Paediatric intensive care

Neil R. Bennett

Department of Paediatric Anaesthesia and Intensive Care, Sheffield Children’s Hospital, Sheffield S10 2TH, UK

Br J Anaesth 1999; 83: 139–56

Keywords: anaesthesia, paediatric; intensive care, paediatric; analgesia, paediatric; children

Children who require intensive care are usually critically ill as a result of an accident, acute medical illness or life-threatening surgical condition. With appropriate management, most should be restored to normal and potentially productive lives. In addition, intensive care may be required when an acute illness is superimposed on a chronic condition or congenital anomaly. Paediatric intensive care is also an essential component in the postoperative management of children undergoing complex surgical procedures.

The pathology and range of critical illness seen during infancy and childhood is different from that in adults. Physiological factors affect the response to critical illness, including the speed of onset and rapidity of clinical deterioration. At least 50% of children requiring intensive care are less than 2 yr of age.45 Significant numbers of neonates may be managed in paediatric intensive care units after, for example, major surgical or cardiothoracic procedures. In addition, babies discharged home shortly after birth may develop airway problems, pneumonia or severe respiratory syncytial virus (RSV) infection and require admission to a paediatric intensive care unit (PICU) during the first 4 weeks of life.

The first multidisciplinary PICU was opened in 1955 at the Children’s Hospital, Gothenborg.37 However, it was not until the following decade that other centres established intensive care units exclusively for children, the main stimulus being development of the technique of prolonged nasotracheal intubation. This heralded a period of rapid progress during which intensive care units were established in most of the leading paediatric centres in Australia, Europe and North America.

More recently, the potential of paediatric intensive care has been enhanced by several factors: developments in paediatric anaesthesia, medicine and surgery; technological and therapeutic advances in both neonatal and adult intensive care medicine; and improved understanding of paediatric physiology and mechanisms of severe illness in children.

There are now well established standards and guidelines for the practice of paediatric intensive care.30 120 The availability of appropriately trained physicians with full-time commitments in paediatric intensive care is of paramount importance. The American Board of Pediatrics granted paediatric critical care medicine subspecialty status in 1987. Training programmes in the USA undergo accreditation and there are examinations leading to Board Certification. In the UK, the Inter-Collegiate Committee on Training in Paediatric Intensive Care Medicine oversees training for doctors who wish to pursue a career in paediatric intensive care. The Committee comprises representatives from three Royal Colleges: anaesthesia, surgery and pediatrics. A detailed syllabus sets out the knowledge and skills which have to be acquired. Training must be obtained in units accredited by the Committee according to criteria which, among others, relate to organization, size, case mix, staffing and supervision.

Organization, assessment and outcome of paediatric intensive care

In industrialized countries, intensive care makes significant demands on health care expenditure. Despite the influence of intensive care on mortality, morbidity and costs, little is known about how its organization affects outcome. There is debate as to the most effective way of providing these services, with particular reference to the relationship between factors such as size, degree of centralization, quality of care, cost and outcome. Those who advocate centralization of specialist services contend that there are economies of scale, with a relationship between patient volume and clinical outcome97; concentrating the provision of more complex treatments should facilitate provision of experienced staff who are able to develop and maintain their expertise. However, recent work in adults undergoing intensive care has demonstrated no apparent relationship between patient numbers and outcome.79 Nevertheless, there is evidence that the availability of trained full-time specialists in paediatric intensive care medicine improves outcome in critically ill children.128 In addition, studies of other specialized paediatric services, including oncology and neonatal intensive care, have demonstrated improved outcome when patients are managed in larger more central-ized tertiary facilities.126 151 152

Paediatric intensive care is a low-volume, high-cost service which comprises several key components: avail-
ability of adequate numbers of doctors and nurses trained specifically in paediatric intensive care; a physical area designed and equipped for the needs of critically ill children; and a paediatric emergency transport team. In addition, there needs to be immediate access to a large multidisciplinary team which includes specialists in paediatric anaesthesia and surgery, physicians in general and sub-specialty paediatrics, and the full range of complementary specialist and ancillary services for children.

Facilities for paediatric critical care should satisfy criteria relating to size, number of admissions and case mix in order to attract appropriately trained staff, maintain expertise and operate effective medical and nurse training programmes. These criteria can be achieved by concentrating paediatric intensive care services in larger units, each of which serves a geographical area with a significant sized population. This model is encountered in parts of North America and throughout Australia where there are a small number of units, each serving a large paediatric population. By contrast, there are parts of the UK where the organization and provision of paediatric intensive care has, in the past, been fragmented and poorly integrated. A recent report from the Department of Health recommended several important changes, including a degree of centralization facilitated by the creation of a number of ‘lead centres’ which will help to coordinate provision of paediatric intensive care services throughout the country.

Although centralization of paediatric intensive care services appears eminently logical, the majority of critically ill children present at local hospitals. Concerns have been voiced that transferring most children who require intensive care to units which may be some distance away could lead to a reduction in skills of staff working in the more peripheral units. It is therefore important that all hospitals which admit children ensure that adequate numbers of staff have received comprehensive training in resuscitation and advanced paediatric life support, regardless of where longer term intensive care is provided. While most paediatric intensive care is provided in hospitals which offer tertiary paediatric services, some smaller scale provision may still be required in more remote and sparsely populated regions of larger countries. This may help avoid the long distance transfer of children with less complex disorders and allow management of acute cases who present with those conditions whose course may be more predictable.

It has been estimated that approximately 1.3 children per 1000 require paediatric intensive care each year. The number of beds required in a PICU therefore depends on the size of catchment population, the average duration of stay and bed occupancy. There may be peaks and troughs of activity, with occupancy rates which vary during the year. This is less likely in larger units located in tertiary paediatric hospitals where there are higher and more sustained levels of activity.

Reported mortality rates for paediatric intensive care vary between 5% and 17%. Hospital mortality rates of 26% have been reported for adults undergoing intensive care, and 66% for preterm infants with birth weights less than 750 g. However, comparisons which use crude mortality rates are limited because outcomes are affected by factors such as co-morbidity, age and severity of acute illness. During recent years, risk adjustment methods have been developed which allow predicted mortality of intensive care patients to be estimated and compared with actual mortality. The APACHE scores were developed for use in adults and incorporate data which relate to the degree of acute physiological derangement together with information on chronic health status.

The most commonly used method to predict mortality in critically ill children is the Paediatric Risk Index of Mortality Score (PRISM); this is based on the values of 14 clinical and laboratory variables measured during the first 24 h after admission to the ICU (Table 1). An equation derived from logistic regression analysis allows mortality risk to be calculated according to the degree of physiological derangement, age and operative status. However, the PRISM score requires reliable collection of a large amount of data. In addition, the 24-h data collection period commences on admission to the PICU, by which time the condition of the child may have improved after initial resuscitation and subsequent stabilization. Alternatively, the child may have died, significant numbers of deaths in critically ill children occurring within 24 h of presentation, often before admission to the PICU. Another problem is that the original version of PRISM does not adjust for co-morbidity: this has been remedied in PRISM III, although a licence fee is required to gain access to the algorithms used for the calculations. Initial verification of the PRISM score used data obtained from tertiary units in the USA. Although subsequent validation has been undertaken in Holland, a study from the UK suggested that PRISM overestimated mortality in critically ill infants. In another study, prediction of short-term survival after cardiac surgery proved to be unreliable. PRISM may therefore be poorly calibrated for certain categories of patients and there remains a need to develop more reliable methods of case mix adjustment and outcome prediction in critically ill children.

Another score, the paediatric index of mortality (PIM), uses six variables together with information concerning operator status and co-morbidity (Table 2). The system is easy to use and has been validated against data collected

<table>
<thead>
<tr>
<th>Table 1 Physiological variables used in calculating the PRISM score (from Pollack, Ruttimann and Getson)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Systolic arterial pressure</td>
</tr>
<tr>
<td>Diastolic arterial pressure</td>
</tr>
<tr>
<td>Heart rate</td>
</tr>
<tr>
<td>$P_{O_2}/P_{CO_2}$</td>
</tr>
<tr>
<td>Total bilirubin</td>
</tr>
<tr>
<td>Potassium</td>
</tr>
<tr>
<td>Calcium</td>
</tr>
<tr>
<td>Glucose</td>
</tr>
<tr>
<td>Bicarbonate</td>
</tr>
</tbody>
</table>


from Australia and the UK. Although it has good predictive power, treatment given immediately before admission to intensive care may again influence the score. Nevertheless, its simplicity makes it feasible to score patients accurately when they first present with a critical illness and facilitates more reliable comparisons.

