Sepsis guidelines and the global pediatric sepsis initiative: implications for treatment

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'...recent guidelines and initiatives show that the progression from sepsis to severe sepsis and septic shock can be effectively halted and reversed with timely therapeutic interventions.'

Sepsis is defined as the systemic response to infection, and clinically manifests as a constellation of tachypnea, tachycardia, fever or hypothermia, and an abnormal white blood cell count. If unrecognized and untreated, sepsis progresses to life-threatening severe sepsis (defined as sepsis associated with organ dysfunction, hypoperfusion or hypotension) and/or septic shock (defined as sepsis with hypotension, despite adequate fluid resuscitation). Sepsis, severe sepsis and septic shock describe the common, underlying pathophysiology of four of the five major killers of children worldwide: severe pneumonia, severe diarrhea, malaria and severe bacterial sepsis [101,102]. The encouraging news is that recent guidelines and initiatives show that the progression from sepsis to severe sepsis and septic shock can be effectively halted and reversed with timely therapeutic interventions [103–105]. Therefore, four of the five major global killers of children can be considered preventable through aggressive sepsis treatment. Indeed, epidemiologic studies have shown that mortality from severe sepsis and septic shock has dropped from 97% in the late 1960s, to as low as 2% in 2003 in previously healthy children [1–4]. Early treatment to circumvent the deterioration to severe sepsis and septic shock is very important, especially in resource-limited environments.

In treating sepsis, a time-sensitive stepwise approach of simple to increasingly complex therapies is recommended. Many children who present to their pediatrician's or family medicine/general practitioner's office or clinic have signs of sepsis, with fever and tachycardia or tachypnea. Most have viral sepsis and require fever control and oral hydration. However, some may require antibiotic treatment, which, when used early, may suffice. The importance of the early antibiotics is demonstrated by Bang and colleagues in a randomized trial of intramuscular gentamicin and oral cotrimoxazole administered to newborns with tachycardia or tachypnea, or diarrhea or poor feeding in rural India by home health workers [5,6]. They observed a reduction in all-cause newborn mortality from 16 to 2%. Of interest, 10% of newborns received antibiotics in this trial. This is the exact percentage of newborns in the western world who receive antepartum or postpartum antibiotics. Sepsis guidelines therefore call for community health workers to be available to administer antibiotics to infants and children in the rural developing world.

Shock is the leading risk factor for mortality in children with sepsis. Sepsis guidelines recommend time-sensitive, stepwise administration of isotonic fluid boluses, escalating to continuous inotrope infusion, to maintain a normal blood pressure and a capillary refill time of less than 3 s. Every hour that goes by without attaining this goal in the community hospital emergency department has been associated with a twofold increase in odds of death from multiple organ failure [7]. Pediatric Advanced Life Support guidelines call for equipping emergency rooms with the means for establishment of intravascular access, isotonic fluid resuscitation and inotrope infusion. The first recommended step is to place high-flow nasal cannula oxygen or continuous positive airway pressure to help with respiratory distress [8,9]. Next, intravascular access should be quickly attained; however, if this is difficult, intraosseous cannulation is recommended. This is followed by repeated 20 ml/kg fluid boluses with isotonic saline or albumin, while always reassessing for signs of fluid overload, including rales and increased hepatomegaly. If this occurs, fluid resuscitation should be stopped, and an inotrope infusion (e.g., epinephrine) should be administered through the intravascular line. Hydrocortisone should also be administered if there is suspicion of adrenal dysfunction. These three interventions and the first dose of antibiotics should all be administered in the emergency room within the first hour. This takes a great deal of organizational determination, but the effort is often well rewarded. Investigators at

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St Mary's hospital in London, UK, and Sophie Hospital in Rotterdam, The Netherlands, have documented reductions in mortality from meningococcemia from 22 to 2% and 20 to 1%, respectively [2,3,10], with implementation of:

- Community education programs instructing parents on early signs of sepsis
- Stepwise resuscitation algorithms using fluid resuscitation followed by inotropic support and airway management in the community emergency department
- Provision of pediatric-specialized transport teams to transport children to the tertiary referral center

Children who remain in shock after this initial resuscitation may require intubation and mechanical ventilation, or placement of central venous lines for pressure and oxygen saturation monitoring. Ketamine remains the recommended sedation agent for these procedures, as etomidate has been associated with increased mortality when used in children and adults with septic shock [11,12]. A recent randomized trial conducted in critically ill children in Brazil showed that goal-directed resuscitation to a central venous oxygen saturation (superior vena cava/right atrium or inferior vena cava/right atrium junction) greater than 70%, using more isotonic fluids if hemoglobin is greater than 10 g/dl or packed red blood cells if hemoglobin is less than 10 g/dl, followed by inotropic support with dobutamine, epinephrine or milrinone, reduced 28-day mortality from 39 to 12% [13]. Children who remain in shock despite this goal-directed approach can benefit from having cardiovascular therapies directed to a cardiac index between 3.3 and 6.0 l/min/m^2. Extracorporeal membrane oxygenation can also be beneficial in rescuing patients with overwhelming cardiac failure (cardiac index: <2.0 l/min/m^2). In addition, children who have multiple organ failure from late resuscitation will commonly benefit from other extracorporeal therapies. Diuretics should be the first line therapy for fluid overload, and fresh frozen plasma infusion is the first-line for prolonged prothrombin time and disseminated intravascular coagulation. However, if fluid overload is more than 10% of the body weight, continuous renal replacement therapy is used to gently remove fluid while avoiding hypotension from acute fluid shifts [14,15]. Plasma exchange therapy is also effective in reversing complex sepsis-induced coagulopathy and thrombotic microangiopathy related in part, to ADAMTS deficiency [8,16,17].

