Management of Septic Shock in Children

Martin C. J. Kneyber
Department of Paediatric Intensive Care, Beatrix Children's Hospital
University Medical Center Groningen, University of Groningen, Groningen
The Netherlands

1. Introduction

Paediatric septic shock is a frequently occurring disease condition that is associated with high morbidity and mortality (Watson et al, 2003). Shock is an acute, complex state of circulatory dysfunction resulting in failure to deliver oxygen (DO_2) and nutrients to meet metabolic demands (VO_2) which are usually increased during shock. If left untreated, multiple organ failure and ultimately death will occur (Smith et al, 2006). This strongly points out the importance of early recognition and aggressive treatment of children with shock. Comparable to adults, such an approach – termed early-goal directed therapy (EGDT) – has been shown to significantly reduce mortality in paediatric septic shock. Paediatric studies have pointed out that the risk of death showed a two-fold increase with each hour delay in the reversal of shock (Carcillo et al, 2009; Han et al, 2003; Inwald et al, 2009; Rivers et al, 2001).

Hypovolaemic shock and septic shock are the most common forms of shock in children. Hypovolaemic shock is characterized by a decrease in intravascular blood volume to such an extent that effective tissue perfusion cannot be maintained. In children hypovolaemic shock is mainly caused by fluid and electrolyte loss due to vomiting and diarrhea or acute haemorrhage. Septic shock is actually a combination of distributive shock (i.e. a decreased total vascular resistance and maldistribution of blood flow in the microcirculation) and relative as well as a absolute hypovolaemia. Furthermore, impairment of myocardial fuction may occur with symptoms of cardiogenic shock.

The great majority of children with septic shock will not be presented in hospitals with PICU facilities. Furthermore, from a pathophysiologic perspective paediatric shock does not resemble adult septic shock. This strongly suggests that every physician that could be faced with these children needs to understand how to recognize paediatric shock and have basic knowledge of the principles of primary management. This chapter summarizes the pathophysiology, clinical manifestations and primary management of paediatric septic shock.

2. Pathophysiology of paediatric shock

The balance between DO_2 and VO_2 is the key factor in the pathophysiology of shock. DO_2 is also in children determined by the cardiac output (CO) and arterial oxygen content (CaO_2) according to the formula

$$DO_2 = CO * (Haemoglobin * 1.36 * SaO_2) + (0.003 * PaO_2) \qquad (1)$$

The CO is determined by the heart rate (HR) and stroke volume (SV), the latter is determined by the pre-load, afterload and contractility of the heart.

The VO_2 is increased in septic shock. Hence, the body will try to compensate for this by increasing the DO_2 through various mechanisms including increasing the HR and the venous vascular tone to optimize cardiac pre-load. Tachycardia is one of the earliest compensatory mechanisms. If this compensation is inadequate to meet cellular oxygen demands, the systemic vascular resistance (SVR) will be increased allowing perfusion of vital organs such as the heart and brain. In addition, oxygen extraction will be increased. Of importance, children are able to maintain normal blood pressure. This phase of shock is termed *compensated shock*.

Oxygen debt will occur if these mechanisms fail when the shock is not reversed. Under normal conditions oxygen debt will occur when the ratio $DO_2 : VO_2$ is 3 : 1. However, as a result of the increase in VO_2 during septic shock oxygen debt will occur already at $DO_2 : VO_2$ 2 : 1. Microvascular perfusion becomes marginal and cellular function deteriorates, affecting all organ systems (*uncompensated shock*). If not adequately managed, *irreversible shock* will occur. Vital organs will be damaged to such an extent that death is inevitable.

