Early care of severe sepsis and multiple organ failure in children

Mark J Peters, Paula Lister

Sepsis is the systemic response to infection, defined in terms of simple clinical and laboratory observations which have been adjusted for age for use in childhood (*Table 1*).

This definition has been a central feature of the many large clinical studies of intervention in sepsis over the last 12 years but has been widely criticized for being too narrow (Bone et al, 1992). Clinicians recognize a wide range of clinical features of sepsis beyond this definition and a much fuller description of infection and the host response has been proposed in terms of predisposition, infection, response and organ dysfunction, along the principles of the tumour, node, metastasis description used to classify cancer (Levy et al, 2003).

Progression of sepsis to cause the dysfunction of one (severe sepsis) or more organs (sepsis-induced multiple organ failure) limits many aspect of high technology medicine and is the principal cause of morbidity and mortality on intensive care units (Angus et al, 2001). Severe sepsis in children is associated with a case-fatality rate of approximately 10% in large epidemiological studies. Community-acquired infection has a better outcome but the precise figure varies widely according to case mix (Watson et al, 2003).

PATHOPHYSIOLOGY

The pathophysiology of sepsis and sepsis-induced multiple organ failure is staggeringly complex. The simple view of severe sepsis as the result of excessive levels of one or a few pro-inflammatory mediators or intracellular signalling processes has failed to produce effective interventions. The clinical picture of any patient with sepsis is now being understood as a dynamic imbalance of pro- and anti-inflammatory responses in individual body compartments as well as a multi-phasic endocrine response (Singer et al, 2004).

Dr Mark J Peters is Consultant in Paediatric Intensive Care and **Dr Paula Lister** is Consultant in Paediatric Intensive Care, Great Ormond Street Hospital, London WC1N 3JH

Correspondence to: Dr MJ Peters

Additional levels of complexity are added by genetic polymorphisms (Fidler et al, 2004), the nature and dose of infecting organism and the presence of pre-existing diseases (Seely and Christou, 2000). Progress has been achieved by identifying individual pathological responses and targeting physiologically meaningful end-points. In short, sepsis is not one disease. Therapy is increasingly tailored to the individual patient at a particular time (Rivers et al, 2001; Annane et al, 2002).

IMMEDIATE ACTION FOR THE CHILD IN SEPTIC SHOCK

The immediate care of a child with suspected septic shock must follow the 'A, B, C' (airway, breathing and circulation) principles and then specific therapy. In septic shock, the majority of cases present with an inadequate circulation as the overriding priority. However, the relatively low functional residual capacity of infants and young children means that respiratory support may be required earlier in the clinical course than might be anticipated from adult data.

Consensus guidelines have been proposed for initial resuscitation with careful attention to the elapsed time (*Figure 1*), based on studies that have suggested improved outcome with this structured approach (Carcillo et al, 1991; Rivers et al, 2001; Han et al, 2003). There are very few randomized trial data in this field – the majority of evidence is grade E (i.e. supported by case series, uncontrolled studies and expert opinion). Some inferences can be made from adult data.

A full discussion of the most appropriate antimicrobial therapy for a child in septic shock is outside the scope of this article. Possible choices for some common scenarios are listed in *Table 2*.

CIRCULATION

Access

If the child is shocked you should not persist with attempting peripheral (or central) venous access for more than 90 seconds. Initial resuscitation via an

TABLE 1.
Sepsis: the systemic response to proven or suspected infection as evidenced by two or more of the following four criteria

Central temperature	>38.0°C or < 36.0°C	
White cell count	$>12 \times 10^9$/litre or $<4 \times 10^9$/litre	
Heart rate	Newborn–3 months	95–145 beats per minute
	3–12 months	110–175 beats per minute
	1–<3 years	105–170 beats per minute
	>3–<7 years,	80–140 beats per minute
	>7–<10 years	70–120 beats per minute
	>10 years	60–100 beats per minute
Respiratory rate	Newborn–3 months	30–40 breaths per minute
	3–12 months	30–40 breaths per minute
	1–<5 years	20–30 breaths per minute
	>5–<12 years	15–20 breaths per minute
	>12 years	12–16 breaths per minute

