Review Article

The Golden Hours in Paediatric Septic Shock—Current Updates and Recommendations

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Abstract

Introduction: Paediatric sepsis is a global health problem. It is the leading cause of mortality in infants and children worldwide. Appropriate and timely initial management in the first hours, often termed as the "golden hours", has great impact on survival. The aim of this paper is to summarise the current literature and updates on the initial management of paediatric sepsis. Materials and Methods: A comprehensive literature search was performed via PubMed using the search terms: 'sepsis', 'septic shock', 'paediatric' and 'early goal-directed therapy'. Original and review articles were identified and selected based on relevance to this review. Results: Early recognition, prompt fluid resuscitation and timely administration of antibiotics remain key in the resuscitation of the septic child. Use of steroids and tight glycaemic control in this setting remain controversial. Conclusion: The use of early goal-directed therapy has had significant impact on patient outcomes and protocolised resuscitation of children in septic shock is recommended.

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Key words: Child, Early goal-directed therapy, Emergency, Sepsis

Introduction

Sepsis in children is a global health issue. The Global Health Observatory estimates that 58% of deaths in children under 5 years old are caused by infectious diseases.[1] Mortality increases as sepsis progresses to septic shock. The implementation of childhood vaccination programmes and the advent of vaccines such as *Haemophilus* influenza and pneumococcal vaccines have resulted in a change in the types of microbial agents responsible for sepsis. Previously common causes of septic shock such as *Haemophilus* influenza type b, *Neisseria meningitides* and *Streptococcus pneumoniae*, are now less commonly seen in countries with widespread immunisation programmes.[2-4] Changing trends in pneumococcal serotypes have also been reported.[5] Despite that, the incidence of sepsis in children has not declined and constitutes a significant economic burden.[6] The World Federation of Pediatric Intensive Care and Critical Care Societies (WFPICCS) has recently launched the Global Sepsis Initiative, a quality improvement programme at an attempt to improve sepsis outcome in children, targeting countries with different level of resources.[7]

The early recognition of septic shock and aggressive, goal-directed treatment is associated with improved outcomes for paediatric patients.[8,9] The objective of this article is to review the latest evidence in treatment strategies during the first hours of management, often referred to as the "golden hours".

Materials and Methods

A comprehensive literature search was performed via PubMed using the search terms: 'sepsis', 'septic shock', 'paediatric' and 'early goal-directed therapy'. Original and review articles were identified and selected based on relevance to this review. Articles that were not written in English were excluded.

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Results

Definitions

The International Paediatric Sepsis Consensus Conference published consensus definitions of various organ dysfunction categories, systemic inflammatory response syndrome (SIRS), severe sepsis, and septic shock specifically for children (Table 1).[10]

Clinical Manifestations of Sepsis

Early recognition of shock and prompt treatment is pivotal in improving patient outcome. In the early phase of shock, the paediatric patient usually mounts a robust tachycardia. There is a compensatory increase in systemic vascular resistance. Both these factors aid in maintaining the blood pressure. Changes in pulse pressure precede a decrease in systolic blood pressure, and the latter is known to be a late sign of shock. Hence, hypotension is not required for the diagnosis of shock.

A child who is in septic shock typically presents with altered sensorium. This may present as inconsolable crying, agitation, or increased drowsiness. The peripheries are cool and mottled, and the capillary refill time is more than 2 seconds. Conversely, in warm shock, the peripheries are warm and flushed, and there is flash capillary refill time. There is decreased urine output of less than 1 mL/kg/hour. The signs of shock should be integrated because no single sign confirms the diagnosis of shock.[11]

Table 1. Definitions for Systemic Inflammatory Response Syndrome, Sepsis and Septic Shock[10]

Condition	Symptoms
Systemic Inflammatory Response Syndrome (SIRS)	The presence of at least 2 of the following 4, one of which must be abnormal temperature or leukocyte count: Core temperature >38.5°C or <36°C, tachycardia (as defined as mean heart rate >2 SD above normal for age) or children <1 year with bradycardia (as defined by mean heart rate <10th percentile for age), mean respiratory rate >2 SD above normal for age or leukocyte count elevated or depressed for age.
Sepsis	SIRS in the presence of or as a result of suspected or proven infection.
Septic Shock	Sepsis and cardiovascular organ dysfunction: (despite administration of isotonic IV fluid bolus >40 mL/kg in 1 hour) Hypotension <5th percentile for age or systolic BP <2 SD below normal for age, or need for vasoactive drugs to maintain blood pressure (BP) in normal range, or 2 of the following – unexplained metabolic acidosis, increased arterial lactate, oliguria, prolonged capillary refill or raised core to peripheral temperature gap.