Risk adjustment methods have been used to assess organizational aspects of paediatric intensive care and efficacy of specific treatments and interventions. One study from the USA using PRISM demonstrated that children with a high risk of mortality were more likely to die when managed in non-tertiary units compared with tertiary facilities. However, there were significantly more patients in the non-tertiary group. There were also major differences in case mix, with more than two-thirds of the non-tertiary group comprising patients with head injuries. In addition, children who were transferred or died before admission to the tertiary centres were excluded from the study.

A subsequent study from the Netherlands demonstrated that high-risk patients managed in tertiary paediatric units had lower than predicted mortality rates: in the non-tertiary units, mortality rates were higher than predicted. Conversely, mortality of low-risk patients managed in tertiary units was higher than expected. However, this was attributed to the fact that several of these children had incurable chronic conditions with little prospect of long-term survival. In addition, PRISM does not adjust for co-morbidity. Higher mortality rates in lower-risk patients were also reported in a study of six PICUs from South America. Although the reasons for this remain unclear, the incidence of tracheal intubation and use of central venous catheters was significantly higher compared with a similar group of low-risk patients who were managed in a large tertiary PICU in the USA.

A more recent study compared risk adjusted outcomes in all children undergoing intensive care over a 12-month period in the Australian state of Victoria and the Trent region of the UK. This study demonstrated that observed mortality was equal to predicted mortality in the Australian group. In comparison, observed mortality was significantly greater than predicted in the British children, differences being greatest in the lower risk categories. Mortality rates in the highest risk category were, however, similar in both countries. Despite geographical differences between the two regions, they have similar sized populations. However, at the time of the study there were important organizational differences: almost all the Australian deaths occurred in one designated PICU which managed virtually every child in the region who required intensive care; in the British group, deaths occurred in nine separate units at a time when there were two designated PICU in the region. This raises the question as to whether British children who died in the non-specialized units would have benefited from transfer to a designated PICU, notwithstanding the fact that many were in the lower mortality risk categories.

There has been much debate about the results of these comparative studies, although they provide contributory evidence that children in medium- and high-risk categories have better outcomes when managed in tertiary units: there is certainly no study which demonstrates the opposite. Nevertheless, further studies are required together with the development and validation of more accurate methods of case mix adjustment in order to allow more reliable comparisons of outcome in different groups of critically ill children.

As regards long-term survival, there is little information about morbidity or health status of those children who have undergone intensive care, mortality being the main outcome measure. However, an Australian study examined long-term outcomes in almost 1000 consecutive children. Patients were categorized according to illness severity on admission to intensive care and detailed follow-up of survivors was undertaken after 3 yr. Mortality at 3 yr was 20%, more than half of whom died during their time on the PICU. Of the survivors, 15% had a mild handicap, 20% were functionally normal but required some medical supervision and 55% were normal. Thus 80% of children survived to 3 yr and 90% of survivors were expected to lead independent lives. Although younger children were more likely to die than older children, those who survived did not have a higher incidence of handicap. In a follow-up study of 1400 North American children, those with previous impairment appeared to have less additional morbidity compared with previously normal children.

More recently, long-term survival and state of health were assessed in 468 Dutch children 1 yr after discharge from intensive care, using the multi-attribute health status classification (MAHSC). This was developed as a comprehensive measure of health status in children and has been used to evaluate survivors of childhood cancer. ICU mortality in this study was 7.5%, increasing to 10.5% after 1 yr. In 73% of survivors, overall health status was equal to pre-admission level. However, MAHSC cannot be used in infants and must be employed with caution in preschool children. Assessment of pre-admission health status is, of necessity, retrospective. Furthermore, it is not possible to exclude the influence of factors which might influence health status following discharge from intensive care.

Most survivors from paediatric intensive care have good functional outcome and go on to lead independent lives. Nevertheless, some need more continuous treatment and

---

Table 2 Information required for calculating PIM score (from Shann and colleagues)

- Booked or elective admission
- Specific underlying condition (e.g. out of hospital cardiac arrest, immune deficiency, etc)
- Response of pupils to bright light
- Base excess (arterial or capillary)
- $P_{A\text{O}_2}$
- $P_{F\text{O}_2}$
- Systolic arterial pressure
- Mechanical ventilation during first hour in ICU

---

Paediatric intensive care
support including a small number who require long-term ventilation which may be provided in separate units or at home. Future studies of children following paediatric intensive care will require development of more refined and sensitive methods of assessment and outcome. These will be important in assessing the efficacy of intensive care and allowing correlation with organizational and quality-of-care factors.

Transfer of the critically ill child

The trend towards centralization of paediatric intensive care services means that significant numbers of critically ill children need to be transferred between hospitals. However, inter-hospital transport of critically ill patients can be hazardous and may result in clinical deterioration. Studies of adults have demonstrated a high incidence of adverse events such as hypotension and hypoxia; acceleration and vertical forces affect cardiovascular stability and may have adverse effects on intracranial pressure in patients with head injury. Transfer of sick children is particularly hazardous, especially when undertaken by inexperienced personnel. Rapid and serious deterioration may result from lack of suitable equipment and deficiencies in management. In one study where the inter-hospital transfer of 56 critically ill children was undertaken without provision of a specialized retrieval team, there were critical incidents in 49 cases.

Common problems included inadequate circulatory and ventilatory support, equipment failures, errors in drug administration and thermal stress; some children even arrived at the referral unit without intravascular access or basic monitoring. A far more satisfactory method of transfer is for the referral unit to send out a paediatric critical care retrieval team. This forms a major component of an integrated paediatric intensive care service, the regional PICU maintaining close links with outlying hospitals which admit children, providing advice when required, arranging emergency transfers and undertaking long-term follow-up.

The benefits of specialized paediatric emergency transfer teams are well documented. A recent study compared inter-hospital transfer of children to two PICUs. Transfers to one unit were undertaken by a dedicated paediatric retrieval team; transfers to the other unit were undertaken by non-specialized teams from the principal referring hospitals. Although illness severity and case mix were similar in both groups, the frequency of critical incidents was 10 times greater when transfers were undertaken by the non-specialized teams. These incidents included loss of i.v. access, depleted oxygen supply and problems with the airway or tracheal tube. A subsequent study of 51 children transferred by a specialized retrieval team demonstrated physiological deterioration in only two cases during transfer, with no adverse incidents related to equipment.

Members of a retrieval team must undergo additional training in paediatric emergency transfer. A paediatric intensivist should be available to provide advice, co-ordinate activity and if necessary accompany the team. On arrival at the referring hospital, the team should ensure that appropriate investigations, monitoring and treatment are initiated; return to the referral unit should normally only take place once the child’s condition is stable. The means of transport depends on geography and demographic factors. Helicopter and fixed-wing transport may be required in more remote areas or when long distances are involved. Carefully managed, a transfer should rarely, if ever, result in deterioration of the patient’s condition.

Airway management in the PICU

The majority of children who undergo intensive care require tracheal intubation to relieve upper airway obstruction, remove secretions or allow some form of respiratory support. Successful management of the paediatric airway remains a sine qua non of paediatric intensive care practice.

Metal tubes were used during the 19th century to relieve airway obstruction caused by diphtheria. However, the technique of prolonged tracheal intubation in children was not described until 1962; by this time, tubes manufactured from polyvinyl chloride were available. Subsequent reports from several major paediatric centres described the successful use of nasotracheal intubation in large cohorts of children undergoing intensive care. Despite concerns about possible long-term sequelae, there was a commendably low incidence of subglottic stenosis, which was reported in one of the early studies to be approximately 1%. The technique therefore became the preferred method for relieving upper airway obstruction caused by conditions such as epiglottitis and acute laryngo-tracheobronchitis, leading to a rapid decline in the requirement for tracheostomy. It also provided a conduit to permit effective ventilatory management of infants and children with respiratory failure arising as a result of pulmonary, cardiac or neuromuscular disease. In addition, it facilitated the provision of IPPV following major trauma, cardiac and other complex surgery.