There are considerable differences in the pathophyiology of septic shock between children and adults. Vasomotor paralysis is the predominant cause of mortality in adults (Parker et al, 1987). Myocardial dysfunction in adult septic shock manifests mainly as decreased ejection fraction with either normal or increased CO. This is because adults are capable of increasing their CO by tachycardia in combination with ventricular dilatation allowing an increase in SV (Parker et al, 1984). In contrast, paediatric septic shock is mainly characterized by severe hypovolaemia; the decrease in CO and not SVR is associated with mortality (Carcillo et al, 2002). This is because especially younger children have higher baseline HR's compared to adults; hence they cannot increase their HR without impairing CO. Furthermore, children are not capable of increasing their SV (Feltes et al, 1994). This means that children need to be resuscitated with fluids aggressively. Nevertheless, the haemodynamic response of fluid-resuscitated children is different from adults. Ceneviva and co-workers evaluated 50 children with fluid-refractory, dopamine resistant septic shock (Ceneviva et al, 1998). The majority had low CO in combination with high SVR, but 22% had low CO and low SVR. Furthermore, haemodynamic profiles changed frequently during the first 48 hours.

Another interesting difference between children and adults relates to the VO_2. The VO_2 is mainly determined by oxygen extraction in adults, whereas in children is it mainly determined by the DO_2 (Carcillo et al, 1989). This indicates that all efforts must be made to maintain adequate DO_2.

3. Symptoms of paediatric shock

The early diagnosis of paediatric shock warrants a high index of suspicion and knowledge of disease conditions that predispose children to shock. It is imperative to understand the reference values for vital parameters in children.

Early signs of septic shock may be subtle and easily missed. Tachycardia is the earliest presenting symptom. Blood pressure will be normal during compensated shock, but the pulse pressure is widened. Children will have plethora, warm extremities and bounding

pulses ("warm shock". If the shock is not reversed, signs of failure of the compensatory mechanisms can be noted including cold extremities and prolonged capillary refill time ("cold shock"). Of note, the capillary refill time has little discriminative value in paediatric shock. Hypovolaemic children may still have a capillary refill time that is within the normal limit (2 seconds).

Age	Heart rate /min (95th percentile)	Respiratory rate /min (95th percentile)	Systolic blood pressure mmHg (5th percentile)
0 – 7 days	180	50	59
8 – 28 days	180	40	69
1 – 12 months	180	34	74
1 – 5 years	140	22	75
6 – 12 years	130	18	83
13 – 18 years	110	14	90

Table 1. Age-related reference values for vital parameters in children (derived from reference values by age, height and weight). Values above the 95th percentile (for heart rate and respiratory rate), and below the 5th percentile (for systolic blood pressure) are abnormal. Adapted from (Anonymous, 2004).

Symptoms of septic shock
General symptoms
Tachycardia
Hypothermia or fever
Decreased consciousness
Decreased urinary output
"Warm shock"
Shortened capillary refill time
Bounding pulses
Widened blood pressure
"Cold shock"
Capillary refill time > 2 secons
Weak pulses
Cold extremities, mottled skin
Hypotension (not necessarily)

Table 2. Symptoms of paediatric septic shock

Many children with fever have tachycardia and warm extremities on physical examination. Not all of these children are in shock. For early recognition of shock it is then absolute necessary to evaluate the mental state of the child. In general, children in shock are lethargic and have decreased consciousness, but the opposite (i.e. agitation, restless, anxious) also occurs. Underlying mechanisms include most likely a combination of cerebral hypoperfusion, metabolic alterations and production of cytotoxic substances.

Oxygen debt will occur when the shock is not recognized and thus not treated properly. Clinically, the child suffers from depressed consciousness, poor skin perfusion, decreased urinary output and hyperventilation to compensate for the metabolic acidosis.

The contribution of laboratory tests is limited. In contrast with adult septic shock, blood gasses and serum lactate levels are not diagnostic for paediatric shock but may be used for monitoring the effectiveness of treatment (Brierley et al, 2009). Repeated evaluation and monitoring of the patient remains the most effective physiologic monitor.

