Mendez D and Lapus R, J Emerg Med Trauma Surg Care 2015, 2: 010
DOI: 10.24966/ETS-8798/100010

HSOA Journal of
Emergency Medicine Trauma and Surgical Care

Research Article

Sepsis in Children

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Abstract

Background: Sepsis in children still accounts for a substantial morbidity and mortality despite the advances in treatment. Rapidly recognizing a child with SIRS or sepsis is key to having favorable outcomes. The purpose of this review is to provide the most current recommendations for evaluation and treatment including differences in the American College of Critical Care Medicine (ACCM) and Pediatric Advanced Life Support (PALS) sepsis guidelines.

Methods: The literature is from a range of sources that was reviewed and synthesized to provide an overview of the most current methods for evaluation and treatment of sepsis in children.

Results: This review summarizes the definitions, clinical manifestations, evaluation and treatment of sepsis in children. Inclusion of the most recent biomarkers of sepsis are included and reviewed.

Introduction

Systemic Inflammatory Response (SIRS) and Sepsis are important to recognize early and treat aggressively since without treatment it can lead to increased morbidity and mortality. Even though pediatric mortality has decreased with the advent of antibiotics and better management, the mortality is still 4-10 percent in pediatric patients with severe sepsis [1-3] and 13 to 34 percent in pediatric patients with septic shock [1-8].

It is important to rapidly recognize SIRS and sepsis early to have favorable outcomes in children. Early recognition and treatment with the American Critical Care Medicine (ACCM)-PALS guidelines has improved outcomes in children. In a study by Han and colleague, they showed a 92% survival versus 62% survival among patients who did not receive ACCM-PALS guidelines [8]. In a prospective study of 91 infants and children presenting to community hospitals with septic shock, each hour delay in initiation of appropriate resuscitation or persistence of hemodynamic abnormalities was associated with a clinically significant increased risk of death [8]. In a trial of goal-directed therapy in 102 children with severe sepsis or fluid-refractory septic shock treated in two pediatric intensive care units, 28-day mortality was lower in patients who received goal-directed therapy versus therapy guided by blood pressure (12 versus 39 percent) [9]. In another study, the implementation of timely goal directed interventions by a mobile intensive care team compatible with the ACCM 2002 guidelines for 331 children with meningococcemia in the United Kingdom was associated with a decrease in the case fatality rate from 23 to 2 percent over five years (annual reduction in the odds of death 0.41, 95% CI: 0.27-0.62) [10].

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Citation: Mendez D, Lapus R (2015) Sepsis in Children. J Emerg Med Trauma Surg Care 2: 010.

Received: March 15, 2015; **Accepted:** August 17, 2015; **Published:** August 31, 2015

Date Collection

We collected all the articles that were published from January 1997 to January 2015, which described children with SIRS or sepsis. These articles were obtained by searching PUBMED using key words "sepsis", "pediatric sepsis", "SIRS", "pediatric SIRS" "CRP and sepsis", "Procalcitonin and sepsis", "CRP and sepsis", and "Lactate and sepsis." Retrospective and prospective studies were included. We excluded studies which did not include children. Opinion articles were also excluded from this review. After selecting the articles, the relevant information was extracted and classified according to evaluation and treatment. After screening the articles, a total of 60 articles were considered to be relevant.

Definitions

As stated before the early recognition of SIRS and sepsis is key to a favorable outcome. In order to identify SIRS and sepsis their definitions will be reviewed. These definitions have been developed by the International Consensus Conference on Pediatric Sepsis (Systemic Inflammatory Response Syndrome-SIRS). SIRS is a widespread inflammatory response that may or may not be associated with infection. Two or more of following criteria (one which needs to be abnormal temp or leukocyte count) indicate SIRS (Table 1).

- Core temp of >38.5˚C (100.4˚F) or <36˚C (96.8˚F)
- Tachycardia (mean HR more than 2 SD above normal for age), or for children younger than 1 year, bradycardia (mean HR <10th percentile for age).
- Mean RR more than 2 SD above normal for a age or mechanical ventilation for acute pulmonary process.
- Leukocyte count elevated or depressed for age or >10 % immature neutrophils.

Sepsis is defined as SIRS in the presence of suspected or proven infection. Severe sepsis is sepsis with cardiovascular dysfunction, Acute Respiratory Distress Syndrome (ARDS), or dysfunction in 2 or more other organ systems [11]. Septic shock is sepsis with cardiovascular dysfunction that persists despite the administration of ≥40cc/kg of isotonic fluid in 1 hour. Refractory septic shock can be divided into fluid refractory and catecholamine resistant. Fluid-refractory shock is when cardiovascular dysfunction persists despite at least 60cc/kg of fluids. Catecholamine-resistant shock is when shock persists despite therapy with dopamine >10mcg/kg/min and/or direct-acting catecholamines (epinephrine, norepinephrine).