A recent study of all infants and children managed during a 4-yr period in a tertiary PICU reported no long-term sequelae following prolonged nasotracheal intubation. Success with the technique requires a thorough understanding of paediatric airway anatomy and adherence to several fundamental principles. The lumen of the subglottic region, between the larynx and trachea, is completely surrounded by the cricoid cartilage and forms the narrowest part of the upper airway in children. In neonates the diameter is approximately 4 mm: 1 mm of circumferential swelling can lead to a reduction in cross-sectional area of 75% and a 16-fold increase in resistance to airflow. Swelling of the ciliated columnar epithelium which lines the larynx at this point may be caused by infection or trauma. The commonest causes of acquired subglottic narrowing in children are therefore acute viral laryngo-tracheobronchitis (ALTB) and mechanical trauma. More permanent narrowing may follow the longer term presence of a large tracheal tube, frequent...
traumatic intubations, burns, inhalation injury, etc. Children with ALTB which is severe enough to require intubation are further predisposed to tube-related injury because of the pre-existing laryngeal swelling caused by infection. Some cases of ALTB may, in addition have a degree of congenital subglottic narrowing which has remained asymptomatic until infection produces oedema with critical narrowing of the airway. Under these circumstances it is necessary to use a tube which is significantly smaller than calculated by age in order to minimize trauma. Unfortunately, cases of acquired subglottic stenosis are still encountered, especially in preterm infants following prolonged neonatal intensive care in whom the reported incidence is up to 8% of intubated infants.132

The pathogenesis of intubation injuries in neonates and small infants has been elegantly described.132 The main factor is the presence of an excessively large tube which causes ischaemic damage and leads to ulceration, necrosis of the mucosa and exposure of the cricoid cartilage; frequent and traumatic intubations can cause similar damage even with an appropriately sized tube. The initial injury is followed by a period of healing and re-epithelialization which can occur with the tracheal tube in place. Healing is impeded by infection, friction caused by tracheal tube movement and trauma caused by frequent re-intubation. This results in further mucosal injury, ulceration of the cartilage, perichondritis and proliferation of granulation and fibrous tissue.

Injury after prolonged intubation can be virtually eliminated by the use of a sterile non-cuffed tracheal tube which allows a small air leak during positive pressure ventilation. The tube should be inserted atraumatically, usually with the aid of a neuromuscular blocking agent and after administration of an anaesthetic or sedative agent. The risks of inadvertent extubation and frictional damage to the larynx from tube movement can be reduced by adequate sedation and meticulous immobilization with tapes and ties. Many units use some form of head harness to immobilize the connecting tubing which confers additional stability and prevents vertical movement of the tracheal tube.

In neonates and small infants, tracheal length is approximately 4 cm and the potential for tube displacement is significant. Apart from increasing the frequency of reintubation, accidental extubation may be associated with serious sequelae, including aspiration, hypoxia and death. The reported incidence of unplanned extubation in neonates undergoing intensive care is 10–13%;11; the incidence in children is 3–13%.95 Predisposing factors include age, duration of intubation, use of an inappropriately short tube and inadequate sedation. Extubation is also more likely when performing bedside procedures and during weaning from ventilation.

The timing of elective extubation is important: early extubation may result in failure, increasing the likelihood of additional intubations and trauma; prolonged intubation increases the duration of ventilation and risk of nosocomial infection.85 Failure rates of 17–19% have been reported after planned extubation in adults51 and 22–28% in preterm neonates.161 In children undergoing intubation for upper airway obstruction caused by infection, criteria for extubation include minimal tracheal secretions, normal white cell count, clear chest x-ray and absence of pyrexia; however, the most important fact is the presence of a leak around the tube.

There is no evidence to support routine administration of steroids before extubation.146 They should be reserved for those cases where there is a significant risk of extubation failure e.g. inadvertent use of a tight tube, multiple intubations, no leak before extubation and ALTB. In a controlled study of the use of steroids in children intubated for ALTB, one group received regular 12-hourly doses of prednisolone 1 mg kg-1 until criteria for extubation were fulfilled. Both duration of intubation and requirement for re-intubation were significantly reduced in those who received steroids compared with the placebo group.157

Several studies of the early use of steroids in children with mild to moderate ALTB have yielded conflicting results. However, recent work suggests a beneficial effect after the use of either oral dexamethasone or nebulized budesonide in unintubated children with mild to moderate ALTB.91 100 Children with severe obstruction should be admitted to the intensive care unit. Regular use of a clinical score provides objective assessment of the severity and progress of the obstruction.58 Nebulized epinephrine has an established role in the management of both severe ALTB and post-extubation stridor. Although it may evoke rapid clinical improvement, the effect may be evanescent; in addition, repeated administration of epinephrine may result in a rebound phenomenon. Early studies used racemic mixtures because of fears of possible cardiac effects; however, the L-isomer used for resuscitation is both safe and effective.134 Children with severe ALTB should receive a combination of nebulized epinephrine together with systemic steroid. Epinephrine should lead to rapid symptomatic improvement and allow time for the steroid to exert its effect, thus, preventing the need for intubation in the great majority of cases of severe ALTB.100

Since the introduction of Hib immunization, the incidence of acute epiglottitis has become extremely rare, although it can be caused by organisms other than Haemophilus influenzae and, on occasion, may occur in infancy. Another cause of upper airway obstruction, in children of all ages, is bacterial tracheitis, caused usually by Staphylococcus aureus. In severe cases, sudden airway obstruction may still occur after intubation due to sloughing of tracheal mucosa, and bronchoscopy may be required.

Sedation

For a child, an intensive care unit is a threatening environment which generates anxiety and fear. Pain and discomfort are caused by drains and tubes, invasive nursing procedures,
and insertion of catheters, cannulae and tracheal tubes. The implications of inadequate analgesia and the neuroendocrine response to stress are well recognized in neonates and infants.7 The emotional and physical stress of critical illness and intensive care can influence both physical and psychological outcome. However, a study from one PICU reported inadequate analgesia and sedation during at least 50% of invasive procedures149, most of which were undertaken without additional medication. More reassuring were the results of a national survey in the UK which showed that analgesic and sedative drugs were used routinely when paediatric anaesthetists managed children undergoing intensive care.105 The most commonly used agents were morphine and midazolam. The nasogastric route was also used when possible to administer supplementary drugs such as trimeperazine and chloral hydrate. Half the respondents used combinations of neuromuscular blockers and sedatives when ventilating neonates.

The purpose of sedation in the PICU is to reduce patient distress, prevent unplanned extubation and facilitate controlled ventilation. Although sedation scores have been developed for adults, pain and agitation may be difficult to assess in children, particularly during infancy. Nevertheless, a number of scores have been devised for the paediatric patient, although several include an assessment of cry which precludes their use in intubated children. One score, the COMFORT scale, rates eight dimensions of behavioural or physiological distress.104 Alertness, calmness/agitation, respiration, physical movement, baseline arterial pressure and heart rate, muscle tone and facial tension are each scored on a five-point scale. A well sedated patient would have a score of 17–26. However, the scale is complex and validation studies excluded patients with head injury and children receiving neuromuscular blocking agents. There remains a need for more reliable scoring systems together with neurophysiological techniques to allow more accurate monitoring of sedation, especially when neuromuscular blocking agents are used.96

There is little information on the effects of prolonged and continuous use of sedative and analgesic agents in critically ill children. There may be considerable variations in response: the pharmacokinetics of analgesic and sedative agents are different during early infancy; drug requirements may be modified by hepatic, renal and cardiac dysfunction; and there may be interactions with other drugs.

Although there is no one drug or combination which can be regarded as ideal, the benzodiazepines are most commonly used to provide sedation, usually in conjunction with opioids. Diazepam is used infrequently because of its long half-life and active metabolites. It has been superseded by midazolam whose properties include rapid speed of onset, water solubility, amnesic effect, short elimination half-life and low incidence of side effects. A slow i.v. loading dose of 0.1–0.2 mg kg⁻¹ is followed by a continuous infusion of 0.1–0.3 mg kg⁻¹ h⁻¹. Hypotension may occur when administered together with fentanyl in small infants;65; colloid-resistant hypotension has also been observed in critically ill neonates receiving midazolam alone.78 Clearance is almost entirely by hepatic metabolism and is dependent on cytochrome P450; duration of action is therefore prolonged if there is hepatic dysfunction, reduced hepatic blood flow or when drugs such as erythromycin or rifampicin are being given simultaneously. Excretion of the active metabolite, 2-hydroxymidazolam, may be delayed if renal function is impaired. In children the elimination half-life of midazolam is shorter and clearance more rapid than in adults. In neonates, elimination half-life is increased and clearance is reduced.78 Both tolerance and prolonged sedation have been described after administration in children.24 Withdrawal symptoms following midazolam have also been reported.73 A recent study recorded adverse effects in 17% of children after infusion of midazolam, including prolonged sedation, abnormal behaviour and hallucinations. Problems were more common in children than in infants, and the risks were increased with doses greater than 0.3 mg kg⁻¹ h⁻¹. The use of midazolam has been described in the management of children with status epilepticus.138 Lorazepam also has potent anticonvulsant properties and can be used for sedation in the PICU. The half-life is longer (4–12 h) and can be administered enterally or i.v. by bolus or infusion; metabolism is by hepatic glucuronidation.

