain signals. Evidently, they are experiencing heightened pain when compared with the healthy population. Morphometric analysis of FM patients via MRI shows a three-fold increase in age-associated grey matter reduction.[5] The loss is more significant in areas correlating to stress, pain, and cognitive function. That could in part explain the flare-up that these patients can have during periods of emotional stress.

Investigations

The diagnosis of FM is mostly clinical as there is no definitive investigation that could confirm the diagnosis. However, since certain rheumatologic conditions such as rheumatoid arthritis may co-exist, there may be an indication for serologic tests in some patients. A complete blood count may be useful to rule out other causes of fatigue such as anaemia and leukaemia. Thyroid function tests need to be performed to rule out hypothyroidism as another cause of fatigue, if the condition is suspected.

Management

Initial management

Treatment is targeted at symptom control with efficacy measured by patient reporting. The initial approach includes patient education, graded exercises, and drug monotherapy. Randomized trials support educating these patients regarding the diagnosis and treatment of FM, the uncertainty of pathogenesis, and the importance of the patient's own role in management. It is important to stress that FM is not 'in the patient's head' and that it is ultimately a benign disease while acknowledging that there can be significant personal distress. Moderate, gradually introduced increases in physical activity show significant benefits in quality-of-life measures. Medications often commenced are

tricyclic antidepressants (TCA) such as amitriptyline. In intolerant individuals, a serotonin–norepinephrine reuptake inhibitor (SNRI), e.g. duloxetine, could be utilized. The success of these medications in some patients with FM suggests that neurotransmitters play a vital role in the maintenance of symptoms.[7]

Refractory FM

Multidisciplinary input is crucial to the management of chronic, recalcitrant FM. Through the involvement of Rheumatologists, Psychologists, physiotherapists, and pain management specialists, FM patients can achieve a moderate reduction in pain intensity and improvement in quality-of-life scores.

Combination drug therapy is usually indicated and is customized to each patient. Side-effect profiles of the drugs need to be balanced to optimize symptom reduction and maintaining daily activities against some unpleasant effects of the prescribed drugs. Common combinations include a TCA or SNRI with an anticonvulsant such as pregabalin. Opioids are now widely recognized to be poor long-term options for FM management.

Irritable bowel syndrome

Introduction

IBS is a gastrointestinal disorder characterized by abdominal pain and altered bowel habits. It is the most common diagnosis in Gastroenterology and represents a significant financial and social challenge. There are two clinical forms: diarrhoea-predominant IBS which seems to be more common in men, and constipation-predominant IBS which is more common in women. Some patients may have mixed symptoms, with diarrhoea alternating with constipation. No conclusive 'gut-based' theory of origin has been demonstrated.

Epidemiology

Worldwide, it is estimated that 11% of the population suffer with IBS. UK prevalence of IBS is reported as anything between 7% and 21%. IBS affects women more than men with ratios varying from 1.5:1 to 3:1. Much like FM, IBS prevalence fades with age. Patients over 50 report less severe symptoms of a shorter duration.

Definition

Diagnosis follows the Rome III criteria (Table 2).[8] NICE guidelines also recommend the use of exclusionary blood tests including full blood count, ESR, CRP, and anti-endomysial antibodies to rule out inflammatory bowel or coeliac disease.[9]

Pathophysiology

Initial research into the pathophysiology of IBS concentrated on bowel dysfunction itself. Investigation into factors such as bacterial overgrowth, food sensitivity, and altered immune response has proven to be of limited use thus far. A number of observations have been made that are starting to elucidate the disease process. Some patients have been noted to have alteration in intestinal permeability, and local immune function probably leading to a change in intestinal and colonic microflora.[10]

Table 2 Rome III diagnostic criteria for IBS

Diagnostic criteria for IBS	
Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months and 2 or more of the following	Improvement with defecation Onset associated with a change in stool frequency Onset associated with a change in stool form

Visceral hypersensivity

Visceral hypersensitivity has been elicited using a computer-controlled distension device known as a barostat. Many laboratories have proven that patients suffering from IBS have an increased sensitivity to rectal, bowel, and gastric stretch. Visceral hypersensitivity has been mooted as a potential 'biological marker' of disease.

Altered sensory modulation

IBS patients have been extensively investigated using fMRI and positron emission tomography (PET). There is altered activation in response to intestinal stimulation in the insula, dorsal anterior cingulate cortex (dACC), and prefrontal cortex.[5]

Genetic factors

There is evidence that a genetic component plays a part in the development of IBS. Twin studies demonstrate familial predictors of functional bowel diseases. Potential specific targets being investigated include serotonin transporter (5HTT) and G-protein (GNβ3) polymorphisms. The 5HTT SLC6A4 polymorphism in particular is significantly associated with the development of IBS.[5]

Management

Diet and lifestyle advice

Diet and lifestyle control are the first stage in symptom management. Advice includes regular meals, reducing caffeine, high fibre intake, limiting fresh fruit, and keeping oral fluid intake high.[11]

Pharmacological interventions

First-line drugs largely target specific symptom relief. For those with diarrhoea-predominant IBS, antispasmodics and loperamide are prescribed. In constipation-predominant sufferers, laxatives are used. Second-line medications include linaclotide, a guanylate cyclase agonist that reduces activation of colonic sensory neurones, and TCA such as amitriptyline. SSRIs such as fluoxetine can also be administered if TCAs have no effect.[8] The side-effect profile of centrally acting antidepressants can be used to good effect in patients who suffer from IBS. Since constipation is a known side-effect of TCAs, these could be prescribed for those patients who have diarrhoea-prominent IBS. Similarly, diarrhoea is a side-effect in patients who are on SSRIs, and those patients who have constipation-dominant IBS, may benefit from an SSRI.[11]

Psychological interventions

NICE guidelines recommend the initiation of cognitive behavioural therapy in those with drug-resistant disease perpetuating beyond a year. Studies highlight multiple significant outcome benefits including a reduction in symptom severity scoring and the work and social adjustment scale. Currently, there is scant evidence for the use of acupuncture or Reflexology.

Temporomandibular dysfunction

Introduction

TMD is a broad term that includes a variety of conditions affecting the jaw complex, both acute and chronic. Chronic or refractory TMD, although uncommon, is being investigated heavily for the genetic factors leading to its development. Care must be taken before labelling someone with TMD as having functional pain. The aetiology for the pain could be either articular (potentially amenable to Orthodontics or to surgery) or myogenic in nature, with the latter fitting more into the pattern of FPS.

Definition

TMD is characterized by spontaneous pain in the mandible and the muscles of mastication and the temporomandibular joint. It has become a collective term covering a cluster of individual disease processes that result in jaw pain. Terms also utilized include temporomandibular pain and dysfunction syndrome (IASP) and temporomandibular joint pain dysfunction syndrome (WHO).

Epidemiology

Estimates for TMD prevalence range from 3% to 15% in the Western population. It affects more women than men with a ratio of ~2:1. The peak onset occurs at reproductive age with a decline in prevalence in the older population. Approximately 31% of patients with TMD go on to become chronic sufferers with symptoms persisting beyond 5 yr.

Pathogenesis

It is unusual for TMD to exist as a sole entity as a cause of pain. Frequently, patients either have symptoms of FM or other regional pains like cervicalgia or migraine. No single external cause or trigger has been identified for TMD. Instead, a complex interaction between environmental influences and genetic predispositions lead to psychological distress and pain amplification, irrespective of the cause.

Advances in high-throughput genotyping methods have rapidly increased the understanding of genes that alter pain sensitivity and psychological distress. Particular examples include genes involved in the regulation of COMT, adrenergic receptor B2 (ADR B2), and serotonin transporter (5HTT). Three haplotypes of COMT have been uncovered that are associated with pain sensitivity and the likelihood of developing chronic TMD.[5]

There is no single locus that defines the phenotype. The targets discovered thus far occur commonly in the healthy population. The resultant clinical phenotypes displayed are likely a result of a complex epigenetic interaction. Environmental influences alter gene penetrance e.g. stressful life events, are more likely to trigger depressive illness in those with functional polymorphism in the 5HTT gene.

Management

Non-pharmacological strategies

Treatment consists of patient education, self-care, and psychological support. Education should focus on trigger avoidance, explaining the nature of the condition and discussing the long-term management rationale. Self-care is customized to the individual patient and includes relaxation and stress management, self-monitoring of symptoms, and supervised exercises.

Pharmacological therapies

There is scant evidence for the pharmacological management of TMD. Acute TMD responds to non-steroidal anti-inflammatory drugs, although care must be taken with long-term use. Benzodiazepines with longer half-life have been utilized to reduce nocturnal symptoms during the first weeks of pain.

Refractory disease responds poorly to classical analgesics and there is no evidence to support the long-term administration of opioids or benzodiazepines. TCAs have been utilized with benefit in chronic TMD, perhaps again pointing to the role of central neurotransmitters in potentiating the pain. A systematic review recommended the use of TCAs in TMD as a type B evidence.[12]

Chronic cardiac chest pain

Introduction

CCCP is a visceral functional pain syndrome. It is a poorly defined syndrome with no globally recognized clinical definition that represents a small element in the spectrum of cardiac chest pain. Response to traditional cardiac medications is poor, although some success is being achieved applying a biopsychosocial approach to symptom management. This condition and its management has been reviewed extensively in a prior article in this journal.[13]

Definition

The definition of CCCP remains unclear in both nomenclature and the clinical picture. At present, syndrome X, CCCP, and sensitive heart syndrome are used interchangeably to define the functional pain syndrome of angina pectoris without cardiac ischaemia.

Clinically, there is no official definition but most require anginal pain in the absence of irregularities on the arteriogram, no bundle branch block on resting or exercise ECG, and no evidence of diabetes mellitus, valvular disease, or cardiomyopathy. These criteria rule out several potential confounding factors.

Epidemiology

The epidemiology of CCCP remains unclear due to unclear definitions. If the above criteria are to be applied, the incidence of the disorder is estimated to be 13% of all patients presenting to a cardiologist with chest pain. Patients with CCCP have an increased use of health resources with 80% of patients reporting one or more hospital admissions over a 6 month period.[13]

Pathogenesis

There is growing evidence through functional neuroimaging and examination of altered pain thresholds that CCCP involves altered central pain processing similar to that seen in other FPS.

Functional neuroimaging

Using PET with ^{15}O-labelled water, syndrome X patients have comparable regional cerebral blood flow (rCBF) responses to dobutamine stress in the hypothalamus, thalami, and right frontal cortices. However, syndrome X demonstrated central chest pain compared with healthy controls. The pain is associated with increased rCBF in the right insula but reduced rCBF in the left insula and right cingulate cortex compared with healthy controls. These areas are involved in the processing and perception of unpleasant pain signals.[5]

Psychological aspects

Compared with patients with true coronary artery disease (CAD), CCCP patients have greater anxiety, more stressful life events, and a tendency to seek reassurance, probably because the investigations are routinely reported as normal.

Altered pain thresholds

Patients with syndrome X demonstrate a reduced pain threshold compared with those with CAD or healthy controls when undergoing direct cardiac stimulation i.e. rapid rotation of an intracardiac catheter. They also demonstrate a reduction in pain thresholds with peripheral stimulation of the forearm.

Management

Management of CCCP requires a multi-departmental approach, including cardiologists, cardiac surgeons, pain specialists, Psychologists, and Physiotherapists.

Therapies directed towards the heart

Many patients presenting with CCCP will have already received coronary revascularization with either percutaneous coronary intervention or coronary artery bypass grafts. Medical therapy typically consists of an anti-platelet medication e.g. aspirin, an angiotensin-converting enzyme inhibitor and a statin. They may also be on either β-blockers or calcium channel blockers. Medical therapy must be maintained and optimized to reduce recurrence of myocardial ischaemia.

Non-cardiac therapies

Imipramine, a tricyclic antidepressant, demonstrates a 52% reduction in chest pain episodes when compared with placebo. Spinal cord stimulators provide beneficial pain relief in ~80% of selected patients with CCCP.[5]

Educational programmes such as the Liverpool Angina Management Programme (LAMP) can significantly improve patients' quality of life. Patients learn about stress management, paced physical activities, dietary advice, and management of the emotional responses to angina. An important aspect of their education is the recognition that pain does not equal damage to the heart.

A unifying hypothesis

Traditionally, IBS has been managed by Gastroenterologists, FM by Rheumatologists, TMD by orofacial surgeons, and CCCP by Cardiologists. These traditional approaches have not proven to be very effective in a majority of these patients. By focusing only on the organ system most evidently affected, the global picture has been ignored.

It is becoming increasingly evident that no FPS is an island. There is extensive comorbid overlap and shared epidemiological spread among FPS. By analysing the similarities in genetic research, functional imaging, and management approaches, these conditions need to be examined under a new light.

Epidemiology

The four FPS examined are more common in women and their incidence reduces with advancing age. A likely explanation for this is the regulation of COMT activity by oestrogen. Higher concentrations of oestrogen in women affect COMT behaviour more than in men, thus amplifying the influence of polymorphisms. COMT activity alters with age, giving a possible explanation for the reduced incidence of FPS in the elderly population.[14]

Comorbid overlap

Extensive comorbid overlap has been demonstrated in these conditions described and the relationship between phenotype and genetic factors has been well studied in two large studies among twins. For example, it has been shown that the most accurate predictor of developing TMD is the presence of another FPS such as FM.[6,15] Table 3 reveals the extent of overlap noted through epidemiological studies of FPS.[16] This fact points to an element of shared physiological process contributing to the pathophysiology.

Genetics

FPS have been linked with polymorphisms of COMT, 5HT transporters, and adrenergic receptor B2.[5,17] An important mechanism of central regulation of peripheral pain inputs is the descending inhibitory pathway. Descending fibres originating in regions such as the periaqueductal grey matter modulate spinal inputs via noradrenergic and serotonergic nerve endings. A reduction in norepinephrine and 5HT at the nerve synapses as a result of these polymorphisms could impair this process and increase pain perception.

Functional neuroimaging

FM sufferers demonstrate increased responses to both noxious and non-noxious stimuli compared with healthy individuals. Similar patterns involving the insula and ACC are seen in IBS and TMD sufferers. This suggests a reduction in the normal gating mechanisms of central inhibition.

Management

TCAs largely work by inhibiting serotonin and norepinephrine reuptake, thus elevating synaptic concentrations. Subsequently, descending inhibitory pathways are bolstered, potentially reducing the negative effects resulting from the gene polymorphisms described above.

Increasingly, antiepileptics such as gabapentin are being used in the treatment of FPS. fMRI studies demonstrate a reduction in fMRI signatures of central sensitization with gabapentinoid use.[18]

Central sensitivity syndrome

These common FPS share, at least partly, an underlying mechanism. Although there are a variety of terms in circulation, the most suitable nosological term is CSS.[19] Individuals have genetic susceptibility through a polygenic mix of common polymorphisms in genes such as COMT, 5HTT, and ADRB2. This susceptibility does not automatically lead to an FPS. A complex network of epigenetic and gene–environment interactions lead to CSS development (Fig. 1).[20]

Environmental triggers may play a key role influencing what phenotypic facet of CSS presents to the healthcare system.

Table 3 Comorbid overlap of common FPS. FM, fibromyalgia; IBS, irritable bowel syndrome; TMD, temporomandibular dysfunction

Primary diagnosis	Degree of overlap with secondary condition (%)		
	FM	IBS	TMD
FM	NA	32–80	75
IBS	32–65	NA	32–65
TMD	13–18	64	NA

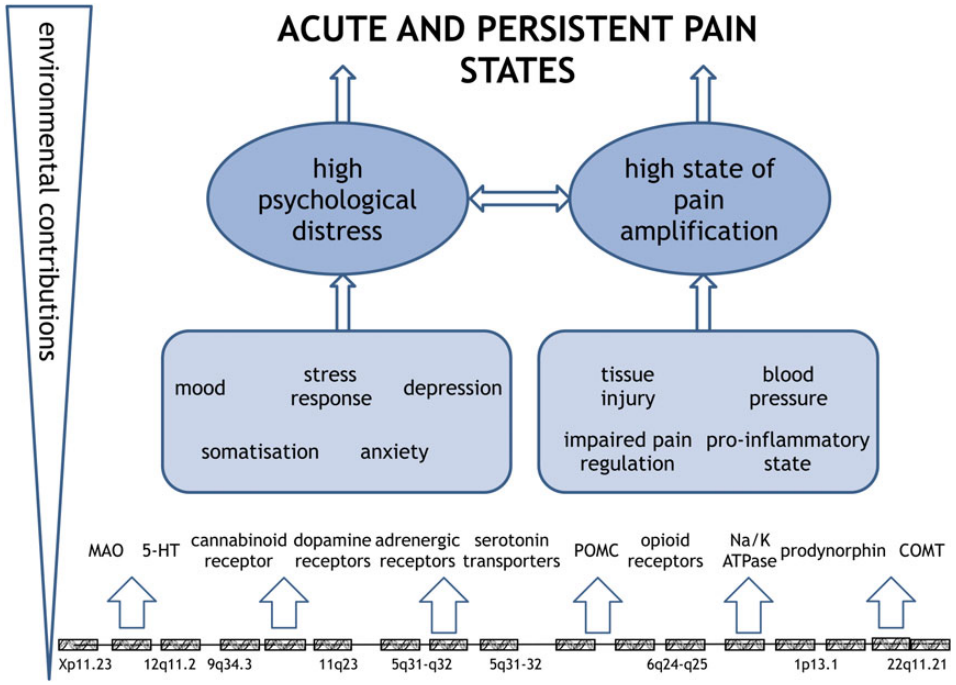

Fig 1 Model depicting likely determinants that contribute to the risk of onset and maintenance of acute and persistent pain states.

Increased peripheral input from the affected organ system, when coupled with CSS, results in the development of predominant symptoms in that system. Examples include hepatitis C and HIV being associated with FM incidence, gastroenteritis triggering IBS, and trauma to the jaw initiating acute and subsequently refractory TMD.[21]

The future

Research

Unifying disparate research targets into one field will allow more rapid understanding of the complex gene–environment reaction. Techniques such as high-throughput SNP (single-nucleotide polymorphism) analysis promote rapid discovery of potential gene targets in those with CSS. These targets must then be analysed in large prospective cohort studies such as the Oral Pain: Prospective Evaluation and Risk Assessment (OPPERA) trials for TMD.[22]

Targeted analgesia

By identifying pain subtypes through clinical trials, we will be able to identify responders to different treatment modalities. The patient's phenotype can then be matched with a treatment responsive to that particular pain subtype and thus pain can then be treated more effectively with a targeted analgesic regime.

Until then, a combination of pharmacological, psychological, and self-help strategies will be the mainstay to treat FPS.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Physiology of oxygen transport

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Key points

- The transport of oxygen is fundamental to aerobic respiration.
- Oxygen transport within the human body occurs through both convection and diffusion.
- Within the pulmonary capillaries, one haemoglobin molecule binds up to four oxygen molecules in a co-operative manner.
- Global oxygen delivery, or oxygen dispatch, describes the total amount of oxygen delivered to the tissues each minute, and is a product of the cardiac output and arterial oxygen content.
- Oxygen diffuses from both the alveoli into the pulmonary capillaries and the systemic capillaries into the tissues, according to Fick's laws of diffusion and the random walk of the diffusing particles.

Oxygen is vital for life-sustaining aerobic respiration in humans and is arguably the most commonly administered drug in anaesthesia and critical care medicine. Within the mitochondrial inner membrane, oxygen acts as the terminal electron acceptor at the end of the electron transport chain whereby oxidative phosphorylation results in the synthesis of adenosine triphosphate (ATP), the coenzyme that supplies energy to all active metabolic processes. This article will discuss the key physiological concepts underpinning the movement of oxygen within the human body and also highlight some clinical applications that serve as examples of these concepts.

Convective *vs* diffusive oxygen transport[1–4]

With respect to human physiology, oxygen transport can be divided into that occurring through convection and that occurring by diffusion. In this context, convection describes the movement of oxygen within the circulation, occurring through bulk transport. This is an active process requiring energy, in this case derived from the pumping of the heart. On the other hand, diffusion describes the passive movement of oxygen down a concentration gradient, for example, from the microcirculation into the tissues (and ultimately the mitochondria).

Section 1: convective oxygen transport

Oxygen uptake into the blood

Deoxygenated venous blood becomes oxygenated in the pulmonary capillaries after diffusion down a concentration gradient across the alveolar capillary membrane (see Section 2: diffusive oxygen transport). The physiology of control of ventilation and the determinants of alveolar oxygen partial pressure, ventilation–perfusion matching, and diffusion within the alveolar–capillary unit are dealt with elsewhere.[1,5]

Haemoglobin and the oxygen dissociation curve[1,5–7]

Oxygen is carried in the blood bound to haemoglobin and dissolved in plasma (and intracellular fluid). Haemoglobin, an allosteric protein, consists of four protein (globin) chains, to each of which is attached a haem moiety, an iron-porphyrin compound. Two pairs of globin chains exist within each haemoglobin molecule. Haemoglobin A consists of two α and two β chains (denoted $\alpha_2\beta_2$), and accounts for more than 95% of normal adult haemoglobin. Mutations in the amino acid sequences in the globin chains give increase to both pathological [e.g. haemoglobin S ($\alpha_2\beta s_2$), sickle-cell disease] and non-pathological haemoglobin variants [such as haemoglobin A2 ($\alpha_2\delta_2$)]. Fetal haemoglobin is denoted haemoglobin F ($\alpha_2\gamma_2$) and is replaced by haemoglobin A during the first year of life.

Once oxygen has diffused across the alveolar membrane, it binds reversibly to haemoglobin within the pulmonary capillaries in a cooperative manner forming oxyhaemoglobin. Up to four molecules of oxygen can be carried simultaneously by one haemoglobin molecule. When a molecule of oxygen binds to haem, the shape of the globin chain is altered, leading an overall change in the quaternary structure of haemoglobin. Subsequent oxygen molecules are then bound with greater affinity. This relationship is best described by the sigmoid-shaped oxyhaemoglobin dissociation curve (ODC, Fig. 1).

Haemoglobin exists in two forms: *taut* (T), which has a low affinity for oxygen; and *relaxed* (R), which has a high affinity for oxygen. The *taut* form predominates in the tissues (a high carbon dioxide, low pH environment) promoting oxygen release, whereas the *relaxed* form binds oxygen more avidly in areas of high pH, low carbon dioxide tension, and high partial pressures of oxygen (such as in the alveoli). This relationship between haemoglobin, oxygen binding, carbon dioxide tension, and pH is known as the Bohr effect.

Carbon dioxide is returned to the lungs from the tissues dissolved in the plasma, either directly or as bicarbonate, and through the formation of carbaminohaemoglobin species within the erythrocyte. Deoxygenated blood has a greater ability to transport carbon dioxide when compared with oxygenated blood, and this is known as the Haldane effect. In combination therefore, the Bohr and Haldane effects promote oxygen binding and carbon dioxide release in the pulmonary capillaries, with the reverse occurring in the tissues.

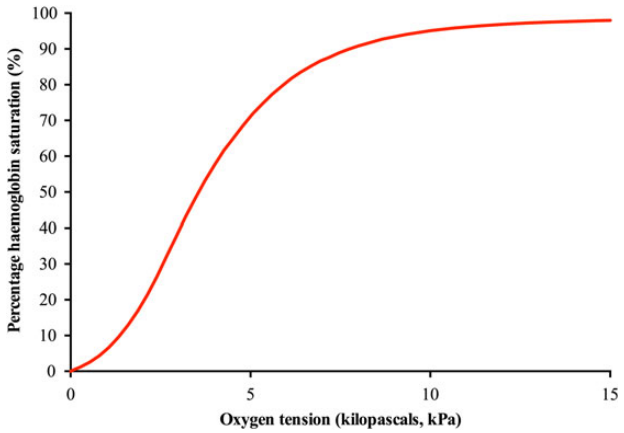

Fig 1 The standard human ODC at pH 7.4, base excess zero, temperature 37°C, and 1 atmosphere. Drawn from equations described by Roughton and Severinghaus[8,9] (subsequently validated).[10]

Haemoglobin has a maximum theoretical oxygen-carrying capacity of 1.39 ml O_2 g^{-1} Hb (known as Hüfner's constant), and therefore, a theoretical maximum oxygen capacity of 20.85 ml O_2 100 ml^{-1} blood at a 'normal' haemoglobin concentration of 15 g dl^{-1} (range 13.5–18.0 in men, 11.5–16.0 in women). However, due in part to the existence of abnormal forms of haemoglobin such as methaemoglobin and carboxyhaemoglobin, which reduce the oxygen-carrying capacity of haemoglobin, empirically this value seems to be closer to 1.31 ml O_2 g^{-1} Hb.[5,11] Haemoglobin oxygen saturation is a percentage expression of the number of oxygen binding sites occupied out of the maximum number of oxygen binding sites available.

P_{50}[1,6,12]

The P_{50} is the partial pressure of oxygen at which haemoglobin is 50% saturated. It is a marker of haemoglobin's affinity for oxygen and is used to compare changes in the position of the curve. The ODC position changes in the face of various chemical and physiological factors, and also with different haemoglobin species. The various factors and their effects on the curve are described in Table 1, and also the effects of a change in position of the curve on oxygen loading and unloading.

2,3-Diphosphoglycerate[6,12,13]

2,3-Diphosphoglycerate (2,3-DPG) is an organic phosphate produced during glycolysis and found in the red blood cell, promoting haemoglobin oxygen release. Of clinical relevance:

- Increased 2,3-DPG production is seen in anaemia, which may minimize tissue hypoxia by right-shifting the ODC and increasing tissue oxygen release.
- 2,3-DPG undergoes metabolism in banked donor blood causing reduced oxygen unloading capacity after transfusion.
- Inorganic phosphate is a substrate for the production of 2,3-DPG and thus capillary haemoglobin oxygen release may be impaired if hypophosphataemia is not corrected. Causes of hypophosphataemia can be divided into: decreased intestinal absorption (e.g. malnutrition); internal redistribution (e.g. in acute leukaemia and recovery from diabetic ketoacidosis); or increased renal excretion (e.g. following corticosteroid use and volume expansion). In critical care, hypophosphataemia is often seen in sepsis, after operation, in refeeding syndrome, in diabetic ketoacidosis (due to increased urinary phosphate excretion), and during renal replacement therapy. Hypophosphataemia is also noted after an acute liver injury caused by, for example, paracetamol overdose and after hepatic resection.

Table 1 Factors that affect the standard human oxygen dissociation curve. Adapted from Thomas and Lumb[6] and Leach and Treacher[12]

	Left-shifted ODC (↓P_{50})	Right-shifted ODC (↑P_{50})
Causes	↑pH (↓H^+) ↓Pa_{CO_2} ↓2,3-diphosphoglycerate ↓Temperature	↓pH (↑H^+) ↑Pa_{CO_2} ↑2,3-diphosphoglycerate ↑Temperature
Effect	Increased haemoglobin oxygen affinity, enhanced oxygen binding	Decreased haemoglobin oxygen affinity, enhanced release of oxygen in the tissues
Others	Fetal haemoglobin Carbon monoxide poisoning Methaemoglobinaemia	Adult haemoglobin

Oxygen content[1,11,12]

The oxygen content of arterial blood is the sum of the oxygen bound to haemoglobin and oxygen dissolved in plasma (where the amount of oxygen dissolved is proportional to the partial pressure exerted by oxygen on the plasma at a given temperature, obeying Henry's law). It is the amount of oxygen in each 100 ml of blood and is calculated by the equation:

$$\text{Arterial oxygen content} = \text{bound oxygen} + \text{dissolved oxygen}$$
$$Ca_{O_2} = (1.31 \times Hb \times Sa_{O_2} \times 0.01) + (0.0225 \times Pa_{O_2})$$

where 1.31 is Hüfner's constant, the directly measured maximum oxygen-carrying capacity per gram of haemoglobin [ml O_2 g^{-1} Hb, reduced from the theoretical maximum binding capacity of 1.39 ml O_2 g^{-1} Hb due to the presence of abnormal haemoglobin species *in vivo* (e.g. carboxyhaemoglobin and methaemoglobin)], Hb the amount of haemoglobin in grams per decilitre (g dl^{-1}), Sa_{O_2} the arterial haemoglobin saturation in per cent, 0.0225 the solubility coefficient of oxygen at body temperature; the number of millilitres of oxygen dissolved per 100 ml of plasma per kilopascal (ml O_2 100 ml^{-1} plasma kPa^{-1}), and Pa_{O_2} the partial pressure of oxygen in arterial blood in kilopascals (kPa).

Therefore, inserting average figures for a 'normal' adult male breathing air at sea level at rest [$F_{I_{O_2}}$ 0.21, 1 atm (101.325 kPa), Sa_{O_2} 100%, Hb 15 g 100 ml^{-1}, Pa_{O_2} 13.3 kPa], the arterial oxygen content can be calculated as 19.95 ml 100 ml^{-1} blood.

Oxygen delivery[5,11,14]

Traditionally, in anaesthesia and critical care medicine, the product of cardiac output and oxygen content has been referred to as 'oxygen delivery', despite the fact that this is inherently incorrect. First of all, the word delivery implies that all the oxygen so described is delivered to, and utilized by, metabolizing cells. This is clearly inaccurate, as we know that the oxygen extraction ratio at rest is ~25%, and that this ratio rarely if ever exceeds 75%, even under conditions of exceptional metabolic stress. The term 'oxygen dispatch' has sometimes been preferred for this reason. Secondly, the word delivery implies an active external process responsible for ensuring arrival of oxygen at the cell. However, this set of processes can just as easily be viewed from the perspective of the cell 'sucking in' oxygen to meet requirements. Notwithstanding these comments, we will continue with oxygen delivery within the context of this article in order to remain consistent with common custom and usage.

Global oxygen delivery describes the amount of oxygen delivered to the tissues in each minute and is a product of the cardiac output and arterial oxygen content.

Thus:

$$\text{Oxygen delivery} = \text{cardiac output} \times \text{arterial oxygen content}$$
$$D_{O_2} = CO \times Ca_{O_2}$$

or

$$D_{O_2} = CO \times \{(1.31 \times Hb \times Sa_{O_2} \times 0.01) + (0.0225 \times Pa_{O_2})\}$$

With a resting cardiac output of 5 litre min^{-1} (and using the same figures as before), a 'normal' adult male has an oxygen delivery of 997.5 ml min^{-1}. It is important to note that this is clearly an overall measure of oxygen delivery and does not describe regional differences—oxygen flux to each tissue bed is not constant throughout the body, rather the microcirculation responds to altering tissue metabolic demands by varying the regional and local blood flow.

Factors affecting oxygen delivery[5,11,14]

As can be seen from the above equation, alterations in cardiac output, arterial oxygen saturation, and haemoglobin concentration will affect oxygen delivery. Sir Joseph Barcroft first presented the causes of reduced oxygen delivery in 1920,[15] classically describing 'stagnant anoxia' (reduced CO or reduced regional blood flow), 'anoxic anoxia' (arterial hypoxaemia), and 'anaemic anoxia' (reduced haemoglobin). Latterly, 'cytopathic hypoxia' (e.g. secondary to sepsis and inflammation) and 'histotoxic hypoxia' (e.g. cyanide poisoning) have been recognized. Under these circumstances, cells have a relative or absolute failure of the capacity to utilize oxygen and increasing D_{O_2} will have little effect in correcting the hypoxia. Any cause of microcirculatory dysfunction will affect oxygen delivery,[16] for example, sepsis where nitric oxide production is increased leading to disorders of autoregulation (matching of supply with demand within the tissues) along with the decreased vascular tone that manifests clinically as hypotension.

Manipulation of global oxygen delivery to improve patient outcome has been the focus of goal-directed haemodynamic therapy (GDT) since its inception in the 1980s. Given that continuing evidence supports equivalent outcome with low blood transfusion triggers in many clinical contexts (haemoglobin concentrations 7.0–9.0 g 100 ml^{-1}),[17] and the increasing interest in limiting hyperoxia,[18] it is clear that the greatest changes in D_{O_2} (convective oxygen delivery) will be achieved through the manipulation of cardiac output.[14] Diffusive oxygen transport will be discussed later.

Oxygen consumption[11,12,14]

Oxygen consumption (V_{O_2}) is the amount of oxygen consumed by the tissues per minute and can be calculated either through direct analysis of respiratory gases or indirectly, using Fick's principle, by measuring the oxygen content of mixed venous blood (i.e. blood in the pulmonary arteries), Cv_{O_2}, and using the equations:

$$Cv_{O_2} = (1.31 \times Hb \times Sv_{O_2} \times 0.01) + (0.0225 \times Pv_{O_2})$$

$$V_{O_2} = CO \times (Ca_{O_2} - Cv_{O_2})$$

Again inserting 'normal' values for an adult male breathing air at sea level at rest [$F_{I_{O_2}}$ 0.21, 1 atm (101.325 kPa), Sv_{O_2} 75%, Hb 15 g 100 ml^{-1}, Pv_{O_2} 5.3 kPa, Ca_{O_2} 19.95 ml 100 ml^{-1}, CO 5 litre min^{-1}], the mixed venous oxygen content can be calculated as 14.86 ml 100 ml^{-1} blood, and therefore the oxygen consumption as 254.5 ml min^{-1}.

Oxygen delivery (oxygen flux) and oxygen consumption are global measures. At tissue level, blood flow is denoted as Q, $[O_2]_{In}$ describes the oxygen content of the afferent blood (analogous to Ca_{O_2} globally), and $[O_2]_{Out}$ describes the oxygen content of the efferent blood (analogous to Cv_{O_2} globally). Therefore, at tissue level:

$$V_{O_2} = Q \times ([O_2]_{In} - [O_2]_{Out})$$

Factors affecting oxygen consumption[14]

The rate of oxygen consumption depends on cellular metabolic demand and can be manipulated. For example, the use of therapeutic hypothermia to reduce cerebral metabolic demand post-cardiac arrest in order to improve neurological outcome is well documented.[19] Commonly encountered factors that affect V_{O_2} are documented in Table 2.

Table 2 Factors that affect oxygen consumption. Adapted from McLellan and Walsh[11]

Factors that increase V_{O_2}	Factors that decrease V_{O_2}
Exercise	Sedation/analgesia/neuromuscular blocking agents/antipyretics
Trauma (including surgery and burns)	Hypovolaemia/shock states
Inflammation/sepsis/pyrexia	Mechanical ventilation
Shivering	Hypothermia
Pain	
Agitation	
Physiotherapy (quoad patients in critical care)	

Oxygen extraction ratio[2,11,12,14,18,20]

This is the fraction of oxygen delivered via the cardiovascular system that is actually utilized by the tissues, and is therefore the ratio of oxygen consumption to oxygen delivery:

$$O_2ER = \frac{V_{O_2}}{D_{O_2}} \text{ (globally)}$$

$$\left(O_2ER = \frac{Ca_{O_2} - Cv_{O_2}}{Ca_{O_2}}\right)$$

or

$$O_2ER = \frac{([O_2]_{In} - [O_2]_{Out})}{[O_2]_{In}} \text{ (at tissue level)}$$

In health, only 20–30% of the oxygen delivered to the tissues is utilized (an O_2ER 0.2–0.3) and it can be seen that by substituting the figures presented earlier (namely V_{O_2} 254.5 ml min^{-1} and D_{O_2} 997.5 ml min^{-1}), an adult male has an O_2ER 0.26 at rest. Under these circumstances, oxygen consumption is said to be 'supply independent' and V_{O_2} is maintained even in the face of a decreasing D_{O_2}.

However, at a critical D_{O_2} (D_{O_2}crit) of ~4 ml kg^{-1} min^{-1} in humans, the O_2ER is maximal (O_2ER 0.6–0.8) and V_{O_2} is said to become 'supply dependent'. If D_{O_2} continues to decrease further below the D_{O_2}crit, or if V_{O_2} increases for a given D_{O_2}crit, tissue hypoxia ensues with resultant anaerobic respiration and lactate production secondary to an imbalance between ATP supply and demand (producing a type A hyperlactataemia).[21] While this theoretical framework underpins our understanding of oxygen physiology in the shocked patient, the empirical evidence supporting these phenomena is limited and the concepts remain controversial. It is also important to highlight that even if global oxygen consumption appears to be supply independent, it does not rule out pathological oxygen supply dependency at a regional or local level, which may only manifest clinically at a later stage.[22]

Figure 2 illustrates the theoretical biphasic relationship between oxygen consumption and oxygen delivery. The solid line 'ABC' depicts what is seen in health, the broken line 'DEF' in critical illness. Points B and E depict D_{O_2}crit in health and critical illness, respectively. In health, V_{O_2} is 'supply independent' between B and C (D_{O_2} is above D_{O_2}crit) and 'supply dependent' between A and B. O_2ER is known to increase during exercise, peaking at maximal exercise at 0.8. This is because although D_{O_2} increases, it does not match the increase in V_{O_2} required by exercise. In critical illness, however, especially sepsis, V_{O_2} may continue to increase, even with increasing D_{O_2} (demonstrated by the line EF), and D_{O_2}crit may be greater than in health. This is termed a 'pathological D_{O_2} dependency' and O_2ER may not increase proportionately with V_{O_2}. Slopes AB and DE represent the maximum O_2ER. The gradient of slope DE is reduced in critical illness as the tissues are less able to extract oxygen.

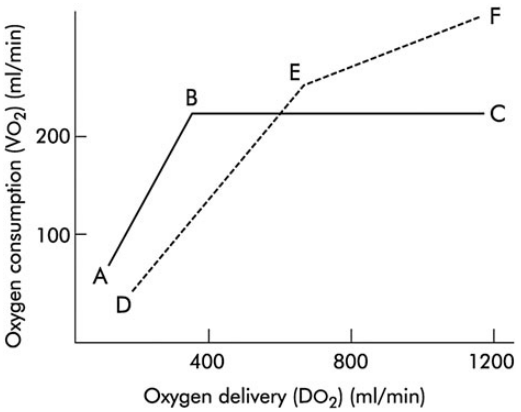

Fig 2 A graph depicting the relationship between V_{O_2} and D_{O_2}. Taken from Leach and Treacher[14] with kind permission from BMJ Publishing Group Ltd.

Another method used clinically to assess D_{O_2} is to measure pulmonary artery mixed venous blood saturation (Sv_{O_2}) using a pulmonary artery catheter (PAC) as this represents unused oxygen returned to the lungs from the tissues. Targeting an Sv_{O_2} of >70% suggests adequate resuscitation of a critically unwell patient has been performed and D_{O_2} optimized. However, under these circumstances, consideration should be given to the possibility that a 'normal' Sv_{O_2} may be an indication of inadequate oxygen utilization, be it through microcirculatory dysfunction or altered cellular oxygen uptake, rather than adequate oxygen delivery. In the absence of a PAC, central venous saturations can be used as a surrogate (Scv_{O_2}), with the normal range only marginally higher than the 68–77% range of Sv_{O_2}.

Section 2: diffusive oxygen transport

Diffusion

Within the lung, oxygen diffuses from the alveoli into the pulmonary capillaries, driven by the gradient between the partial pressure of oxygen in the alveolar space and that in the deoxygenated pulmonary capillary blood. In the tissues, oxygen diffuses down a gradient between oxygenated blood in the systemic capillaries and the oxygen-consuming cells.

Diffusion can be described by either a phenomenological approach using Fick's laws or an atomistic approach applying the principle known as the random walk of the diffusing particles (another example of which is Brownian motion).

Fick's laws of diffusion[1–4]

Adolf Fick (1829–1901) derived two laws of diffusion in 1855. His first law states that at steady state, particles move from an area of high concentration to an area of low concentration, the rate of which is proportional to the difference in their concentrations (i.e. it relates flux to concentration gradient). Thus:

$$J = -D\frac{\partial C}{\partial x}$$

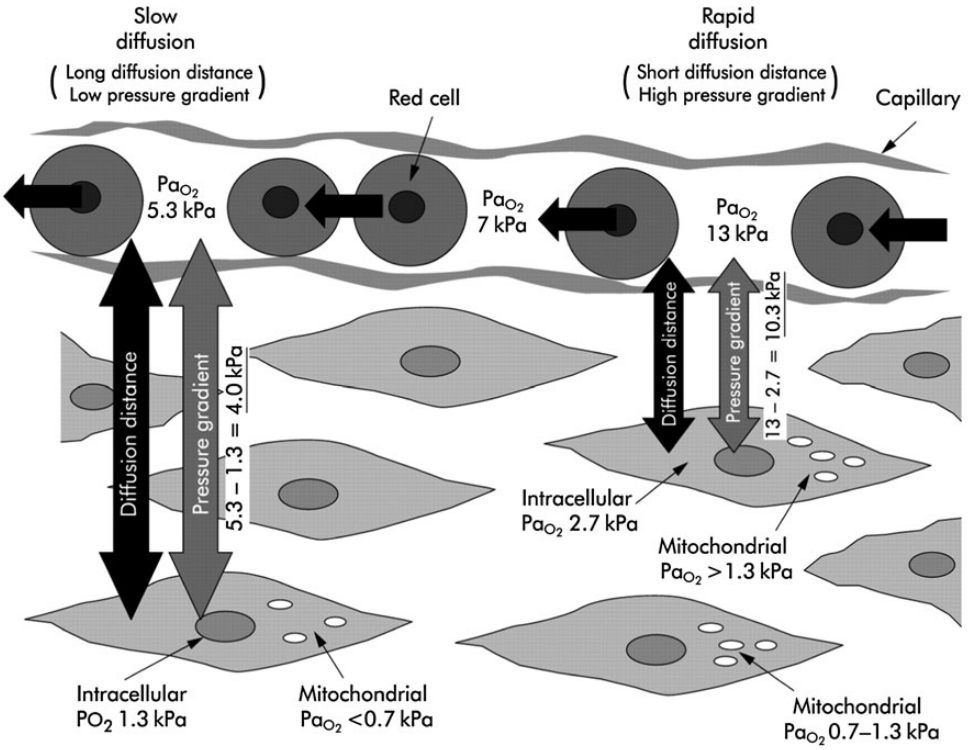

Fig 3 A diagram illustrating the importance of diffusion distance from capillary to cell and local oxygen tension in determining diffusive oxygen flow rate. Taken from Leach and Treacher[14] with kind permission from BMJ Publishing Group Ltd.

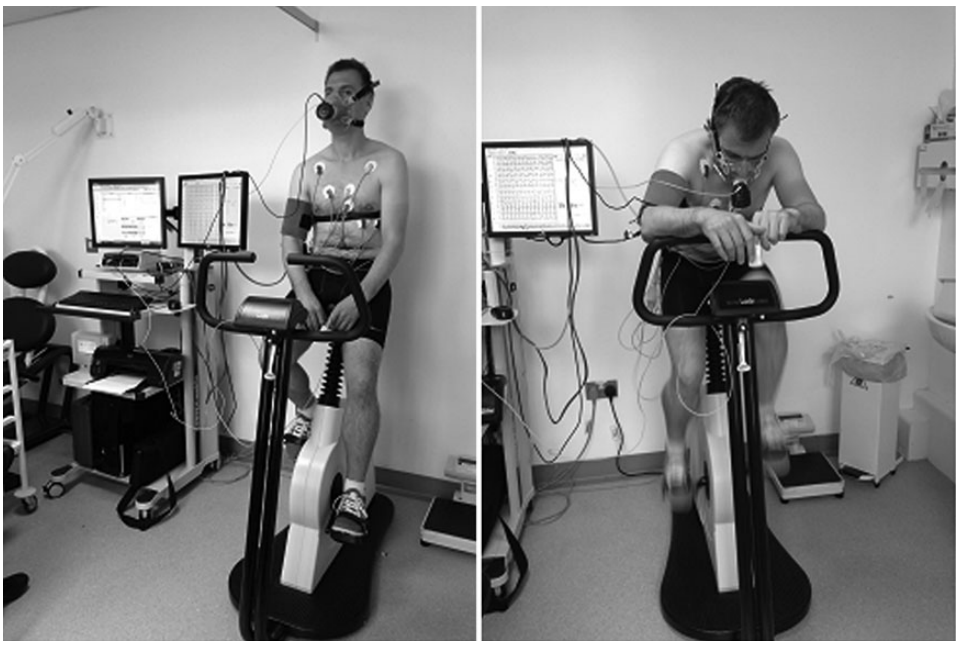

Fig 4 A participant undergoing CPET. Reproduced with permission.

where J is the diffusion flux [(amount of substance) area^{-1} time^{-1}], D the diffusion coefficient or diffusivity of the diffusing species (length^2 time^{-1}), C the concentration (amount of substance volume^{-1}), and x the position (diffusion length).

Fick's second law describes how diffusion causes the concentration gradient to change with respect to time:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2}$$

where C is the concentration (amount of substance volume^{-1}), t the time, D is diffusion constant or diffusivity of the diffusing species (length^2 time^{-1}), and x the position (length).

Therefore, adapting Fick's first law to human physiology, it can be shown that the rate of diffusion (rate of flux) for a gas across a capillary wall is:

$$\text{Flux} = \frac{DA(C_1 - C_2)}{T}$$

$$D \propto \frac{\text{Sol}}{\sqrt{\text{MW}}}$$

where D is the diffusion constant (or capillary permeability) for a specific gas at a specified temperature, combining the factors that affect diffusion of a substance such as molecular size, charge, and lipid solubility, A the capillary surface area, $C_1 - C_2$ the concentration gradient (or difference in partial pressures) of the gas across the membrane (flow is from C_1 to C_2), T the capillary wall thickness, Sol the gas solubility, and MW the molecular weight.

Thus, although the global oxygen delivery (oxygen flux) may be manipulated through changes in cardiac output and oxygen content, at a tissue level diffusion distance and partial pressure gradients will have the greatest effect in altering the diffusive oxygen flux. This is shown in Figure 3.

Section 3: clinical applications of oxygen transport

Whole-body oxygen transport and utilization can be estimated using two principle approaches:

- Estimation of oxygen mass transport, through separate measurement of cardiac output and the elements of oxygen content. In combination with the latter approach, additional measurement of mixed venous oxygen content allows calculation of oxygen extraction and therefore oxygen consumption.
- Evaluation of oxygen consumption through measurement of steady state, or dynamically changing, oxygen uptake using expired gas analysis to measure gas flows and concentrations [cardiopulmonary exercise testing (CPET), metabolic cart].

It is worth noting that expired gas analysis, although less invasive, is more direct in its measurement of cellular oxygen consumption.

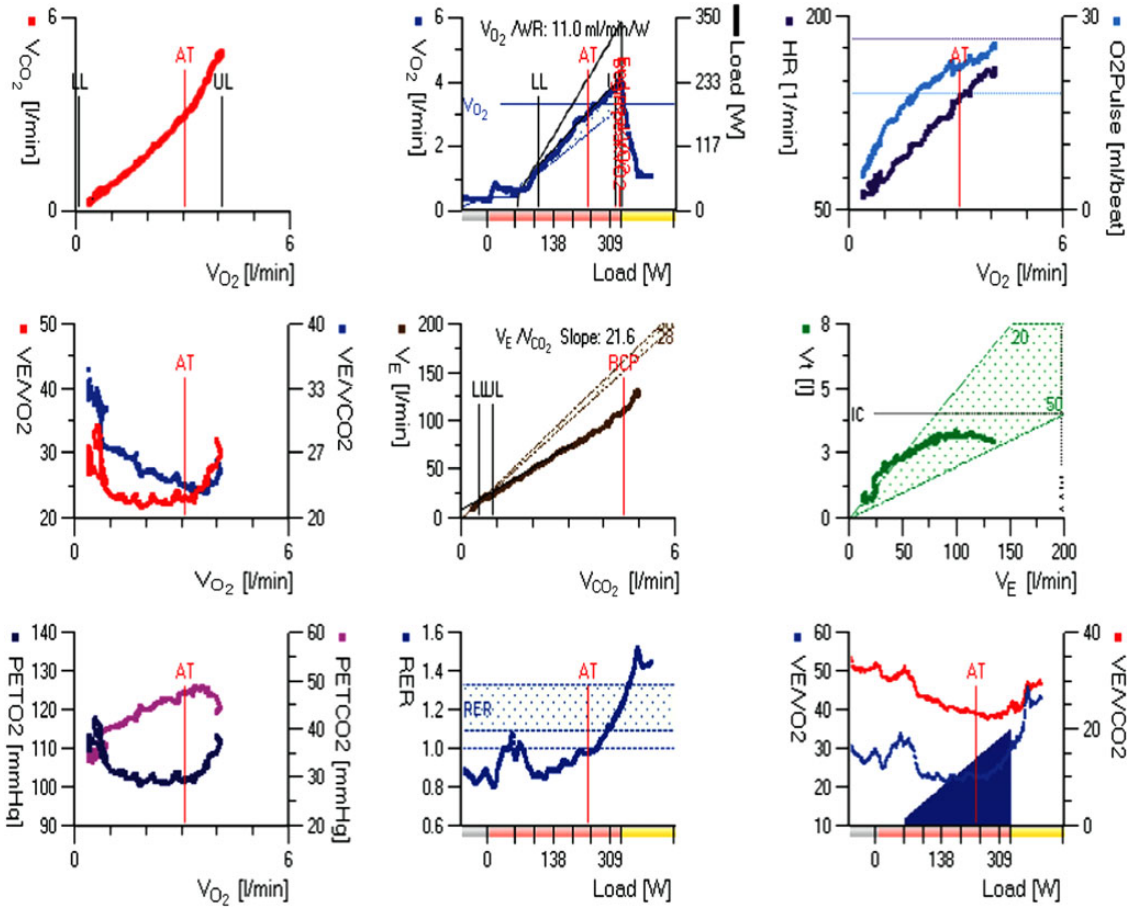

Fig 5 An example of a CPET nine-panel plot (data from authors' laboratory). Panels 1–3 are in the first row, 4–6 in the second row, and 5–9 in the third row. Panel 1 plots V_{CO_2} *vs* V_{O_2} and illustrates the *V*-slope (linear regression analysis) method to determine (ventilatory) AT: at the AT, the gradient of the V_{O_2}/V_{CO_2} relationship increases above 1. The AT can also be ascertained by evaluating: the ventilatory equivalents for oxygen and carbon dioxide in panel 4; end-tidal oxygen tension in panel 7; and ventilatory equivalents against workload in panel 9. The vertical red line denotes the AT. V_{O_2}, oxygen consumption; V_{CO_2}, carbon dioxide elimination; IC, inspiratory capacity; V_E, minute ventilation; V_E/V_{O_2}, ventilatory equivalent for oxygen (i.e. the ratio of minute ventilation to oxygen consumption); V_E/V_{CO_2}, ventilatory equivalent for carbon dioxide; $P_{E'_{O_2}}$, partial pressure of end-tidal oxygen; $P_{E'_{CO_2}}$, partial pressure of end-tidal carbon dioxide; RER, respiratory exchange ratio; HR, heart rate; O_2pulse, oxygen pulse (the amount of oxygen consumed per heart beat, V_{O_2}/HR; can also be used to estimate cardiac stroke volume); V_t, tidal volume; Load, exercise workload.

