Update in
Anaesthesia

Management of paediatric sepsis

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Summary

Sepsis and septic shock have recently been redefined. Sepsis results when the host response becomes dysregulated.

The term 'severe sepsis' is no longer in use.

Septic shock is sepsis with a high mortality.

In contrast to adults, two thirds of children present in 'cold shock'.

Give antibiotics within 1 hour of diagnosis.

Traditional fluid resuscitation in septic children has recently been challenged by the FEAST trial.

INTRODUCTION

The aim of this article is to provide the reader with an overview of the current guidelines and evidence for the management of sepsis in children. Sepsis is a major cause of morbidity and mortality in children and, although mortality rates are lower in children than in adults, they are estimated at about 10% in severe sepsis.[1] In 2003, the World Federation of Paediatric Intensive and Critical Care Societies (WFPICCS) launched an international paediatric sepsis initiative to reduce mortality and morbidity from sepsis in children[2] by promoting early diagnosis and guiding effective treatment. The provision of dedicated neonatal and paediatric intensive care units, outreach teams and retrieval teams and the dissemination of guidelines to aid early recognition and treatment has contributed to falling mortality rates in paediatric sepsis.[3]

DEFINITIONS

Adult systemic inflammatory response syndrome (SIRS) criteria are modified to produce paediatric specific definitions.[4] However, sepsis and septic shock have recently been redefined and the term 'severe sepsis' is no longer in use (Table 1).[5] The former definition of sepsis was sensitive but very non-specific. The new definition takes into account that SIRS is an appropriate response to an insult, whereas in sepsis the inflammatory response is *dysregulated* and causes life-threatening organ dysfunction.

PRESENTATION

Adult and paediatric shock can be quite different. Adults tend to present with tachycardia, hypotension, low systemic vascular resistance (SVR) and a reduced ejection fraction, but with a relatively maintained cardiac output.[6] In children, the sympathetic nervous system responds to sepsis by increasing heart rate and SVR to maintain mean arterial pressure (MAP). Loss of this compensatory mechanism leads to hypotension, usually a late sign. Two-thirds of children present in 'cold' shock (normal/low cardiac output and high SVR); adults and the remaining one-third of children present in 'warm' shock (normal/high cardiac output and low SVR) (Table 2).[7] Mortality in children with sepsis is associated with severe hypovolaemia and a low cardiac output. It has been stated that for every extra hour a child remains in shock their mortality rate doubles.[8]

Tissue oxygen delivery is the major limitation to oxygen consumption in children with sepsis and treatment should be targeted to improve this. The use of cardiac output measurements or surrogate measures, such as superior vena cava oxygen saturation ($ScvO_2$) and lactate may act as guides to optimise treatment and improve oxygen delivery.[9]

TREATMENT

Consensus guidelines exist for the management of infants and children with septic shock.[10] There is some evidence that adherence to these recommendations has improved survival.[8,11] The treatment algorithm produced by the American College of Critical Care Medicine (ACCM) is available free at the following address: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4447433/.[10]

Management can be broadly divided into two main phases:

1. **ABCs**. During the first hour of resuscitation, fluid and inotropic drug therapy is directed towards maintaining goals of age-appropriate heart rate and blood pressure, and a normal CRT ≤ 2 seconds (Table 3). Oxygenation and ventilation should be supported as appropriate.
2. **Stabilisation**. Beyond the first hour, management should move to an intensive care setting for further haemodynamic support and

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Table 1. *New definitions of sepsis*

SIRS – the definition is unchanged	A response to a stimulus, which results in two or more of the following:[4] • Temperature > 38.5°C or < 36°C • Heart rate more than two standard deviations above normal, or bradycardia in children < 1 year old (< 10th centile for age) • Respiratory rate more than two standard deviations above normal (or $PaCO_2$ <32 mmHg) • Leucocyte count >12 000 cells mm^{-3}, <4 000 cells mm^{-3}, or > 10% band forms • Hyperglycaemia, altered mental status, hyperlactaemia, increased capillary refill time (CRT).
Sepsis is now the old 'severe sepsis'	Life-threatening organ dysfunction caused by a dysregulated host response to infection
Septic shock is defined by its increased mortality compared with sepsis	A subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone
Clinical criteria for septic shock	Hypotension requiring use of vasopressors to maintain mean arterial pressure ≥ 65 mmHg and Persistent serum lactate > 2 mmol L^{-1} despite adequate fluid resuscitation

goal-directed therapy. Treatment targets include normal perfusion pressure for age, $ScvO_2$ > 70% and cardiac index (CI) 3.3–6 L min^{-1}.