Morphine remains the most commonly used analgesic agent in the PICU, and is usually administered in conjunction with a sedative agent. Its respiratory depressant effects are useful in improving synchronization with IPPV. An initial slow i.v. bolus of 0.05–0.2 mg kg⁻¹ is followed by continuous infusion of 20–40 µg kg⁻¹ h⁻¹. Increments may be administered to cover painful procedures. Elimination half-life is increased and clearance decreased in neonates, with even greater variations in preterm neonates;108 adult values are usually attained by the age of 3–6 months. Problems include vasodilatation, suppression of gastrointestinal function and urinary retention: inhibition of gastric emptying and intestinal absorption may interfere with enteral nutrition. Administration of bolus doses of morphine to hypovolaemic infants may cause hypotension. The hepatic immaturity of neonates may lead to cumulation of morphine 3-glucuronide which can alter the response to the analgesic and sedative effects of morphine. During extracorporeal membrane oxygenation (ECMO), infants require higher morphine dose rates to maintain a constant level of sedation.118

Fentanyl and its analogues are shorter-acting and are associated with less histamine release and vasodilatation compared with morphine. In children undergoing ventilation, doses of 4–10 µg kg⁻¹ h⁻¹ may be used and fentanyl is often preferred in patients with haemodynamic instability. It can be used to obtund responses to tracheal suction and physiotherapy in neonates and infants with conditions such as congenital diaphragmatic hernia, where pulmonary vascular resistance may be labile.67 Chest wall rigidity may interfere with ventilation.103 especially when using high doses in the absence of an additional sedative drug or...
neuromuscular blocker; however, increased compliance has also been reported after administration of fentanyl to infants. Concerns have been expressed about the possible effects of fentanyl and its analogues in patients with increased intracranial pressure; in practice this does not seem to be a problem. There is wide variability in dose requirement and tolerance has been observed in infants during long-term use. As fentanyl is rapidly redistributed to peripheral compartments, these may become saturated after prolonged infusion causing extended duration of action; in addition, the half-life of fentanyl is increased and clearance decreased in preterm infants and neonates. Withdrawal symptoms have been reported following its use in children undergoing intensive care; in a recent prospective study, 57% of cases developed withdrawal symptoms which were related to total dose and duration of infusion.

Potent inhalation agents. Isoflurane has many desirable characteristics, although it can cause vasodilatation and hypotension. While seizures, hallucinations and disorientation have been reported following prolonged use in critically ill children, other possible causes were implicated in several of these cases. Isoflurane can be used as a short-term supplementary sedative agent to cover painful and distressing procedures in selected patients.

I.v. anaesthetic agents. Thiopental is not used for sedation, although it may be employed for its therapeutic actions, for example, in the management of status epilepticus and increased intracranial pressure. Ketamine is used infrequently but has properties which are beneficial in some cases. It provides amnesia and analgesia, systemic vascular resistance is well maintained and the effects on respiratory mechanics are minimal. The sympathomimetic effects may be useful in the ventilated asthmatic and in children who have cardiac lesions where systemic vascular resistance must be maintained to avoid shunt reversal. It may also reduce the need for inotrope support in septic patients, an effect which may be related to inhibition of catecholamine uptake. Disadvantages include hallucinations, emergence phenomena and effects on intracranial pressure and cerebral activity. In children, ketamine is particularly useful in the management of painful and distressing procedures such as changing burns dressings. Emergence phenomena are less frequent than in adults and can be obtunded by benzodiazepines.

Propofol has pharmacokinetic and clinical properties which would appear to make it particularly suitable for use in patients undergoing controlled ventilation in the intensive care unit. Initial descriptions of its successful use in critically ill children were followed by reports of serious complications, including CNS irritability. Subsequently, a study from the UK described five children undergoing IPPV who died unexpectedly from myocardial failure after long-term infusion of propofol used as the sole sedative agent in high doses which often exceeded 10 mg kg⁻¹ h⁻¹; metabolic acidosis, lipaemic serum, hepatomegaly, intractable hypotension and multi-organ failure occurred in all cases. Although the contribution of factors such as severe sepsis could not be excluded, a safety warning was issued and the use of propofol was abandoned in most British PICUs. A recent survey has identified another 12 fatalities in critically ill children who had received propofol; in all cases mean infusion rates were greater than 4 mg kg⁻¹ h⁻¹ and duration of administration exceeded 48 h.

The use of propofol in critically ill children is reported to be more widespread in the USA than in the UK. However, there are few studies describing its use in low doses as a supplementary agent for sedating critically ill children. In a recent retrospective comparative study, propofol (mean dose 3.39 mg kg⁻¹ h⁻¹) was administered to 106 children. Although metabolic acidosis occurred in several patients, the incidence was similar in the control group and mortality was similar in both groups. In another study, metabolic, biochemical and haemodynamic effects were monitored in infants undergoing ventilation receiving propofol (up to 4 mg kg⁻¹ h⁻¹) together with fentanyl, administered over a period of 48 h after cardiac surgery: no patient demonstrated metabolic acidosis or hepatic dysfunction and there were no significant alterations in serum creatinine, glucose or triglyceride concentrations during infusion of propofol. Nevertheless, until more information is available, considerable caution is advised before using propofol in younger children undergoing intensive care. It is best avoided in the presence of sepsis, primary respiratory infection or an underlying metabolic problem. It should not be used as the sole sedative agent, the infusion rate should be limited to less than 4 mg kg⁻¹ h⁻¹ and duration of administration should not exceed 48 h; close monitoring should be undertaken, including regular measurements of metabolic status, liver function and acid–base balance.

Other commonly used sedative agents include pheno-thiazine derivatives and chloral hydrate. These can be administered enterally, providing useful background sedation in small children and infants. Analgesic requirements can also be influenced by appropriate use of local anaesthetics when inserting drains, cannulae and sutures. Reference has already been made to problems of withdrawal which may occur after opioids or benzodiazepines. Clinical manifestations include restlessness, tachycardia, tachypnoea, vomiting and seizures. Weaning from prolonged sedation should be performed slowly and may, if necessary, be covered by the use of agents such as lorazepam and the α2 agonist, clonidine. Clonidine can also be used as a sedative in patients undergoing ventilation in whom it may allow the use of lower doses of benzodiazepines or opioids.

The development of more sophisticated ventilators has led to a reduction in the use of neuromuscular blocking agents in critically ill adults for whom there are established practice directives. Disadvantages of neuromuscular blocking agents include risks associated with unrecognized ventilator disconnection, suppression of cough reflex, sputum retention, hypostatic oedema and muscle atrophy.
Recent work has demonstrated impaired diaphragmatic endurance and strength in baboons after prolonged mechanical ventilation with neuromuscular blocking agents. Prolonged weakness after long-term use of neuromuscular blocking agents such as pancuronium and vecuronium has been described in both adults and children, although neuromuscular dysfunction may also be associated with sepsis, multiple organ failure, administration of steroids and prolonged intensive care. Nevertheless, synchronization with the ventilator may be particularly difficult to achieve in children with non-compliant lungs without resort to inappropriately large doses of sedative and analgesic drugs. The ability to reduce oxygen consumption, carbon dioxide production and swings in intrathoracic pressure is particularly important when managing an infant with severe respiratory disease and marginal oxygenation who is fighting the ventilator and is likely to develop air leaks and secondary lung injury. In some units, neuromuscular blocking agents are also used in children with increased intracranial pressure and in circumstances where certain specialized therapies and procedures may be jeopardized by patient movement.

