

Review Article

Beyond the guidelines of paediatric septic shock: A focused review

Mohamad-Hani Temsah

Paediatric Intensive Care Unit, King Saud University Medical City,
Riyadh, Saudi Arabia.

ABSTRACT

Severe sepsis and septic shock continue to cause major morbidity and mortality among children, especially in the resource-limited areas. Guidelines that focus on these entities, such as “Surviving Sepsis” and “Paediatric Advanced Life Support” guidelines, are revised and updated on regular basis to incorporate new evidence based medicine. There is ongoing need to review these updated guidelines, and address potentially best available solutions for adapting them into suitable practical steps for paediatricians worldwide, especially those working in resource-limited areas. The available recommendations may help to improve sepsis management in middle- and low-income countries; however, guidelines must be wisely implemented according to the available resources, with follow up auditing to ensure appropriate implementation.

Key words:

Audit; Guidelines; Resource-limited; Sepsis; Shock; Child.

Correspondence to:

Mohamad-Hani Temsah

Assistant Professor of Paediatrics and Paediatric Intensivist, King Saud University and King Saud University, Medical City, Riyadh, Saudi Arabia.
Email: mtemsah@ksu.edu.sa

How to cite this article:

Temsah M-H. Beyond the guidelines of paediatric septic shock: A focused review. Sudan J Paediatr 2015;15(2):16 - 22.

INTRODUCTION

Severe sepsis and septic shock continue to cause major morbidity and mortality among children. Sepsis is the most common cause of death in infants and children worldwide [1,2]. Expansion of critical care to handle such a burden with inadequate primary care and higher-risk medical therapies will be challenged by high costs at a time of economic constraint [3]. Policy makers and healthcare providers will need to balance global burden of critical illness and available critical-care resources, and develop both preventive and therapeutic interventions that are feasible and suitable across countries [3].

When we use the term “sepsis” in paediatrics, it usually refers to an infection that overwhelms the patient, causing capillary leak, hypotension, and/or respiratory failure [4]. Many stable children who are hospitalized with infections, such as pneumonia or cellulitis, could be given the diagnosis of “sepsis” according to the definitions published in 2005 from the International Consensus Conference on Paediatric

Sepsis (Table 1) [5]. Those sepsis definitions were created to facilitate enrolment of children into clinical trials of anti-sepsis agents [5]. In this review, we will address some management guidelines for children with severe sepsis. There is a continuity of severity ranging from sepsis to severe sepsis and septic shock. “Septic child” must have a suspected or confirmed infection with signs of a systemic response to that infection. In severe sepsis, there is dysfunction of ≥ 2 organ systems (i.e. end organ system involvement), while in septic shock there is associated cardiovascular dysfunction. These definitions were derived from adult SIRS criteria initially, and the goal of these paediatric definitions was to facilitate performance of clinical trials in children with sepsis [5]. It is useful to understand sepsis as a continuum, and it is crucial that healthcare workers aim at identifying sepsis in earlier stages, to facilitate early intervention, with the goal of stopping further spread of infection and preventing a severe life-threatening inflammatory reaction to this infection (Table 1).

Table 1 – Definition of clinical syndromes in the context of a sepsis continuum

Clinical Syndrome:	Criteria	Comments for practitioners
Systemic Inflammatory Response Syndrome (SIRS)	<p>The presence of at least 2 of the following criteria, one of which must be abnormal temperature or leukocyte count</p> <p>Abnormal temperature: Fever (core temperature more than 38.5°C) or hypothermia (less 36°C).</p> <p>Abnormal heart rate: either tachycardia (HR-2 SD above normal for age in the absence of external stimulus, drugs, or painful stimuli, or otherwise unexplained elevation over 0.5–4 hours) or bradycardia (HR <10th percentile for age in absence of external vagal stimulus, drugs, congenital heart disease; or otherwise unexplained HR depression for more than 30 minutes)</p> <p>Abnormal respiratory rate: Tachypnea: 2 SD above normal for age or mechanical ventilation for process other than anaesthesia or underlying neuromuscular disease</p> <p>Abnormal leukocyte profile with counts either elevated or depressed for age (not due to chemotherapy); or >10% immature neutrophils</p>	SIRS is nonspecific inflammatory process occurring after trauma, infection, burns, pancreatitis, and other diseases [6]