Pediatric Systemic Inflammatory Response Syndrome Criteria					
Age Group	Heart Rate (beats/min)		Respiratory Rate (beats/min)	Leukocyte Count (Leukocytes X 10^3/mm^3)	Systollic Blood Pressure (mmHg)
	Tachycardia	Bradycardia			
Newborn (0 days to 1 week)	>180	<100	>50	>34	<59
Neonate (1 week to 1 month)	>180	<100	>40	>19.5 or <5	<79
Infant (1 month to 1 year)	>180	<90	>34	>17.5 or <5	<75
Toddler and preschool (>1 to 5 years)	>140	NA	>22	>15.5 or <6	<74
School age (<5 to 12 years)	>130	NA	>18	>13.5 or <4.5	<83
Adolescent (>12 to <18 years)	>110	NA	>14	>11 or <4.5	<90

Table 1: Demonstrates the SIRS criteria according to age [11].

NA: Not Applicable

Multiple organ failure is useful for tracking clinical changes and response to treatment in children with septic shock. The International Consensus on Pediatric Sepsis developed criteria for organ dysfunction [11].

Cardiovascular

Hypotension or reliance on a vasoactive drug to maintain blood pressure, or two of the following: metabolic acidosis, elevated arterial lactate, oliguria, or prolonged capillary refill.

Respiratory

Arterial oxygen tension/fraction of inspired oxygen (PaO_2/FiO_2) <300, arterial carbon dioxide tension ($PaCO_2$) >65 torr or 20mmHg over baseline $PaCO_2$, need for >50 percent FiO_2 to maintain oxygen saturation ≥92 percent, or need for nonelective mechanical ventilation.

Neurologic

Glasgow coma score ≤11 or acute change in mental status.

Hematologic

Platelet count <80,000/microL or a decline of 50 percent from highest value recorded over the past three days or Disseminated Intravascular Coagulation (DIC), a consumptive coagulopathy diagnosed by clinical findings of hemorrhage and microthrombi and laboratory abnormalities including thrombocytopenia, prolongation of clotting times (PT and aPTT), and evidence of fibrinolysis (low fibrinogen with elevated fibrin degradation products), which is a common hematologic manifestation in sepsis.

Renal

Serum creatinine ≥2 times upper limit of normal for age or twofold increase in baseline creatinine.

Hepatic

Total bilirubin ≥4mg/dL (not applicable to newborn) or Alanine Aminotransferase (ALT) >2 times upper limit of normal for age.

Clinical Diagnostics of Septic Shock

Vital signs

Children with septic shock have alterations in their vital signs. Tachycardia is a sensitive, though non-specific indicator in early stages of shock. Hypotension is a late sign. Tachypnea, bradypnea, or apnea are other signs of septic shock. Fever or hypothermia (especially in infants) are also signs of shock. Fever effects heart rate by increasing heart rate as fever becomes elevated. This rise in heart rate can be adjusted for fever. For each 1 degree F above 100 F, the correction was 5 beats per minute or 9.6-10 beats per minute for each 1 degree C [12,13] (Table 2).

Temperature (F)	0-1 year old	2-5 year old	6-12 year old	≥12 year old
<100	180	140	130	110
101	185	145	135	115
102	190	159	140	120
103	195	155	145	125
104	200	160	150	130
105	205	165	155	135
106	210	165	155	140

Table 2: Heart rate corrected for temperature [12].

Other physical findings

Other physical findings of shock include: Ill appearance, prolonged capillary refill (>3 sec), diminished peripheral pulses, mottled extremities and altered mental status (irritability, anxiety, confusion, lethargy, and somnolence).

Presentation of shock in children versus adults

Early in shock, children have circulatory compromise which is exhibited by tachycardia and subtle alteration in mental status. When stroke volume is decreased because of hypovolemia or reduced cardiac function, tachycardia is the compensatory mechanism used to maintain cardiac output (cardiac output = heart rate X stroke volume). The ability of children to compensate with tachycardia is less than in adults. Adults can easily double their heart rate but children cannot. This tachycardia in children may compromise cardiac output because of inadequate ventricular filing time. Because of this "limited cardiac reserve," as cardiocirculatory compromise progresses, children vasoconstrict their peripheral tissue microvascular beds in attempt to maintain cardiac preload and perfusion pressure to central organs. If circulatory insufficiency progresses, hypotension occurs, circulatory collapse, circulatory failure and eventual cardiac arrest.

Types of shock and clinical findings

Distributive shock which is also called warm shock is characterized by hyperdynamic physiology with decreased systemic vascular resistance and elevated cardiac output. The physical findings for warm shock are: flash capillary refill (<1 second), bounding pulses, warm dry extremities, and wide pulse pressure (typically greater than 40 mmHg in older children and adults).

Cold shock is characterized by an increased systemic vascular resistance and decreased cardiac output. The physical findings are: delayed capillary refill (>2 seconds), diminished pulses and mottled or cool extremities.

Etiology

Bacteria and viruses are the most frequent cause of sepsis.

Bacteria

In table 3, the most common bacteria by age group is listed. Also listed are the recommended antibiotic coverage for each bacterium.

Viruses

Viral pathogens can present with the same symptoms as bacterial sepsis. The following viral etiologies are:

- Respiratory (RSV, influenza, parainfluenza, adenovirus, metapneumovirus)
- H1N1
- EBV, CMV
- Herpes simplex, enterovirus.