Patients who receive neuromuscular blocking agents require constant evaluation; monitoring of neuromuscular function should be performed and attempts made to restart some spontaneous respiratory effort at the earliest appropriate opportunity. A recent study of children undergoing ventilation with acute respiratory disease demonstrated significant improvements in oxygenation on discontinuing neuromuscular block, similar findings have been reported in a study of preterm infants with hyaline membrane disease.

Severe sepsis—meningococcal disease

The clinical manifestations of severe sepsis result from persistent inflammation which causes widespread endothelial damage and is described as the systemic inflammatory response syndrome (SIRS). In adults it may develop after infection, trauma, burns, pancreatitis and haemorrhagic shock. Criteria for defining sepsis have been adapted for paediatric use to allow the manifestations of infection to be graded (Fig. 1). Mortality rates of 10–30% have been reported for children with severe sepsis, blood lactate concentrations providing an early predictor of outcome. Several groups are particularly susceptible: neonates; children with myeloproliferative disorders and congenital or acquired immunodeficiency; children with congenital cardiac or renal tract anomalies.

An important cause of severe sepsis in children is Neisseria meningitidis, a gram-negative diplococcus which commonly resides in the nasopharynx. The outer membrane is surrounded by a highly antigenic capsule whose composition forms the basis for subdivisions into groups A, B and C; further subtypes can be identified using monoclonal antibodies. Although group B is the commonest cause of meningococcal disease in developed countries, recent reports suggest an increase in group C infection. Vaccines are available for groups A and C although infants mount a poor response following immunization.

The three clinical manifestations of meningococcal disease are meningitis, septicemia and meningitis with septicemia. The incidence of septicemia is much lower than that of meningitis but the clinical effects are far more devastating. Mortality from meningococcal disease is approximately 10% but increases to more than 50% in children with severe meningococcal sepsis.

It is not clear why the organism migrates from the nasopharynx into the blood and causes such a profound response, although patients deficient in properdin and abnormalities of the terminal components of the complement pathway are thought to be particularly susceptible. Severe meningococcal septicemia is triggered by the lipid A component of the endotoxin molecule. This initiates an intense inflammatory response, with release of cytokines and other inflammatory mediators, together with activation of the complement, coagulation and kinin cascades. Physiological effects include disturbed regulation of temperature and vascular tone, myocardial dysfunction, coagulopathy, platelet aggregation and bone marrow suppression. Hypovolaemia occurs as a result of increased vascular permeability and capillary leak; this may be caused by loss of negatively charged surface glycosaminoglycans which are normally present on the endothelial surface.
Table 3 Glasgow Meningococcal Septicaemia Prognostic Score (from Sinclair, Skeoch and Hallworth147)

| AP <75 mm Hg systolic, age <4 yr | 3 |
| AP <85 mm Hg systolic, age ≥4 yr | 2 |
| Skin-rectal temperature difference >3°C | 3 |
| Modified coma scale score <8 or deterioration of >3 points in 1 h | 3 |
| Deterioration in hour before scoring | 2 |
| Absence of meningism | 2 |
| Extending purpuric rash or widespread echymoses | 1 |
| Base deficit >8.0 | 1 |
| Maximum score | 15 |

Paediatric intensive care

Table 3 Glasgow Meningococcal Septicaemia Prognostic Score (from Sinclair, Skeoch and Hallworth147)

| AP <75 mm Hg systolic, age <4 yr | 3 |
| AP <85 mm Hg systolic, age ≥4 yr | 2 |
| Skin-rectal temperature difference >3°C | 3 |
| Modified coma scale score <8 or deterioration of >3 points in 1 h | 3 |
| Deterioration in hour before scoring | 2 |
| Absence of meningism | 2 |
| Extending purpuric rash or widespread echymoses | 1 |
| Base deficit >8.0 | 1 |
| Maximum score | 15 |

muscle pain. The characteristic petechial rash may be subtle in the early stages; thereafter, it can progress very rapidly. Tachycardia and diminished capillary refill are manifestations of hypovolaemia: severe cases may initially receive large volumes of i.v. fluid, including colloid, at a time when they may be developing progressive capillary leak and myocardial dysfunction. These children should therefore receive early and aggressive inotropic support. Hypocalcaemia is common and administration of a bolus followed by a continuous infusion of calcium may be beneficial in hypotensive children requiring inotropic support. In these severe cases, intubation and IPPV are mandatory to reduce work of breathing, protect the airway, optimize gas exchange and facilitate placement of lines and use of invasive techniques. In addition, gas exchange can be optimized in patients at risk from developing pulmonary oedema and acute respiratory distress syndrome (ARDS). Early administration of antibiotics is essential: although benzylpenicillin or chloramphenicol have been standard initial therapy, the incidence of resistant strains is increasing. In addition, other organisms, including Haemophilus influenza type B and Streptococcus pneumoniae, can cause a similar clinical picture. Until culture results are available, a third-generation, broad-spectrum cephalosporin should be commenced.

Early identification of patients who require more intensive and aggressive early management is facilitated by the use of prognostic indicators. A poor outcome is associated with onset of a petechial rash less than 12 h before admission, a normal or low leucocyte count and ESR, shock, acidosis and absence of meningism. An obtunded conscious level in the absence of meningism is a harbinger of severe illness. The Glasgow Meningococcal Septicaemia Prognostic Score (GMSPS) is a clinical tool which facilitates rapid assessment of severity (Table 3).147 A retrospective study demonstrated a mortality rate of 74% in cases with scores of 9 or more.156 More recent studies have demonstrated lower mortality rates at this threshold143; this may be a result of improvements in management and greater awareness of the importance of early intensive treatment.

In recent years, several supplementary therapies have been used, although not all have undergone thorough evaluation. I.v. prostacyclin 5–20 ng kg⁻¹ min⁻¹ is a vasodilator which inhibits platelet aggregation and may also improve oxygen delivery and uptake.21 It should be used in conjunction with inotropes and titrated to avoid severe hypotension. Continuous veno-venous haemofiltration can remove circulating cytokines, including TNFα17; whether this influences outcome remains to be demonstrated. A recent study described the early use of haemofiltration in four children with severe meningococcal sepsis (GMPS 9–11)20: all survived with normal cerebral and pulmonary function. Although this therapy remains speculative, especially if renal function is adequate, there are attractions to a procedure which may remove inflammatory mediators and facilitate accurate control of fluid balance in patients who have capillary leak and are receiving significant volumes of fluids, including blood products.

In young children, assessment of cardiac function and response to inotropes is facilitated by serial cardiac ultrasound examination. The use of extracorporeal membrane oxygenation (ECMO) has been described in patients with shock or severe respiratory failure who remain refractory to maximal medical treatment and conventional intensive therapy.59 The hazards of transporting such critically ill patients to a paediatric ECMO centre highlights the need for early identification of those cases who are likely to require this treatment.

Disturbed haemostasis is common and requires replacement of clotting factors. In addition, there may be reduced concentrations of both protein C and tissue plasminogen activator (TPA): the former has antithrombotic effects, the latter is a fibrinolytic activator. Administration of protein C concentrates and TPA have been reported to improve coagulation and circulatory status.137 167 Intra-arterial infusions of TPA may also improve circulation in ischaemic limbs of children with meningococcal disease.12 Anti-cytokine or anti-endotoxin therapy may be expected to modulate development of the more severe manifestations of meningococcal septicaemia. The introduction of a monoclonal antibody (HA-1A) against the lipid A portion of endotoxin stimulated considerable interest. After several equivocal studies, one of which demonstrated increased mortality after its use in adults with sepsis, the agent was withdrawn. As yet there is no evidence of improved outcome from meningococcal sepsis after the use of interleukin-1 receptor antagonist48 or human-TNFα monoclonal antibody.2 A prospective, randomized, controlled study of recombinant bacterial permeability increasing protein (BPI) is currently being undertaken. BPI can bind to endotoxin and has been shown to inhibit biological responses to lipopolysaccharide.

There are conflicting views on the use of corticosteroids. Although early use of corticosteroids may reduce the inflammatory response to sepsis in animals, evidence from multicentre studies and systematic reviews has failed to demonstrate reduced mortality in adults with septic shock.2 However, recent work suggests that they may benefit patients who are pressor-dependent.23 There is also a subgroup of patients with septic shock who, despite normal or high cortisol concentrations, have relative adrenocortical insufficiency with an adrenal response which is not consistent
with the degree of insult; improvements in physiological status and short-term survival may occur after administration of glucocorticoids. In meningococcal septicaemia, steroids may also be required where there is adrenal infarction or haemorrhage and in children requiring high doses of inotropes.

