Sepsis is broadly understood to be the systemic response to infection. It can be said to exist when an infectious process has triggered the systemic inflammatory response syndrome (SIRS). The term 'SIRS' was coined in 1992 by the American College of Chest Physicians and Society of Critical Care Medicine to describe the non-specific inflammatory process occurring in adults after trauma, infection, burns, pancreatitis and other diseases.

Severe sepsis is a major problem in children. It has been estimated that there are more than 42,000 cases per year in the US in children 19 years old or less, causing 4,400 deaths (Table 1). The incidence varies among children by age, with neonates experiencing the highest incidence at 3.6 per 1,000 population (23% of all children with severe sepsis are low-birth-weight neonates). Severe sepsis has been found to be 15% more common in boys, and this is accounted for by an increased incidence in boys under 4 years old. Today, there is an overall hospital mortality of 10.3%, accounting for 4,383 deaths annually in the USA. Outcomes in children with severe sepsis have improved from 97% mortality in the 1960s and 60% in the 1980s. In the USA, survival was three times better in children than in adults in 1999 (9% vs 27% mortality). An underlying disease was present in 49% of children—commonly respiratory or cardiovascular disease in infants, neuromuscular disease in children between 1 and 9 years old and neoplastic disorders in older children. Severe sepsis represents a significant financial burden on health care systems, with a mean length of stay of 31 days and a mean admission cost of $40,600, giving an annual total cost of $1.97 billion in the USA.

Traditional theory has been that sepsis represents an uncontrolled inflammatory response fuelling vascular endothelial injury and the so-called sepsis cascade. Advances in our understanding of sepsis pathophysiology and cell signalling pathways have questioned this thinking, and the current understanding is that sepsis is the result of a loss of homeostasis between inflammation, coagulation and fibrinolysis.

### Pathophysiology of sepsis

The pathophysiology of sepsis varies according to age. The commonest cause of death in children is cardiac failure, but in adults it is vasomotor paralysis. In adults with sepsis, myocardial dysfunction usually results in a decreased ejection fraction, but cardiac output is usually maintained as a result of tachycardia and ventricular dilation. Where this adaptive process fails to maintain cardiac output, the prognosis is poor. In contrast, paediatric septic shock is frequently associated with profound hypovolaemia, and aggressive volume resuscitation is often helpful, although children who have been fluid-resuscitated show more varied haemodynamic responses than adults. Reduced cardiac output, rather than systemic vascular resistance, is associated with mortality in paediatric septic shock, and achieving a cardiac index (CI) of 3.3–6.0 litre min⁻¹ m⁻² may result in improved survival. In children, oxygen...

### Table 1: Annual incidence, case fatality and national estimate of deaths associated with severe sepsis in the US by age

<table>
<thead>
<tr>
<th>Age</th>
<th>Incidence (per 1000 population)</th>
<th>National estimate of cases</th>
<th>Case fatality (%)</th>
<th>National estimate of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1yr</td>
<td>5.16</td>
<td>20,145</td>
<td>10.6</td>
<td>2,135</td>
</tr>
<tr>
<td>0-28 days</td>
<td>3.60</td>
<td>14,049</td>
<td>10.3</td>
<td>1,361</td>
</tr>
<tr>
<td>29-364 days</td>
<td>1.56</td>
<td>6,096</td>
<td>13.5</td>
<td>774</td>
</tr>
<tr>
<td>1-4 yr</td>
<td>0.49</td>
<td>7,583</td>
<td>10.4</td>
<td>786</td>
</tr>
<tr>
<td>5-9 yr</td>
<td>0.22</td>
<td>4,168</td>
<td>9.9</td>
<td>413</td>
</tr>
<tr>
<td>10-14 yr</td>
<td>0.20</td>
<td>3,836</td>
<td>9.6</td>
<td>368</td>
</tr>
<tr>
<td>15-19 yr</td>
<td>0.37</td>
<td>6,633</td>
<td>9.7</td>
<td>644</td>
</tr>
<tr>
<td>All children</td>
<td>0.56</td>
<td>42,364</td>
<td>10.3</td>
<td>4,383</td>
</tr>
</tbody>
</table>
delivery, rather than oxygen extraction, is the major determinant of oxygen consumption, and achieving an oxygen consumption goal of >200 ml min⁻¹ m⁻² may also be associated with improved outcome.