Cardiopulmonary exercise testing[23,24]

In addition to its use in the physiological assessment of elite athletes, CPET has been developed as a tool to assess a patient's preoperative functional capacity, that is, their ability to do external physical work, before major surgery. Also determining $V_{O_{2peak}}$, a subject's (ventilatory) anaerobic threshold (AT) may be calculated. The AT is the V_{O_2} (in ml kg^{-1} min^{-1}) at which, with increasing work, anaerobic metabolism commences. While this is often presented as being evidence of the demand for oxygen outstripping supply, it may in fact be more closely related to the recruitment of muscle fibres with different patterns of metabolism.

During CPET, anaerobic metabolism is shown when carbon dioxide production (V_{CO_2}) outstrips V_{O_2}, whereas during aerobic metabolism, V_{CO_2} increases proportionately with V_{O_2} (see panel 1 in Fig. 5). A high level of functional capacity (physical fitness) is an index of a substantial physiological reserve over and above resting values. This in turn is inferred to provide benefit in withstanding the physiological challenge of major surgery. In patients undergoing major surgery, postoperative morbidity and mortality are consistently increased in individuals with lower values of AT and $V_{O_{2peak}}$. A standard CPET set-up is shown in Figure 4 and an example of a nine-panel plot in Figure 5. See the American Thoracic Society/American College of Chest Physicians Joint Statement[25] and the American Heart Association Scientific Statement[26] on CPET for more in-depth reviews.

Goal-directed hemodynamic therapy

In GDT, blood flow and/or oxygen delivery (D_{O_2}) is augmented through the use of supplemental oxygen and fluids (both crystalloids and colloids), and in some cases, additional inotropes, vasopressors, and vasodilators are also used to achieve the stated goals. Blood flow measurements are obtained using haemodynamic monitoring equipment such as the oesophageal Doppler (Deltex Medical Ltd), LiDCO (LiDCO Ltd), and PiCCO (PULSION Medical Systems SE, Germany). A variety of physiological variables have been targeted including D_{O_2}, cardiac index (CI), stroke volume (SV), and indexed systemic vascular resistance (SVRI). Originally, measurement of these variables required thermodilution techniques and a pulmonary artery (right heart) catheter;[27] however, this modality has subsequently gone out of favour following concerns about its safety.[28]

GDT is used perioperatively in anaesthesia and critical care. Theoretically, by improving D_{O_2} (*convection*) to the tissues, the oxygen concentration gradient between the microcirculation and the cells increases, causing increased oxygen *diffusion* (or rather increased *diffusive flux*). However, although GDT may provide more oxygen at tissue level, this will not necessarily affect oxygen utilization (in the absence of supply-dependency). It is also assumed that capillary surface area and diffusion coefficient remain constant, which may not hold if tissue fluid status changes, for example, in the case of the tissue oedema often seen in critically unwell patients. A more in-depth review of GDT is beyond the scope of this article; however, see the clinical reviews by Lobo and de Oliveira,[29] Ramsingh and colleagues,[30] and Lees and colleagues,[31] and also the Cochrane Review by Grocott and colleagues[32] for further information.

Conclusion

The convective and diffusive transport of oxygen from the air into the tissues is clearly complex, with each step in the process affected by multiple factors. However, understanding how our respiratory and cardiovascular systems combine to facilitate the movement of oxygen from where it enters the circulation in the pulmonary capillary to where it is ultimately utilized in mitochondria within cells is fundamental for anaesthetists.

Declaration of interest

M.G.M. is Smiths Medical Professor of Anaesthesia and Critical Care UCL and a Consultant at UCLH. He is Director of the UCL Centre for Anaesthesia and The UCL Discovery Lab and a resident PI at the Institute of Spots Exercise and Health. He is a paid Consultant for Edwards Lifesciences (via UCL Consulting and independently) and Deltex in the USA. He was a National Clinical Advisor for the Department of Health Enhanced Recovery Partnership until May 2013; Stock holder and advisory board for Medical Defence Technologies LLC (³Gastrostim² patented); Director Bloomsbury Innovation Group a community interest company owned by UCLH Charity; Co-Inventor of ³QUENCH² (fluid managementsystem) IPbeing exploited by UCL Business. His institution has also received charitable donations and grants from Smiths Medical Endowment, Deltex Medical and Fresenius-kabi. He was also co-author of the GIFTASUP guidelines on perioperative fluid management; Editor in Chief of Peri-operative Medicine; on the Editorial Board of the BJA and Critical Care; a member of the Improving Surgical Outcomes Group; Expert advisor to the NICE IV fluids guideline development group; Chairman of the Board of The National Institute of Academic Anaesthesia; Co-Director Xtreme Everest; Co-Chair Evidence Based Perioperative Medicine (EBPOM). In the past 20 years he has also received honoraria and travel expenses from Fresenius-kabi, BBraun, Baxter, Cheetah, LidCo, AQIX, Hospira and Massimo. He does a small amount of Private Medical Practice.

M.P.G. serves on the Medical Advisory Board of Sphere Medical Ltd through a consulting contract via the University of Southampton. He also serves (no renumeration for any of these roles) as a director of Oxygen Contol Systems Ltd, as a director of the Bloomsbury Innovation Group (a novel community interest group using an innovative low-cost open source IP model to drive innovation and development in medical devices in the areas of anaesthesia and critical care within the NHS) and is chair of the board of the Xtreme-Everest Community Interest Company (jointly owned by University of Southampton and UCL; maintenance, development and exploitation of the Xtreme Everest Bioresource). He also leads the Xtreme-Everest Oxygen Research Consortium which has received unrestricted research grant funding paid to his institution (UoS/UHS/UCL/UCLH) from BOC Medical (Linde Group), Ely-Lilly Critical Care, Smiths Medical, Deltex Medical, London Clinic, Rolex, UCLH Special Trustees, and the Royal Free Special Trustees. He has also received honoraria for speaking and/or travel expenses from Edwards Lifesciences (2009 and 2016), Fresenius-Kabi (2008), BOC Medical (Linde Group)(2008), Ely-Lilly Critical Care (2008) and Cortex GmBH (2008 & 2009).

J.-O.C.D. has no conflicts of interest to declare.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Implications of complexity theory for clinical practice and healthcare organization

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Key points

- Non-linear systems are not amenable to investigation by reductionist methods.
- Complexity theory offers an alternative approach to quantifying the degree of physiological derangement in multi-system disorders such as sepsis.
- The normal, healthy human heart rate displays fractal variation which is lost in numerous disease states.
- Statistical techniques, such as approximate entropy, allow us to quantify the degree to which this variation is lost.
- Large, multi-faceted organizations such as the NHS frequently behave as complex systems and as such may benefit from alternative management strategies, informed by complexity theory.

Medicine, like many other scientific fields, is founded upon the classical Cartesian method of reductionism, where a problem is broken down into its smallest components, examined, and then the information gleaned used to draw conclusions about the nature of the larger reality. Fundamental to this approach is the requirement that the problem being examined is a linear system (Table 1). When this is the case, the reductionist approach is a great success and the clinician may rightly feel confident in predicting the outcome of an intervention. An example of this might be the response of blood glucose to a dose of exogenous insulin.[2] Frustrations arise however when the problem we wish to examine is not a simple linear system but rather shows non-linear behaviour (Table 1). Our inability to predict the outcome in these situations is all too painfully familiar, yet it was at this problematic interface, between reductionism and real life, that the science of complexity theory was born.

Edward Lorenz was a meteorologist at the Massachusetts Institute of Technology who in 1961 was trying to develop a computer model to allow accurate long-range weather forecasting. While inputting the data to rerun a previous weather model, he abbreviated one number from 0.50612 to 0.506 to save time. When he returned later that day to examine the 'weather' pattern generated by the computer, to his surprise, it was markedly different from the previous model he was trying to recreate. Rather than ignore it, he had the presence of mind to publish his findings that non-linear systems appeared to display what he later coined 'sensitive dependence on initial conditions'.[1] This has since been more poetically paraphrased by the expression that if 'butterfly flaps its wings in Brazil will it set off a tornado in Texas?' This was the first step towards identifying the characteristics that all complex systems share (Table 2) regardless of whether the system in question is biological, meteorological, or social. Furthermore, a certain number of these characteristics may present us with novel opportunities to better understand and even predict the outcome in conditions characterized by non-linear behaviour.

Examples of complex systems in clinical medicine

Examples of non-linear or complex systems abound in medicine and perhaps the most relevant to our speciality is that of the multiple organ dysfunction syndrome (MODS). This is a clinical syndrome precipitated by any number of insults (i.e. infection, trauma, burns), whose response is orchestrated by several components (immune, humoral, neurological, and inflammatory) and whose outcome remains difficult to predict at the outset. When viewed in this light, MODS does indeed display features consistent with a complex system in that we have sensitive

dependence on initial conditions, interdependent components, and an outcome that is not necessarily proportional to the original insult. It has also been suggested that this may be an underlying reason why multiple trials of pharmacological agents targeting individual inflammatory mediators have failed to improve mortality[3] as we are adopting a linear approach to solve a non-linear problem. However, it would be a mistake to view disease as a complex state while viewing normal homeostasis as an ordered linear state.

Much work has already been done to show that health itself (i.e. normal homeostasis) can also be thought of as a complex system characterized by a high degree of biological variability, negative entropy, and emergent order.[4,5] It is this variability that provides us with the resilience to withstand physiological insults. The loss of biological variability, with an attendant increase in entropy, is characteristic of several disease states, including MODS and even normal ageing.[6] Therefore, although MODS represents an example of a complex system, it may also be viewed as a higher entropy state than health and therefore as a step on the decomplexification pathway that may lead ultimately to death (Table 2). The challenge exists therefore to identify decomplexification before it becomes irreversible.

Table 1 Features of linear and non-linear systems

Linear system	Non-linear system
Output is proportional to input	Output disproportionate to input
Output is reproducible over time for a given input	Output for the same input value may not be constant over time,[1] or be reproducible
Events occur sequentially	Events occur both sequentially and simultaneously
Each variable within a linear system acts independently of another	Each component of the system influences the other, i.e. shows interdependence
Example: Response of blood sugar to insulin	Example: Human immune response to a pathogen

Identifying loss of complexity

As already mentioned in Table 2, one hallmark of a 'healthy' complex system is the degree of connectivity between individual components. This connectivity manifests itself by encouraging various physiological parameters to oscillate between a number of steady states. The physiological parameter in question will then display variability which rather than being purely random will be seen to display self-similarity over time or in other words show temporal fractal variation. One such physiological parameter that displays this is the human heart rate. In a healthy individual, the inter-beat variation, as measured by the R–R interval, fluctuates in a stable manner that is hypothesized to be due to the influence of biological 'strange attractors' (Table 2).[4] In plain English, this means that the heart receives information from other organs, including the sympathetic nervous system and various endocrine glands while also being affected by changes in breathing and posture; an ability to respond to these (and therefore show variability) is clearly a requirement for normal homeostasis.

Several studies have now demonstrated a correlation between loss of heart rate variability (HRV) and various disease states including congestive cardiac failure and MODS, the same pattern is also seen in normal human ageing[3–7] (see Fig. 1 where HRV on the *y*-axis changes over time on the *x*-axis). Here, we can clearly see decomplexification in action; there is a marked reduction in the degree of fractal variation present which implies a loss of connectivity and an increase in the entropy of the system. HRV therefore provides us with a window into complex systems and may

Table 2 Common features of complex (non-linear) systems

Feature	Definition
Sensitive dependence on initial conditions	Tiny, even imperceptible, factors at the onset of the event can have a disproportionately large effect upon the ultimate endpoint
Mathematical simplicity (determinism)	Paradoxically even the most complex systems are governed and can therefore be explained by relatively simple mathematical equations or 'rules'
Strange attractors	A mathematical concept whereby non-linear systems tend to settle at a finite number of non-repeating fixed points in phase space. It is the main difference between a difficult to predict complex system and a truly unpredictable random system. Also underlies the principle of 'variability as health' whereby a system will oscillate between several stable states over a period of time
Fractal variation	Complex systems tend to display a striking degree of self-similarity at different scales of length. They can be geometrical (i.e. the human vascular tree) or temporal (i.e. heart rate variability)
Connectivity and synchronization	Each component of a complex system responds to and influences each other. This can allow information to spread more rapidly through such a system, i.e. a murmuration of starlings or a nervous system
Emergent order	This is the tendency of complex systems to adopt macroscopically ordered structures despite being composed microscopically of seemingly disordered components and is due to the properties described above. This is also the feature most likely to be missed if a reductionist approach is taken to investigate a complex system
Negative entropy	Complex systems are highly ordered with low entropy and as such stand opposed to the second law of thermodynamics which states that the entropy in a system will trend towards maximum, i.e. a system is always trying to move from a highly ordered state to a less ordered state. The implication here is that a huge amount of energy is required to maintain a system in a state of low or negative entropy. Biologically speaking, health or life in general could be thought of as a state of negative entropy
Decomplexification	This may be simply thought of as the biological manifestation of entropy in progress. It occurs when a biological system moves from a highly ordered state (health) towards a less ordered state (disease or ultimately death)

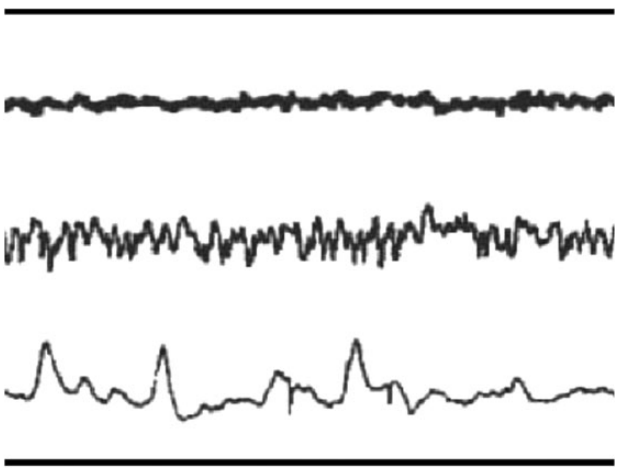

Fig 1 Examples of changes in heart rate variability with ageing and disease. The middle tracing is from a healthy young patient. The bottom tracing is from a healthy but aged patient. The top tracing was obtained from a critically ill patient. The image is reproduced with permission from Wolters Kluwer Health Inc.

Table 3 Techniques to quantify HRV

Technique	Explanation
Time domain analysis	Relatively simple technique whereby the standard deviation of a collection of R–R intervals is used to generate a measure of variability (as standard deviation is equal to the square root of variance from the mean). Highly sensitive to artifact
Frequency domain analysis	A time domain analysis can be converted into a frequency domain analysis (FDA) via a Fourier transform. FDA may then be used to identify the relative contributions of different systems to HRV (i.e. sympathetic, parasympathetic and humoral) Subject to the same limitations as time domain analysis
Entropy analysis	Statistical technique whereby the degree of connectivity between data sets is quantified Principle advantage over other methods is its ability to be applied to shorter, 'noisier' data sets

represent a novel means of monitoring and identifying critically ill patients; of particular note is the fact that these changes appear to precede the clinical manifestation of disease by several hours.

Various methods exist to analyse HRV (Table 3), all of which at present are experimental[8] but of particular interest is the statistical technique of approximate entropy (ApEn). This tool allows us to measure the degree of variability within a data set obtained over a given period of time. A low ApEn correlates to a high rate of variability (i.e. normal homeostasis), while a high ApEn represents randomness and therefore decomplexification. Furthermore, a derivative of this method, Cross-ApEn, allows us to quantify the degree of connectivity between two separate data sets, potentially giving an even more accurate insight into the degree of connectivity within the system as a whole.[4] A further advantage of the ApEn method is that it can be performed on a relatively small data set (100–900 data points).

HRV monitoring has already demonstrated its utility as a means of predicting patients at risk of developing postoperative cardiac failure or increased mortality post-myocardial infarction;[3] however, the challenge now remains to refine the technique so as to be amenable to real-time bedside monitoring. In this role, HRV analysis could potentially represent a highly individualized, patient-specific, technique to detect and monitor the progress of MODS, allowing clinicians to escalate and de-escalate treatment regimens with greater accuracy.

Implications of complexity theory in healthcare management

A full description of the myriad ways in which complexity theory has influenced thinking on organizational behaviour is beyond the remit of this article; however, the reader could do a lot worse than start with an excellent series of articles published in 2001 in the *British Medical Journal* edited by Plsek and Greenhalgh.[9,10] Just as reductionism has influenced generations of scientific investigation by encouraging participants to adopt the classical Newtonian viewpoint of the 'clockwork universe', so too have traditional management models tended to view organizations as machines, composed of multiple individual components each of which can be 'fine-tuned' separately to improve performance within the organization as a whole. In this model, effective leadership involves introducing best practice via a top-down approach and any resistance to change is frequently viewed as symptomatic of a poorly working machine. Likewise, any variation in practice from a predetermined norm can be eliminated via the imposition of protocols and guidelines which can be fitted into the machine rather like new spark plugs on a car. When a true consensus exists as to what constitutes best practice (i.e. antibiotics before knife to skin), then such an approach may be perfectly valid; however, more frequently genuine uncertainty may exist as to how to meet a particular challenge (i.e. how to improve operating theatre efficiency). It is in these situations that adopting an alternative viewpoint, informed by complexity theory, may allow more productive solutions to emerge.

By viewing an organization as a complex system, then a greater focus is placed upon the connections between individual components, how their interactions may lead to the emergence of novel, unpredictable outcomes, and the understanding that human behaviour shows 'attractor patterns'[10] whereby individuals will tend to default to a certain set of attitudes which can be misconstrued as resistance to change. In these situations, effective leadership would involve placing a greater emphasis upon finding out how different services interact and influence each other and engaging with staff to introduce new 'attractors' to influence behaviour and attitudes. More importantly is the understanding that meaningful change may be more likely to occur if it is allowed to emerge spontaneously from the interactions of the individual services involved; rather than imposed from the top down. Clearly, this has to be guided and this may achieved by the use of 'minimum specifications'.[10] This is a management strategy where the emphasis is placed upon 'direction pointing', setting 'boundaries' and 'resources', and then giving 'permission' for the system to generate its own solutions. In addition to this, there must be effective feedback mechanisms in place to allow solutions to be shared throughout the organization.

As an example, one might consider how the best way to reduce anaesthetic drug errors within a theatre complex might be achieved. An organization could issue top-down warnings to promote vigilance and create a sense of heightened awareness or it could engage with theatre teams to discover if there are any

recurrent themes (or attractors) in these errors, suggest options for how to minimize these in the future (direction pointing) but also encourage staff to take ownership of the problem themselves to ideally find their own solutions (permission). Any solutions generated would then be shared with the organization as a whole.

Conclusion

The science of complexity theory has already led to advancements in other fields as diverse as mathematics, economics, meteorology, and ecology, yet its potential utility for clinical medicine and healthcare organization remains to be fully explored. However, it represents an exciting avenue for future research in the hope of yielding novel solutions to age old problems.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Trigeminal neuralgia

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Key points

- Trigeminal neuralgia (TN) is a relatively rare but debilitating facial pain condition.
- Classical TN occurs without any apparent cause other than possible microvascular compression.
- TN is a clinical diagnosis, but MRI is helpful to exclude secondary causes.
- Many patients respond to pharmacological therapy and carbamazepine remains the first-line drug.
- Microvascular decompression has the best outcome in terms of quality and duration of pain relief.

Trigeminal neuralgia (TN) is a characteristic neuropathic pain involving the trigeminal nerve distribution. The International Association for the Study of Pain (IASP) defines TN as 'a unilateral painful disorder that is characterised by brief, electric shock like pains, is abrupt in onset and termination, and is limited to the distribution of one or more divisions of the trigeminal nerve'. The annual incidence of TN in the UK is around 26/100 000.[1] Worldwide prevalence varies from 10 to 300/100 000. The peak age of onset is between 50 and 60 yr with a male-to-female ratio of 1:2. In this article, we present a review of the pathophysiology, diagnosis, and treatment of TN based on available evidence.

Aetiology and pathophysiology

The exact aetiology and pathophysiology of TN remains to be clearly elucidated. According to the 'ignition theory' (the most common hypothesis), TN is the result of abnormalities in the afferent neurones of the trigeminal root or ganglion.[1] Any injury to the axons can make them hyperexcitable, leading to this painful neuropathic condition. It has been suggested that central sensitization also plays a role in TN. Some of the risk factors in developing TN are multiple sclerosis (MS), increased age, stroke, hypertension (in women), Charcot–Marie–Tooth disease, and tumours in the region of the trigeminal nerve root.

In the majority of TN cases, the cause is thought to be demyelination of the trigeminal nerve root near its entry into the pons.[2] This area (called the root entry zone) is where the peripheral myelin of Schwann cells meet the central myelin of the astrocytes. The area of nerve root that has been affected can spontaneously discharge impulses that trigger TN. A-β fibres (carrying touch sensation) lie in close proximity with A-δ and C fibres (carrying pain sensation) in the root entry zone, leading to ephaptic cross-talk between them. This might explain precipitation of attacks of TN by trivial tactile stimulation.[1,3] The trigeminal ganglion itself can show pathological changes like hypermyelination.[4] In many patients, the demyelination is caused by compression by a vascular structure. MS, tumours, and arteriovenous malformations can lead to primary demyelination. TN when associated with MS may show plaques of demyelination at the root entry zone. These patients present at a younger age and although do not tolerate anticonvulsants very well, their response to interventions is similar to patients with classical TN.

The theory of vascular compression leading to TN has been supported by the results of surgical decompression and evidence from MRI and nerve conduction studies. However, vascular contact is not a consistent finding in all TN patients and cadaveric studies have shown vascular compression as an incidental finding in people who did not suffer from TN.[4]

Diagnosis

TN is essentially a clinical diagnosis based on its characteristic presentation.

A: Paroxysmal attacks of pain lasting from a fraction of a second to 2 min, affecting one or more divisions of the trigeminal nerve and fulfilling criteria B and C
B: Pain has at least one of the following characteristics:
Intense, sharp, superficial, or stabbing
Precipitated from trigger areas or by trigger factors
C: Attacks are stereotyped in the individual patient
D: There is no clinically evident neurological deficit
E: Not attributed to another disorder

Ref: NICE Clinical Knowledge Summaries: Trigeminal Neuralgia, December 2014.

Differential diagnosis

TN has to be differentiated from other causes of orofacial pain and headaches.

Headache disorders: cluster headache, trigeminal autonomic cephalalgia
Dental pain: cracked tooth, dental abscess
Temporo-mandibular joint disorders
Other neuralgias: occipital neuralgia, glossopharyngeal neuralgia, post-herpetic neuralgia, atypical facial pain
Tumours: acoustic neuromas, meningiomas
Sinusitis

Classification

TN is classified[5] as:

(i) Classical TN—occurs without any apparent cause other than microvascular compression. It is further subdivided as:
  (a) purely paroxysmal: where the patient is pain free between attacks and
  (b) with concomitant persistent facial pain(also called as atypical TN or TN type 2): a low-grade background facial pain persists between the attacks. Central sensitization may account for the persistent pain. Neurovascular compression may not be demonstrable in this type and is resistant to several treatment modalities.
(ii) Symptomatic TN—caused by another recognizable disorder that leads to neural damage (e.g. MS, herpes zoster, trauma, space-occupying lesion).

Investigations

TN is diagnosed on the basis of typical history and clinical features. Although there are no specific investigations to confirm the diagnosis, it may be necessary to undertake some to rule out symptomatic TN:

(i) A neurological examination would help to detect any neurological deficit, area of involvement, and trigger areas. A sensory deficit, absent trigeminal reflexes, and bilateral involvement suggests symptomatic TN.[6]
(ii) MRI scanning of the brain is useful to detect any secondary causes like MS or tumours. Routine neuroimaging may identify a cause in up to 15% of patients.[6,7] High-resolution MRI may be able to identify vascular compression.[2,6]
(iii) Evoked potentials, quantitative sensory testing, and electrophysiological studies can also help detect symptomatic TN, but as yet do not have enough evidence to be routinely recommended.[2,6]
(iv) Preoperative magnetic resonance tomographic angiography has been suggested as useful in patient selection and outcome prediction for microvascular decompression (MVD).[7]

Relevant clinical anatomy

The trigeminal nerve is the fifth and largest cranial nerve and composed of both sensory and motor components. The sensory nuclei are present throughout the brainstem. It is a paired nerve and exits the lateral surface of pons bilaterally as separate sensory and motor roots. The sensory root forms the trigeminal (Gasserian) ganglion in the middle cranial fossa and is located in a cavity called Meckel's cave. This ganglion divides into ophthalmic (V1), maxillary (V2), and mandibular (V3) nerves. The motor root passes along with the sensory root, but is distributed only to the mandibular division.

The ophthalmic nerve exits the cranium through the superior orbital fissure and innervates the skin above the eye, forehead, and globe. The maxillary nerve exits the cranium through the foramen rotundum and supplies the skin between the eye and mouth. The mandibular nerve exits through the foramen ovale. Sensory fibres of V3 innervate the skin of the lateral part of the head and lower jaw, tongue, mucosa of oral cavity, and teeth. Motor fibres innervate the muscles of mastication.

The trigeminal nerve, through its branches, carries parasympathetic supply to ganglia and the lacrimal glands (V1, V2), nasal glands (V2), submandibular, sublingual, and parotid glands (V3).

Treatment

Pharmacological

Optimal pharmacotherapy should be the first line of treatment in the majority of patients with TN. Symptomatic TN needs to be managed by addressing the treatment of the causative condition.

Carbamazepine (200–1200 mg) remains the drug of choice, with good evidence[1] of efficacy in TN and a number needed to treat of 1.8. It is an anticonvulsant drug that blocks the use-dependent sodium channels and may also prevent synaptic transmission in the trigeminal nucleus. The major limiting factor in its use is the high incidence of side-effects, including drowsiness, dizziness, rash, liver damage, hyponatraemia, and ataxia. Patients on carbamazepine should therefore have their liver function, blood count, and serum electrolytes checked at regular intervals. Oxcarbazepine, a derivative of carbamazepine, has a better side-effect profile and similar efficacy.

Gabapentin, pregabalin, and amitriptyline are commonly used in TN because of their efficacy in treating neuropathic pain conditions; however, evidence of their effectiveness specific to TN is not strong. Baclofen and lamotrigine have been used as add-on therapy. Baclofen may be useful in patients with MS suffering from TN.[1] Similarly, phenytoin has been used with limited benefit in some cases of TN.

Surgical

Patients who fail to benefit from pharmacological therapy or experience significant side-effects should be considered for surgical interventions. These procedures can be carried out at three levels.

Peripheral

Peripheral techniques involve neurolysis of the trigeminal nerve branches distal to the gasserian ganglion. This can be accomplished by using laser therapy, alcohol injections, or neurectomy. These procedures are less invasive than other surgical interventions, but the pain relief is short term, lasting 6 months to 1 yr. Patients may also develop dysesthesias post-procedure.[6]

However, they can be useful in patients who are not fit for any other surgical interventions, or as an emergency procedure.

At the gasserian ganglion

The gasserian ganglion can be ablated using thermal (radiofrequency), chemical (glycerol, phenol, alcohol), or mechanical (balloon compression) techniques. A needle is passed percutaneously into the foramen ovale to reach the ganglion to facilitate these procedures.

The procedure is usually performed under local anaesthetic and sedation, as the patient's co-operation is necessary. Fluroscopy-guided technique is more precise in localizing the foramen ovale. The patient is placed supine, with neck slightly extended. A submental view X-ray is obtained. Then, by gradually moving the C arm obliquely towards the affected side, the foramen ovale is located between mandibular process and maxilla. A needle is directed towards the foramen ovale using X-ray guidance (Fig. 1). Needle tip position is confirmed using lateral views (Fig. 2). Once the needle is in a satisfactory position, rhizotomy is achieved by radiofrequency, glycerol injection, or balloon compression.

These interventions provide longer duration of pain relief, lasting around 4–5 yr in 50% of patients.[2,6] However, there is a high incidence of sensory loss and dysaesthesias, with around 4% developing anaesthesia dolorosa.[6] Balloon compression can lead to arrhythmias, aseptic meningitis, and temporary diplopia.

Posterior fossa

(i) MVD: The trigeminal nerve in the posterior fossa is accessed by a suboccipital craniotomy. The nerve root is freed from vessels compressing it (most commonly superior cerebellar artery) and a teflon felt is placed between them. MVD has a very good initial success rate (80–90%) and provides the most sustained pain relief of all the procedures available. The relapse rate at the end of 10 yr is about 30–40%.[8,9] Since MVD is a major neurosurgical procedure, it is associated with a mortality of 0.5%. Other complications include aseptic meningitis (11%), hearing loss (10%), sensory loss (7%), cerebrospinal fluid leaks, haematomas, and infarcts. The complication rate is lower in centres that perform MVD regularly.

(ii) Gamma knife stereotactic radiosurgery: is a destructive procedure that aims at delivering a focused beam of radiation to trigeminal nerve root in the posterior fossa where there is a proven vascular compression. MRI mapping is used to locate the exact site of microvascular compression. This procedure provides complete pain relief in up to 69% of patients by the end of 1 yr,[6] but the benefits may not be sustained, although it can be repeated in recurrent TN. Complications include facial numbness and paraesthesia. It remains a useful option in patients not suitable for MVD.

Psychological interventions

TN, like any other chronic pain condition, can have a significant impact on the patient's psychological well-being. Although there is a lack of good quality studies assessing usefulness of psychological interventions, it is worth having a multidisciplinary team including psychologist in managing these patients and considering psychological interventions such as cognitive behavioural therapy and acceptance and commitment therapy.[10]

Other modalities

Neuromodulation techniques targeting the trigeminal nerve, occipital nerves, peripheral nerves, spinal cord, and motor cortex are being performed at some centres, although at present, the evidence is not robust enough to warrant routine use.

Non-invasive repetitive transcranial magnetic stimulation of motor cortex has been shown to be of benefit in orofacial pain, including that involving the trigeminal nerve. However, its role in managing TN is yet to be established.

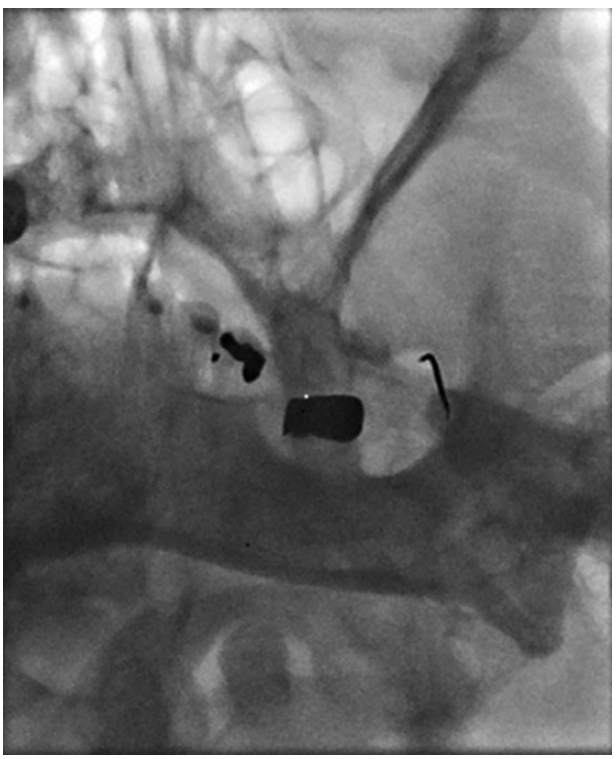

Fig 1 Submental view of needle in foramen ovale.

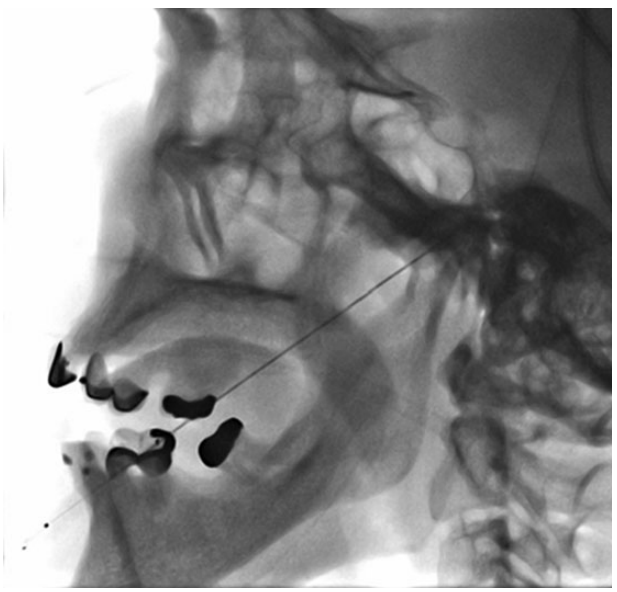

Fig 2 Lateral view of needle in foramen ovale.

There are some case reports and open-ended studies regarding the use of botulinum toxin type A in TN. Well-conducted studies with large samples are required before it can be recommended in TN.

Transcutaneous electrical nerve stimulation, acupuncture, and 5% lidocaine patches have also been tried in TN with varying results.

Conclusion

Patients with TN suffer one of the most severe pains described. Appropriate and early diagnosis is important to formulate an optimal management plan. Pharmacotherapy with carbamazepine is worth trying in the first instance before considering invasive procedures. As treatment options become more invasive, the results improve, but at the cost of increased side-effects. Hence, it is important to individualize the management plan according to the patient's circumstances.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Migraine

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Key points

- Migraine is a neurological disorder with genetic predisposition.
- Diagnosis is essentially clinical, which is based upon compatible history and normal neurological examination.
- Current literature supports that primary headache disorders are principally neurally mediated.
- If treated early in the course of attacks, abortive strategies may be more effective if given as a large single dose.
- Prophylaxis should be considered in patients who have ≥4–5 headache days per month to avoid medication overuse headache, which is reported for ≥8 treated days per month.

Migraine is considered to be a common disabling primary headache disorder. It has a high prevalence with epidemiological studies documenting high socio-economic and personal impact. It is one of the most common clinical presentations to neurologists in routine practice. In a systematic analysis of Global Burden of Disease Study 2010,[1] it was found that migraine is the seventh most common cause globally of years lived with disability with a global prevalence of 14.7% and nearly 3% worldwide disability attributable to any specific disease. Migraine is about twice as common in women (12–14%) than men (6–8%). If untreated, the median duration of a migraine attack is 18 h with the median attack frequency 1 per month. In Europe, 12–28% of people get affected by migraine at some stage in their lives, which includes about 6–15% of adult men and 14–35% of adult women.[2]

Clinical features and diagnosis

A typical migraine attack is a spectrum that may consist of: premonitory symptoms, headache, and the postdrome. Nearly 20–30% of people experience one or more focal reversible neurological symptoms, called the migraine aura. Although the majority of individuals have episodic migraine, about 2–3% of the population has chronic migraine currently defined as migraine headache on at least 15 days per month for at least 3 months.

Premonitory symptoms

Prevalence varies from 7% to 88% and symptoms may commence 24–72 h before the onset of headache. Commonly reported premonitory symptoms include feeling tired and weary (72%), difficulty in concentration (51%), neck stiffness (50%), irritability, depression, craving for specific foods, constipation, and increased yawning. A recent study[3] demonstrated 72% patients correctly predicted migraine headache through their premonitory symptoms.

Headache

Although not always, but commonly, the headache is unilateral in presentation. The headache presents with a throbbing or pulsatile characteristic, increasing in proportion with the intensity of the headache. During an attack, patients commonly experience nausea, whereas vomiting, photophobia, and phonophobia are less frequent. Additionally, osmophobia and cutaneous allodynia may occur. A headache episode may last from few hours to several days if left untreated. Some attacks resolve while sleeping.

Postdrome

A postdromal phase may follow the headache episode. Postdrome may be characterized by the symptoms of exhaustion although could alternate between mild elation or euphoria.

Aura

Migraine aura, consisting of focal neurological symptoms, has an incidence of 20–30%. Although these symptoms usually precede the headache, they may occur concurrently with the pain, after or independent to headache. Aura is not specifically associated with migraine, it can occur in all primary headaches.[4]

Auras are most commonly visual (90%), although may also be sensory or associated with language or motor abnormalities. Typical aura evolves gradually, usually no longer than an hour, has a mix of positive and negative features and complete reversibility.[5] The positive features may include visual symptoms (bright lines, shapes, visual loss), auditory symptoms (tinnitus), and somatosensory features (paresthesia). Negative features may include a loss of function, such as visual or hearing loss and inability to feel or move a part of the body. The majority of aura symptoms last <60 min.

A differential diagnosis of transient ischaemic attack (TIA) should be considered if neurological symptoms have a very rapid onset with a simultaneous rather than sequential pattern. In TIA, the characteristic visual phenomenon is a descending curtain deficit (amaurosis fugax) contrary to scintillating visual disturbance of migraine aura.

Precipitating and exacerbating factors

In a study of migraine performed retrospectively,[6] at least one trigger was associated with acute attacks by 75% of the patients. These trigger factors include: emotional stress (80%), hormones (65%), weather (53%), sleep disturbances (50%), odours (44%), neck pain (38%), light (38%), alcohol (38%), smoke (36%), sleeping late (32%), heat (30%), food (27%), exercise (22%), and sexual activity (5%). Migranous neck pain/stiffness can be misdiagnosed as pain originating from the neck.

As initially stated, migraine is essentially a clinical diagnosis which is based upon a compatible history and normal neurological examination. The International Classification of Headache Disorders (ICHD), 3rd edition,[5] has classified migraine without aura (MwoA) and migraine with aura (MwA) (Table 1).

Migraine without aura

(A) At least five headache attacks fulfilling criteria B–D
(B) Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
(C) Headache has at least two of the following four characteristics:
  (i) Unilateral location
  (ii) Pulsating quality
  (iii) Moderate or severe pain intensity
  (iv) Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
(D) During headache at least one of the following:
  (i) Nausea and/or vomiting
  (ii) Photophobia and phonophobia

Table 1 Migraine classification based on the International Classification of Headache Disorders, 3rd edition (beta version)

1.1	Migraine without aura
1.2	Migraine with aura
1.2.1	Migraine with typical aura
1.2.1.1	Typical aura with headache
1.2.1.2	Typical aura without headache
1.2.2	Migraine with brainstem aura
1.2.3	Hemiplegic migraine
1.3	Chronic migraine

Migraine with aura

(A) At least two attacks fulfilling criteria B and C
(B) One or more of the following fully reversible aura symptoms:
  (i) Visual
  (ii) Sensory
  (iii) Speech and/or language
(C) At least two of the following four characteristics:
  (i) At least one aura symptom spreads gradually over 5 min, and/or two or more symptoms occur in succession
  (ii) Each individual aura symptom lasts 5–60 min
  (iii) At least one aura symptom is unilateral
  (iv) The aura is accompanied, or followed within 60 min, by headache

Although not essential in diagnosis, imaging (CT/MRI) should be considered in the following patients:[7]

(i) Patients with sudden severe headache (thunderclap onset). The pain escalates from no pain to maximum intensity within 5 min. The most common presentation of subarachnoid haemorrhage is with thunderclap headache. The diagnosis of subarachnoid haemorrhage is based upon CT within 24 h of ictus and if normal, CSF examination for xanthochromia detected with spectrophotometry within 12 h to 2 weeks after ictus.
(ii) Patients presenting with headache and focal neurology (including seizures).
(iii) Patients presenting with headache and systemic ill-health.
(iv) There should be a lower threshold for investigating headache in individuals >50 yr, particularly with new onset or change in character/pattern.

Pathophysiology

Migraine was originally thought to be of vascular origin and was supposedly attributed to the dilatation of blood vessels, while the vasoconstriction was thought to cause aura.[8] Migraine is now considered to be a disorder of the brain in individuals with an inherited predisposition.

It has been estimated that genetic inheritance may account for 40–50% of an individual's susceptibility to migraine. Three genes have been identified to cause one of the more uncommon forms of migraine—familial hemiplegic migraine (FHM). FHM has been linked to CACNA1A, ATP1A2, and SCN1A gene mutation-related channelopathies. The more common forms of migraine with and without typical aura may have a more complex pattern of inheritance.

The pathophysiology of migraine involves activation of the trigeminovascular system, consisting of sensory neurones supplying large cerebral and pia vessels, the duramater, and large venous sinuses. These sensory, small caliber pseudo-unipolar neurones originate from the trigeminal ganglion and upper cervical dorsal roots. The anterior structures of the cranial fossa are innervated via the ophthalmic division of the trigeminal nerve, whereas the posterior structures receive a greater contribution from upper cervical roots.

Central projections from the upper cervical nerve roots and the trigeminal nerve converge at the trigeminal nucleus caudalis and extend to the C2–3 segment in the dorsal horn forming the trigemino-cervico complex (TCC).[9] This may explain frontal, occipital, and cervical distribution of the symptoms.

Activation of this network releases various neurotransmitters including serotonin, substance P, calcitonin gene-related peptide, glutamate, and neurokinin A, which may in turn lead to the process of sensitization. This phase is characterized by an increased responsiveness to nociceptive and non-nociceptive stimulation.[10]

From the TCC, second-order neurones project to the thalamus and hypothalamus via the trigeminothalamic and trigeminohypothalamic tracts *en route* to cortical structures. In addition numerous subcortical connections including projections to periaqueductal grey, nucleus raphe magnus, brain stem, cerebellum, and midbrain play important role in central modulation of pain.

The hypothalamus has been associated with migraine premonitory symptoms through its projections to TCC and the sensitization of thalamic neurones has been implicated in the spread of cutaneous allodynia.

Although not shown in humans, animal work has demonstrated that the phenomenon of cortical spreading depression (CSD) may cause aura symptoms:[11] CSD is a slowly propagating wave (2–6 mm min^{-1}) of neuronal and glial depolarization which is followed by inhibition of cortical activity (15–30 min). How aura is linked to headache remains largely speculative.

Treatment

Migraine management is targeted as acute and preventive treatment.

Acute

This should be tailored to an individual's requirements depending upon the severity and frequency of attacks, co-existing symptoms, comorbidities, and the patient choice. A step-wise ladder approach may be used, initiating with an analgesic and anti-emetic and escalating to 5HT1 receptor agonist (triptan) as needed. However, a stratified approach in which attacks are treated according to the severity at the time of treatment has been demonstrated to be more cost-effective. During the acute phase, options include a non-steroidal anti-inflammatory drug (NSAID), such as aspirin (1000 mg) or ibuprofen (400–800 mg), paracetamol (1 g), or triptan. Acute treatments can also be taken in combination and with an anti-emetic, which has been shown to improve gastric absorption and efficacy. A single adequate dose of acute treatment (or combination of acute treatments) is more effective than suboptimal doses taken throughout the day.

A meta-analysis[12] has shown that in comparison with sumatriptan 100 mg: rizatriptan 10 mg demonstrates better efficacy, consistency, and equal tolerability; eletriptan 80 mg a lower tolerability; almotriptan 12.5 mg an equal efficacy but better consistency and tolerability; naratriptan l2.5 mg lower efficacy but better tolerability. Zolmitriptan 5 mg/10 mg, eletriptan 40 mg, and rizatriptan 5 mg were comparable with each other. In the UK, sumatriptan is also available as a subcutaneous and intranasal preparation, rizatriptan has a melt, and zolmitriptan both intranasal and melt formulations.

In the absence of enough good quality evidence, ergot alkaloids are not recommended routinely and are no longer available in many parts of the Europe.

During the aura phase, acute attack treatment is not effective at preventing the migraine headache, hence should be taken when the headache evolves.[13] Successful treatment of migraine attacks in recent randomized controlled trials achieve the following endpoints:

- no pain after 2 h,
- headache improves from moderate/severe to mild/none after 2 h,
- the treatment is consistently effective in two of three attacks,
- no further recurrence of headache and no need to take the drug within 24 h after successful treatment.

Acute treatment for more than 8 days a month has been associated with medication overuse headache (MOH). As it is the frequency of treatment rather than the dosing which has been implicated in MOH, the acute-relief medication use should be restricted to once or twice a week at most. If the frequency starts to increase towards the higher end of the range, preventive strategies should be introduced early to avoid the development of MOH and ensure that any prophylactic benefit remains maximal.

All acute-relief medications are associated with MOH. The most protracted withdrawal occurs with opioids followed by simple analgesics; hence, opioids should be avoided in migraine. NSAIDs have been the least implicated in MOH, hence use is advised as first line. If not tolerated, paracetamol can then be considered. Although triptans are associated with the most rapid development of MOH, they are the most effective acute treatments and withdrawal faster than with other acute treatment options.

Preventive

Prophylactic treatment in migraine may be indicated if headache frequency is more than four in a month, or if less but without adequate response to acute treatments. After 6–12 months of effective prophylaxis, gradual reduction or withdrawal of medication can be considered. The aim is to tailor treatment according to the symptoms. Thus, if on withdrawal or reduction in the preventive treatment, symptoms recur, the treatment can be re-established at effective doses. Some patients may need a combination of preventive treatments to minimize disability from their headache disorder. Migraine prophylaxis may be deemed successful if there is a decrease in 50% frequency of migraine attacks per month.

Recommendations based on the scientific evidence from clinical trials and the expert consensus by the task force of the European Federation of Neurological Societies (EFNS)[14] on the drug treatment of migraine have been summarized in Tables 2 and 3.

