Special Article ========================================

# Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock*

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*Background:* The Institute of Medicine has called for the development of clinical guidelines and practice parameters to develop "best practice" and potentially improve patient outcome.

*Objective:* To provide American College of Critical Care Medicine clinical guidelines for hemodynamic support of neonates and children with septic shock.

*Setting:* Individual members of the Society of Critical Care Medicine with special interest in neonatal and pediatric septic shock were identified from literature review and general solicitation at Society of Critical Care Medicine Educational and Scientific Symposia (1998–2001).

*Methods:* The MEDLINE literature database was searched with the following age-specific keywords: sepsis, septicemia, septic shock, endotoxemia, persistent pulmonary hypertension, nitric oxide, and extracorporeal membrane oxygenation. More than 30 experts graded literature and drafted specific recommendations by using a modified Delphi method. More than 30 more experts then reviewed the compiled recommendations. The task-force chairman modified the document until <10% of experts disagreed with the recommendations.

*Results:* Only four randomized controlled trials in children with septic shock could be identified. None of these randomized trials led to a change in practice. Clinical practice has been based, for the most part, on physiologic experiments, case series, and cohort studies. Despite relatively low American College of Critical Care Medicine–graded evidence in the pediatric literature, outcomes in children have improved from 97% mortality in the 1960s to 60% in the 1980s and 9% mortality in 1999. U.S. hospital survival was three-fold better in children compared with adults (9% vs. 27% mortality) in 1999. Shock pathophysiology and response to therapies is age specific. For example, cardiac failure is a predominant cause of death in neonates and children, but vascular failure is a predominant cause of death in adults. Inotropes, vasodilators (children), inhaled nitric oxide (neonates), and extracorporeal membrane oxygenation can be more important contributors to survival in the pediatric populations, whereas vasopressors can be more important contributors to adult survival.

*Conclusion:* American College of Critical Care Medicine adult guidelines for hemodynamic support of septic shock have little application to the management of pediatric or neonatal septic shock. Studies are required to determine whether American College of Critical Care Medicine guidelines for hemodynamic support of pediatric and neonatal septic shock will be implemented and associated with improved outcome. (Crit Care Med 2002; 30:1365–1378)

O utcomes in neonatal and pediatric sepsis have improved with the advent of neonatal and pediatric intensive care (reduction in mortality from 97% to 9%) (1–3) and are markedly better than in adults (9% compared with 28% mortality) (3). The clinical practice parameters presented in this document are an attempt to provide a consensus statement on state-of-the-art hemodynamic support for neonates, infants, and children with septic shock. This document is designed to be an addendum to the previously published practice parameters for hemodynamic support of adult sepsis (4). The reader who is in search of more detailed discussion of general principles in sepsis and cardiovascular support, or a more extensive reference list that concentrates on adult animal and human literature, is directed to this comprehensive document (4).

More than 30 clinical investigators and clinicians who were affiliated with the Society of Critical Care Medicine and who had special interest in hemodynamic support of pediatric patients with sepsis, were contacted and volunteered to be members of the task force. Three invitees declined to participate. Subcommittees were formed to review and grade the literature by using the evidence-based scoring system of the American College of Critical Care Medicine. The literature was accrued by using MEDLINE and indexing the following age-limited keywords: sepsis, septicemia, septic shock, endotoxemia, persistent pulmonary hypertension, nitric oxide, and extracorporeal membrane oxygenation (ECMO). The clinical parameters and guidelines were drafted by using a modification of the Delphi method. Briefly, the initial step included review of the literature and grading of the evidence by topic-based subcommittees during a 1-yr period. Of interest, the committee found only four randomized controlled trials in children that examined the effect of a hemodynamic support therapy on outcome from septic shock (5–8). Because of the pau-

city of outcome-directed, randomized controlled trials, the recommendations for hemodynamic support of term newborns and children in this document are primarily expert opinion rather than irrefutable evidence.

Subcommittees were formed to evaluate each subtopic. The report from each subcommittee was compiled into a comprehensive document by the task-force chairperson. All members commented on the unified draft, and modifications were made until <10% of the task force disagreed with any specific or general recommendation. This process occurred during a 6-month period. Reviewers from the American College of Critical Care Medicine then requested further modifications that were performed. The document was designed to meet the maximum criteria possible as recommended by the American Medical Association. Grading of the literature and levels of recommendations were based on published American College of Critical Care Medicine criteria (Table 1).

The task force did not follow the adult guideline format (4) because children have age-specific considerations in hemodynamic support of septic shock. The task force drafted this document to provide practitioners with an expert opinion and an evidence-based, age-specific, stepwise approach to hemodynamic support of septic shock in term neonates and children.

## DEVELOPMENTAL DIFFERENCES IN THE HEMODYNAMIC RESPONSE TO SEPSIS IN NEWBORNS, CHILDREN, AND ADULTS

The predominant cause of mortality in adult septic shock is vasomotor paralysis (9). Adults have myocardial dysfunction manifested as a decreased ejection fraction; however, cardiac output is usually maintained or increased by two mechanisms, tachycardia and ventricular dilation. Adults who do not develop this adaptive process to maintain cardiac output have a poor prognosis (10). Pediatric septic shock is associated with severe hypovolemia, and children frequently respond well to aggressive volume resuscitation; however, the hemodynamic response of children who are fluid resuscitated seems diverse compared with adults. Contrary to the adult experience, low cardiac output, not low systemic vascular resistance, is associated with mortality in pediatric septic shock (11–20). Attainment of the therapeutic goal of a cardiac index (CI) of 3.3–6.0 L/min/m$^2$, may result in improved survival (20). Also contrary to adults, oxygen delivery, not oxygen extraction, is the major determinant of oxygen consumption in children (13). Attainment of the therapeutic oxygen consumption goal of >200 mL/min/m$^2$ may also be associated with improved outcome (12).