Differences Between Children and Adults

The adult patient responds to the shock state by increasing the heart rate and reducing the systemic vascular resistance (SVR), giving rise to the classical warm shock state. SVR is diminished due to decreased vascular response to catecholamines and alterations in alpha-adrenergic receptor signal transduction.[12] This hyperdynamic state is displayed in almost 90% of adults. Vasomotor paralysis is the main cause of death in adults with septic shock.

In contrast to adults who typically present with high cardiac output vasodilatory shock, the physiological response to sepsis varies in children. In children, the ability to increase the heart rate is limited. Doubling the heart rate in an infant would result in a tachycardic response that cannot be sustained, because the diastolic phase would be too short to allow for adequate cardiac refill. The variability in the physiological response was shown in a small case series of 50 children with fluid-refractory, dopamine-resistant shock.[12] Fifty-eight percent of them showed a low cardiac index and high systemic vascular resistance state, 20% had a high cardiac index and low systemic vascular resistance, 22% had a low cardiac index and low systemic vascular resistance. This difference has a direct impact on the choice and timeliness of fluid resuscitation and the use of inotropes.[13] Children with sepsis often have absolute or relative hypovolaemia and respond well to aggressive fluid resuscitation.[14]

First Hour Management

The role of early fluid resuscitation has been demonstrated to improve outcomes in paediatric septic shock.[14] The landmark randomised controlled study by Rivers et al[15] further highlighted the significance of early goal-directed therapy of septic shock in adults.

Airway Management

Oxygen should be given to any patient who is in shock. A child with a Glasgow coma scale (GCS) of less than 8, or one that is rapidly decreasing, should be intubated. In a patient who is able to maintain his or her own airway but requires large amount of fluid resuscitation (60 mL/kg or more), elective intubation should be considered. Up to 40% of the cardiac output supports the work of respiratory muscles.[13] By taking over the work of breathing through

assisted ventilation, this amount can be directed to other vital organs. The effect of left ventricular afterload reduction with positive pressure ventilation also improves cardiac output. Early intubation should also be considered for young infants and neonates as they have a lower functional residual capacity.[16]

Induction agents before intubation may cause vasodilatation and worsen the shock. Ensuring adequate intravascular volume may ameliorate this effect. Positive pressure ventilation, and particularly excessive ventilation, also decreases the effective preload to the heart. Although etomidate is an induction agent with relatively less side effects on the haemodynamic state, it should be avoided in the septic child, as adrenal suppression has been demonstrated after the use of etomidate and is associated with a higher mortality rate.[17,18]

Intravenous (IV) Access

Vascular access is of critical importance in the resuscitation of shock. Intravenous (IV) access may be more challenging in children compared to adults. However, fluid resuscitation and inotropic infusion should not be delayed in cases of difficult IV access. Depending on available expertise, the emergency physician should institute resuscitation via intraosseous access if vascular access is not readily secured. The intraosseous route is safe and can be used to administer all medications that would otherwise have been administered intravenously.[11,19-23] It has been recommended that no more than 3 attempts or 90 seconds be taken to obtain IV access before considering the intraosseous route.[24]

Fluid Resuscitation

Fluid resuscitation is indicated early, in the presence of tachycardia and changes in pulse pressure, or with physical examination findings consistent with septic shock, as stated above.