SPECIFIC RECOMMENDATIONS

Antibiotics

Antibiotics need to be administered within 1 hour of identification of severe sepsis, after appropriate cultures have been taken. Early antibiotic therapy and identification of the possible source of infection is critical. Broad-spectrum antibiotics should be commenced first; appropriate to the likely source of infection, the age of the child, and knowledge of local disease prevalence and drug-resistant organisms. Antibiotic cover can then be rationalised as the clinical picture, culture results and local microbiology team advice dictates. Therapeutic drug monitoring should be used to ensure adequate target levels and avoid drug toxicity. Courses of antibiotics must be completed and intravenous conversion to oral drugs taken at appropriate stages. Source control strategies are important and include drainage or debridement of infected tissues and removal of infected devices or foreign bodies.

Table 2. *Types of shock*

Type of shock	Clinical signs
Cold shock	CRT > 3 seconds, reduced peripheral pulses, cool mottled peripheries, narrow pulse pressure, commonly seen with community-acquired sepsis
Warm shock	Instantaneous capillary refill, bounding pulses, warm to edges, wide pulse pressure, more likely to be associated with central venous catheter infections.

Neonatal sepsis

A distinction can be drawn between early (age < 72 hours) and late (age > 72 hours) phases of neonatal sepsis.[13]

In early-onset neonatal sepsis causative agents are organisms commonly present in the maternal genital tract (e.g. group B *Streptococcus*, *Escherichia coli*, *Klebsiella*, *Enterobacter* and *Listeria monocytogenes*).[13] Typical broad-spectrum antibiotic cover is ampicillin and gentamicin (or amikacin), with therapeutic drug monitoring.

Late-onset neonatal sepsis is due to pathogens in the post-natal environment (e.g. transmission from the caregiver, aspiration of feeds and central line contamination). Initial broad-spectrum cover is often similar, ampicillin and either gentamicin or amikacin, but if meningitis is suspected then cefotaxime instead of gentamicin is used.[13] Vancomycin is used for suspected central line sepsis instead of ampicillin.

Paediatric sepsis

Common infecting organisms include *Staphylococcus*, *Streptococcus*, *Pseudomonas* and *Meningococcus.* Antibiotic choice depends on the likely pathogens involved and should vary depending on clinical presentation, e.g. pneumonia, bloodstream infection, intra-abdominal sepsis or meningitis. Antibiotic regimens need to cover both Gram-positive and Gram-negative organisms.

Table 3. *Age-appropriate heart rates and perfusion pressures*[11,12]

Age	Heart rate (bpm)	MAP – CVP (mmHg)
Term newborn	120–180	55
Up to 1 year	120–180	60
Up to 2 years	120–160	65
Up to 7 years	100–140	65
Up to 15 years	90–140	65

Anaesthesia and ventilation

Neonates and infants have a low functional residual capacity and a high work of breathing; early intubation and ventilation must be considered, especially in patients who show little response to aggressive fluid resuscitation and peripheral inotropes.

Induction drugs need to be carefully selected and administered to guard against excessive cardiovascular depression. Avoid large doses of thiopentone, propofol, midazolam and high inspired concentrations of volatile anaesthetic agents. Etomidate is associated with increased severity of illness in septic shock[14] and is generally not recommended. Ketamine (1–2 mg kg^{-1}) is a good alternative. Consider the need for a rapid sequence induction with cricoid pressure, and a nasogastric tube. Preoxygenation with 100% oxygen is desirable, but often practically difficult. There is potential for deterioration in cardiovascular parameters at this time and appropriate fluid boluses and inotropes should be prepared in advance.