Chronic migraine

About 2–3% of the population have chronic migraine, defined as more than 15 headache days a month for at least 3 months. The treatment of chronic migraine should focus on prophylactic drug treatment as a first-line therapy (Table 3). More invasive treatments such as greater occipital nerve block with local anaesthetic and steroid, botulinum toxin type A administration and neuromodulation including occipital nerve stimulation (ONS) are reserved for individuals with refractory migraine. Acute headache medication intake should be limited in order to avoid MOH, but severe superimposed migraine headaches are treated in the same manner as episodic migraine headaches. The pertinence of this is that prophylactic treatments are rendered less efficacious in the presence of acute-relief medication overuse.[15]

Table 2 Acute drug treatment of migraine: Based on the European Federation of Neurological Societies (EFNS) guidelines 2009. *Level A: (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies. Level B: (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence. Level C: (possible effective, ineffective, or harmful) rating requires at least two convincing class III studies

NSAIDs, paracetamol, and other analgesics, antiemetics and triptans			
Substance	Dose (minimum to maximum)	Recommendation level*	Comment
Acetylsalicylic acid (ASA)	1000 mg (oral or i.v.)	A	Gastrointestinal side-effects, risk of bleeding
Ibuprofen	200–800 mg	A	Side-effects as for ASA
Naproxen	500–1000 mg	A	Side-effects as for ASA
Diclofenac	50–100 mg	A	Including diclofenac
Paracetamol	1000 mg (oral), 1000 mg (supp.)	A	Caution in liver and kidney failure
ASA plus, paracetamol plus, and caffeine	50 mg (oral), 200–250, and 50 mg	A	As for ASA and paracetamol
Metoclopramide	10–20 mg (oral) 20 mg (suppository) B 10 mg (i.m., i.v., or s.c.)	B	Side-effect: dyskinesia; contraindicated in childhood and in pregnancy
Domperidone	20–30 mg (oral)	B	Side-effects less severe than in metoclopramide; can be given to children
Sumatriptan	25, 50, and 100 mg (oral including rapid-release), 25 mg (suppository), 10 and 20 mg (nasal spray), 6 mg (subcutaneous)	A	General side-effects for all triptans: chest symptoms, nausea, distal paresthesia, fatigue. General contraindications: arterial hypertension (untreated), coronary heart disease, cerebrovascular disease, Raynaud's disease, pregnancy and lactation, age under 18 (except sumatriptan nasal spray) and age above 65 yr, severe liver or kidney failure
Zolmitriptan	2.5 and 5 mg (oral including disintegrating form), 2.5 and 5 mg (nasal spray)	A	
Naratriptan	2.5 mg (oral)	A	Less side-effects and efficacy than sumatriptan
Rizatriptan	10 mg (oral)	A	5 mg when taking propranolol
Almotriptan	12.5 mg (oral)	A	Probably less side-effects than sumatriptan
Eletriptan	20 and 40 mg (oral)	A	80 mg allowed if 40 mg not effective
Frovatriptan	2.5 mg (oral)	A	Less side-effects and efficacy than sumatriptan

Table 3 Prophylactic drug treatment of migraine: Based on the European Federation of Neurological Societies (EFNS) guidelines 2009. Certain other drugs for prophylaxis with probable efficacy are gabapentin, magnesium, riboflavin, coenzyme Q10 (level C evidence).

Substance	Dose (minimum to maximum)	Recommendation level*	Comment
β-Blockers			
Metoprolol	50–200 mg	A	Cautious use: asthma, diabetes, bradycardia, peripheral vascular disease, comorbid depression
Propranolol	40–240 mg	A	Preferred in: comorbid anxiety
Anti-epileptics			
Valproic acid	500–1800 mg	A	Cautious use: obesity, liver disease, pregnancy Preferred in: depression
Topiramate	25–200 mg	A	Cautious use: renal stone, angle closure glaucoma, pregnancy, anorexia Preferred in: comorbid obesity
Amitriptyline	50–150 mg	B	Cautious use: angle closure glaucoma Preferred in: comorbid depression, sleep disturbance
Bisoprolol	5–10 mg	B	

I.V. dihydroergotamine has been associated with the improvements in headache and disability in chronic refractory migraine patients[16] and can be effective in the presence of MOH. However, the effect tends to be self-limiting.

Botulinum toxin type A

Botulinum toxin type A is recommended by NICE for adults with chronic migraine, who have not responded to at least three preventive medications and have been managed appropriately for medication overuse. In recent data from the pooled analyses of the PREEMPT 1 and PREEMPT 2 trials of more than 1300 patients, nearly half of patients (47%) who received Botox reported a 50% or higher decrease in headache days 24 weeks after treatment.[17]

Greater occipital nerve block

Although limited, evidence has shown benefit from the greater occipital nerve block, but the treatment usually requires repeat procedures over time.

Occipital nerve stimulation

ONS peripherally stimulates the occipital nerves with a subcutaneous battery-powered implantable pulse generator has proven to be effective in managing some patients with chronic refractory migraine. A 52 week open-label extension study has reported 30% responder rate of 59.5% and 50% responder of 47.8% with headache days being significantly reduced by 6.7 days per month at the end of 52 weeks.[18] NICE is currently reviewing its clinical commissioning policy for ONS (at the time of print).

Migraine in pregnancy

Migraine tends to improve in pregnancy. Nevertheless, if problematic during the pregnancy, paracetamol is safe. Codeine may also be used, although there is a risk of MOH with both treatments. There is post-marketing data for the safety of sumatriptan during the first trimester.[19]

Declaration of interest

V.M. is an editor of *BJA Education*. Other authors: none declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Dental knowledge for anaesthetists

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Key points

- Dental damage is the leading cause of complaint and medicolegal claims against anaesthetists.
- Direct laryngoscopy is implicated in most cases of dental injury.
- Severe periodontitis is an independent risk factor for cardiovascular disease.
- A thorough preoperative dental assessment, explanation of risk, and clear documentation in the anaesthetic record is essential, particularly in individuals with risk factors for dental injury.
- Departments should have an agreed management pathway for patients who have sustained dental injury as prompt treatment can improve tooth survival.

Anaesthetists routinely instrument patients' airways and may inadvertently cause dental injury. Detailed knowledge of dental anatomy and development, risk factors for dental injury and its management, however, is often lacking. Dental injury remains the most common area for complaint and litigation against anaesthetists. The cost and complexity of treatment and restorative dentistry has significantly increased in the last 5 yr. This article aims to review these topics to aid anaesthetists in making accurate preoperative dental assessments, provide appropriate consent, minimize the risk of perioperative dental injury, and manage it correctly, should it occur.

Development and anatomy of teeth

The role of teeth primarily concerns the processes of mastication and digestion but extends to provision of structural support to facial architecture, influencing facial aesthetics, and facilitation of speech.

Dental buds of primary (interchangeably called milk or deciduous) teeth develop from the 6th week *in utero*, forming in the opposing maxillary and mandibular bones. Adult teeth begin to develop behind their primary counterparts from 20 weeks *in utero* but do not undergo calcification until early infancy. 'Primary eruption' is the first appearance of teeth in infants, and occurs around the age of 6–12 months. This first dentition comprises 20 teeth (8 incisors, 4 canines, and 8 molars) (Fig. 1A).

Tooth development starts with formation of the crown. Completion of the root lags behind by many months or even years, rendering them prone to injury for some time. The maxillary incisors are the first to undergo full calcification by ~18 months of age, while the last stage of molar root development is usually completed by 3 yr. Primary teeth begin to fall out (termed 'exfoliation') by the age of 6 to allow eruption of the permanent dentition. A period of mixed dentition follows and may last until the age of 12, when complete exfoliation of all primary teeth has usually occurred.

Development of permanent teeth variably lasts into late adolescence or early adulthood, with root formation usually completed in the early part of the third decade of life. Complete permanent dentition consists of 32 teeth, with each quadrant containing, in antero-posterior orientation, one central and one lateral incisor, one canine, two premolars, and the first, second, and third molars (Fig. 1A).

Structure of individual tooth

Each tooth is made up of a crown (the visible portion projecting into the mouth) and a root. The root is anchored into the jawbone by the periodontal apparatus (Fig. 2).

Teeth are subjected to immense loads generated by the muscles of mastication. The forces exerted on posterior teeth during

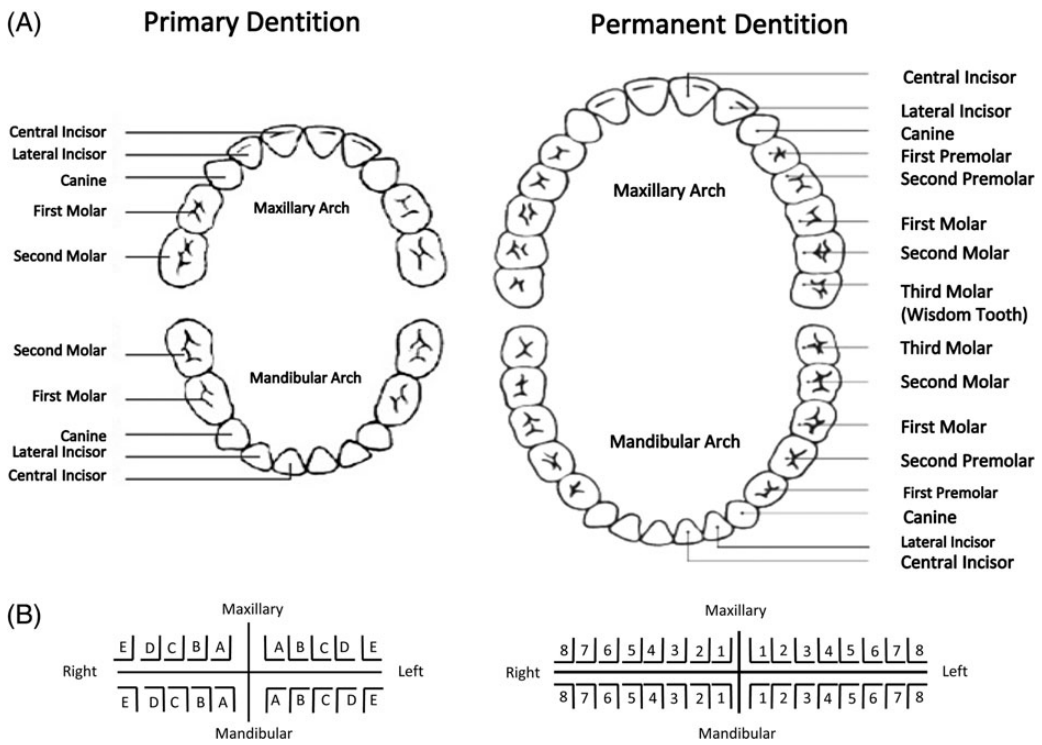

Fig 1 (A) Paediatric and adult dentition. (B) Palmer notation for paediatric and adult dentition.

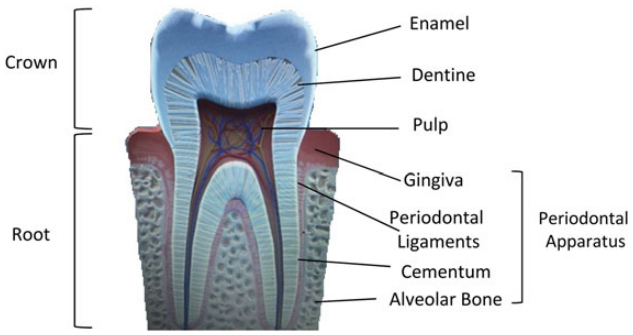

Fig 2 Tooth structure.

normal chewing are ~70–150 N, but may exceed 800 N[1] during involuntary tooth grinding (bruxism). Their multi-layered structure and anchorage into the jawbones offers teeth some protection from these common stressors.

The crown

The crown is covered by enamel, a translucent, highly mineralized substance recognized as the hardest tissue in humans, albeit at the expense of brittleness. Produced by ameloblasts which lose function once a tooth is fully developed, damaged enamel cannot be regenerated.

The bulk of the tooth is formed by yellowish dentine—a bone-like, porous matrix of fluid-containing tubules. Its composition (60% mineral, 20% protein including type 1 collagen) provides flexibility and allows absorption of the forces encountered during mastication.

Dentine is produced throughout the tooth's lifespan by cells in the underlying pulp, which occupies the central part of the crown and root canals. Pulp also contains neurovascular tissue and performs nutritive, sensory, and restorative functions. The amount of pulp decreases with age and dental disease, resulting in diminished regenerative capacity.

The root and periodontium

Incisors are single-rooted, while premolars and molars have two to three roots. The root is covered by cementum, a collagen–proteoglycan substance structurally akin to bone. A key part of the periodontal apparatus, cementum forms crucial bonds between the root and alveolar bone while preventing the resorption of the root into bone.

The periodontium is the unit supporting each tooth within its bony socket. In addition to cementum, this unit consists of periodontal ligaments (PDL), alveolar bone, and the gingiva.

PDL cells have fibroblast and osteoblast-like functions, forming the PDLs. These wrap around the dental root in a sling-like fashion, anchoring it into the bone while allowing small physiological movements to withstand the forces of mastication.

Alveolar bone is named after the bony sockets (alveoli) within it that accommodate individual teeth. It provides anchorage and, together with the gingival epithelial cuff, acts as a shock-absorber by dissipating forces away from teeth.

Dental disease

Dental disease is common, affecting 15–20% of middle-aged individuals and increasing significantly above the age of 65. Bacteria found in plaques that lie either above (dental caries) or below the dental margin (periodontitis) cause infection which weakens teeth and periodontium, ultimately leading to tooth loss. Interaction between host and microbial factors determines the severity of disease. Some common medical conditions predispose to

Table 1 Factors associated with periodontitis. The order of associated factors has been amended to present the most significant factors first, as suggested by the reviewers

Predisposing/risk factors	
Smoking	Single biggest modifiable risk factor; promotes cytokine proliferation and inflammation, connective tissue destruction
Poor oral hygiene	Leads to a favourable environment for bacterial growth
Diet	Sugary and acidic conditions promote bacterial growth
Substance misuse	Alcohol, (Meth)amphetamines, and opiates may cause xerostomia; cocaine (mucosal application makes tissues susceptible); poor oral hygiene
Glycaemic control	
Xerostomia (reduced salivary flow)	Age-related Sjogren's syndrome Radiotherapy Pharmacologically induced (see 'Drugs' and 'Substance misuse')
Drugs	Dry mouth: antidepressants, antihypertensivesGingival hypertrophy (difficult to maintain oral hygiene): anticonvulsants, calcium channel blockers, cyclosporine
Genetic predisposition	
Anxiety/stress	
Associated systemic disorders	
Diabetes mellitus	Multifactorial aetiology (microvascular disease, hyperglycaemia, immune dysfunction)
Autoimmune conditions	Rheumatoid arthritis, Crohn's disease, Sjogren's syndrome
Immunocompromise	HIV, hypogammaglobulinaemia, haematological malignancies, and their treatments
Down syndrome	Likely multifactorial (reduced salivary flow, immune deficiency)
Connective tissue diseases	Ehlers–Danlos syndrome, Marfans disease

dental disease and these should be considered in individuals who present with severe periodontitis (Table 1). Studies indicate that severe periodontitis predisposes to cardiovascular disease due to endothelial dysfunction and systemic inflammation caused by seeding of bacterial endotoxins during chewing.[2]

Spread of periodontal infection

Spread of infection results from a breakdown in local and systemic defences. Spread can result in either localized complications, systemic seeding of the infection, or both. Supragingival plaques spread infection to dental pulp, resulting in pulpitis which can ultimately perforate alveolar bone and cause abscess formation. Infection in subgingival plaques leads to gingivitis, periodontal abscesses, and spreading infection to the orofascial planes of the head and neck. Anaesthetic considerations for patients with dental abscesses are covered elsewhere.[3]

Dental disease in children

Primary teeth are particularly vulnerable to injury as their enamel and dentine is thin. Equally, as root development lags behind, alveolar attachment is weaker. Due to the proximity of primary dental roots to the non-calcified permanent crowns, damage to primary teeth—either traumatic or carious—may directly affect the development of the underlying successor, potentially causing disturbance of growth or abnormal shape of the permanent tooth.

Restorative dentistry

The range of restorative and reconstructive treatments has vastly expanded over the last decade (Tables 2 and 3). Moreover, with increasingly sophisticated materials used, recognition of these vulnerable restorations and prostheses is becoming more difficult. The presence of restorative treatments should alert the anaesthetist not only to the potential for damage to the prosthesis, but also to the presence of underlying periodontal disease.

Perioperative dental assessment

Examination

While it is usually impractical to carry out a full dental assessment routinely, in cases where there is significant concern about the state of dental health, evaluation, and documentation of the following may be valuable:

- presence of periodontal disease as evidenced by an erythematous, retracted gumline; visible roots;
- evidence of infective complications of periodontal disease, e.g. abscesses or sinuses;
- presence of cracks, chips, and severe discolouration;
- identification of loose teeth by gentle palpation with a gloved hand;
- position of missing or loose teeth;
- position and condition of dental restorations.

Notation

Several methods for the identification of individual teeth exist. The Palmer notation is most commonly used by dentists in the UK. Symbols (⌜⌝ ⌞⌟) mark the relevant quadrant and teeth are numbered 1–8 starting in the midline, as viewed by the assessor. For primary dentition, the letters A–E replace the numbers (Fig. 1B).

The Palmer notation is further adapted in the 'letters and numbers' system; each quadrant is assigned two letters (for instance, LL, left lower; RU, right upper) followed by a number 1–8.

Internationally, the World Health Organization's ISO system is often used. Each quadrant is designated a number 1–4, and each individual tooth a further number 1–8 as per the Palmer notation.

In the USA, the Universal Numbering System is primarily used. Adult teeth are labelled with a number 1–32 starting with the third right maxillary molar and moving in an anti-clockwise direction. For primary dentition, letters A–T are used.

Table 2 Restorative and reconstructive dental treatments. Natural lifespan of most treatments ~10–15 yr unless indicated specifically

Type of treatment	Description and associated problems
Direct restoration (cavity filled *in situ*)	
'Filling'	Usually made from amalgam, gold, or composites ('white fillings') Prone to expansion or shrinkage when setting, leading to tooth fracture or further decay Approximate lifespan 7–12 yr
Indirect restorations (filling created *ex situ*)	
Inlays/onlays	Gold or porcelain. Inlay is a filling made and set outside the mouth, then bonded and thus is less prone to expansion or shrinkage. Onlay refers to an inlay which covers a dental cusp
Crown	Commonly referred to as a 'cap', this is an Onlay which completely covers the tooth surface. Usually required when significant damage to the tooth exists
Veneer	A thin layer bonded to tooth surface to improve appearance of fractured or discoloured teeth. Made from porcelain or composite resin
Prosthesis	
Bridge	Fixed partial denture, anchored to adjacent teeth
Denture	Partial removable prosthesis—attached to adjacent teeth via clasps Complete prosthesis—may be associated with underlying mucosal irritation or gingivitis. Chronic irritation may cause hyperplasia and granuloma formation
Implant	Titanium screw inserted into alveolar bone undergoes ossointegration, tightly bonding to bone. A prosthesis (single tooth, bridge or denture) is then added via an abutment Recession of gingiva can occur over time causing weakening of implant Approximate lifespan 10–20 yr

Table 3 Materials used for dental restorations

Material	Properties
Gold–alloy	Inert, durable substance; comparable hardness to enamel, therefore does not damage opposing teeth. Expensive and visually noticeable
Amalgam	Affordable, prone to expansion when sets, thus causing cracking or fracture of tooth
Ceramic/porcelain	Expensive; tooth coloured, thus frequently used in anterior restorations Older types brittle and prone to cracking New harder porcelain may cause excessive wear on opposing teeth
Composite resin	Affordable, tooth coloured, therefore aesthetically suitable for anterior dental restorations However, less durable than other materials and may shrink, crack or chip
Glass ionomer cement (GIC)	Tooth coloured but aesthetically inferior to porcelain or composite resin Brittle but less prone to shrinkage and cracking than composite resin

Dental injuries under anaesthesia

Dental injuries under general anaesthesia (GA) are the most common cause of complaint and medicolegal claims against anaesthetists. While the true incidence is unknown, retrospective studies estimate an incidence between 0.02% and 0.1% of all GAs.[4] Prospective studies report rates up to 25% in patients undergoing direct laryngoscopy when examined closely after operation.[5] The Royal College of Anaesthetists' guidance on dental damage quotes a risk of 1:4500,[6] in line with US figures from analysis of nearly 600 000 cases.[3]

Retrospective data suggest a five-fold risk of injury to teeth with pre-existing pathology, highest in patients between 50 and 70 yr as these are more likely to have teeth weakened by periodontal disease while remaining dentulous.[7] Patients with dental restorations are 3.4 times more likely to sustain dental injury.[8] Interestingly, studies demonstrated no increase in risk for emergency intubations and even from inexperienced laryngoscopists,[9, 10] although the risk is 20-fold in individuals deemed difficult to intubate.[8] Risk factors for dental injury are summarized in Table 4.

Direct laryngoscopy is implicated in 50–75% of all cases of dental injury. Maxillary incisors are the most commonly injured under GA. Representing 50% of cases, they are particularly prone to fracture, being small-rooted, of narrow cross-sectional area with a slight anterior axis.[11] The left central maxillary incisor is most vulnerable to damage from the flange of the laryngoscope blade if used as a fulcrum, usually when attempting to improve the view during a difficult intubation. It is important, therefore, to avoid blade-to-tooth contact or transmission of any oblique or vertical forces through the incisors and canines. The posterior teeth are injured less frequently, being wider, multiple-rooted, and generally remote from laryngoscope positioning. Contact with the right third molar during laryngoscope insertion is the most common mechanism for posterior dental injury.

Aside from laryngoscopy, dental injury can also result from mouth-opening manoeuvres ('scissors manoeuvre'), forcible removal of tracheal tubes, vigorous oropharyngeal suctioning, and insertion or removal of oropharyngeal and supraglottic airway devices (SAD). Up to 20% of injuries occur during emergence from anaesthesia. Involuntary biting during emergence is hazardous, particularly on the hard stem of some

Table 4 Risk factors for dental injury

Anaesthetic factors	Dental factors
Difficult airway predictors • Prominent incisors ('Buck teeth') • Mallampati 3/4 • Inter-incisor gap <5 cm • Limited head and neck movement • Limited mandibular subluxation • Receding mandible • Obesity BMI >35 kg m^{-2}	Restorative dental work any crowns, veneers, prostheses are at risk; in particular: • Anterior restorations • Brittle restorative materials, e.g. some ceramics or composite resin • Recent restorative/orthodontic treatment
Direct laryngoscopy; tracheal intubation	Pre-existing dental pathology, previous root canal treatment
Placement of double-lumen tubes	Periodontitis
Biting during emergence	Caries
Forceful removal of tracheal tubes/supraglottic airways	Isolated teeth
Vigorous oropharyngeal suctioning	Mixed dentition (children aged 5–12)

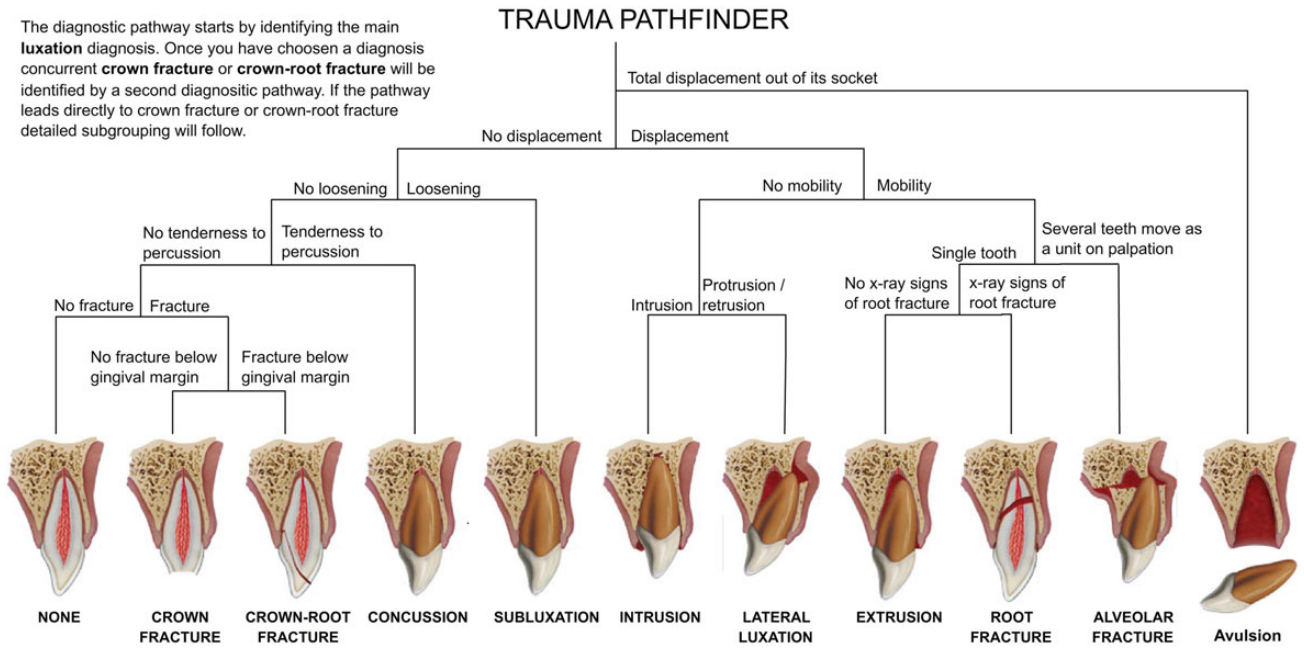

Fig 3 Trauma pathfinder for identifying the nature of dental injuries. Supplied and reproduced with kind permission from J.O. Andreasen and E. Fernandez-Rugerio.

SADs. Approximately 85% of dental injuries are recognized at the time of injury by the anaesthetist;[8] up to 15% are identified after operation by either the patient or recovery staff.

Nature of dental injuries

The nature of the injury sustained can be diagnosed using the trauma pathfinder (Fig. 3).

Over 50% of dental injuries under GA are crown fractures or subluxations.[8] Tooth avulsion (completely out of socket) occurs in ~10% of cases. Crown fractures are more common in younger patients, while avulsion and subluxation injuries are more common with advancing age as the anchoring periodontium weakens with age and periodontal disease.

Strategies to minimize the risk of dental injury

If severe dental pathology is identified before operation, patients should be advised to consult their dentist for restorative treatment or dental extraction before surgery. When preoperative treatment is not feasible and airway instrumentation unavoidable, the following strategies may be used to mitigate the risk of dental injury.

A loose tooth recognized before operation may be stabilized by knotting a suture or tie around its base and, where possible, to a fixed neighbouring tooth with the suture ends brought out and secured to the cheek using adhesive tape.[12] This technique has the advantage of not only supporting the loose tooth by splinting it to an adjacent one, but also minimizes risk of aspiration and aids retrieval in the event of avulsion.

Blind intubation, using nasal tracheal tubes or intubating SADs, eliminate the need for instrumenting the airway with a laryngoscope; however, the success of these techniques depends on operator skill and anatomical factors. Furthermore, the risk of dental injury from SADs remains significant either from direct injury or from involuntary biting. Nasal fibreoptic intubation may be a more reliable technique as it bypasses the oral cavity completely and allows intubation under direct vision.

When laryngoscopy is the technique of choice, tooth-to-blade contact may be reduced with the use of alternative blades such as the McCoy, a modified Macintosh with a short flange, plastic blades, or a retromolar approach with a straight blade.[13]

Similarly, studies in simulated difficult airway scenarios on manikins suggest that videolaryngoscopes may be associated with a significantly lower risk of tooth-to-blade contact and thus dental injury.[14]

The use of dental guards, as used to protect maxillary teeth during rigid bronchoscopy or in contact sports, has not been proven to avoid dental injury.[11] Moreover, damage can result from the guard itself and may render laryngoscopy more difficult by narrowing the inter-incisor gap.

During emergence, shivering or pain may promote involuntary biting and must be avoided. The use of Guedel oropharyngeal airways as bite guards is not advocated, as the anterior teeth are subjected to significant forces during involuntary biting, risking fracture. A softer bite block of rolled gauze swabs placed between the molar teeth performs the same function while carrying a lower risk of dental injury.

Management of dental injury

General

Appropriate management after dental injury depends on the type of injury and whether it involves primary or permanent teeth. In all cases, the nature of the injury and the circumstances in which it occurred must be clearly documented in the patient record. A full explanation should be provided to the patient when fully awake and a plan for further management and follow-up with a dentist initiated.

When dental injury is recognized during anaesthesia, it is essential to localize avulsed, broken teeth, or prostheses. Laryngoscopy and retrieval of missing teeth, prostheses, or fragments using Magill's forceps should be attempted. If these cannot be found or retrieved, imaging in the form of a chest radiograph should be performed to determine if they have been aspirated into the lungs or oesophagus. It must be remembered, however, that not all dental prostheses are radiopaque and primary teeth are difficult to visualize on a chest radiograph. If there is doubt, a discussion with a radiologist as to the appropriate imaging should occur. If aspiration into the tracheobronchial tree is suspected, advice from a senior ENT or thoracic surgeon should be sought urgently.

Specific dental management

Avulsion of a permanent tooth is one of the most serious dental injuries and timely management determines tooth survival. In most situations, replantation, by pushing the tooth into its socket for several minutes, is the immediate treatment of choice. This may, however, not be appropriate in immunocompromised patients or those with severe periodontal disease due to the risk of bacterial seeding.

The viability of the avulsed tooth depends on the condition of the PDL cells, found on the root of the tooth which must not be handled. These, in turn, are dependent on the storage medium in which the avulsed tooth is placed and also the 'dry time' (the time the tooth spends either outside the mouth or a storage medium). After 60 min dry time, no PDL cells survive. It is therefore essential the tooth is either replanted or placed in a storage medium immediately. Tissue or cell culture transport media are optimal but may not be immediately available in theatre; alternatively, an osmolality balanced medium such as cold saline or milk may be used.

While immediate replantation may save the tooth, it may still be lost or extracted at a later stage. Replantation while the patient is still anaesthetized also poses the risk of redisplacement and aspiration into the lungs or oesophagus. Replantation of primary avulsed teeth in children must not be attempted due to risk of damage to the underlying permanent successor. In other types of injury such as crown fractures or broken prostheses, the fragments should be placed into a storage medium and given to the patient until urgent dental review can take place. A local protocol for the ongoing management of damage should be available in anaesthetic departments.

Medicolegal aspects of dental injury

Eleven per cent of anaesthesia-related claims made to the NHS litigation authority (NHSLA) from 1995 to 2007 were for dental damage. The cost of claims ranged from £0 to £20 800, with a total cost to NHSLA of £177 000.[15] While this data set has limitations, there is a general trend towards increased cost of claims in the last 5 yr as dental treatments become more sophisticated. The total costs to NHSLA from 2009 to 2014 increased to £443 753 (personal communications). Analysis of claims made to the Medical Defence Union estimated that 63% of private claims made against anaesthetists were for dental injury.

Negligence claims require the claimant to prove, in a three-part test, that a duty of care existed and was breached, and that this directly led to the harm experienced. Lack of a clear record of the preoperative condition of a patients' dentition can make rebuttal of a subsequent claim difficult even if this is brought for a dental injury that is not typically associated with laryngoscopy or SAD insertion. Presently, the majority of dental claims are settled informally as the cost of defending cases in court is usually vastly disproportionate to the cost of dental repairs.

Documentation of a thorough preoperative dental assessment and any explanation of risk provided to the patient is essential. Individuals with risk factors for dental injury should be warned of a higher likelihood of damage. A simple diagrammatic representation using the Palmer notation is effective in indicating the locations and condition of dental prostheses and restorations, broken, vulnerable, or missing teeth. An overall impression of the state of the dentition and presence of periodontal disease should be recorded in addition.

Conclusion

Dental injury under anaesthesia is a common area for complaint against anaesthetists. A thorough preoperative dental assessment with explanation of risk is essential, particularly in individuals in whom severe periodontal disease is identified. These individuals may also be at increased risk of cardiovascular disease. Prompt recognition and treatment in the event of dental injury can improve tooth survival.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Paediatric total intravenous anaesthesia

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Key points

- Paediatric total i.v. anaesthesia (TIVA) can facilitate surgery, reduce airway responsiveness, and minimize complications such as postoperative nausea and vomiting and emergence agitation.
- Bolus doses of propofol are largely determined by the volume of distribution, while required infusion rates are predominantly determined by the clearance.
- Manual infusions remain an important option in clinical practice due to variability within and between target-controlled infusion models.
- Adjuvant agents, such as remifentanil and dexmedetomidine, play an important role in minimizing propofol requirements.
- Avoidance of neuromuscular block, and the adjuvant use of processed EEG, is recommended to aid titration and lower the potential risk of awareness.

Total i.v. anaesthesia (TIVA) has been used in adult practice since 1982 with target-controlled infusion (TCI) regimes available since 1989. Conversely, the use of TIVA in paediatric practice is far less routine with a survey finding only 10% of paediatric anaesthetists using it weekly or more.[1] It has previously been the subject of a special edition of the journal *Pediatric Anaesthesia*[2] and the use for paediatric anaesthesia care is an increasing component at international meetings: educational sessions at the European Society for Paediatric Anaesthesia (2013), ASA (2014), and the Society for Intravenous Anaesthesia meeting in November 2015.

Despite a number of obstacles (including interindividual pharmacokinetic and pharmacodynamic variability and safety concerns regarding propofol infusion syndrome—PrIS), there are notable benefits to TIVA and particular areas where it is indicated for anaesthetic or surgical reasons, where it may surpass volatile anaesthesia.[3] It is a mandatory technique when inhalation agents are contraindicated.

Indications (see Table 1)

Advantages and disadvantages

For physiological and clinical[3] reasons (Table 2), TIVA has increasingly established a significant role in surgery in or around the airway (e.g. ENT) by obtunding airway reflexes (Table 2). The changes in airway reactivity facilitate extubation and result in a minimal incidence of laryngospasm and stridor after extubation. It is readily titratable, so that spontaneous ventilation (SV) may be maintained.[4] It does not rely on the airway for delivery or on airway and pulmonary dynamics for anaesthetic maintenance. Therefore, there is no risk of ambient pollution and exposure of surgical and operating theatre staff to volatile anaesthetics when the airway is shared. TIVA has been seen to be beneficial in those with preoperative respiratory symptoms by reducing the frequency of complications.[5]

Emergence delirium (or agitation) (ED/EA) is common, especially subsequent to sevoflurane anaesthesia, and may

precipitate maladaptive behaviour, memory impairment, and problems with subsequent anaesthetic experiences in paediatric practice. Propofol use, at induction and as maintenance of anaesthesia, has been seen to reduce the risk of ED in comparison with sevoflurane.[6]

Prevention of postoperative nausea and vomiting (PONV) with propofol improves patient experience and may avoid associated complications such as dehydration, electrolyte abnormalities, and delayed discharge. The incidence of PONV in children over 3 yr is double that of adults. Propofol reduces early PONV with number needed to treat quoted as 5.53 in adult practice and is therefore felt likely to benefit children over 3 yr old.[7]

With the current concern surrounding the effects of anaesthesia on the developing brain, propofol may exert some neuroprotective effects; animal studies have shown reduced 'hypoxia-mediated increases in lactate dehydrogenase' and increased neurogenesis.[4] The reduced incidence of emergence delirium has been hypothesized to be a result of this neuroprotective effect. This is thought not to be true for the neonatal brain as propofol does cause apoptosis similarly to isoflurane and ketamine in this population in animal studies.[8]

Table 1 Indications for use or consideration of TIVA in paediatric cases

Patient	Malignant hyperthermia history, susceptibility, or risk
	Muscular dystrophy, core myopathy, or neuromuscular disease
	Previous history of PONV or motion sickness
	Risk or previous history of emergence delirium
	History of acute or chronic reactive airways
	Fear of facemask
	Minimization of allergy risk
Surgical	Airway surgery or shared airway procedures
	Requirement for evoked potential monitoring, e.g. scoliosis surgery
	Neurosurgical procedures
	Middle ear surgery
	Procedures with high PONV risk, e.g. strabismus, T&A
Procedural	Remote site anaesthesia, e.g. MRI
	Muscle biopsy for neuromuscular diagnosis

The disadvantages of TIVA in children include practical issues such as pain on injection and others seen in Table 2. If i.v. access, without undue distress, is not possible in the awake child, then a TIVA infusion may still be used for maintenance of anaesthesia subsequent to an inhalational induction once the cannula is placed. Methods of preventing the pain of injection include co-administered lidocaine (0.2–0.5 mg kg^{-1}, common practice), pre-treatment with other agents such as opioids (e.g. 0.5 μg kg^{-1} remifentanil),[9] use of a larger vein, lower initial infusion rates, or alternative propofol formulations with altered lipid content (the addition of lidocaine nullifies the differences between formulations).[7]

Overall cost-effectiveness is difficult to assess with drug costs, disposables, equipment, and patient outcomes all requiring consideration. Propofol and remifentanil have decreased in cost since their introduction and usage is inversely proportional to weight; becoming cheaper in comparison with sevoflurane or desflurane anaesthesia as weight decreases[3] (cost for 60 min: sevoflurane $54.75, TIVA 10 kg patient $2.95, TIVA 20 kg patient $5.91—unpublished hospital data).

There are concerns about awareness when TIVA is used in children, although one study has shown the risk to be lower with TIVA compared with inhalation anaesthesia in paediatric practice.[3] In the recent Fifth National Audit Project, the incidence was higher with TIVA (compared with volatile anaesthesia) in adults, but there was only one paediatric vignette, in a 15 yr old, associated with TCI propofol and neuromuscular block. The risk may be reduced by avoiding neuromuscular block and by using processed EEG (pEEG) monitoring in patients over 2 yr of age or dependent on the monitor available (monitors are not well validated in children and are not valid in infants less than age 2 yr). Caution should be exercised in the light of the recent publication regarding pEEG in awake patients.[10]

Pharmacokinetic and pharmacodynamic variability between paediatric patients,[11, 12] the effect of maturation on propofol metabolism in early life and specific issues in the critically ill, limits use; the extremely variable pharmacokinetics of propofol in neonates and the non-linear changes in both volume of distribution and clearance indicate that it should be used with extreme caution in neonates and ex-premature infants and in the critically ill with organ dysfunction. Caution is also required where vasodilatation would be hazardous, such as in the shocked child or those with certain types of congenital heart disease.

Table 2 Advantages and disadvantages of TIVA in paediatrics[3]

	Advantages		Disadvantages
Clinical	Reduced airway reactivity, laryngospasm and bronchospasm	Clinical	Risk of bacterial contamination
	Improved ciliary function		Pain on injection
	Bronchodilation and preserved hypoxic pulmonary vasoconstriction		Risk of associated metabolic phenomena; PrIS, lactic/metabolic acidosis
	Reduced emergence delirium	Practical	Need for i.v. access and infusion pump(s)
	Reduced PONV		Potential for disconnection, risk of awareness
	Use in neuromuscular disease, core myopathies		Lack of EEG monitoring availability or reliable depth of anaesthesia monitor
Practical	No interference with evoked potential monitoring		No practical, cost-effective point–of-care propofol measurement systems
	Titratable, ease of delivery via pump		
	Maintenance of SV for remote site anaesthesia	Other	Caution in prolonged procedures or obese patients due to long context-sensitive half-life of propofol
Other	No vapour atmospheric pollution		Environmental effect of plastic waste and waste propofol
	Associated with overall reduced costs		Disposables may be costly

Propofol infusion syndrome is a concern with the use of propofol for TIVA; it is associated with high propofol infusion rates (>4 mg kg^{-1} h^{-1}) for a prolonged period (usually >48 h).[7] It has been seen in the sedated intensive care unit population, but there are no reports in healthy children undergoing routine anaesthesia. Care is required in those with defects in lipid metabolism[7] or with metabolic disorders. Restricting duration, using regional or local anaesthesia and using adjunct agents (opiates, α-2-adrenergic agonists), will reduce the propofol requirement and associated potential risk. The use of a 2% propofol preparation can also reduce the lipid load; 1% and 2% solutions have 0.1 g ml^{-1} of lipid, the volume required for the same dose may be halved with the use of 2% preparation. Hospital guidelines suggest a maximum of 3–4 g kg^{-1} day^{-1} of lipid may be given to children on parenteral infusions, greater than the above rate associated with PrIS.

Pharmacology

Propofol and pharmacokinetic modelling in adults has been described recently in this journal.[13] Manual and TCI techniques in children have been described.[14] The differences in propofol pharmacokinetics in children vary with age.

- There is a larger central compartment and volume of distribution; greatest in infants and decreasing with age to adult levels. This requires a higher bolus dose and initial infusion rate.
- There is a greater rate of clearance, peaking at around 1 yr of age. This requires higher maintenance rates.

Manual infusion regimens for children, as seen in Tables 3 and 4, are markedly different when compared with adult regimens. The former, McFarlan and colleagues,[15] based on the Kataria pharmacokinetic data for 3–11 yr olds. The latter, Steur and colleagues,[16] proposed more recently for children under 3 yr of age. These suggestions cannot be applied rigidly to the clinical setting without taking into account other factors such as the level of preoperative anxiety of the child, the desired depth of anaesthesia for the specific surgical stimulus, the use of adjuvants or regional blocks, and, perhaps most importantly, the significant variability between individual children. Initial bolus doses may need to be much higher in toddlers, but then maintenance infusion rates may decrease below those of older children with increased infusion duration. In children, the dose is typically modelled as an allometric relationship (typically to the power of 0.75) between weight and volume of distribution or clearance. Maturation and organ dysfunction are also crucial covariate factors.[17] In the obese population, propofol induction doses are proportional to lean body mass, while maintenance doses are linked to total body weight.[3] Processed EEG feedback may be particularly useful for titration of anaesthesia in this population.

TCI models are commonly used for adults in Europe. Numerous paediatric TCI models have been developed but two are widely available: the Paedfusor and Kataria (Fig. 1). Paedfusor uses age and weight as covariates; it can be used between 5 and 61 kg, and 1–16 yr of age. Kataria can be used from 3 to 16 yr of age and works with a minimum weight of 15 kg.

There is a marked degree of variability both within and between population-based pharmacokinetic models; as much variation may be seen within a model as between models and so they are not generalizable. There is a good concordance with projected Paedfusor infusion rates when using typical simple manual infusion techniques.[18] The context-sensitive half-life in children has been derived to be longer than in adults; 10.4 *vs* 6.7 min after 1 h infusion, 19.6 *vs* 9.5 min after 4 h.[15] This is infrequently clinically significant, but infusion rates can be tapered towards the end of longer cases to avoid prolonged recovery times.

Anaesthetists may titrate infusion rates to traditional clinical signs of depth of anaesthesia, such as vital signs, and use pEEG for titration in lengthier cases or where neuromuscular block is required; titrating to a target and recognizing potential limitations of the monitor.[10] Investigation continues into the 'closed loop' systems where physiological data and pEEG provide feedback directly to infusion pumps with anaesthetic supervision. These systems may lead to less variability in titration of anaesthesia, lower drug requirements, improvement in haemodynamic stability, and more rapid smooth emergence from anaesthesia.[19]

Remifentanil is the ultra-fast-acting titratable opioid that has a unique synergistic effect with propofol and is a valuable adjunct. There is an associated incidence of respiratory depression with its use, but a higher dose is tolerated for SV in children compared with adults; between 0.05 and 0.3 μg kg^{-1} min^{-1}, with younger children maintaining SV more effectively at higher doses. The reduction in respiratory rate can be used as a marker for titration (see airway example), either aiming for a respiratory rate of <15 or a 50% reduction in younger children. Remifentanil can be given as a weight-based infusion or via TCI models; a weight-based infusion has an almost linear relationship between target level and infusion rate. The Rigby-Jones and Davis models are not widely available. The Minto model has a minimum weight of 30 kg, minimum age of 12 yr, and uses height as a covariate. This makes it less practical in a large proportion of the paediatric population.

Propofol and remifentanil can be combined in the same syringe in varying proportions for practicality and ease of delivery depending on the clinical situation (see example); concentrations of 2.5, 5, and 10 μg of remifentanil per millilitre of propofol are infused. They can be weaned or stopped together for emergence. The practice is endorsed by clinicians but not by regulators. The combination of agents is not recommended for patients under 10 kg or where individual agent titration is required (see Example 1).

Table 3 Propofol infusion rate recommendations in children aged 3–11 yr targeting blood concentrations of 3.0 μg ml^{-1}, McFarlan and colleagues[15]

Bolus dose Propofol infusion rates	2.5 mg kg^{-1} μg kg^{-1} min^{-1}	mg kg^{-1} h^{-1}
0–15 min	250	15
15–30 min	215	13
30–60 min	185	11
1–2 h	165	10
2–4 h	150	9

Table 4 Steur recommendation for propofol dosing in under 3 yr.[16] Doses in mg kg^{-1} h^{-1}

Time	0–10 min	10–20 min	20–30 min	30–40 min	40–100 min	Remaining time
<3 months	25	20	15	10	5	2.5
3–6 months	20	15	10	5	5	2.5
6–12 months	15	10	5	5	5	2.5
1–3 yr	12	9	6	6	6	6

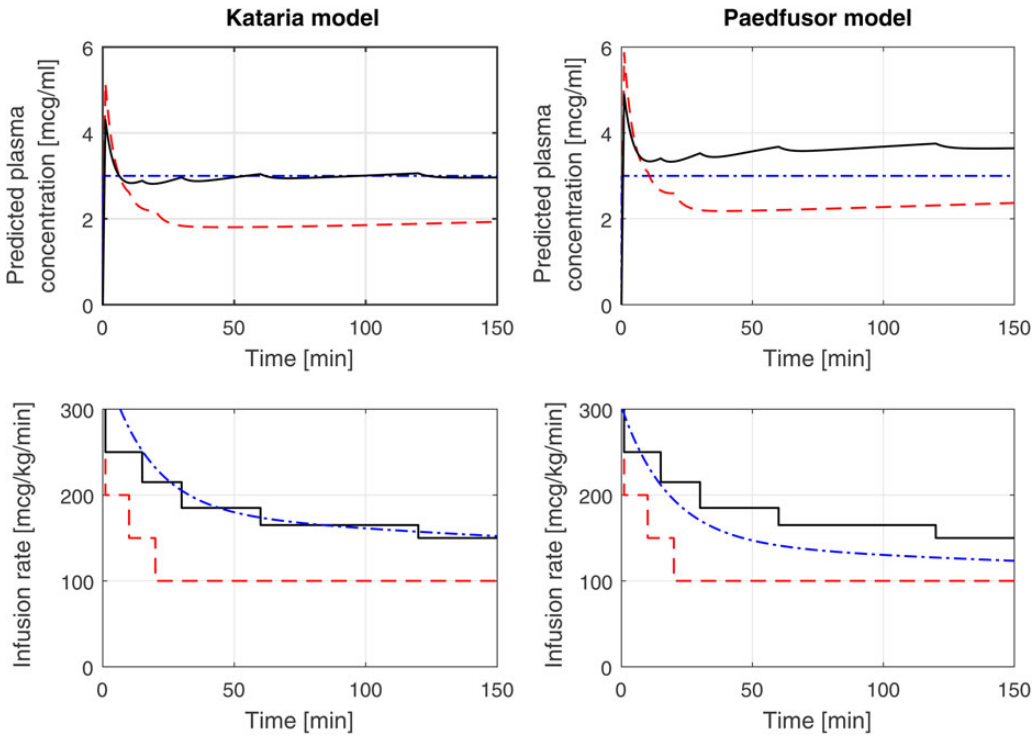

Fig 1 Modelled plasma concentrations and infusion rates for a 3 year old weighing 18 kg targeting 3 mcg/ml; using the Kataria model (left, blue) and Paedfusor model (right, blue) in comparison to manual Mcfarlan (black) and Steur (red) schemes.

Other adjuvants to consider utilizing are the α-2-adrenergic agonists, clonidine or dexmedetomidine, depending on availability. These agents have been seen to add further analgesic, sedative, and anxiolytic properties. Dexmedetomidine is around 8 times more selective but is not licensed anywhere for use in the paediatric population. Despite this, it is in increasing use and has been found to be a valuable adjunct at this centre in reducing propofol and remifentanil requirements and also further enhancing the quality of recovery.[3]

Newer agents such as fospropofol and other propofol, etomidate, and midazolam-related compounds are in development; PF0713 and AZD3043, MOC-etomidate, carboetomidate, remimazolam (CNS7056), and JM-1232.[3]

Clinical examples

(1) Airway surgery (maintaining SV and avoiding an airway device)

Coordination and communication with the surgeon is required regarding the anticipated surgical plan and the use of a ventilating laryngoscope/bronchoscope. The aim is to achieve an appropriate depth of anaesthesia with SV and the avoidance of an airway device to distort the airway or increase the risk of fire

Attach the monitoring, including a pEEG monitor. Proceed with inhalation or i.v. induction followed by separate propofol and remifentanil infusions. Titrate propofol boluses to maintain SV and then 200–400 μg kg^{-1} min^{-1} titrated against a target pEEG index of 30–40

Use remifentanil 0.2–0.3 μg kg^{-1} min^{-1} (less with increasing age) titrated to target a respiratory rate at the low end of normal for the age of the child; beware of marked tidal volume variation as this may indicate imminent apnoea. The margin between an awake and an apnoeic patient becomes narrower with age. The addition of 0.5–1 μg kg^{-1} bolus of dexmedetomidine widens this margin

Adequate topical anaesthesia of the airway is vitally important. Coordinate handover of the airway to the surgeons and provide continuing oxygenation supplementation to the spontaneously breathing patient. Minimize oxygen levels based on S p_{O_2} if laser is being used. Transcutaneous CO2 monitoring is useful if available. An accessory monitor of respiratory rate, such as a hand on the abdomen or ECG impedance, can be very useful

(2) Anaesthesia for an MRI scan

Aiming for settled conditions for MRI with a well-maintained airway and SV

Routine pre-assessment with standard monitoring attached as tolerated. I.V. cannula placement with cooperation of the parent if present. Subsequent slow, titrated i.v. induction with propofol 2–3 mg kg^{-1} (with lidocaine 0.5 mg kg^{-1}) aiming to maintain SV. Gas induction if i.v. access not possible. The use of nasal cannulae providing oxygen with carbon dioxide sampling. Attach complete monitoring if not already present. Stop sevoflurane if used. Commence propofol 1%, with 2.5 μg ml^{-1} remifentanil added, initially at 180 μg kg^{-1} min^{-1} but titrated down in response to respiratory rate

Top tips

- Patient, parent, and support staff preparation is invaluable in achieving i.v. access awake while avoiding distress to the patient or family. Distraction techniques and assistants may facilitate this.