Children with septic shock have traditionally been believed to have severe hypovolaemia and aggressive fluid resuscitation has been recommended.[14] In an earlier landmark study, there was clear survival benefit for those with septic shock and given fluid resuscitation in excess of 40 mL/kg.[14] Fluids should be given in aliquots of 20 mL/kg over 5 to 10 mins,[25] and commonly up to 60 mL/kg in the first hour in the emergency department, as per ACCM/PALS guidelines.[13] Concerns for large volumes of resuscitation fluid include the development of cerebral oedema or acute respiratory distress. It has been recommended that in the absence of clinical signs of fluid overload (such as increased work of breathing, lung crepitations, gallop rhythm or hepatomegaly), fluid boluses can be administered to as much as 200 mL/kg.[13] Early involvement of community paediatricians with rapid fluid resuscitation has also been shown to reduce mortality.[8] Every hour that passes without restoring appropriate circulatory volume is associated with a 2-fold increase in mortality.[8]

Worldwide, the priority has moved to improve access to facilities capable of time-critical IV fluid resuscitation.[14] Four randomised controlled studies involving children with dengue and WHO classification stage 3 and stage 4 shock have shown that isotonic fluid resuscitation in the emergency department attains nearly 100% survival.[26-29] Mortality from diseases associated with hypovolaemic shock has also been shown to decrease by more than 10-fold with the availability and rapid administration of IV fluids,[30] including in children with meningococcaemia.[31] The World Sepsis Initiative has included early IV fluid administration in the clinical bundle for non-industrialised countries.[7]

More recently, the FEAST trial[32] showed, however, that fluid boluses increased 48-hour mortality in critically ill children with impaired perfusion. This study was a multicentre trial performed in resource-limited settings with a high prevalence of malarial disease and anaemia. In their population, routine fluid challenge could worsen severe anaemia, cause fluid overload and worsen hypoxaemia.[33] Reperfusion injury caused by rapid increase in plasma volumes, and exacerbation of capillary leak from the transient hypervolemia or hyperosmolality in susceptible patients may also account for the adverse effects of the fluid boluses.[34] Murthy et al also commented that the late presentation may result in decreased fluid-responsiveness in the cohort studied by the FEAST trial, and cautioned against a "one-size-fits-all" approach, because the pathophysiological mechanisms differ significantly between different causative agents and infections.[35]

In children with meningitis and pneumonia, levels of antidiuretic hormone (ADH) are raised[36,37] and aggressive fluid resuscitation may result in cerebral oedema. Standard recommendations still support timely and aggressive fluid resuscitation, in children with septic shock, while awaiting more specific research directing specific therapies for different aetiologies.

Type of Resuscitation Fluids

While evidence supports timely fluid resuscitation, there is insufficient evidence to support the use of either crystalloid or colloid. The initial study that showed a significantly improved outcome with aggressive fluid resuscitation used a combination of crystalloids and colloids.[14] Previous meta-analysis showed the use of human albumin solution or 0.9% saline resulted in similar survival outcomes.[38] This meta-analysis included a large Australian study (SAFE) reflecting the same outcomes.[39] The general trend has been

a decline in the use of albumin in paediatric intensive care units in the UK.[40]

A more recent systematic review published in 2010 showed few trials that specifically examined fluid resuscitation strategies in children.[41] The objective of the review was to include sepsis and sepsis-like conditions, in which there may be a theoretical benefit for the use of colloids. The inclusion criteria resulted in the studies mainly centred on those with malaria and dengue, with only one studying sepsis.[26,27,29,42-47] The trials for dengue shock showed a superior efficacy of colloids for restoring circulation in severe dengue shock. One randomised controlled trial comparing the use of colloid with crystalloid in children with dengue shock showed that those who received Ringer's lactate took the longest time to recover from shock.[26] One study for malaria showed a significant overall reduction in mortality in the albumin group compared to the saline group, specifically in the subgroup where acidosis and shock was complicated by coma.[43]

The single trial in children with sepsis showed no difference in the risk of mortality between saline and gelatin polymer.[47] The study was too small to detect differences, but did show that a larger volume of crystalloid was required to achieve the same resuscitation endpoint as colloid. Specifically, meningococcal sepsis is associated with microvascular injury, increased vascular permeability and capillary leak syndrome.[48] It has been recommended that in children with suspected or confirmed meningococcal septicaemia, if signs of shock persist after the first fluid bolus of 20 mL/kg of sodium chloride 0.9%, human albumin can be considered in subsequent aliquots of fluid resuscitation.[49]

Caution has to be exercised with the use of colloids, as they are known to be associated with allergic reactions, coagulation abnormalities and renal toxicity (the latter more so if used in large doses).[50-52] The use of hydroxyethyl starch (HES) has been reported to be associated with increased risks of acute kidney injury, need for renal replacement therapy and increased mortality.[53-56] Colloids are also more costly and are not uniformly available, especially in resource-limited countries.