It was not until 1998 that investigators reported outcome when aggressive volume resuscitation (60 mL/kg fluid in the first hour) and goal-directed therapies (12) (CI goal of 3.3–6.0 L/min/m$^2$ and normal pulmonary capillary occlusion pressure) were applied to children with septic shock (20). Ceneviva et al. (20) described 50 children with fluid-refractory ($\geq$60 mL/kg in the first hour), dopamine-resistant shock. The majority (58%) showed a low cardiac output and high systemic vascular resistance state, and only 22% had low cardiac output and low vascular resistance. Hemodynamic states frequently progressed and changed during the first 48 hrs. Persistent shock occurred in 33% of the patients. There was a significant decrease in cardiac function over time, requiring addition of inotropes and vasodilators. Although decreasing cardiac function accounted for the majority of patients with persistent shock, some showed a complete change from a low output state to a high output and low systemic vascular resistance state (21–24). Inotropes, vasopressors, and vasodilators were directed to maintain normal CI and systemic vascular resistance in the patients. Mortality from sepsis in this study (18%) was markedly reduced compared with mortality in the 1985 study (58%) (12, 20), in which aggressive fluid resuscitation was not used.

Neonatal septic shock can be complicated by the physiologic transition from fetal to neonatal circulation. *In utero,* 85% of fetal circulation bypasses the lungs through the patent ductus arteriosus and foramen ovale. This flow pattern is maintained by suprasystemic pulmonary artery pressures prenatally. At birth, inhalation of oxygen triggers a cascade of biochemical events that ultimately result in reduction in pulmonary artery pressure and transition from fetal to neonatal circulation with blood flow now being directed through the pulmonary circulation. Closure of the patent ductus arteriosus and foramen ovale complete this transition. Pulmonary artery pressures can remain elevated and the ductus arteriosus can remain open for the first 6 wks of life, whereas the foramen ovale may remain probe patent for years. Sepsis-induced acidosis and hypoxia can increase pulmonary artery pressure and maintain patency of the ductus arteriosus, resulting in persistent pulmonary hypertension of the newborn (PPHN) and persistent fetal circulation. Neonatal septic shock with PPHN is associated with increased right ventricle work. Despite *in utero* conditioning, the thickened right ventricle may fail in the presence of systemic pulmonary artery pressures. Decompensated right ventricular failure can be clinically manifested by tricuspid regurgitation and hepatomegaly. Newborn animal models of group B streptococcal and endotoxin shock have also documented reduced cardiac output and increased pulmonary, mesenteric, and systemic vascular resistance (25–29). Therapies directed at reversal of right ventricle failure, through reduction of pulmonary artery pressures, are commonly needed in neonates with fluid refractory shock and PPHN.

The hemodynamic response in premature, very low–birthweight infants with septic shock (<32 wks gestation, <1000 g) is least understood, in part, because

**Table 1.** American College of Critical Care Medicine guidelines for rating evidence-based medicine for strength of recommendation and quality of evidence supporting the references

Rating system for references
- a: Randomized, prospective controlled trials
- b: Nonrandomized, concurrent or historical cohort investigations
- c: Peer-reviewed, state of the art articles, review articles, editorials, or substantial case series
- d: Non-peer reviewed published opinions, such as textbook statements or official organizational publications

Rating system for recommendations
- Level I: Convincingly justifiable on scientific evidence alone
- Level II: Reasonably justifiable by scientific evidence and strongly supported by expert critical care opinion
- Level III: Adequate scientific evidence is lacking but widely supported by available data and expert opinion

pulmonary artery catheterization is not possible in this population. Most information has been assessed from echocardiographic evaluation alone. There is a paucity of studies devoted to septic shock. Literature is available, for the most part, on the hemodynamic response in premature infants with respiratory distress syndrome or shock of undescribed pathogenesis. Echocardiographic analysis has documented reduced right ventricular and left ventricular function in premature newborns (30). This and other literature indicates that premature infants with shock can respond to volume and inotropic therapies with improvements in stroke volume, contractility, and blood pressure.

Several other developmental considerations influence therapies for shock. Relative initial deficiencies in the thyroid, and parathyroid hormone axes have been appreciated and can result in the need for thyroid hormone, calcium replacement, or both (31, 32). Hydrocortisone has been examined in this population as well (33). Immature mechanisms of thermogenesis require attention to external warming. Reduced glycogen stores and muscle mass for gluconeogenesis require attention to maintenance of serum glucose. Standard practices in resuscitation of premature infants in septic shock employ a more graded approach compared with resuscitation of term neonates and children. This more cautious approach is a response to anecdotal reports that premature infants at risk for intraventricular hemorrhage (<30 wks gestation) can develop hemorrhage after rapid shifts in blood pressure; however, some now question whether long-term neurologic outcomes are related to periventricular leukomalacia (a result of prolonged underperfusion) more than to intraventricular hemorrhage. Another complicating factor in very low–birthweight infants is the persistence of the patent ductus arteriosus. This can occur because immature muscle is unable to constrict. The majority of infants with this condition are treated medically with indomethacin or surgically with ligation. Rapid administration of fluid may cause left-to-right shunting through the ductus, with ensuing congestive heart failure induced by ventricular overload. Studies of therapies specifically directed at premature very low–birthweight infants with septic shock are needed. One single-center, randomized controlled trial reported improved outcome with use of daily 6-hr

pentoxifylline infusions in very premature infants with sepsis (5). This promising therapy deserves evaluation in the multicentered trial setting (34).

## WHAT CLINICAL SIGNS AND HEMODYNAMIC VARIABLES CAN BE USED TO DIRECT TREATMENT OF NEWBORN AND PEDIATRIC SHOCK?

The University of Minnesota hospitals reported a 97% mortality in children with Gram-negative sepsis in 1963 (1). With the advent of modern pediatric intensive care therapy, mortality has been reduced to 9% (3). The task-force consensus is that early reversal of shock results in improved outcome (35). In the absence of survival-directed trials, the task force agreed to evaluate the literature and make recommendations on therapy by using resolution of shock as the gold standard outcome.

Shock can be defined by clinical variables, hemodynamic variables, oxygen use variables, or cellular variables. After review of the literature, the committee chose to define septic shock by clinical, hemodynamic, and oxygen use variables only. Septic shock can be recognized, before hypotension occurs, by a clinical triad that includes hypothermia or hyperthermia, altered mental status, and peripheral vasodilation (warm shock) or cool extremities (cold shock). Therapies should be directed to restoring normal mental status and peripheral perfusion. Restoration of urine output can also be a reassuring measure of successful resuscitation.

