

This discussion outlines the current management strategies for infants and young children with septic shock. Septic shock is diagnosed in the clinical context of suspected infection and persistent signs of decreased perfusion. While antimicrobial therapy is directed against the common age-associated pathogens, "goal-directed" hemodynamic support is the critical focus of resuscitation of the child with septic shock. Aggressive fluid therapy and the use of inotropic drugs to attain and maintain normal cardiac index constitute the current recommendations of goal-directed therapy. Administration of up to and more than 60 ml/kg of crystalloid may be necessary during the first 30 to 60 minutes of resuscitation. In the absence of randomized controlled trials in infants and children with septic shock, dopamine is the consensus first-line drug for fluid refractory shock. Hydrocortisone therapy is reserved for use in children with catecholamine resistance and suspected or proven adrenal insufficiency.

*Clin Ped Emerg Med* 5:20-27.  
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# Management of Septic Shock in the Pediatric Emergency Department in 2004

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**T**HIS DISCUSSION OUTLINES THE CURRENT management strategies for infants and young children with septic shock. Of note, several recent publications have provided exhaustive review of the definitions pertinent to the systemic inflammatory response syndrome (SIRS),<sup>1,2</sup> including sepsis and septic shock, as well as clinical guidelines for the hemodynamic support of neonates, infants, and children with septic shock.<sup>3</sup>

The mortality in adult patients with sepsis has declined slightly during recent decades, but remains high (>30-40%).<sup>4</sup> In contrast, the mortality associated with pediatric septic shock has declined significantly, in some reports to levels lower than 10%.<sup>5,6</sup> The most important influence on outcome is early recognition of shock and rapid and aggressive therapy in the emergency department.<sup>7,8</sup>

## Diagnosis

Septic shock is diagnosed in the clinical context of suspected infection (fever or, less commonly, hypothermia) and persistent signs of decreased perfusion, including tachycardia, decreased peripheral pulses compared with central pulses, decreased alertness, flash capillary refill or capillary refill > 2 seconds, and mottled or cool extremities (Table 1).

Notably, hypotension (systolic arterial blood pressure < 2 standard deviations [SD] below the mean for age) is not a diagnostic criterion for shock in infants or young children. Normal measured blood pressure in the context of a low volume state is more likely to be sustained by maintenance of high vascular tone

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1522-8401/\$—see front matter  
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doi:10.1016/j.epem.2003.11.007

**TABLE 1. Definition and Characteristics of Shock\* in the Infant and Young Patient**

	Cold Shock	Warm Shock
Capillary refill	> 2 seconds	Flash capillary refill
Peripheral pulses	Diminished	Bounding
Mottling of skin	Present	Absent

\*Shock is defined as a change in mental status (persistent irritability, decreased interactions with caretakers, lethargy, or obtundation)

in pediatric patients relative to adults. Hence, hypotension is a marker of decompensated shock in children.

Septic shock in adults refers to a state of acute circulatory failure characterized by persistent arterial hypotension with a clinical suspicion of infection. Hypotension is defined by a systolic arterial pressure below 90 mm Hg, a mean arterial pressure (MAP) < 60 mm Hg, or a reduction in systolic blood pressure of > 40 mm Hg from baseline, despite adequate volume resuscitation, in the absence of other causes for hypotension.<sup>1</sup>

## Management of Septic Shock

### Etiology and Antimicrobial Therapies

Age is the primary determinant of risk of bacterial infection, whether related to maturation of the immune defenses or exposure to microbes or viruses common to an environment or peer group. Table 2 provides an outline of common pathogens against which antimicrobial (and anti-viral) therapies are directed in the pediatric patient in whom septic shock is suspected. The rate of invasive disease from *Haemophilus influenzae* type b has declined by 99%, and by 90% from *Streptococcus pneumoniae*, in infants and young children since the licensure of the protein conjugate vaccines in 1988<sup>9</sup> and 2000 (Black S, unpublished data), respectively.

Suspicion of invasive bacterial disease initiates an immediate search for the source(s), and antimicrobial agents should be administered promptly. Body fluid (blood, urine, and cerebrospinal fluid) and surface (oral, nasal, rectal, vaginal, and wound) cultures, as well as a chest radiograph, are consid-

ered for inclusion in the initial evaluation of a patient with septic shock. The clinical status of the patient will determine the extent of the evaluation.