Opinion is divided about the use of steroids in meningococcal meningitis. Dexamethasone reduces the incidence of hearing loss after meningitis caused by *Haemophilus influenzae* and is claimed to reduce mortality after pneumococcal meningitis. The Committee on Infectious Diseases of the American Academy of Pediatrics recommends that steroids be administered to children with meningitis caused by *Haemophilus influenzae* and should be considered in cases caused by pneumococcus and meningococcus. In the UK, dexamethasone is recommended only for meningitis caused by *Haemophilus influenzae*.

**Management of acute respiratory failure**

Approximately 30% of children admitted to a PICU have a primary respiratory disorder and require intubation and ventilation. Significant numbers whose primary diagnosis involves other systems also require periods of intubation and ventilation. Of those with primary respiratory disorders, a proportion develop severe acute respiratory failure. Despite therapeutic and technological advances, this remains a major cause of morbidity and mortality.

In quantifying the severity of respiratory failure, several physiological indices of oxygenation have been used, including alveolar–arterial oxygen tension difference (P\textsubscript{A\textsubscript{O}}\textsubscript{2}–P\textsubscript{a\textsubscript{O}}\textsubscript{2}), arterial/alveolar ratio (P\textsubscript{a\textsubscript{O}}\textsubscript{2}/P\textsubscript{A\textsubscript{O}}\textsubscript{2}) and P\textsubscript{a\textsubscript{O}}\textsubscript{2}/F\textsubscript{O}\textsubscript{2} ratio. Oxygenation index (OI) is used increasingly in neonatal and paediatric intensive care, relating P\textsubscript{a\textsubscript{O}}\textsubscript{2} to both oxygen requirement and mean airway pressure:

\[
\text{Oxygen Index} = \frac{\text{Mean Airway Pressure (cm H}_2\text{O)} \times F\textsubscript{O}_2(\%)}{P\textsubscript{a\textsubscript{O}}\textsubscript{2} (\text{mm Hg})}
\]

Acute respiratory distress syndrome (ARDS) arises as a result of pulmonary injury and inflammation which is caused by a variety of direct or indirect insults. Within the lungs there is damage to the alveolar–capillary membrane, permeability pulmonary oedema and abnormal surfactant function. ARDS may be caused by conditions such as bacterial pneumonia, viral pneumonitis, aspiration pneumonia, septicaemia and near drowning.

The incidence of ARDS in children is not known because of inconsistencies in the use of diagnostic criteria: cases previously described as acute respiratory failure did not necessarily fulfil criteria for ARDS. In many cases, measurements of pulmonary capillary wedge pressure, a major component of earlier definitions, will not have been available. More recently, the diagnosis of ARDS has been facilitated by the use of the lung injury score which dispenses with the need for pulmonary wedge pressure: a score >2.5 indicates ARDS. Diagnosis has been further simplified by excluding values of positive end-expiratory pressure (PEEP). Acute lung injury is therefore present if there are bilateral pulmonary infiltrates on radiography, the ratio of P\textsubscript{a\textsubscript{O}}\textsubscript{2} to P\textsubscript{A\textsubscript{O}}\textsubscript{2} is \(\leq 300\) mmHg, irrespective of the level of PEEP, and there is no clinical or radiographic evidence of increased left atrial pressure. The definition of ARDS is the same with the exception that the ratio of P\textsubscript{a\textsubscript{O}}\textsubscript{2} to P\textsubscript{A\textsubscript{O}}\textsubscript{2} is \(\leq 200\) mmHg.

In a recent report from a large tertiary PICU, patients with ARDS comprised 3% of admissions; mortality was 62%, accounting for 33% of all unit deaths; children with cancer or following bone marrow transplantation had a particularly poor prognosis. Other studies have variously reported mortality rates of 40–75% and analysis of the most recent reports suggests an overall mortality of 52%. ARDS may also occur in neonates, the commonest causes being group B streptococcal septicaemia and perinatal asphyxia.

Significant numbers of preterm neonates who undergo IPPV for infant respiratory distress syndrome (IRDS) develop chronic lung disease (bronchopulmonary dysplasia). Follow-up studies of children surviving ARDS have also demonstrated abnormalities in both lung mechanics and gas exchange. Although lung injury may result from the underlying disease process, artificial ventilation causes additional damage to lung parenchyma; in addition, high concentrations of inspired oxygen can cause pulmonary oxidative damage.

A significant cause of lung injury induced by positive pressure ventilation is the volume change occurring during the respiratory cycle. Attempts to achieve normal blood gases, by using large volumes and high inflation pressures, can cause repetitive over-distension of lung units and damage the alveolar–capillary membrane. Studies in rats have demonstrated a relationship between high peak inspiratory pressures and lung injury, while the use of increasing levels of PEEP appears to exert a protective role by preventing closure of lung units at the end of expiration. Another study demonstrated similar degrees of lung injury in groups using identical ventilatory volumes, irrespective of whether they were generated by positive or negative pressure. Animal models of ventilator-induced lung injury confirm that changes in lung volume occurring during the respiratory cycle are important causes of pulmonary damage and demonstrate that PEEP affords a degree of protection. It has been demonstrated that maintenance of a constant lung volume throughout the respiratory cycle whilst minimizing changes in both alveolar pressure and volume results in significantly less mechanical ventilator-related lung injury. It is thought that one of the mechanisms leading to lung damage is shearing injury associated with cyclical opening and closing of alveolar units. Damage can be reduced by using techniques which facilitate recruitment of lung units and prevention of end-expiratory closure, expansion being maintained by appropriate levels of mean airway pressure. The level of PEEP required for maximum
recruitment is close to the inflection point on the pressure–volume loop; above this point, further increases in pressure may cause over-distension of lung units which have already been recruited.

These studies have led to a re-appraisal of techniques of ventilation with limitation of peak inspiratory pressure (PIP), moderately increased inspiratory times and provision of sufficient PEEP to maintain an adequate end expiratory lung volume. PIP can be reduced in the volume control mode by limiting tidal volume. Alternatively, the pressure control mode may be used, with limitation of PIP, which results in decelerating gas flow and ensures that a preset inspiratory pressure is not exceeded. Prolongation of inspiratory time allows generation of a sustained square wave which permits recruitment of alveoli at lower peak pressures. Interestingly, this concept was first espoused in 1971 by Reynolds who demonstrated improved oxygenation using square wave, pressure-limited ventilation and prolonged I:E ratios in neonates with hyaline membrane disease. However, use of an excessively long inspiratory time can cause gas trapping in terminal lung units leading to hyperinflation, generation of intrinsic PEEP, and reductions in cardiac output and oxygen delivery. Injudicious prolongation of inspiratory time must therefore be avoided.

Less aggressive methods of respiratory therapy aim to achieve acceptable rather than normal blood-gas values. In adults with ARDS, significant reductions in mortality have been reported using low tidal volumes and permissive hypercapnia. PEEP was used to maintain oxygenation, although saturations as low as 90% were accepted. A more recent study of this technique in adults with ARDS demonstrated improved survival at 28 days. While there are no prospective, randomized, controlled studies in children, there are reports of improved survival from observational studies which used permissive hypercapnoea and limitation of peak inspiratory pressure. However, in children neither the maximum permissible $P_{aCO_2}$ nor the minimum acceptable $P_{aO_2}$ have been established. Until further information is available, this technique should be used with caution; oxygen delivery to the tissues should be optimized and regular monitoring of acid–base status performed.

**High-frequency ventilation**

The limitations of conventional mechanical ventilation (CMV) have stimulated interest in techniques which deliver reduced tidal volumes at high respiratory frequencies. There are three distinct types of high-frequency ventilation: high-frequency positive pressure ventilation (HFPPV, 1–3 Hz), high-frequency jet ventilation (HFJV) and high-frequency oscillatory ventilation (HFOV). Tidal volumes generated with HFJV and HFO are smaller than the anatomical deadspace. The ability of high-frequency oscillation to maintain adequate gas exchange was described in 1972, although its role in the management of respiratory failure has only recently been appreciated.

HFJV involves generation of small square wave pulses of gas, delivered from a high pressure source, via a tube into the trachea at frequencies of 2–10 Hz: expiration is passive. The ability to achieve adequate carbon dioxide clearance and oxygenation using low volumes and airway pressures provides ideal conditions for surgery of the larynx and tracheobronchial tree. It is not used widely in the PICU, although some benefit has been observed when used in children with ARDS complicated by barotrauma. Improvements have been described in neonates with pulmonary interstitial emphysema (PIE) after switching from CMV to HFJV. Doubts have been raised about adequacy of humidification following reports of children who developed necrotizing tracheobronchitis.