Fungi

Fungal infections more common in children with the following risk factors:

- Malignancy
- Indwelling vascular catheters
- Prolonged neutropenia (>4 days) [14]
- Other - Parasitic or Rickettsial

Culture negative sepsis

Between 30-75% of children with sepsis have no infectious etiology identified [5,15,16]. Culture negative sepsis may indicate host response to bacterial components, such as endotoxin, or prior antibiotic treatment. It may be due to insensitive detection with a blood culture. New Polymerase Chain Reactant (PCR) testing may improve detection of the organism [17,18].

Evaluation

Clinical evaluation

As the definition of SIRS and sepsis include the vital signs parameters, this emphasizes how important the clinical evaluation is. Evaluating the patient for prolonged capillary refill, diminished peripheral pulses, change in mental status and mottled extremities is vital prior to using laboratory studies as a guide in defining SIRS and sepsis.

Laboratory Studies

- Rapid glucose-Hypoglycemia is associated with sepsis in children. Children have less glycogen stores than adults so they become hypoglycemia more frequently those adults with sepsis. Hypoglycemia is defined as < 60 mg/dl in children, < 45 mg/dl in neonates. Treat hypoglycemia with 2.5-5mL/kg of 10% Dextrose solution (D10W) for infants to children up to 12 years, and 1-2mL/kg of 25 percent Dextrose (D25W) in adolescents.
- Arterial Blood Gas (ABG) or Venous Blood Gas (VBG)-Children with sepsis frequently have acidosis from poor tissue perfusion.
- Complete Blood Count (CBC)-Sepsis in children frequently is associated with leukocytosis or leukopenia.
- Blood lactate -Elevation of blood lactate (arterial >3.5mmol/L or venous >4.0mmol/L) is associated with sepsis.
- Serum Electrolytes-Electrolyte abnormalities (eg: Hyponatremia, hyperkalemia, hypokalemia, and hypophosphatemia) may be associated with sepsis through syndrome of inappropriate secretion of antidiuretic hormone and capillary leak.
- Serum calcium-Ionized calcium <1.1mml/L, or nonionized (4.8mg/dL) may affect myocardial function & vascular tone. Treat with calcium gluconate 10% at dose of 50-100mg/kg up to 2g slowly by IV or IO (don't give with bicarbonate). Treat hypocalcemia with calcium chloride 10% in dose of 10-20mg/kg up to 1g in central line or IO. Infants under 12 months may rely on extracellular calcium to maintain cardiac contractility. Animal models suggest improvement, but no human studies do, so it is recommended only to treat if hypocalcemia.
- Serum creatinine-Renal insufficiency suggested by a serum creatinine >2 times upper limit of normal for age or twofold increase in baseline creatinine is support the diagnosis of septic shock.
- Alanine Serum total bilirubin and Alanine aminotransferase- A total bilirubin ≥4mg/dL, (not in newborn) or Alanine aminotransferase (ALT) >2 time upper limit of normal for age indicates liver dysfunction in sepsis.
- Prothrombin Time (PT) Partial Thromboplastin Time (aPTT), and International Normalized Ratio (INR)-An elevation of PT and aPTT or INR suggests Disseminated Intravascular Coagulopathy (DIC).
- Fibrinogen & D-Dimer-Decreased fibrinogen and increased D-Dimer support DIC
- Cultures- blood, urine, CSF, wound

Biomarkers

Distinguishing SIRS from sepsis can be confusing because there are a number of noninfectious conditions that present like SIRS, such as burns, trauma, pancreatitis, and autoimmune disorders. It is important to make the distinction between SIRS and sepsis because it would dictate whether antibiotics would be administered and the duration of antibiotic therapy. Diagnostic biomarkers establish the presence or absence of clinical conditions and in this case, sepsis, they would help in distinguishing SIRS from sepsis.

C-reactive protein CRP

Some of the first applications of CRP in pediatrics were related to identifying neonates with sepsis in whom clinical manifestations of severe illness were often nonspecific. CRP was also used in a variety of other clinical scenarios to distinguish infection from inflammation. CRP alone lacks the specificity to consistently discriminate between infection and non-infection [19] McCabe and Remington reported that CRP values did not differ significantly among patients with or without bacteremia [20]. Owing to its poor specificity, it is often used in combination with other biomarkers as part of a panel of tests to assist clinicians with diagnosis [21,22].

Age	Pathogen	Antibiotic Coverage	Adminster
≤28 days	*Staphylococcus aureus* Listeria Gram negative (especially *E Coli*) Group B *Streptococcus* Herpes simplex virus	Vancomycin Ampicillin & Gentamicin Gentamicin or Cefotaxime Ampicillin & Gentamicin Acyclovir with clinical signs	Ampicillin & Gentamicin Or Cefotaxime +/-Acyclovir
29 days- 3 mos	*Staphylococcus aureus* Gram negative (especially *E Coli*) Group B *Streptococcus* (rare)	Vancomycin Gent or Cefotaxime Zosyn for GI source Ampicillin & Gentamicin	Vancomycin & Ceftriaxone or Cefepime
>3 mos	*Streptococcus pneumonia* *Neisseria meningitidis*	Cefotaxime/Ceftriaxone & Vanc (meningitis) Cefotaxime/Ceftriaxone	Vancomycin Ceftriaxone or Cefepime
Febrile neutropenia	Gram positive (Coagulase-negative staphylococci, *Staphylococcus aureus*, *Streptococcus pneumonia*, viridans streptococci) Gram negative (*Pseudomonas aureus*, *E coli*, *Klebsiella*)	Vancomycin Cefepime or Ceftazidime	Vancomycin Cefepime or Ceftazidime
In hospital-acquired	Coagulase-negative staphylococci Gram negatives	Vancomycin Cefepime or Ceftazidime	Vancomycin Cefepime or Ceftazidime

Table 3: Bacterial etiology based on age.