Maintain sedation and paralysis post intubation and adopt a lung-protective ventilator strategy, maintaining low lung volumes (6–7 mL kg^{-1} tidal volume) with adequate positive end-expiratory pressure (PEEP) and low mean airway pressure. Evidence for this is derived from adult practice.

High-frequency oscillatory ventilation may be required where conventional ventilation alone proves inadequate.

Fluid resuscitation and intravenous access

Resuscitation should begin with boluses of 10–20 mL kg^{-1} crystalloid or 5% albumin over 5–10 minutes with further aliquots titrated to clinical condition (e.g. heart rate, urine output, CRT and level of consciousness). Aggressive fluid resuscitation is a key stage to improved survival, provided there is also access to inotropic therapy and mechanical ventilation.[15] Large fluid deficits are common and volumes of over 40–60 mL kg^{-1} can often be required (but see below for resuscitation in special circumstances).

The optimal choice of fluid is not known, and a recent systematic review of resuscitation fluid in children was unable to find evidence to support the use of colloid over crystalloid.[16] A large randomised study in adults, the SAFE trial, compared crystalloid and albumin fluid resuscitation, finding a trend towards improved outcomes in septic shock with albumin.[17] The 2007 updated consensus guidelines[9] suggest a preference towards the use of colloid resuscitation and there are two particular studies that support this in children.[18,19]

Malnourished children are a special category of patients who do not tolerate aggressive fluid resuscitation, as they are at greater risk of congestive heart failure from overhydration. Septic shock can be difficult to recognise and treat in these patients. Malnourished children require slow IV rehydration with careful and regular observation (every 5–10 minutes). An infusion of 15 mL kg^{-1} Ringer's lactate–5% glucose should be given over 1 hour; if there are signs of improvement, a repeat bolus can be given slowly, followed by oral or nasogastric rehydration. If the patient does not improve after 1 hour, a blood transfusion should be considered (10 mL kg^{-1} slowly over 3 hours). If the child deteriorates during treatment (increased respiratory rate or heart rate), the infusion should be stopped.[20]

The practice of high-volume fluid resuscitation in sepsis has been challenged by the recent Fluid Expansion As Supportive Therapy (FEAST) study, which investigated fluid resuscitation in a large cohort of children with a diagnosis of sepsis (but without hypotension) in Uganda, Kenya and Tanzania.[21] Resuscitation with a fluid bolus of 20–40 mL kg^{-1} saline or albumin was compared with the local practice of no fluid bolus resuscitation. The results of the study were surprising: mortality at 48 hours was higher in the fluid bolus groups than in the group that did not receive a fluid bolus, and at 4 weeks the risk of death and neurological sequelae was 4% higher. Most deaths were early, 87% occurring in the first 24 hours. The study included many children with malaria (57%), severe anaemia (32%), hypoxia (25%) or coma (15%), and 6% had hypotension. This may represent a population in whom overhydration will not be well tolerated, particularly if mechanical ventilation and inotropic support are not available. The implications of the FEAST study are not completely clear at present, but it is likely that aggressive bolus fluid resuscitation, as traditionally recommended, should not be used in children with severe anaemia or malaria, or other common febrile illness associated with a significant stress response but not hypotension (i.e. associated with antidiuretic hormone release and fluid retention). Particular caution should be used when using aggressive fluid resuscitation in patients in low-income countries given the absence of mechanical ventilation and inotropic support in many centres.[22]

Intravenous access is often difficult to achieve in critically ill children. Early intraosseous access should be considered to avoid repeated or prolonged attempts at venepuncture and enable resuscitation to begin in a timely manner. In children with fluid-refractory shock, CVP and arterial pressure monitoring can guide on-going resuscitation. Ultrasound guidance can be a useful tool to facilitate this.

Inotropic and vasoactive drug therapy

In fluid-refractory shock, persistent hypotension is treated with either inotropes, vasopressors or a suitable combination of both. Regular reassessment of the child with appropriate changes to the choice and rate of cardiovascular drug used is essential.

