PEDIATRIC SEPTIC SHOCK

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Septic shock in children is the prototype combination of hypovolemic, cardiogenic and distributive shock. Recently published American college of critical care medicine (ACCM) made recommendations for hemodynamic support of neonatal and pediatric patients with sepsis, Surviving sepsis campaign and its pediatric considerations and subsequent revision of definitions for pediatric sepsis.

Sepsis is a problem that presents a management challenge to those who care for infants and children; however, early recognition and intervention clearly improves the outcome for infants and children with infections or intoxications that lead to sepsis. Based on the 1992 Consensus Conference on definitions for sepsis and organ failure, severe sepsis was defined in adult patients as sepsis associated with at least one acute organ dysfunction [1]. This definition was upheld in the recent 2001 Consensus Conference [2]. With the exception of certain pediatric-specific diagnostic criteria for sepsis introduced in the 2001 Consensus Conference report, little guidance or consensus exists in the literature for the definition of pediatric systemic inflammatory response (SIRS) with infection, more generally termed pediatric sepsis. Sepsis remains a major cause of morbidity and mortality among children [3,6]. Sepsis-associated mortality in children decreased from 97% in 1966 [7] to 9% among infants in the early 1990s [8]. A recent population-based study by Watson and colleagues [9] of US children with severe sepsis (bacterial or fungal infection with at least one acute organ dysfunction) reported 42,000 cases in 1995 with a mortality rate of 10.3%. Although this represents a significant improvement over the past few decades, severe sepsis remains one of the leading causes of death in children, with 4,300 deaths annually (7% of all deaths among children).

Generally, sepsis is considered to comprise a spectrum of disorders that result from infection by bacteria, viruses, fungi, or parasites or the toxic products of these micro-organisms. Bacteremia, viremia, fungemia, and parasitemia refer to bloodstream invasion that may be associated with fever but no other signs or symptoms of circulatory compromise or end-organ malperfusion or dysfunction.

The spectrum of sepsis ranges from microbial invasion of the bloodstream or intoxication with early signs of circulatory compromise, including tachycardia, tachypnea, peripheral vasodilation, and fever (or hypothermia), to full-blown circulatory collapse with multiorgan system failure and death. All these manifestations are part of the more appropriately termed systemic inflammatory response syndrome (SIRS), which is used interchangeably with sepsis to signify any of these manifestations, whatever the etiology. SIRS results from an insult, whether infectious, traumatic, chemical, malignant, autoimmune, or idiopathic, and the host response that follows. The outcome depends on the intricate interplay of upregulating and downregulating cytokines and inflammatory cells and the direct effects of the insult itself.

Pathophysiology

Fever is the most common presenting symptom of children with SIRS. Fever is one component of the triad
of hyperthermia (or hypothermia), tachypnea, and tachycardia that typifies the earliest and/or mildest manifestation of SIRS. If SIRS is identified and reversed early, the subsequent inflammatory cascade can often be avoided or mitigated. However, in some situations, further damage occurs because the insult or the resultant host immune response is too great. This damage can result in increased cardiac output, peripheral vasodilation, increased tissue oxygen consumption, and a hypermetabolic state (i.e., warm shock). If SIRS is not identified and reversed early, cardiac output may fall, peripheral vascular resistance may increase, and shunting of blood may ensue (i.e., cold shock). This results in resultant tissue hypoxia, end-organ dysfunction, metabolic acidosis, end-organ injury and/or failure, and death.

Definitions

Hypovolemia is the most common cause of pediatric shock.

Septic shock is the prototype combination of hypovolemia and cardiogenic and distributive shock. Following are the latest definitions published in 2005, related to sepsis and septic shock.

**Systemic inflammatory response syndrome**

At least two of the following four criteria are present, one of which must be abnormal temperature or leukocyte count.

\(i\) Core temperature of more than 38.5°C or less than 36°C.

\(ii\) Tachycardia, defined as the mean heart rate of more than 2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli. Otherwise, unexplained persistent elevation over a 0.5-4 h time period or bradycardia for children aged less than 1 year, defined as the mean heart rate.