Parenteral antibiotics are administered when septic shock is suspected, preferably immediately after cultures are obtained. Antimicrobial strategies are outlined in Table 3. Importantly, the administration of acyclovir is appropriate for the neonate with septic shock when Herpes simplex virus is a consideration.

### Hemodynamic Support: Goal-directed Therapy

Recent literature emphasizes early "goal-directed therapy" that requires careful and quantitative monitoring of physiologic responses to ameliorative interventions. The majority of infants and young children with septic shock are in a low cardiac output and high vascular resistance state,<sup>8</sup> and much evidence suggests that a low cardiac output state is associated with mortality.<sup>10-13</sup> Consequently, in addition to aggressive fluid resuscitation, the use of vasopressors and inotropic drugs to attain and maintain normal cardiac index (CI; 3.3-6.0 L/min/m<sup>2</sup>) constitute the current strategies of goal-directed therapy, particularly in the adult population.<sup>2</sup> Goal-directed therapy is increasingly well supported in the literature and in practice in the pediatric intensive care unit. In particular, though, while the measurement of indices of cardiac function (eg, CI, pulmonary capillary wedge pressure

**TABLE 2. Pathogens Associated With Septic Shock**

Neonate and young infant	<i>Streptococcus agalactiae</i>
	<i>Escherichia coli</i>
	<i>Listeria monocytogenes</i>
	Other Gram-negative enterics
	<i>Staphylococcal</i> species
	Enterococcus
Infant and young child	Herpes simplex virus
	<i>Neisseria meningitidis</i>
	<i>Streptococcus pneumoniae</i>
	<i>Hemophilus influenzae</i> type B
	<i>Streptococcus pyogenes</i>
	<i>Staphylococcus</i> species
	<i>Rickettsiae</i>

**TABLE 3. Age-specific Antimicrobial and Antiviral Therapies for Infants and Children With Suspected Septic Shock**

	Agent	Dose (mg/kg)	Comment
Neonate $\geq$ 7 days	1. Ampicillin	50	
	2a. Gentamicin or	2.5-3	Based on gestational age
	2b. Cefotaxime	50	
	3. Acyclovir	20	If risk of infection with herpes simplex virus
	<b>Typical regimen:</b> 1 + 2a or 2b		
Neonate > 7 days	1. Ampicillin	50	
	2a. Gentamicin or	2.5	
	2b. Cefotaxime or	50	
	2c. Ceftriaxone	50	
	Vancomycin	10	If CNS infection present or suspected
	<b>Typical regimen:</b> 1 + 2a or 2b or 2c (if hyperbilirubinemia not present)		
Infants and children > 1 month	Ceftriaxone	50	
	Vancomycin	10	CNS infection or suspected resistant <i>S. pneumoniae</i>
	Metronidazole	7.5	For intraabdominal infections
	<b>Typical regimen:</b> Ceftriaxone alone unless other indications present		
Infants and children, immunocompromised	1a. Ceftazidime or	50	
	1b. Cefepime or	50	
	1c. Piperacillin/tazobactam	100	
	2. Vancomycin	10	If suspected skin or mucous membrane focus
	<b>Typical regimen:</b> 1a or 1b or 1c, sometimes combined with 2		

[PCAWP], superior vena cava [SVC] O<sub>2</sub> saturation) is not a goal of the first hour of resuscitation, the principles derived from this approach can be applied to the early management of the patient with septic shock in the emergency department.

Figure 1 summarizes a rapid and step-wise approach to the management of septic shock, based on reviewed literature and the consensus statement of the American College of Critical Care Medicine (ACCCM)/Society for Critical Care Medicine (SCCM) Task Force Committee members.<sup>3</sup> Specific discussions of the elements of treatment follow.

**The ABCs.** The early recognition of shock and prompt treatment is paramount for survival of the pediatric patient with sepsis. Maintenance of the airway and attention to oxygenation and adequate

ventilation are the priorities of initial resuscitation. In contrast to adults, oxygen delivery, not oxygen extraction, is the primary determinant of oxygen consumption in children.<sup>13,14</sup> Importantly, then, oxygen is provided as the “drug of first choice” for any infant or child with evidence of shock.