- Similar precautions as in adults should be used;[20] reliable access, visible infusions or concurrent fluid infusion, anti-reflux valves. Infusion line dead-space should be especially minimized in children.
- To avoid pain on induction: lidocaine (before or mixed with propofol) may be administered, the rate of induction can be slowed, or use of opioid analgesia.
- Propofol alone will not provide good surgical conditions. The use of an opioid, with or without other adjuncts (e.g. dexmedetomidine), or good regional blockade will limit the required dose of propofol and improve surgical conditions.
- The use of an inhalation induction is not a contra-indication to TIVA use: techniques of conversion after inhalation induction include slower loading dose administration or starting TCI at a lower target and slowly increasing it. Beware the potential for severe bradycardia associated with administration of remifentanil after inhalational induction when there is significant residual sevoflurane present.
- Be cautious in the critically ill, or shocked, patient and those with congenital heart disease, metabolic disorders, or abnormal lipid metabolism.
- Processed EEG monitoring is a useful adjunct to aid titration of TIVA, especially for lengthy procedures and where neuromuscular block is indicated. Continue using clinical judgement and do not rely only on the infusion pump.

Conclusion

TIVA in paediatrics is an accessible technique with published advantages for the patient in terms of facilitating specific surgical procedures, optimizing surgical conditions, and reducing postoperative complications. It has previously been infrequently used, but in order to gain the benefits, it may be advantageous to develop expertise as part of paediatric anaesthetic practice. Familiarity with the technique is required when inhalational agents are contraindicated.

There is no single method for using TIVA in paediatrics. A variety of techniques can be seen in the literature and have been described at international meetings. What is safe and practical in different centres with different anaesthetists can be derived from these examples. We hope this provides a starting point for the development of individual practice with the 'top tips' and safety issues taken into account.

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Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Challenges, solutions, and advances in ultrasound-guided regional anaesthesia

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Key points

- Challenges to successful ultrasound-guided regional anaesthesia include the acquisition of acceptable ultrasound images of the nerve while avoiding artifacts.
- The most common ultrasound artifacts are acoustic or anatomic.
- Physiological and pathological factors attributable to the patient affect image quality and interpretation.
- Needle artifacts may cause confusion and error during ultrasound-guided nerve blocks.
- The combination of ultrasound guidance and peripheral nerve stimulation, 'dual guidance', may offer reassurance when the nerve or needle image is suboptimal.

Ultrasonography offers significant advantages in the practice of regional anaesthesia, including faster sensory onset and improved success rates compared with landmark-based techniques.[1] Adequate visualization of neural and surrounding structures together with monitoring the spread of local anaesthetic (LA) are absolute prerequisites for the safe and successful practice of ultrasound-guided regional anaesthesia (USGRA). The creation of an ultrasound (US) image is based on the physical properties of the US beam formation, propagation of sound in matter, interaction of sound with reflective interfaces, echo detection, and machine processing. However, there are often a number of significant challenges to acquiring the optimal US images necessary to achieve successful nerve blocks. Such challenges include the acquisition and interpretation of optimal US images of the target structure and needle while avoiding tissue and needle artifacts. Other difficulties may include physiological, pathological, and anatomical factors attributable to the patient and which may affect image quality and interpretation. This article will describe some of these problems, discuss strategies to avoid them, and highlight current and future advances which may assist the practice of USGRA.

Challenges presented by the ultrasound machine

The spatial resolution of any imaging system is defined as its ability to distinguish two points as separate entities in space. Spatial resolution is commonly subcategorized into axial and lateral resolution.[2] Axial resolution is defined as the US machine's ability to differentiate two objects located at different depths in the direction parallel to the direction of the US beam. If the distance between two objects is greater than half the length of the US pulse then the two objects will be distinguished. Axial resolution can be improved by increasing the US pulse frequency and reducing the pulse length. High-frequency transducers having shorter pulse lengths will therefore provide optimal axial resolution but is limited to superficial structures. When viewing deeper structures, the operator should chose a transducer with the highest frequency which permits adequate tissue penetration of the US beam.

Lateral resolution refers to the ability of the US machine to differentiate two objects which are adjacent to each other, e.g. the tibial and common peroneal nerves in the popliteal fossa. The width of the US beam and depth of imaging both influence lateral

resolution.[2] All US beams typically diverge at greater depth, while wider beams diverge further in the far field. Therefore, lateral resolution is best at shallow depths and worse with deeper imaging. Lateral resolution is improved by positioning the focal zone, the narrowest part of the US beam, at the level of the target object.

Temporal resolution refers to the US machine frame rate which is the speed at which an imaging device produces consecutive images and is important in real-time imaging during USGRA.[3] The rate at which consecutive image frames are generated and viewed affects the visualization of moving structures. A low frame rate may obscure motion during a procedure including probe movement, needle insertion, and the placement of LA during USGRA. Temporal resolution is influenced by the speed of sound in tissue and may be improved by decreasing the imaging depth to just below the target and minimizing tissue movement by the slow injection of LA.

Table 1 Errors associated with ultrasound artifacts

Artifact	Error
Acoustic	Presentation of ultrasound information
Anatomic or pitfall	Interpretation
Optical illusion	Perception
Other	Electrical noise

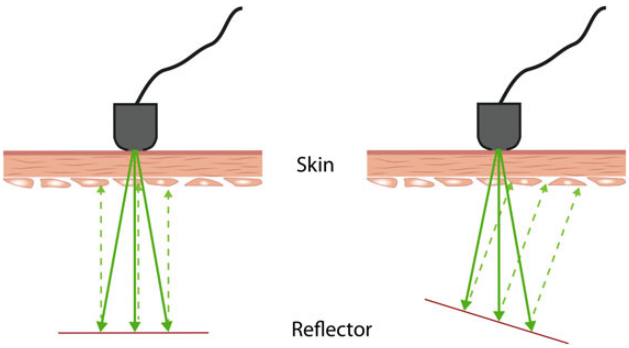


Fig 1 Angle of insonation. When the ultrasound beam is perpendicular to the reflector, the ultrasound beam is returned to the transducer. When the angle of insonation is reduced, the ultrasound beam is reflected away from the transducer and the view of the target is suboptimal.

Challenges presented by the ultrasound image

Artifacts are presentations on the display which are added or omitted, or are of improper location, brightness, shape, and size compared with the true anatomical features. Some artifacts are useful in interpretation, while others may cause confusion and error. A good understanding of artifacts, why they arise and how to deal with them when they occur, is important in the practice of USGRA. Failure to recognize imaging artifacts may lead to complications, including incorrect needle placement or deposition of LA in the wrong location or hazardous areas. Artifacts are commonly observed during ultrasound-guided nerve blocks and may be related either to the tissues, the block needle, or both (Table 1). The most common artifacts observed during USGRA are either acoustic or anatomic.

Acoustic artifacts

Acoustic artifacts are usually the result of incorrect assumptions during processing by the instrumentation. These assumptions include sound travels in straight lines; the intensity of returning echoes is directly related to scatter from the imaged object and distance of structures on the image is directly proportional to the time taken for the sound wave to return to the transducer. Some acoustic artifacts are also secondary to operator error, including improper transducer placement or scanning technique. A common operator error is a suboptimal angle of insonation resulting in a significant portion of the returning US beam being transmitted away from the transducer producing a degraded image (Fig. 1). As the incident angle of the US beam to the nerve approaches 90°, the target image becomes optimal. This artifact can be reduced by sweeping the transducer through an arc to determine the position of the transducer which provides the best available image of the target nerve. Classification of common acoustic artifacts together with their origins and imaging errors are listed in Table 2.

Acoustic errors may also be subdivided into missing or falsely perceived structures and are often due to errors in gain setting. Gain refers to the degree of amplification applied to all US signals returning to the transducer. Too high a gain will make the image too bright and obscure structures, while too little gain will darken the image and may make a structure appear absent. This artifact is avoided by adjusting the gain setting to permit an optimal view of the target nerve and surrounding tissues. Attenuation is the progressive loss of acoustic energy and signal strength as the US wave passes through tissue. Attenuation can be reduced by increasing the overall gain control and image brightness. Time gain

Table 2 Ultrasound artifacts and their origins

Acoustic artifact group	Origin	Artifact
Attenuation	Reduced amplitude of echoes by intervening structures with high attenuation	Shadowing
	Increased relative amplitude of echoes caused by an intervening structure of low attenuation	Enhancement
Resolution	Pulse frequency	Axial resolution
	Beam divergence	Lateral resolution
	Interference patterns from echoes generated by closely spaced reflectors	Speckle
Propagation path	Sound pulse reverberates back and forth between two strong parallel reflectors	Reverberation
	Change in direction of a sound pulse when it crosses a boundary and when a change of speed of sound occurs	Refraction
	Reflection of the sound pulse from a highly reflective surface	Mirror image
	Side beams from the transducer cause objects to be viewed in a lateral location	Side lobe
Miscellaneous	Two closely spaced reflective surfaces and generated echoes with a conical shape	Comet tail

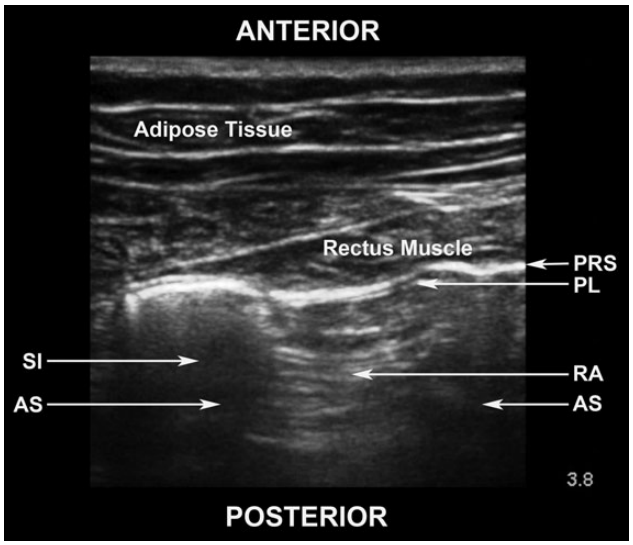


Fig 2 Reverberation artifact and acoustic shadowing. AS, acoustic shadowing; PL, peritoneal layer; PRS, posterior layer of rectus sheath; RA, reverberation artifact; SI, small intestine.

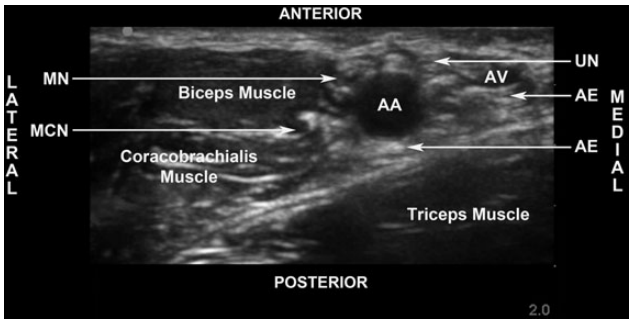


Fig 3 Acoustic enhancement. AA, axillary artery; AE, acoustic enhancement; AV, axillary vein; MCN, musculocutaneous nerve; MN, median nerve; UN, ulnar nerve.

compensation (TGC) is a setting applied in ultrasonography to account for tissue attenuation of the US beam. TGC independently increases the gain of reflected signals with increasing time from the transmitted pulse and is equivalent to increasing the gain of a reflected US signal with increasing tissue depth.

Acoustic shadowing may also cause structures to appear less echogenic and occurs when a target lies below a structure which strongly absorbs or reflects US waves. Air and bone are common causes of acoustic shadowing during USGRA and may be avoided by changing the transducer position (Fig. 2).

Acoustic enhancement occurs when an area behind a weakly attenuating structure produces stronger echoes than the surrounding structures. This artifact commonly occurs behind blood vessels and may lead to confusion with neural structures lying posterior to arteries and veins. This is particularly important when scanning the axilla where the radial nerve lies behind the axillary artery and may be confused with acoustic enhancement artifact (Fig. 3). In such instances, the use of a nerve stimulator may be helpful to confirm the presence or absence of the radial nerve.

Image degradation is often the result of reverberation which results from US waves reflecting off two strong reflectors, for example, the pleura, peritoneum, or a fascial plane. The image

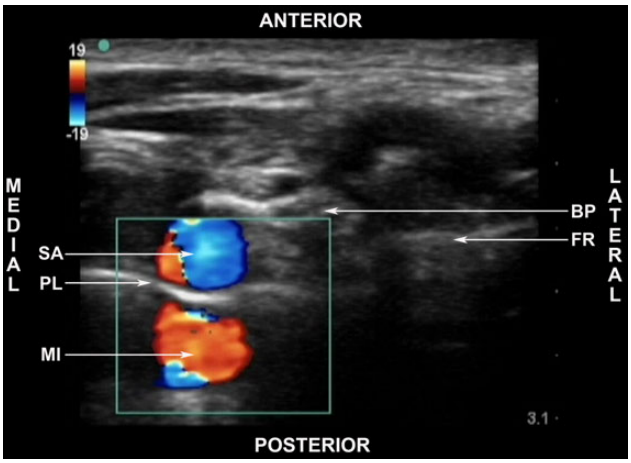


Fig 4 Mirror artifact. BP, brachial plexus; FR, first rib; PL, pleura; MI, mirror image; SA, subclavian artery.

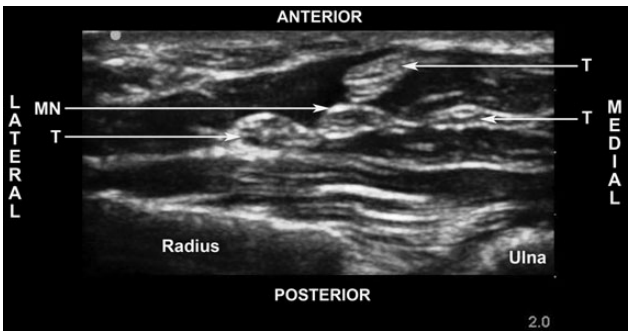


Fig 5 Tendons and nerves. MN, median nerve; T, tendon.

shows multiple linear and hyperechoic areas distal to the reflecting surface (Fig. 2). The comet tail sign refers to the mergence of multiple reverberation artifacts in a tapered band adjacent to the object.[4] Increasing the pressure of the probe on the skin may eliminate the reverberation artifact. The 'double-barrelled subclavian artery' is also an example of a reverberation artifact (Fig. 4). This results from the US beam bouncing within the lumen of the subclavian artery and creating a mirror image of the subclavian artery deep to the first rib. It is important to recognize that the image of the subclavian artery under the first rib is an artifact and attempted needle insertion towards this point may lead to a pneumothorax.

Anatomic or pitfall error

Anatomic artifacts are tissue structures which resemble the target nerve. These errors are also referred to as 'pitfall errors'. Tendons and nerves may be difficult to distinguish by ultrasonography (Fig. 5). This is a particular problem in the wrist, but tracking structures proximally often assist in differentiating the two structures since tendons will integrate within their respective muscles. Blood vessels are not normally mistaken for nerves. Arteries are anechoic and pulsatile, while veins are compressible. Nerves are usually hyperechoic (echo bright) or hypoechoic (echo dark) and non-compressible. However, the roots of the brachial plexus may sometimes appear similar to a small diameter vessels. Colour Doppler is useful in identifying vascular structures but may be misleading if the transducer is placed perpendicular

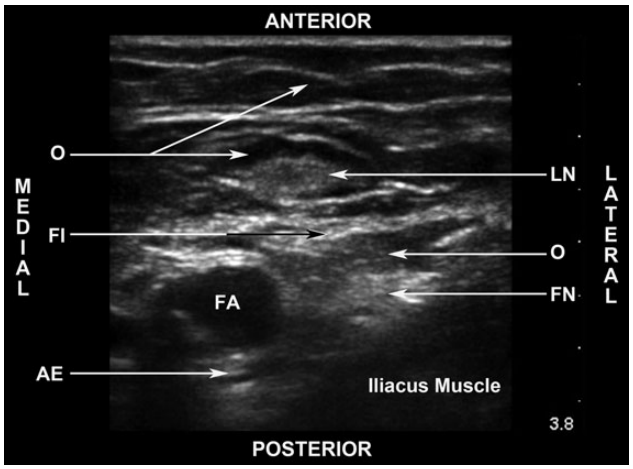


Fig 6 Tissue oedema. AE, acoustic enhancement; FA, femoral artery; FI, fascia iliaca; FN, femoral nerve; LN, lymph node; O, oedema.

to the blood vessels and detection of blood flow is suboptimal. Flow detection is best when the transducer is aligned in the direction of blood flow.

Inflamed lymph nodes may also be mistaken for nerves, but the former are often well circumscribed, non-compressible anechoic structures with small, hypoechoic internal features (Fig. 6). Additionally, a nerve stimulator will differentiate between a lymph node and motor nerve.

Optical illusion

Illusions may be categorized as illusions of sensation, perception, and image formation.[5] They represent alterations in the appearance of reality due to the process of image formation and may result in misinterpretation.

Random noise

Noise degrades the quality of an US image and often appears as low-amplitude echoes in echolucent areas. The origins of random noise are extensive and often include excessive gain and other changes in machine settings. A common source of noise in the operating theatre is electrocautery. Ultrasound machines are often fitted with filters to limit the amount of electrical interference.

Challenges presented by the patient

Obesity

Obesity is a rapidly growing pandemic disease and regional anaesthesia offers many potential advantages to the obese patient. Airway manipulation and cardiopulmonary depression are avoided, while postoperative pain control is improved. However, peripheral and centroneuroaxis nerve block may be technically difficult in the obese patient. While US guidance has revolutionized the practice of regional anaesthesia, it has several limitations, particularly in the obese patient. Neural structures are more deeply situated in obese patients and the US beam is highly attenuated as it travels a greater distance through the tissue layers. Sound attenuation in adipose tissue is defined as the product of the attenuation coefficient (decibels per centimetre at 1 MHz), the transducer frequency (MHz), and thickness of the adipose tissue (cm).[6] Adipose tissue is also associated with phased aberration of the US beam due to the uneven speed of sound within the irregularly shaped layers of adipose tissue.[7] Whenever an US beam crosses a tissue boundary, a portion of the sound energy is reflected back to the transducer creating more echoes and further artifacts including speckling and clutter which are particular problems in the obese patient. Speckling artifact refers to interference patterns from echoes generated by closely spaced reflectors and which are too small to resolve.[8] The resulting US image appears to have a granular structure which obscures the underlying anatomy. Clutter artifact appears as a diffuse haze in hypoechoic areas overlying areas of interest and degrading image quality.[9] Sources of acoustic clutter include sound reverberation in tissue layers, US beam distortion, and random acoustic noise. Consequently, the acquired US image in obese patients is often suboptimal.

US imaging in obese patients may be improved by using a lower frequency transducer, while the US machine should be set to 'penetrate' to enable greater depth penetration of the US beam at the lower frequency. Signal attenuation is reduced and more of the primary beam penetrates the subcutaneous adipose tissue. The needle should be aligned as parallel as possible to the probe by carefully choosing the entry site and by tilting the far end of the probe down ('heel in' manoeuvre). Harmonic imaging is a technique in ultrasonography which provides images of better quality by exploiting non-linear propagation of US through body tissues.[10] Distortion of the US beam leads to the generation of harmonics, multiples of the transmitted US frequency. These harmonic waves which are generated within the tissue increase with increasing depth. Near field clutter is reduced and resolution increased, thus improving image quality. Spatial compound imaging which combines overlapping image frames from different US beam angles to form a single real-time image may also assist in reducing artifacts.[8] Other processing filters including speckle reduction may also improve image quality.

Oedema

Tissue oedema offers a number of challenges during ultrasound-guided nerve blocks. Diffuse oedema may amplify sound absorption and decrease the echo contrast that normally exists between nerves and the surrounding tissues (Fig. 6). Oedema may also compress or displace neural structures changing its anatomic position or shape.

Tissue oedema is a particular problem in the ankle and may obscure the anatomy and make identification of neural structures and the observation of LA spread particularly difficult. In extreme cases, it is often necessary to choose a more proximal area where tissue oedema is less prevalent to permit effective and safe execution of the ultrasound-guided nerve block.

Air

Air forms an impenetrable barrier to sound and casts a shadowing artifact (Fig. 2). Image quality is degraded and underlying structures obscured. Air may be present secondary to a pathological process including subcutaneous emphysema but may also be due to air injection during the ultrasound-guided procedure. The presence of microbubbles in an injectate may degrade an image by reflecting the US beam, thus obscuring the target and surrounding structures (Fig. 7; Online video 1). Care should be taken to remove air bubbles before undertaking the procedure and to minimize the number of syringe changes. Additionally, pre-warmed LA may assist in reducing microbubble formation.

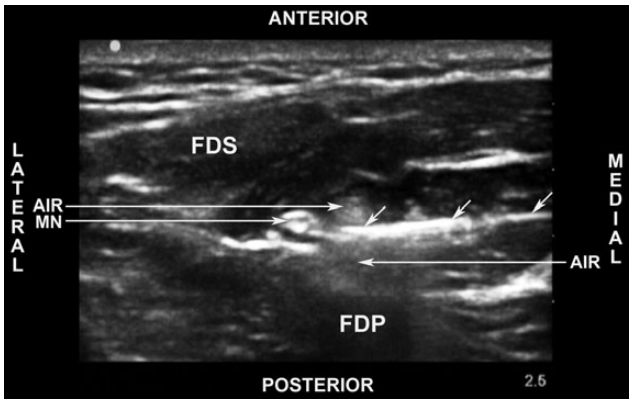
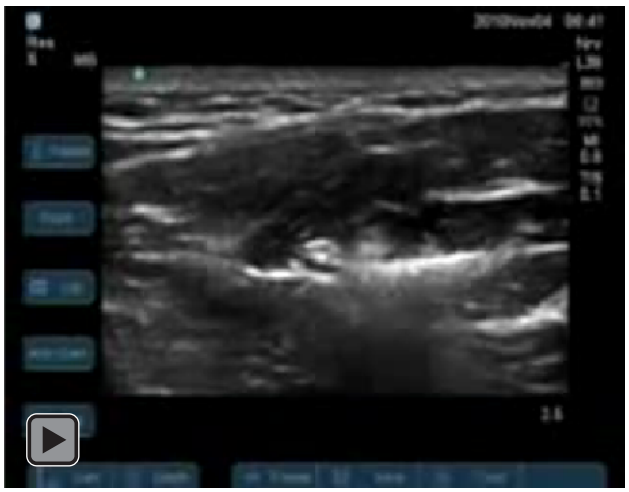


Fig 7 Degradation of the ultrasound image by injected air. Air within reflects the ultrasound beam and degrades the view of the median nerve and needle tip. FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis; MN, median nerve. The small unlabelled arrows indicate the block needle.



Video 1 If reading the pdf online, click on the image to view the video.

Muscle atrophy

Muscle atrophy due to chronic myositis and muscle degeneration in the elderly is commonly observed during USGRA. The atrophied muscles reflect the US beam and are shown as hyperechoic structures. Failure of the US beam to adequately penetrate atrophied muscle obscures deeper structures. In such circumstances, it is often unsafe to proceed and an alternative location for the ultrasound-guided nerve block should be chosen.

Anatomical abnormalities

The observation of anatomical anomalies is not uncommon during USGRA and is important to recognize. The musculocutaneous nerve is absent in 1.4–6% of the population in whom branches originate either from a common trunk arising from the median nerve or directly from the median nerve itself (Fig. 8; Online video 2).[11] However, the majority of anatomical abnormalities in the upper limb are related to vascular anomalies which may impact on the practice of USGRA as blood vessels are often used as landmarks for peripheral nerve blocks. Anatomical variation of the brachial artery may be observed in up to 25% of the population and includes high proximal division into the terminal branches.[12] The brachial artery is often used as a landmark for the median nerve block at the elbow, but this advantage is

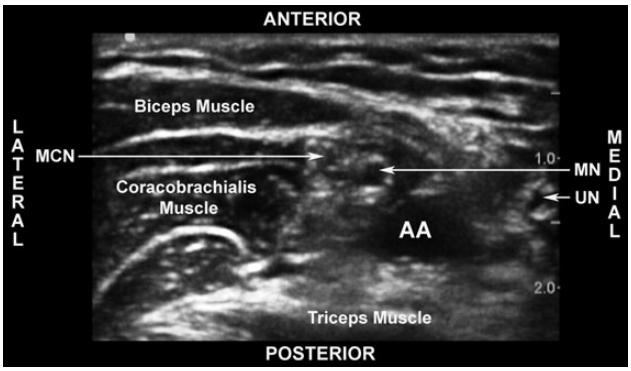
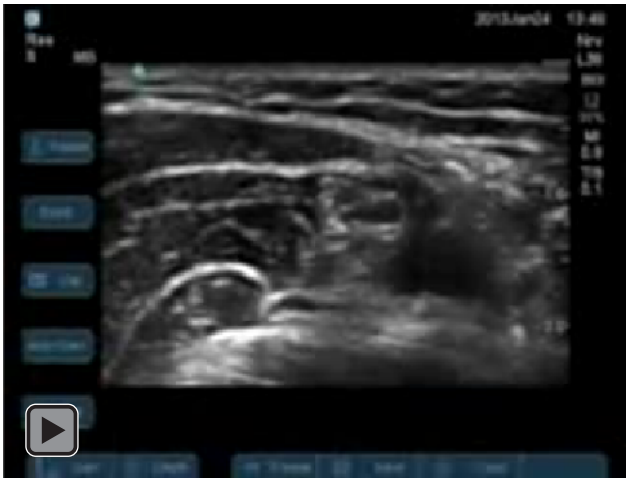


Fig 8 Fusion of the median and musculocutaneous nerves. The median and musculocutaneous nerves are fused proximally in the axilla and separate distally in the arm. AA, axillary artery; MCN, musculocutaneous nerve; MN, median nerve; UN, ulnar nerve.



Video 2 If reading the pdf online, click on the image to view the video.

lost if the brachial artery has already divided. Other anatomic variants include the persistent median artery and veins which accompany the median nerve in the forearm in ~19% and 6% of patients, respectively.[13] These vessels normally evolute and are not often noted in the adult population. When present, the needle should approach the nerve on its non-vascular aspect to avoid inadvertent vessel puncture. Another common anatomical anomaly is the superficial ulnar artery (SUA) and may be observed in up to 10% of individuals.[14] While the ulnar artery usually accompanies the ulnar nerve (UN) in the distal forearm, the SUA lies superficial to the flexor muscles throughout its course and is an unreliable landmark for identification of the UN which may be difficult to distinguish from surrounding tendons. In this instance, the use of a peripheral nerve stimulator is advantageous before the deposition of LA.

Challenges presented by the block needle

Real-time assessment of needle position is vital during USGRA. However, observation of the regional block needle and needle tip can also pose challenges during the practice of USGRA. Needles are strong reflectors of the US beam and are subject to reverberation artifacts evident as multiple linear densities behind the needle and which occur due to US waves bouncing back and forth within the lumen of the needle (Fig. 9). It is

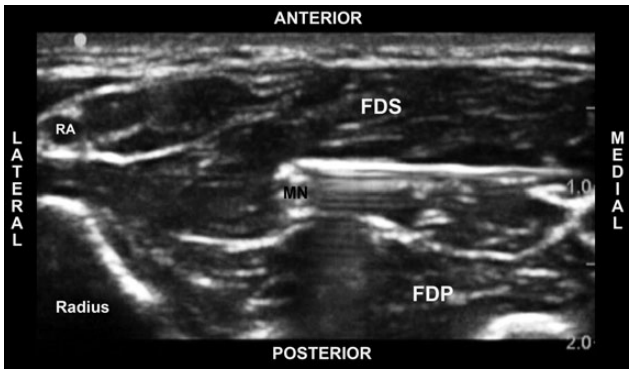


Fig 9 Needle artifacts: bayonet and reverberation. FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis; MN, median nerve; RA, radial artery.

important to note that the true needle image is the one nearest the transducer. Such artifacts most commonly occur when the needle is completely perpendicular to the US beam and can therefore be reduced by decreasing the angle of the US beam to <90°. In addition, a reduction in far gain will darken the distal artifacts.

A mirror artifact is a type of reverberation artifact and is produced when an object is located in front of a strong US reflector, e.g. needles and bone. A second representation of the needle is observed in an incorrect location behind the strong reflector and may cause confusion. It is important to note that the true needle image is the one nearest the transducer.

Another common needle artifact is the bayonet artifact in which the needle appears broken or bent (Fig. 9). This artifact occurs because of differences in the speed of sound in different tissues which are adjacent to the needle. The speed of sound is reduced in adipose tissue compared with muscle and takes longer to return to the transducer. Therefore, a needle placed in adipose tissue will appear to be deeper than that part of the needle which is in muscle.

The side lobe artifact is often seen during USGRA and may cause confusion in image interpretation.[15] Several low-intensity beams, side lobes, are often located peripheral to the main axis of an US beam. Although they are of a much lower intensity than the main beam, these peripheral beams are sufficiently high to create significant artifacts when they interact with highly reflective acoustic surfaces, including a metallic needle path. In contrast, other US artifacts, the side lobe artifact is visible anterior to the true needle path. The artifact is divergent and diffuse while the needle tip projected beyond the true needle pathway. The side lobe artifact is a particular problem with but not unique to linear transducers and can be observed with both static and real-time equipment. The artifact is minimized by careful repositioning of the US transducer.

Improving needle visibility

Maintaining optimal needle visibility during the ultrasound-guided nerve block remains a significant challenge even to experienced practitioners. Needle-beam alignment may be improved by the use of a mechanical guide attached to the transducer, but needle realignment may be restricted and the freehand technique is often preferred. Needle visibility may be improved by using needle with a larger diameter but at the expense of increased tissue damage and patient discomfort. Needle tip and shaft visibility is improved by keeping the needle shaft at more than 55° to the US beam while keeping the needle tip at 0 or 180° to the US beam. Priming the needle with air or fluid does not improve needle echogenicity.

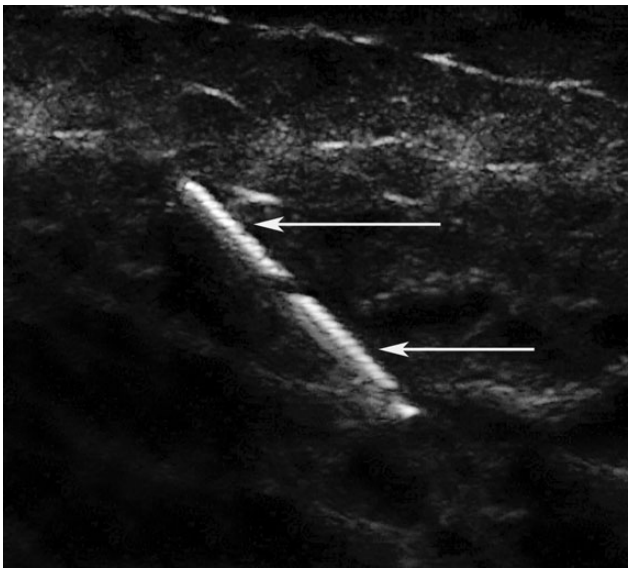


Fig 10 An echogenic needle. The arrow indicates cornerstone technology. Image reproduced with permission from Pajunk GmbH Medizintechnologie.

Combined neurostimulation and ultrasound guidance

The parallel contribution of US guidance and peripheral nerve stimulation (PNS) or 'dual guidance' may offer versatility and reassurance when localizing nerves. Although ultrasonography has the advantages of real-time imaging of nerves and monitoring the spread of LA, it also encourages multiple injections and needle realignments during ultrasound-guided nerve block. However, PNS also has some disadvantages including a reliance on eliciting a motor response which may be affected by numerous factors, including disease processes. Failed nerve block in the presence of an adequate motor response is not uncommon and may be due to the presence of fascial planes inhibiting the spread of LA and delivery of asymmetric current from the needle tip. PNS combined with ultrasonography is useful for identifying neural structures when there is doubt about the sonoanatomy and as a warning system when there is uncertainty about the position of the needle tip. Dual guidance may also be useful as an aid when learning USGRA. However, it is sometimes difficult to distinguish between intra- and extra-fascicular injection by current resolution. Triple monitoring (US, PNS, and measurement of injection pressure) has been proposed as the standard to minimize nerve injury.[16]

New technology and future directions

US technology continues to advance. Recent advances have included additions to both needle and machine technology. Advances in needle technology to improve the reflective signal have included dimpling, roughing, scoring, and the application of a polymeric coating to the needle with the aim of increasing the return of the US signal to the transducer (Fig. 10).[17] These needles may improve needle tip visibility when the insonation angle is steep but are of limited value in superficial ultrasound-guided blocks. Needles with piezoelectric polymer sensors at the tip

have also been designed. Other approaches to improving needle visibility include beam steering technology and the use of proprietary software algorithms within the US machine software to adjust the needle-beam angle to 90°. Ultrasound characterization of tissue elasticity or elastography offers the ability to distinguish key anatomical features and differentiate between neural and extraneural tissue.[18]

In recent years, technology has improved enormously in areas such as transducer sensitivity, beam formation, image processing, and final data display. Three-dimensional US offers several advantages over two-dimensional views. Multiple planes of view can be visualized providing information about the spatial relationship between structures and tracking of LA spread. However, the technology is currently limited by a slower frame rate and reduced image quality while needle visibility is not enhanced. Other recent advances include the use of metamaterials which permit US to pass through tissues with a high acoustic index including bone.[19] Machine recognition and automated nerve block systems may also prove useful for enhancing the accuracy of identification of peripheral nerves.

Online videos

The videos associated with this article can all be viewed from the article in *BJA Education* online.

Declaration of interest

None declared

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Autonomic nervous system: anatomy, physiology, and relevance in anaesthesia and critical care medicine

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Key points

- The autonomic nervous system (ANS) regulates involuntary functions. Anaesthesia, surgery, and critical illness lead to a varied degree of physiological stress that alters the ANS.
- The organization of ANS is on the basis of the reflex arc and it has an afferent limb, efferent limb, and a central integrating system.
- Neurotransmitters and receptors are an integral part of the ANS.
- Autonomic neuropathy refers to damage to the autonomic nerves and diabetes mellitus is the most common cause.
- Autonomic neuropathy involves a number of organs and has serious clinical consequences in the perioperative period and during their management in the critical care unit.

The autonomic nervous system (ANS) is the part of the nervous system that regulates involuntary functions.[1] Examples are the heartbeat, the digestive functions of the intestines, control of respiration, and secretion by glands.

Basic anatomy and physiology

The organization of the ANS is on the basis of the reflex arc and it has an afferent limb, efferent limb, and a central integrating system.[1]

Afferent limb

The afferent limb transmits information from the periphery to the central nervous system (CNS). The receptors are present in the abdominal and thoracic viscera.[1] The transmissions from these receptors are conducted along neural pathways into the spinal cord via the dorsal root ganglion or to the brain stem via cranial nerves. Baroreceptors and chemoreceptors are examples of the afferent pathway. These are present in the aortic arch and carotid sinus. The sensory impulses from these receptors are transmitted via glossopharyngeal and vagus nerves to the brain stem.

Efferent limb

The efferent limb is made up of preganglionic and post-ganglionic fibres and an autonomic ganglion. The efferent limb is further subdivided based on its anatomic and physiological differences into sympathetic and parasympathetic components. A useful generalization is that the sympathetic system responds for 'flight-or-fight' and prepares the body for such a response by increasing the heart rate, arterial pressure, blood flow to the skeletal muscles, heart, and brain.[1] The parasympathetic system prepares the body for 'rest and digest' by depressing the central venous system and increasing the activity of the abdominal viscera.[1]

Central integration

Simple reflexes are completed within the organ system involved. More complex reflexes are regulated by higher autonomic centres present in the CNS, mainly the hypothalamus and the brain stem.[1]

Structure of the ANS

Preganglionic fibres of both the sympathetic and parasympathetic system are myelinated, whereas the post-ganglionic fibres are

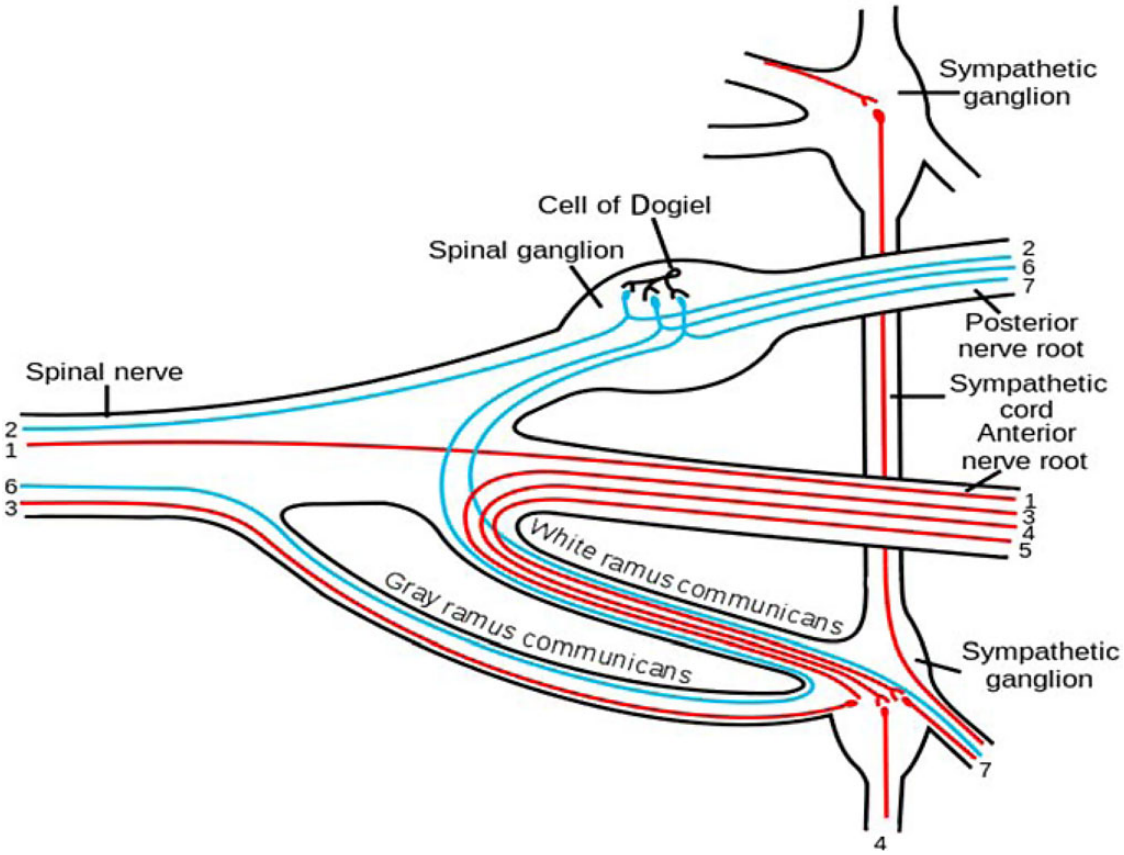

Fig 1 Sympathetic nervous system anatomy at the spinal cord level. 1, Somatic efferent; 2, somatic afferent; 3–5, sympathetic efferent; 6 and 7, sympathetic afferent. This image is from the 20th US edition of *Gray's Anatomy of the Human Body* and is in the public domain.

unmyelinated. Both the divisions of the ANS innervate most of the organs in the body, usually with opposing effects. The effects may also be parallel as seen in the salivary glands.

Sympathetic nervous system

Preganglionic fibres originate from cell bodies in the grey matter of the lateral horn of the spinal cord between the first thoracic segment down to the second or third lumbar segment (T1 to L2/3). The so-called 'thoraco-lumbar' outflow.[2] These preganglionic fibres synapse with the post-ganglionic neurones in the ganglia of the sympathetic chain (Fig. 1). The ganglia form the sympathetic chain arranged as two paravertebral chains. The post-ganglionic fibres leave the ganglia and join the spinal nerves or visceral nerves to innervate the target organs.[1]

The paravertebral sympathetic chain[2]

The paravertebral sympathetic chain is divided into four parts.

(i) *A cervical part*: consists of three ganglia (superior, middle, and inferior) supplying the head, neck, and thorax. The inferior cervical ganglion fuses with the first thoracic ganglion to form the stellate ganglion.
(ii) *A thoracic part*: consists of series of ganglia from each thoracic segment. T1–T5 branches supply the aortic, cardiac, and pulmonary plexus.
(iii) *Lumbar part*: situated in front of the lumbar vertebral column as the prevertebral ganglia. Branches from the lumbar part form the coeliac plexus.

Table 1 Neurotransmitters and receptors of the ANS

ANS efferent pathway	
Preganglionic cholinergic fibres	
Release acetylcholine	
Ganglia	
Acetylcholine nicotinic receptors	
Sympathetic nervous system	Parasympathetic nervous system
Post-ganglionic adrenergic fibres	Post-ganglionic cholinergic fibres
Release predominantly norepinephrine	Release acetylcholine
Release acetylcholine at sweat glands, piloerector muscles of the hairs, and few blood vessels	
Adrenergic receptors	Acetylcholine (Ach) receptors
α1, α2, β1, β2, β3	Muscarinic receptors
	Nicotinic receptors

(iv) *Pelvic part*: lies in front of the sacrum and consists of the sacral ganglia.

Parasympathetic nervous system

Preganglionic fibres arise from the CNS from both the cranial (from brain stem) and sacral nerves called 'craniosacral' outflow. Cranial parasympathetic fibres arise from brainstem motor nuclei of the 3rd, 7th, 9th, and 10th cranial nerves. Sacral outflow arises from the second, third, and fourth sacral segments of the spinal cord. Fibres emerge from ventral rami of nerves S2–4 and form the pelvic splanchnic nerves.

Table 2 ANS effects on various organs of the body

Organ	Sympathetic response	Parasympathetic response
Eyes	Dilatation (α1)	Constriction
Heart	Increase heart rate (β1, β2)	Decrease heart rate
	Increase contractility (β1, β2)	Decrease contractility
	Increase conduction velocity	Decrease conduction velocity
Arterioles	Vasoconstriction (α)	Vasodilatation
	Vasodilatation (β)	
Systemic veins	Vasoconstriction (α)	
	Vasodilatation (β)	
Lungs	Bronchodilatation (β2)	Bronchoconstriction
Kidney	Increase renin secretion (β1)	
Gut	Decrease peristalsis and tone	Increase peristalsis and tone
	Contraction of sphincter (α)	Relaxation of sphincter
Liver	Glycogenolysis (α1, β2)	Slight glycogen synthesis
	Lipolysis	
Bladder	Detrusor relaxation (β2)	Detrusor contraction
	Sphincter contraction (α1)	Sphincter relaxation
Uterus	Contraction in pregnancy (α1)	
	Relaxation of pregnant and non-pregnant uterus (β2)	
Basal metabolism	Increased	
Adipose tissue	Lipolysis (α1, β1, β3)	
Salivary glands	Thick, viscous secretion (α1)	Profuse, watery secretion

The physiology of the ANS

Neurotransmitters and receptors are integral to the automatic functioning of the ANS (Tables 1 and 2). Receptors mediate actions of the neurotransmitters involved in the ANS by activation of a second messenger, or by a change in ion channel permeability.

Pathophysiology

Autonomic neuropathies

Autonomic neuropathy refers to damage to the autonomic nerves. They are a group of disorders affecting the autonomic neurones, either sympathetic or parasympathetic, or both (Fig. 2). In developed countries, diabetes is the most common cause of autonomic neuropathy.[3]

Aetiology and pathogenesis

The pathophysiology of autonomic neuropathies is variable and depends upon the medical condition or the complication that lead to it. Exact mechanism of damage to the ANS is still unclear. Poor blood sugar control may be an important contributing factor in many of the proposed mechanisms[4] (Table 3).

Anaesthetic management of a patient with autonomic neuropathy

Preoperative assessment

Autonomic neuropathy involves a number of organ systems and has serious clinical consequences during the perioperative period. Anaesthetists therefore must be aware of the clinical conditions that are associated with autonomic neuropathy (Table 4). It is vital to look for evidence of dysfunction (Table 5) in order to anticipate and possibly prevent perioperative complications.[5]

Cardiac autonomic neuropathy (CAN) is a clinically significant and life-threatening complication of diabetic autonomic neuropathy. Significant intraoperative haemodynamic instability and major cardiac events can occur. Poor glycaemic control and duration of diabetes are mainly responsible for the severity and it is also known to exist in patients with advanced diabetic complications like retinopathy and nephropathy.[4] Resting tachycardia is a feature of diabetic neuropathy and a heart rate between 90 and 130 beats min^{-1} is a feature of cardiac autonomic dysfunction.[4] This occurs due to sympathetic over-activity as parasympathetic dysfunction occurs first.[4]

The loss of afferent nerve fibres in the ischaemic areas of the heart may be responsible for the 'defective anginal warning' in diabetic patients with autonomic neuropathy. Not only can acute myocardial infarction occur without symptoms, but chronic painless ischaemia is also common.[5] Even in the absence of any cardiac disease, autonomic neuropathy may be associated with LV systolic and diastolic abnormalities.

Prolonged QTc on ECG is seen in patients with CAN. These patients are more at risk of developing perioperative cardiac complications like painless myocardial ischaemia, arrhythmias such as torsades de pointes, and sudden death.[3,4] Altered cardiac sympathetic innervation (imbalance in the right and left stellate ganglion activity) is suggested to be the reason for the prolongation of the QTc interval.[4,6]

Exercise tolerance is impaired in patients with autonomic dysfunction because the compensatory responses of heart rate and arterial pressure are decreased in response to exercise. Poor exercise tolerance would warrant further evaluation of the cardiopulmonary function and assessment of the ANS.[4]

Orthostatic hypotension may be present in patients with diabetic autonomic neuropathy due to damage to the efferent sympathetic fibres. Sympathetic dysfunction leads to a decrease in norepinephrine release and reduced vasoconstriction causing hypotension during postural changes.[4] Any history of fainting, dizziness, visual impairment, and syncope in these patients should be actively sought and would be suggestive of orthostatic hypotension due to autonomic neuropathy.