\(iii\) Less than 10% for age in the absence of external vagal stimulus, β-blocker drugs, or congenital heart disease, or otherwise, unexplained, persistent depression over a 0.5 h time period.

\(iv\) Mean respiratory rate of more than 2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.

\(v\) Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or more than 10% immature neutrophils.

**Infection**

A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen or a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans).

**Sepsis**

Systemic inflammatory response syndrome in the presence of or as a result of suspected or proven infection.

**Severe sepsis**

Sepsis plus either cardiovascular organ dysfunction or acute respiratory distress syndrome (ARDS), or two or more other organ dysfunctions. Organ dysfunctions are defined in (Fig. 1).

**Septic shock**

Sepsis and cardiovascular organ dysfunction are defined in (Fig. 1).

The detection of altered organ function in the acutely ill patient constitutes multiple organ dysfunction syndrome (two or more organ involvement). The terminology dysfunction identifies this process as a phenomenon in which organ function is not capable of maintaining homeostasis. This process, which may be absolute or relative, can be more readily identified as a continuum of change over time.

**ORGAN DYSFUNCTION CRITERIA**

**Cardiovascular dysfunction**

Despite administration of isotonic intravenous fluid bolus _40 mL/kg in 1 hr_

- Decrease in BP (hypotension) < 5th percentile for age or systolic BP < 2 SD below normal for age OR
- Need for vasoactive drug to maintain BP in normal range (dopamine >5 mcg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose) OR
- Two of the following
Fluid refractory - dopamine/dobutamine resistant shock

- Catecholamine-resistant shock

 fluids refractory shock

 Fluid responsive*

 Establish central venous access, begin dopamine or dobutamine therapy and establish arterial monitoring

 Fluid refractory - dopamine/dobutamine resistant shock

 Titrates epinephrine for cold shock, norepinephrine for warm shock to normal MAP-CVP difference for age and SVCO₂ saturation >70%

 At risk of adrenal insufficiency? Not at Risk?

 Normal Blood Pressure Cold Shock
 AVCO₂ Sat < 70%
 Add vasodilator or type III PDE inhibitor with volume loading

 Low Blood Pressure Cold Shock
 SVCO₂ Sat < 70%
 Titrate volume resuscitation and epinephrine

 Low Blood Pressure Warm Shock
 SVCO₂ Sat ≥ 70%
 Titrate volume and norepinephrine

 Persistent Catecholamine-resistant shock

 Start cardiac output measurement and direct fluid, inotrope, vasopressor, vasodilator, and hormonal therapies to attain normal MAP-CAP and CI > 3.3 and < 6.0 L/min/m²

 Refractory shock

 Consider ECMO

 Fig. 1. Sepsis and cardiovascular organ dysfunction
Emergency management

Management of child with septic shock is best started by aggressive goal-directed management in the emergency department.

The treatment of septic shock in children is aimed at optimizing perfusion of critical vascular beds and preventing or correcting metabolic abnormalities arising owing to cellular hypoperfusion. The ultimate goals are to prevent or reverse the defects in cellular substrate delivery and metabolism and to support the patient until homeostasis is restored.

For all forms of shock, treating the underlying cause is mandatory and speed is essential. Delays in making the diagnosis and initiating treatment (fluid resuscitation as well as appropriate antibiotics), as well as suboptimal resuscitation, contribute to the developments of peripheral vascular failure and irreversible defects in oxygen use, which can culminate in vital organ dysfunction.

Priorities of Treatment

Two major priorities in treatment of septic shock are given below:

(i) Rapid assessment of patient’s disease process.
(ii) Achievement of cardiopulmonary stability.

VIP approach can be used in initial treatment of shock, in which “V” stands for ventilation, “I” for infusion, and “P” for pumping or cardiovascular support.

Initial resuscitation of a child in shock involves assessment of airway, administration of oxygen, and establishment of intravenous access.