Shock should also be evaluated and resuscitated by using hemodynamic variables. Flow (Q) varies directly with perfusion pressure (dP) and inversely with resistance (R). This is mathematically represented by $Q = dP/R$. For the whole body, this is represented by cardiac output = mean arterial pressure (MAP) − central venous pressure (CVP)/systemic vascular resistance. This relationship is also evident for organ perfusion. In the kidney, for example, renal blood flow = mean renal arterial pressure − mean renal venous pressure/renal vascular resistance. Some organs, including the kidney and brain, have vasomotor autoregulation that maintains blood flow in low blood pressure (MAP or renal arterial pressure) states. At some critical point, perfusion pressure is reduced below the ability of the organ to maintain blood

flow. The purpose of treatment of shock is to maintain perfusion pressure above the critical point below which blood flow cannot be effectively maintained in individual organs. Because the kidney receives the second highest blood flow of any organ in the body, measurement of urine output (with the exception of patients with hyperosmolar states leading to osmotic diuresis) and creatinine clearance can be used as an indicator of adequate perfusion pressure. In this regard, maintenance of MAP with norepinephrine has been shown to improve urine output and creatinine clearance in hyperdynamic sepsis (36). Maintenance of supranormal MAP above this point is likely not of benefit (37)

Reduction in perfusion pressure below the critical point necessary for adequate organ perfusion can also occur in disease states with increased intraabdominal pressure (IAP) such as bowel wall edema, ascites, or abdominal compartment syndrome. Increased IAP is associated with increased CVP. If this is not compensated for by an increase in MAP, then perfusion pressure is decreased. Therapeutic reduction of IAP (measured by intrabladder pressure) results in restoration of perfusion pressure and has been shown to improve renal function in children with burn shock (38).

Shock can also be treated according to oxygen use measures. Measurement of cardiac output and oxygen consumption (CI × [arterial oxygen content − mixed venous oxygen]) has been proposed as being of benefit in patients with persistent shock because a CI between 3.3 and 6.0 L/min/m$^2$ and oxygen consumption >200 mL/min/m$^2$ are associated with improved survival (12). Assuming a hemoglobin concentration of 10 g/dL and 100% arterial oxygen saturation, then a CI of >3.3 L/min/m$^2$ would correlate to a mixed venous oxygen saturation of >70% in a patient with a normal oxygen consumption of 150 mL/min/m$^2$ (oxygen consumption = CI × arterial oxygen content × oxygen extraction; therefore, 150 mL/min/m$^2$ = 3.3 L/min/m$^2$ × [1.36 × 10 g/dL × 100 + Pao$_2$ × 0.003] × [100% − 70%]). Low cardiac output is associated with mortality in pediatric septic shock (11–20). In one study, children with fluid-refractory dopamine-resistant shock were treated with goal-directed therapy (CI, 3.3–6 L/min/m$^2$) and found to have predicted improved outcomes compared with historical reports (20). Low cardiac output is associated with in-

creased oxygen extraction (13). In an emergency room study in adults with septic shock, maintenance of superior vena cava oxygen saturation at >70% by use of blood transfusion to a hemoglobin of 10 g/dL and inotropic support resulted in a 50% reduction in mortality compared with a group in which MAP-CVP was maintained without attention to superior vena cava oxygen saturation (39).

## DEVELOPMENTAL CONSIDERATIONS IN MONITORING AND TREATMENT OF SHOCK IN NEWBORNS AND CHILDREN

*Intravascular Access.* Intravenous access for fluid resuscitation and inotrope-vasopressor infusion is more difficult to attain in newborns and children compared with adults. The American Heart Association and American Academy of Pediatrics have developed neonatal resuscitation program and pediatric advanced life support guidelines for emergency establishment of intravascular support (40, 41).

*Fluid Therapy.* Two clinical case series have evaluated fluid resuscitation in pediatric septic shock (19, 42). The larger of the two case series used a combination of crystalloid and colloid therapies (42). There is only one randomized controlled trial comparing the use of colloid to crystalloid resuscitation (dextran, gelatin, lactated Ringers, or saline) in children with dengue shock (8). 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. On the basis of these and other studies, the committee agrees that fluid resuscitation with crystalloids and colloids is of fundamental importance to survival of septic shock (8, 19, 42–53). Debate on the efficacy of exclusive colloid resuscitation is ongoing. In a recent clinical practice position paper, a group chosen for outstanding results in resuscitation of meningococcal septic shock (5% mortality) reported that they use 5% albumin exclusively (20 mL/kg boluses over 5–10 mins) and intubate all patients who require >40 mL/kg (54). The Cochrane Group meta-analysis that implied harmful effects of colloid use in critical illness evaluated no studies examining fluid resuscitation in children or newborns with septic shock. (55). Beneficial or harmful effects of colloids remain to be studied in this population (56). The use of blood as a fluid expander has been examined in two small pediatric studies, but no recommendations were given by the investigators (57, 58). There are no published studies of or recommendations on targeted hemoglobin concentration in children. The last National Institutes of Health consensus conference recommended a target hemoglobin concentration of 10 g/dL in adults with cardiopulmonary compromise. An emergency room protocol directed to maintenance of hemoglobin at 10 g/dL in adults with a superior vena cava oxygen saturation of <70% was associated with improved outcomes (39).

Fluid infusion is best initiated with boluses of 20 mL/kg titrated to clinical monitors of cardiac output, including heart rate, urine output, capillary refill, and level of consciousness. Large fluid deficits typically exist, and initial volume resuscitation usually requires 40–60 mL/kg but can be as much as 200 mL/kg (19, 42–50). Patients who do not respond rapidly to initial fluid boluses, or those with insufficient physiologic reserve, should be considered for invasive hemodynamic monitoring. Filling pressures should be increased to optimize preload to attain maximal cardiac output. In most patients, this will occur with a pulmonary capillary occlusion pressure between 12 and 15 mm Hg. Increases above this range usually do not significantly enhance end-diastolic volume or stroke volume and may be associated with decreased survival. Large volumes of fluid for acute stabilization in children have not been shown to increase the rate of the acute respiratory distress syndrome (42, 49) or cerebral edema (42, 50). Increased fluid requirements may be evident for several days (19). Fluid choices include crystalloids (normal saline) and colloids (dextran, gelatin, or 5% albumin) (8, 51–53, 55–58). Experience with the use of starch, hypertonic saline, or hyperoncotic albumin was limited among members of the task force. Fresh-frozen plasma may be infused to correct abnormal prothrombin time and partial thromboplastin time but should not be pushed because it has hypotensive effects likely caused by vasoactive kinins. In the absence of data, it is reasonable to maintain hemoglobin concentration within the normal range for age in children with shock. Oxygen delivery depends significantly on hemoglobin concentration (oxygen delivery = CI × [1.36 × % hemoglobin × % oxygen saturation + $Pa_{O_2}$ × 0.003). Hemoglobin should be maintained at a minimum of 10 g/dL (39).