**Vascular access.** Rapid peripheral vascular access is necessary for any patient in whom shock is suspected. Intraosseous access is indicated if peripheral access is delayed or unreliable. Patients responsive to fluid resuscitation are monitored with non-invasive blood pressure measurements and pulse oximetry. Central venous access is preferred for patients with refractory shock who will require centrally delivered drugs (epinephrine, norepinephrine). In addition, central access should be

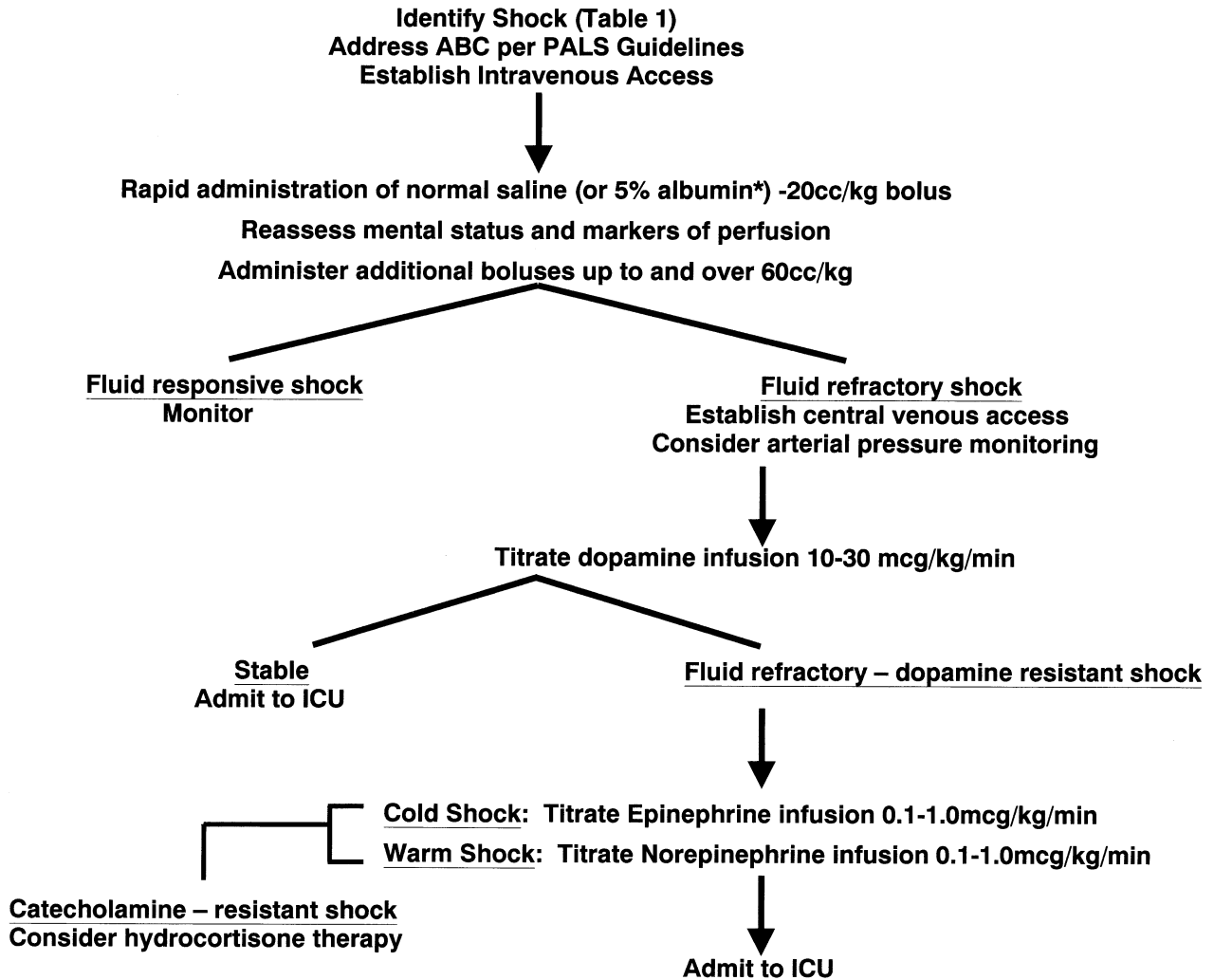


Figure 1. Step-wise approach to management of septic shock in the infant and young child. Adapted from Carcillo JA, Fields MD: Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. Crit Care Med 30:1365-1378, 2002.

considered if (1) peripheral access is unsuccessful, or (2) more intensive monitoring (eg, cardiovascular pacing) or treatment is necessary or likely to be so. Arterial catheterization is appropriate if (1) intra-arterial pressure monitoring, or (2) the use of vasoactive drugs is anticipated.