Need for early intubation and ventilation

Owing to low functional residual capacity, young infants and neonates with severe sepsis may require early intubation [10]. Unfortunately, no objective clinical criteria specific to pediatric septic shock for timing of endotracheal intubation (other than the standard indications, which include shock) exist in literature. Therefore, it is reasonable to consider endotracheal intubation when shock is persistent even after a volume resuscitation of more than 40-60 mL/kg. Children with sepsis requiring aggressive fluid resuscitation frequently have worsening tachypnea and increasing oxygen requirement, clinically depicting early ARDS. These patients will require early intubation and mechanical ventilation.

Unexplained metabolic acidosis: base deficit >5.0 mEq/L
Increased arterial lactate >2 times upper limit of normal
Oliguria: Urine output <0.5 mL/kg/hr
Prolonged capillary refill: >5 secs
Core to peripheral temperature gap <3°C

Respiratory

- \( \text{PaO}_2 / \text{FiO}_2 < 300 \) in absence of cyanotic heart disease or preexisting lung disease
- \( \text{PaCO}_2 > 65 \) torr or 20 mm Hg over baseline \( \text{PaCO}_2 \)
- Proven need or >50% \( \text{FiO}_2 \) to maintain saturation >92%
- Need for nonelective invasive or noninvasive mechanical ventilation.

Neurologic

- Glasgow Coma Score <11 (57)
- Acute change in mental status with a decrease in Glasgow Coma Score >3 points from abnormal baseline

Hematologic

- Platelet count <80,000/mm³ or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients)
- International normalized ratio >2.

Renal

- Serum creatinine >2 times upper limit of normal for age or 2-fold increase in baseline creatinine.

Hepatic

- Total bilirubin >4 mg/dL (not applicable for newborn)
- ALT 2 times upper limit of normal for age.
ventilation. The principles of lung-protective strategies (low tidal volumes and permissive hypercapnea) are applied to children as they are to adults. In premature infants, additional attention is paid to avoiding hyperoxemia to prevent retinopathy.

Fluid resuscitation

Intravenous access for fluid resuscitation and inotrope/vasopressor infusion is more difficult to attain in children than in adults. The American Heart Association has well-established pediatric advanced life support guidelines for emergency establishment of intravascular support, including intraosseous access [11]. On the basis of many studies, it is accepted that aggressive fluid resuscitation with crystalloids or colloids is of fundamental importance to survival of septic shock in children [12-13]. There is only one randomized, controlled trial comparing the use of colloid with crystalloid resuscitation (dextran, gelatin, lactated Ringers or saline) in children with dengue shock [12]. All these children survived, regardless of the fluid used, but the longest time to recovery from shock occurred in children who received lactated Ringers. Among patients with the narrowest pulse pressure, there was a suggestion that colloids were more effective than crystalloids in restoring normal pulse pressure. Fluid infusion is best initiated with boluses of 20 mL/kg over 5-10 min and titrated to clinical monitors of cardiac output, including heart rate, urine output, capillary refill, and level of consciousness. A 60 mL syringe filled with fluid drawn via the fluid bag with a three-way connection can be conveniently used to push fluid boluses in the absence of a volumetric pump.

Children normally have a lower blood pressure than adults and can prevent reduction in blood pressure by vasoconstriction and increasing heart rate. Therefore, blood pressure by itself is not a reliable endpoint for assessing the adequacy of resuscitation. However, once hypotension occurs, cardiovascular collapse may soon follow.

Hepatomegaly occurs in children who are fluid-overloaded and can be a helpful sign of the adequacy of fluid resuscitation. Other practical ways to assess fluid overload are jugular venous distension, heart size, and pulmonary congestion on chest X-ray. Gold standard still remains the measurement of a central venous pressure.

Large fluid deficits typically exist, and initial volume resuscitation usually requires 40-60 mL/kg but can be much higher [13-15]. As a word of caution in neonates, the use of aggressive fluid therapy may be limited by patency of ductus arteriosus, risk of intraventricular hemorrhage, and right heart failure owing to pulmonary hypertension.