Some special considerations exist for specific organisms. Streptococcal toxic shock syndrome toxin released by *Streptococcus pyogenes*; Panton–Valentine leukocin toxin released by community-associated methicillin resistant *Staphylococcus aureus*; and *Clostridium difficile* toxin can be neutralized with intravenous immunoglobulin *in vitro*, and this treatment is recommended for these patients. Resistant organism strains are very challenging, as each hour that goes by without being given the appropriate antibiotic or antifungal is associated with a 7% increased risk of death [18]. Hence, empiric antibiotic/antifungal therapy requires an in-depth understanding of the child's past infections and general immune status, and the community's endemic infection flora.

'The three therapeutic determinants of sepsis survival in children are rapid resuscitation, source control and immune suppression withdrawal/immune restoration.'

Special considerations also exist for some children. For instance, children with dengue or malarial shock require slower fluid infusion in the first hour than children with bacterial septic shock [19–21]. However, children with malaria have bacterial septic shock for as much as 40% of the time. Children with malaria may also benefit from initial albumin resuscitation more than from crystalloid resuscitation [22,23]. Children with primary or acquired immune deficiencies are at greater risk of unrelenting sepsis. Withdrawal or rapid tapering of immune suppressants, including high-dose corticosteroids, is recommended in children undergoing therapeutic immune suppression who develop septic shock or severe sepsis. Children with primary immune deficiencies may also require immune therapy. Children with chronic granulomatous disease should be treated with white blood cell transfusions and children with hypocomplementemia should be treated with plasma. Children with hypogammaglobulinemia should be treated with intravenous immunoglobulin, children should be treated with neutropenia with granulocyte-colony stimulating factor and children should be treated with immune paralysis with granulocyte macrophage colony-stimulating factor.

The three therapeutic determinants of sepsis survival in children are rapid resuscitation, source control and immune suppression withdrawal/immune restoration [24]. Indeed, if sepsis

does not resolve after 5 days, one of three possibilities must be considered: the organism is resistant; there is an immune-deficient state; or the nidus has not been removed. Barie and colleagues demonstrated a 96% survival with removal of surgical nidus of infection, compared with only 1% without [25]. Areas of abscess and necrotic tissue should be aggressively removed and antibiotics switched to those with a minimum inhibitory concentration of less than 1 when possible. Immune suppressants should be held and immune restoration used as indicated if immune deficiency is suspected.

In an effort to increase global awareness of sepsis as the major preventable cause of child mortality and to prevent sepsis deaths worldwide, the World Federation of Pediatric Intensive and Critical Care Societies has begun the free web-based Pediatric Sepsis Initiative [106,107]. The site has four offerings. First is guideline provision, with web access to international guidelines including the WHO Handbook and the American College of Critical Care Medicine (ACCM) guidelines. Both are symptom-based guidelines. However, the WHO guidelines provide recommendations, for the most part, for when physicians are not available and allied health workers are the major patient assessors and treatment providers. The ACCM guidelines assume that physicians are available as patient assessors and treatment providers. Second is education provision, with access to lectures and 'real TV' videos to instruct caretakers in assessment and treatment. Third is provision of the Bundle Registry. Here, practitioners join an exciting and ambitious worldwide epidemiology and quality-assurance initiative. Each participant lists whether they come from a setting that is either:

- Nonindustrialized developing region with more than 30 deaths/1000 children
- Nonindustrialized developing region with less than 30 deaths/1000 children
- Industrialized developing region
- Industrialized developed nation

Each level has an administrative checklist that characterizes resources that the initiative expects to be available for children with sepsis. Next, the participant lists the diagnosis, organism, site and underlying disease of the individual patient. The participant then lists whether the patient received the goal-directed therapies expected for the level of administrative support provided. Finally, the participant lists the patient's outcome. Ambassadors throughout the world are responsible for recruiting participants in the initiative. Participants' results will be provided anonymously on a quarterly basis according to level A–D, allowing the participant to identify which areas do and do not require improvement. A yearly global report will be prepared to inform the global community of progress in eradicating sepsis deaths in children.

'The Global Pediatric Sepsis Initiative is a new program, dependent on healthcare provider participation, that is designed to inform the community of both the ongoing challenges and successes in eradicating pediatric sepsis death and morbidity.'

In summary, sepsis is a major pediatric health problem worldwide. It is estimated that 10% of newborns develop sepsis and receive antibiotics with improved health outcomes worldwide. Septic shock deaths in infants and children have decreased almost 50-fold since the 1960s, with the best centers now reporting 1–2% mortality in previously healthy children. Despite success in the developed industrial world, sepsis remains the leading killer of children in the developing world. The best outcomes require organized emergency medicine, transport medicine and critical care medicine systems. Sepsis guidelines provide the framework for this organizational approach. The Global Pediatric Sepsis Initiative is a new program, dependent on healthcare provider participation, that is designed to inform the community of both the ongoing challenges and successes in eradicating pediatric sepsis death and morbidity. Early recognition of sepsis (tachypnea/tachycardia with fever) and treatment with antibiotics, and early recognition of septic shock (prolonged capillary refill or hypotension) and treatment with intravenous fluids and inotropes all but eradicate morbidity and mortality from this disease. Our challenge is an organizational one: to achieve these goals within a time-sensitive framework in clinics and emergency departments throughout the world.

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