*Intravascular Catheters and Monitoring.* Minimally invasive monitoring is necessary in children with fluid-responsive shock; however, central vein access and arterial pressure monitoring should be considered and used in children with fluid-refractory shock. Maintenance of perfusion pressure (MAP-CVP, or MAP-IAP if the abdomen is tense secondary to bowel edema or ascitic fluid) was considered necessary for organ (particularly renal) perfusion (38). Echocardiography was also considered an appropriate noninvasive tool to rule out the presence of pericardial effusion. Superior vena cava oxygen saturation of >70% is associated with improved outcome during the first 6 hrs of presentation of septic shock(39). The decision to use pulmonary artery catheter monitoring should be reserved for those who remain in shock despite therapies directed to clinical signs of perfusion, MAP-CVP, and superior vena cava oxygen saturation.

Consensus opinion on adult use of the pulmonary catheters has been summarized in the Society for Critical Care Medicine *Pulmonary Artery Catheter Consensus Conference* document (59). A clear reduction in mortality with pulmonary artery catheter use has not been demonstrated in adults. We recommend use of the pulmonary artery catheter in selected pediatric patients for the following reasons. Although the risk of pulmonary artery catheter–associated complications exists, many published studies evaluating use of hemodynamic support therapies in children have used the pulmonary catheter without reporting complications from its use (11–13, 15, 20, 42, 57, 58, 60–64), supporting safety in this population. A relatively large study showed that in children with fluid-refractory and dopamine-resistant shock, placement of the pulmonary artery catheter diagnosed improper cardiovascular support strategies that had been based on incorrect assessment of hemodynamic state. This new information guided a change to appropriate therapies that reversed shock (20), supporting potential efficacy from pulmonary artery catheter–derived data in this population. An independent review of this topic interpreted the results in this study to support the

use of the pulmonary artery catheter in the select group of children with septic shock that has not been reversed by peripheral arterial and CVP pressure and oxygen saturation–directed therapies (65). The committee concluded that there was not yet enough information or general experience to recommend for or against the use of echocardiography, gastric tonometry, or femoral artery thermodilution to direct therapy in children with septic shock (60, 65–73).

*Vasopressor Therapy.* Dopamine remains the first-line vasopressor for high output, low vascular resistance shock in adults. Although the task force chose dopamine as the first-line drug for fluid-refractory hypotensive shock in the setting of low systemic vascular resistance, it was also aware of the literature demonstrating an age-specific insensitivity to dopamine (74–82). Dopamine causes vasoconstriction by releasing norepinephrine from sympathetic vesicles. Immature animals and young humans (<6 months) may not have developed their full component of sympathetic vesicles. Dopamine-resistant shock commonly responds to norepinephrine or high-dose epinephrine (20, 83, 84). Some in the committee promote use of low-dose norepinephrine as a first-line agent for warm hyperdynamic shock. Phenylephrine is limited to use as a pure vasopressor because it has no β–adrenergic activity (85). Angiotensin or arginine vasopressin can be successful in patients who are refractory to norepinephrine because it does not use the α receptor and its efficacy is therefore not affected by ongoing α-receptor down-regulation (86, 87). Use of vasopressors can be titrated to end points of perfusion pressure (MAP-CVP) or systemic vascular resistance that ensure optimum urine output and creatinine clearance (20, 36, 38, 83, 84). Nitric oxide inhibitors and methylene blue are considered investigational therapies (88–98).

*Inotrope Therapy.* As in adults, dobutamine or mid-dosage dopamine can be used as the first line of inotropic support (20, 39, 99–110); however, children <12 months can be less responsive (107). Dobutamine- or dopamine-refractory shock can be reversed with epinephrine infusion (20, 110). Epinephrine is more commonly used in children than in adults. Some members of the committee recommended use of low-dose epinephrine as a first-line choice for cold hypodynamic shock. Recommendations in the adult literature have been driven by the observation that epinephrine transiently reduces intramucosal pH in adults with hyperdynamic sepsis (111), but there are no data available to evaluate whether gut injury does or does not occur with epinephrine use in children. Pediatric patients requiring inotropy are in a low cardiac output, not a high cardiac output, state.

When pediatric patients remain in a normotensive low cardiac output and high vascular resistance state, despite epinephrine and nitrosovasodilator therapy, then the use of milrinone (if liver dysfunction is present) or amrinone (if renal dysfunction is present) should be strongly considered (62–64, 112–115). Amrinone and milrinone are rarely used in adults because catecholamine refractory low cardiac output and high vascular resistance is so uncommon; however, this hemodynamic state can represent a major proportion of children with fluid-refractory, dopamine-resistant shock (20). These type III phosphodiesterase inhibitors prevent hydrolysis of cyclic adenosine monophosphate and therefore potentiate the effect of β-receptor stimulation in cardiac and vascular tissue. Down-regulation of the $\beta_1$ and $\beta_2$ receptor can be overcome by these drugs. Fluid boluses are likely to be required if amrinone or milrinone are administered with loading doses. Although recommended in the literature (62, 63), many in the committee choose not to use boluses of amrinone or milrinone. This group administers the drugs as a continuous infusion only, recognizing that it will take more than four half-lives to reach a steady-state effect. Because of the long half-life elimination, these drugs should be discontinued at the first sign of tachyarrhythmias, hypotension, or diminished systemic vascular resistance. Hypotension-related toxicity with these drugs can be potentially overcome by stopping epinephrine and beginning norepinephrine (62, 63). Norepinephrine counteracts the effects of increased cyclic adenosine monophosphate in vascular tissue by stimulating the α receptor. Norepinephrine accomplishes this without further $\beta_2$ stimulation.

