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MANAGEMENT OF PEDIATRIC SEPTIC SHOCK IN THE EMERGENCY DEPARTMENT

September 2003

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The pathophysiology and response to therapy in septic shock are highly age dependent. Children are different from adults in a number of important ways including usual lack of myocardial disease, normal coronary arteries and greater diversity in their hemodynamic response to fluid resuscitation. Despite these differences much of how septic shock is managed in children is based on experience and research from adult populations. Few randomized controlled trials have been done in the pediatric population. This article explores the aspects of septic shock that are relevant to the initial emergency management of the septic child. The discussion of the management of the premature infant with sepsis is not covered in this article.

Epidemiology of Pediatric Septic Shock

The incidence of sepsis has increased across all age groups in the last two decades, however, the overall mortality of patients with sepsis has declined significantly in that time period.[1] Improvement in mortality for children has been particularly impressive, decreasing from 97% to 9%.[2,3] While advances in critical care technology are credited for this decrease, the increase in overall incidence is thought to be attributable to more common use of invasive procedures and immunosuppressive drugs as well as increased microbacterial resistance.[4] Better reporting and coding of sepsis has also been thought to contribute to the increase in overall incidence.[1]

There are a number of well known host-related risk factors for sepsis. They include extremes of age, a compromised immune system, malnourishment, asplenia, and chronic antibiotic or steroid use. Additionally, any insult (shock, trauma, burn) that makes the gastrointestinal tract permeable to gram negative bacteria puts individuals at risk for gram negative sepsis.

For many years, the most common causative organisms for sepsis in the United States were gram negative bacteria. However, in the year 2000, gram positive bacteria accounted for 52.1% of all cases of sepsis while gram negative bacteria accounted for 37.6%. Additional causes included multiple organisms (4.7%), fungi (4.6%), and anaerobes (1.0%).[1] During the 22 year time period from 1979 to 2000 gram positive infections increased an average of 26.3% per year and fungal infections increased a total of 207% during that time period.[1]

Diagnosis

The rapid recognition of septic shock is essential as early reversal of shock results in an improved outcome.[5] Sepsis is a clinical diagnosis and does not rely on the isolation of the causative infectious organism. Since signs of early septic shock may be subtle and the condition dynamic there is a danger of overlooking them in a busy emergency department. The patient may not always adhere to the classic stages of shock described in textbooks. The hallmark of septic shock is decreased perfusion. For children changes that occur **before** the onset of hypotension are the recognized clinical triad of hyper or hypothermia, altered mental status and peripheral vasodilation ("warm" shock) or vasoconstriction ("cool" shock). Any change in mental status (inconsolable, inability to recognize parents, unarousable) of a febrile child should prompt immediate consideration of septic shock. In warm shock there is evidence of decreased perfusion, including decreased mental status but bounding peripheral pulses and quick capillary refill. Patients with cold shock have diminished peripheral pulses and prolonged capillary refill.

Since septic shock is a clinical diagnosis, laboratory data are of limited utility in establishing the diagnosis. A positive body fluid culture is helpful but not required to establish the diagnosis of septic shock and clearly of little use in the emergency department. Identification

of the organism causing the shock is useful in narrowing antibiotic medication later in treatment. Cultures of blood or any other body fluid suspicious of being infected should be taken prior to antibiotics being given.

In recent years there has been an increased understanding of the pathophysiology of sepsis with identification of a number of different cytokines, and markers of inflammation such as C-reactive protein. Certain markers such as procalcitonin have been found to be even more sensitive for predicting severity of shock and poor outcome than traditional makers such as CRP or white cell count.[6] In recent years laboratory measurement of these markers has become a reality. Potential benefits of such testing include early recognition of shock, grading of severity of shock and prediction of mortality. Unfortunately, despite this theoretical attractiveness, they have not been found to be independent predictors of mortality and their usefulness as in the clinical management of sepsis has yet to be established.[7]

Initial Management

Other than antibiotics and/or surgery to definitively treat infection, therapy in septic shock is limited to supportive care. Evidence-based treatment guidelines for the hemodynamic support of pediatric and neonatal septic shock have been recently published by the American College of Critical Care Medicine.[8] The group that developed these guidelines acknowledges that there is little high grade evidence (randomized controlled trials, meta-analysis, etc) for the management of pediatric septic shock so that, in large part the guidelines are based on expert/consensus opinion.