Gastroparesis leading to delayed gastric emptying and increased risk of acid reflux and aspiration is an important concern for the anaesthetist even in fasted patients. The presence

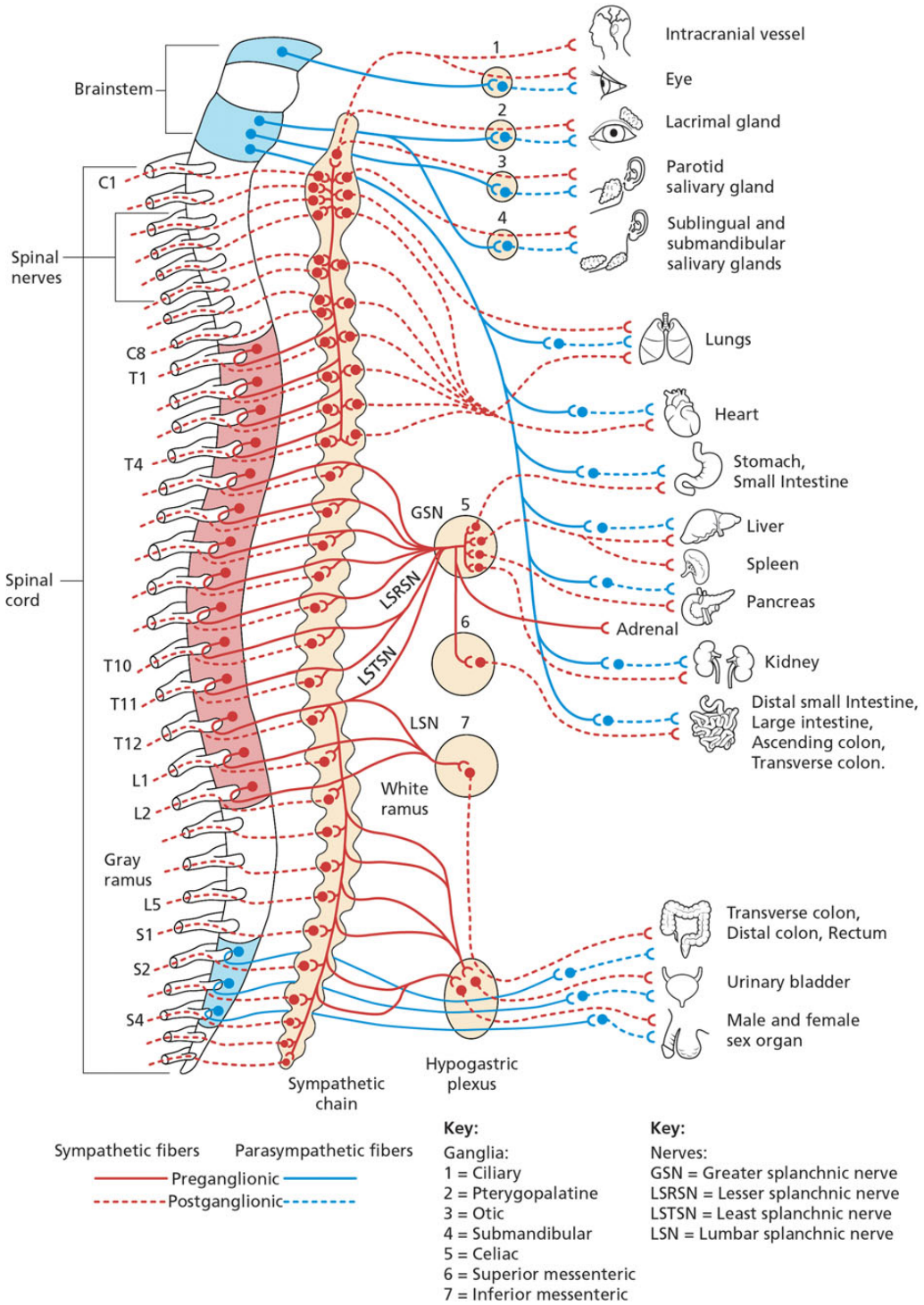

Fig 2 ANS overall anatomy. Parasympathetic pathways represented by blue and the sympathetic pathways in red. The interrupted red lines indicate post-ganglionic rami to the cranial and spinal nerves. This image is from the 20th US edition of *Gray's Anatomy of the Human Body* and is in the public domain.

of cardiovascular autonomic dysfunction is in no way evidence of the presence of gastroparesis.[3] If acid reflux is present, it is prudent to prescribe these patients with H2 receptor antagonists like ranitidine and prokinetics like metoclopramide as premedication.

Recent studies have shown the presence of obstructive sleep apnoea (OSA) in diabetic patients with autonomic neuropathy.[7] Impaired vagal input to inspiratory phasic dilator muscles has been suggested as the mechanism for the sleep apnoea.[6,7]

Assessment of ANS

Methods for the evaluation of cardiovascular autonomic reflexes were described by Ewing and Clarke.[8] These methods were

Table 3 Mechanisms of nerve damage in diabetic autonomic neuropathy[4]

Vascular endothelial damage
Caused by increased oxygen free radicals and intracellular hyperglycaemia
Degeneration of nerve fibres due to hyperglycaemia
Hyperglycaemia causes destruction of nerve growth factors
Autoimmune-mediated nerve damage
Occurs due to changes in the immune system due to the disease process

Table 4 Causes of autonomic neuropathy

Inherited
Amyloidosis
Porphyria
Fabry disease
Hereditary sensory autonomic neuropathy
Acquired
Diabetes mellitus
Uraemic neuropathy, chronic liver diseases
Nutritional deficiency: vitamin B12
Toxic/drug induced: alcohol, amiadarone, chemotherapeutic agents
Infections: human immunodeficiency virus, leprosy, botulism, diphtheria, Lyme disease, Chagas disease, tetanus
Autoimmune: Guillain–Barré, Sjogren, rheumatoid arthritis, systemic lupus erythematosis, Lambert–Eaton myasthenic syndrome
Neoplasia: paraneoplastic syndromes, brain tumours

described by them for the assessment of diabetic autonomic neuropathy. The simplicity and effectiveness of these methods have led to its use in the evaluation of patients with non-diabetic causes of autonomic dysfunction as well (Table 6).[3]

Power spectral analysis

New methods using analysis of biomedical signal variability to assess autonomic function have been developed and are gaining popularity. Heart rate (R–R interval) or arterial pressure variability is analysed using power spectral analysis.[6] Power spectral analysis consists of breaking down variability into its component sinusoidal waves by means of fast Fourier transformation. Information derived from applying Fourier transformation on biomedical signal variability is indirectly used to assess ANS activity.[6]

Intraoperative considerations

Monitoring should be consistent with the standards of the Association of Anaesthetists of Great Britain and Ireland. Additional monitoring would depend on the cause of autonomic neuropathy, comorbidities present, and the nature of surgery.

Induction and intubation responses

During induction of anaesthesia and intubation of the trachea, increased cardiovascular instability and abnormal cardiovascular responses have been described with diabetic autonomic neuropathy.[9]

Table 5 Clinical features of autonomic neuropathy

Cardiovascular
Postural hypotension
Resting tachycardia
Fixed heart rate
Gastrointestinal
Dysphagia (oesophageal atony)
Gastroparesis causing nausea and vomiting, abdominal fullness
Constipation
Nocturnal diarrhoea
Genitourinary
Atonic bladder causing urinary incontinence, recurrent infection, urgency, retention
Sexual
Erectile dysfunction, retrograde ejaculation
Sudomotor
Anhidrosis
Gustatory sweating
Nocturnal sweats
Vasomotor
Dependent oedema due to loss of vasomotor tone and increased vascular permeability
Cold feet due to loss of skin vasomotor responses
Pupillary
Decreased pupil size
Absent or delayed light reflexes

The pressor response to tracheal intubation and extubation is reduced with less tachycardia and hypertension when compared with patients with no autonomic neuropathy.[3,4] The defective cardiac autonomic fibres lead to loss of compensatory mechanisms like increasing heart rate and vasoconstriction. The decrease in arterial pressure and heart rate is more significant and exaggerated in these patients due to these reasons and hence an increased need for vasopressor support post-induction of anaesthesia.[4]

Although the risk of hypotension appears to be significantly higher with induction agents like thiopental and propofol, there is no evidence available to suggest any one single induction agent is superior in this patient group.

Intraoperative cardiovascular instability

Significant hypotension may develop in patients with orthostatic hypotension in response to changes in position. Volatile anaesthetic agents can cause exaggerated hypotension because of the loss of compensatory mechanisms. The institution of positive pressure ventilation may profoundly decrease cardiac output and worsen the hypotension. There is evidence to suggest an increased requirement of intraoperative vasopressor support in these patients.[3,4]

Close monitoring is vital due to the possibility of these significant cardiac complications. Invasive arterial and central venous pressure monitoring is hence advisable in these patients. Detection and rapid treatment of silent ischaemia and myocardial infarction may be assisted through CM5 lead ECG configuration.

Other important factors

There is an association between cardiovascular autonomic neuropathy and severe intraoperative hypothermia.[10] Temperature should be monitored and normothermia maintained with the use of warming devices. Maintenance of anaesthesia may be

Table 6 Non-invasive tests for assessing the ANS[3,6,8]

	Normal	Borderline	Abnormal
Tests reflecting parasympathetic function			
Heart rate response to valsalva manoeuvre (valsalva ratio)	>1.21	1.11–1.20	<1.10
The valsalva ratio is the ratio of the longest R–R interval (slowest heart rate) to the shortest R–R interval (fastest heart rate)			
Heart rate (R–R interval) variation during deep breathing (max–min heart rate)	>15 beats min^{-1}	11–14 beats min^{-1}	<10 beats min^{-1}
The subject takes six deep breaths in 1 min and heart rate is recorded. The maximum and minimum heart rate during each cycle is measured. The mean difference (maximum heart rate–minimum heart rate) is the average of the differences in the heart rates for all six breaths			
Immediate heart rate response to standing (30:15 ratio)	>1.04	1.01–1.03	<1.00
The 30:15 ratio is the ratio of the longest R–R interval (around 30th beat) to the shortest R–R interval (around 15th beat)			
Tests reflecting sympathetic function			
Arterial pressure response to standing (decrease in systolic arterial pressure)	<10 mm Hg	11–29 mm Hg	>30 mm Hg
Postural decrease in arterial pressure is the difference between the systolic arterial pressure in the supine and systolic arterial pressure in the standing position			
Arterial pressure response to sustained handgrip (increase in diastolic arterial pressure)	>16 mm Hg	11–15 mm Hg	<10 mm Hg
Subject maintains handgrip of 30% of the maximum handgrip for up to 5 min or for as long as possible. The mean of the three diastolic readings before the testing is subtracted from the highest diastolic pressure during the handgrip			

complicated by the absence of autonomic 'signs' of depth of anaesthesia. Monitors of depth of anaesthesia provide dual advantage of reducing risk of awareness and excessive anaesthetic depth.

Central neuraxial block

Significant hypotension may be seen while establishing central neuraxial block due to sympathetic block in the presence of autonomic neuropathy. Central neuraxial anaesthesia may carry greater risks as profound hypotension may have deleterious consequences if they are associated with coronary artery, cerebrovascular, or renovascular disease.

Postoperative

Supplemental oxygen should be provided as these patients may have chronic silent ischaemia and are also prone to myocardial infarction without symptoms. If symptoms of OSA are present, they might need high dependency unit (HDU) care for the provision of non-invasive ventilation. If the patient is considered haemodynamically unstable, admission to intensive care or HDU should be arranged and invasive haemodynamic monitoring continued. Emerging issues from anaesthesia (e.g. pain, bleeding) should be identified and managed effectively to reduce the likelihood of increased cardiovascular instability and abnormal cardiovascular responses.

ANS dysfunction relevant to critical care

Autonomic changes in spinal cord injury

Spinal shock describes the initial phase of neurological dysfunction, consisting of loss of reflexes and autonomic control below the level of spinal cord injury. 'Spinal shock is a neurological, not a cardiovascular condition'.[11] This leads to flaccid paralysis, areflexia, and associated loss of sensory and motor activity below the injury.

Injury to the spinal cord at or above T6 results in significant loss of sympathetic tone and if it is above T4, cardiac sympathetic supply is also lost. This causes hypotension due to vasodilatation and bradycardia, both resulting due to loss of sympathetic outflow. This is called neurogenic shock. 'Neurogenic shock=hypotension+bradycardia+peripheral vasodilatation'.[11]

Initial management of the patient with spinal cord injury should involve the same principles as is used for the management of trauma patients. Bradycardia can be treated with anticholinergics like atropine and glycopyrrolate. Care must be exercised when suctioning trachea as unopposed vagal activity may cause profound bradycardia. Treatment of hypotension includes fluid resuscitation and may require vasopressor administration. Catecholamine surge due to the initial injury must be borne in mind during fluid resuscitation as there is the risk of pulmonary oedema. Invasive haemodynamic monitoring should be established to guide the management of neurogenic shock.

Autonomic hyperreflexia

Supraspinal feedback and inhibition of many autonomic reflexes are lost after spinal cord injury. Small stimuli below the level of injury can cause exaggerated, disordered autonomic response. This phenomenon is usually seen between 3 weeks and 9 months of the initial injury and is a significant risk with lesions above the T6 level. The stimulation is usually bladder or bowel distension but can be cutaneous stimulation or pain from surgery. The response causes severe hypertension, with risk of seizures and brain haemorrhage. Severe reflex bradycardia may develop. Treatment consists of preventing or removing the stimulus and using short-acting anti-hypertensive drugs to decrease arterial pressure.

Guillian–Barré syndrome

Autonomic dysfunction involving both sympathetic and parasympathetic systems is seen in Guillian–Barré syndrome. Sinus tachycardia is the most common manifestation. Orthostatic and persistent hypotension, paroxysmal hypertension, fluctuations in heart rate, paralytic ileus, urinary retention, and abnormalities of sweating are commonly present.[6]

Tetanus

Basal sympathetic activity is higher and episodic sympathetic hyper responsiveness is seen in tetanus. Features of autonomic dysfunction present in tetanus are hypertension, tachycardia, arrhythmias, sweating, and fever. Epinephrine and norepinephrine levels are very high during episodes of autonomic hyperactivity. Combination of α and β adrenergic blockers are used during sympathetic crisis. Unopposed β-block can precipitate acute congestive cardiac failure and hence avoided. Sedatives in the form of benzodiazepines and morphine are also used to decrease catecholamine output. Magnesium sulphate is used in severe tetanus as an adjunct to sedation and adrenergic block.[6]

HIV infection

Autonomic dysfunction is a common occurrence in HIV infection. Awareness of this complication of HIV infection is important to decrease the morbidity and mortality in this patient group.[3]

Porphyria

Sympathetic hyperactivity is a feature of autonomic dysfunction in porphyria. Hypertension, tachycardia, abdominal pain, and altered bowel movements are some of the features present during the crisis.[6]

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Perioperative management of patients with cardiac implantable electronic devices

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Key points

- The number of patients with cardiac implantable electronic devices (CIEDs) presenting for surgery is increasing.
- Electromagnetic interference (EMI) is frequently encountered in the theatre environment and can interfere with the function of CIEDs.
- Bipolar diathermy should be used in preference to monopolar diathermy to reduce the risk of EMI.
- The degree of dependency on the implanted device and the potential consequences of pacing inhibition should be established.
- The defibrillator function of an implantable cardioverter defibrillator should be deactivated immediately before surgery where EMI is likely.

Pacemakers effectively treat a broad range of cardiac arrhythmias by generating an electrical impulse to re-establish regular myocardial contraction. The implantation rate of pacemakers in the UK continues to increase.[1] The design and capability of these devices have become increasingly complex and can encompass treatment modalities for patients with heart failure by provision of cardiac resynchronization therapy (CRT) and defibrillator functions to treat tachyarrhythmias.

This article comprises two parts. The first part will review the relationship between the underlying cardiac pathophysiology and the physics of recording, pacing, and defibrillation. The implications of electromagnetic interference (EMI) will then be introduced. The second part will focus on the safe perioperative management of a patient with a CIED who presents for unrelated surgery; procedure-specific considerations will be discussed.

Indications

Permanent pacemakers

Within the UK in 2010, 58% of permanent pacemakers (PPMs) were inserted for symptomatic bradycardia caused by atrioventricular (AV) block.[2] AV block is classified according to the extent of the delay (first-degree block, P–R interval >0.2 s), or interruption (intermittent—second degree, or complete—third degree) to electrical conduction between the atria and ventricles. The pathophysiology of AV block is varied and includes ischaemic, degenerative, and infiltrative processes or may be iatrogenic after AV nodal ablation.

The second most frequent indication for PPM insertion (23.6% in 2010) is sick sinus syndrome. This describes sinus node dysfunction with intermittent loss of P-waves or sinus arrest causing episodes of symptomatic bradycardia.

Biventricular PPMs

Biventricular pacemakers are specific types of pacing devices indicated for symptomatic patients with moderate-to-severe cardiac failure with a left ventricular ejection fraction of <35% and a widened QRS interval.[3] Biventricular pacing optimizes the timing of right and left ventricular contraction which is otherwise uncoordinated with sole right ventricular pacing; hence, the term CRT. The latest published implantation rate of these devices is 145 per million of the UK population.[1]

Implantable cardioverter defibrillators

Implantable cardioverter defibrillators (ICDs) sense and analyse myocardial electrical activity and are capable of pacing and shock therapy when necessary. Most ICDs are implanted (in accordance with NICE guidance), for secondary prevention in patients who have survived a cardiac arrest or other significant haemodynamic compromise after ventricular arrhythmias.[3] ICD implantation is indicated in selected patients after myocardial infarction [usually with scar-related ventricular tachycardia (VT) risk] or those with significant left ventricular dysfunction. Other patient groups at high risk of sudden death due to ventricular arrhythmias include those with familial cardiac conditions such as long QT syndrome, Brugada syndrome, cardiomyopathies, and selected patients with congenital heart disease. There are specialized ICDs available which permit CRT for patients with indications for biventricular PPMs at risk of arrhythmias. These devices, predominantly inserted for primary prevention, are referred to as CRT-Ds ('D' denotes defibrillator).

Implantable loop recorders

These leadless cardiac monitoring devices function solely as a diagnostic tool. They are indicated for patients with recurrent unexplained syncope and/or palpitations and as a long-term monitoring device for some patients with atrial fibrillation (AF). Implantable loop recorders (ILRs) have self-contained electrodes capable of recording an ECG and can be automatically or patient triggered (via an external activator) when arrhythmias or symptoms arise.

Physics and nomenclature of CIEDs

Pacemakers

A PPM system comprises a pulse generator (which contains a battery and electronic circuitry) and one or more pacing leads. The pulse generator consists of a silicon chip and electronic sensing and output circuitry which analyses the cardiac rhythm and paces as programmed. Pacing configuration may entail current delivery to a single cardiac chamber or to multiple chambers. Unipolar leads have a single electrode at the pacing tip which acts as the current emitting cathode; the PPM box serving as the anode. With more commonly encountered bipolar leads, the anode lies on the lead itself just proximal to the cathode tip; reducing the susceptibility of the device to EMI.

The PPM box generates an electrical current between the anode and cathode which is transmitted to the myocardium via a lead to achieve a wave of depolarization. Successful pacing-induced depolarization is referred to as 'electrical capture'. The stimulation threshold is defined as the minimum electrical stimulus that consistently exceeds the excitation threshold of the myocardial cells to produce cardiac depolarization. Depending on the number of leads and the programming of the device, the box responds to sensing of intrinsic electrical activity in single or multiple chambers by either inhibiting or triggering pacing in one or more chambers.

The Generic Pacemaker Code describes the PPM function; positions 1–3 refer to the chamber paced, the chamber sensed, and the response to sensing, respectively (Table 1).[4] For example, VVI would denote a ventricular paced and sensed PPM with an inhibiting response to sensing. The commonly encountered DDD mode can have essentially four responses according to the detected intrinsic cardiac rhythm:

(i) Atrial sensing and ventricular sensing

If both atrial and ventricular activity are detected within the appropriate pre-programmed time interval (which depends on the desired heart rate), then there will be inhibition of any pacing activity.

(ii) Atrial pacing and ventricular sensing

Atrial pacing leads to intrinsic ventricular activity within the programmed time interval which is sensed by the ventricular lead and therefore inhibits pacing (e.g. sick sinus syndrome with a normal P–R interval).

(iii) Atrial sensing and ventricular pacing

Sensed intrinsic atrial activity triggers ventricular pacing when spontaneous ventricular depolarization is not sensed within a programmed time interval (e.g. with complete AV block and normal sino-atrial node function).

(iv) Atrial pacing and ventricular pacing

In this scenario, there is pacing of both the atrium and ventricle if intrinsic electrical activity is undetected within the specified preset time interval (e.g. with complete heart block and inadequate intrinsic atrial rate).

The fourth position of the generic PPM code refers to rate-responsive pacing whereby the pacemaker can alter the paced heart rate in response to motion or sensed physiological conditions. Most commonly, an accelerometer detects activity during exertion and increases the paced rate to optimize cardiac output. Other sensing mechanisms may detect an increase in physiological parameters, including minute ventilation or myocardial contractility, adjusting heart rate accordingly.

Implantable cardioverter defibrillators

Conventional ICDs are analogous to pacemaker devices but with a larger generator which houses electronic circuitry, batteries, and a capacitor. Defibrillation requires ~750 V (to deliver an output of 30–45 J); achieved by charging the capacitor and then dissipating this energy. The device continuously senses and analyses native electrical activity (the R–R interval) to detect VT or ventricular fibrillation. It incorporates anti-tachycardia pacing (ATP) capabilities whereby a programmed burst of overdrive

Table 1 The Generic Pacemaker Code (adapted from Bernstein and colleagues[4] with permission from John Wiley & Sons Ltd)

Position I: pacing chamber(s)	Position II: sensing chamber(s)	Position III: response(s) to sensing	Position IV: programmability
O = None	O = None	O = None	O = None
A = Atrium	A = Atrium	I = Inhibited	R = Rate modulation
V = Ventricle	V = Ventricle	T = Triggered	
D = Dual (A+V)	D = Dual (A+V)	D = Dual (A+V)	

pacing is used to attempt to terminate VT. In the case of VF, or if ATP fails, a capacitor within the ICD will charge and then release a shock which passes between the defibrillator coils. These coils are either both located on the ventricular lead or alternatively the box acts as one coil with a single ventricular lead coil. Shock delivery is painful and utilizes more battery life or capacity (measured in ampere-hours) than ATP. An ICD has the anti-bradycardia capabilities of a pacemaker and is able to pace in the event of 'post-shock' bradyarrhythmias.

Sensing and the implications of EMI

Sensitivity of a PPM describes the minimum intrinsic atrial or ventricular electrical activity measured in millivolts that is sensed by the device. This is set as a margin around the amplitude of a sensed signal and depends on origin (atrial or ventricular) and lead type (unipolar or bipolar). If incorrectly set, the device may 'under-sense' and fail to detect intrinsic atrial or ventricular activity. Consequently, 'over-pacing' can occur whereby the pulse generator fires, despite intrinsic activity with the potential risk of triggering malignant tachyarrhythmias. An alternative scenario of 'over-sensing' is when the device inappropriately registers myocardial activity when none exists, leading to failure to pace in the context of no intrinsic electrical activity. The most frequent PPM interaction with EMI is over-sensing.[5] EMI is particularly important to consider in a patient who is PPM-dependent since over-sensing may result in inappropriate inhibition and significant haemodynamic compromise. In the case of ICDs, EMI may be falsely interpreted as a shockable rhythm and as such, there is a risk of intraoperative shock delivery. Disabling the defibrillator function of a device before exposure to EMI is therefore advised.

CIED insertion

PPMs are usually implanted subcutaneously below the left clavicle with trans-venous access commonly via the left cephalic, subclavian, or axillary veins. In paediatric patients, the PPM may be implanted in other locations including the abdominal wall. The atrial lead is generally positioned in the right atrial appendage and the ventricular lead in the right ventricular apex. Biventricular systems require the additional positioning of a lead to stimulate the wall of the left ventricle; this is usually achieved by passing a lead into the coronary sinus via the right atrium (Fig. 1). A retrospective study reported a 7.5% complication rate, most commonly from lead displacement (4.8%), pneumothorax (3.7%), or infection (1.5%).[6] Recently developed leadless PPMs have a small sensing and pacing device entirely contained within the right ventricle with no leads (Fig. 2).

ICDs are implanted similarly to pacemakers with trans-venous leads which sense and deliver shock therapy as required. A less invasive, subcutaneous ICD has been developed (S-ICD), primarily for patients with difficult venous access or complex cardiac anatomy. A lead is placed subcutaneously in the midline, connecting to a pulse generator sited in the left axilla (Fig. 3). The device analyses and treats ventricular arrhythmias by delivering an 80 J biphasic shock without the need for endovascular lead placement and the potential associated complications. The anticipated battery longevity is shorter than conventional ICDs; pacing capabilities are limited to post-shock pacing only.

Preoperative assessment of patients with CIEDs

History and examination

The presence of a CIED indicates a high likelihood of coexisting significant cardiac disease and warrants conduct of a thorough history and examination. Direct inquiry of any symptoms suggesting device malfunction should be made, including dizziness, syncope, or indicators of deteriorating cardiac function. Prescribed anti-arrhythmic agents should be continued in the perioperative period. Electrolyte abnormalities (including hypomagnesaemia), acid–base disturbances, or blood gas abnormalities should be corrected since they may influence the stimulation and/or defibrillation thresholds.

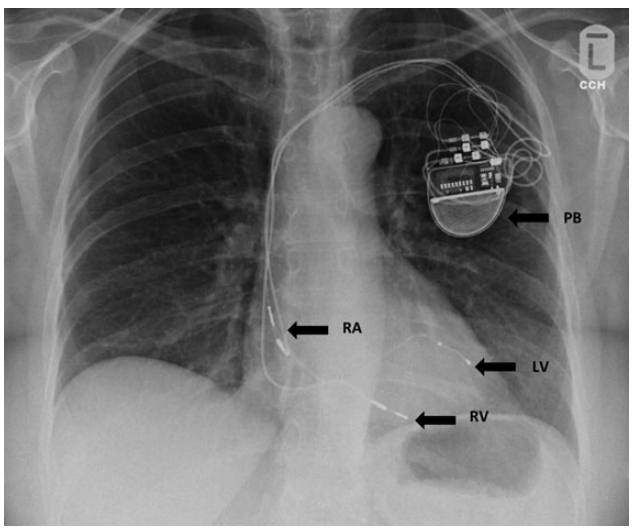

Fig 1 Chest radiograph of a biventricular pacing system (CRT-P). PB, pacing box; RA, right atrial lead; RV, right ventricular lead; LV, coronary sinus lead stimulating the left ventricle.

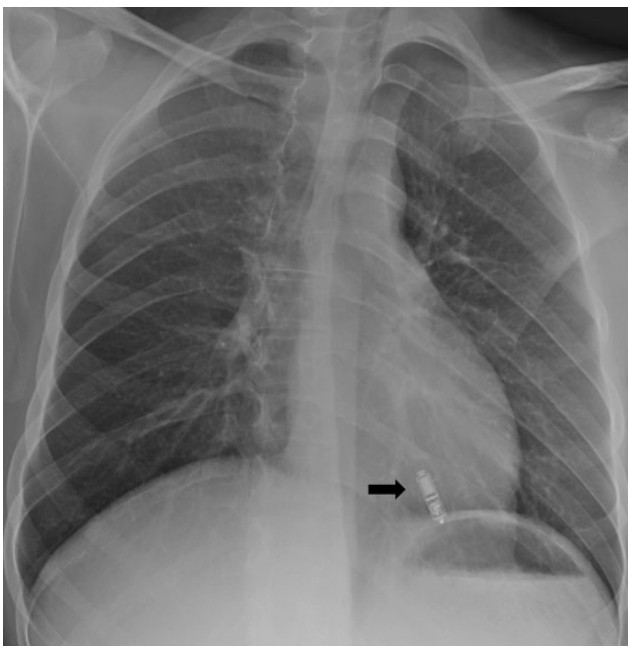

Fig 2 Chest radiograph demonstrating a leadless pacemaker system (arrowed) within the right ventricle.

Investigations

A recent ECG should be examined and may demonstrate pacing activity; sole atrial pacing is seen as a single stimulus (spike) followed by a p-wave and then the patient's own QRS complex (Fig. 4). Ventricular pacing results in a spike followed by a broad QRS complex (Fig. 5). Dual-chamber pacing shows features of both atrial and ventricular pacing. Spikes preceding all p-waves, QRS complexes or both would indicate potential PPM dependency.

Chest radiograph

Important information regarding the nature and function of a CIED can be determined from a chest radiograph. This includes device-specific identifiers and the number and configuration of leads together with other findings including the presence of cardiac failure. An ICD can be distinguished from a pacemaker by the presence of one or two thick, linear, radiopaque shock coils on the right ventricular lead (Fig. 6). Radiographic appearances may also suggest potential malfunction of the device such as lead fracture or migration (Fig. 7).

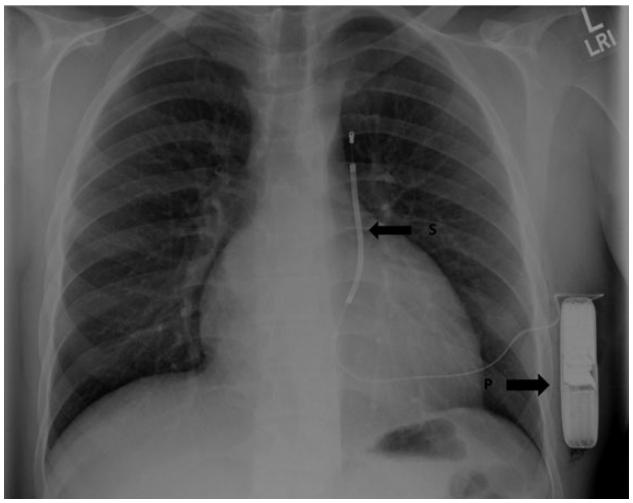

Fig 3 Chest radiograph demonstrating a subcutaneous pacemaker system. P, pulse generator; S, subcutaneous lead with shock coil.

Device analysis and interpretation of the preoperative check

The patient should carry a European Pacemaker Patient Identification Card which provides detailed information including the pacemaker centre details, the date and indication of implantation, and the manufacturer, model, and serial number of the device (Fig. 8 and Supplementary Fig. S1). Guidelines vary, although it is generally considered acceptable for a PPM to have been checked within 12 months and an ICD within 6 months. Conventional in-person interrogation involves external placement of a programming head onto the implant for recognition; a 'cardiac dashboard' displayed on the attached programmer provides a summary of CIED performance during the follow-up interval. Most modern ICDs and some PPMs have the ability to communicate wirelessly; permitting device interrogation in the patient's home with data transmitted automatically to secure websites.

The key features that should be identified when interpreting a CIED check before a surgical procedure are summarized in Table 2. The format of CIED checks varies between devices and manufacturers. The check will not provide comprehensive information about the patient's underlying cardiac condition but will provide some insight into clinical issues that may be relevant in the perioperative period.

ICD-specific analysis

Although advances in technology have limited the repeated need to check the defibrillator function of ICDs, a patient may recently have been sedated for a defibrillator safety margin test. This test involves inducing VF under controlled conditions (providing there is no contraindication such as cavity thrombi) to ensure that the device senses, detects, and terminates the arrhythmia reliably and with adequate energy delivery.

Device re-programming considerations

Reprogramming of a CIED before surgery should be considered in the following circumstances:

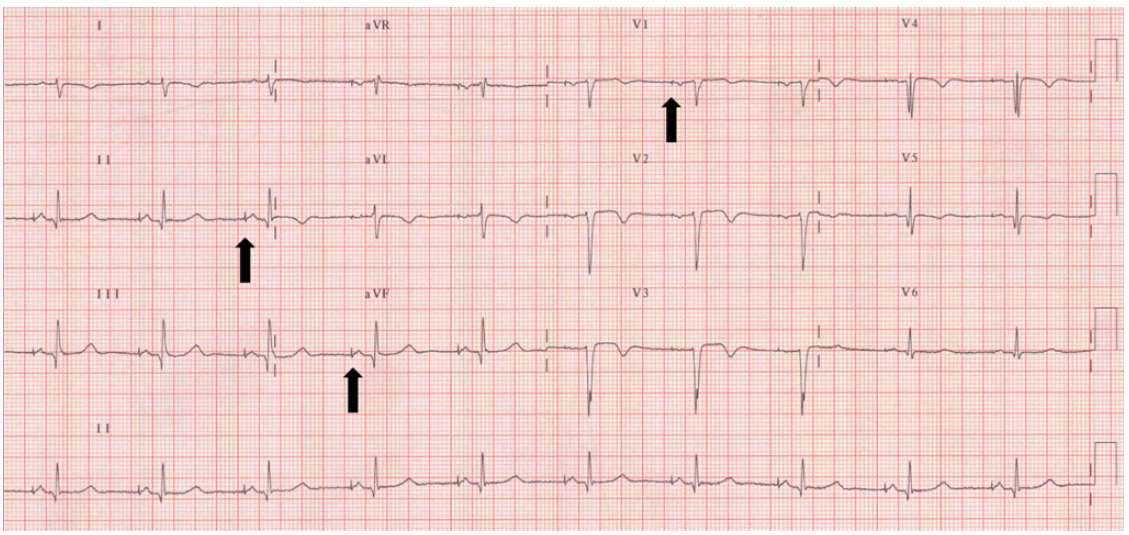

Fig 4 ECG demonstrating sole atrial pacing—atrial pacing spikes (arrowed) are followed by atrial capture and normal width QRS complexes.

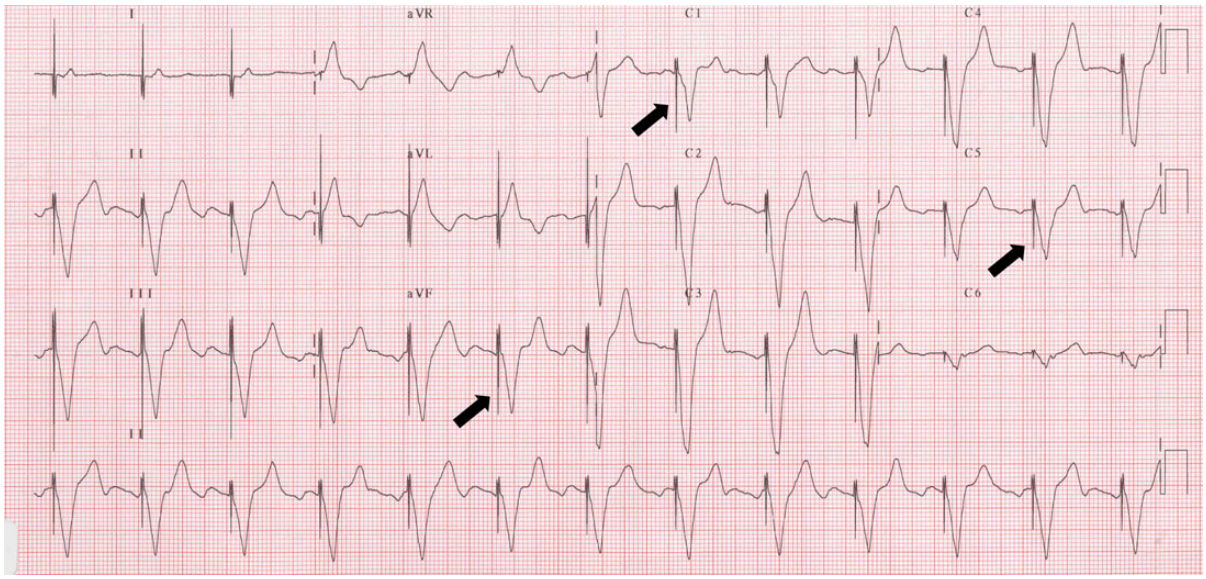

Fig 5 Sole ventricular pacing—pacing spikes (arrowed) are followed by broad QRS complexes.

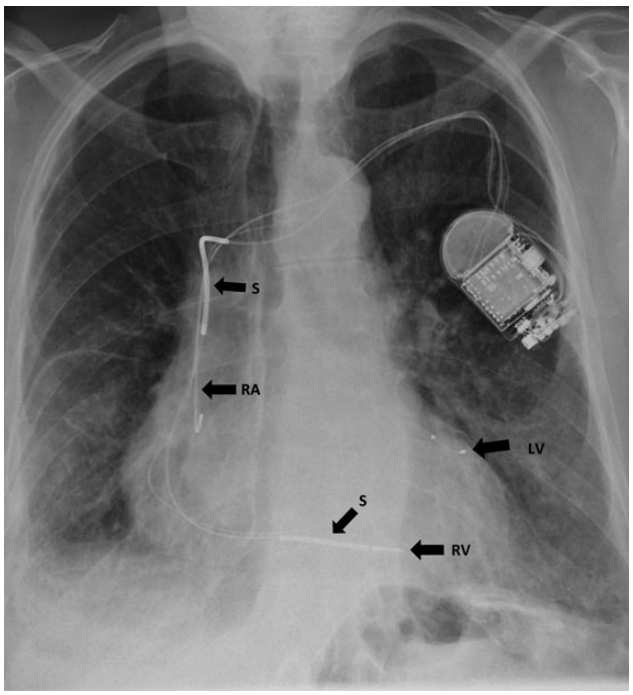

Fig 6 A chest radiograph demonstrating a CRT-D device—note the widened shock coils (S) located on the right ventricular (RV) lead, in contrast to the right atrial (RA) lead and the narrow left ventricular (LV) pacing lead.

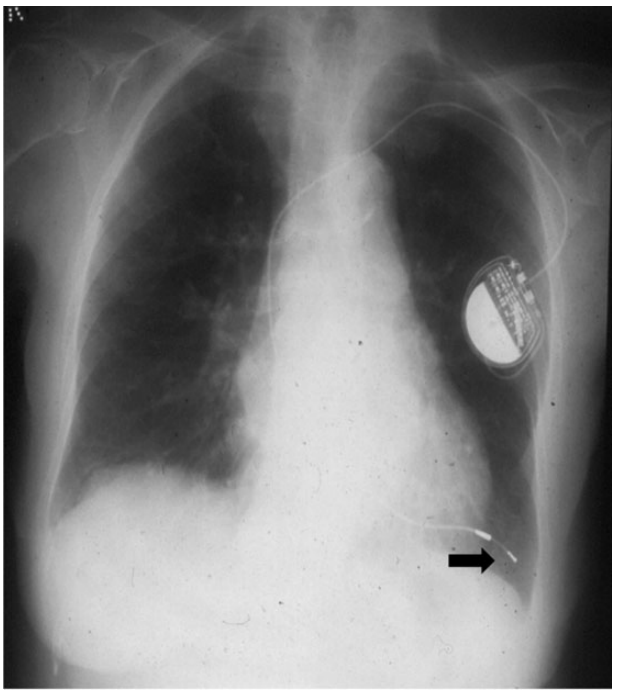

Fig 7 Chest radiograph demonstrating right ventricular lead migration (arrowed) outside of the heart.

(i) Significant pacemaker dependency

If the patient is highly pacemaker-dependent, and the procedure involves potential EMI, a cardiac physiologist should be consulted as temporary reprogramming of the device to an asynchronous (non-sensing) mode (A00, V00, or D00 depending on the set configuration) may be required.

(ii) Advanced CIED functions

Any device with a *rate response* function using minute ventilation as the mechanism of regulating pacing should have this programmed off during surgery since mechanical ventilation may stimulate excessive pacing rates. *Sleep/rest mode* is another example of an advanced function whereby the programmed base rate is gradually reduced during a specified sleep phase. This should be deactivated if late surgery is planned.

(iii) Defibrillator function

The defibrillator function should be deactivated immediately before any surgery where EMI is deemed likely. If this is not possible, the application of a magnet should be considered.

European Pacemaker Patient Identification Card

1. Patient ID Nr.: **NHS#:** Sex: F
Patient Name:
Address Line 1:
Address Line 2:
City: Post Code:
Country: Tel. Nr.:
Date of Birth: First Implant: 2012 03 16
Symptom Primary: D2 ECG: C5 Aetiology: E3
Symptom Secondary: ECG: Aetiology: E1

2. Pacemaker Centre
Cardiologist:
Hospital: Southampton General Hos
Address:
City/Postal Code: Tel. Nr.:
Country: Fax Nr.:

3.IPG Basic Rate Mode: VVIR
Model: C3TR01 Consulta CRT-P Manufacturer: Medtronic
Date of Implantation: 2013 09 18 Serial Nr.: PZI615601S

4. Leads
(1) Type: Ventricle Right Ventricle Manufacturer: Vitatron
Model: ICL08B Crystalline Serial Nr.: VMN08323V Date of Implantation: 2002 02 08
NBG Lead Code:
(2) Type: Atrium Right Atrium Manufacturer: Vitatron
Model: ICL08JB Crystalline Serial Nr.: VMP03824V Date of Implantation: 2002 02 08
NBG Lead Code:
(3) Type: Ventricle Coronary Sinus (Left) Manufacturer: Medtronic
Model: 4396 Attain Ability Straight Serial Nr.: RAE610959V Date of Implantation: 2013 09 18
NBG Lead Code:

4.1 Partially Explanted Leads
(1) Type: Manufacturer:
Model: Serial Nr.: Date of Implantation:
NBG Lead Code:

General Practitioner
Name:
Address Line 1:
Address Line 2:
City: Post Code: SO16 6YD
Country: United Kingdom Tel. Nr.:

5. Brady Parameters at Time of Implant

	Blank	Refr	Sens	Pol	Amp	Dur	Pol	
Mode VVIR Lower 70 Tracking Sensor 120 Hyst./Sleep			0.3	B	@			A
			0.9	B	3.5 @ 0.4		B	VR
					4 @ 1		U	VL

6. Comments

Fig 8 Example of a European Pacemaker Patient Identification Card for a patient with a CRT device programmed to VVI-R ('D2, C8, E3' indicates a patient with heart failure and chronic AF who required a PPM due to AV-block caused by nodal ablation—see Supplementary Fig. S1).

Magnets

A magnetically activated switch is incorporated into CIEDs to enable alteration of the pacing or defibrillator modes. Application of a magnet to a PPM varies according to the model and settings of the device. Usually, it delivers an asynchronous mode at a rate specific to the manufacturer; however, it may initiate a diagnostics function and then revert to its programmed mode of pacing. It is important to appreciate that an asynchronous mode may be suboptimal in a patient with an underlying native rhythm and rarely may induce malignant arrhythmias.[5] The device should revert to programmed baseline settings upon removal of the magnet.[7]

It is possible to deactivate the defibrillator function of an ICD in an emergency by placing and securing (with surgical tape) a medical grade magnet on the device for the duration of surgery. This is the case with all commonly encountered ICDs, provided that this magnet function has not been disabled. Some manufacturers (including Medtronic and Boston Scientific) have incorporated audible tones emitted from the ICD to indicate when a magnet has been applied and defibrillator functions have been deactivated. Removal of the magnet at the end of surgery should promptly reactivate the defibrillator function.[7]

Implantable loop recorders

These devices do not deliver any treatment and they present no risk to the patient when EMI is encountered. Since noise created by diathermy may fill up the memory banks of the device and

Table 2 Key features of a preoperative CIED check

- Device type—pacemaker/ICD/CRTD
- Pacing percentages—sensing (S), pacing (P), and chamber (A and V) will be given for all four combinations, i.e. ASVS, ASVP, APVS, APVP. A high percentage of pacing will indicate a higher degree of pacemaker dependency
- Pacing threshold—the report should confirm an adequate safety margin with the output on the lead (pacing amplitude) programmed to at least double the pacing threshold (in volts) to ensure capture
- Lead impedance—resistance to current flow (measured in ohms) and trends. Abnormal lead impedance may suggest lead crush or fracture (excessively high impedance) or an insulation defect (excessively low impedance)
- Sensed P/R amplitude (mV)—confirmation of appropriate sensing parameters
- Battery life—presented as a graph, figure, or battery life in years
- ICD features—therapy since last interrogation will be displayed in the form of ATP or shock therapy. Some devices will indicate the total number of therapies that the device has delivered
- 'Current EGM (endocardial electrogram)'—will display the current signals from the atrial and ventricular channels allowing the underlying rate and rhythm to be seen. Some devices will indicate any episodes of AF
- 'Alerts'—most devices will provide a summary box that highlights any clinical or device functionality issues

overwrite existing data, it is prudent to contact the cardiac physiology department to allow them an opportunity to download any relevant clinical data before planned surgery.

Intraoperative considerations

Anaesthesia should be tailored to the patient's cardiac state, existing comorbidities, and the intended surgical intervention. Hypoxia, hypercapnia, acidosis, and electrolyte abnormalities (especially of potassium and magnesium) should be avoided since they may precipitate arrhythmias and/or interfere with pacemaker capture. If re-programming of the device is required, this may be done by a cardiac physiologist in the anaesthetic room immediately before induction. If an asynchronous mode is deemed necessary, reliable capture at an appropriate rate with haemodynamic stability should be confirmed.

Management of intraoperative arrhythmias

There is a possibility of intraoperative arrhythmias, particularly in susceptible patients with ICDs when the defibrillator function has been temporarily disabled. Equipment should be immediately available for external defibrillation and/or temporary pacing. External defibrillator/pacing pads should be attached to patients with CIEDs before surgery, particularly when access to the chest wall might be difficult. Pads should be placed at least 10–15 cm away from the edge of the CIED to avoid the remote possibility of damage to the device or the theoretical risk of damage to the myocardium as a consequence of excess current flow. Arrhythmias should be treated conventionally following standard ALS procedures and using the usual recommended external defibrillation energy levels. Should external pacing become necessary, capture can usually be achieved at currents of ~50–100 mA using external pads.

Monitoring

Patients should receive standard recommended monitoring; an appropriate ECG lead should be displayed that demonstrates any pacing spikes. The ECG should be monitored throughout surgery with particular attention paid to the effects of diathermy. Note that the monitored heart rate may be inaccurate due to double-counting of the pacing spike and the QRS complex. Monitoring must also include a plethysmographic pulse measurement and display. Invasive arterial pressure monitoring will provide additional beat-to-beat evidence of mechanical capture and may add valuable information in patients with cardiac failure.

Where central venous access in the upper body is deemed necessary, sites should be chosen well away from the site of lead implantation. Caution should be taken to avoid passing guide wires into the heart precipitating arrhythmias or potentially (in recently implanted devices) lead dislodgement. Peripheral nerve stimulators are considered safe, providing that they are distant from the device and that the stimulus is not in a vector parallel to that of the pacemaker current.

Drug and fluid considerations

Succinylcholine should be used with caution since fasciculations may cause over-sensing and result in pacing inhibition;[8] ICDs have robust sensing algorithms and inappropriate shock delivery is unlikely. Antibiotic prophylaxis should be carefully considered depending on the surgery. CIED infection, predominantly staphylococcal, is difficult to diagnose and treat with a mortality of up to 35%.[9]

Many patients with CIEDs will have impaired cardiac function and the potential for development of malignant arrhythmias. Monitoring and anaesthetic technique should reflect the need to ensure myocardial optimization in these patients. Whilst negative inotropic drugs should be avoided, positive inotropes may precipitate (catecholamine sensitive) tachyarrhythmias in susceptible patients.

Fluid balance is an important consideration since patients with a fixed ventricular rate will be unable to respond to hypovolaemia with an increase in heart rate; this may compromise end organ perfusion and oxygen delivery. Cardiac output monitoring is recommended for surgery with the potential for significant haemodynamic compromise.

Reducing EMI

Bipolar electrodes and engineered shielding protection have reduced the risk of EMI; however, sources of EMI around the patient should be avoided. If the device has been recently checked and the surgical site is remote, the likelihood of malfunction is minimal. Although mobile phones are generally considered safe, care should be taken to avoid direct placement of any phone onto the CIED since they remain a source of EMI and could potentially activate the 'magnet mode' of the device. Medical equipment which incorporates wireless technology, for example, some infusion pumps, monitoring devices, and ultrasound probes, should also be distanced from a CIED since these devices may provide a source of EMI. Diathermy should be avoided where possible; bipolar electrical diathermy is considered safer than monopolar.

Should monopolar diathermy be required, it should be used in short 1–2 s bursts with 10 s pauses and (where possible) the use of the cutting rather than coagulation current. The pathway from the diathermy to the return electrode should not pass near the CIED and the current field should be at right angles to the pacing leads. Diathermy cables should be kept well away from the site of the implant.

Procedure-specific considerations

The likely risk of EMI should be considered with reference to the site and type of procedure to be undertaken, and the diathermy required. Broadly speaking, over-sensing as a complication of EMI is unlikely for procedures where the application of diathermy and the return electrode are below the level of the umbilicus.[5]

(i) Radiofrequency ablation

Radiofrequency ablation involving the continuous application (several minutes) of radiofrequency energy via an emitting electrode to cause local heating and tissue coagulation is used in many kinds of surgery. The risk of prolonged current exposure leading to EMI with this technique means that it is especially important to disable the defibrillation function of ICDs. Direct contact between the ablation catheter and any CIED should be avoided and the radiofrequency current path should be as far away as possible from the CIED and lead.[10]

(ii) Tissue expanders in breast surgery

Tissue expanders that use magnets to orientate a needle to allow fluid filling to occur should be avoided. Their close proximity to a CIED may risk magnetic switch activation with conversion to asynchronous pacing, or failure of an ICD to detect a tachyarrhythmia.

(iii) Electroconvulsive therapy

The brief (1–2 s) electrical stimulus with electroconvulsive therapy (ECT) may cause pacemaker inhibition, although this is unlikely to be clinically significant. Subsequent seizure activity, however, may cause more prolonged over-sensing. Reprogramming to an asynchronous mode may be appropriate for selected patients before ECT, although this may also risk arrhythmias when intrinsic electrical activity exists. The defibrillator function of an ICD should be disabled since seizure activity may trigger an inappropriate shock either due to EMI or if there is a marked reactive sinus tachycardia that encroaches on the ICD tachycardia trigger rate. ECT often occurs in isolated sites which adds complexity to planning.

(iv) Transcutaneous electric nerve stimulation

Transcutaneous impulses may cause inappropriate sensing and subsequent inhibition of pacemaker function or inappropriate shock administration by an ICD; transcutaneous electric nerve stimulation is therefore considered contraindicated in patients with CIEDs.