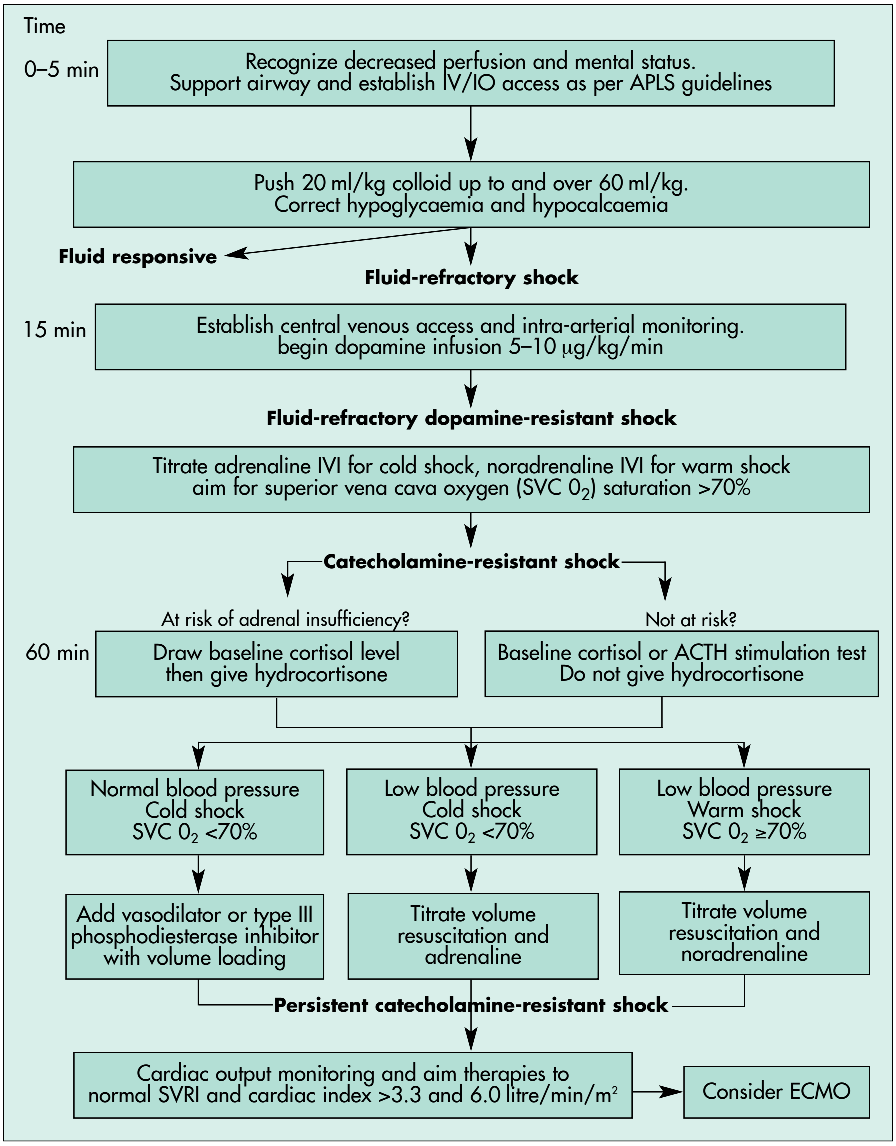

Figure 1. Guideline for initial resuscitation of child presenting with sepsis and shock outside the neonatal period. Adapted from Carcillo and Fields (2002); Dellinger et al (2004). ACTH = adrenocorticotrophic hormone; APLS = Advanced Paediatric Life Support; ECMO = extracorporeal membrane oxygenation; IV/IO = intravenous/intraosseous, IVI, = intravenous infusion; SVRI = systemic vascular resistance index.

TABLE 2.
A regimen for antibacterial choices for children presenting with septic shock beyond the neonatal period

Community-acquired sepsis	Cefotaxime	50 mg/kg/dose 6-hourly
In-hospital acquired sepsis	Pipatazobactam	90 mg/kg/dose 6-hourly >2 months
		90 mg/kg/dose 12-hourly <2 months
	and an aminoglycoside, e.g. gentamicin	10 mg/kg/dose 24-hourly <2 months
		20 mg/kg/dose 24-hourly >2 months
Likely abdominal origin for sepsis	Benzylpenicillin	50 mg/kg/dose 4–6-hourly
	and metronidazole	7.5 mg/kg 8-hourly
	and amikacin	10 mg/kg/dose 24-hourly <2 months
		20 mg/kg/dose 24-hourly >2 months

anterior tibial intra-osseous needle is easy and effective. You will not be criticized for placing an intra-osseous line early and it will improve the chances of securing central venous and arterial lines later. The first choice site for a central venous line is femoral. Many of these children will be severely coagulopathic, so neck lines carry an increased risk of complications.