*Vasodilator Therapy.* The use of vasodilators can reverse shock in pediatric patients who remain hypodynamic with a high systemic vascular resistance state, despite fluid resuscitation and implementation of inotropic support (20, 116–119). Most in the committee use nitrosovasodilators (nitroprusside or nitroglycerin have a very short half-life elimination) as first-line therapy for children with epinephrine-resistant low cardiac output and elevated systemic vascular-resistance shock because hypotension-associated toxicity can be immediately reversed by stopping the infusion. Milrinone or amrinone can be used for their vasodilating properties in patients with nitrosovasodilator-resistant, low-output syndrome or nitrosovasodilator-associated toxicity (cyanide or isothiocyanate toxicity from nitroprusside or methemoglobin toxicity from nitroglycerin) (20, 62, 63). Other vasodilators used and reported in neonatal and pediatric septic shock include prostacyclin, phentolamine, pentoxifylline, and dopexamine (120–123).

*Glucose, Calcium, Thyroid, and Hydrocortisone Replacement.* It is important to maintain metabolic and hormonal homeostasis in newborns and children. Hypoglycemia can cause neurologic devastation when missed. Hypoglycemia must be rapidly diagnosed and promptly treated. Hypocalcemia is a frequent, reversible contributor to cardiac dysfunction (32, 124, 125). Calcium replacement should be directed to normalize ionized calcium levels. The committee agreed that replacement with thyroid or hydrocortisone could be lifesaving in children with thyroid or adrenal insufficiency and catecholamine-resistant shock (6, 7, 20, 31, 124–134). Infusion therapy with triiodothyronine has been shown to be beneficial in postoperative patients with congenital heart disease but has yet to be studied in children with septic shock (135). Hypothyroidism can be commonly found in children with trisomy 21 and children with central nervous system disease (e.g., pituitary abnormality) (128).

The adult literature is examining the use of hydrocortisone in patients with catecholamine-dependent septic shock without adrenal insufficiency. The adult literature is also exploring new definitions of relative hypoadrenal responses in septic shock (129–141) (Table 2). Our committee consensus was that until similar pediatric studies are performed, hydrocortisone (not methylprednisolone) therapy should be reserved for use in children with catecholamine resistance and suspected or proven adrenal insufficiency. Adrenal insufficiency, and particularly a low aldosterone state, may be more common in children with septic shock than previously thought (127–129,

134, 135). Patients at risk include children with purpura fulminans and associated Waterhouse-Friedrichson syndrome, children who have previously received steroid therapies for chronic illness, and children with pituitary or adrenal abnormalities (128). The committee chose the most conservative diagnostic approach and defines adrenal insufficiency as a total cortisol level between 0 and 18 mg/dL (138, 139). Review of the pediatric literature found several case series and two randomized trials that used "shock dose" hydrocortisone in children (6, 7). The first randomized controlled trial showed improved outcome with hydrocortisone therapy in children with dengue shock. The second study was underpowered and showed no effect of hydrocortisone therapy on outcome in children with dengue shock. The reported shock dose of hydrocortisone is 25 times higher than the stress dose (6, 7, 133–141).

*Therapy for PPHN.* Although inhaled nitric oxide therapy is the treatment of choice for uncomplicated PPHN (142, 143), the committee agreed that metabolic alkalinization remains an important initial resuscitative strategy during shock (144). PPHN in the setting of septic shock can reverse when acidosis is corrected. For centers with access to inhaled nitric oxide, this is the only selective pulmonary vasodilator reported to be effective in reversal of PPHN (142, 143, 145–150). ECMO remains the therapy of choice for patients with refractory PPHN and sepsis (151–154).

*ECMO Therapy.* ECMO is not routinely used in adults (with the notable exception of the University of Michigan) (151). However, ECMO is a viable therapy for refractory shock in neonates (151–154). The Extracorporeal Life Support Organization registry suggests that neonates have a similar outcome (survival rate of approximately 80%) whether the indication for ECMO is refractory respiratory failure or refractory shock. Although the outcome is similar, neonates with septic shock have more complications (e.g., bleeding and infection) associated with therapy. The Extracorporeal Life Support Organization registry and other reports in the literature suggest outcome is less successful when ECMO is used for refractory pediatric septic shock (37% to 50% survival) (155–157). Therefore, the committee agreed that its use in pediatric septic shock is less successful, yet it seems to be reasonable according to clinical judgment. Of interest, ECMO is effective for pediatric

cardiogenic shock (158). It is also effective in adult victims of hantavirus with low cardiac output and high systemic vascular resistance shock (159–160). The committee speculates that ECMO therapy is likely most successful in patients with refractory low cardiac output septic shock.

## RECOMMENDATIONS FOR PEDIATRIC SEPTIC SHOCK

### Diagnosis

The inflammatory triad of fever, tachycardia, and vasodilation is common in

children with benign infections. Septic shock is suspected when children with this triad have a change in mental status manifested as inconsolable irritability, lack of interaction with parents, or inability to be aroused (Fig. 1). The clinical diagnosis of septic shock is made in children who have a suspected infection manifested by hypothermia or hyperthermia and have clinical signs of decreased perfusion, including decreased mental status, prolonged capillary refill of >2 secs (cold shock) or flash capillary refill (warm shock), diminished (cold shock) or bounding (warm shock) peripheral