Infection:	A suspected or proven infection by any pathogen (bacterial, viral, fungal, or rickettsial). Presence of high probability of infection is also considered, with evidence including positive findings on physical exam, laboratory, or radiologic findings.	Confirmation is by positive culture, tissue stain, or molecular testing.
Sepsis	SIRS resulting from or occurring in the presence of suspected or proven infection	
Severe Sepsis	Sepsis plus one of the following: cardiovascular organ dysfunction <u>OR</u> acute respiratory distress syndrome <u>OR</u> two or more other organ dysfunctions	
Septic Shock	Sepsis and cardiovascular organ dysfunction despite administration of isotonic intravenous fluid bolus of at least 40 mL/kg in 1 hr. The Cardiovascular dysfunction is either: <ul style="list-style-type: none"> • Hypotension (BP less than 5th percentile for age) • OR: Need for vasoactive drug to maintain BP in normal range • OR: Two of the following: Unexplained metabolic acidosis, Increased arterial lactate more than 2 times upper limit of normal, oliguria (urine output 0.5 mL/kg/hr), prolonged capillary refill: more than 5 secs, core to peripheral temperature gap more than 3°C 	As a quick reference, hypotension is: For term neonates (0 to 28 days of age), SBP <60 mm Hg For infants from 1 month to 12 months, SBP <70 mm Hg For children >1 year to 10 years, SBP <70+(2×age in years) Beyond 10 years, hypotension is defined as a SBP <90 mm Hg [7]

Recommended published resources:

The followings are adapted from recent published guidelines that may help better management of severe sepsis and septic shock in children. A capsule summary of paediatric-specific consensus recommendations for sepsis management from the 2012 Surviving Sepsis and Paediatric Advanced Life Support guidelines,

Adapted & Updated from: Paediatric sepsis: important considerations for diagnosing and managing severe infections in infants, children, and adolescents (Table 2) [4,8,9]. The healthcare providers are advised to review the original publications and to adopt the most suitable approach in their settings with limited available resources (Table 2).

Table 2 - Summary of paediatric-specific consensus recommendations for sepsis management and their feasibility in resource-limited countries

Consensus recommendations	Feasibility in Resource-limited countries / Comments
Initial Resuscitation: Paediatric Specific Considerations	
1. Infants anatomically have low pulmonary functional residual capacity and can desaturate very quickly. Supplemental oxygen should be delivered via facemask or nasal cannula or other devices to children with septic shock even if oxygen saturation levels appear normal with peripheral monitoring devices.	Usually readily available

<p>2. Peripheral intravenous access is often difficult to obtain in hemodynamically unstable infants and young children. If unable to obtain peripheral intravenous access quickly, early use of intraosseous access is recommended for fluid resuscitation, inotrope infusion and delivery of antibiotics when central venous access is not easily obtainable. If mechanical ventilation is required then cardiovascular instability during intubation may be less likely after appropriate cardiovascular resuscitation.</p>	<p>Maybe available, may need some skills training.</p>
<p>3. The 2015 Paediatric Life Support (PALS) guidelines [8] ^{4t} are recommended for the management of septic shock in children.</p>	<p>For Healthcare Workers dealing with critically ill children, updated recommendations with full text Open Access are available online [10].</p>
<p>Antibiotics and Source Control</p>	
<p>1. Empiric antibiotics should be administered within the first hour of determining that the patient has severe sepsis. Obtaining blood cultures prior to antibiotics is preferred, when possible, but should not delay antibiotic administration.</p>	<p>The Golden Hour: Early reversal of shock and early antibiotics administration is crucial for better outcome in Septic Shock</p>
<p>2. The empiric drug choice must be tailored to epidemic and endemic ecologies and consideration for treatment of resistant organisms is essential.</p>	<p>Antimicrobial choice should be tailored to the hospital/ setting susceptibility and potential organisms based on the patient's setup</p>
<p>3. Clindamycin and anti-toxin therapies for toxic shock syndromes with refractory hypotension are recommended.</p>	
<p>4. Early and aggressive source control is essential. Because infants and young children have difficulty communicating the location of their pain, radiologic imaging is an essential part of the workup in children with severe sepsis.</p>	<p>Maybe available, may need some skills training.</p>
<p>Fluid Resuscitation</p>	
<p>1. In the industrialized world with access to inotropes and mechanical ventilation, initial resuscitation of hypovolemic shock begins with infusion of isotonic crystalloids (or albumin equivalent) with repeated boluses of up to 20 mL/kg of crystalloids (or albumin equivalent) over 5–10 min, titrated to reversing hypotension, increasing urine output, and attaining normal capillary refill, peripheral pulses, and level of consciousness.</p>	<p>Initial fluid bolus of 20 mL/kg is reasonable for most Paediatric Septic Shock patients. However, in settings with limited access to critical care resources (like mechanical ventilation and inotropic support), administration of bolus IV fluids should be undertaken with caution, as it may be harmful. Individualized treatment and frequent clinical reassessment are emphasized to titrate fluid and inotropes as per patient's status.</p>
<p>2. In a child with hepatomegaly or rales, early inotropic support should be implemented, and fluid resuscitation carefully titrated.</p>	
<p>3. In children with compensated shock in resource-limited settings without access to inotropes or mechanical ventilation, fluid boluses may be harmful.⁹² Blood transfusion should be considered in patients with compensated shock who are profoundly anaemic.</p>	