As in all emergent resuscitation the initial ABC's should be addressed as per Pediatric Advanced Life Support (PALS) guidelines.[9] 100% Oxygen should be delivered to all patients and if necessary a definitive airway should be secured through endotracheal intubation. No evidence indicates the most appropriate timing of intubation but the decision to secure the airway should not depend on laboratory studies. Increased work of breathing, hypoventilation and altered mental status are indications for intubation. Venous access must be established as quickly as possible or an intraosseous failing venous access.

Early fluid resuscitation is widely accepted as the frontline treatment for septic shock. Therapeutic endpoints include objective measures such as urine output >1ml/kg/hr, normal mental status, normal blood pressure and pulse, and capillary refill < 2 seconds. Pediatric Advanced Life Support guidelines call for an initial intravenous bolus of 20ml/kg followed by reassessment and re-bolus to a total of 60ml/kg in the first hour of resuscitation.[9] Some patients require additional volumes of fluid with 100 to 200ml/kg total not unusual in the first few hours of resuscitation. During rapid fluid resuscitation constant monitoring of the patient for rales, hepatomegaly and increased work of breathing is required. Fluids should be isotonic but may include dextrose if hypoglycemia is documented. Studies document the effectiveness of rapid, high volume intravenous fluid resuscitation. In the 1980's Caricillo, et al. examined the association of fluid given with survival in pediatric septic shock and complications including ARDS, pulmonary edema and persistent hypovolemia. In this nonrandomized study of 34 patients with documented septic shock a positive association was found between volume of fluids given in the first hour and improved outcomes. Children who received more than 40ml/kg (mean 69ml/kg $\pm$ 19 ml/kg) of intravenous fluid in the first hour had greater survival and were far less likely to be persistently hypovolemic at six hours after presentation than children who

received less than 40 ml/kg. The higher volume group did not have greater risk of ARDS or cardiogenic pulmonary edema than those given a smaller volume of fluid in the first hour. [10]

Isotonic crystalloid solutions are most commonly the fluids of choice in initial volume restoration but debate on whether exclusive use of colloids improves outcomes exists. One randomized controlled trial compared colloids to crystalloids in children with dengue shock. There were no survival differences between the groups but longer time to recovery was documented in the group who received lactated ringers.[11] The Cochrane Collaboration found that, among different types of colloid solution there was no difference in clinical response of outcome.[12] If shock lasts more than one hour despite aggressive fluid resuscitation vasopressor support becomes mandatory.

Vasopressor Therapy

Typically, children with septic shock require vasopressor support during the initial stages of resuscitation. Recent guidelines have reiterated dopamine as the first line vasopressor for the treatment of fluid resistant septic shock.[8] The guidelines call for dosages from 5 to 10 μg/kg IV. It should be remembered that insensitivity to dopamine in very young children (< 6 months) has been documented.[13,14] This is thought to be due to the lack of development of the full component of sympathetic vesicles, upon which dopamine acts to release norepinephrine. Shock which is not responsive to dopamine will typically be responsive to norepinephrine (0.03-1.5 mcg/kg/min) or epinephrine (0.1-0.5 mcg/kg/min). [15-17] The consensus guidelines recommend epinephrine for cold shock and norepinephrine for warm shock. Other agents which may be considered once the patient is transferred to the pediatric intensive care include inotropes to increase cardiac contractility (dobutamine), other vasopressors (vasopressin, angiotensin), vasodilators to reduce

systemic and pulmonary vascular resistance (sodium nitroprusside) and Type III phosphodiesterase inhibitors which act as inotropes and vasodilators (milrinone).