Information from up to Date 2014, Septic Shock: Rapid recognition and initial resuscitation in children

CRP and Procalcitonin (PCT)

These inflammatory biomarkers are not recommended in routine testing [23,24]. CRP and procalcitonin have been helpful in certain cases. Procalcitonin and C-reactive protein have been shown to be useful in predicting serious bacterial infection in infants and young children who present to an emergency department with fever and no apparent source of infection [25,26]. In a study by Luaces-Cubells and colleagues, 868 children were studied. In this study, either PCT or CRP had a higher diagnostic reliability than WBC and Absolute Neutrophil Count (ANC). More importantly, in children with duration of fever <8 hours, PCT was the biomarker with the highest predictive value. CRP and PCT may also be useful in predicting bacterial infection in patients with fever and neutropenia [27,28].

Procalcitonin (PCT)

PCT elevation has been associated with sepsis. In a prospective study in children, procalcitonin's usefulness in distinguishing bacteria from viral infection in early and rapid diagnosis in neutropenic children with Acute Lymphoblastic Leukemia (ALL) was shown. The study included five groups (A, B, C, D and E) of children with ALL undergoing intensive chemotherapy. Groups A and B consisted of neutropenic children with bacterial and viral infection, respectively. Groups C and D consisted of non neutropenic children with bacterial and viral infection, respectively. Group E consisted of children without neutropenia and without fever. In all groups, blood samples were collected upon admission and then for 7 days on a daily basis. Levels of CRP, PCT, Tumor Necrosis Factor (TNF)-a, Interleukin (IL)-1b, IL-8, and sTNFRII were determined in all blood samples. They found a highly significant difference in PCT levels between bacterial and nonbacterial episodes. Sensitivity and specificity of PCT were 94 and 96.5%, respectively [27]. In a study by Samransamruajkit and colleagues, they investigated the prognostic value of initial plasma N-terminal (NT) pro- B-type Natriuretic Peptide (BNP) and procalcitonin in children. Infants and children (0-15 years with severe sepsis or septic shock) were prospectively enrolled and treated according to the ACCM guidelines. Initial blood drawn was saved for NT-pro-BNP, procalcitonin measurements and clinical data were also recorded. A total of 47 subjects were recruited. There was a significant difference between the initial NT-proBNP levels between survivors and non survivors, (6280.3 ± 9597ng/L, $P < 0.001$), but not for procalcitonin (12.7 ± 24.8, 29.3 ± 46μg/L, $P = 0.1$), respectively [29].

Soluble adhesion molecules

During sepsis it is postulated that aberrant leukocyte activation and recruitment into host tissues plays a role in causing breakdown of the vascular endothelium [30]. Inflammatory leukocyte recruitment is initiated by soluble mediators (for example, cytokines or bacteria-derived lipopolysaccharide) which upregulate adhesion molecule expression on both leukocytes and the endothelium. This upregulation results in a multistep adhesion cascade whereby circulating immune cells sequentially roll on, firmly adhere to, and transmigrate across the endothelium [31-33] during the progression of inflammatory responses, soluble isoforms of the leukocyte recruitment adhesion molecules are shed from cell surfaces and accumulate within the circulating blood plasma [34]. These soluble isoforms have been considered promising as biomarkers of sepsis. Five soluble adhesion molecules are associated with sepsis: E-selectin, L-selectin, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1. Briassoulis and colleagues showed significant increase of sE-selectin, as well as sL-selectin and ICAM-1, especially amongst survivors [35]. The authors concluded that inadequate or suppressed shedding during sepsis might be associated with increased mortality, and they hypothesize that the shedding process is indeed protective for the host. Similarly, in a large pediatric ICU study on microcirculatory dysfunction in meningococcal sepsis in children, levels of sE-selectin, sVCAM-1 and sICAM-1,but not sP-selectin, were significantly increased in septic patients but negatively correlated with the degree of microcirculatory dysfunction (a measure of sepsis severity), as assessed by sublingual imaging [36].