Extracorporeal Membrane Oxygenation (ECMO)	
1. Consider ECMO for refractory paediatric septic shock with respiratory failure.	Not readily available in most resource-limited settings
Blood Products and Plasma Therapies	
1. Haemoglobin targets are similar in children as in adults. In hemodynamically unstable children in shock on vasopressor infusions, haemoglobin levels of ≥ 10 g/dL are targeted. In stable critically ill children, a lower haemoglobin target of ≥ 7.0 g/dL is recommended.113	Tailor to patient's condition and available resources
2. Similar platelet transfusion targets in children as in adults.	Tailor to patient's condition and available resources
3. Consider plasma therapies in children to correct sepsis-induced thrombotic purpura disorders, including progressive disseminated intravascular coagulation, secondary thrombotic microangiopathy, and thrombotic thrombocytopenic purpura.	May not be readily available in most resource-limited settings

Recommendations for sepsis management in resource-limited settings:

A special review article by Dunser et al was published in Intensive Care Med in 2012 [11]. This extensive medical literature review aimed to provide clinicians in resource-limited settings with a framework to improve the management of paediatric and adult patients with sepsis. The authors made specific attention to identify clinical evidence on sepsis management from resource-limited settings, and they highlighted the limited evidence that existed regarding the management of sepsis in resource-limited settings. Their recommendations were grouped into acute and post-acute interventions [11]. For example, acute interventions included liberal fluid resuscitation to achieve adequate tissue perfusion, normal heart rate and arterial blood pressure, use of epinephrine or dopamine for inadequate tissue perfusion despite fluid resuscitation, frequent measurement of arterial blood pressure in hemodynamically unstable patients, administration of hydrocortisone or prednisolone

to patients requiring catecholamines, oxygen administration to achieve acceptable oxygen saturation more than 90%, semi-recumbent and/or lateral position, non-invasive ventilation for increased work of breathing or hypoxemia despite oxygen therapy, timely administration of adequate antimicrobials. Regarding the fluid management, the role of fluid resuscitation in the treatment of children with shock and life-threatening infections who live in resource-limited settings is not established. The study by Maitland et al. reported increased mortality in African children with sepsis who received fluid boluses in addition to maintenance fluids [12]. Harmful effects of fluid boluses were mainly observed in children with compensated shock and profound anaemia [12]. More than half of the children in that study had malaria. The general lack of intensive care facilities among study centres may have contributed to harmful effects of aggressive fluid loading. The results of this study challenge the importance of bolus resuscitation as a lifesaving intervention in resource-limited settings for children with shock who

do not have hypotension, and raise questions regarding fluid-resuscitation guidelines in other settings as well. Based on these data, patients with sepsis and tissue hypoperfusion (Hypotensive Septic Shock) appear to benefit from a rapid bolus of intravenous crystalloid solution of 20 mL/kg. Further fluid resuscitation should be guided by the response to fluid loading, and early start of inotropic support may be helpful. Further research is needed to clarify this issue.

In a recent publication, Fusco et al found that time to first antimicrobial administration after onset of sepsis was not optimal in their setting (Median time to first antibiotic dose was 2.7 (0.5-5.1) hours), and exceeded the recommendations set for th in international guidelines [13]. This highlights the significance of not only adopting the guidelines, but also working as a multidisciplinary team to implement such guidelines & audit the process to ensure it is being utilized appropriately.

Post-acute interventions that were suggested by Dunser et al included administration of antimicrobials for an

adequate but not a prolonged duration, avoidance of hypoglycaemia, pharmacological or mechanical deep vein thrombosis prophylaxis, resumption of oral food intake after resuscitation and regaining of consciousness, careful use of opioids and sedatives, early mobilization, and active weaning of invasive support [11]. Specific considerations for malaria sepsis and HIV/AIDS patients with sepsis were also included in that review [11].

CONCLUSION

Little evidence exists for the specific management of paediatric and adult sepsis in resource limited settings, and this warrants further research. The available recommendations may help to improve sepsis management in middle- and low-income countries; however, guidelines must be wisely implemented according to the available resources. Auditing process should follow to ensure that the guidelines are appropriately implemented.

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