Acid Base and Electrolyte Abnormalities

Hypoglycemia may develop rapidly in the septic child due to high glucose needs and low glycogen stores and can result in neurologic sequela if untreated. Serum glucose should be monitored and hypoglycemia promptly treated. Serum ionized calcium levels are frequently low (< 4.5 mEq/L) in children with septic shock which contributes to myocardial dysfunction.[18] Replacement therapy should be directed to normalize ionized calcium levels. Patients in septic shock usually have an anion gap acidosis from lactic acid. Previously sodium bicarbonate was commonly used to correct this acidosis, and it was argued that response to catecholamines was improved by correcting the acidosis in this manner. Evidence does not support this approach, however. A study by Cooper and others did not find that sodium bicarbonate improved the hemodynamics of acidotic septic patients nor did it improve responsiveness to catecholamines.[19]

Antibiotic Therapy.

Initially the selection of antibiotics is empiric and should be broad spectrum. A complete discussion of antibiotic selection in the child with septic shock is beyond the scope of this article but certain general principles can be recommended. Choice of specific antibiotic should be based on a consideration of 1) the suspected site of infection 2) the suspected organism. 3) whether infection was acquired in the community or a hospital setting and 4) host factors – eg: immune status. An additional consideration are the local antibiotic resistance patterns. Important to the

pediatric population is the increasing incidence of penicillin resistant streptococcus pneumonia.[20] Although it is optimal to obtain cultures prior to antibiotic administration, they should never be delayed secondary to need for cultures.

Steroids

It is thought that severe septic shock is associated with relative adrenal insufficiency or resistance to glucocorticoids.[21-23] The role of steroids in septic shock remains controversial and undefined. Randomized controlled trials in children are lacking and the results of studies in adults have been mixed. Two meta-analyses in adults found that steroids provided no benefit.[24.25] A recently published placebo controlled, randomized study concluded that a 7 day treatment with low doses of hydrocortisone and fludrocortisone significantly reduced the risk of death of adults with septic shock and relative adrenal insufficiency.[26] The two pediatric trials used "shock doses" of hydrocortisone in children with dengue fever.[27,28] Some authors recommend the measurement of serum cortisol and adrenocorticotropic hormone in children with septic shock and in those with low levels, low-dose hydrocortisone (25-50mg) followed by an infusion of 0.18mg/kg/hr.[29] In the emergency department usefulness of this approach is limited by the time it takes to determine the results of such laboratory studies. The American College of Critical Care Medicine recently published guidelines recommend that adrenal insufficiency should be clinically suspected in catecholamine-resistant hypotensive shock in children with a history of CNS abnormality, chronic steroid use or purpura fulminans and that hydrocortisone use should be reserved for these patients.[8] Dose recommendations in these guidelines are not specific and vary from a bolus of 1-2 mg/kg for to 50mg/kg followed by the same dose as a 24 hour infusion.[8]

Immunotherapy

Sepsis is characterized by the release of proinflammatory cytokine mediators such as tumor necrosis factor (TNF), interleukins (IL-1, IL-2, IL 18) and interferon. This response is commonly called "systemic inflammatory response syndrome" (SIRS). Antibodies or antagonists to various mediators of infection have held much theoretical promise in the treatment of septic shock among they anti-tumor necrosis factor, antithrombin III replacement, anti-interleukin. Disappointingly, little clinical benefit has, so far, been demonstrated.

Endotoxin, or lipopolysaccharide (LPS) is a component of the outer cell wall of gram negative bacteria and is thought to be an important mediator in gram negative sepsis. Several investigative efforts in adult patients have focused on using antibodies to LPS to modulate the effects of sepsis and to improve survival. The vast majority of treatment trials and prophylaxis trials have not shown promise.[30] The Cochrane Database review of randomized trials comparing intravenous immunoglobulin (monoclonal or polyclonal) with placebo or no intervention in patients of all ages with sepsis found that polyclonal IVIG significantly reduced morality. However, this review commented that all trials were small and that the totality of the evidence was insufficient to support conclusion of a benefit.[31] A recent systematic review of randomized controlled trials by Cohen concluded that no particular adjunctive immunoactive drug has altered the risk of death for children.[32] Perhaps further investigation will yield useful results.

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