Dopamine is the first-line agent. If central venous access will delay starting inotropes, then the American College of Critical Care Medicine guidelines recommend the use of peripheral inotropes (not vasoconstrictors) with close monitoring of the IV access site to prevent extravasation injury.[10]

Subsequent inotropic support depends on the clinical presentation of the child: low cardiac output and high SVR (cold shock), high

Table 4. *Recommended infusion rates*

Adrenaline	0.05–2 μg kg^{-1} min^{-1}
Dobutamine	5–20 μg kg^{-1} min^{-1}
Dopamine	5–15 μg kg^{-1} min^{-1}
Noradrenaline	0.05–1 μg kg^{-1} min^{-1}
Glycerine trinitrate	1–5 μg kg^{-1}.min^{-1}
Milrinone	0.3–0.75 μg kg^{-1} min^{-1}
Sodium nitroprusside	1–5 μg kg^{-1} min^{-1}

cardiac output and low SVR (warm shock), or low cardiac output and low SVR. Where dopamine is ineffective, add adrenaline in cases of cold shock and noradrenaline in warm shock (Table 4 gives guide infusion rates). Other agents to consider are vasodilators (e.g. sodium nitroprusside or glyceryl trinitrate) or phosphodiesterase inhibitors (e.g. milrinone) in the case of low cardiac output and high SVR despite adrenaline infusion. Vasopressin is used in adult practice for the treatment of extremely low SVR despite high doses of noradrenaline, but there is currently no clear evidence to support its use in paediatrics.[23]

Therapeutic end points

In the first hour, the aim of resuscitation should be to achieve normalisation of heart rate, a CRT ≤ 2 seconds, normal pulses with no differential between central and peripheral, warm extremities, urine output ≥ 1 mL kg^{-1} h^{-1}, and normal mental status. Progress towards these targets can be used to monitor the progress of resuscitation.

Early goal-directed therapy originated in the management of severe sepsis in adults and has been shown to have the largest mortality reduction of any sepsis study.[24] Timely use of cardiac output monitoring and surrogate markers of organ perfusion is recommended in the management of paediatric sepsis, including lactate, improved base deficit, $ScvO_2$ ≥ 70% or SvO_2 ≥ 65%, CVP 8–12 mmHg or cardiac output monitoring (cardiac output 3.3–6 L min^{-1} m^{-2}).

An indirect measure of oxygen delivery can be made using $ScvO_2$. and a study of children with sepsis compared the use of the ACCM guidelines with and without the goal of $ScvO_2$ > 70%.[8] When this goal-directed approach was used, patients received more crystalloid, blood and inotropic support, resulting in a reduction in 28-day mortality from 39.2% to 11.8% in the $ScvO_2$-monitored group. Normalising lactate clearance may be as effective as the use of $ScvO_2$ as a resuscitation goal in the initial treatment of sepsis.[25]

Cardiac output monitoring in the form of echocardiography, trans-oesophageal Doppler, pulse contour analysis or suprasternal ultrasound cardiac output monitors can be helpful. Blood flow is difficult to determine clinically and blood pressure is a poor substitute, as it is affected by both cardiac output and systemic vascular resistance. There is no good evidence for improved outcome with any of these monitoring tools, only observational data. A large multicentre randomised controlled trial is needed.

Steroids

Evidence for the use of steroids in paediatric sepsis is lacking. A randomised controlled trial in children with septic shock is required and until then steroids should not be used routinely.[26] Current *retrospective* studies of steroids in children with severe sepsis have shown their use to be an independent predictor of increased mortality.[27]

Hydrocortisone therapy is reserved for children with catecholamine resistance and suspected or proven adrenal insufficiency. Children at risk of adrenal insufficiency should be treated with steroids, but the recommended doses of hydrocortisone vary; the dose for stress cover is 1–2 mg kg^{-1} day^{-1} whilst that for shock reversal is 50 mg m^{-2} day^{-1}. Note the different units for these doses. Those at risk of adrenal insufficiency include children taking steroids for chronic disease, those with pituitary or adrenal abnormalities, and cases of catecholamine resistant severe septic shock. Adrenal insufficiency can be identified by random blood cortisol levels < 18 μg dL^{-1} or a cortisol level increase of < 9 μg dL^{-1} after an adrenocorticotrophic hormone (ACTH) stimulation test.