4. Management of paediatric shock

The American College of Critical Care Medicine (ACCM) has published clinical guidelines for the haemodynamic support of neonates and children with septic shock in 2002 and revised them in 2009 (Brierley et al, 2009; Carcillo et al, 2002). These guidelines advocate amongst others early recognition, adequate fluid resuscitation and timely and appropriate antibiotic therapy. Notwithstanding the fact that the efficacy of these guidelines has not been confirmed in a randomized clinical trial, data strongly suggests that adherence to these guidelines results in improved survival (de Oliveira et al, 2008; Dellinger et al, 2008; Han et al, 2003). Han and co-workers evaluated 91 patients with septic shock who were referred to their PICU (Han et al, 2003). Shock reversal within 75 minutes and adherence with the ACCM guidelines was associated with > 90% survival. Worrisome however was that adherence to these guidelines was only achieved in < 30% of all patients. A study of 200 children with severe sepsis in the United Kingdom showed a drop from 25% to 6% in mortality when shock was reversed, although only 8% of patients were managed according to the ACCM guidelines (Inwald et al, 2009).

The primary goal of the primary management of paediatric shock is to prevent organ failure caused by oxygen debt through optimalisation of and balancing DO_2 and VO_2. This means that is important to maintain blood pressure above the critical point which below flow cannot be effectively maintained. Thus, shock should be clinically diagnosed before hypotension occurs. Clinical targets include age-appropriate HR and blood pressure, normalisation of the capillary refill time, normal consciousness and adequate urinary output (> 1 mL/kg/hour) (Figure 1) (Brierley et al, 2009). After each intervention it is evaluated whether or not these clinical targets have been achieved.

4.1 Recognition and management during the first 15 minutes

Within the first five minutes the child is evaluated according to the Paediatric Advanced Life Support approach – i.e. a structural approach examining Airway, Breathing and Circulation (Figure 1). The diagnosis septic shock is confirmed when tachycardia, fever and symptoms of inadequate tissue perfusion are present. These symptoms include altered consciousness, as well as shortened capillary refill time, bounding pulses and widened pulse pressure (in case of "warm shock") or prolonged capillary refill time, weak pulses, mottled skin and decreased urinary output (in case of "cold shock").

The next step then is to administer 100% oxygen via a non-rebreathing mask (flow 10 – 15 L/min) and to insert two peripheral lines. Blood is drawn for haematological, biochemical studies and blood culture. Subsequently, aggressive fluid resuscitation is mandated (Carcillo et al, 1991). This means that within 15 minutes three fluid boluses of 20 mL/kg (max 500 mL) are administered. Crystalloid fluids are the first choice. After each bolus the child is evaluated if the clinical targets have been met. Rapid and sufficient fluid administration is significantly associated with improved survival (Ceneviva et al, 1998).