(v) Diagnostic radiation

Diagnostic imaging in general does not have a significant impact on CIED function. However, there are rare case reports of inappropriate sensing and electronic reset with the higher radiation doses utilized by new-generation multi-slice computerized tomography scanners. Magnetic resonance imaging (MRI) is usually contraindicated in patients with CIEDs. MRI-conditional PPMs and ICDs which can be used only in certain well-defined conditions are produced by some manufacturers. Stipulations include specific MRI systems, combined use of generator and leads designated MRI-compatible, the pacing system in place for longer than 6 weeks, and specific programming of the device outside the MRI safety zone.[11] Programming will be set to an asynchronous or non-pacing mode by a cardiac physiologist depending on the device and the degree of dependency.[12] Device design modifications include a reduction in ferromagnetic components, a sensor designed to resist the magnetic field, and robust well-insulated circuitry.

(vi) Radiation therapy

This is usually considered safe, although direct radiation of the CIED should be avoided and the device may need to be re-sited if it is located directly within the field of radiation.[10] Device function should be verified frequently in the case of radiation-induced reversion to a backup safety mode (usually VVI, but manufacturer-specific).[7]

(vii) Extracorporeal shock wave lithotripsy

Shock waves are acoustic pressure waves created from electromagnetic, piezoelectric, electroconductive, or electrohydraulic sources. The wave form comprises a compressive and tensile phase which generates acoustic energy for stone disintegration (lithotripsy).[13] Generally, the risk of CIED dysfunction is low but devices should be checked within 1 month of the procedure.[7] There have been case reports of pacing suppression and backup safety mode reversion. The lithotripter should be kept at least 6 inches away from the CIED and the beam should not be focused near the CIED.[10] Lithotripsy pulses should be timed with the ECG, and rate modulation should be deactivated.

Postoperative considerations

Patients with CIEDs are ideally managed in a high dependency recovery environment with continuous monitoring and full resuscitation equipment immediately available. The defibrillator function of an ICD and any rate modulator pacing function which has been suspended needs reactivating by a cardiac physiologist after surgery. The device should be checked at the earliest opportunity if a magnet is used to deactivate a CIED intraoperatively. Any adverse incident relating to a CIED in the perioperative period should be addressed by a cardiac physiologist as soon as possible.

Conclusion

An increasing number of patients are presenting for surgery with varying forms of cardiac implantable electronic devices. It is important to consider the indications for insertion of the device, the degree of pacemaker dependency, the nature of the procedure being performed, and the likelihood of EMI. Careful preoperative and intraoperative preparation can help reduce complications and permit timely intervention if required.

Supplementary material

Supplementary material is available at *BJA Education* online.

Declaration of interest

H.C.B. and P.D. have no declarations of interest. P.R.R. has received consultancy fees from Medtronic and Boston Scientific, companies that manufacture CIEDs.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

Podcasts

This article has an associated podcast which can be accessed at http://www.oxfordjournals.org/podcasts/bjaed_Cardiac_Electronic_Implantable_Devices_Dr Diprose_BJAEducation_Nov2016.mp3

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Analgesia in intensive care: part 2

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Key points

- Pain is a common problem in intensive care; regional anaesthesia (RA), although less studied, offers excellent pain relief while avoiding opioid-induced side-effects.
- Performance of RA in intensive care is fraught with challenges. The pharmacology of local anaesthetics (LAs) is greatly influenced by pathophysiological states common in this setting, and understanding this is important in minimizing the complications.
- Despite numerous dilemmas like sepsis, coagulopathy, inotrope dependence, and sedation, risk–benefits of RA have to be considered on an individual basis and the reasons clearly documented.
- In intensive care, a high index of suspicion and close monitoring is necessary to promptly identify the development of neuraxial infections or LA toxicity.
- The risk due to RA can be minimized by adopting local and national guidelines, using modern technologies, and considering available alternatives and local expertise.

Pain is a common cause of distress in the intensive care unit (ICU) and a vast majority of patients experience it at some point during their stay. Systemic analgesia, most notably opioids, remains the mainstay in its management. However, opioids are associated with significant side-effects like delirium, ileus, respiratory depression, and increased duration of mechanical ventilation, especially when used as continuous prolonged infusions.[1] There has been a general trend in ICU to move towards targeted analgesia and avoidance of sedation.

In the ICU, regional anaesthesia (RA) when indicated has the potential to offer excellent pain relief but avoiding the unwanted side-effects of opioids. Unlike the perioperative setting, its role in the ICU has not been thoroughly evaluated. However, the potential benefits offered by RA can be significant and extend beyond just provision of analgesia (Table 1). Despite its numerous advantages, RA remains an underutilized modality, due to various challenges and perceived disadvantages (Table 1).

The objective of this article is to provide an overview of the use of RA in the ICU: to discuss the advantages and disadvantages, to debate the commonly faced dilemmas, and to highlight the specific circumstances where RA may be beneficial. It is beyond the scope of the article to cover individual RA techniques.

Specific challenges in intensive care

RA in the ICU setting poses unique challenges, which can be divided into:

- drug factors;
- patient factors;
- human and environmental factors.

Drug factors

Pharmacology of local anaesthetics

The pharmacokinetics and pharmacodynamics of the local anaesthetics (LAs) may be altered due to the derangements in physiological and metabolic parameters commonly seen in ICU patients. Derangements in acid–base balance, hypoalbuminaemia, and organ failure (hepatic and renal) influence the ionization, unbound free fraction, and distribution of the LAs between body fluid compartments and their clearance. The impact of these derangements may be subtle like prolonged onset and

Table 1 Advantages and disadvantages of RA in intensive care

Advantages	Disadvantages
1. Excellent pain relief	1. Need for expertise and high-resolution ultrasound machines
2. Reduction in stress response	2. Variable failure rate
3. Reduction in use of opioids and their side-effects	3. Difficulty in obtaining consent
4. Reduced sedation, delirium, and ileus	4. Possible, but unproven higher incidence of rare and serious complications (e.g. epidural haematoma)
5. Ability to better assess neurology in the absence of opioids (especially polytrauma)	5. Difficulty in monitoring for side-effects in sedated patients (e.g. nerve injury)
6. Possible reduced duration of mechanical ventilation and early ambulation	6. Repeated position change leading to dislodgement and disconnection
7. Minimizes progression to chronic pain (e.g. in amputations)	7. Potential for errors—route and drug
8. Promotes gut motility and splanchnic perfusion	
9. Reduces sympathetic tone, useful in promoting blood flow in critical ischaemia	

duration of action or dramatic like LA toxicity. To factor these, adjustments to the choice and dose of LA may be needed.

The degree of ionization of an LA depends on the difference between its dissociation constant (pKa) and the pH in the tissues. As LAs are weak bases and have a pKa higher than the physiological pH, they exist predominantly in the ionized form in an acidic environment. As only the unionized form is lipid-soluble and hence can cross the cell membrane freely, onset of action will be delayed in both local (e.g. abscess) and systemic (e.g. septic shock, renal failure) acidosis. Hypoalbuminaemia, which is commonly found in acutely ill patients, increases the unbound free fraction of the LA, and can increase the risk of LA toxicity.

LA toxicity

Impaired ability to clear LA due to factors discussed above predisposes to LA toxicity, especially when administered in large doses or as prolonged infusions. Cardiovascular collapse or seizures may be the only sign, especially in sedated patients, and hence a high index of suspicion is necessary. The British National Formulary (BNF) recommends a maximum bupivacaine dose of 2 mg kg^{-1} over a 4 h period and 400 mg over 24 h. For ropivacaine, depending on the site of injection, the maximum recommended bolus dose varies between 200 and 300 mg and when used as an epidural infusion can be given up to a maximum of 28 mg h^{-1} (cumulative dose of 675 mg over 24 h).[2] The maximum allowable LA dose should be calculated on the basis of ideal body weight, with adjustments for organ impairment.

The use of adjuvants (opioids, clonidine, ketamine, epinephrine, and dexamethasone) allows for a reduction in the dose of LA, and in the case of epinephrine also reduces the plasma concentration. Every unit should have a protocol for management of LA toxicity and use of Intralipid® rescue as suggested by the Association of Anaesthetists of Great Britain and Ireland (AAGBI) guidelines.

Spread of LA

Spread of LA in the epidural or intrathecal space is influenced by changes in position, changes in intrathoracic pressure such as in intermittent positive pressure ventilation (IPPV) and the LA volume. In a study by Visser and colleagues,[3] after a test dose with 4 ml of 2% lidocaine through a low thoracic epidural catheter, application of 7.5 cm H_2O of CPAP resulted in a greater segmental spread of sensory blockade when compared with spontaneously breathing patients. The median increase in the spread was four segments, but this increase was predominantly found caudad to the injection site.

Patient factors

There are insufficient data on the incidence of complications due to RA in ICU and whether it is higher than the perioperative population. However, complications are more difficult to diagnose due to factors commonly found in ICU patients like use of sedation and the presence of abnormal neurology. In addition, peripheral oedema can obscure landmarks and result in poor ultrasound images; neuromuscular weakness can mask motor responses to nerve stimulation.

Owing to these challenges, it is reasonable to assume that RA techniques may run a higher risk of complications like failure, infection, bleeding, neuronal injury, pneumothorax, and haemodynamic compromise. In addition, the development of a complication is likely to have a greater impact on the recovery and rehabilitation of the patient, prolonging their length of ICU stay (LOIS). As an example, diaphragmatic paresis from interscalene block in a patient with chronic obstructive pulmonary disease may hamper successful weaning from ventilatory support. Immunosuppression is very common in ICU either due to pathological insults or pharmacological interventions (sepsis, steroids, drug-induced side-effects, etc.). This not only increases the risk, but may also mask the typical signs and symptoms of neuraxial infections. A high index of suspicion and regular monitoring for rare complications of RA (e.g. meningitis, vertebral abscess, epidural/subdural haematomas, and LA toxicity) is required. Daily nursing observations should include monitoring of neurological function and checking the catheter insertion site for signs of infection.

Organ dysfunction

Renal failure and uraemia can result in hyperdynamic circulation, resulting in rapid absorption and higher peak plasma concentration. This combined with lower plasma clearance of LA may lead to sustained high plasma concentrations. Hence, a 10–20% dose reduction relative to the degree of renal dysfunction is recommended in situations where a high bolus dose [e.g. brachial plexus, paravertebral blocks (PVB)] or prolonged continuous infusion techniques or where repeated boluses/blocks (<5 half-lives) are needed.[4]

In hepatic dysfunction, marked derangements in physiology can occur, including coagulopathy, increased volume of distribution, reduced plasma clearance, hyperdynamic circulation, and concomitant renal dysfunction. Usually, LA doses need not be decreased for single-shot techniques. However, doses need to be reduced by 10–50% for continuous infusion or repeated boluses/blocks (<5 half-lives) depending on the extent of the hepatic and renal dysfunction.[4]

In cardiac failure, the low cardiac output state results in a reduction in the hepatic and renal clearance of drugs. As a consequence, LAs with high first-pass metabolism (e.g. lidocaine) may reach a high plasma concentration. In contrast, strongly protein-bound drugs like ropivacane and bupivacaine have a relatively low first-pass metabolism and hence are not greatly affected. In the presence of advanced heart failure, dose reduction to the order of 10–20% is recommended. Also, epinephrine should be avoided as an additive to LA in these patients due to the risk of arrhythmias.[4]

Human and environmental factors

Infrequent use of RA in ICU results in lack of opportunities for training and familiarity among the nursing staff, and increases the risk of human errors. Using non-interchangeable connectors in RA reduces the chances for drug errors or LA toxicity from inadvertent i.v. infusion.

There is an increased risk of catheter dislodgement due to repeated changes in position for routine aspects of ICU care and to aid oxygenation. Tunnelling catheters intended for longer use and securing the connectors firmly with specialized devices could mitigate this risk. Other environmental factors like space constraints (e.g. indwelling drains, lines and tubes, ICU equipments) and availability of necessary RA equipment can also be an impediment.

Indications for RA

The indications for performing RA in ICU are similar to the perioperative period and in many cases is only a continuum. For example, thoracic epidural analgesia (TEA) facilitates early weaning from ventilatory support in lung surgery, lung transplant, and thoracic trauma.[5] The medical and surgical conditions, which are specific to ICU, which benefit from RA are summarized in Table 2.

RA in ICU: controversies

There are many clinical dilemmas, which clinicians often face when deciding to perform RA in ICU. In a survey of ICUs in the Northwest critical care network, systemic sepsis and vasopressor therapy were cited as the most common contraindications for the performance of RA, followed by coagulopathy and sedation.[6]

It is impossible to provide specific guidance on the suitability of RA in these circumstances, but the generic recommendations in these areas of controversy are:

(i) To perform a risk–benefit analysis on an individual basis and clearly document the reasons. For continuous techniques, the risk–benefit analysis must be reviewed on a daily basis.

(ii) To minimize the risk of RA by:
- availing best local expertise;
- avoiding multiple needle passes;
- using advanced technology like ultrasound;
- appropriate case selection;
- consideration of available alternatives;
- meticulous monitoring for complications.

RA in a septic patient

Serious central neuraxial infections such as arachnoiditis, meningitis, and abscess after neuraxial anaesthesia are rare but can have catastrophic consequences. From the NAP 3 report,[7] the incidence of epidural abscess in the perioperative period after neuraxial instrumentation is approximately one in 47 000, the incidence of permanent harm from vertebral abscess is approximately one in 88 000, and the incidence of paraplegia is one in 236 000. The incidence of bacterial meningitis is <1:200 000.

These incidences are based on perioperative data and not specifically from patients with raised inflammatory markers, bacteraemia, or sepsis. Risk factors for neuraxial infections are

Table 2 Indications of RA in intensive care

Indications of RA	Regional anaesthetic options
Surgical indications	
Thoracotomy—lung transplant/lung resections	Thoracic epidural Paravertebral blocks
Laparotomy	Neuraxial-epidural/spinal TAP blocks: classical and subcostal approaches Rectus sheath blocks Local infiltration analgesia
Rib fractures	Thoracic epidural Paravertebral blocks Interpleural block Intercostal blocks Serratus plane blocks
Limb fractures (traumatic and pathological)/amputations	Lower limb: spinal/epidural Plexus (lumbar+sacral), fascial plane blocks (fascia iliaca blocks), and peripheral nerve blocks (femoral, sciatic, popliteal) Upperlimb: brachial plexus blocks and peripheral nerve blocks
Non-surgical indications	
Acute pancreatitis	Thoracic epidural; coeliac plexus block
Neuralgia, complex regional pain syndromes (CRPS) and ischaemic limb	Sympatholytic blocks
Procedures in ICU	
Chest drains	Intercostal blocks
Tracheostomy	Superficial cervical plexus block
Debridement/dressing changes	Upper and lower limb blocks as above

diabetes, immunosuppression, neuraxial trauma or instrumentation, and systemic or local infection. Despite the frequent presence of the above risk factors in the ICU population, there is not enough evidence to suggest that this poses an increased risk.

In neuraxial infections, bacterial seeding can be due to endogenous (haematogenous or local spread) or exogenous (staff and equipment) factors. Despite the lack of data, there is a general belief that neuraxial blocks must be avoided in patients with systemic sepsis, raised inflammatory markers, or both. Clinical cohort studies and retrospective reviews mainly in paediatric patients with bacteraemia report conflicting results.

There is a disconnect between the organisms that commonly cause systemic sepsis and those that are incriminated in neuraxial infections. Sepsis is not infrequently caused by gram-negative organisms, whereas the commonly isolated organism from a vertebral abscess is *Staphylococcus aureus*. In a prospective audit, catheter colonization was a very common occurrence with an incidence of 29%, but none of the patients with catheter colonization developed neuraxial infection.[8]

Neuraxial infections are medical emergencies, which require prompt diagnosis and urgent treatment to avoid permanent disability. The classical clinical features of meningitis (headache, confusion, neck stiffness, and photophobia) and vertebral abscess (back pain, temperature, neurological deficit in the lower limbs, and raised inflammatory markers) are very inconsistent findings. Neuromuscular block, sedation, confusion and delirium, inability to communicate, raised temperature, and inflammatory markers due to other infections, pre-existing antibiotic therapy, and bacteriostatic effects of LA infusions are some of the confounding factors that could mask the presentation of neuraxial infections; hence, a high index of suspicion is necessary for early intervention and a favourable outcome.

Recommendations for performing neuraxial blocks in the presence of sepsis are (adapted from Wedel and Horlocker):[9]

(i) Except in the most extraordinary circumstances, central neuraxial block should not be performed in patients with untreated systemic infection.
(ii) Patients with evidence of systemic infection may safely undergo spinal anaesthesia, provided appropriate antibiotic therapy is initiated before dural puncture and the patient has shown a response to therapy, such as a decrease in fever (placement of an indwelling epidural catheter in this group of patients remains controversial).
(iii) Epidural catheters should be removed in the presence of local erythema, discharge, or both; there are no convincing data to suggest that concomitant infection at remote sites or the absence of antibiotic therapy are risk factors for infection.
(iv) Close monitoring of neurology and signs of local infection at the injection site may help in early diagnosis, especially when epidural catheters are *in situ* for >48 h. A delay in diagnosis and treatment of major central nervous system infections of even a few hours may significantly worsen neurological outcome.

There is no guidance available for performance of peripheral nerve blocks (PNBs) (single shot or continuous) in the presence of systemic sepsis. It would be safe to assume that the risks may be less than that posed by neuraxial techniques.

Vasopressor therapy

Neuraxial anaesthesia commonly produces hypotension and bradycardia due to sympathetic block and requires administration of vasopressors. In ICU, neuraxial analgesia aggravates hypotension in patients with reduced venous return (e.g. hypovolaemia, IPPV). Avoidance of LA boluses, use of continuous infusions, dilute concentrations of LA, and inclusion of additives may mitigate some of the haemodynamic effects. Alternative RA techniques with fewer propensities to cause haemodynamic instability should be considered. For example, in patients undergoing laparotomy, rectus sheath catheters, when compared with epidural analgesia (EA), have been shown to be equally efficacious, while decreasing the need for vasopressors or fluid therapy.[10]

There are no contraindications for PNB in patients on pre-existing vasopressor therapy, although theoretically, the risk of nerve injury can be higher due to constriction of the vasa-nervorum and alteration of the microcirculation.

Haemostatic abnormalities

Coagulation and platelet abnormalities are common in the intensive care setting: thrombocytopenia (platelets $<100\times10^{-9}$ litre^{-1}) occurs in 35–41% of surgical patients in ICU and coagulation abnormalities can occur in 14–18% of ICU patients. The commonly encountered disease pathologies in the ICU that result in abnormal haemostasis are sepsis, polytrauma and massive transfusion, disseminated intravascular coagulation, liver failure, and uraemia. In addition to this, pharmacological anti-coagulation is almost universally used in ICU due to the risk of deep venous thrombosis, atrial fibrillation, myocardial infarction, and hypercoagulable states due to malignancy. Both acquired and iatrogenic derangements of coagulation may influence the use of RA in ICU. Hence, a careful assessment on the presence of coagulation abnormalities and a review of the prescription chart must be diligently performed.

There is no specific guidance for RA in ICU in the presence of pathological haemostatic derangements; however, the generic guidance published by the American Society of Regional Anaesthesia (ASRA) and AAGBI[11] can be used for decision-making. Haemostatic abnormalities are a relative contraindication to the performance of neuraxial and PNBs. The risk is not the same for all RA blocks: proximal, deep, and perivascular blocks are at higher risk compared with distal, superficial, or 'plane' blocks and it is helpful to refer to the AAGBI stratification of relative risk due to various RA techniques (Fig. 1). The current thinking is, deeper blocks should share the same stringent criteria as the neuraxial blocks on acceptable haemostatic parameters. The advent of ultrasound to perform RA blocks widens the margin of safety in expert hands, and can reduce the risk for some of the deeper and perivascular blocks compared with landmark techniques.

The factors to consider in the risk–benefit analysis include: haemostatic pathology, extent and rapidity of progression of haemostatic derangement, the feasibility for correction of the haemostatic abnormality, the proposed RA block, and its available alternatives.

Haematological abnormalities may develop newly or the existing abnormality may worsen when a continuous RA catheter is still *in situ*. Criteria for catheter removal are exactly the same as catheter insertion, and in the presence of abnormal haemostasis, correction of the abnormality should be aimed for, with haematologist's advice.

Unconscious and sedated patients

RA in the ICU poses two unique challenges, consent and the risk of complications in sedated/anaesthetized patients. Of the two,

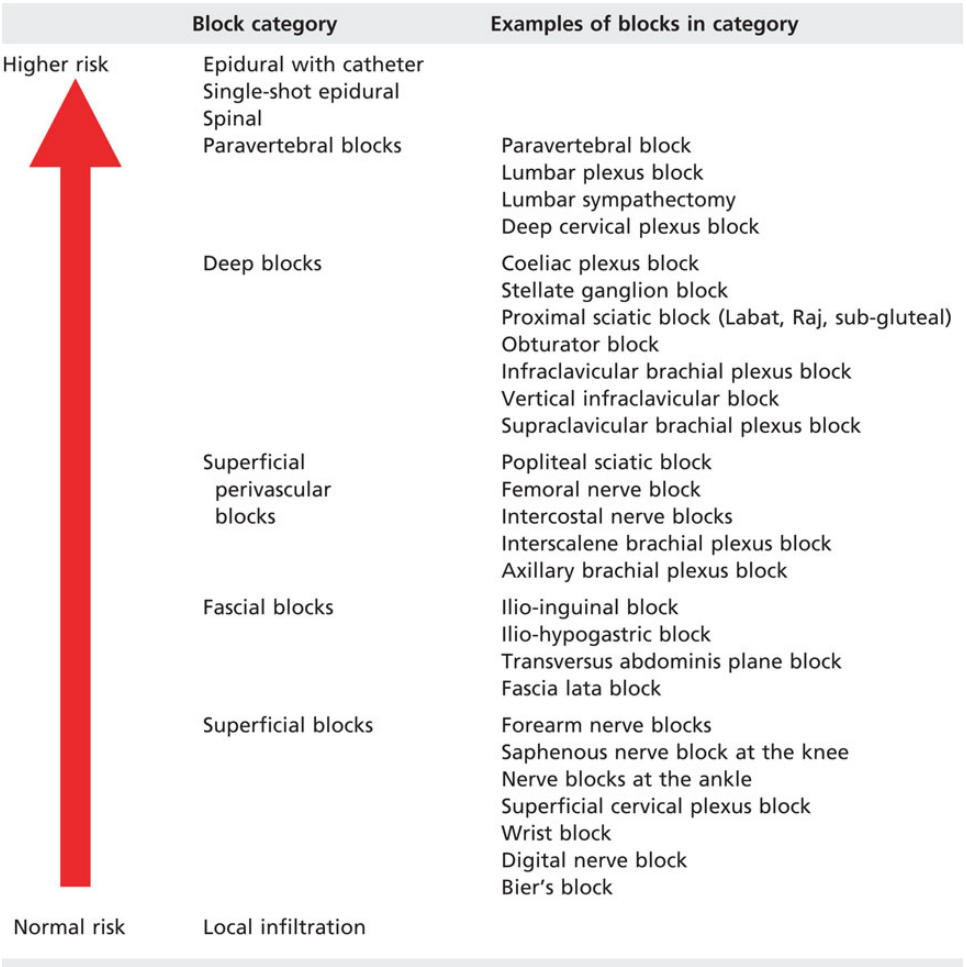

Fig 1 Relative risk of RA in patients with haemostatic abnormality (reproduced with kind permission from the Association of Anaesthetists of Great Britain and Ireland).[11]

the issue of consent is much clearer. Numerous procedures that are performed in a sedated patient in ICU (e.g. tracheostomy and invasive vascular access) are performed keeping the best interests of the patient in mind, carefully weighing the benefits and risks of the procedure to be performed. Consent for RA in ICU is no different from these other procedures, and should be considered if the benefits outweigh the risks.

Many anaesthetists prefer to perform RA in awake patients and would not perform it in anaesthetized patients. However, there is no evidence of increased risk of complications when RA is performed under anaesthesia and it is the only option in paediatric patients. Similarly, the ICU environment does not give one the luxury of performing the blocks awake. Despite the lack of evidence, utmost care must be taken when performing RA in the ICU and monitoring for complications.

Trauma and compartment syndromes

Severe pain and paresthesia are the main symptoms of an evolving compartment syndrome (CS). The incidence of complications and poor outcomes increases with the increasing time from diagnosis to fasciotomy. Complications include muscle necrosis, neurological deficit, rhabdomyolysis, acute kidney injury, amputation, and not infrequently death. In ICU, these symptoms may be masked in head-injured or sedated patients and difficulties in sedation or pain management may be the only clue for an ongoing progression of CS. Under these circumstances, compartment perfusion pressures (diastolic pressure minus compartment pressure) and absolute compartment pressures should be used to diagnose CS, although there are no universally agreed cut-off thresholds.

The clinical symptoms and signs of CS are often variable and unreliable with a very high false-positive rate. Pain is an inconsistent symptom; patients can have CS with no pain or severe pain. Even though all analgesic modalities (PCA, nerve blocks, and EA) have been implicated in the delayed diagnosis of CS, it could easily be averted if patients have regular monitoring of pain, sensation, movement, and function.[12] Despite a commonly held belief that RA should be avoided in situations where there is a risk of developing CS, there are no randomized controlled trials evaluating the influence of RA on delaying its diagnosis and the evidence is limited to case reports and case series. Many experts believe that EA does not contribute to delayed diagnosis of CS. In the published review by Mar and colleagues,[12] >90% of the patients still demonstrated classical signs and symptoms of CS, in the presence of EA. Fifty-one per cent of patients had breakthrough pain and delays in diagnosis occurred only when the motor blocks were dense.[13] Of the PNBs, there is no evidence that they delay diagnosis of CS in the upper limbs and thigh CS (femoral block) in lower limbs. Traumatic mid-shaft tibial fractures were most commonly missed in the presence of PNB.

A high concentration LA infusion can mask many of the symptoms of CS, by causing complete limb anaesthesia and

paralysis. Hence, avoiding dense blocks by using weak concentrations of LA with adjuncts like opioids and using continuous infusions aid good pain management and facilitate early diagnosis. Providing suboptimal analgesia for identification of CS is a bad practice, and in most cases, breakthrough pain or increasing analgesic requirements precedes the development of clinical signs. Triaging high-risk patients, a high index of suspicion and regular clinical monitoring with early measurement of compartmental pressures form the cornerstones in the early diagnosis and management of CS.

Analgesia in intensive care: specific situations

Rib fractures

The prevalence of rib fractures is 4–10% among the trauma population, with mortality ranging from 3% to 13%, pulmonary complications from 16% to 60%, and they account for up to 25% of the trauma-related fatalities. The mortality and pulmonary complications increase with age, pre-existing conditions, number of ribs fractured, presence of flail segments, and lung injury.

Development of pulmonary complications (pneumonia, atelectasis) determines the duration of mechanical ventilation, LOIS, and length of hospital stay (LOHS) and severe pain is a contributory factor in development of this associated morbidity.

Effective analgesia is able to reverse some of the pulmonary complications. Both systemic (oral, i.v. opioids and PCA) and regional analgesia (epidural, paravertebral, interpleural, intercostal blocks) can be used.

There is ongoing debate about systemic or TEA on mortality, LOIS, and LOHS in patients with rib fractures. In patients with three or more rib fractures, Gage and colleagues[14] reported a reduction in the odds of death for up to a year, in those receiving TEA when compared with systemic analgesia. In contrast, other reviews did not find a difference in mortality, LOHS, or duration of mechanical ventilation.[5,15] But none of these studies looked into significant adverse effects of opioids like delirium.

PVB provide good-quality sensory block of the hemithorax with reduced incidence of hypotension, motor block, and urinary retention that are common with TEA. Continuous PVB for unilateral rib fractures provides significant improvement in pain scores at rest and on coughing, improves peak expiratory flow rates and oxygenation. In patients with unilateral rib fractures, PVB provides equivalent analgesia when compared with TEA, with no difference in LOHS, LOIS, or pneumonia rates. PVBs are technically challenging to perform and carry a 1–2% risk of pneumothorax. Ultrasound guidance improves the success rate and minimizes the complications of PVB. In a retrospective audit in the author's centre (M.N.), continuous paravertebral analgesia provides effective pain relief and may be associated with fewer ICU admissions with respiratory failure (unpublished data).

Continuous intercostal nerve block has been shown in a prospective case series to significantly reduce the pain on rest and coughing and decrease the LOHS, whereas interpleural analgesia has not been shown to be of any benefit.

Based on the current evidence, it is not possible to recommend any single technique for pain management in patients with fractured ribs, which can be applied in all possible circumstances.

Laparotomy

Laparotomy is one of the most common surgical reasons for admission to ICU and until recently, only EA was the commonly used RA technique to provide pain relief. EA does not reduce mortality when compared with systemic opioids, but has a favourable influence on numerous morbidity factors: reduction in the incidence of paralytic ileus, delirium, LOIS, and duration of mechanical ventilation. EA, when compared with i.v. analgesia, increases functional residual capacity by 27% and decreases the rate of pulmonary complications,[16] which carries a greater significance in ICU. In the MASTER trial involving patients undergoing major abdominal and oesophageal surgeries, even though there was no difference in mortality rates, TEA was associated with significantly reduced pulmonary complications and lower pain scores, without an increase in catheter-related complications.[17] In a retrospective study, there was a 70% risk reduction in the TEA group for anastomotic leak after oesophagectomies.[18]

There are instances in ICU where EA is contraindicated or the side-effects undesirable (hypotension and bradycardia), where continuous trunk blocks [rectus sheath blocks, transversus abdominis plane (TAP) blocks, and wound infiltration catheters] are effective alternatives. They offer equivalent analgesia while reducing the need for rescue vasopressors, fluid therapy, and urinary catheterization.[10] EA has a high failure rate, more so in the ICU, and trunk blocks can be used as a rescue analgesic technique. Trunk blocks when compared with opioid-based techniques offer equivalent analgesia but with quicker recovery of bowel function.

It is important to understand the anatomy to choose the most appropriate technique for the patient. Rectus sheath blocks are effective in providing analgesia by blocking the anterior cutaneous nerves of the abdomen. They carry many advantages over EA —they can be sited either by the anaesthetist or by the surgeon, intraoperatively or after operation, and without the need for a change in position of the patient. Complications are rare, but one needs to be aware of the risk of rectus sheath haematoma, which can mimic an acute abdomen or sepsis by causing haemodynamic instability.

TAP blocks, unlike rectus sheath blocks, are effective for transverse incisions, but are inadequate for covering dermatomes above T10 level. A variant of TAP block, the subcostal oblique TAP block, can be used for incisions above the T10 dermatome, for example, 'roof-top' incisions for cholecystectomy and liver resections. In a retrospective study, TAP blocks were as effective as EA for open abdominal aortic aneurysm repair.

Acute pancreatitis

Acute pancreatitis is a very common surgical emergency with an annual incidence of 15–35 per 100 000 and with a mortality of up to 30% in severe types. It is associated with severe pain, and opioid-based strategies remain the mainstay of analgesia. However, opioids can cause or worsen ileus, sedation, and reduce respiratory drive, which may be detrimental to these patients, who generally present with multi-organ impairment.

There has been inertia for adopting TEA as a normal component of pain management in acute pancreatitis, even though there have been successful reports dating back to 1950. There is encouraging evidence derived from animal studies, that thoracic epidural block may play a vital role in modifying splanchnic tissue microperfusion, protecting vulnerable microcirculatory units from ischaemic damage and improving end-organ perfusion, regardless of its effects on macro-haemodynamics.[19] In a prospective study of 121 patients with acute pancreatitis, 72% obtained excellent analgesia with TEA without the need for other added analgesia; only 8% required vasopressor support, with no reported complications.[20] The optimal timing and the duration of TEA remain unclear. In another prospective case series, continuous coeliac plexus block provided effective pain relief in patients

who failed to respond to TEA, especially with a history of alcohol or opioid dependence.

Vasospasm and sympathetically mediated pain

Stellate ganglion block has a unique role in providing analgesia for complex regional pain syndromes and refractory ischaemic chest pain, despite medical management. It provides sympatholysis and hence finds use in the salvage of ischaemic limbs in patients with peripheral vascular disease and in the treatment for vasopressor extravasation. It has also been shown to reduce the incidence of vasospasm of intracranial and extracranial arteries after subarachnoid haemorrhage or aneurysm coiling, resulting in improvement of GCS.[21] There are case reports of the usefulness of stellate ganglion block in the management of ventricular arrhythmias and sustained ventricular fibrillation refractory to electrical and pharmacological management.

Hip fractures

Annually, about 64 000 patients are admitted with hip fracture in the UK and the average 30 day mortality is around 8%. Achieving adequate analgesia in the population could be a challenge and conventional systemic analgesics like opioids carry significant adverse effects, as discussed above. RA techniques like fascia iliaca compartment block (FICB) and femoral nerve block can minimize or circumvent these adverse effects and provide superior quality of analgesia. In comparison with femoral nerve block, FICB being a 'plane block' is anatomically distant from the neurovascular structures and thereby minimizes the risk.

The benefits of these blocks extend beyond just provision of pain relief—they decrease the incidence of sedation and delirium, nausea and vomiting, need for supplemental oxygen, morphine requirements, and LOHS. Both the incidence and the duration of delirium are reduced in patients receiving FICB.

Conclusion

RA is an under-utilized modality, but has the potential to provide excellent pain relief while avoiding the side-effects of systemic drugs in intensive care. There are many common dilemmas faced while considering RA in the ICU, and risk–benefits have to be individualized. Risks can be minimized by following local and national guidelines, using modern equipment and techniques and maintaining expertise in RA.

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Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Anaesthesia for transjugular intrahepatic portosystemic shunt insertion

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Key points

- Anaesthesia for transjugular intrahepatic portosystemic shunt (TIPS) procedures requires consideration of the physiological and pharmacological changes in advanced liver disease, and haemodynamic instability in variceal bleeding.
- The logistics of anaesthesia in the angiography suite must be considered, particularly positioning of the patient, equipment, and personnel in relation to moving imaging equipment.
- General anaesthesia with tracheal intubation is preferred as it ensures airway protection, adequate ventilation, and optimal conditions for the radiologist.
- Complications during the procedure include arrhythmias and haemorrhage due to vascular injury or liver capsule rupture.
- Early post-procedure complications include ventricular failure, encephalopathy, renal failure, liver failure, and sepsis.

Background

The prevalence of liver disease in the UK has increased substantially over recent decades, principally due to alcohol, non-alcoholic fatty liver disease associated with obesity, and viral hepatitis B and C. Liver cirrhosis may lead to the development of portal hypertension, which has a significant impact on patient outcomes and survival. These patients are clinically challenging and costly to manage, often requiring treatment for consequences of liver failure such as ascites, variceal haemorrhage, sepsis, and renal failure. Transjugular intrahepatic portosystemic shunt (TIPS) insertion offers a minimally invasive option for lowering raised portal pressure, which can provide symptomatic relief and confer a survival benefit in selected patients suffering the complications of portal hypertension. The first TIPS procedures were carried out in the 1980s, and success rates have increased as endovascular and radiological technologies have developed. There are, however, considerable challenges to delivering an effective TIPS service, including the organization of multidisciplinary input with appropriate anaesthetic expertise and support.

Portal hypertension

The liver receives ~25% of the cardiac output, via a dual blood supply. The hepatic arteries carry oxygenated blood via the aorta and coeliac axis, while the portal vein carries nutrient-rich blood from the gastrointestinal tract to process within the hepatic parenchyma. The portal vein is formed by union of the mesenteric veins and splenic vein posterior to the head of the pancreas, and divides into right and left branches which enter the respective liver lobes. Venous drainage is via the hepatic veins to the inferior vena cava.

Portal hypertension occurs when there is increased resistance to portal venous blood flow through the liver as a result of structural disruption, which can have many causes (Table 1). The most common cause in the Western world, accounting for around 90% of cases, is liver cirrhosis. In addition to the fixed obstruction resulting from structural disruption, there can be a dynamic component due to stellate cell contraction within the liver as a result of acute events such as sepsis or acute high alcohol intake.

Diagnosis

The diagnosis of portal hypertension may be suspected clinically in patients with features of cirrhosis, suggestive haematology (thrombocytopenia), or diagnostic radiological findings (splenomegaly, recanalization of the umbilical vein, or reversal of flow in the portal vein). Diagnosis can be confirmed by measurement of the hepatic venous pressure gradient (HVPG), which is the gold standard for assessing portal hypertension and also has prognostic value. HVPG is a surrogate for the portal pressure gradient and is measured at hepatic venous catheterization as the difference between the balloon-wedged hepatic venous pressure and free hepatic venous pressure. Normal HVPG is up to 5 mm Hg; portal hypertension is defined as an HVPG ≥6 mm Hg, with clinical manifestations including variceal haemorrhage or liver decompensation typically occurring at ≥10 mm Hg as the increased portal venous pressure results in development of a collateral circulation.[1]

Clinical manifestations of portal hypertension include ascites, hydrothorax (a transudative pleural effusion, on the right side in 90% of cases), varices (oesophageal, gastric, periumbilical, rectal), portal hypertensive gastropathy, hepatorenal syndrome, and hepatopulmonary syndrome. The physiological effects which result from the consequences of advanced liver disease and portal hypertension have been described in detail elsewhere.[2]

Treatment options

Treatment of portal hypertension aims to reduce HVPG either pharmacologically or by TIPS in order to manage these complications. In addition, treating the underlying cause, such as achieving abstinence from alcohol or using antiviral regimes, frequently limits or reverses complications.

Ascites and hepatic hydrothorax may respond to a sodium restricted diet or diuretics (e.g. spironolactone, furosemide) to promote sodium excretion. Diuretic-resistant ascites may require repeated large-volume paracentesis with i.v. albumin replacement.

Table 1 Some causes of portal hypertension

Pre-hepatic
Portal vein thrombosis
Splenic vein thrombosis
Intra-hepatic
Alcoholic cirrhosis
Non-alcoholic fatty liver disease (NAFLD)
Viral hepatitis B and C
Drugs (e.g. methotrexate)
Wilson's disease
Haemochromatosis
Primary biliary cirrhosis
Sarcoidosis
Polycystic liver disease
Idiopathic fibrosis
Post-hepatic
Hepatic venous obstruction
Budd–Chiari syndrome

In any patient with established cirrhosis, endoscopic surveillance for varices should be performed at diagnosis and repeated every 2–3 yr. Primary prophylaxis with non-selective β-block (e.g. carvedilol or propranolol) or endoscopic variceal band ligation is equally effective in reducing the risk of a first bleed. When medical or endoscopic therapy fails and portal pressure remains persistently high, shunt procedures such as TIPS may be beneficial.

Selection of patients for TIPS

TIPS provides symptomatic benefit and improves survival in patients with diuretic-resistant ascites which requires frequent paracentesis.[3] It confers a survival advantage when used for the control of variceal bleeding,[4] in which it can be used to control haemorrhage from oesophageal and gastric varices, and to prevent recurrence once initial control has been established. There are other uses for TIPS, which have limited supportive evidence (Table 2). Clinical outcomes, including mortality, after TIPS can be predicted using liver disease severity scores such as the model for end-stage liver disease or Child–Pugh scores.[5]

There are several absolute and relative contraindications[6] (Table 3). Where possible, clinical assessment by a hepatologist, echocardiography, and triple-phase computed tomography (CT) should be performed in all patients.

Procedure and complications

TIPS insertion requires expertise in interventional radiology and is usually performed in the angiography suite. Internal jugular

Table 2 Indications for TIPS insertion

Significant evidence
Refractory ascites
Variceal bleeding
Limited evidence
Portal hypertensive gastropathy
Gastric antral vascular ectasia
Refractory hepatic hydrothorax
Hepatorenal syndrome
Budd–Chiari syndrome
Hepatic veno-occlusive disease
Hepatopulmonary syndrome

Table 3 Contraindications to TIPS insertion[6]

Absolute contraindications
Heart failure
Severe tricuspid regurgitation
Severe pulmonary hypertension (mean pulmonary pressure >45 mm Hg)
Multiple hepatic cysts
Sepsis
Biliary obstruction
Relative contraindications
Hepatocellular carcinoma
Obstruction of all hepatic veins
Portal vein thrombosis
Severe coagulopathy
Thrombocytopenia (platelet count $<20\times10^9$ litre^{-1})
Prior encephalopathy
Moderate pulmonary hypertension

vein cannulation allows passage of a catheter into the hepatic vein where wedge pressure is measured and HVPG calculated.

Hepatic venography (using contrast or carbon dioxide), often ultrasound-assisted by a second operator, is used to delineate the vascular anatomy of the liver and a communication between a branch of the hepatic venous and portal venous circulation is created by the cutting tip of the catheter under fluoroscopic control. After balloon dilatation of this communicating track, a polytetrafluoroethane-covered nitinol (e.g. Gore Viatorr®; typical dimensions 10 mm×80 mm) stent is deployed to maintain patency. Procedure duration varies and challenges include guidewire positioning and adequate HVPG reduction with stent placement; the objective is to reduce the HVPG to near normal levels and at a minimum to <12 mm Hg.

Internal jugular vein access can be complicated by carotid or tracheal puncture, pneumothorax or haemothorax, thoracic duct, or brachial plexus injury. The passage of the catheter through the right atrium may cause irritation precipitating arrhythmias, and rarely damage to the myocardium. Technical difficulty can occur in puncture of the portal vein, which may result in liver capsule puncture and potentially fatal haemorrhage into the peritoneal cavity. Portal venous rupture, inadvertent puncture of the hepatic arteries, biliary structures, and right kidney have also been reported. Late complications such as stent occlusion, thrombosis, or dislodgement may also occur. Major complications occur in 3–5% of procedures and mortality rates vary with the indication for TIPS, being higher for emergency procedures.[7]

Anaesthesia

Patients undergoing TIPS are medically complex as a result of chronic liver disease causing multisystem physiological disruption. They should receive multidisciplinary input as part of comprehensive preoperative assessment and optimization before undergoing the procedure.

Patients who are potential or confirmed transplant candidates must be carefully considered as TIPS may rarely precipitate sudden decompensation to fulminant hepatic failure. These cases should be discussed with a transplant centre and transferred if appropriate.

Pre-procedure work-up and optimization

A full evaluation of co-existing conditions should be undertaken in the usual manner before anaesthesia, although there are several particular areas to which attention must be directed in order to ensure optimal outcomes. The urgency of the procedure will determine the extent of preoperative work-up that is feasible.

Cardiovascular status must be assessed. Patients with cirrhosis often exhibit a hyperdynamic circulation with low-normal arterial pressure due to persistent splanchnic vasodilatation. Cardiac output will increase after TIPS insertion as pooled venous blood returns to the systemic circulation; hence, any degree of heart failure must be assessed before shunt insertion as this is likely to deteriorate with the effective fluid challenge post-procedure. Symptomatic heart failure and tricuspid regurgitation should be assessed using transthoracic echocardiography and treatment optimized before TIPS is considered. All patients should undergo echocardiography to determine left ventricular function and to exclude severe pulmonary hypertension; this would contraindicate the procedure due to the expected increase in right heart and pulmonary pressures with increased preload after shunting.

Reduced functional residual capacity due to ascites and hepatic hydrothorax impairs respiratory function. This is exacerbated by the supine position required for the procedure. Baseline ventilatory observations may reveal respiratory dysfunction, while a chest radiograph will indicate the presence and extent of hydrothorax. Consideration should be given to drainage of any intraperitoneal or intrathoracic fluid collection in patients with severe respiratory compromise. This is normally performed on the day before the TIPS procedure and should involve the use of albumin for volume replacement (8 g per 2.5 litres drained) to avoid post-paracentesis circulatory dysfunction and renal impairment.

Thrombocytopenia and coagulopathy are common in cirrhotic patients and these abnormalities should be corrected before shunt insertion. Targets are controversial; a platelet count more than 50×10^9 litre^{-1} and INR <1.5 are recommended in cases of gastrointestinal bleeding and are reasonable aims when considering TIPS.[8]

Cross-matched blood should be requested according to local policy, bearing in mind that patients have often had multiple transfusions in the past after repeated variceal haemorrhage and may therefore have atypical antibodies requiring extended cross-matching and import of blood products from regional centres. In cases of variceal bleeding, a restrictive transfusion threshold (7 g dl^{-1}) has been shown to improve outcomes in Child–Pugh class A or B patients, but not Child–Pugh C, when compared with a liberal transfusion threshold (9 g dl^{-1}).[9]

Baseline renal impairment must be investigated further, as this may represent intrinsic renal damage or a degree of hepatorenal syndrome. In either case, the receipt of a significant contrast load during TIPS insertion may adversely affect renal function. This may be attenuated by correction of hyponatraemia, volume expansion with human albumin solution, and the use of acetylcysteine for 48 h, although there is a lack of trial evidence to support this.

The presence and severity of hepatic encephalopathy should be assessed and graded,[2] as this may occur or worsen after shunt insertion due to entry of unprocessed portal blood into the systemic circulation. The presence of overt hepatic encephalopathy may contraindicate TIPS in the elective situation.

In the emergency situation, such a detailed work-up is not feasible and the results of historical investigations may need to be acquired. Baseline laboratory testing should be performed—haemoglobin, platelet count, coagulation screen, and renal and hepatic function—as these will guide optimization and influence post-procedure destination. Haemodynamic stability should be the aim, but may be unattainable with ongoing variceal bleeding, and temporizing measures such as a Sengstaken tube insertion may have a place. I.V. fluid and blood product administration is required to maintain circulating volume and correct coagulopathy to an acceptable level for jugular and hepatic puncture. Patients with acute variceal haemorrhage will usually receive vasopressors (e.g. terlipressin) and broad-spectrum antibiotics (e.g. piptazobactam) as part of their medical therapy.

Anaesthetic technique

Complexities of remote site anaesthesia should be considered and include the delivery of care in an unfamiliar environment, often distant from theatres (and their inherent safety due to staff and equipment availability), with staff not necessarily trained in anaesthetic practice.

For elective TIPS procedures, the choice between sedation or general anaesthesia will depend on patient factors and local practice. There is little literature comparing different methods

and so the advantages and disadvantages of each must be considered for each individual case.

Conscious sedation can be used, using combinations of short-acting sedative agents that include midazolam, propofol, and remifentanil. Although sedation may avoid the need for general anaesthesia, many patients experience significant discomfort in the supine position for a prolonged period of time. Airway protection is not guaranteed, ventilation may be compromised, agitation caused by encephalopathy may hinder safe completion of the procedure, and discomfort during balloon dilatation of the intrahepatic tracts may be severe. In cases managed under sedation, equipment and personnel should be immediately available for conversion to general anaesthesia, which may then present a significant challenge with a patient positioned on the imaging table.

General anaesthesia is recommended by many as the preferred technique on the grounds of safety, particularly when complications occur.[10] This requires the appropriate equipment, monitoring, and assistance as mandated by the AAGBI. Sedative premedication should be avoided, as this will have a prolonged effect, and may exacerbate encephalopathy. An H_2-receptor antagonist or proton pump inhibitor can be used.

The logistics of anaesthetizing a patient in the interventional radiology suite will be dictated by the configuration of each individual angiography suite (an example is shown in Fig. 1). The induction of anaesthesia requires appropriate space and a tilting table in the case of regurgitation, and as this cannot be easily achieved on most angiographic tables, a separate location for induction and emergence from anaesthesia is sometimes required.

I.V. access should be secured, which may be difficult in the patient with chronic liver disease. Central venous access may be required, in which case the femoral veins or the left internal jugular vein can be used after discussion with the radiologist. Invasive arterial pressure monitoring should be used as haemodynamic instability is a frequent complication. Insertion of lines on the side most accessible to the anaesthetist in the interventional suite is advisable, along with the use of multi-lumen extension devices. A double pressure transducer is essential, as this will allow one port for connection of the arterial line and a second port for transduction of the venous pressure line inserted by the radiologist. Urinary catheterization and patient warming are required as procedures may be prolonged. A broad-spectrum antibiotic (e.g. piptazobactam or a third-generation cephalosporin) should be administered before the procedure and continued for 24 h after.

In most cases, tracheal intubation is the safest option, as patients with ascites have disrupted respiratory mechanics and a raised intra-abdominal pressure which will increase the risk of regurgitation of gastric contents. Rapid sequence induction of anaesthesia with application of cricoid pressure is often warranted. Controlled ventilation is useful as a motionless patient and the ability to provide frequent breath holds will aid the radiologist in positioning the shunt. Good communication between radiologist and anaesthetist is essential.