**Fluid resuscitation.** Aggressive fluid resuscitation is imperative for survival from septic shock.<sup>15</sup> Isotonic crystalloid solution (normal saline) is the optimal resuscitative fluid for the pediatric patient with septic shock.<sup>3</sup> Colloids (5% albumin) can also be considered as initial resuscitation fluid, based in large part on studies of children with dengue and meningococcal septic shock.<sup>16,17</sup> The exclusive use of colloid, though, remains controversial. The 1998 Cochrane review suggests that mortality was higher

when albumin was used in adult patients with sepsis, but none of the studies addressed children, and other systematic reviews have shown conflicting results.<sup>18</sup>

An initial bolus of 20 ml/kg of crystalloid fluid is given as rapidly as possible (eg, over 5-10 min). This should be followed by immediate re-evaluation of airway, breathing, and circulation, including mental status, pulse, and capillary refill time. Administration of up to and more than 60 ml/kg of crystalloid may be necessary during the first 30 to 60 minutes, titrated against objective measures of perfusion. Large volumes of fluid may be required, as increased vascular permeability results in peripheral and third-space losses. Despite this, the risk of cerebral or pulmonary edema remains tolerable.<sup>3,15,19</sup>

TABLE 4. Indications and Dose Range for Hydrocortisone Therapy

	Dose	Clinical Examples
Adrenal insufficiency	2 mg/kg	Purpura fulminans Chronic steroid use: asthma, rheumatic diseases, inflammatory bowel disease Known disorders of the hypothalamic-pituitary axis (eg, hypopituitarism, congenital adrenal hyperplasia), recent surgery
Catecholamine-resistant shock	50 mg/kg	Refractory shock Purpura fulminans with dopamine-resistant shock

**Vasopressor and inotropic therapy.** Following fluid resuscitation, the continued presence of inadequate perfusion or hypotension warrants the use of vasopressor therapy. In the absence of randomized controlled trials in infants and children with septic shock, consensus opinion<sup>3,10,20</sup> holds that dopamine is the first-line drug for fluid refractory shock. Dopamine reverses low vascular resistance and will therefore be most effective in warm septic shock (Fig 1), but in addition provides increases in cardiac output and CI regardless of the type of shock.<sup>2</sup> As with fluid resuscitation, the dopamine infusion dose is titrated to physiologic response.

The use of epinephrine and norepinephrine is extensively discussed in the consensus paper.<sup>3</sup> Of note, epinephrine may be particularly effective for infants who are dopamine-insensitive<sup>21,22</sup> and for patients with cold shock (Fig 1).

All patients requiring vasopressor and inotropic support require invasive monitoring in an intensive care unit setting. Invasive blood pressure measurement will allow accurate initial titration of vasopressors and should be considered for stabilization in the emergency department.<sup>23</sup>

**Hydrocortisone therapy.** Currently, no convincing data exist with regard to the benefit of hydrocortisone replacement in the pediatric patient with septic shock, except for a single study in patients with dengue shock.<sup>24</sup> A recent report in adults suggests that patients with septic shock who are “non-responders” to adrenocorticotropic hormone (ACTH) stimulation (inability to raise cortisol following ACTH stimulation by 10 mcg/dl or greater) benefit from treatment with stress-dose hydrocortisone (decreased mortality and decreased vasopressor use) compared with “responders.”<sup>25</sup>

Based on these data, but without other supportive pediatric studies, the current consensus committee recommendation on the use of hydrocortisone for

the pediatric patient with septic shock states that “hydrocortisone therapy should be reserved for use in children with catecholamine resistance and suspected or proven adrenal insufficiency.”<sup>3</sup> The stress-dose of hydrocortisone is 2 mg/kg. Given that the study of patients with dengue fever used 25 times the stress dose of hydrocortisone,<sup>24</sup> the “shock dose” of hydrocortisone is 50 mg/kg (Table 4). The committee allows for discretion when selecting the dose of hydrocortisone (between stress dose and shock dose; personal communication, Carcillo, J), based on the severity of shock and response to other therapies. Before the initial administration of hydrocortisone, it is recommended that a blood cortisol concentration be obtained to direct subsequent hydrocortisone therapy.