In the neonatal population, septic shock may be complicated by the transition from fetal circulation to the normal neonatal circulation. Acidosis and hypoxia, which may occur in sepsis, can increase pulmonary artery pressure and maintain patency of the ductus arteriosus. This may result in persistent pulmonary hypertension of the neonate, increased right ventricle work and right ventricular failure.

**Principles of management**

Septic shock may be recognized before hypotension occurs by the presence of pyrexia or hypothermia, altered mental status and either peripheral vasodilation (warm shock) or cool extremities (cold shock). Therapies should be directed to restoring normal peripheral perfusion and mental status (Fig. 1).

Aggressive early resuscitation and early goal-directed therapy should be used in the management of septic shock. This approach involves adjustments of cardiac preload, contractility and afterload to balance oxygen delivery with oxygen demand. The use of markers of global metabolic well-being, including lactate concentration, base deficit, pH and central venous oxygen saturation, is recommended.

Carcillo and colleagues evaluated the association of the volume of fluid administered at 1 and 6 h after presentation with survival and the occurrence of the acute respiratory distress syndrome, cardiogenic pulmonary oedema and persistent hypovolaemia during the resuscitation of children with septic shock. Rapid fluid resuscitation in excess of 40 ml kg⁻¹ in the first hour after emergency-department presentation was associated with improved survival, decreased occurrence of persistent hypovolaemia and no increase in the risk of pulmonary oedema or acute respiratory distress syndrome.

In 1998, it was reported that the outcome of children with septic shock was better with aggressive volume resuscitation (60 ml kg⁻¹ fluid in the first hour) and goal-directed therapy (CI goal of 3.3–6.0 litres min⁻¹ m⁻² and normal pulmonary capillary occlusion). Ceneviva and colleagues described 50 children with fluid-resistant (≥60 ml kg⁻¹ in the first hour) dopamine-resistant shock. The majority of children (58%) were in a low cardiac output state with high systemic vascular resistance. Only 22% had a low cardiac output state with low vascular resistance. Haemodynamic conditions changed frequently during the first 48 h. Persistent shock occurred in a third of patients. Cardiac function decreased significantly with time, requiring the additional use of inotropes and vasodilators. However, variation between patients was so marked that several children with persistent shock showed a complete change from a low cardiac output state to a high output state with low systemic vascular resistance. Inotropes, vasopressors and vasodilators were adjusted to maintain normal CI and systemic vascular resistance. Mortality in this study was 18%, significantly lower than the 58% in a previous study in 1985 when aggressive fluid resuscitation was not used.

A recent study by Rivers and colleagues has shown that early aggressive therapy which optimizes cardiac preload, afterload and
contractility in adult patients with severe sepsis and septic shock improves survival. The investigators used infusions of colloid or crystalloid vasoactive agents and blood transfusions to increase oxygen delivery, which was assessed using mixed venous oxygen saturation, lactate concentration, base deficit and pH. Patients receiving early goal-directed therapy received more fluid, inotropic support and blood transfusions during the first 6 h than control patients receiving standard resuscitation therapy. Between 7 and 72 h, patients receiving early goal-directed treatment had a higher mean central venous oxygen concentration, a lower mean lactate concentration, a lower mean base deficit and a higher mean pH. Mortality was 30.5% in the treatment group and 46.5% in the control group ($P = 0.009$).

**Fluid resuscitation**

Fluid resuscitation with crystalloids and colloids is of fundamental importance to survival of septic shock. There is ongoing debate regarding the relative merits of colloids and crystalloids. Two Cochrane group meta-analyses of randomized trials that compared crystalloids with colloids or crystalloids with albumin concluded that the use of both colloids was associated with increased mortality in critically ill patients. There are major methodological concerns with these meta-analyses, and the fact remains that early aggressive fluid resuscitation with 5% albumin and prompt transfer to a paediatric intensive-care unit (ICU) for patients with meningococcal sepsis in the UK has reduced mortality from 50% in severely ill children to less than 5%.