The choice of drugs demands consideration of the physiological and pharmacokinetic changes seen in chronic liver disease patients.[2] A cautious dose of propofol or thiopental is suitable for induction of anaesthesia, with muscle relaxation provided by succinylcholine followed by a renally excreted

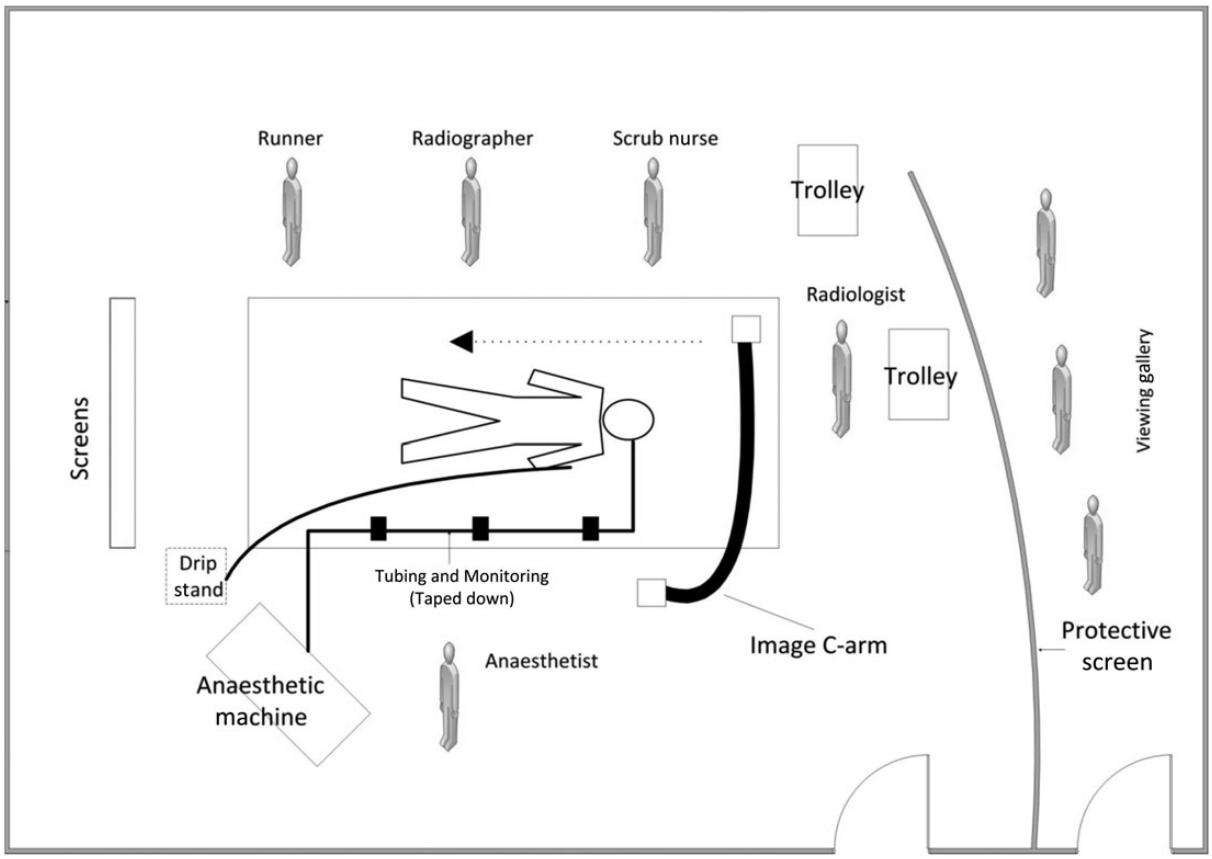

Fig 1 Set up of an interventional radiology suite for a TIPS procedure under general anaesthesia.

non-depolarizing neuromuscular blocking agent (e.g. atracurium). Short-acting opiates (e.g. alfentanil, fentanyl) can be used in carefully titrated doses to aid tube tolerance and cover stimulating parts of the procedure. Maintenance of anaesthesia with a volatile agent or a total i.v. anaesthesia technique is appropriate.[9] The aim should be to use appropriate doses of short-acting agents in order to allow rapid post-procedure recovery.

Emergency TIPS for control of acute variceal haemorrhage is usually undertaken when endoscopic therapy has failed, or more commonly as a proactive early measure for those with Child–Pugh B with active bleeding or Child–Pugh up to C13. These patients are likely to possess a compromised airway, haemodynamic instability, coagulopathy, and susceptibility to sepsis and risk of hepatic encephalopathy. For acute haemorrhage, urgent stabilization will be required and measures may have already been instituted to facilitate endoscopic therapy. Airway protection by rapid sequence induction of anaesthesia and tracheal intubation is mandatory. Large-bore peripheral venous access and invasive arterial pressure monitoring will be required and correction of haematological abnormalities is essential, as is judicious blood transfusion.[8] It is not uncommon to require activation of a major haemorrhage pathway in this situation.

For those patients undergoing TIPS after successful endoscopic therapy but with a high risk of re-bleeding, management principles can broadly follow the elective route. However, there may not be sufficient time to perform a full preoperative work-up. The anaesthetist should be aware of an increased aspiration risk due to residual blood in the stomach, the potential for continued haemodynamic instability, and the effects of recent massive transfusion.

Post-procedure care

Haemodynamic instability may remain after the procedure in those with blood loss, so haemodynamic monitoring and correction of anaemia and coagulopathy is required. The increased venous return to the heart can precipitate heart failure, which will require initial medical stabilization followed by diuresis. The application of continuous positive airway pressure may also be considered in treating pulmonary oedema. A haemolytic anaemia may develop between 7 and 14 days post-procedure, due to mechanical shear stress on blood cells as they pass through the shunt.

Encephalopathy occurs in up to 20% of patients after TIPS. This can occur at any time after the procedure and is caused by shunting of hepatic venous blood containing neurophysiologically active compounds such as ammonia and benzodiazepine-like substances, which may enhance cerebral GABA-ergic tone. Hepatic encephalopathy can be managed with a combination of lactulose and non-absorbable antibiotics (e.g. rifaximin), TIPS shunt size reduction, or TIPS occlusion in intractable cases.[7] If iodine-based contrast is used, there is a risk of contrast nephropathy and an exacerbation of hepatorenal syndrome if this was present, even subclinically, before the procedure. Fluid management and renal replacement therapy should be considered in discussion with critical care and renal specialists.

There is a risk of post-procedural sepsis, principally caused by gram-negative organisms (e.g. *Escherichia coli, Klebsiella, Enterococcus*). Early identification and administration of antibiotics (piptazobactam or a third-generation cephalosporin) is essential in order to avoid deterioration in organ function. Fluid and vasopressor therapy may be required.

Patients are managed either on critical care, hepatology, or gastroenterology wards and are subject to early warning scoring and frequent medical review. Given the potential for multisystem decompensation, access to critical care outreach and high dependency care in the post-procedure period is necessary. However, given the nature of the underlying disease and often guarded prognosis, escalation of care must be carefully considered with appropriate ceilings of care set in a multidisciplinary environment, ideally in advance of any intervention.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Anaesthetic management for craniosynostosis repair in children

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Key points

- Craniosynostosis occurs isolated in 80% of patients.
- Syndromic craniosynostosis is often combined with midface hypoplasia, skull base, and limb abnormalities.
- Treatment is predominantly surgical and depends on the age of the child, associated complications, and the type of craniosynostosis present.
- Specific risks related to surgery include major blood loss and venous air embolism.
- Newer surgical techniques are emerging which adopt a minimally invasive approach with the intended benefits of reducing morbidity, hospital length of stay, and costs. These techniques remain controversial and are as yet not widely practiced.

Craniosynostosis is a condition in which premature fusion of one or more of the cranial sutures occurs, leading to abnormal skull development and head shape. The infant skull is made up of a series of bony plates separated by sutures that allow distortion of the head shape during birth and permit growth and development of the infant brain into adulthood. Abnormal premature fusion of one or several of these sutures results in restricted growth of the skull perpendicular to the affected suture. Compensatory bone growth occurs parallel to the affected suture in order to allow for continued brain growth and results in distinct clinical skull characteristics (Fig. 1).

Children may present with a broad range of conditions requiring correction, from otherwise well children with single suture craniosynostosis (80% of cases) to syndromic children with multiple synostoses with other cranial and extracranial anomalies. The overall incidence of craniosynostosis is about one in 2500 live births.

Correction may require extensive surgery that is commonly performed at a young age, and although the incidence of adverse events is low, potential risks and complications exist.

Uncorrected craniosynostosis may result in complications that include:

- Raised intracranial pressure (ICP)—this is more common in syndromic craniosynostosis and particularly when multiple sutures are affected. Factors causing this include hydrocephalus, craniocerebral disproportion, airway obstruction, or abnormalities in the venous drainage from the brain.[1]
- Cognitive and neurodevelopmental impairment—including global developmental delay, problems with speech and hearing, and poor feeding may occur.
- Psychological implications of poor self-esteem and isolation due to an abnormal appearance.

Syndromes associated with craniosynostosis

Syndromes most frequently associated with craniosynostosis include Apert, Crouzon, Pfeiffer, Saethre–Chotzen, Carpenter, and Muenke syndromes (Table 1). Most show autosomal-dominant inheritance, although they are often sporadic and may involve mutations in genes encoding for fibroblast growth-factor receptors (FGFR), leading to defective intracellular signalling, and in *TWIST* genes.[1] Syndromes often include midface hypoplasia, skull base, and limb abnormalities that may lead to associated problems such as raised ICP, airway obstruction, feeding difficulties, behavioural, and psychological issues (Table 1).

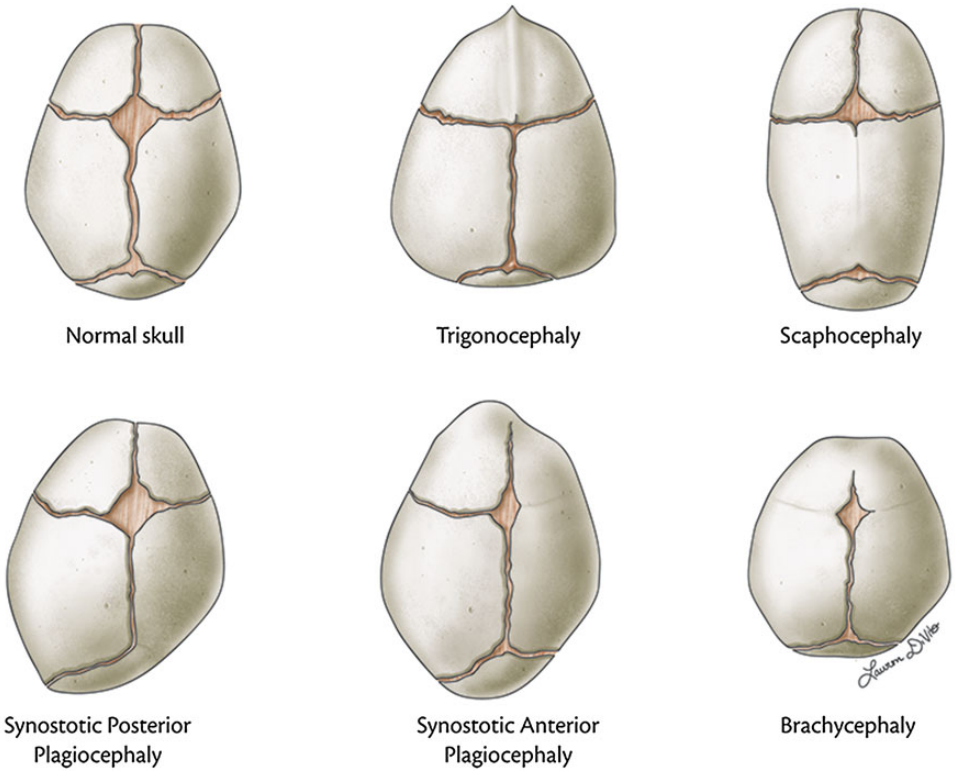

Fig 1 Anatomical variations of craniosynostosis. Illustration by Lauren Divito. (Rights reserved).

Surgical options

The treatment of craniosynostosis is predominantly surgical and requires a coordinated and integrated approach between a large multi-disciplinary team, including, but not limited to, combined plastics and neurosurgical teams, anaesthesia, and specialist nursing. Surgical correction is not solely cosmetic; corrective procedures are performed early in life to allow normal brain growth and cognitive development. It is important to remember that every patient is different in terms of the cosmetic appearance and functional problems faced and treatment is therefore highly individualized. For this reason, a range of procedures and techniques exist (Table 2), varying between centres across the world particularly between the UK and North America.

The timing of surgical intervention is controversial. Indications for emergency surgery include an immediate threat to the airway or eyes, or the presence of raised ICP. Advantages of early surgical intervention include increased malleability of the softer younger bone and the ongoing brain growth encouraging continued growth of the cranial vault. This comes at the cost of performing complex surgery and anaesthesia in a younger child, increased complications associated with blood loss, and the increased likelihood of the need for re-do surgery at a later date. In older children, the re-operation risk is lower and surgery and anaesthesia are potentially safer; however, surgery can be more challenging due to increasing severity of deformities and thicker, less malleable bone. There may also be reduced ability of the skull to ossify small defects necessitating the use of bone grafts. Surgery is often performed around 8–12 months of age to balance these challenges.

Surgery is often specific to the particular synostosis involved, but some general principles apply for all of the surgeries; these are to prevent progression and correct the abnormality and to reduce the risks of raised ICP that may occur without surgery.[1] Three-dimensional CT scanning provides useful anatomical information and can clearly demonstrate the abnormally fused suture(s) and allowing surgeons to plan. There is a trend away from the more traditional invasive open surgery towards less invasive endoscopic techniques with the potential advantages of reduced morbidity and length of stay balanced against surgical outcomes and risk of re-operation rate in the less invasive surgeries.

Invasive surgery

Correction of sagittal synostosis

Surgery performed before 6 months of age

In craniosynostosis diagnosed before 6 months of age, the best cosmetic and functional results are often obtained if the surgery is performed early in the child's life for the reasons previously discussed. This type of corrective surgery is performed at around 4–6 months of age with an extended strip craniectomy and, in some institutions, subsequent helmet moulding therapy which relies on early rapid brain growth to drive remodelling.[1] This surgery comprises excision of the fused suture, usually sagittal, and expansion of the adjacent bone using cuts to allow brain growth. Surgical time is usually around 1–3 h and, when used, a helmet may be fitted around 7–10 days later to ensure a more symmetrical skull shape and to protect from any undue pressure. This is worn for 23 h a day for usually around 4–6 months. Although early surgery may be beneficial for many reasons, it comes at the compromise of increased inherent risks of anaesthesia and surgery in a younger infant and concerns regarding restenosis rate and poorer resolution of the cephalic index compared with other more invasive surgical techniques.

Table 1 Characteristics of syndromes associated with craniosynostosis. AD, autosomal dominant; AR, autosomal recessive

Syndrome	Gene mutation and inheritance	Synostosis	Facial features	Extracranial features	Anaesthetic considerations
Apert	FGFR-2 AD	Bicoronal Brachycephaly	Maxillary hypoplasia Low set ears, cleft palate, exorbitism, hypertelorism, strabismus, hearing loss	Complex syndactyly Developmental delay	Potentially difficult facemask ventilation and airway management OSA Corneal abrasions/eye injury
Crouzon	FGFR-2 (FGFR-3) AD	Bicoronal	Midface hypoplasia (less severe than Aperts, cleft palate rare) Tall flattened forehead, proptosis	Cervical spine abnormalities (present in 1/3rd) Normal hands and feet Normal development	Cervical spine must be evaluated before surgery Potentially difficult facemask ventilation/airway management Corneal abrasions/eye injury
Pfeiffer	FGFR-1 and 2 AD	Ranges—bicoronal to fusion of all sutures (cloverleaf skull)	Midface hypoplasia (varying degrees)	Broad thumbs, wide great toes, partial syndactyly Radiohumeral synostosis of elbow, hydrocephalus, imperforate anus may occur	Raised intracranial pressure in severe forms
Muenke	FGFR-3 AD	Uni- or bicoronal	Midface hypoplasia—usually mild Wide set eyes Low set ears	Broad toes, brachydactyly Potential developmental delay	Usually mild compared with other syndromic forms but higher risk of re-operation than non-syndromic craniosynostosis
Carpenter	RAB23 (RAS-associated protein) AR	Coronal, sagittal, and lamboidal with brachycephaly	Midface hypoplasia Low set ears, high arched palate, shallow orbital ridges, flat nasal bridge	Limb defects—preaxial polydactyly Up to 50% have cardiac defects (ASD, VSD, PDA, PS, TofF, TGA) Hypogonadism, omphalocoele Developmental delay	Must be assessed for congenital heart disease
Saethre–Chotzen	TWIST/FGFR-2 AD	Coronal, lamboidal±metopic (mild)	Towering forehead, low set hairline, facial asymmetry with septal deviation Ptosis upper eyelid	Cutaneous syndactyly Normal intelligence	

Table 2 Surgery for craniosyntosis

Surgery	Age	Indication	Position	Anaesthetic considerations	Length of procedure
Extended strip craniectomy	4–6 months	Usually sagittal synostosis	Supine, head-up tilt	Young infant Oral or nasal TT Arterial line May require redo surgery	1–3 h
Spring-assisted cranioplasty	4–6 months	Sagittal synostosis, Scaphalocephaly or posterior plagiocephaly	Supine, head-up tilt	May not need invasive monitoring in some procedures	45 min–1.5 h
Total vault reconstruction	>10–12 months	Usually sagittal synostosis	Modified prone with head extension	Oral or nasal TT Arterial line Cell salvage	4–6 h
Minimally invasive endoscopic surgery	<3 months (3–6 months acceptable)	Usually sagittal, also metopic, coronal	Supine or modified prone position	Blood transfusion uncommon May not need invasive monitoring May be discharged day 1 postop	1–2 h
Fronto-orbital remodelling	Between 12 and 18 months	Metopic, coronal synostosis	Supine, head-up tilt	South facing RAE TT Lacrilube to eyes Arterial line	3–4 h
Posterior calvarial vault expansion	6 months or younger	Lamboidal synostosis	Modified prone with head extension	Arterial line Oral or nasal TT	2–3 h

Surgery performed after 6 months of age

Later diagnosis requires more extensive surgical correction called a total cranial vault reshaping. This is a more invasive procedure and not only aims to repair the fused suture but also directly addresses the compensatory calvarial anomalies that have occurred. It involves removal and reconstruction of the bones with plates and screws and usually lasts around 4–6 h. Owing to the more invasive nature of the procedure and risks involved, it is usually performed later in life usually around 10–12 months of age, or in some centres, at around 15–18 months of age.

Frontal advancement and posterior expansion

Frontal advancement procedures are used to remodel abnormal frontal bone and advance the supraorbital rims, particularly in metopic and coronal synostosis. It is most commonly performed around age 12 months and involves a frontal craniotomy to release the involved sutures and elevate the forehead to provide eye protection and improved brain growth. It may be performed as a first-stage procedure when eye protection is needed, or later after another procedure such as a posterior vault expansion. Posterior cranial vault procedures aim to expand the posterior aspect of the skull and may be used in severe cases of turricephaly due to bicoronal and lamboidal synostosis.[1] It is commonly performed around age 6 months.

Midface hypoplasia

Midface hypoplasia is found in many forms of syndromic craniosynostosis and may be addressed at the time of cranial vault surgery or at a later time by Le Fort III advancement. The Le Fort III advancement involves repositioning the midface in the forward position and is typically performed as a single-stage procedure at around 4–8 yr, or later around 9–12 yr if the abnormality is less severe.

Monobloc frontofacial advancement

In some patients, it may be possible to advance the forehead and midface in one procedure rather than the above combination of fronto-orbital and subsequent Le Fort III advancements. This is usually performed at age 4–12 yr and involves a frontal craniotomy followed by osteotomies of the orbits and midface.

Facial bipartition and box osteotomies for hypertelorism

Facial bipartition is a technically challenging procedure. It involves the mobilization and advancement of the bony orbits, the midface, together with splitting of the midfacial segment. After this, the central nasal and ethmoid bones are removed, and the two facial partitions rotated towards each other to correct the hypertelorism. Box osteotomies involve the medial rotation of one or both orbits to correct the hypertelorism, requiring a 360° incision around the base of each orbit to release them. Box osteomtomies are typically performed on children who have reached puberty.

Minimally invasive surgery for craniosynostosis

Spring-assisted cranioplasty

Spring-assisted cranioplasty is a newer minimally invasive technique in craniosynostosis surgery. It involves a sagittal strip craniectomy with placement of two springs across the defect to gradually separate the narrowing. These are then subsequently removed at a second procedure usually around 6 months or even earlier once the desired result has been achieved. Early data suggest that the clinical outcomes do not differ between different surgical techniques; however, the outcomes regarding operation time, blood loss, intensive care unit (ICU) stay, and hospital stay are in favour of the spring-assisted surgery. The quality of evidence is low,[2] and therefore, it is not currently a widely accepted technique.

Endoscopic suture release with helmet moulding

Endoscopic suture release with subsequent postoperative helmet moulding is emerging as another minimally invasive alternative

in some centres. The procedure depends on brain growth for remodelling of the bones and uses a helmet after operation to direct this growth. Surgery is performed in the supine or modified prone position and burr holes are used to pass a rigid endoscope for visualization. When compared with more extensive surgical techniques, it promises a shorter surgical time, reduced blood loss, associated transfusions, and reduced hospital stay and costs.[3] The ideal age for this procedure is typically <3 months, but children aged 3–6 months are good candidates. This technique may lead to a change in perioperative practice as blood transfusion is unusual; incidence of venous air embolism (VAE) is reduced compared with open surgery.

Anaesthetic management

Preoperative concerns

A thorough preoperative assessment tailored to the individual child and the proposed surgical procedure is essential. Preoperative airway assessment and cardiac evaluation are important to identify the need for specific interventions, particularly when associated with syndromes such as Aperts or Crouzons. It is important to consider the presence of intracranial hypertension and to adjust the anaesthetic technique, particularly induction, accordingly. Obstructive sleep apnoea and respiratory complications occur more frequently in these children requiring the review of sleep studies and consultation with ear, nose, and throat surgeons. In cases of severe respiratory obstruction, where extensive facial osteotomies are planned or the airway is found to be extremely challenging, a covering tracheostomy may be considered. This should be considered as part of a preoperative multi-disciplinary team discussion.

Baseline haematological, biochemical, and coagulation studies should be performed and blood products ordered. Patients who are anaemic should be considered for preoperative optimization, with iron therapy or recombinant human erythropoietin. Parents should be appropriately counselled as to the specific anaesthetic and surgical risks involved with the procedure, particularly regarding blood transfusion and the risk of VAE.

Intraoperative concerns

Premedication is often not necessary but when used; concerns for possible effects on raised ICP should be taken into account.

Induction of anaesthesia may be inhalation or i.v. depending on the anaesthetist's, patients, and parents' preference with the considerations of potential airway compromise and difficult venous access in this age group, particularly in syndromic children. Midface hypoplasia can cause difficulties with mask ventilation and appropriate airway adjuncts should be considered in advance.

The type of tracheal tube used and the route of intubation may vary between the procedure type and individual centres, anaesthetists, or surgeons; nasal intubation is often preferred in our institution due to the added stability it offers in different positions. Tube position should be checked with the head flexed and extended to avoid accidental extubation or endobronchial intubation during position changes. In our institution, the preference is for the surgeons to suture the tracheal tube to the nasal septum to prevent dislodgement. During surgery, access to the tracheal tube will be limited; therefore, it is imperative to cross-check all airway and tube connections before draping the patient and surgery commencing.

Monitoring includes standard monitors with the addition of invasive arterial pressure monitoring due to the need for repeated blood samples and rapid haemodynamic changes secondary to rapid blood loss. Two large-bore peripheral i.v. cannulae should be placed. With the advent of minimally invasive surgery, some now prefer not to place arterial access. In our institution, it is not current practice to routinely use central venous access in these cases, except if large-bore peripheral access is unobtainable, the risk of VAE is high or in patients undergoing complex major surgery. This may differ in other centres where central venous access may be considered mandatory. Temperature monitoring should be used throughout the case and methods of active warming should be used, such as forced-air warming blankets and fluid warmers from the start of the case.

Positioning must be done in conjunction with the surgeons and may be supine, prone, or a modified prone position with the head extended. Care should be taken to ensure pressure areas are protected and particular attention should be paid to the eyes to avoid direct pressure or corneal abrasion. It is important to consider the position of the surgical field relative to the heart as this may increase the risk for VAE. A compromise between this risk and reducing venous bleeding in the head-up position must be discussed as a team. Care to avoid hyperextension of the neck must be taken and attention paid to the potential for jugular venous obstruction.

Maintenance of anaesthesia with a balanced technique involving inhalation agent in an air/oxygen mix with opioid allows for manipulation of depth of anaesthesia during various different stages in the procedure. Remifentanil infusions are often used in our institution to allow titration of the arterial pressure. A total i.v. technique using propofol may be also be used in older children.

Attention should be paid to the management of raised ICP with consideration of cerebral perfusion pressure, particularly until craniectomy is performed with avoidance of factors known to increase ICP such as hypercapnia, hypoxia, and raised venous pressures.

Intraoperative mishaps and management

Haemorrhage and massive blood transfusion

Blood loss may be slow and insidious or sudden and acute. It is important that the anaesthetist is aware of the timings in surgery where blood loss is more likely and that communication is maintained between the surgical and anaesthesia teams.

Massive blood transfusion can be required in craniosynostosis surgery. Studies have shown that the average transfusion is in the region of 50 ml kg^{-1},[4] although may be in excess of 100 ml kg^{-1}. Factors that increase the likelihood of large-volume blood loss include:

- Younger age and lower weight—along with a disproportionately larger head size meaning larger surface area for blood loss and increased circulating blood volume directed to the head
- Prolonged surgery—particularly occurring in syndromic craniosynostosis where surgery may be more complex.[5]

Complications associated with massive transfusion such as hypothermia, dilutional coagulopathy, and metabolic and electrolyte disturbances (hypocalcaemia, hyperkalaemia) should be considered and managed appropriately. Consideration of the use of coagulation factors with large-volume transfusion may reduce the volume of blood needed both intraoperatively and after operation.[5]

Blood conservation strategies

Preoperative optimization of haemoglobin using iron or erythropoietin remain a vital part of blood conservation. Intraoperative

blood loss management is one of the most challenging aspects of craniosynostosis surgery and estimation of blood loss can be difficult due to losses occurring into the surgical drapes and surrounding area. Elevation of the vascular periosteum is a significant source of bleeding; the dural sinuses are often the source of sudden and rapid blood loss requiring immediate resuscitation with fluids or blood products. Both insidious and rapid blood loss and electrolyte changes may occur necessitating regular point-of-care testing for haematocrit, electrolytes, and acid–base balance and allogeneic blood transfusion; blood loss may be >100% of the circulating volume.

For all but the most minor cases, blood products should be in the room and checked before surgery starts. Blood conservation strategies have been used in an attempt to reduce the amount of donor blood transfusion required (Table 3).[6 7]

Preoperative autologous blood donation involves the patient donating blood in the weeks before surgery, allowing time for self-correction of the subsequent anaemia and then re-transfusing the patient's own blood. This is sometimes combined with recombinant human erythropoietin to encourage production of red blood cells. This method does not always remove the need for allogeneic blood and still carries risks surrounding handling and storage and transfusion side-effects and requires careful coordination to prevent wastage of the blood if not used within its expiry date. Similarly, acute normovolaemic haemodilution involves collecting the patients' own blood at the start of surgery and replacing it with crystalloid to create normovolaemia with a lower haematocrit with a view to replacing the blood once blood loss occurs. These strategies are generally not useful in this paediatric population due to a small circulating blood volume and difficulty collecting blood before operation without sedation.

Similarly, intraoperative and postoperative cell salvage can be used to collect either intraoperative blood loss from the surgical field or from postoperative losses from the surgical drains. Again, these techniques are more limited in infants and small children due to the slow processing times, high priming volumes, and limited ability to concentrate the washed shed blood,[6] but can be useful techniques to consider particularly in complex major surgery.

The use of antifibrinolytic agents, such as tranexamic acid, has been shown in some studies to reduce blood loss and the need for transfusion in children having craniosynostosis surgery.[6 7] Tranexamic acid acts to competitively block formation of plasmin from plasminogen and inhibits the proteolytic action of plasmin on fibrin clot and platelet receptors inhibiting fibrinolysis at the surgical site. The dose of tranexamic acid varies between different surgical types and populations and varies from 10 to 100 mg kg^{-1} loading dose followed by an infusion of 5–10 mg kg^{-1} h^{-1} for the duration of the surgery.

Fibrin can be used at the site of surgery to encourage haemostasis and reduce blood loss. It is a naturally occurring substance and has been shown to reduce the need for allogeneic blood transfusions both intraoperatively and after operation.

Induced hypotension is not a widely accepted technique for blood conservation due to the increased risk of VAE with low venous pressures and the potential haemodynamic instability associated with rapid blood loss.

Current evidence related to the above strategies is limited and further trials are needed to fully assess their safety and efficacy in this population.

In our institution, preoperative optimization of nutrition and iron levels, meticulous surgical technique, positioning, arterial pressure control, and tranexamic acid are routinely used to minimize blood loss and allogeneic transfusions.

Table 3 Blood conservation strategies in craniosynostosis

Blood conservation strategies
• Preoperative autologous blood donation
• Acute normovolaemic haemodilution
• Intraoperative cell salvage
• Postoperative cell salvage
• Perioperative recombinant erythropoietin
• Antifibrinolytic drugs (tranexamic acid)
• Fibrin sealants or fibrin glue

Table 4 Intraoperative VAE

Symptoms
• Bronchoconstriction/wheezing
• Hypotension/circulatory collapse
• Hypoxaemia (V/Q mismatch)
• Dysrhythmias
• Myocardial ischaemia
Signs
• Abrupt decrease/loss end-tidal CO_2
• Turbulent flow detected on transoesophageal echo or Doppler ultrasound
Management
• Notify surgeon, call for help
• 100% oxygen
• Discontinue nitrous oxide/volatile
• Flood surgical wound with saline
• Position head below the heart
• Perform valsalva with manual ventilation
• Chest compressions (even if not in cardiac arrest, these may help break up bubbles)
• Treat cardiovascular compromise with usual inotropes, e.g. epinephrine
• Standard PALS protocol if in cardiac arrest
• Call for emergent transoesophageal echocardiography to confirm diagnosis

Venous air embolism

VAE is a complication seen in craniosynostosis repair and is most likely to occur when the head is positioned above the heart and the bony venous sinusoids or dural sinuses are exposed. The incidence of VAE during craniosynostosis surgery has been reported as high as 83%,[8] most without haemodynamic compromise and only about 1–2% being clinically significant. Routine precordial Doppler has been recommended to increase the chance of early diagnosis; however, most centres use capnography for detection. Rapid cardiovascular collapse can occur and treatment is predominantly supportive (Table 4). A central venous line (CVL) can be used to aspirate large volumes of air from the right ventricle; however, placement can be difficult in an emergency setting. It is recommended that a CVL is placed at induction of patients with high risk for VAE, particularly related to surgical position and technique, presence of intracardiac shunts, and volume deplete patients. A discussion should take place as to whether surgery should proceed after the event.

Postoperative concerns

Most patients are extubated at the completion of surgery. Factors that may delay extubation include a prolonged procedure, marked fluid shifts, large-volume transfusions, and effects of prolonged prone positioning and patient factors such as

preoperative obstructive sleep apnoea or airway concerns.[9] Most patients will be cared for on the ICU or high dependency units and observed for haemodynamic and volume status changes with close monitoring of haematological and coagulation profiles. Analgesia is predominantly with i.v. opiate infusions with progression to oral regimens within 24–48 h for more complex surgery with oral regimens commenced immediately after operation for less complex surgery. The use of NSAIDs in craniosynostosis surgery remains controversial.

Careful attention should be paid to postoperative electrolyte disturbances, particularly hyponatraemia. This may be related partly to the use of crystalloid infusions intraoperatively and also to anti-diuretic hormone release (SIADH) as a result of the surgical insult. A retrospective record review of patients developing hyponatraemia post-craniosynostosis surgery suggested that patients at increased risk of this complication included those with preoperative raised ICP, increased volume blood transfusion, and female sex (regardless of ICP).[10] The use of hyponatraemic fluids intraoperatively further increases the risk.

Summary

Craniosynostosis is a condition in which premature fusion of the bony plates of the skull leads to abnormal head shape and the potential for complications such as raised ICP. The main method of treatment is surgical and has anaesthetic concerns associated with surgery in young children with the specific risks related to blood loss and VAE. Newer techniques are emerging that may help to mitigate these risks and may change the way we manage these patients both in the operating theatre and in the immediate postoperative period. These techniques remain controversial and are as yet not widely practiced.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Cerebral oximetry

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Key points

- Cerebral oximeters enable continuous non-invasive monitoring of cerebral oxygenation.
- Cerebral oximeters utilize similar physical principles to pulse oximeters.
- Cerebral oximeters use the Beer–Lambert law and spatial resolution to provide estimates of cerebral haemoglobin oxygen saturation.
- Baseline cerebral oximetry values should be obtained before induction of anaesthesia.
- Cerebral oximetry values represent a balance between cerebral oxygen delivery and consumption.

The maintenance of adequate oxygen delivery to tissues and organs, especially the brain, is a fundamental objective of the anaesthetic process. The dangers of prolonged hypoxia and reduced oxygen delivery to the brain are well documented; however, the brain remains one of the least monitored organs during anaesthesia.[1]

Cerebral oximeters are non-invasive, continuous monitoring devices, used to monitor adequate cerebral oxygenation. They utilize similar physical principles to pulse oximeters. The first commercially available cerebral oximeters were used in the 1990s; however, Jobsis[2] first introduced the concept of using near-infrared spectroscopy (NIRS) to measure cerebral oxygenation in 1977. Although the majority of published data on cerebral oximetry have demonstrated improved outcomes among cardiac surgical patients, studies are emerging identifying improved outcomes in the non-cardiac surgical population.[3] Studies have demonstrated an increased incidence of adverse perioperative outcomes in patients who demonstrate substantial cerebral oxygen desaturation during surgery.[4]

This article aims to explain the underlying physical principles surrounding cerebral oximetry, and evaluate evidence supporting their use in different clinical situations.

Physics

Cerebral oximeters use NIRS to obtain continuous non-invasive measurements of cerebral oxygenation values.[5] Cerebral oximeters consist of a monitor that is connected to oximeter probes. Adhesive pads attach probes to the patient's scalp. Probes are most commonly applied to the scalp overlying the frontal lobe. Probes contain a fibreoptic light source and light detectors.[6] Light sources release light in the infrared range through a process of either stimulated emission of radiation or through light-emitting diodes.[7] Emitted light in the infrared range is able to penetrate the skull to reach underlying cerebral tissue. The skull is transparent to light in the near-infrared range.[1] Emitted light is either absorbed, redirected, scattered, or reflected.[8] When infrared light contacts haemoglobin, a change in the light spectrum occurs, depending upon the oxygenation status of the haemoglobin molecule.[8] Reflected light returns towards the surface and is detected by the light detectors within the oximetry probes.[8]

Cerebral oximeters calculate cerebral oxygenation using the Beer–Lambert Law.[9] The Beer–Lambert law is a combination of two physical laws.

Beer's law

The intensity of transmitted light decreases exponentially as the concentration of a substance the light passes through increases.

Two containers of equal size are filled with identical volumes of a solution. The concentration of solution in Figure 1A is less than the concentration of solution in Figure 1B. Light from identical light sources are shone through the containers. The amount of light passing through each container is detected by a photodetector. The amount of light reaching the photodetector in

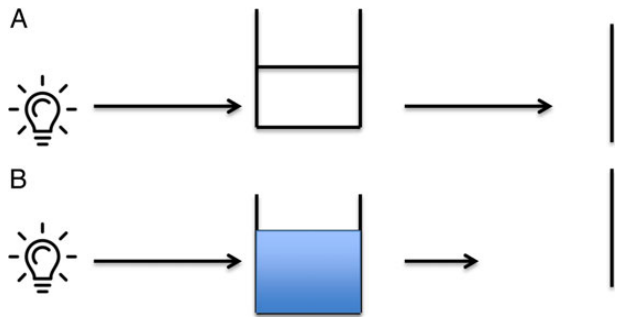

Fig 1 Diagrammatic representation of Beer's Law.

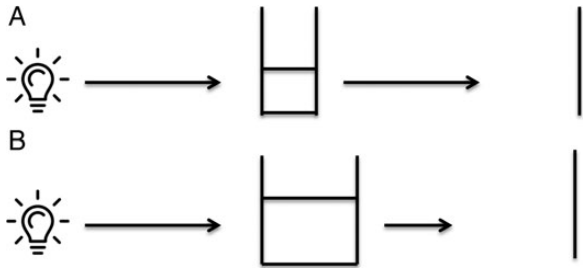

Fig 2 Diagrammatic representation of Lambert's Law.

Figure 1A is greater than the amount of light reaching the detector in Figure 1B. As the concentration of a substance increases, the amount of light absorbed by the substance increases and the amount of light detected by the photodetector decreases.

Lambert's law

The intensity of transmitted light decreases exponentially as the distance travelled by the light through a substance increases.

Two containers of differing size are each filled with volumes of solution of identical concentration. Light from identical light sources are shone through each container. The amount of light passing through each container is detected by a photodetector. Light passing through the container in Figure 2A has less distance to travel through the substance, than light passing through the container in Figure 2B. The amount of light reaching the photodetector in Figure 2A is greater than that in Figure 2B. As the distance a light travels through a substance increases, the amount of light absorbed increases, and the amount of light detected by the photodetector decreases.

According to these laws, an amount of a substance, that is, oxygen, can be determined by how much light the substance absorbs.[10]

Near-infrared light with a wavelength of 650–940 nm is able to penetrate the skull to underlying cerebral tissue.[9] Primary light absorbing molecules within tissues are metal complex chromophores: haemoglobin, bilirubin, and the cytochromes.[1] Haemoglobin exists in either an oxygenated or deoxygenated form. The absorption spectra for each haemoglobin state are different. The absorption spectrum for deoxygenated haemoglobin is 650–1000 nm and oxygenated haemoglobin 700–1150 nm.[1] The isobestic point where the absorption spectra for oxygenated and deoxygenated haemoglobin are the same can be used to calculate total tissue haemoglobin concentration (Fig. 3).[1]

Extracranial blood is a potential source of error in cerebral oximetry measurements. In order to limit this, cerebral oximeters

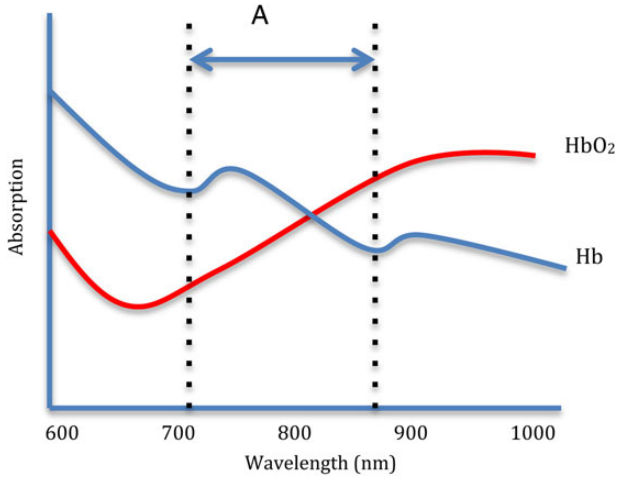

Fig 3 Absorption spectra for oxygenated and de-oxygenated haemoglobin. Area A represents light wavelengths used by Cerebral oximeters.

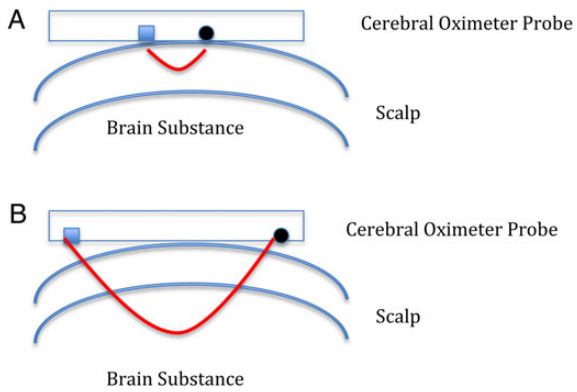

Fig 4 Diagrammatic representation of Spatial Resolution.

utilize multiple probes[6] and a process of spatial resolution.[4] Spatial resolution is based on a principle that the depth of tissue investigated is directly proportional to the distance between the light emitter and light detector (Fig. 4).[11] Increasing the distance between the emitter and detector will increase the depth of tissue sampled.

Cerebral oximeters use mathematical algorithms involving subtraction of values obtained from the emitters near and far from the photodetector to limit contamination from extracranial blood, and obtain a reading representative of cerebral oxygenation values. There are numerous commercially available cerebral oximetry devices for clinical use. Inter-device variability with regard to measurements exists. Variability occurs as a result of different wavelengths of light emitted by the probes, different light sources,[4] and different mathematical algorithms used to obtain cerebral oxygenation values.

Cerebral oximetry values are derived mainly from venous blood, and in contrast to pulse oximeters are independent of pulsatile blood flow.[12] Cerebral oximetry values reflect a balance between oxygen consumption and oxygen delivery to the brain.

Clinical interpretation of cerebral oximetry measurements

Baseline cerebral oximetry values should be obtained before induction of anaesthesia. Normal values range from 60% to 80%;

however, lower values of 55–60% are not considered abnormal in some cardiac patients.[8]

Adequate cerebral oxygenation is dependent upon adequate cerebral blood flow and oxygen content. Factors affecting either of these will result in a reduction in cerebral oxygenation and a reduction in cerebral oximetry values. Anatomical variations, for example, an incomplete Circle of Willis, or severe carotid artery stenosis can create errors in cerebral oximetry values; therefore, it is recommended that cerebral oximetry is performed bilaterally. Table 1 summarizes some factors that may result in reduced cerebral oxygenation values caused by alterations in blood flow or oxygen content.

Table 1 Factors resulting in reduced cerebral oxygenation values

Cerebral blood flow	Oxygen content
Cardiac output	Haemoglobin concentration
Acid–base status	Haemoglobin saturation
Major haemorrhage	Pulmonary function
Arterial inflow/venous outflow obstruction	Inspired oxygen concentration

Cerebral oximetry values must not be interpreted in isolation; alterations in cerebral oximetry measurements must take into consideration all available clinical information and physiological state of the patient. One of the most common limitations in cerebral oximetry monitoring has been the absence of an intervention protocol to treat a decrease in regional brain oxygenation.[1] Denault and colleagues[13] have devised a potential treatment algorithm based on optimizing cerebral oxygen delivery and consumption to treat a reduction in cerebral oximetry values (Fig. 5).

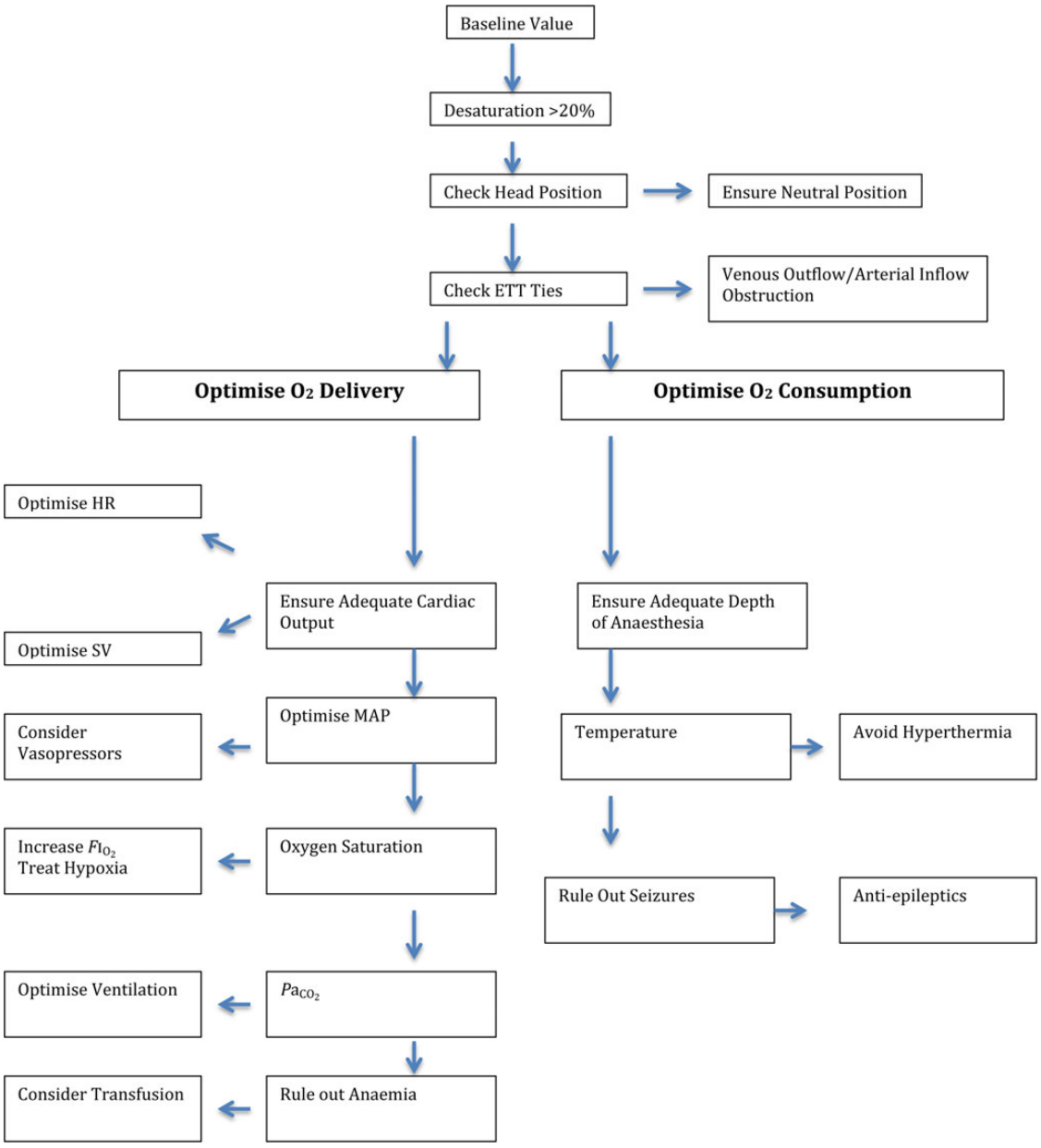

Fig 5 Treatment algorithm for managing cerebral desaturation. Adapted from original by Denault and colleagues.[13]

Limitations in cerebral oximetry measurements

All monitoring devices have limitations. Limitations associated with cerebral oximetry include:

(i) Blood from an extracranial source can create erroneously low measurement.[4]
(ii) Electrosurgical equipment, that is, diathermy, can affect the accuracy of measurement.[4]
(iii) Cerebral oximeters only measure regional cerebral oxygenation. Large areas of the brain remain unmonitored.[4]
(iv) Cerebral oximeters are unable to identify a cause for the desaturation.[14]

Clinical applications

Questions have been raised with regard to the clinical utility of cerebral oximetry monitoring.[1] An increasing number of studies are demonstrating the ability of cerebral oximetry monitoring to detect clinically silent episodes of cerebral ischaemia.[1] Cerebral oximeters have the potential to be an important safeguard for cerebral function.[1]

Cardiac surgery

Patients undergoing cardiac surgery are at risk of adverse perioperative neurological events. Cerebral oximetry monitoring can be used, potentially reducing the incidence of these devastating events.

Coronary artery bypass surgery

Studies have been conducted investigating cerebral oximetry in patients undergoing cardiac surgery. Salter and colleagues[15] carried out a study involving 265 patients undergoing coronary artery bypass surgery (CABG) surgery. Patients were randomized to two groups. Cerebral oximetry was used in both groups. One group received cerebral oximetry monitoring and interventions to improve cerebral oximetry values if they decreased by 20% from a baseline preoperative measurement. The second group was a control group. The study found an association between cerebral desaturation and early postoperative cognitive dysfunction. However, the study did not identify an association between the use of a cerebral oximetry-guided intervention protocol, and a reduction in the incidence of postoperative cognitive dysfunction.[15]

Persistent postoperative cognitive dysfunction after cardiac surgery is controversial. Meta-analyses[16] have identified that persistent cognitive decline is not as common as previously thought. Some patients may even show an improvement in cognitive function after CABG surgery.

Deep hypothermic circulatory arrest

A number of cardiac surgical procedures are performed using cardiopulmonary bypass (CPB). Certain complex procedures, however, require a cessation of all blood flow. Deep hypothermic circulatory arrest describes the rapid reduction in core body temperature, followed by the cessation of CPB. The brain is vulnerable to ischaemia during this time. Cerebral oximetry monitoring may provide a means of monitoring and detecting the onset of cerebral ischaemia.[1] However, there is insufficient evidence surrounding the sensitivity of cerebral oximetry monitoring during profound hypothermia (temperatures <25°C).