**The inflammatory response and anti-mediator therapies.** The systemic response to infection is complex, and both host and microbial factors influence the magnitude of the inflammatory response. Briefly, the systemic inflammatory response syndrome is induced by cell wall products of circulating microbes or toxins released from sites of local infection, or both. The inflammatory response of the host is comprised of the induction of intracellular pro- and anti-inflammatory mediators (cytokines), activation of the coagulation cascade and alteration of the function of vascular endothelial cells. Infection may be associated with an imbalanced and exuberant inflammatory response and can result in a failure to maintain homeostatic cytokine production, coagulation, and vascular integrity. In its severest form, inflammatory mediators of this host response produce shock, multiple organ failure, and mortality.

Anti-mediator therapies are intended to down-regulate the SIRS associated with sepsis and septic shock. During the last 20 years, a number of experimental anti-mediator molecules (Table 5) have

**TABLE 5. Therapies Directed Against Mediators of the Systemic Inflammatory Response Syndrome**

Mediator	Therapeutic Strategy	Molecule	Reference
Endotoxin	Bind or neutralize endotoxin	Monoclonal antibody directed against lipid A moiety	36
		Endotoxin neutralizing protein	37
		Bactericidal/permeability increasing protein	38,39
	Endotoxin receptor antagonism	Soluble CD14 (recombinant)	40
Interleukins	Cytokine antagonism	IL-1 receptor antagonist	41,42
Tumor necrosis factor	Cytokine antagonism	Anti-TNF antibody	43-46
Platelet activating factor	Factor antagonism	PAF antagonist	47
Coagulation cascade	Replacement of depleted protein C	Drotrecogin alfa (recombinant human activated protein C)	30-33

been studied as ameliorative agents for sepsis. Results have been predominantly disappointing. Anti-endotoxin therapies have resulted in no effect, and anti-mediator trials have shown either no or minimal survival benefit.<sup>26-29</sup>

Recently, drotrecogin alfa (recombinant human activated protein C) was shown to significantly improve 28-day survival in adults with severe sepsis.<sup>30-33</sup> Of note, treatment with protein C concentrate in children with purpura fulminans and meningococcal septic shock was shown to result in dose-related increases of plasma activated protein C and resolution of coagulation imbalances.<sup>34</sup> Despite these encouraging data, criteria for selecting appropriate children to receive drotrecogin alfa have not been delineated. Morbidity associated with administration of drotrecogin alfa may be a barrier to its use in children. Nonetheless, a recent safety study in infants and children with severe sepsis suggests that the pharmacodynamic and safety profile of drotrecogin alfa in children may be similar to that in adults.<sup>35</sup>

Disappointing clinical results and the absence of data from the pediatric population regarding anti-mediator therapies exclude these compounds from current consideration for the treatment of young infants and children with septic shock.

### Summary

The current management strategy for septic shock focuses on antimicrobial and hemodynamic goal-directed therapies. In summary, all therapies are directed at bacterial killing and restoration of a normal mental status and perfusion to vital organs and the peripheral circulation.

### First Hour

- Assess airway, breathing, circulation.
- Establish intravenous access.
- Obtain cultures of pertinent body fluids or sites of local infection. Administer antibiotics and antivirals as indicated.
- Aggressive fluid resuscitation: up to (and over if needed) 60 cc/kg based on physiologic responses.

### Second Hour

- First-line vasopressor: dopamine
- Fluid refractory dopamine-resistant shock
  1. Consider epinephrine: cold shock or shock in the young infant unresponsive to dopamine;
  2. Consider norepinephrine (warm shock).
- Catecholamine-resistant shock
 

Consider hydrocortisone therapy:

Stress dose: 2 mg/kg

Shock dose: 50 mg/kg

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