Interleukin 6 (IL-6)

Cytokines are diagnostic markers and their levels are increased early in the infectious process [37,38], Interleukins are pro-inflammatory cytokines predominantly produced by monocytes, activated macrophages and endothelial cells. IL-6 has been shown to be a sensitive marker in the early phase of infection but cannot be used as a reliable marker in the later stages of disease, due to its short half-life [37,39,40]. In a study by Hassan Boskabadi and colleagues they showed that the median serum level of IL-6 is higher in cases with sepsis in comparison with control healthy infants. IL-6 has also the highest sensitivity (89%) and negative predictive value (91%) at the onset of infection compared with other biochemical markers, including CRP, TNF, and E-selectin [41]. Maamouri and colleagues

reported a higher mean serum level of IL-6 in clinical sepsis compared with a control group (185 vs. 5Pg/ml) [42]. In a study by Krueger et al., infants were classified into documented infection, possible infection and healthy groups and mean serum IL-6 levels were found to be 1920, 50 and 8Pg/ml, respectively [43]. In another study by Romagnoli et al., higher serum IL-6 and 10 levels were associated with neonatal sepsis [44].

IL-6 has been shown to be a sensitive biomarker for predicting bacteremia/clinical sepsis in children with febrile neutropenia [45,46]. In severe sepsis, the best diagnostic accuracies were found for I-6 and procalcitonin and these were significantly higher than those for Lipopolysaccharide-Binding Protein (LBP) on admission [46].

Lactate

Blood lactate may help identify presence and severity of septic shock at presentation but evidence is limited in children. A study of 239 children younger than 19 years of age with SIRS who presented to a pediatric ED, investigated whether early hyperlactatemia (serum lactate 4.0mmol/L) would be associated with increased risk of organ dysfunction. The primary outcome was organ dysfunction within 24 hours of triage; secondary outcomes included disposition, Serious Bacterial Infection (SBI), treatments, and mortality. The hyperlactatemia group had a relative risk of 5.5 (95% Confidence Interval [CI] = 1.9 to 16.0) of developing 24-hour organ dysfunction. As a test for organ dysfunction, hyperlactatemia had a positive likelihood ratio of 5.0, a sensitivity of 31% (95% CI = 13% to 58%), and specificity of 94% (95% CI = 90% to 96%). Subjects with hyperlactatemia were significantly more likely to receive Intravenous (IV) antibiotics and fluid boluses; despite increased therapy, they were at significantly increased risk for Intensive Care Unit (ICU) admission and bacterial infection. They concluded among undifferentiated children with SIRS, early hyperlactatemia is significantly associated with increased risk of organ dysfunction, resuscitative therapies, and critical illness [47].

In another study by Duke and colleagues of children with sepsis syndrome or septic shock, blood lactate level was the earliest predictor of outcome in children with sepsis. The following data were recorded at admission, 12, 24 and 48 h: heart rate, mean arterial pressure, arterial pH, base deficit, arterial lactate, gastric intramucosal pH (pHi) and DCO (intramucosal carbon dioxide tension minus arterial partial pressure of carbon dioxide). The principal outcome measure was survival. The secondary outcome measure was the number of organ systems failing at 48 h after admission. There were 10 deaths and 21 survivors. No variable discriminated survival from death at presentation. Blood lactate level was the earliest discriminator of survival. Using univariate logistic regression, lactate discriminated survivors from those who died at 12 and 24 h after admission, but not at 48 h ($p = 0.049$, 0.044 and 0.062, respectively [48,49].

Management

Clinical management

Airway and breathing: Patients with septic shock should receive 100 percent supplemental oxygen to optimize blood oxygen content and delivery to tissues. Once adequate perfusion has been restored, supplemental oxygen should be titrated to avoid SpO_2>97 percent to prevent the adverse effects (eg: lung injury and oxygen and microcirculatory vasoconstriction) associated with hyperoxia and free radical generation [32].

Endotracheal intubation with Rapid Sequence Intubation (RSI) is often necessary in children with septic shock to protect the airway, assist with ventilation and/or promote oxygenation. Endotracheal intubation and sedation reduces the work of breathing which will retain cardiac output to other organs than the muscles of respiration. As per the updated CCM guidelines in 2007, high-flow heated and humidified oxygen is recommended by nasal cannula until intubation is done [18].

The decision to intubate and ventilate should be based on clinical assessment of increased work of breathing, hypoventilation or impaired mental status. Waiting for confirmatory laboratory tests is discouraged since 40% of cardiac output is used for work of breathing and delay of intubation could be deleterious [18].

Overview of RSI:

- Preoxygenate: Preoxygenate with 100% for 2-5 minutes. Also preoxygenate with high flow oxygen 15L/min with Nasal Cannula (NC). Preoxygenation is essential due to a child's intolerance for apnea. A high-flow NC (15L in adolescents, up to 8L in toddlers) can be used for preoxygenation in addition to the face mask and while intubating. It has been shown to decrease apnea and desaturations during RSI [50,51].
- Preparation of equipment and medications
- Pretreatment: Atropine- All children <1 year, children <5 receiving succinylcholine and older children receiving a second dose of succinylcholine. Dose: 0.02mg/k IV (Minimum single dose 0.1mg, Maximum single dose child 0.5mg, Maximum singledose adolescent 1.0 mg; if no IV access, can be given IM).
- Sedation
  - Etomidate- Not recommended per the 2007 Clinical Guidelines for Hemodynamic Support of Neonates and Children with Septic Shock from American College of Critical Care Medicine.
  - Ketamine: Safe with hemodynamic instability if patient is not catecholamine depleted. Dose 1-2mg/kg IV (If no IV access, can be given IM at dose of 3-7mg/kg)
  - Midazolam- May cause hemodynamic instability at doses required for sedation. Dose: 0.2-0.3mg/kg IV (maximum dose 2mg, onset of effect requires 2-3 minutes).
  - Thioopental- Not recommended with hemodynamic instability. Dose: 3-5mg/kg iV.
- Paralytic
  - Succinycholine- Not recommended with chronic myopathy or denervating neuromuscular disease: 48-72 hours after burn, crush or denervating injury: malignant hyperthermia; or pre-existing hyperkalemia. Dose: infants and young children: 2mg/kg IV, older children: 1-1.5mg/kg IV. (If IV access unobtainable, can be given IM at dose of 3-5mg/kg)
  - Rocuronium- Has none of the adverse effects of succinylcholine, making it an ideal alternative. Dose: 1mg/kg.