Vascular surgery

Carotid endarterectomy

Carotid endarterectomy is associated with postoperative stroke. Monitoring devices are commonly used to detect periods of cerebral ischaemia. Common monitoring devices include transcranial Dopplers, EEGs, and monitoring of somatosensory evoked potentials (SSEPs).

Transcranial Dopplers provide an indirect measure of cerebral blood flow by measuring blood velocity in a cerebral artery. Measurements are obtained through transcranial windows. Transcranial windows are found across the thinnest parts of the skull—the temporal bone, or where bone is absent—the orbit. One-fifth of patients lack a transcranial window, and as a result, transcranial Doppler studies cannot be used.[1] SSEPs and EEG monitoring are affected by anaesthetic agents and surgical diathermy.[1] Cerebral oximetry monitoring can be used as a tool for detection of cerebral ischaemia.

A reduction in cerebral oximetry values >12% from a baseline preoperative value has been identified as a reliable, sensitive, and specific threshold for detection of brain ischaemia.[1] A reduction in cerebral oximetry values after cross-clamping of the internal carotid artery may indicate the need for shunt placement during the procedure. Moritz and colleagues[17] compared different monitoring modalities in identifying cerebral ischaemia during carotid surgery. Results highlighted similar accuracy for the detection of onset of ischaemia with transcranial Doppler and cerebral oximetry monitoring, least accuracy was identified for SSEP monitoring.

Carotid endarterectomy hyperperfusion syndrome

Carotid endarterectomy hyperperfusion syndrome is caused by an increase in cerebral blood flow after repair of carotid stenosis. It occurs as a result of impaired cerebral auto-regulation. The syndrome is characterized by headache, cerebral oedema, seizures, intracerebral haemorrhage, and death.

A correlation exists between cerebral oxygen saturation values and changes in cerebral blood flow after de-clamping of the internal carotid artery.[1] Cerebral oximetry could be used to identify patients at risk of cerebral hyperperfusion syndrome.[18]

Paediatrics

Neonates born prematurely have impaired cerebral auto-regulation and are at risk of intraventricular haemorrhage and periventricular leucomalacia.[9] Periventricular leucomalacia is usually diagnosed by transcranial ultrasound. Areas of ischaemia are identified in white matter surrounding the lateral ventricles. By the time a diagnosis of periventricular leucomalacia has been made, permanent neurological damage such as visual disturbance and cerebral palsy has occurred. Changes in cerebral oxygen values as detected by cerebral oximeters provide an indirect measure of alterations in cerebral blood flow. Continuous cerebral oxygenation monitoring may enable the early detection and prevention of periventricular leucomalacia and intraventricular haemorrhage.[9]

Additional uses

Cerebral oximetry monitoring is being increasingly used to monitor the adequacy of tissue and organ perfusion when placed on sites other than the scalp.[1] NIRS is being investigated as a

potential marker of perfusion for hepatic, renal, and splanchnic tissues.[1]

NIRS is further being evaluated as a potential screening tool for the need for blood transfusion in trauma patients at risk of haemorrhagic shock.[1]

Conclusion

Cerebral oximetry is a simple, non-invasive monitoring methodology that may improve patient outcome in a variety of different clinical situations; evidence for its use beyond cardiac surgery is continuously emerging. This article has highlighted some of the increasing roles and evidence for cerebral oximetry in clinical practice, further research is required to validate cerebral oximetry monitoring in improving patient outcomes in both cardiac and non-cardiac surgical patients.[3]

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

Podcasts

This article has an associated podcast which can be accessed at http://www.oxfordjournals.org/podcasts/bjaed_cerebral_oximetry.mp3.

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Paediatric mechanical ventilation in the intensive care unit

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Key points

- With appropriate sizing, both cuffed and uncuffed tracheal tubes are acceptable for use in infants. Cuff pressures should be <20 cm H_2O, and uncuffed tubes should allow for air leak at ~20 cm H_2O.
- The resistance of the small airways of children may increase dramatically with subtle reductions in airway diameter.
- Equipment factors may significantly contribute to dead space ventilation in children.
- High-frequency oscillation remains an option for refractory respiratory failure in paediatrics.
- Neurally adjusted ventilatory assist technology, while not in routine use in paediatrics, may benefit select patients.

The care of the ventilated paediatric patient requires an extensive understanding of respiratory mechanics and pathophysiology of cardiopulmonary disease. Many of the fundamental principles of respiratory physiology and gas exchange are similar to those of adults and will not be the focus of discussion. Instead, our aim is to review features of mechanical ventilation that are distinctive to the paediatric population. Ventilation of premature infants is a unique subset of paediatric ventilation and will not be addressed in this article.

As the adage says, 'children are not small adults', and management of ventilated paediatric patients requires an appreciation of the susceptibility of developing lung tissue to injury, congenital anomalies, disease processes specific to the paediatric population, and the potential equipment-related difficulties associated with small patients. Considered together, each paediatric patient who requires mechanical ventilation represents a unique clinical problem.

Airway

While the majority of tracheal tubes (TTs) placed in critically ill children are for the purposes of facilitating mechanical ventilation, decisions at the time of airway placement may have important implications. Features specific to paediatric patients (e.g. size, anatomy, inability to follow instructions) leave them at particular risk for compromising their airway security.

Tracheal tube type and route

Uncuffed TTs have traditionally been used in children due to historic anatomical surveys revealing the conical shape of the airway during the first several years of life. However, due to the common occurrence of ineffective ventilation and the egress of anaesthetic vapour in the presence of a large leak, cuffed TTs in paediatrics have grown in popularity. Early investigations showed that TTs with high-pressure, low-volume cuffs had similar rates of post-extubation stridor when compared with uncuffed TTs,[1] but their use was eschewed in children due to concerns of subglottic stenosis. More recent evaluations of modern low-pressure, high-volume cuff technology have shown similar airway outcomes and significantly reduced rates of re-intubation for air, gas leakage, or both compared with uncuffed TTs.[2,3]

Despite this information, the choice of TT type in young children remains controversial, as long-term data on airway injury are lacking. Currently, the use of cuffed or uncuffed TTs is considered an acceptable standard of practice. If cuffed TTs are used, cuff pressure should be routinely monitored and kept below 20 cm H_2O. Uncuffed TTs should be sized to allow a leak ~20 cm H_2O.

Another debate is that of orotracheal intubation *vs* nasal intubation in infants. Proponents of nasal TTs suggest that it improves TT security and reduces unplanned extubations. However, a Cochrane review of small studies comparing oral *vs* nasal TTs in infants has shown no differences in complication rates.[4] Concerns with nasotracheal intubation in infants are that it is considered more technically difficult by inexperienced providers and inappropriately time-consuming during resuscitation situations. Currently, both routes of tube placement are commonly used.

Tracheal tube sizing

A number of methods for estimating appropriate TT size in paediatrics exist, including measurement of the fifth finger or fingernail. However, estimations based on body size may be inaccurate as airway growth tends to occur in a relatively constant fashion, independent of individual body habitus. It is likely for this reason that age-based formulas have been shown to more reliably predict appropriate TT size. The most commonly used is Cole's formula, which predicts an uncuffed TT size=[(age in years)/4+4]. If a cuffed TT is being placed, the predicted size would be 0.5 mm smaller than the uncuffed calculation.

It should be recognized that infant-sized TTs have proportionally higher resistances to flow compared with those used in adults. For example, a 6-month-old infant weighing 7 kg would be anticipated to require a 4.0 uncuffed or 3.5 cuffed TT. Compared with a 70 kg adult male intubated with an 8.0 TT, the resistance of a 4.0 TT is 16-times higher, and a 3.5 TT is 27-times higher (based on Poiseuille's law). In addition, while being ventilated, small reductions in TT diameter (such as due to secretions or bending) will have a more pronounced effect on smaller sized TTs. As a result, even minute changes to TT patency or position may significantly compromise the ventilation of infants and small children. Finally, due to the higher resistance of smaller tubes, infants require additional pressure support when breathing spontaneously while intubated.

Breathing

The majority of intubations in the paediatric intensive care unit (ICU) are performed to facilitate oxygenation, clearance of carbon dioxide (CO_2), decrease work of breathing, or a combination of these clinical issues. Each will be discussed.

Oxygenation

Hypoxaemia in ventilated patients is treated in several ways: increasing the fraction of inspired O_2 (F_{IO_2}) to increase the partial pressure of oxygen in the alveoli, optimizing alveolar patency via recruitment manoeuvres, and providing adequate PEEP to maintain functional residual capacity (FRC).

Adjusting F_{IO_2} to maximize haemoglobin oxygen saturation remains a safe strategy in paediatrics with a few notable exceptions: some patients with unrestrictive single-ventricle cardiac physiology or large ventricular septal defects may suffer from excessive pulmonary blood flow due to the decreased pulmonary vascular resistance (PVR) associated with increased oxygen delivery. This can lead to pulmonary over-circulation and decreased systemic cardiac output. Excessive F_{IO_2} may also lead to atelectasis[5] and oxygen toxicity.[6] A general principle in determining what F_{IO_2} to select is that oxygen delivery should be limited to the minimum necessary to meet oxygenation goals.

Optimization of ventilation–perfusion matching and FRC is most effectively accomplished by adjusting the mean airway pressure, largely by making changes to the PEEP in combination with recruitment manoeuvres. However, there are occasions where oxygenation remains inadequate, despite these adjustments and maximizing F_{IO_2}. High-frequency oscillatory ventilation (HFOV) is a mode of ventilation whose theoretical benefit is based on the ability to recruit and maintain gas exchange units by using a higher mean airway pressure compared with conventional ventilation. HFOV has recently decreased out of favour in adult critical care due to trials involving patients with acute respiratory distress syndrome (ARDS) indicating no benefit and possibly harm with its use.[7] In contrast, there is no such literature in paediatrics. HFOV may still be used as a rescue method for children with severe ARDS,[8] and considered in those with refractory hypoxia, hypercapnia, or both.

In addition to its ability to maintain lung recruitment, other theoretical advantages of HFOV include reducing the risk of lung injury and pneumothorax associated with volutrauma and atelectrauma. However, there is no robust literature supporting or refuting these claims. Disadvantages to HFOV include often requiring significant levels of patient sedation, poor secretion clearance, noisiness, and limited ability for patient monitoring (e.g. auscultation, end-tidal CO_2 monitoring).

CO_2 clearance

The main clinical target involved in regulating CO_2 clearance is alveolar ventilation (minute ventilation less dead space ventilation). A patient's Pa_{CO_2} is directly proportional to CO_2 production by the body, and inversely proportional to CO_2 clearance by alveolar ventilation.

Permissive hypercapnia continues to be used regularly in ventilated paediatric patients in the ICU. Typical strategies aim for a gradual increase in Pa_{CO_2} to <8–10 kPa and allow for a corresponding mild acidosis (e.g. pH 7.25–7.33). This permits patients to be ventilated with lower plateau pressures and tidal volumes in an effort to reduce ventilator-induced lung injury. However, caution should be exercised because although moderate hypercapnia is known to increase cardiac output and regional systemic blood flow, it occurs at the costs of impaired stroke volume and increased cardiac metabolic activity.[9] While most otherwise healthy paediatric patients will tolerate these demands, those who are particularly sensitive to elevated Pa_{CO_2} or acidosis, such as those with pulmonary hypertension, cardiac dysfunction, increased intracranial pressure (ICP), or sickle cell disease, should not be ventilated according to this strategy.

The simplest way to predictably alter minute ventilation, and thus alveolar ventilation, is to adjust the respiratory rate (RR). While there is often no specific lower limit, an upper limit to RR will be reached based on the expiratory time required to avoid gas trapping. This limit will vary based on airway resistance. Conditions resulting in severe airway obstruction, such as asthma, may necessitate the use of a low RR and long cycle times in order to facilitate full expiration.

There is a large body of evidence which supports the use of low tidal volume (Vt) ventilation strategies in adult ARDS[10,11] and in premature infants with developing lungs.[12] Although the pathophysiology of volutrauma and barotrauma are not specific to these conditions, the superiority of a low-Vt strategy has not been clearly established outside these clinical circumstances.

Goal Vt is comparable between children and adults. Paediatric patients are often ventilated with Vt ~ 6 ml kg^{-1} which is similar to or at the lower end of the adult range. However, clinical circumstances may warrant the use of higher or lower Vt.

Modern ventilators have attempted to combine the advantages of volume and pressure control modes by introducing dual or hybrid modes such as pressure-regulated volume control. These modes deliver pressure-cycled breaths to the patient, with the goal of achieving a user-defined Vt. As such, pressure is constant across the inspiratory phase of ventilation, in contrast to the classic volume control mode where flow is constant across the inspiratory phase and airway pressure is subject to variability. Using the measured Vt as feedback, the ventilator will adjust its pressure control as needed to maintain the target Vt, up to a user-defined limit. This essentially makes it an efficient volume control mode that is able to independently account for dynamic breath-to-breath variability in patient compliance. Such modes are useful in conditions requiring strict Pa_{CO_2} control, such as increased ICP.

Work of breathing

Many infants and children are able to utilize increased respiratory effort (e.g. grunting, retractions) in order to maintain relatively normal oxygenation and CO_2 clearance. The decision to mechanically support such a patient becomes a clinical judgement based on knowledge of the underlying disease process and its anticipated trajectory. Compared with adults, infants and young children expend proportionally more metabolic effort with increased work of breathing and are at risk of rapid deterioration. Although diaphragmatic fatigue itself has been demonstrated in cases of extreme, prolonged stress, the deterioration these patients face is likely multi-factorial with progression of the underlying disease, hypoxaemia, and/or CO_2 retention. When compounded with conditions such as heart failure or severe infection, ventilatory support may be particularly helpful in improving the balance between oxygen delivery and consumption.

Non-invasive positive pressure ventilation (NIPPV) has become a common and effective ventilation modality for many indications in paediatrics, including increased work of breathing. In heterogeneous disease processes such as viral bronchiolitis, excessive respiratory effort is thought to be attempting to both overcome atelectatic regions of low compliance, and further distend obstructed, hyperinflated regions. NIPPV is often able to ameliorate both of these issues and significantly decrease work of breathing. In addition, recruitment of atelectatic regions and improving compliance generally result in improved oxygenation and CO_2 clearance. NIPPV may also be used in a similar fashion to manage the severe airway obstruction associated with asthma exacerbations. However, attention should be directed to limiting positive pressure delivery to the minimum necessary to overcome the critical airway opening pressure, and avoid further gas trapping and hyperinflation. Additionally, NIPPV may be an effective intermediary therapy for children experiencing post-extubation de-recruitment or stridor/stertor. Although NIPPV is often administered to infants and children using mild sedation, or none at all, some children do not tolerate it or are unable to maintain an adequate seal. The increasing availability of NIPPV interfaces for infants and children of all ages and sizes has significantly reduced the need and duration for invasive mechanical ventilation in paediatrics.

Circulation

The majority of paediatric patients have a normally functioning cardiovascular system. Despite this, knowledge of cardiorespiratory interactions is important when managing all mechanically ventilated paediatric patients.

Extra-thoracic venous effects

The introduction of positive pressure into the thoracic cavity reduces the pressure differential that drives systemic venous return. As a result, progressive increases in mean airway pressure are often associated with impairments in right ventricular preload. In addition, the impedance of venous blood flow may affect other organs more drastically in paediatric patients compared with adults. As children utilize lower systemic arterial pressures, reducing the arterial–venous pressure gradient by impeding venous return, for example, from the abdomen, may result in the earlier development of renal dysfunction and ascites. Similarly, young infants have limited abilities to auto-regulate cerebral blood flow and obstructing venous return may result in intracranial haemorrhages.

Extra-thoracic arterial effects

In contrast to its effects on venous return, positive intrathoracic pressure effectively decreases left ventricular afterload by reducing the transmural pressure gradient. The result is improved systemic blood flow. For this reason, positive pressure ventilation, whether delivered by TT or NIPPV, may be considered as a method to support cardiac output in those with left ventricular dysfunction. Although it is far less common in paediatrics in comparison with adults, some children with left ventricular dysfunction due to mitral insufficiency or coronary artery abnormalities may benefit from positive pressure ventilation.

Intra-thoracic venous/arterial effects

Structures that are intra-thoracic (e.g. the heart, pulmonary arteries, and pulmonary veins) are similarly affected by changes in intra-thoracic pressure. As such, it may be predicted that blood flow from the right ventricle to the pulmonary vascular bed is unaffected by positive pressure ventilation. However, changes in pulmonary blood flow do become apparent when positive pressure is introduced. While impaired venous return and right ventricular preload may be a factor, even patients with corrected volume status will demonstrate altered pulmonary blood flow. The mechanism is not clearly understood, but is possibly due to positive pressure effects within the airways. PVR appears to be the lowest when the airways are optimally distended to FRC. Accordingly, PVR begins to increase with either under- or over-distension of the airways; likely as a result of interference with blood flow through the neighbouring vessels. In contrast to adults, this is an important consideration for newborns in whom PVR is universally elevated at the time of and in the weeks after birth, and also other patients with pulmonary hypertension.

Ventilation in the operating theatre

Mechanical ventilation of the paediatric patient for surgery follows many of the same principles. There are, however, some additional considerations in the operating theatre. An appropriately sized TT should be selected in order to allow for adequate ventilation with minimal gas leak. This helps facilitate procedures where airway pressure may be increased, such as those performed in the lithotomy position and laparoscopic surgery. In addition, the desire to minimize waste anaesthetic gas pollution

in the operating theatre necessitates TT sizing that does not allow for excessive leak.

One limitation of traditional anaesthesia ventilators has been the inability to deliver an accurate tidal volume to the lungs of the patient. This was largely due to interactions with the fresh gas flow and not accounting for circuit compliance. In contrast to adults, seemingly minor inaccuracies in volume delivery due to equipment factors may have a significant overall impact on the minute ventilation of small children. Modern anaesthesia ventilators have been designed to prohibit fresh gas flow during tidal volume delivery, and adjust for volume changes related to circuit compliance. The result of improved tidal volume delivery has allowed for more precise monitoring of changes in pulmonary compliance for paediatric patients during surgery.

Another factor with implications for paediatric patients in the operating theatre is equipment-related dead space which can impair CO_2 clearance. Routinely used apparatus such as tubing extensions and heat and moisture exchangers may significantly increase dead space ventilation. When infants are being ventilated in the operating theatre, care should be taken to minimize the volume of connections between the 'Y' piece of the breathing system and the TT.

Novel techniques in paediatric ventilation

Novel modes of ventilation are continually being studied and investigated for use in paediatrics. High-frequency jet ventilation (HFJV) and neurally adjusted ventilatory assist (NAVA) are two examples of emerging technologies. Although experience with these modalities continues to increase, with the exception of premature infants, neither is currently used routinely in paediatrics.

High-frequency jet ventilation

Jet ventilation has existed for decades, with low-frequency techniques used in the early days of bronchoscopy and tracheal surgery, and a method of rescue ventilation.[13] HFJV relies upon a second separate ventilator to provide consistent PEEP, while the jet nozzle itself releases bursts of high-velocity, high-pressure gas over fractions of a second (typically ~20 ms). The brief interruptions between jet bursts allow for passive expiration. Theoretically, the high-velocity jet bursts create a funnelling channel of expired air to assist with secretion clearance. Also, the inspiratory pressures associated with the jet bursts dissipate in the large conducting airways, exposing the smaller airways and alveoli only to PEEP; a property thought to be beneficial to patients with air leak.

HFJV is still new to paediatric intensive care and there is little literature available to support its use beyond the theoretical advantages described. There is, however, increasing support for its use in the neonatal ICU as a lung-protective and haemodynamically stable method of ventilating premature neonates.[14,15]

Neurally adjusted ventilatory assist

The theory underpinning NAVA is that the most physiological means of determining the need for minute ventilation arises from the patient's own respiratory centre. NAVA uses an oesophageal catheter to measure diaphragmatic electrical activity and uses this information to direct ventilation.[16] It is suspected that coordinating the timing of ventilator breaths based on diaphragmatic electrical activity is superior to current techniques based on sensing changes in circuit gas flow, as there is less of a delay. Diaphragmatic electrical activity also permits some estimation of the magnitude of ventilator breath to deliver. The combination of these features is thought to result in improved patient–ventilator synchrony and may potentially benefit those with neuromuscular conditions in particular.

Despite the promising theoretical advantages of NAVA, more experience and study is needed. Oesophageal catheters designed to monitor diaphragmatic activity are costly and appropriately positioning them can be difficult. In addition, it is unknown whether the intact respiratory centre can appropriately regulate ventilation during critical illness.

Illustrative case #1

A 3-month-old infant is admitted to the paediatric ICU for severe bronchiolitis. Despite the provision of non-invasive positive pressure ventilation, he continues to demonstrate haemoglobin oxygen saturations of 88% with $F_{I_{O_2}}$ 100%. His blood gas reveals a worsening acute respiratory acidosis, with pH 7.12 and Pa_{CO_2} 9.9 kPa. In addition, physical examination reveals grunting and significant supra-sternal and inter-costal retractions. The decision is made to intubate, and thus, he has a size 3.5 cuffed TT placed successfully and position is verified by chest radiograph.

Pressure-control ventilation is initiated with peak inspiratory pressures of 22 cm H_2O, and PEEP 6 cm H_2O. In the hours after intubation, his oxygenation improves and his end-tidal CO_2 reads 7.5 kPa. Through the course of the night, he once again begins demonstrating hypoxia and the end-tidal CO_2 increases to 9 kPa. A follow-up chest radiograph confirms TT position, progression of the bilateral patchy infiltrates/atelectasis, and no pneumothorax. His PEEP is increased to 9 cm H_2O and peak inspiratory pressure up to 27 cm H_2O. With these changes, his oxygen saturations improve and his end-tidal CO_2 stabilizes at 7.2 kPa. As there is no contraindication to permissive hypercapnia, the RR and peak inspiratory pressures are gradually weaned to maintain end-tidal CO_2 <8 kPa. A blood gas is sampled periodically to ensure the infant's pH remains >7.25, and that the end-tidal monitoring equipment is trending appropriately.

The following day, the infant demonstrates improved oxygenation, maintaining saturations with $F_{I_{O_2}}$ 45% and an improved chest X-ray. As a result, the PEEP is slowly decreased. The ventilator parameters are gradually reduced over the following days and sedation is weaned to promote spontaneous respiratory effort. The infant maintains adequate oxygenation and CO_2 clearance with spontaneous breathing and pressure support of 10 cm H_2O above an end-expiratory pressure of 5 cm H_2O. Given the minimal degree of ventilator support being provided, the infant undergoes a trial of extubation. With the TT removed, he breathes comfortably and is able to maintain a normal blood gas and adequate oxygen saturations with supplemental oxygen by nasal prongs at 0.5 litre min^{-1}.

Illustrative case #2

An 8-yr-old boy with a history of asthma presents to the emergency department with respiratory distress. His parents report that he developed viral upper respiratory tract infectious symptoms the previous day, and his usual salbutamol inhaler was only providing minimal relief. On examination, he exhibits moderate work of breathing with a prolonged expiratory phase, haemoglobin oxygen saturation 88% in room air, and decreased breath sounds bilaterally with polyphonic wheezing. He is diagnosed with a severe asthma exacerbation, and is administered supplemental oxygen, consecutive treatments of nebulized

salbutamol and ipratropium, an oral dose of prednisone, and an i.v. bolus of magnesium sulphate.

Six hours later, the patient is transferred to the ICU for continuous nebulized salbutamol therapy. Despite his bronchodilator and anti-inflammatory therapies, he continues to demonstrate significant work of breathing and diminished breath sounds. A chest X-ray is unremarkable aside from prominent hyperinflation. He is carefully initiated on continuous positive airway pressure (CPAP) at 5 cm H_2O, and the salbutamol treatment is changed to a continuous i.v. infusion. In the following hours, his respiratory effort and breath sounds improve. He is continued on CPAP at 5 cm H_2O and the salbutamol infusion and regular i.v. steroids for 24 h. After this, he tolerates removal of the CPAP mask and the transition back to regular nebulized salbutamol and oral steroid therapy. In the subsequent days, he completes a course of systemic steroids and transitions back to his usual inhalers.

Authors' contributions

R.G. conceptualized the article, drafted the initial version of the manuscript, and approved the final manuscript as submitted. D.R. assisted with conceptualization of the article, reviewing the initial draft, and approved the final manuscript as submitted.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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Rheumatological conditions in critical care

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Key points

- The management of rheumatological conditions now focuses on early, aggressive immunosuppression, using a variety of disease-modifying and biological agents.
- Rheumatological therapies can cause immunosuppression, and both specific and general side-effects of relevance to the intensivist.
- Atypical infection, such as Pneumocystis pneumonia, tuberculosis, and fungi, should be considered in all rheumatological patients on treatment who present to intensive care.
- Signs of underlying disease flare and sepsis are often indistinguishable; patients with rheumatological disease who are not responding to treatment on the intensive care unit may need further rheumatological/immunosuppressive treatment.
- Prompt rheumatology consultation is paramount.

Traditionally thought of as disorders of the joints and musculoskeletal system, rheumatological diseases (RDs) can affect any organ system and many have debilitating systemic effects. These conditions, and the sequelae of the immunosuppressive medications used to treat them, can also cause catastrophic complications and can pose many diagnostic and therapeutic challenges to the intensivist (Table 1). While RDs are relatively common in the general population, they remain a comparatively rare cause of intensive care admission. However, such patients have a reported intensive care unit (ICU) mortality of 15–55% and poor long-term outcomes.[1]

The most common rheumatological causes for admission to the ICU include:[2]

- development of new manifestations/end-organ sequelae of RD,
- infection secondary to immunosuppressive treatment of RD,
- adverse effects of disease-modifying drugs,
- acute critical compromise unrelated to but exacerbated by the underlying RD.

In reality, these presentations tend to overlap, further complicating the ICU course. A common scenario, for example, would be attempting to differentiate between sepsis and a flare-up of underlying inflammatory disease. This can be a major diagnostic challenge, given that the management of infection differs substantially from control of the underlying disease. Early consultation with a rheumatologist is therefore paramount and treatment of both infection and the RD may be required in tandem.

Three-quarters of those patients admitted to the ICU because of RD have rheumatoid arthritis (RA), systemic lupus erythromatosus (SLE), or scleroderma. Other less prevalent conditions include antiphospholipid syndrome (APS), the vasculitides, and dermatomyositis.[2] There is not scope in this article to discuss every rheumatological condition and how it may present to the intensivist. Instead, we will concentrate on some important presentations that should not be missed, and critical problems potentially posed by the different therapies used within rheumatology.

Table 1 Why rheumatological diseases are important

Predominantly affect young females
Multi-system diseases
Potential multi-organ failure
High mortality on ICU
Complicated pharmacotherapy
Result in immunocompromise, secondary to disease, medication, or both
Many rheumatological conditions coexist/overlap

Rheumatological presentations not to be missed

Macrophage activation syndrome

Macrophage activation syndrome (MAS) is a rare, but potentially lethal complication of several rheumatological diseases and is one of the conditions grouped under the umbrella of 'haemophagocytic lymphohistiocytosis' (HLH). There is a significant mortality rate in MAS quoted between 15% and 20%,[3] although a recent study demonstrated a mortality of 8%.[4] In MAS/HLH, there is a loss of regulation within the immune system leading to inappropriate activity of macrophages and T-cells and a state of uncontrolled, self-perpetuating hyperinflammation. This 'cytokine storm' is characterized by unregulated release of tumour necrosis factor-α (TNF-α), IFN-γ, IL-6, IL-10, and IL-1B and marked decrease in natural killer cell activity.

Primary HLH is caused by genetic defects in perforin genes and presents mainly in infants. Secondary, acquired forms of MAS/HLH occur in malignant disease, those with acquired immune deficiency states, such as organ transplant recipients, and in those with RD. MAS/HLH is most often seen in association with systemic juvenile idiopathic arthritis (SJIA). It is also reported with SLE, adult-onset Still's disease, and vasculitis and may occur at any stage of the disease; at onset, during periods of active disease or during periods when the underlying condition is quiescent.[3] Importantly, MAS can also develop *de novo* in non-rheumatology patients on the ICU suspected to have sepsis and multi-organ dysfunction, or with commonly identified triggers such as lymphoma and Epstein–Barr virus infection.

Clinical features

Features are mainly due to the underlying hyper-inflammatory state:

- cytopaenias—often decreasing platelet count is the first abnormality noted,
- hyperferritinaemia,
- unremitting fever,
- coagulopathy/disseminated intravascular coagulation,
- splenomegaly and lymphadenopathy,
- hypertriglyceridaemia,
- neurological features, such as confusion, headache, seizures, and coma,
- multiple organ failure.

The most common presenting features in a recent multinational study were fever (96%), hepatomegaly (70%), and splenomegaly (58%).[4]

Diagnosis

It is often difficult to differentiate MAS from underlying RD or overwhelming sepsis. Diagnosis requires a high degree of clinical suspicion and trends in serum values are more important than absolute values. High levels of serum ferritin and a low percentage of glycosylated ferritin have been shown to be useful in the diagnosis of MAS/HLH (hyperferritinaemia>10 000 μg litre^{-1} is pathognomic and levels >5000 very suggestive). Furthermore, there is evidence that consecutive ferritin levels can be used as a marker of response to therapy.[5] Other serum markers showing marked change include aspartate and alanine aminotransferases (increased by 346 and 325%, respectively), D-dimer (122%), and lactate dehydrogenase (121%). C-reactive protein is expected to increase, while the erythrocyte sedimentation rate may decrease.[4]

Treatment

While the majority of studies and recommendations for the treatment of MAS are in children, a multinational group proposed guidelines in 2005 for treatment in adults.[6] These include:

- early, aggressive supportive therapy,
- high-dose corticosteroids, such as dexamethasone or methylprednisolone with escalation to additional immune suppression with ciclosporin,
- elimination of known or suspected triggers,
- infection control.

The use of i.v. immunoglobulin therapy (1 g kg^{-1} for 2 days), plasma exchange, and treatment with biological agents have all been advocated in refractory cases of acquired MAS/HLH.

Minoia and colleagues[4] documented that almost 98% of MAS patients received corticosteroids, ciclosporin (61.2%), and i.v. immunoglobulin (36.3%). Only 15.2% of the patients required biological agents, with anakinra being the most commonly selected agent.

Case report: MAS in a 17-yr-old male with arthritis

A 17-yr-old male with SJIA, controlled with methotrexate and tocilizumab, was admitted to the ICU with respiratory failure secondary to lobar pneumonia. His immunosuppression was stopped, he was sedated, his lungs mechanically ventilated, and he was turned prone for refractory hypoxaemia. Broad-spectrum antibiotics and antiviral drugs were commenced and his urine was positive for pneumococcal antigen.

After improvement in his respiratory parameters, a surgical tracheostomy was performed on day 11 because of repeated failed sedation holds. He then became more unwell, having developed a widespread rash and spiking temperatures. A full septic screen was undertaken and broad-spectrum antibiotics commenced to no avail. He was turned prone again for acute respiratory distress syndrome and worsening hypoxaemia.

Rheumatology review raised the possibility of MAS/HLH and suggested high-dose methylprednisolone if his platelet count decreased. Several days later, a blistering chest wall rash was noted, his platelets did decrease, he developed cerebral irritation, and then had a seizure. A diagnosis of MAS was made clinically and supported by laboratory features (ferritin >16 500 μg litre^{-1}, triglycerides 10.3 mmol litre^{-1}, and a pancytopaenia). Methylprednisolone was started after advice from a regional specialist rheumatologist and he was transferred to a regional centre for further treatment, including ciclosporin, IVIG, and etoposide and ultimately made a full recovery.

Scleroderma renal crisis

Systemic sclerosis is an autoimmune disease characterized by fibrosis and inflammation of internal organs and the skin. A life-threatening complication of this disease is scleroderma renal crisis (SRC), affecting ~5–10% of patients with scleroderma.[7]

SRC is characterized by a rapid-onset hypertension that becomes malignant, combined with acute oliguric/anuric renal failure. This is a true rheumatological emergency as rapid diagnosis and treatment may save lives and renal function. The pathogenesis is not fully understood, but is thought to involve thickening of the inter-lobar and arcuate arteries within the kidneys, leading to reduced renal perfusion and excessive renin release.

Risk factors include:

- corticosteroid therapy,
- rapidly progressive skin disease,
- diffuse cutaneous systemic sclerosis.

The male:female incidence of SRC is roughly 1:3, with an average age of 53 yr and a mean interval of 3.2 yr between diagnosis of systemic sclerosis and developing SRC.[8]

Clinical features

- New-onset hypertension >150/80
- Acute deterioration in renal function >30% reduction in eGFR
- Left ventricular insufficiency
- Hypertensive encephalopathy

Classically, patients present with headaches, visual disturbances, encephalopathy, and seizures. They may also have cardiac involvement leading to pulmonary oedema, arrhythmias, and myo/peri-carditis.[9] A proportion of patients (~10%) do not have hypertension and progressive fatigue and malaise may be the only symptoms, combined with renal failure; therefore, a high degree of clinical suspicion is required.
Laboratory investigations show increased creatinine, thrombocytopenia, potentially a microscopic angiopathic haemolytic anaemia, and hyper-reninaemia.

Treatment

Aggressive management of hypertension is required to prevent irreversible renal damage. Angiotensin-converting enzyme inhibitors are the cornerstone of treatment and have achieved a decrease in acute mortality, but there is often resistance to their use in non-specialist ICUs because patients have renal failure. Further treatment may involve calcium channel blockers, labetalol, and nitrates (especially with pulmonary oedema) or plasma exchange if there is extensive thrombotic microangiopathy.

Approximately 25% of SRC patients require dialysis in the short term; however, 40–66% of all SRC patients do not recover full renal function and require chronic dialysis, transplantation, or both.[10] Recovery of renal function occurs slowly, taking up to 24–36 months, and prognosis is worse in those who are male, aged >53 yr, and those who are normotensive on presentation.[10] The overall 5 yr survival for systemic sclerosis patients with full SRC remains low (65%), despite improving treatments.[9]

Catastrophic antiphospholipid syndrome

APS is an autoimmune condition characterized by recurrent venous and arterial thrombosis, pregnancy disorders (miscarriage, preterm birth, and eclampsia), and the presence of antiphospholipid (APL) antibodies. It is most prevalent in women of reproductive age. There is also a higher incidence in Afro-Caribbean populations. APS is often found in conjunction with other inflammatory autoimmune conditions such as SLE, RA, systemic sclerosis, and Bechet's disease. It is thought to account for 10–15% of recurrent miscarriages and 20% of recurrent thromboses in young people.[11] Cardiac involvement in APS is common, with patients under 40 at increased risk of myocardial infarction and sudden death. These patients are also at high risk of re-stenosis after percutaneous intervention or coronary artery bypass grafting and can pose major therapeutic challenges.

Table 2 Clinical features of CAPS

Body system	Features
Pulmonary	PE
	Pulmonary hypertension
	Acute respiratory distress syndrome
Cardiac	Myocardial infarction
	Valvular lesions
	Heart failure
Renal	Renal failure
	Malignant hypertension
Central nervous system	Coma
	Seizures
	Cerebrovascular infarctions
	Retinal artery thrombosis
Abdominal	Abdominal pain
	Vascular occlusion of bowel, splenic, hepatic, pancreatic, and adrenal vessels all common in CAPS
Skin	Livedo reticularis
	Digital ischaemia
	Splinter haemorrhages
	Ulcerations
	Superficial gangrene in lower limbs

The pathogenesis of APS is still not fully understood. It is thought that APL antibodies activate endothelial cells, monocytes, and platelets and a pro-coagulant state is induced. This appears to be primarily mediated by the increased production of tissue factor and thromboxane-A2.[12]

Catastrophic APS (CAPS) is the rarer form, representing <1% of APS cases. In CAPS, there is an accelerated, widespread course of disease, leading to rapid multi-organ failure and over 50% mortality despite treatment. Histological studies show a thrombotic microangiopathy of small vessels, resulting in organ failure and a systemic inflammatory response syndrome (SIRS)-like state. The majority of CAPS events are preceded by a precipitating event which may be unknown. Identifiable triggers include infection, but also surgical procedures, trauma, and withdrawal of anticoagulation therapy.

Diagnosis

Diagnosis is challenging with many causes of false-positive and false-negative results, and validated diagnostic criteria are currently not available.[13] Early recognition of CAPS is essential to ensure the best clinical course possible for the patient. Presentation may be suspected with clinical history and common clinical features (Table 2), but a high index of suspicion and early liaison with haematology/rheumatology specialists is vital.

Treatment

Treatment is not currently standardized due to the rarity of the condition. In addition to supportive care for specific organ involvement, it is important to recognise those at high risk (surgery/trauma) and aggressively treat any precipitating factors, for example infection. A three-pronged approach is then recommended:[13]

(i) Prevent and treat the ongoing thrombotic events, usually with i.v. heparin.

(ii) Consider IVIG and/or plasma exchange.
(iii) Suppress the excessive cytokine 'storm' with high-dose steroids and other immunomodulatory therapies if indicated.

Anti-neutrophil cytoplasmic antibodies-associated vasculitides

The anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) are a subgroup of multi-system, autoimmune diseases that affect small to medium-sized blood vessels and are characterized by the presence of ANCA in the circulation. In addition, there is an absence of immune deposits within vessel walls that differentiates AAV from other small vessel vasculitides.[14]

The clinicopathological variants of AAV were revised in 2012[15] and are as follows:

- microscopic polyangiitis (MPA),
- granulomatosis with polyangiitis (GPA, formerly Wegener's)
- eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg–Strauss),
- single-organ AAV (e.g. renal-limited AAV).

It is important to note that AAV is not a single disease entity but rather a group of multisystem disorders that share certain features. The respiratory tract and kidneys are most commonly affected by AAV.

Complications

Many of these patients will be well established on corticosteroid therapy and other immunosuppressive drugs and as such are at high risk of opportunistic infections and overwhelming sepsis.

Pulmonary involvement is more frequent in GPA (90%) and EGPA (70%) and less frequent in MPA (50%).[16] In granulomatosis with polyangiitis (Wegener's), all parts of the respiratory tract can be affected from the nasal mucosa to the pleura and pulmonary artery. Complications of particular interest to the intensivist are the development of subglottic stenosis, leading to difficult tracheal intubation, and the potential for diffuse alveolar haemorrhage, requiring invasive ventilation. In EGPA (Churg–Strauss), there may be multiple nasal polyps and an eosinophilic asthma that progresses in severity with disease course.

Renal involvement occurs more frequently in MPA (90%) and in GPA (80%) and less frequently in EGPA (45%).[16] Renal AAV can present as rapidly progressive glomerulonephritis, quickly leading to end-stage renal disease.[17]

The heart is involved most commonly in EGPA, with presentations including heart blocks, myocarditis, pericarditis, and myocardial infarction. Gastrointestinal presentations include bowel perforation, resulting from vasculitic ulceration of the small and large intestine, and pancreatic or liver involvement.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a complex, multi-system disease with numerous critical complications that may present to the intensivist. These range from common (coronary artery disease, overwhelming sepsis, and renal failure) to rare (pericarditis, alveolar haemorrhage, and transverse myelitis). Owing to the vast scale of this disease, it is out of the scope of this review article.

Rheumatological pharmacotherapies

The pharmacological management of RD has changed dramatically over recent years. A paradigm shift has occurred where the 'inflammatory burden' a patient is exposed to is increasingly recognized; the greater the burden and the longer a patient's exposure, the greater the risks of complications such as cardiovascular disease developing in later life. Therefore, by attenuating the inflammatory burden, the risks of associated complications are lowered. For example, suffering from RA is an independent risk factor in the 'QRISK2 score' (a widely used cardiovascular risk scoring algorithm for determining the likelihood of having a cardiac event within the next 10 yr).[18]

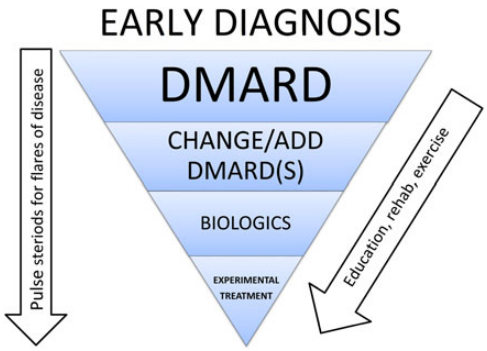

Fig 1 The new inverted pyramid approach to treatment of RD.

In 2009, NICE recognized this and described the need for the early use of disease-modifying anti-rheumatic drugs (DMARDs) in their guidelines.[19] This strategy is described as the 'inverted pyramid approach' (Fig. 1). Aggressive immunosuppressant therapy is now started early. Consequently, this means many more people are receiving DMARDs and often as dual- or triple-therapy. First-line DMARDS are usually started in combination as standard therapy for RA, e.g. methotrexate and sulphasalazine. For resistant disease, biological agents are usually given alongside an oral DMARD, e.g. methotrexate plus infliximab. Further biologics are then added as per NICE guidance. In other RDs such as SLE, hydroxychloroquine, azathioprine, or mycophenolate mofetil may also be used first line and again in combination (Table 3).

Methotrexate

Methotrexate is the most commonly used DMARD in the treatment of RA. It is an analogue of folic acid, with anti-proliferative, immunosuppressive, and anti-inflammatory properties. It is taken orally or subcutaneously once weekly. Methotrexate has many recognized side-effects including methotrexate pneumonitis (MX-P) and methotrexate-induced bone marrow failure.

Methotrexate pneumonitis

Methotrexate can cause pulmonary toxicity by exacerbating pulmonary fibrosis, the exact mechanism of which is unknown. One rare but important form of pulmonary toxicity is MX-P. The incidence of MX-P is between 2% and 7%, with the greatest risk being within the first year of treatment. Although rare, acute MX-P can have a mortality of up to 20%. Onset may be acute or subacute, within days to months of taking methotrexate.

Clinical features include:

- breathlessness,
- cough,
- fever,
- hypoxia,
- bibasal lung crackles.

Table 3 Examples of common rheumatological drugs, classes, uses, and side-effects

Drug type	Examples	Use	Side-effects
First-line DMARDS	Methotrexate Sulphasalazine Leflunomide Hydroxychloroquine (less commonly gold and penicillamine)	First-line RA treatment	Methotrexate pneumonitis (RARE), methotrexate bone marrow toxicity All DMARDs have a potential to cause myelosuppression conferring a high risk of neutropenic sepsis. Many also cause renal or liver toxicity, skin rash, or gastrointestinal disturbance
New-generation biologics	Anti-TNF agents, e.g. infliximab, etanercept, and adalimumab B-cell depletion, e.g. rituximab IL-6 antagonists, e.g. tocilizumab T-cell co-stimulators, e.g. abatacept	Used in combination with first-line DMARDs for resistant RA Used if anti-TNF agent/DMARD fails	Primary infection with TB or other atypical infections, e.g. PCP, aspergillus, and cytomegalovirus Reactivation of latent TB Antibody depletion can lead to JC virus reactivation and progressive multifocal leukoencephalopathy Bone marrow suppression Worsening of demyelinating diseases such as multiple sclerosis and optic neuritis
Alkylating agents	Cyclophosphamide	SLE, granulomatosis with polyangiitis	Bone marrow suppression, pancreatitis, SIADH, renal dysfunction, hepatotoxicity
NSAIDs Steroids	Ibuprofen, naproxen, celecoxib Methylprednisolone	For acute flare management	Renal dysfunction, bleeding, increased cardiovascular events

Investigations and the expected findings are:

- pulmonary function tests—gas transfer usually decreased,
- high-resolution CT—bilateral, patchy ground-glass opacities,
- trans-bronchial tissue biopsy—marked eosinophilia.

Diagnosis of MX-P can be challenging as MX-P is initially difficult to differentiate from acute pulmonary infection, and organisms such as *Pneumocystis* should be excluded. Several sets of diagnostic criteria have been developed; the one most commonly used is Searles' criteria (Table 4).[20] MX-P is characterized as 'definite' if one of the major criteria is present in conjunction with three minor criteria. 'Probable' MX-P is present if major criteria 2 and 3 plus two of the five minor criteria are present.

Treatment of MX-P involves simply discontinuing methotrexate therapy and this may be enough to halt the pathological process and improve the clinical condition. In those who do not respond to the cessation of methotrexate, high-dose corticosteroid therapy may be required (e.g. methylprednisolone 1 mg kg^{-1} initially). Empirical antibiotics should be commenced in those in whom infection, especially with *pneumocysitis*, cannot be ruled out. In severe cases, inotropic and ventilatory support may be required.

Patients usually improve clinically within days of cessation of methotrexate and radiologically within weeks to months. Pre-methotrexate screening with pulmonary function tests and chest X-ray are standard to ensure if the rare complication of MTX pneumonitis is encountered, the patient has sufficient respiratory reserve to recover when MTX is withdrawn.

Methotrexate bone marrow toxicity

Methotrexate bone marrow toxicity may present as a moderate to severe pancytopenia. Risk factors include impaired glomerular filtration rate, advanced age, low serum albumin levels, and concurrent liver disease. Treatment begins with cessation of methotrexate, organ support, and administration of folinic acid. Appropriate replacement of red blood cells and platelets, granulocyte colony-stimulating factor, and i.v. methylprednisolone may also be required.

Biological agents

The 'biologics' are usually second-line treatments and fall into four broad categories.

Anti-TNF agents

TNF is a family of cytokines that have key functions in immunity, cell proliferation, and inflammation. TNF-α inhibitors have revolutionized the treatment of RA and other inflammatory diseases.

Table 4 Searles criteria' for diagnosis of MX-P[20]

Major criteria
- Hypersensitivity pneumonitis by histopathology without evidence of pathogenic organisms
- Radiological evidence of pulmonary interstitial or alveolar infiltrates
- Blood cultures (if febrile) and initial sputum cultures (if sputum is produced) that are negative for pathogenic organisms

Minor criteria
- Shortness of breath for <8 weeks
- Non-productive cough
- Oxygen saturation ≤90% on room air at the time of initial evaluation
- Diffusing capacity of lung for carbon monoxide (DLCO) ≤70% of predicted for age
- White cell count ≤15 000 cells mm^{-3}

Owing to their powerful inhibitory action on TNF-α, they suppress the immune system significantly and are relatively contraindicated in those already at risk of infection, e.g. patients with uncontrolled diabetes or those on high-dose steroid therapy. Currently, they can only be given under specialist supervision. Infliximab, adalimumab, certolizumab, and golimumab are monoclonal antibodies, while etanercept is a construct of TNF-α receptors, coupled to a human monoclonal antibody.

As patients may be admitted to the ICU already taking these agents, it is useful to know dosing schedules. Broadly, these drugs are usually given subcutaneously weekly (etanercept), fortnightly (certolizumab), or monthly (golimumab). Infliximab is given 8-weekly by i.v. infusion. This should allow ample time to gain rheumatology involvement to discuss dosing and whether to continue administration or not.

Anti-TNF agents put patients at risk of atypical and opportunistic infections. Examples include:

- bacterial, e.g. Listeria, Salmonella,
- mycobacterial, e.g. *Mycobacterium tuberculosis*,
- viral, e.g. varicella,
- fungal, e.g. *Pneumocystis jirovecii* (previously Pneumocystis carinii pneumonia), Aspergillus.

B-cell depletors

Rituximab is a monoclonal antibody against CD20, a protein found on the surface of B-lymphocytes. It therefore has potent anti-B-cell action. It is licensed for the treatment of resistant RA in combination with methotrexate. It is given 6–12 monthly as two i.v. infusions 2 weeks apart.

Antibody depletion confers a high risk of the reactivation of latent infections such as tuberculosis. Reactivation of the John Cunningham virus can lead to the serious and potentially fatal progressive multifocal leukoencephalopathy.

IL-6 antagonists

Tocilizumab is a monoclonal antibody licensed for the treatment of juvenile idiopathic arthritis and RA that has failed to respond to DMARDs and a TNF-α inhibitor. It is administered by monthly i.v. infusion and weekly s/c injection.

T-cell co-stimulators

Abatacept is a fusion protein that binds to CD80 and CD86 receptors on the surface of T-cells, thus preventing T-cell activation. It is licensed for resistant RA and polyarticular juvenile idiopathic arthritis. It is usually given by monthly i.v. infusion.

Conclusions

The recent paradigm change in rheumatology where inflammatory disease is treated early with combination immunosuppressant therapies means patients are more susceptible to sepsis including atypical and opportunistic infection. Rheumatological disease flares can cause acute illness or can be a sequelae of acute illness, especially sepsis. In patients on intensive care who initially improve with antibiotics but then worsen, there should be consideration that a flare of the underlying rheumatic disease is responsible and requires treatment. Intensivists should be aware of hyper-inflammatory states such as MAS and CAPS as these are treatable when recognized. Intensivists should be aware of the rare but specific rheumatological emergencies.

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Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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