**Table 2.** Definitions of shock

Cold or warm shock: Decreased perfusion including decreased mental status, capillary refill >2 secs (cold shock) or flash capillary refill (warm shock), diminished (cold shock) or bounding (warm shock) peripheral pulses, mottled cool extremities (cold shock), or decreased urine output <1 mL/kg/hr
Fluid-refractory/dopamine-resistant shock: Shock persists despite ≥60 mL/kg fluid resuscitation in first hour and dopamine infusion to 10 μg/kg/min
Catecholamine resistant shock: Shock persists despite use of catecholamines epinephrine or norepinephrine
Refractory shock: Shock persists despite goal-directed use of inotropic agents, vasopressors, vasodilators, and maintenance of metabolic (glucose and calcium) and hormonal (thyroid and hydrocortisone) homeostasis
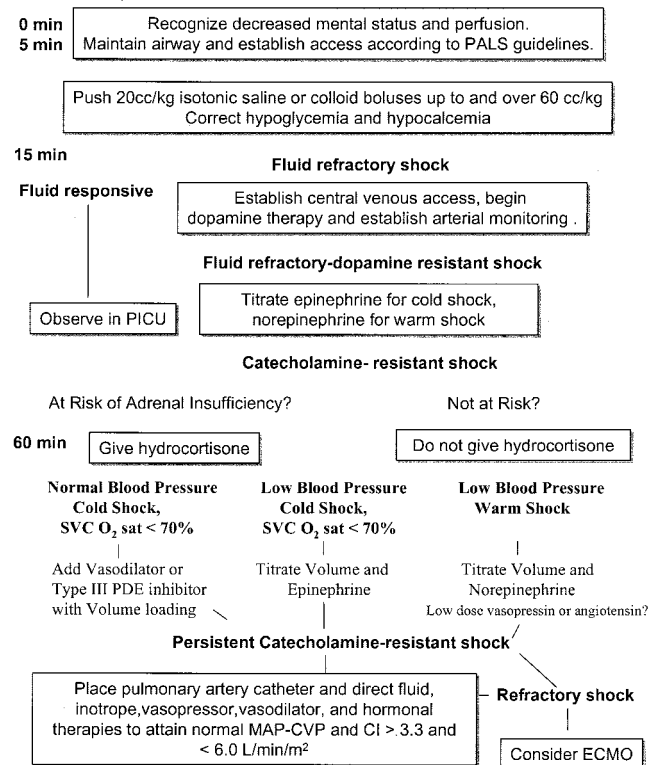


**Figure 1.** Recommendations for stepwise management of hemodynamic support in infants and children with goals of normal perfusion and perfusion pressure (mean arterial pressure − central venous pressure [*MAP − CVP*]). Proceed to next step if shock persists. *PALS*, pediatric advanced life support; *PICU*, pediatric intensive care unit; *SVC $O_2$*, superior vena cava oxygen; *PDE*, phosphodiesterase; *CI*, cardiac index; *ECMO*, extracorporeal membrane oxygenation.

pulses, mottled cool extremities (cold shock), or decreased urine output of <1 mL/kg/hr. Hypotension is not necessary for the clinical diagnosis of septic shock; however, its presence in a child with clinical suspicion of infection is confirmatory.

## ABCs: First Hour of Resuscitation

*Goals (Level III).*

Maintain airway, oxygenation, and ventilation

Maintain circulation (defined as normal perfusion and blood pressure)

Maintain threshold heart rates (Table 3)

*Therapeutic End Points (Level III).* Therapeutic end points include capillary refill of <2 secs, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output >1 mL/kg/hr, normal mental status, and normal blood pressure for age.

*Monitoring (Level III).*

Pulse oximeter

Continuous electrocardiography

Blood pressure

Temperature

Urine output

Glucose and ionized calcium

*Airway and Breathing (Level III).* Airway and breathing should be rigorously monitored and maintained. Lung compliance and work of breathing may change precipitously. Patients typically manifest hypoxemia and metabolic acidosis and are at high risk to develop respiratory acidosis. The decision to intubate and ventilate is made on clinical diagnosis of increased work of breathing, hypoventilation, impaired mental status, or presence of a moribund state. Waiting for confirmatory laboratory tests is discouraged. Volume loading may be required during intubation because of relative or absolute hypovolemia. Induction agents that maintain cardiovascular integrity should be used.

*Circulation (Level II).* Vascular access should be rapidly attained. Establish intraosseous access if reliable venous access cannot be rapidly attained. Placement of central catheter access will usually be required for vasoactive infusions.

*Fluid Resuscitation (Level II).* Rapid fluid boluses of 20 mL/kg (isotonic saline or colloid) should be administered by push while observing for the development of rales, gallop rhythm, hepatomegaly, and increased work of breathing. In the absence of these clinical findings, fluid can be administered to as much as 200 mL/kg in the first hour. The average requirement is 40–60 mL/kg in the first hour. Fluid should be pushed with the goal of attaining normal perfusion and blood pressure.

*Hemodynamic Support (Level II).* Patients with severe shock uniformly require vasoactive support during fluid resuscitation. Vasoactive agents should be administered when a second catheter, preferably a central catheter, has been established. Dopamine can be used as the first-line agent; however, dopamine-resistant shock should be quickly recognized and epinephrine used for cold shock or norepinephrine used for warm shock to restore normal perfusion and blood pressure.

*Hydrocortisone Therapy (Level III).* Adrenal insufficiency should be suspected in catecholamine-resistant hypotensive shock in children with a history of CNS abnormality or chronic steroid use or with purpura fulminans. Use of hydrocortisone in this situation may be lifesaving. Dose recommendations vary from a bolus of 1–2 mg/kg for stress coverage to 50 mg/kg for shock, followed by the same dose as a 24-hr infusion.

## Stabilization: Beyond the First Hour

*Goals (Level III).*

Normal perfusion

Perfusion pressure (MAP-CVP or MAP-IAP) appropriate for age

Superior vena cava or mixed venous oxygen saturation of >70%

CI of >3.3 L/min/m² and <6.0 L/min/m²

*Therapeutic End Points (Level III).* Therapeutic end points are capillary refill of <2 secs, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output >1 mL/kg/hr, normal mental status, CI >3.3 and <6.0 with normal perfusion pressure (MAP-CVP or MAP-IAP) for age, and superior vena cava or mixed venous oxygen saturation >70%. Maximize preload to maximize CI.

*Monitoring (Level III).*

Pulse oximetry

Continuous electrocardiography

Continuous intraarterial blood pressure

Temperature

Urine output

Central venous pressure and oxygen saturation

Pulmonary artery pressure and oxygen saturation

Cardiac output

Glucose and calcium

*Fluid Resuscitation (Level II).* Fluid losses and persistent hypovolemia secondary to diffuse capillary leak can continue for days. Ongoing fluid replacement should be directed at clinical end points, including perfusion, pulmonary capillary occlusion pressure, and cardiac output. Crystalloid is the fluid of choice in patients with hemoglobin >10 g/dL. Packed red blood cell transfusion can be given to children with hemoglobin <10 g/dL.