Management of hemodynamic support: Goal-directed therapy for septic shock involves an aggressive systematic approach to resuscitation targeted to improve physiologic indicators of perfusion and vital organ function within the first six hours.

The first hour goals include restoring and maintaining normal heart rate, capillary refill <2 seconds, and normal blood pressure. Also this includes support of oxygenation and ventilation.

The following therapeutic endpoints should be targeted goals:

- Strong, distal pulses equal to central pulses
- Capillary refill <2 seconds
- Normal mental status
- Urine output (>1mL/kg/hour, up to 40mL per hour).
- Blood pressure in children 1 month to 10 years (systolic pressure at least fifth percentile for age: 60 mmHg<1month of age, 70 mmHg + (2 x age in years). Blood pressure in children 10 years of age or older (90 mmHg)
- Lactate (<4mmol/L or ≥10 percent decrease per hour until normal)
- Central venous oxygen saturation (ScvO2), (≥70 percent)

Treatment Guidelines

There are 2 guidelines for goal directed treatment for sepsis in children.

The 2007 American College of Critical Care Medicine (ACCM) guidelines

The ACCM guidelines emphasize early goal-directed therapy (Figure 1). The guidelines recommend: 1) Recognition of sepsis in the first 5 minutes, begin oxygen and establish IV/IO; 2) Initial resuscitation with 20cc/kg boluses up to and over 60cc/kg until perfusion improves or unless rales or hepatomegaly develop within the first 15 minutes; 3) If the child is fluid refractory start low dose dopamine or epinephrine. If dopamine resistant start an epinephrine drip. One must monitor for peripheral infiltration/ischemia and reduce the dose if this occurs. Central dopamine, epinephrine or norepinephrine can be administered as a first line drug as indicated by hemodynamic state. For cold shock with normal blood pressure epinephrine is recommended. For cold shock with low blood pressure epinephrine is recommended. For warm shock with low blood pressure norepinephrine is recommended; 4) If patient is catecholamine resistant then hydrocortisone is recommended.

Using these ACCM guidelines has shown a reduction in mortality of severe sepsis in children [9,52,53]. In a trial of goal-directed therapy in 102 children with severe sepsis or fluid-refractory septic shock treated in two pediatric intensive care units, 28-day mortality was lower in patients who were treated by the ACCM guideline versus therapy guided by blood pressure (12 versus 39 percent, respectively) [9]. In a single centered center in Pittsburgh, patients treated according to ACCM guidelines found that every hour's delay in resuscitation in the emergency room was associated with a 40% increase in mortality in children with septic shock [8]. In another study, institution of the ACCM guidelines by a mobile intensive care team, in the care for 331 children with meningococcemia in the United Kingdom was associated with a decrease in the case fatality rate from 23 to 2 percent over five years (annual reduction in the odds of death 0.41, 95% CI: 0.27-0.62) [10].

Pediatric Advanced Life Support (PALS) guidelines for septic shock

The PALS guidelines are comparable to the American College of Critical Care Medicine guidelines but do not have as tight a time frame for optimal delivery of initial intravenous fluid boluses (Figure 2).

Implementation of the PALS septic shock guidelines has also shown a reduction in mortality and morbidity. In a retrospective study over a 4-year period from 5 regional pediatric centers' specialty care transport teams showed a significant decrease in morbidity and mortality. Four thousand eight hundred fifty-six patients ranging in age from newborn to 18 years of age were included. Use of the PALS guidelines resulted in a 2 fold reduction in mortality (5.06% vs 16.37%) and functional morbidity (1.56% vs 4.11%) [54].