Deep vein thrombosis prophylaxis

In older, post-pubertal, children appropriate measures to consider include unfractionated or low-molecular-weight heparin or mechanical prophylactic devices such as compression stockings. In young children, the majority of thrombotic events are associated with the use of central venous catheters, and there is some evidence that heparin-bonded central venous lines may reduce thrombosis rates.[28] A multicentre randomised controlled trial under way at present is looking at catheter-related infections in children and comparing the effectiveness of heparin-bonded catheters and antibiotic-impregnated catheters for the prevention of hospital-acquired bloodstream infections (CATCH trial[29]). A side-arm of this study will investigate the incidence of thrombosis.

Stress ulcer prophylaxis

Early enteral feeding or, where this is not possible, stress ulcer prophylaxis with H_2 blockers or proton pump inhibitors should be used routinely in patients with severe sepsis. This is aimed at reducing the risk of gastrointestinal bleeds and at the prevention of ventilator-associated pneumonia. H_2 blockers were previously used in nil-by-mouth neonates, but there is now evidence of increased risk of infections, necrotising enterocolitis and fatal outcome.[30]

Glycaemic control

Blood glucose should be kept within the normal range. Hypoglycaemia can cause neurological damage and should be treated promptly with 2 mL kg^{-1} 10% glucose. Neonates will require a 10% glucose infusion (8 mg kg^{-1} min^{-1}) whilst children and adolescents have lower requirements, 5 mg kg^{-1} min^{-1} and 2 mg kg^{-1} min^{-1} respectively. Requirements may be higher in children with metabolic disease or liver failure.

Hyperglycaemia is also a risk factor for increased mortality[31] and should be treated with an insulin infusion and frequent glucose monitoring to avoid inadvertent hypoglycaemia.

Transfusion

Consider targeting transfusion to a haemoglobin goal of greater than 10 g dL^{-1} to achieve an $ScvO_2$ > 70%, so enhancing oxygen delivery.[10]

After the initial resuscitation is complete, we do not know the best haemoglobin level for critically ill children. Common practice is to use conservative blood transfusion thresholds to reduce potential risks and complications. The Transfusion straTegies in Paediatric Intensive Care Units (TRIPICU) study looked at transfusion thresholds in stable, critically ill children.[32] The authors reported that a haemoglobin threshold of 7 g dL^{-1} decreased transfusion requirements without increasing adverse outcomes.

Renal replacement therapy

With large volumes of initial resuscitation fluid being given and often an on-going fluid requirement due to capillary leak, there can be significant tissue oedema and fluid overload. Diuretics, peritoneal dialysis or renal replacement therapy may be required once the child has been stabilised. Early implementation of continuous renal replacement therapy is associated with improved survival compared with late implementation.[33]

Protein C and activated protein C

The use of activated protein C in children is not recommended due to a lack of evidence of benefit and an increase in bleeding complications.[34]

Extracorporeal membrane oxygenation (ECMO)

Extracorporeal membrane oxygenation (ECMO) may be considered in those cases of severe septic shock, which have not responded to all conventional treatment strategies,[35] where it may be associated with improved survival.

Intravenous Immunoglobulin

Intravenous immunoglobulin therapy may be associated with a reduction in mortality and should be considered in severe sepsis.[35]

CONCLUSION

Mortality rates in paediatric sepsis have fallen due to improvements in its management. Early recognition and aggressive treatment in line with protocol-driven algorithms (such as the guidelines produced by the ACCM) form the mainstay of initial management. Subsequent early referral and transfer to intensive care units for on-going care, and the use of early goal directed therapy are essential to improve outcomes. For many therapeutic interventions there is a paucity of good supporting evidence. The guidelines provided by the ACCM provide an expert consensus approach to the management of septic children.

There is some emerging evidence that children in low-income countries represent a patient cohort in whom traditional recommendations of fluid resuscitation may not be applicable.

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