*Hemodynamic Support (Level II).* Hemodynamic support can be required for days in children with fluid-refractory shock. Children can present with low cardiac output and high systemic vascular resistance, high cardiac output and low systemic vascular resistance, or low cardiac output and low systemic vascular

**Table 3.** Threshold heart rates and perfusion pressure (MAP-CVP or MAP-IAP) for age[a]

| Term Newborn (yrs) | Heart Rate (beats/min) | MAP-CVP (cm H₂O) |
|---|---|---|
| | 120–180 | 55 |
| ≤1 | 120–180 | 60 |
| ≤2 | 120–160 | 65 |
| ≤7 | 100–140 | 65 |
| ≤15 | 90–140 | 65 |

MAP-CVP, mean arterial pressure–central venous pressure.

[a]Adapted with permission from Johnson KB: The Harriet Lane Handbook. 13th Edition. St. Louis, Mosby Year-Book, 1993; and Report of the Second Task Force on Blood Pressure Control in Children–1987 (161, 162).

resistance shock. Although children with persistent shock frequently have worsening cardiac failure, hemodynamic states may completely change over time. A pulmonary artery catheter should be placed when poor perfusion, including reduced urine output, acidosis, or hypotension, persists despite use of hemodynamic therapies guided by clinical examination, blood pressure analysis, echocardiographic analysis, and arterial and superior vena cava oxygen saturation analysis. Children can respond to a change in hemodynamic therapeutic regimen with resolution of shock. Therapies should be adjusted to maintain mixed venous oxygen saturation >70%, CI of >3.3 L/min/m$^2$, and a normal perfusion pressure for age (MAP-CVP), with the ultimate goal of restoration of normal perfusion. There is no benefit to increasing oxygen delivery beyond the point of oxygen consumption plateau (critical point of oxygen delivery).

*Shock with Low CI (Level II).* Epinephrine is usually the first-line drug for dopamine-resistant shock. If hemodynamics are dependent on epinephrine and the cortisol level is <18 mg/dL, hydrocortisone at stress or shock doses may begin. If T$_4$ or T$_3$ level is low and sick euthyroid syndrome has been excluded, oral levothyroxine or, if necessary, intravenous liothyronine can be used to restore normal values for age.

*Shock with Low CI, Normal Blood Pressure, and High Systemic Vascular Resistance (Level II).* Nitroprusside or nitroglycerin are first-line vasodilators in patients with epinephrine-resistant shock and normal blood pressure. If cyanide or isothiocyanate toxicity develops from nitroprusside, or methemoglobin toxicity develops from nitroglycerin, or there is a continued low cardiac output state, then the clinician should substitute milrinone or amrinone. As noted above, the long half-life elimination of these drugs can lead to slowly reversible toxicities (hypotension or tachyarrhythmias), particularly if abnormal renal or liver function exists. Such toxicities can be reversed in part with norepinephrine infusion. Additional volume loading is necessary to prevent hypotension when loading doses are used.

*Shock with High CI and Low Systemic Vascular Resistance (Level II).* Norepinephrine is the drug of choice for age-dependent dopamine resistance. If hemodynamics are dependent on norepinephrine and the cortisol levels are <18 mg/dL, then hydrocortisone at stress or

shock doses may be initiated. If the T$_4$ or T$_3$ level is low and sick euthyroid syndrome is excluded, then oral thyroxine or, if necessary, intravenous liothyronine can be given.

*Refractory Shock (Level II).* Children with catecholamine-refractory shock must be suspected to have unrecognized morbidities, including pericardial effusion, pneumothorax, hypoadrenalism, hypothyroidism, ongoing blood loss, intraabdominal catastrophe, necrotic tissue, and others. When these morbidities have been excluded, ECMO becomes an important alternative to consider. Currently, however, the expected survival is no greater than 50%. If the clinician suspects that outcome will be better with ECMO, flows >110 mL/kg may be required if vasodilation exists. Calcium concentration should be normalized in the red blood cell pump prime (usually requires 300 mg of CaCl$_2$ per unit of packed red blood cells).

## RECOMMENDATIONS FOR NEWBORN SEPTIC SHOCK

### Diagnosis

Septic shock should be suspected in any newborn with respiratory distress and reduced perfusion, particularly in the presence of a maternal history of chorioamnionitis or prolonged rupture of membranes. It is important to distinguish newborn septic shock from cardiogenic shock caused by closure of the patent ductus arteriosus in newborns with ductal dependent complex congenital heart disease. Any newborn with shock and hepatomegaly, cyanosis (a cardiac murmur), or differential upper and lower extremity blood pressures or pulses should be started on prostaglandin E$_1$ until complex congenital heart disease is ruled out by echocardiographic analyses. Newborn septic shock is typically accompanied by increased pulmonary artery pressures. Persistent pulmonary hypertension can cause right ventricle failure (Fig. 2).
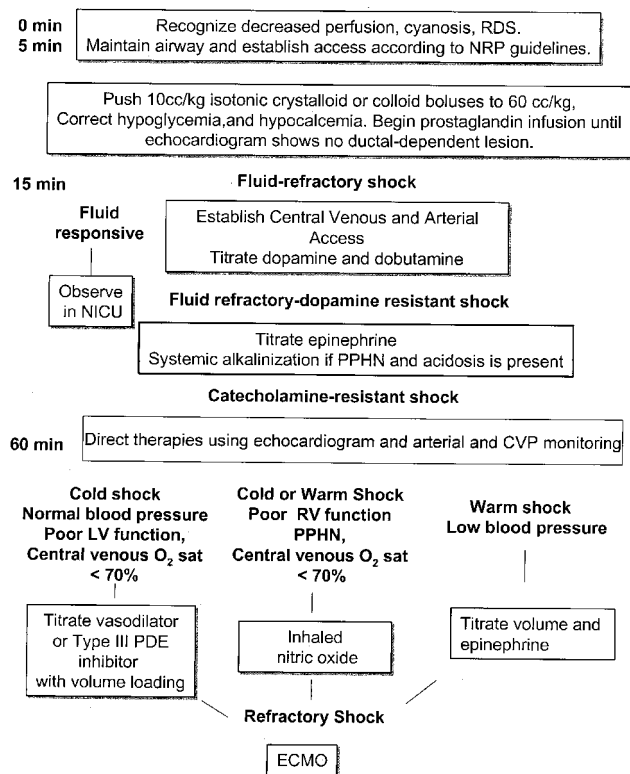


Figure 2. Recommendations for stepwise management of hemodynamic support in term newborns with goals of normal perfusion and perfusion pressure (mean arterial pressure − central venous pressure) and preductal and postductal oxygen saturation difference of <5%. Proceed to next step if shock persists. *RDS*, respiratory distress syndrome; *NRP*, neonatal resuscitation program; *NICU*, neonatal intensive care unit; *PPHN*, pulmonary hypertension of the newborn; *CVP*, central venous pressure; *LV*, left ventricular; *RV*, right ventricular; *PDE*, phosphodiesterase; *ECMO*, extracorporeal membrane oxygenation.