Of importance, antibiotics must be administered within the first 15 minutes. Although not confirmed in paediatric studies, adult data indicated that mortality doubled for each hour
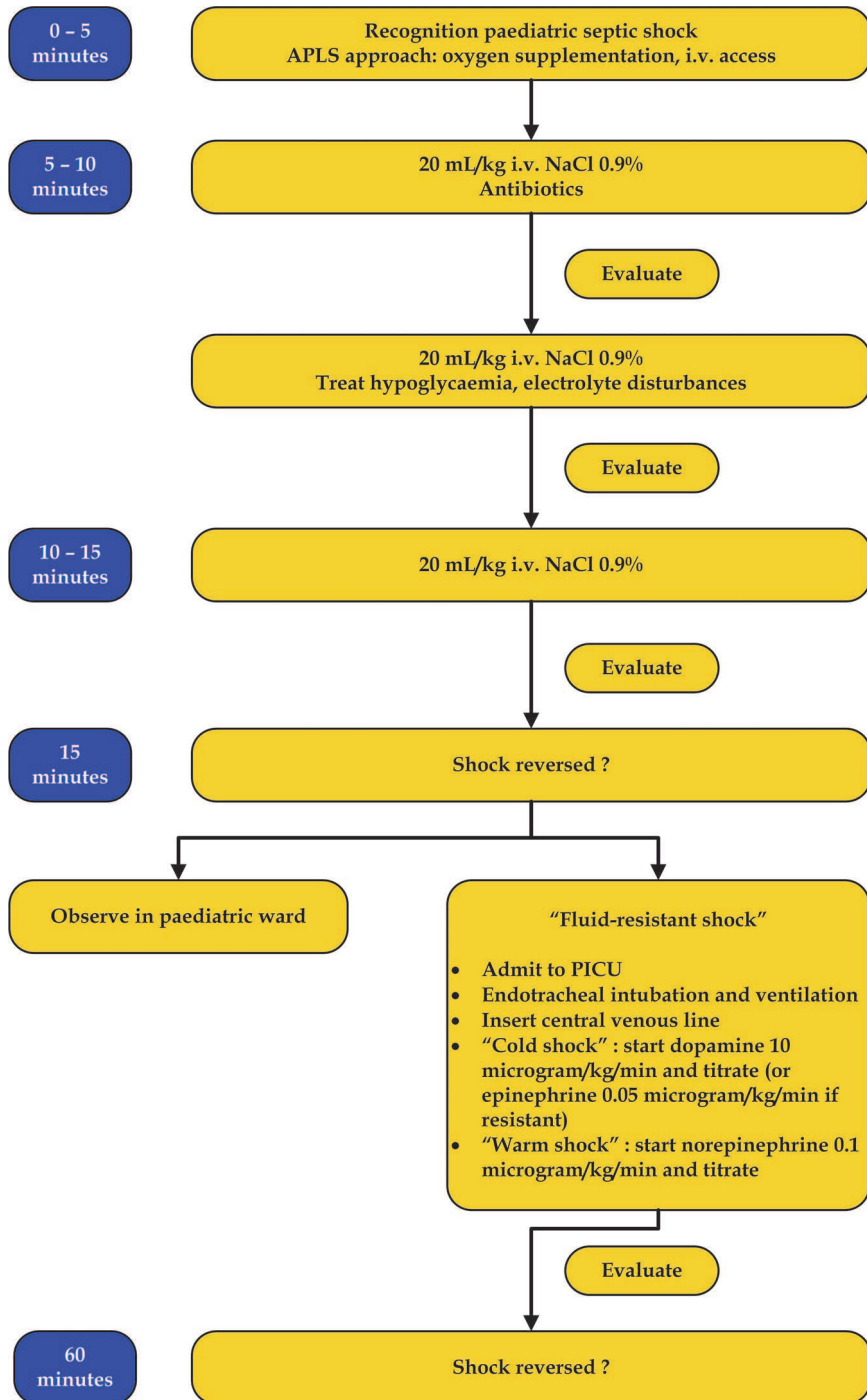
delay in administration of antibiotic treatment (Kumar et al, 2006). Electrolyte disturbances or hypoglycaemia is corrected in this first phase of primary management.

4.2 Management after the first 15 minutes

After 15 minutes it is evaluated if the clinical targets have been met. If not, the shock is classified as "fluid-resistant". The next step then would be to refer the patient to a PICU facility. It now depends upon the haemodynamic profile of the child what the next therapeutic intervention would be. If the child has a haemodynamic profile that is compatible with "cold shock", fluid administration is continued and dopamine 10 microgram/kg/minute is started via a peripheral line while in the mean time a central venous line is inserted. If the child has a haemodynamic profile that is compatible with "warm shock", fluid administration is continued and norepinephrine 0.1 microgram/kg/minute is started. Fluid administration will be continued until the liver becomes palpable enlarged or crackles are noted at pulmonary auscultation. Nevertheless, cumulative fluid administration up to 200 mL/kg may be necessary (Maar, 2004). Fluid administration should not be discontinued because of assumed possible development of pulmonary oedema, acute respiratory distress syndrome (ARDS) or cerebral oedema (Brierley et al, 2009). As an alternative to crystalloids, colloids such as albumin may be considered at this stage (Boluyt et al, 2006).

Also, endotracheal intubation and initiation of mechanical ventilation should be strongly considered in order to optimize DO_2. As discussed, in paediatric shock VO_2 is dependent upon DO_2. Furthermore, especially small children have a small functional residual capacity (FRC) that is easily compromised by pulmonary capillary leakage or if the child gets fatigued. Also, VO_2 may rise with 15 – 30% due to increased work of breathing during septic shock (Butt, 2001; Carcillo et al, 1989). Last, but not less important, sedation and mechanical ventilation may be needed to facilitate invasive procedures such as insertion of central lines. Also, increased intrathoracic pressure reduces left ventricular afterload that may be beneficial when there is a low CI/high SVR state. Nevertheless, early intubation may still be subject of debate. One of the arguments often used is the vasodilatory effect of agents used for induction. This effect may further compromise DO_2 in the septic child. We advocate the use of ketamine as induction agent (Yamamoto, 2000). Ketamine is a centrally acting N-methyl-D-aspartate (NMDA) receptor antagonist allowing cardiovascular stability. We would also advocate refraining from the use of etomidate because of its negative effects on adrenal gland function (Brierley et al, 2009).