HFOV has been shown to be an effective means of ventilating experimental animals, both with and without lung disease, and neonates with respiratory failure. Tracheal gas mixes with a bias flow of fresh gas which is oscillated at high frequency (10–40 Hz) by means of a piston or vibrating diaphragm; a sine wave is generated and the expiratory phase is active. The gas transport which occurs along airways at high frequencies may be enhanced by coupling of oscillatory longitudinal flow with secondary motions caused by the effects of airway curvature.

An early multicentre study of HFOV failed to demonstrate beneficial effects in preterm infants with respiratory failure and reported an increased risk of intraventricular haemorrhage. However, more recent studies of infants with IRDS have demonstrated improved gas exchange together with a reduction in the incidence of air leaks and chronic lung disease. HFOV is particularly effective in neonatal IRDS, used early, in conjunction with exogenous surfactant. It also provides a valuable alternative therapy in full-term neonates with acute respiratory failure who fulfil the criteria for ECMO. Unlike the early unsuccessful trials, these studies used an ‘open lung’ strategy whereby values of mean airway pressure were selected to promote alveolar recruitment and maintain optimal lung volume throughout the respiratory cycle. High peak inspiratory pressures (PIP) are avoided, as are the large cyclical changes in airway pressure and lung volume which usually occur during CMV. Initially, mean airway pressure is set slightly higher than the level being used with CMV and is subsequently titrated against oxygenation and chest expansion, the latter being assessed by radiography. Carbon dioxide clearance is related to amplitude of oscillation together with ventilatory frequency, which is set initially at approximately 10 Hz.

A similar volume recruitment strategy has been used in a controlled crossover study of children with ARDS. HFO was associated with a reduced incidence of barotrauma, significant enhancement of gas exchange and improved outcome. A recent pilot study has also demonstrated encouraging results using HFO in adults with ARDS. Reduction of PIP and the possible avoidance of ECMO make HFO an attractive method of respiratory support. Further work is required to define, more precisely, its role in paediatric respiratory failure, its indications and whether...
earlier deployment will lead to improved outcome and reduced duration of ventilation.

**Nitric oxide**

The identification of nitric oxide as endothelium-derived relaxing factor and the appreciation that endogenous nitric oxide caused selective pulmonary vascular dilatation stimulated interest in the use of this agent in patients with pulmonary hypertension and acute lung disease.

Nitric oxide plays a regulatory role in numerous physiological processes, including neurotransmission, vascular tone, immune function and coagulation. In animals, nitric oxide selectively reverses the pulmonary vascular constriction induced by hypoxia or thromboxane. Therapeutically, inhaled nitric oxide is used to simulate the dilator effects of endogenous nitric oxide on pulmonary vascular smooth muscle. In children, indications include persistent pulmonary hypertension of the newborn (PPHN), control of pulmonary hypertensive crises and acute respiratory failure in the neonate.

PPHN is characterized by high pulmonary vascular resistance, low pulmonary blood flow and shunting of blood from right to left through the ductus arteriosus and foramen ovale. Pulmonary vasodilatation normally occurs at birth and is modulated by endogenous nitric oxide production. PPHN may result from failure or reversal of this normal adaptive process; it may be primary or secondary to conditions such as meconium aspiration syndrome, congenital diaphragmatic hernia, hyaline membrane disease, exomphalos and group B streptococcal sepsis. Some cases respond to treatment with high concentrations of oxygen and mechanical ventilation. I.v. vasodilators such as nitroprusside, tolazoline and prostacyclin may help but are not selective and can have systemic effects, causing hypotension and an increase in right to left shunting; extracorporeal membrane oxygenation (ECMO) may be life-saving. However, a dose-dependent improvement in pulmonary blood flow has been demonstrated in fetal lambs receiving inhaled nitric oxide. Administration of nitric oxide to neonates with PPHN reduces pulmonary vascular resistance without causing systemic hypotension; this results in improved oxygenation and a reduced requirement for ECMO. Pulmonary hypertension may also occur in children undergoing cardiac surgery for lesions associated with large left to right shunts or pulmonary venous obstruction; vascular reactivity may be increased after cardiopulmonary bypass and life-threatening pulmonary hypertensive crises may occur during the postoperative period, thus requiring administration of low-dose nitric oxide.

There are several studies describing the use of nitric oxide in ventilated neonates with acute hypoxic respiratory failure. A recent multicentre, randomized study of 235 infants demonstrated significant improvements in oxygenation and a reduced requirement for ECMO. Although there was no effect on overall mortality, nitric oxide may produce dramatic effects in selected neonates with acute respiratory failure while the response in others is disappointing. This may be because of the range of underlying pulmonary pathophysiology, responders having a greater degree of pulmonary hypertension than non-responders.

Nitric oxide has also been used in children with ARDS in order to improve matching between ventilation and perfusion. Although some studies have demonstrated improved oxygenation, these involved small numbers and lacked control groups. However, one prospective study of nitric oxide administered to 17 children with ARDS demonstrated improved oxygenation: all survived despite a mean mortality risk of 54% and no child required ECMO. In addition, a recent randomized, phase II study of nitric oxide in adults with ARDS demonstrated improvements in oxygenation, although there was little discernible effect on outcome. However, caution is required when using mortality statistics as an end-point for these studies as death in patients with ARDS often occurs as a result of the underlying primary condition or some other non-respiratory cause. When administering nitric oxide to children with ARDS, it would seem logical to combine it with a lung recruitment strategy (HFO). Undesirable effects of nitric oxide include nitrogen dioxide toxicity, methaemoglobinemia, negative inotropic actions, platelet dysfunction and rebound pulmonary hypertension on cessation of treatment.

**Surfactant**

IRDS, caused by surfactant deficiency, is responsible for most of the mortality and morbidity seen in preterm neonates. Surfactant forms a monolayer at air–water interfaces throughout the lung, altering alveolar surface tension during respiration. Without surfactant, small airways and respiratory saccules collapse, while larger ones become distended resulting in a combination of atelectasis and hyperinflation. The pre-term neonate is at risk from developing chronic neonatal lung disease (bronchopulmonary dysplasia) if surfactant deficient lungs are exposed to positive pressure ventilation.

Surfactant is a mixture of phospholipids and surfactant-specific proteins. Dipalmitoyl phosphatidylcholine (DDPC) is responsible for the effects on surface tension, although surfactant has several other actions: it is thought to have anti-inflammatory properties, facilitate mucus clearance and protect against infection. Surfactant replacement preparations are synthetic or naturally occurring, the former comprising predominantly DDPC. Natural preparations contain surfactant proteins and are animal extracts, although no immunological problems have been reported following administration to humans.

Surfactant replacement therapy is well established in the prevention and treatment of IRDS in preterm neonates and has been associated with a highly significant reduction in both mortality and pulmonary air leak. Its effect on the incidence of chronic lung disease has been less dramatic; similarly, the incidence of intraventricular haemorrhage has
not been reduced. In the preterm neonate, surfactant may be administered prophylactically, shortly after birth, through a tracheal tube. Rescue treatment involves administration of surfactant to intubated babies with established IRDS. Term neonates with meconium aspiration, sepsis and pulmonary hypertension also have abnormalities of the surfactant system leading to reductions in pulmonary compliance.

The role of surfactant therapy outside the neonatal period remains unclear. There is evidence that surfactant can influence small airway patency in normal lungs: cells lining the bronchioles secrete surfactant proteins A and B which may prevent small airway closure as luminal diameter decreases. Analysis of bronchoalveolar aspirates from infants with acute bronchiolitis has demonstrated abnormal surfactant composition and function. Surfactant activity and production can also be inhibited in children with inflammatory lung disease. Surfactant therapy might be of benefit in older infants with conditions such as pneumonia and bronchiolitis and there have been reports describing improved respiratory function after its administration to children with acute respiratory failure. However, there have been no randomized, controlled trials, apart from one study in adults with ARDS in which there were no detectable benefits associated with administration of surfactant.