### ABCs: First Hour of Resuscitation

*Goals (Level III).*

Maintain airway, oxygenation, and ventilation

Maintain circulation (defined as normal perfusion and blood pressure)

Maintain neonatal circulation

Maintain threshold heart rates

*Therapeutic End Points (Level III).* Therapeutic end points include capillary refill of $<2$ secs, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output of $>1$ mL/kg/hr, normal mental status, normal blood pressure for age, difference in preductal and postductal oxygen saturation of $<5\%$, and oxygen saturation of $>95\%$.

*Monitoring (Level III).*

Temperature

Preductal and postductal pulse oximetry

Intra-arterial (umbilical or peripheral) blood pressure

Continuous electrocardiography

Blood pressure

Arterial pH

Urine output

Glucose and calcium

*Airway and Breathing (Level III).* Airway and breathing should be rigorously monitored and maintained. The decision to intubate and ventilate is made on clinical diagnosis of increased work of breathing or the moribund state. Volume loading is necessary during intubation and ventilation because of hypovolemia.

*Circulation (Level III).* Vascular access should be rapidly attained according to NRP. Placement of an umbilical arterial and venous catheter is preferred. If these catheters cannot be placed, a peripheral arterial and peripherally positioned central catheter can be placed.

*Fluid Resuscitation (Level II).* Rapid fluid boluses of 10 mL/kg should be administered, observing for the development of rales, hepatomegaly, and increased work of breathing. Up to 60 mL/kg may be required in the first hour. Fluid should be pushed, with a goal of attaining normal perfusion and blood pressure.

*Hemodynamic Support (Level II).* Patients with severe shock uniformly require vasoactive support during fluid resuscitation. Although dopamine can be used as the first-line agent, its effect on pulmonary vascular resistance should be taken into account. Usually, a combination of dopamine at low dosage ($<8$ mg/kg/min) and dobutamine (up to 30 μg/kg/min) is used; if the patient is not responsive to therapy, then epinephrine should be infused to restore normal blood pressure and perfusion.

*PPHN Therapy (Level II).* Hyperoxygenate initially with 100% oxygen, and institute metabolic alkalinization (up to pH 7.50) with $NaHCO_3$ or tromethamine. Mild hyperventilation can also be instituted until 100% oxygen saturation and $<5\%$ difference in preductal and postductal saturations are obtained. Therapeutic narcosis with fentanyl and paralysis with neuromuscular blockers should be considered to reduce pulmonary blood pressures in ventilated patients without response to the PPHN therapy outlined above. Inhaled nitric oxide should be administered when available.

### Stabilization: Beyond the First Hour

*Goals (Level III).*

Maintain threshold heart rate

Maintain normal perfusion and blood pressure

Maintain neonatal circulation

Central venous oxygen saturation $>70\%$

*Therapeutic End Points (Level III).*

Capillary refill $<2$ secs, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output $>1$ mL/kg/hr, normal mental status, normal blood pressure for age

$>95\%$ peripheral oxygen saturation

$<5\%$ difference in preductal and postductal saturation

Central venous oxygen saturation $>70\%$

Absence of right-to-left shunting, tricuspid regurgitation, or right ventricular failure on echocardiographic analysis

*Monitoring (Level III).*

Pulse oximetry

Arterial pH

Continuous electrocardiography

Continuous intra-arterial blood pressure

Temperature

Glucose and calcium

Urine output

Central venous pressure and oxygen saturation

*Fluid Resuscitation (Level II).* Fluid losses and persistent hypovolemia secondary to diffuse capillary leak can continue for days. Ongoing fluid replacement should be directed at clinical end points, including perfusion and CVC. Crystalloid is the fluid of choice in patients with hemoglobin $>12$ g/dL. Packed red blood cell transfusion can be added in newborns with hemoglobin $<12$ g/dL.

*Hemodynamic Support (Level II).* The pulmonary vascular reactivity will tend to decrease after 5 days of life, although this should be evaluated carefully before stopping therapies directed at PPHN. In the patient with suprasystemic pulmonary hypertension, right ventricle failure may accompany shock. This can make inotrope and vasopressor therapies less effective at supporting cardiac output. Therapies directed at reducing pulmonary artery pressure are paramount. Inhaled nitric oxide can be given with greatest effects usually found at 20 ppm. In newborns with poor left ventricle function and normal blood pressure, the addition of nitrosovasodilators or type III phosphodiesterase inhibitors can be effective but must be monitored for toxicities. It is important to volume load when using these systemic vasodilators.

*ECMO Therapy for Refractory Shock (Level II).* Newborns with refractory shock must be suspected to have unrec-

ognized morbidities, including pericardial effusion, pneumothorax, ongoing blood loss, hypoadrenalism, hypothyroidism, inborn errors of metabolism, or cyanotic or obstructive heart disease. When these causes have been excluded, ECMO becomes an important therapy to consider. The expected ECMO survival rate for newborn septic shock is currently 80%. Most centers accept refractory shock or a Pao$_2$ <40 mm Hg after maximal therapy to be sufficient indication for ECMO support. ECMO flows of >110 mL/kg may be required when vasodilation exists. When administering venoarterial ECMO, persistent hypotension or shock should be treated with dopamine or epinephrine because vasodilation is the likely cause. The venoarterial system provides inotropic support. Inotrope requirements frequently lessen when venoarterial ECMO is used. Calcium concentration should be normalized in the red blood cell pump prime (usually requires 300 mg of CaCl$_2$ per unit of packed red blood cells).

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## APPENDIX

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