The use of corticosteroids and sodium bicarbonate during the first hour of primary management of paediatric shock is also subject of heavy scientific debate. Corticosteroids are definitely indicated for children with purpura fulminans, or children with a recent history of prolonged corticosteroid use of proven abnormalities in the hypothalamic-pituitary-adrenal gland axis (Langer et al, 2006). In addition, the use of corticosteroids may be considered when children do not respond to infusion of vaso-active drugs ("*catecholamine-resistant shock*") (Brierley et al, 2009). Sodium bicarbonate is usually administered to correct metabolic acidosis as it is presumed that vaso-active drugs function less well in an acidic environment (Tabbutt, 2001). However, the metabolic acidosis is caused by insufficient tissue perfusion. This indicates that is necessary to optimize tissue perfusion rather than correcting the acidosis with sodium bicarbonate (Dellinger et al, 2008). Also, two studies performed in critically ill adults with septic shock and pH ≥ 7.15 have shown no beneficial effect on haemodynamic variables when patients were treated with

| 0 – 5 minutes | **Recognition paediatric septic shock**
APLS approach: oxygen supplementation, i.v. access |

| 5 – 10 minutes | **20 mL/kg i.v. NaCl 0.9%**
Antibiotics |

Evaluate

| | **20 mL/kg i.v. NaCl 0.9%**
Treat hypoglycaemia, electrolyte disturbances |

Evaluate

| 10 – 15 minutes | **20 mL/kg i.v. NaCl 0.9%** |

Evaluate

| 15 minutes | **Shock reversed ?** |

Observe in paediatric ward

"Fluid-resistant shock"

- **Admit to PICU**
- **Endotracheal intubation and ventilation**
- **Insert central venous line**
- **"Cold shock" : start dopamine 10 microgram/kg/min and titrate (or epinephrine 0.05 microgram/kg/min if resistant)**
- **"Warm shock" : start norepinephrine 0.1 microgram/kg/min and titrate**

Evaluate

| 60 minutes | **Shock reversed ?** |

sodium bicarbonate. Recent adult recommendations indicate to use sodium bicarbonate when pH < 7.00 (Boyd et al, 2008).

It is unclear if optimizing haemoglobin (Hb) levels through transfusion of red blood cells (RBC) is beneficial. One group of investigators could not confirm a beneficial effect on VO_2 despite optimalisation of CaO_2 in paediatric shock (Mink et al, 1990). Nevertheless, it is currently recommended to maintain Hb > 10 g/dL (Brierley et al, 2009). Fresh Frozen Plasma (FFP) is indicated for active haemorrhage or a prolonged activated partial thromboplastin time (APTT); in clinical practice usually twice the age-dependent reference value (Brierley et al, 2009).

4.3 Management after the first hour

One hour after presentation it is determined whether or not the shock has been reversed. If not, then the patient is recognized as having a fluid refractory dopamine-resistant shock. The patient is managed in the PICU. Treatment goals in this phase are similar to the golden hour (i.e. age-appropriate HR and blood pressure, normalisation of the capillary refill time, normal consciousness and urinary output > 1 mL/kg/hour), but now also include maintainance of age-appropriate perfusion pressure (mean airway pressure minus central venous pressure), cardiac index (CI) between 3.3 and 6.0 L/min/m2, central venous oxygen saturation (SvO_2) > 70%, normal anion gap and normal lactate. Fluid replacement should be continued and directed at these endpoints.