Fluid resuscitation is best initiated with boluses of 20 ml kg$^{-1}$ titrated to clinical parameters, including heart rate, capillary refill, blood pressure, urine output and level of consciousness. Large fluid deficits typically exist, and initial volume resuscitation usually requires 40–60 ml kg$^{-1}$ but can be as much as 200 ml kg$^{-1}$, particularly in meningococcal sepsis. Invasive haemodynamic monitoring should be considered in patients who do not respond rapidly to initial fluid boluses. Filling pressures should be increased to optimize preload and attain maximal cardiac output. Oxygen delivery depends significantly on haemoglobin concentration, and haemoglobin should be maintained at a minimum of 10 g dl$^{-1}$. Broad-spectrum antibiotics should be continued using a ‘third generation’ cephalosporin such as cefotaxime until more specific microbiological information is available.

Bedside estimation of cardiac output is possible on the paediatric ICU using a variety of methods, although all have their limitations. The use of pulmonary artery catheters should be restricted to centres and physicians who use them frequently; sporadic use is not recommended.

**Vasopactive drugs**

In the recently published clinical practice parameters for haemodynamic support of paediatric and neonatal patients in septic shock produced by a Task Force from the American College of Critical Care Medicine, dopamine or dobutamine are recommended as the first line of inotropic support.

Dopamine has an agonistic effect on a variety of different receptors, depending on the dose used. At doses less than 5 µg kg$^{-1}$ min$^{-1}$, it acts predominantly on dopamine receptors (mainly the vascular D$_1$ receptor); at doses between 5 and 10 µg kg$^{-1}$ min$^{-1}$, its β-adrenergic agonist effects are dominant; and at doses more than 10 µg kg$^{-1}$ min$^{-1}$, its α$_2$-adrenergic agonist action predominates. Dopamine increases CI, primarily because of an increase in stroke volume but also partly because of an increase in heart rate.

Patients less than 12 months old may be resistant to dopamine. This age-specific insensitivity to dopamine is believed to be the result of immaturity of sympathetic vesicles. Dopamine-resistant shock commonly responds to norepinephrine or high-dose epinephrine. Norepinephrine is a potent α$_1$-adrenergic agonist with a weaker, but still significant, β-adrenergic agonist effect. It increases blood pressure mainly by increasing systemic vascular resistance as a consequence of its vasoconstrictive effects. It increases the blood pressure with little change in the heart rate. Vasopressin has been successfully used in patients who are refractory to norepinephrine.

As long as blood pressure can be maintained, vasodilators can have a role in the management of paediatric patients who remain in a low cardiac output state with a high systemic vascular resistance, despite fluid resuscitation and implementation of inotropic support. Sodium nitroprusside should be used as first-line therapy, because stopping the infusion can immediately reverse any hypotension. If children are resistant to nitroprusside, the use of milrinone or enoximone should be considered. These drugs are type III phosphodiesterase inhibitors which prevent hydrolysis of cyclic adenosine monophosphate and therefore potentiate the effect of β-receptor stimulation in cardiac and vascular tissue. Significant hypotension may occur with the administration of bolus doses of these drugs and, in the setting of sepsis, they should only be used as continuous infusions. Because of the long half-life elimination, they should be discontinued at the first sign of hypotension, diminished systemic vascular resistance, or tachyarrhythmias.

**Mechanical ventilation**

Acute lung injury is common in patients with sepsis, and the traditional approach to mechanical ventilation in these patients is to use tidal volumes of between 10 and 15 ml kg$^{-1}$ body weight (almost twice the average tidal volume at rest) and to maintain a low positive end-expiratory pressure (PEEP). The aim of this approach is to achieve normal values for the pH and partial pressure of arterial carbon dioxide. However, this strategy leads to high inspiratory airway pressures and to damaging stretch of the aerated lung. The Acute Respiratory Distress Syndrome Network in the USA carried out a large, prospective, multicentre, randomized trial into the use of low-tidal-volume ventilation in acute lung injury or acute respiratory distress syndrome. The trial was stopped during an interim analysis when the use of lower tidal volumes was found to be associated with a significantly reduced mortality ($P = 0.005$). When mechanical ventilation is indicated.
for treatment of patients with severe sepsis, the tidal volume should be limited to 6–7 ml kg \(^{-1}\) ideal body weight, with a PEEP of at least 8–9 cm H\(_2\)O, using a strategy of permissive hypercapnoea.