Fluid resuscitation

Fluid resuscitation is of fundamental importance to survival of septic shock in children. Large fluid deficits typically exist, and initial volume resuscitation usually requires 40–60 ml/kg but can be much higher. Administration of >40 ml/kg in the first hour is associated with a significant reduction in mortality (Carcillo et al, 1991). Fluid infusion should use 20 ml/kg aliquots over 5–10 minutes, titrated to the clinical response reflecting cardiac output, including heart rate, urine output, capillary refill and level of consciousness.

Children can delay a reduction in blood pressure by tachycardia and vasoconstriction. Blood pressure alone is not a reliable end-point for assessing the adequacy of resuscitation. Hypotension should be considered a late sign indicating that cardiovascular collapse is imminent.

There no definite evidence that colloid or crystalloid is more effective as an initial resuscitation fluid. However, a recent 7000-patient adult study of saline *vs* 4% albumin in all intensive care unit (ICU) patients demonstrated that when 1.4x the volume of saline was given *vs* 4% albumin, there was an clear trend toward increased mortality with saline in the large septic shock subgroup (odds ratio for survival 0.87, 95% confidence interval 0.76–1.02, P=0.09) (Finfer et al, 2004). Previous studies suggesting excess mortality with colloid pre-date modern ventilatory support and were not conducted in patients with septic shock. Until further evidence is available, initial resuscitation fluid in septic shock should be colloid.

FLUID-REFRACTORY SHOCK

If the child has not been fully resuscitated from shock (i.e. is displaying some evidence of end-organ hypoperfusion) after 15 minutes of aggressive fluid resuscitation then therapy should be escalated to include vasoactive drugs. In severe cases this need might be anticipated and the timing reduced but fluid therapy should always be provided before vasopressor or inotropic support.

While this is happening the need for respiratory support must be reassessed frequently – consider that a semi-elective induction is likely to be much safer than an emergency induction. In the presence of persistent end-organ hypoperfusion despite adequate filling, intubation and ventilation is strongly recommended.

Children with septic shock may have:

- A normal or high cardiac output with low systemic vascular resistance ('warm shock')
- Low cardiac output and high systemic vascular resistance ('cold shock'). This is a higher risk group, which occurs more frequently in children than adults.

There is significant debate about the first-line choice of vasoactive drugs. The adult recommendations are either noradrenaline or dopamine as the first-choice vasopressor agent to reverse hypotension in septic shock (grade D).

In paediatrics there is no clear consensus as to the first-choice vasoactive drug. The issue is to provide a drug that will be an appropriate first line in both the warm and cold shock scenarios. While dobutamine may be given peripherally it carries a risk of worsening hypotension in warm shock. As clinical distinction of these two entities is very unreliable, and for simplicity, dopamine 5–15 μg/kg/min is recommended as the first-line drug in all scenarios. There are two exceptions that should be considered:

1. In individual cases with striking evidence of profound vasodilatation (flash capillary refill, low diastolic pressure with wide pulse pressure) noradrenaline may be the most appropriate choice.
2. Children with the most profound cardiovascular collapse secondary to sepsis (e.g. following resuscitation from cardiac arrest or with very poor or intermittent pulse volume) should receive an adrenaline infusion (0.1–0.5 mg/kg/min or more).

Vasodilators or inodilators should not be used early in resuscitation from septic shock and should not be used in the absence of cardiac output monitoring.

FLUID- AND DOPAMINE-REFRACTORY SHOCK

Consideration should be given to whether increasing blood pressure or cardiac output is the clinical priority. Ideally this requires continuous assessment of blood pressure, cardiac output and systemic vascular resistance.