The type of haemodynamic support depends upon the haemodyamic profile of the child (i.e. low CO/high SVR, high CO/low SVR, or low CO/low SVR) (Figure 2). It seems therefore rational to use haemodynamic monitoring devices such as pulse contour analysis or Doppler ultrasound to assess the haemodynamic profile especially since frequently change. Irrespective of haemodynamic profile, support should be targeted at a CI between 3.3 and 6.0 L/min/m2. Pollack and co-workers have shown that a CI within this range was associated with the best outcome in paediatric shock (Pollack et al, 1985). Also, SvO_2 should be maintained > 70%. The SvO_2 can be used as a surrogate marker of the CO. Oliveira and co-workers randomized 102 children with septic shock to be managed using the ACCM guidelines with or without monitoring the SvO_2 (de Oliveira et al, 2008). Their SvO_2 goal-directed therapy resulted in less mortality (28-day mortality 11.8% vs. 39.2%, p = 0.002), and fewer new organ dysfunctions (p = 0.03). However, this strategy was associated with more crystalloid (28 (20-40) vs. 5 (0-20 ml/kg, p<0.0001), blood transfusion (45.1% vs. 15.7%, p =0.002) and inotropic (29.4% vs. 7.8%, p = 0.01) support in the first 6 hours of admission.

For patients with low CI, normal blood pressure and high SVR (i.e. "cold shock" with normal blood pressure), it is recommended to reduce ventricular afterload. This can be achieved using either epinephrine or dobutamine. Some have argued to additionally use a short-acting vasodilator such as nitroprusside or nitroglycerin to recruit the microcirculation. Alternatively, the use of type III phosphor-diesterase inhibitors such as milrinone may be considered (Barton et al, 1996). These agents have a synergistic effect with beta-adrenergic agents because they stimule intracellular cyclic adenosine monophosphate.

Patients with low CI, low blood pressure and low SVR (i.e. "cold shock with low blood pressure) it is recommended to titrate vasopressor therapy. In general, dopamine is the first-line vasopressor therapy. At high infusion rates, the alpha-adrenergic effects of dopamine predominate. Alternatively, norepinephrine or high dosage epinephrine may be considered. Once adequate blood pressure is achieved, a vasodilator can be added to improve the SvO_2 by recruiting the microcirculation.

Finally, patients with persisting high CI and low SVR despite fluid administration and norepinephrine may benefit of agents such as vasopressin or phenylephrine. Of importance, CO may be reduced when these agents are used so close monitoring of the CO and/or SvO_2 is mandated.

When the shock cannot be reversed and co-morbidities that fuel the shock (such as pericardial effusion, pneumothorax, hypoadrenalism, ongoing blood loss, increased intra-abdominal pressure, or necrotic tissue) high-flow veno-arterial extra-corporeal membrane oxygenation (ECMO) or high-flux continues renal replacement therapy (CRRT) with flows > 35 mL/kg/hour may be considered. Yet, these modalities may be qualified as last resort and their effects on final outcome need to be established.

5. Conclusion

Early recognition and aggressive primary management of paediatric septic shock is significantly associated with improved patient survival. Tachycardia, fever and altered consciousness are the first clinical manifestations of paediatric septic shock. Primary management includes aggressive fluid resuscitation, adequate oxygen delivery through early intubation and mechanical ventilation, and early referral to a paediatric intensive care unit. Future research should be directed towards obtaining stronger scientific evidence to confirm the components of the ACCM guidelines.

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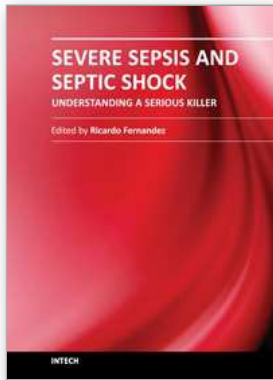
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Despite recent advances in the management of severe sepsis and septic shock, this condition continues to be the leading cause of death worldwide. Some experts usually consider sepsis as one of the most challenging syndromes because of its multiple presentations and the variety of its complications. Various investigators from all over the world got their chance in this book to provide important information regarding this deadly disease . We hope that the efforts of these investigators will result in a useful way to continue with intense work and interest for the care of our patients.

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