### Adjunctive treatments

#### Protein C

Recombinant human activated protein C (an anticoagulant) is the first anti-inflammatory agent that has been shown to be effective in the treatment of sepsis. Endogenous activated protein C interrupts the amplification cycle of coagulation and inflammation that is the hallmark of sepsis. It has direct anti-inflammatory properties, decreasing levels of tumour necrosis factor-\(\alpha\) and interleukin-1\(\beta\) production and it inhibits thrombin formation.

PROWESS (recombinant human activated protein C worldwide evaluation in severe sepsis) was a large, randomized, double-blind, placebo-controlled, international Phase III study evaluating the safety and efficacy of recombinant human activated protein C (drotrecogin alfa activated) for severe sepsis. The study was stopped during an interim analysis that showed a significant benefit in those given the drug. A 4-day infusion of drotrecogin was associated with a 19.4% reduction in the relative risk of death and an absolute risk reduction of 6.1%. Subsequently, it was approved by the Food and Drug Administration (FDA) in November 2001 for use in adults with severe sepsis who have a high risk of death. A further trial mandated by the FDA will evaluate the safety and efficacy of drotrecogin alfa in around 500 children with severe sepsis.

A major risk associated with the use of activated protein C is haemorrhage, with 2.5% of a series of patients suffering intracranial haemorrhage. Drotrecogin alfa is therefore contraindicated in clinical situations where bleeding could be associated with a high risk of death or significant morbidity.

#### Insulin

There is evidence that intensive insulin therapy to maintain blood glucose concentrations between 4.4 and 6.1 mmol litre \(^{-1}\) can improve the outcome of septic adult patients. The mechanism for this effect is not clear but may be related to the prevention of apoptotic cell death. More stringent control of glucose concentrations is now common practice in critically ill adults, but there are no equivalent studies in children, where the consequences of inadvertent hypoglycaemia are different and where hypoglycaemia is a common cause of myocardial depression.

#### Steroids

Whilst the administration of high doses of steroids does not improve the outcome of patients with sepsis and may worsen mortality by increasing the frequency of secondary infection, there is evidence to suggest that the most severely ill adult patients with septic shock benefit from small ‘physiological’ doses of corticosteroids. Benefits have included reversal of shock and trends toward decreased organ system dysfunction and decreased mortality. There remains controversy in this area and little high-grade evidence to support the routine use of corticosteroids.

### Intravenous immunoglobulin

Several studies have addressed the issue of intravenous immunoglobulin as an adjunctive treatment for bacterial sepsis and septic shock. A recent meta-analysis has demonstrated a significant reduction in mortality among adult patients with sepsis and septic shock treated with polyclonal intravenous immunoglobulin. However, all of the relevant trials were small, and the weight of evidence is insufficient to support their routine use at present.

### Blood purification techniques

Extracorporeal therapies designed to remove substances from the circulation include haemodialysis, haemofiltration, haemoadsorption, plasma filtration, cell-based therapies and combinations of these. In recent years, there have been considerable advances in technical capabilities, but there remains a lack of randomized trials. The available studies show an absence of benefit for haemofiltration. Studies of plasma filtration in sepsis in children are ongoing.

### Potential therapies

Many agents have shown beneficial effects in laboratory studies of sepsis and offer potential avenues for new therapies. These include interleukin-12 and antibodies against the complement activation product C5a and macrophage migration inhibitory factor. Agents designed to interrupt the apoptotic death of lymphocytes and epithelial cells are a major area for future development.

### Key references


See multiple choice questions 11–15.