Liquid ventilation

In recent years, there has been considerable interest in the use of liquid perfluorocarbons for severe respiratory failure. Theoretical advantages to ventilating the lungs with liquid include removal of the air–liquid interface within the alveolus leading to reduction in surface tension and increased compliance. Lung volume may be enhanced by expansion and recruitment of atelectatic alveoli; continuous alveolar lavage may help to clear inflammatory mediators.

Perfluorocarbons (PFC) are dense biologically inert liquids with surface tensions which are significantly lower than water. Carbon dioxide is four times more soluble and oxygen 20 times more soluble in PFC than in water. Instillation of PFC into the lungs supplies a medium with good gas solubility which reduces surface tension, allows the use of lower distending pressures and offers some protection against development of lung injury.

Total liquid ventilation involves replacement of all gas in the lungs with PFC and requires a ventilator with extracorporeal removal of carbon dioxide. Partial liquid ventilation (perfluorocarbon-associated gas exchange (PAGE)) is a more practical technique with instillation of a smaller volume of liquid, equivalent to FRC, and use of a conventional ventilator.

Beneficial effects of liquid ventilation have been observed in animals and in models of acute lung injury. The use of PAGE has been reported in small numbers of neonates. One study demonstrated improved compliance and oxygenation, although survival rates were unaffected. Another study of preterm neonates with severe IRDS resulted in survival rates which were greater than predicted, although there was no control group. Perfluorocarbons have also been studied in older children undergoing ECMO. Improvements in compliance and A–a \(D_O2\) were demonstrated during trial periods of withdrawal from ECMO and institution of conventional ventilation. However, until definitive studies have been performed, liquid ventilation remains an experimental technique and its use must be evaluated in randomized, controlled studies. In addition to anecdotal reports of an increased incidence of pneumothoraces, there are also concerns about possible long-term effects; there is some systemic absorption with trace amounts of perfluorocarbons detectable in the tissues of animals 3 yr after administration.

Extracorporeal membrane oxygenation (ECMO)

ECMO has evolved from cardiopulmonary bypass technology. Blood is drained into the ECMO circuit from a large central venous cannula. In veno-arterial ECMO, blood is returned usually via the right common carotid artery: in veno-venous ECMO, it is returned to the vein through a double-lumen cannula.

Although an early multicentre study in adults demonstrated no effect on outcome, results in neonates with severe respiratory failure were more promising: two randomized, prospective studies demonstrated improved outcome when ECMO was compared with conventional mechanical ventilation. However, these studies used an adaptive randomized design and relatively small numbers received conventional treatment. Nevertheless, the study by O’Rourke and colleagues showed an overall survival rate of 97% for the ECMO group compared with 60% for the group which received conventional treatment.

More than 10 000 neonates have now been treated with ECMO, of whom 83% have survived. Predicted mortality rates for these cases would be 80% with conventional treatment, although this value is based on historical controls who would not have had access to the more recently introduced innovative techniques and therapies for managing respiratory failure. However, a recent randomized, multicentre study of neonatal ECMO in the UK fulfilled strict randomization criteria; infants with severe respiratory failure (oxygen index >40) were assigned to receive ECMO or conventional ventilatory management according to study guidelines. The end-point of this study was survival which was significantly better in the ECMO group (60%) compared with the control group (30%).

ECMO has been used in neonates with meconium aspiration syndrome, congenital diaphragmatic hernia, pneumonia, respiratory distress syndrome and persistent pulmonary hypertension of the newborn. Overall survival is 80% but differs according to diagnosis: meconium aspiration 94%; IRDS 84%; primary pulmonary hypertension 82%; sepsis 77%; and diaphragmatic hernia 58%. ECMO is only one of several strategies which have been used in the management of congenital diaphragmatic hernia and recent reports from paediatric units in Boston and
Toronto suggest that neither ECMO nor HFOV improve outcome significantly in the most severe cases.13 166

ECMO has also been used outside the neonatal age group, although survival rates are lower. Specific criteria for initiating ECMO therapy in older infants and children may vary between centres, although it is usually reserved for cases with a potentially reversible condition where maximum conventional therapy has or is likely to fail. Primary diagnoses include severe bacterial, viral or pneumocystis pneumonia, aspiration, near drowning and smoke inhalation. ECMO is a rescue treatment which allows ‘lung rest’ and is particularly helpful in those infants born prematurely who, after IPPV as neonates, have chronic lung disease, then subsequently develop severe pneumonia or RSV infection but fail to respond to conventional ventilatory management. In a report of the use of ECMO in 24 infants with severe RSV bronchiolitis who were refractory to conventional management, there was one fatality.84 In a comparative study of the use of ECMO in 38 infants and children with acute respiratory failure and high mortality risk scores, the observed mortality was significantly lower compared with a similar group who received conventional treatment.61 ECMO has also been used to provide circulatory support after cardiac surgery and in children with severe meningococcal septicaemia.59

ECMO is not without risks and availability may be limited. There has also been a proliferation of alternative innovative techniques for use in children with severe respiratory disease; these have been described above, and some have been shown to be efficacious in significant numbers of cases. For example, there is evidence that inhaled nitric oxide reduces the requirements for ECMO in term infants with persistent pulmonary hypertension and acute respiratory failure.114 130 However, further clinical trials and comparative studies are required to define more precisely the indications for using each of these treatments, including ECMO.

Conclusions

The principles underlying the practice of paediatric intensive care have been established over the past 30 yr. Paediatric intensive care has facilitated the development and introduction of many advanced medical and surgical treatments for infants and children. While the development and introduction of new and innovative treatments must be informed by high quality research, their full potential can only be realized through the availability of well organized and high-quality intensive care services for children which are multi-disciplinary, led by full-time specialists in paediatric intensive care medicine and staffed by appropriately trained critical care nurses. Whichever organizational model is used, it is imperative that any critically ill child should be able to gain speedy access to these specialized services in order to take advantage of the staff, facilities, treatments and expertise which they provide. These objectives are consistent with the principles enshrined in the UN convention on the Rights of the Child.155

References

6 American Academy of Pediatrics Committee on Hospital Care. Guidelines for air and ground transportation of pediatric patients. Pediatrics 1986; 78: 943
15 Barry PW, Ralston C. Adverse events occurring during inter-hospital transfer of the critically ill. Arch Dis Child 1994; 71: 8–11


30 Committee on Hospital Care and Pediatric Section of the Society of Critical Care Medicine. Guidelines and levels of care for pediatric intensive care units. *Pediatrics* 1993; 92: 166–75


33 Dargaville PA, South M, McDougall PN. Surfactant abnormalities in infants with severe viral bronchiolitis. *Arch Dis Child* 1996; 75: 133–6


38 Downes JJ, Raphaely RC. Pediatric intensive care. *Anesthesiology* 1975; 43: 238–50


42 Eckenhoff JE. Some anatomical considerations of the infant larynx influencing endotracheal anesthesia. *Anesthesiology* 1951; 12: 401–16


44 Extracorporeal life support organisation registry. *Ann Arbor, Michigan, 1997


48 Fischer CJ, Dhairait JF, Pribble JP. A study evaluating the efficacy of human recombinant interleukin 1 receptor antagonist (IL-1RA) in the treatment of patients with sepsis syndrome. *Clin Intensive Care* 1993; 4: 85


116 O’Dwyer J. Two cases of group treated by tubage of the glottis. NY Med J 1885; 42: 605


126 Phibbs SC, Bronstein JM, Buxton E, Phibbs RH. The effect of patient volume and level of care at the hospital of birth on neonatal mortality. JAMA 1996; 276: 1054–9


133 Rees JG, Owen Thomas JB. A technique of pulmonary ventilation with a nasotracheal tube. Br J Anaesth 1966; 38: 901


144 Sham F. Paediatric intensive care. Lancet 1993; 342: 1240


146 Shemie S. Steroids for anything that swells: dexamethasone and myocardial failure after propofol infusion in children: five case reports. BMJ 1992; 305: 613–16

147 Shemie S. Steroids for anything that swells: dexamethasone and myocardial failure after propofol infusion in children: five case reports. BMJ 1992; 305: 613–16


150 Sperry RJ, Bailey PL, Reichman MV, Peterson JC, Peterson PB, Pace NC. Fentanyl and sufentanil increase intracranial pressure in head trauma patients. *Anesthesiology* 1992; 77: 418–20


152 Stiller CA, Draper GJ. Treatment centre size, entry to trials and survival in acute lymphoblastic leukaemia. *Arch Dis Child* 1989; 64: 657–61