Vasopressors / Inotropes

These should only be used after appropriate volume resuscitation. Children with severe sepsis can present with low cardiac output and high systemic vascular resistance (cold shock, more common scenario), high cardiac output and low systemic vascular resistance, or low cardiac output and low systemic vascular resistance shock. Early inotropic support should be started in the case of fluid-refractory shock or a life-threatening hypotension when fluid bolus has been initiated. Dopamine is the first choice of support for the pediatric patient with hypotension refractory to fluid resuscitation. The choice of vasoactive agent is determined by the clinical examination. Dopamine-refractory shock may reverse with epinephrine (adrenaline) or norepinephrine (noradrenaline) infusion [15]. Pediatric patients with low cardiac output states may benefit from use of dobutamine. The use of vasodilators can reverse shock in pediatric patients who remain hemodynamically unstable with a high systemic vascular resistance state, despite fluid resuscitation and implementation of inotropic support [15-16]. Nitrosovasodilators with a very short half-life (nitroprusside or nitroglycerin) are used as first-line therapy for children with epinephrine-resistant low cardiac output and elevated systemic vascular-resistance shock. Inhaled nitric oxide reduced extracorporeal membrane oxygenation use when given to the term neonates with persistent pulmonary artery hypertension of the newborn and sepsis in a randomized, controlled trial [17]. When pediatric patients remain in a normotensive, low-cardiac-output, and high-vascular-resistance state, despite epinephrine and nitroso-vasodilator therapy, the use of a phosphodiesterase inhibitor should be strongly considered, such as milrinone [18-20]. Vasopressin therapy should be considered in warm shock unresponsive to fluid and norepinephrine.

Early antibiotics

After appropriate cultures are taken, the early use of a broad-spectrum systemic antimicrobial therapy based on clinical suspicion is reasonable, although no randomized studies exist in children. Adult data support the use of early appropriate antibiotics to impact favorably on morbidity from septic shock.
**Therapeutic end points**

Therapeutic endpoints are capillary refill of less than 2s, normal pulses with no differential between peripheral and central pulses, warm limbs, urine output of more than 1 mL/kg/h, normal mental status, decreased lactate, and increased base deficit and superior vena cava or mixed venous oxygen saturation of more than 70%. When employing measurements to assist in identifying acceptable cardiac output in children with systemic arterial hypoxemia such as cyanotic congenital heart disease or severe pulmonary disease, the arterial-venous oxygen content difference is a better marker than mixed venous hemoglobin saturation with oxygen. Optimizing preload optimizes cardiac index. As noted above, blood pressure by itself is not a reliable endpoint for resuscitation. Rarely, if a pulmonary artery catheter is utilized, therapeutic endpoints are cardiac index of more than 3.3 and less than 6.0 1/m/m² with normal perfusion pressure (mean arterial pressure minus central venous pressure) for age. Use of pulmonary artery catheter has declined over the years owing to no well-demonstrated therapeutic benefit in patients with septic shock.

**Electrolyte balance**

An attempt should be made to check and correct common electrolyte problems related to sodium (hyponatremia), potassium, and ionized calcium (ionized hypocalcemia).

**Steroids**

Hydrocortisone therapy should be reserved for use in children with catecholamine resistance and suspected or proven adrenal insufficiency. Patients at risk include children with severe septic shock and purpura [21-22], children who have previously received steroid therapies for chronic illness, and children with pituitary or adrenal abnormalities. There are no strict definitions, but adrenal insufficiency in the case of catecholamine-resistant septic shock is assumed at a random total cortisol level of less than 18 mg/dL (496 nM / l). There is no clear consensus for the role of steroids or best dose of steroids in children with septic shock. A post-30-min or –60-min adrenocorticotropic hormone stimulation test increase in cortisol of <9 mg/dL (248 nM / l) also makes that diagnosis. There are two randomized, controlled trials that used shock dose hydrocortisone (25 times higher than the stress dose) in children, both in dengue fever. The results were conflicting. Dose recommendations vary from 1 to 2 mg/kg for stress coverage (based on clinical diagnosis of adrenal insufficiency) to 50 mg/kg for empirical therapy of shock followed by the same dose as a 24 h infusion. Thus, the dose of steroids remains controversial.