Red Cell Transfusion

There is no known optimal haemoglobin target in children with septic shock. A randomised controlled trial of stabilised critically ill children comparing a haemoglobin target of >7 g/dL and >9.5 g/dL did not show a difference in rate of new or progression of organ dysfunction.[57] In the acutely ill septic child, it is imperative to optimise oxygen delivery by optimising cardiac output and blood oxygen content. A randomised controlled trial of early goal-directed therapy was conducted in paediatric patients with septic shock, with the multimodal intervention arm targeting a central venous oxygen saturation ($S_{CV}O_2$) of more than 70%.[58] One of the interventions included transfusing red cells to achieve a haemoglobin level of ≥10 g/dL when the $S_{CV}O_2$ was ≤70%. This study showed a reduced 28-day mortality in the intervention arm. The current recommendation is to target a haemoglobin level of >10 g/dL during active resuscitation. In children with invasive monitoring, this can be guided by the $S_{CV}O_2$. After stabilisation with recovery from shock and hypoxaemia, a more conservative haemoglobin goal of >7 g/dL can be considered.[25,59]

Use of Inotropes and Vasopressors

Physiological response in septic shock varies in children. Inotropes (and vasopressors or vasodilators) should be individualised to the type of response. The physician must remember that septic shock is a dynamic process and the choice of agents have varying effects on systemic vascular resistance, cardiac contractility and heart rate. The septic child may have a combination of low cardiac output and high systemic vascular resistance, high cardiac output with low systemic vascular resistance or low cardiac output with low vascular resistance.[12] Inotropic support should not be delayed due to the absence of central venous access, and can be administered peripherally. As recommended, dopamine is the first choice of support in a child who is in fluid-refractory shock, up to 10 mcg/kg/min.[25] In dopamine-refractory shock, adrenaline may be used. The use of adrenaline may result in hyperglycaemia from gluconeogenesis, increased lactate, and gut injury from decreasing intestinal mucosal pH. Noradrenaline is particularly useful in cases of warm shock.[12] A small series published showed that the use of peripheral noradrenaline (IV or IO) was safe without significant side effects.[60] Dobutamine should be considered in cases with low cardiac output states. In cases with persistently low cardiac output and raised vascular resistance, phosphodiesterase inhibitors should be considered.[61,62]

Early Antimicrobial Therapy

Administration of effective antibiotics within the first hour of recognition of septic shock or severe sepsis is strongly recommended.[25] Broad spectrum antibiotics should be given as early as possible. In the event that blood cultures are difficult to obtain, this should not delay the first dose of antibiotics. The initial choice of antibiotic should take into account the initial source of the infection, local bacteriology trends and patient's immunity status. With the isolation of the causative organism and known sensitivities, the antibiotics should then be quickly scaled down to target the detected organism specifically. In an adult septic shock study, effective antimicrobial administration within the

first hour of documented hypotension was associated with increased survival to hospital discharge.[63] An observational study demonstrated a reduced odds of death for patients who received antimicrobial agents within 60 minutes of emergency department triage time.[64]