Comparing the ACCM and PALS Guidelines

The 2007 American College of Critical Care Medicine (ACCM) guidelines and Pediatric Advanced Life Support are similar but the ACCM guidelines provide a tighter time frame of delivery of initial intravenous fluids boluses. The ACCM guidelines recommend fluid boluses within the first 15 minutes and PALS recommend fluid boluses within first 60 minutes. Literature has shown the quicker shock treatment is administered the better the morbidity and mortality in children with septic shock. Acting quickly and it's relation to morbidity was shown in a study by Han. Every hour's delay in resuscitation was associated with a 40% increase in mortality [8]. Other observational evidence from pediatric studies suggest that vigorous fluid resuscitation may play a major role in preventing end-organ damage and improve survival in sepsis [9,10,37]. In a recent quality improvement study, a reduction in severe sepsis mortality (4.0-2.4%) was shown with the delivery of fluid boluses and antibiotics in the first hour in a pediatric emergency department [55]. The improved morbidity and mortality associated with fluid boluses is due to it disrupting the normal progression of sepsis. The normal progression of patients in shock is for them to be initially tachycardic then as shock progresses; they become vasoconstricted (prolonged capillary refill of more than 3 seconds) and then eventually hypotensive. Mortality risks increase as the patient progresses through shock. Carcillo and colleagues examined over 5,000 children and found the mortality with tachycardia alone was 4.5% and increased to 33.7% when tachycardia was associated with hypotension and prolonged capillary refill. If shock treatment guidelines are initiated rapidly one can reverse this mortality. By treating with normal saline boluses early when the patient is tachycardic prevents their progression to tachycardia associated with hypotension and prolonged capillary refill. It makes sense that the ACCM guidelines would prove to be superior to the PALS guidelines since the ACCM guidelines recommend fluid boluses be administered in the first 15 minutes and the PALS guidelines recommend this within the first 60 minutes.

Pharmacological Treatment

Antibiotics

The recommended antibiotics are listed in the table under bacterial pathogens. Current guidelines recommend obtaining blood, urine and other cultures and administer empiric broad-spectrum antibiotics within one hour of presentation [56]. Antibiotic therapy should not be delayed beyond one hour and not delayed waiting for cultures to be obtained. Mortality increases for each hour that the patient does not receive appropriate antibiotics [57,58]. If IV access is limited, consider administration of cephalosporin prior to vancomycin, due to the former's shorter infusion time.

Corticosteroids

Patients who persist with shock in spite of rapid fluid administration and continuous infusions of epinephrine or

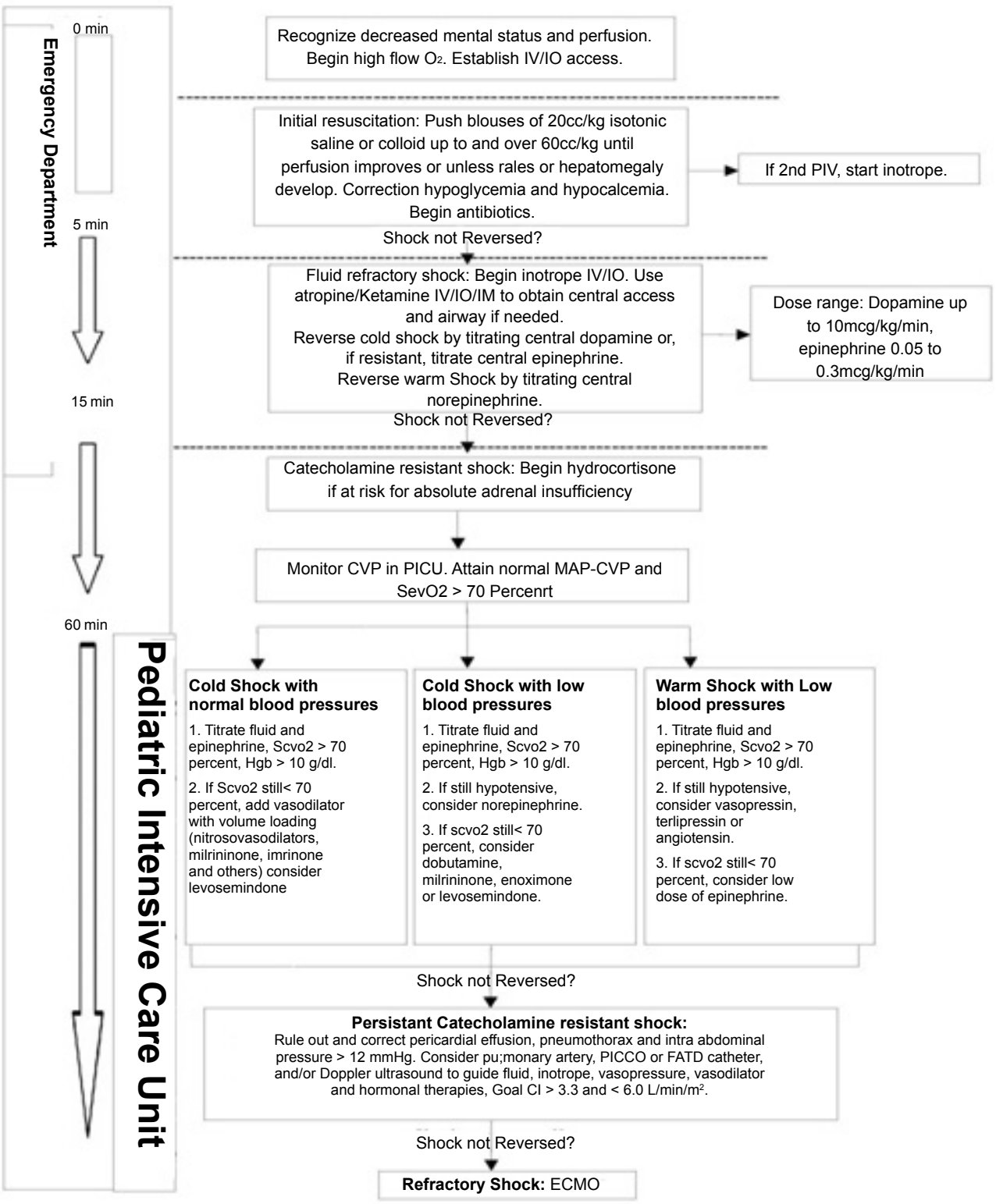

Figure 1: ACCM Guidelines.