**Protein C and activated protein C**

Protein C concentrations in children reach adult values at the age of 3 yrs. This might indicate that the importance of protein C supplementation either as protein C concentrate or as rhAPC is even greater in young children than in adults. There has been one dose finding, placebo-controlled study performed using protein C concentrate. This study was not powered to show an effect on mortality rate but did show a positive effect on sepsis-induced coagulation disturbances [23,24]. No randomized studies using rhAPC have been performed.

**Granulocyte macrophage colony stimulating factor**

Growth factors or white blood cell transfusions are given to patients with neutropenic sepsis secondary to chemotherapy or white blood cell primary immune deficiency. A randomized, controlled trial showed improved outcomes in neonates with sepsis and an absolute neutrophil count <1500/microL treated with a 7-day course of granulocyte macrophage colony stimulating factor [25,26].

**DVT prophylaxis**

Most DVTs in young children are associated with central venous catheters. Femoral venous catheters are commonly used in children, and central venous catheter-associated DVT occurs in approximately 25% of children with a femoral central venous catheter. There are no data on use of heparin prophylaxis to prevent DVT in children.

**Stress ulcer prophylaxis**

No studies have been performed in children analyzing the effect of stress ulcer prophylaxis. Studies have shown that the rate of clinically important gastrointestinal bleeding in children occurs at rates similar to adults [27,28]. As in adults, coagulopathy and mechanical ventilation are risk factors for clinically important gastrointestinal bleeding. Stress ulcer prophylaxis strategy is commonly used in mechanically ventilated children, usually with H₂ blockers. Its effect is not known.
Renal replacement therapy

Continuous venovenous hemofiltration may be clinically useful in children with anuria/severe oliguria and fluid overload, but no large RCTs have been performed.

Glycemic control

In general, infants are at risk for developing hypoglycemia when they depend on intravenous fluids. This means that a glucose intake of 4-6 mg/kg/min or maintenance fluid intake with glucose 10% in NaCl 0.45% is advised. There are no studies in pediatric patients analyzing the effect of rigid glycemic control using insulin. This should only be done with frequent glucose monitoring in view of the risks for hypoglycemia.

Sedation / Analgesia

Appropriate sedation and analgesia for children who are mechanically ventilated are the standard of care, although there are no data supporting any particular drugs or drug regimens.

Intravenous immunoglobulin

Polyclonal intravenous immunoglobulin has been reported to reduce mortality rate and is a promising adjuvant in the treatment of sepsis and septic shock. In children, however, all the trials have been small, and the totality of the evidence is insufficient to support a robust conclusion of benefit. Adjunctive therapy with monoclonal intravenous immunoglobulins remains experimental [29].

ECMO

ECMO has been used in septic shock in children, but its impact is not clear.

Survival from refractory shock or respiratory failure associated with sepsis is 80% in neonates and 50% in children. There is one study analyzing 12 patients with meningococcal sepsis on ECMO; eight of the 12 patients survived, with six leading functionally normal lives at a median of 1 yr (range, 4 months to 4 yrs) of follow-up. Children with sepsis on ECMO do not perform worse than children without sepsis at long-term follow-up [30-32].

CONCLUSIONS

Pediatric recommendations for management of severe sepsis in children include a more likely need for endotracheal intubation and mechanical ventilation owing to low functional residual capacity. Infants and children are recognized to have more difficult intravenous access, therefore necessitating the use of intraosseous access, as required. Early fluid resuscitation based on weight with 40-60 mL/kg or higher may be needed.

Decreased cardiac output and increased systemic vascular resistance tends to be the most common hemodynamic profile. Dopamine is recommended as the initial agent for hemodynamic support. Pediatric recommendations include greater use of physical examination therapeutic endpoints.

The issue of high-dose steroids for therapy of septic shock remains unsettled, although recommendation include use of steroids for catecholamine-unresponsive shock in presence of a suspected or proven adrenal insufficiency.

There is greater risk of hypoglycemia with aggressive glucose control.

REFERENCES


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