Glycaemic Control

Hypoglycaemia must be avoided and treated at all costs in children. However, optimal glycaemic control in sepsis is still widely debated. Much interest was drawn to glycaemic control in critically ill patients when an adult randomised controlled trial in a cardiac surgical unit demonstrated a reduction in intensive care unit (ICU) mortality with intensive IV insulin therapy targeting blood glucose of 4.4 to 6.1 mmol/L.[65] However, subsequent adult studies in mixed populations of ICU patients, including patients with sepsis, did not show consistent reductions in mortality and in fact demonstrated increased incidence of hypoglycaemia with intensive insulin therapy. [51,66-70] The NICE-SUGAR trial, a multicentre randomised controlled trial, showed an increase in 90-day mortality and an increased incidence of hypoglycaemia in those who received intensive insulin therapy (blood glucose range, 4.5 to 6 mmol/L) compared to those with target blood glucose of less than 10 mmol/L.[71] In a post hoc analysis of this trial, moderate and severe hypoglycaemia was associated with increased risk of death.[72]

One randomised controlled trial of critically ill children showed an improvement in inflammatory markers and reduced length of ICU stay in patients with tight glycaemic control but also an increased risk of hypoglycaemia.[73] The most recent randomised trial in young children post cardiac surgery did not show benefit in terms of infection rate with intensive therapy.[74] Current evidence does not support tight glycaemic control but hyperglycaemia (blood glucose >10 mmol/L) should be avoided.

Use of Steroids

There is a strong controversy on the use of steroids in sepsis. While data suggest that sepsis causes a state of relative adrenal insufficiency,[75-84] there is no consensus on the exact definition of this insufficiency state. The administration of low dose steroids may hasten the reversal of shock and reduce inotropic-vasopressor requirement in adults.[18,85-87] One study in children similarly reported earlier shock reversal when low dose hydrocortisone was used for septic shock.[88] However, steroid therapy has not been conclusively shown to reduce mortality.[89,90] The CORTICUS trial, a multicentre randomised controlled trial involving adults with septic shock, did not show a difference in 28-day mortality with low dose hydrocortisone treatment compared to placebo.[91] Although earlier reversal of shock was observed in the treatment arm, there was no difference in the total number of patients with reversal of shock between the groups. A recent study reviewing the use of low dose steroids in the Surviving Sepsis Campaign showed a higher adjusted odds of hospital mortality in those who received steroids for fluid refractory shock.[92] A retrospective cohort analysis of a large paediatric sepsis trial showed no reduction in mortality attributable to use of adjunctive steroids.[93] Presently, the evidence for the use of steroids in children with septic shock is scarce and hence, does not provide a good basis to guide treatment. Steroids may be recommended for use in children with catecholamine-resistant shock and suspected or proven adrenal insufficiency.[25] These include children who are on exogenous steroids for chronic illnesses, those with known pituitary or adrenal insults, or children with severe shock and purpura. [84,88]

Parameters for Improvement

The therapeutic endpoint is the reversal of shock. Clinical parameters include normalisation of heart rate and respiratory rates, restoration of normal conscious level, normal volume pulses with no difference between peripheral and central pulses, capillary refill time of less than 2 seconds and a urine output of more than 1 mL/kg/hour.

Early goal-directed therapy[15] has been shown to have a significant impact on improved organ function in the adult population, and protocolised resuscitation of patients with septic shock is recommended.[25] In the paediatric population, the implementation of a goal-directed protocol resulted in earlier recognition of suspected sepsis and reduction in time to interventions and decreased treatment variation.[94] With the development of an emergency department (ED) septic shock protocol,[95] it has been shown to decrease the median hospital length of stay. The authors noted more complete recording of triage vital signs, timely fluid resuscitation and antibiotic administration, and serum lactate determination.

Biochemical markers include decreasing lactate levels, improving base deficit and superior vena cava or mixed venous oxygen saturation of >70%.[15,58] Improvements in lactate and central venous saturations have demonstrated stabilisation of haemodynamic status leading to improved clinical outcomes.[58]

Conclusion

Recommendations for Direction of Future Research

Many of the current recommendations are still consensus-based. In which septic shock child would aggressive fluid resuscitation be beneficial? Better stratification by different specific causative agents and biologically-derived mechanisms[35] would allow for more specific and appropriate

protocol application. The development of biomarkers of sepsis to allow early detection and risk stratification is another important area of research to help in early diagnosis and target appropriate treatment. More specific strategies should be explored in order to derive clearer guidelines on glycaemic control and the use of steroids during the golden hours in paediatric septic shock.

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