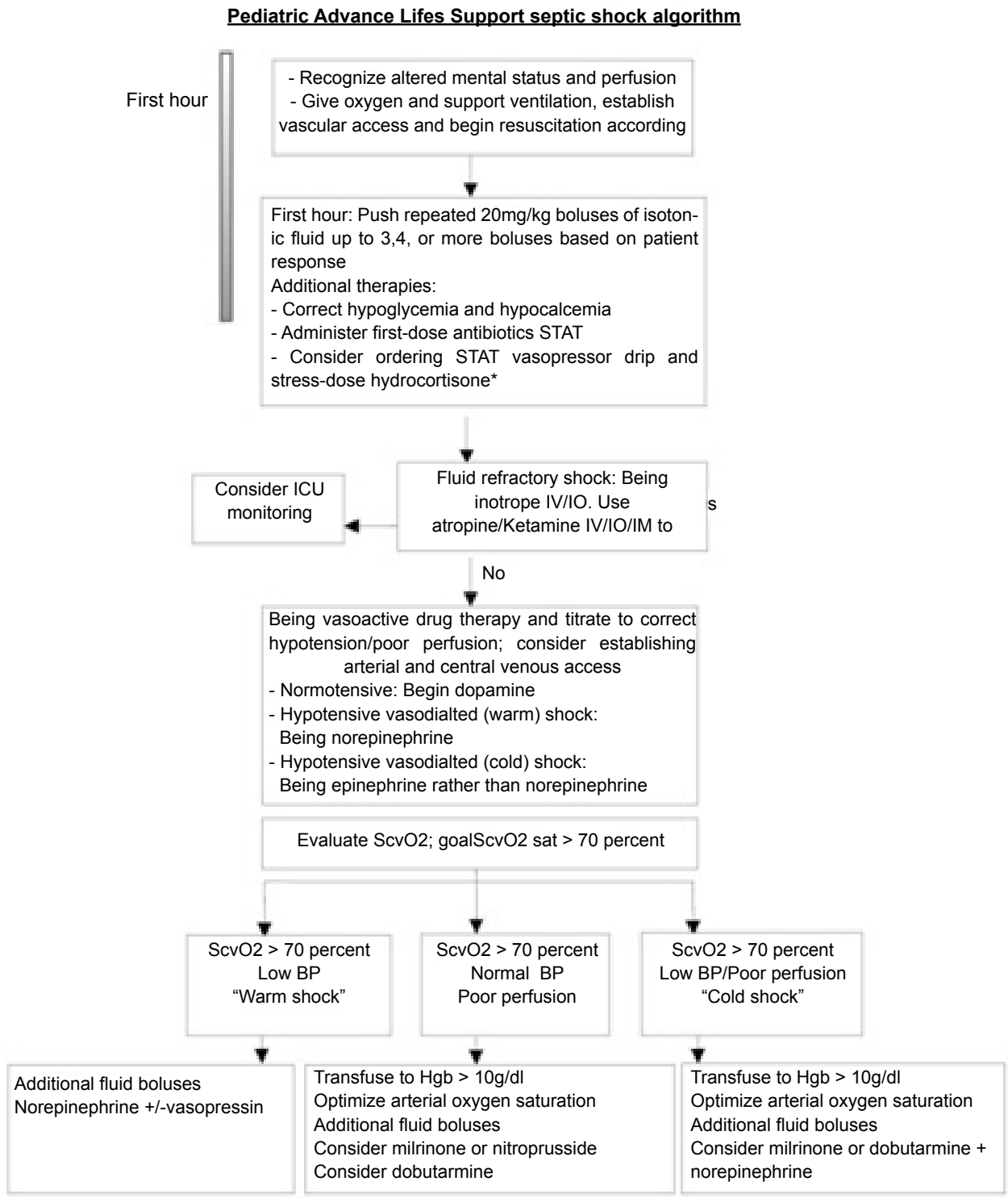

Figure 2: PALS Guidelines.

norepinephrine may have adrenal insufficiency. Risk factors include purpura fulminans, recent or chronic treatment with corticosteroids, hypothalamic or pituitary abnormalities, or adrenal insufficiency (congenital or acquired). When adrenal insufficiency is suspected, administration of hydrocortisone in stress doses (50mg/m^2/day or 2mg/kg per day, intermittent or continuous infusion, maximum dose 50mg/kg per day) is suggested [59]. Although evidence is lacking regarding the best method to identify adrenal insufficiency in children with refractory septic shock, assessment of adrenal status (either baseline serum cortisol or adrenocorticotropin hormone stimulation testing) is advised prior to corticosteroid administration.

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