This information is rarely available in the first hour of resuscitation, so proxy measures such as the oxygen saturation in the superior vena cava (SVC $O_{2\ sat}$) or right atrium may be used as an indicator of the adequacy of cardiac output. While this measurement should also be interpreted with caution, low values occur with an inadequate cardiac output – cold shock – (SVC $O_{2\ sat}$ <70%) resulting in increased tissue oxygen extraction, whereas in warm shock with a high cardiac output SVC $O_{2\ sat}$ would typically be higher (>70%). In principle adrenaline is the key component of resuscitation for cold shock and noradrenaline for warm shock. Catecholamine-resistant shock is addressed below.

In adults, adopting the following goals during the first 6 hours of resuscitation from sepsis-induced hypoperfusion improves survival (Rivers et al, 2001):

- Central venous pressure (8–12 mmHg)
- Mean arterial pressure >65 mmHg
- Urine output >0.5 ml/kg
- SVC $O_{2\ sat}$ or mixed venous oxygen saturation >70%.

These may be considered appropriate targets in older children. The principle of tailoring resuscitation to relevant physiological goals such as SVC $O_{2\ sat}$ is likely to apply to children of all ages.

AIRWAY/BREATHING

All children presenting in septic shock require high flow oxygen via a reservoir mask and prompt anaesthetic or intensivist review. Any of the following indicate an impending need for assisted ventilation:

- Fluid-refractory shock
- Depressed conscious level (Glasgow Coma Score < 9)
- Poor airway reflexes
- Worsening tachypnoea (especially the grunting infant) and requirement for supplemental oxygen.

Induction presents a significant risk of relative hypoxia, myocardial depression and afterload reduction. This risk can be reduced by:

1. Aggressive volume replacement (see above)
2. Pre-oxygenation
3. Intravenous (IV) atropine 10–20 mg/kg
4. Adrenaline bolus prepared (0.05–0.1 ml/kg of 1 in 10 000) and available
5. Range of endotracheal tubes sizes prepared (a good fit may be necessary to ensure adequate ventilation in the face of pulmonary oedema). Consider use of a cuffed tube even in infants
6. Use of optimal drugs for induction (dictated by availability and experience). Good combinations include fentanyl 10 mg/kg and suxamethonium 1 mg/kg, or atracurium 0.5 mg/kg or pancuronium 0.1 mg/kg. Ketamine 1–2 mg/kg can be used in addition to fentanyl, although not if there is any suspicion of raised intracranial pressure
7. Modified rapid sequence induction should be considered (nasogastric tube, cricoid pressure). There is a balance of risk to be considered using continuous positive airways pressure (CPAP) alone with a risk of relative hypoxia. Some would consider ventilation with a bag-mask system to be an appropriate modification during induction of anaesthesia in order to limit the immediate risk of hypoxia. Children with a significant coagulopathy should be orally intubated.

There is a significant risk of pulmonary oedema (cardiogenic and non-cardiogenic) and in severe cases it may be impossible to achieve adequate recruitment and oxygenation in the absence of positive end-expiratory pressure (PEEP). Bag-valve ventilation is therefore not adequate. All children in septic shock must be ventilated with PEEP.

CATECHOLAMINE-RESISTANT SHOCK

Steroids

Adult data have demonstrated improved ICU mortality with physiological replacement doses of steroids (hydrocortisone 1 mg/kg 6-hourly iv, fludrocortisone 1 mg/kg 24-hourly nasogastric). However, this study was unusual in that a very high proportion of cases (76%) demonstrated adrenal hyporesponsiveness and the benefit was entirely seen within this group (Annane et al, 2002).

Adult recommendations are that IV corticosteroids (hydrocortisone 200–300 mg/day, for 7 days in three or four divided doses or by continuous infusion) should be given in patients with septic shock who, despite adequate fluid replacement, require vasopressor therapy to maintain adequate blood pressure. The necessity of fludrocortisone in this regimen and the ideal length of a course are not known. However, doses of >300 mg hydrocortisone daily should not be used in this context.

The prevalence of adrenal hyporesponsiveness in paediatric septic shock is unclear, therefore steroid therapy cannot be routinely recommended. However, there are a number of situations in which (relative) adrenal hyporesponsiveness may be inferred:

- Chronic diseases requiring steroid medication
- Pituitary or adrenal disease
- Purpura fulminans
- Lack of the normal hyperglycaemic stress response.

In addition, one approach supported by consensus statements is to assume that all children with catecholamine-resistant shock have adrenal insufficiency. There are no paediatric data to help determine dosage and therefore the authors have adopted a 'stress' dose equivalent to that used in the adult study. A random serum cortisol level should be collected (but not analysed) before administration of hydrocortisone. Some investigators recommend doses in excess of the stress doses investigated in the adult study (Annane et al, 2002) but to date these are unsupported by clinical data. Therefore the authors' approach is that all children with catecholamine-resistant septic shock should receive hydrocortisone 1 mg/kg 6-hourly.

PERSISTENT CATECHOLAMINE-RESISTANT SHOCK

Cold shock – normal blood pressure

Potential additional therapies in the face of catecholamine-resistant shock include type III phosphodiesterase inhibitors (e.g. milrinone infusion at up to 0.7 μg/kg/min) for resistant cold shock (with volume loading) with a normal blood pressure. This treatment requires very careful attention to the risk of hypotension, and should ideally be undertaken with continuous cardiac output monitoring.

Cold shock – low blood pressure

Occasionally a child will demonstrate such severe cardiovascular depression that escalating doses of adrenaline are ineffective in maintaining adequate systemic perfusion. This is not sustainable.

At this stage (and before complete cardiovascular collapse) it may be appropriate to discuss the case with the extracorporeal membrane oxygenation (ECMO) team. Survival is at least 50% in appropriately selected cases. ECMO can be very effective in treating shock but is not appropriate in cases of very profound multiple organ failure where the additional risk of bleeding is extremely high (Goldman et al, 1997).

Warm shock – low blood pressure

In cases with hypotension that is resistant to noradrenaline, vasopressin (0.0003–0.002 iu/kg/min) is often effective at increasing systemic vascular resistance.

KEY POINTS

- Early aggressive fluid resuscitation saves lives in paediatric septic shock.
- 'Watch the clock' – outcome is closely related to the duration of shock.
- Constant re-evaluation and adjustment of therapy is required.
- Discuss cases with the local paediatric intensive care team early on.

CONCLUSIONS

The immediate care of the child with severe sepsis and shock involves simple interventions and a constant need for reassessment. Early administration of fluid resuscitation is life-saving and ongoing care should be titrated to the clinical situation. Early involvement of specialist paediatric intensive care staff is advisable. HM

Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* **29:** 1303–10

Annane D, Sebille V, Charpentier C et al (2002) Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* **288:** 862–71

Bone RC, Balk RA, Cerra FB et al (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* **101:** 1644–55

Carcillo JA, Fields AI (2002) Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. *Crit Care Med* **30:** 1365–78

Carcillo JA, Davis AL, Zaritsky A (1991) Role of early fluid resuscitation in pediatric septic shock. *JAMA* **266:** 1242–5

Dellinger RP, Carlet JM, Masur H et al (2004) Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* **32:** 858–73

Fidler KJ, Wilson P, Davies JC, Turner MW, Peters MJ, Klein NJ (2004) Increased incidence and severity of the systemic inflammatory response syndrome in patients deficient in mannose-binding lectin. *Intensive Care Med* **30:** 1438–45

Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R (2004) A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* **350:** 2247–56

Goldman AP, Kerr SJ, Butt W et al (1997) Extracorporeal support for intractable cardiorespiratory failure due to meningococcal disease. *Lancet* **349:** 466–9

Han YY, Carcillo JA, Dragotta MA, Bills DM, Watson RS, Westerman ME, Orr RA (2003) Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. *Pediatrics* **112:** 793–9

Levy MM, Fink MP, Marshall JC et al (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* **31:** 1250–6

Rivers E, Nguyen B, Havstad S et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* **345:** 1368–77

Seely AJ, Christou NV (2000) Multiple organ dysfunction syndrome: exploring the paradigm of complex nonlinear systems. *Crit Care Med* **28:** 2193–200

Singer M, De SV, Vitale D, Jeffcoate W (2004) Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. *Lancet* **364:** 545–8

Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC (2003) The epidemiology of severe sepsis in children in the United States. *Am J Respir Crit Care Med* **167:** 695–701