Special Article

American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock

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DOI: 10.1097/CCM.0000000000002425

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Group leaders and subgroups are identified in **Appendix 1**.

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The American College of Critical Care Medicine (ACCM), which honors individuals for their achievements and contributions to multidisciplinary critical care medicine, is the consultative body of the Society of Critical Care Medicine (SCCM) that possesses recognized expertise in the practice of critical care. The College has developed administrative guidelines and clinical practice parameters for the critical care practitioner. New guidelines and practice parameters are continually developed, and current ones are systematically reviewed and revised.

Dr. Davis served as an expert witness regarding a patient who herniated post operatively. Dr. Aneja received funding from UpToDate royalties. Dr. Relvas participates in AAP PrepICU (editorial board member). Dr. Williams participates in American Academy of Pediatrics (guidelines committee work). Dr. Yeh participates in American Academy of Pediatrics (guidelines committee work). Dr. Brierley received funding from Astellas Pharmaceuticals Speakers Bureau (regarding anti-fungals in the ICU). He participates as a member in the American Academy of Pediatrics, Academic Pediatric Association, and Society for Academic Emergency Medicine. Dr. de Caen participates in the Royal College of Physicians and Surgeons of Canada and the American Heart Association. Dr. Cheifetz received funding from Philips (medical advisor) and Ikaria (medical advisor). He participates in various volunteer activities for AARC and ATS, and he has served as an expert witness for testimony for medical malpractice cases. Dr. Choong participates as an Executive Member of the Canadian Critical Care Trials Group, and is an employee of the Hamilton Health Sciences. Dr. Conway participates as Chair of Section on Pediatric CCM for the AAP. He has served as an expert witness for pediatric CCM/ED defense cases. Dr. Cornwell received grant funding from the Coulter Foundation. He participates in the Society of Pediatric Research. Dr. Doctor received funding from consulting for Novartis, Galera Pharmaceuticals, and Terumo BCT. Dr. Fortenberry participates in American Academy of Pediatrics, Extracorporeal Life Support Organization. He served as an expert witness for review of PICU cases and testimony in support of physicians providing PICU care. Dr. Greenwald served as an expert witness for testimony regarding course of illness and risk of mortality. Dr. Hall serves as the Editor for the ATS Online Journal Club. Dr. Irazuzta participates in the National Institutes of Health. Dr. van der Jagt received grant funding from University of Rochester (employee/faculty). She participates in NYS Emergency Medical Services for Children Advisory Committee (Vice-Chair); University of Rochester School of Medicine (faculty); AHA Pediatric Advanced Life Support Advanced Life Support Writing Group (member); IPSO National Expert Advisory Committee (member); FAAP, Sr. Fellow Society of Hospital Medicine; and Fellow College of Pediatricians. Dr. Jeffries participates in AAP, Ped Cardiac Intensive Care Society, and ACC. Dr. Kache participates on the Global health Educators Committee in Association of Pediatric Program Directors, and on the Global Health Education Sub-Comittee in Consortium of Universities for Global Health. Dr. Kon participates as the President-elect for the American Society for Bioethics and Humanities. He disclosed he is a government employee. He has served as an expert witness for peds critical care and bioethics. Dr. MacLaren received funding from UpToDate (royalties). He participates in the Asia-pacific Chapter of ELSO (Chair) and the Pediatric Cardiac Intensive Care Society (Vice President). Dr. Maul received funding from consulting for Mallinkrodt, Thoratec, and Alung. He received grant funding. He participates in ASAIO (editor) and ELSO (committee member). Dr. Odetola participates as a member of the Sub-Board of Critical Care Medicine, American Board of Pediatrics. Dr. Parbuoni participates in the American Society of Health-System Pharmacists and California Society of Health-System Pharmacists. Dr. Reuter-Rice received funding from J & B Learning (textbook royalties). She received grant funding from RWJK. She participates in PNCB-IPN, AAN, and ISONG. Dr. Schnitzler participates in Sociedad Argentina de Terapia Intensiva, Sociedad Argentina de Calidad en Asistencia Sanitaria, and Instituto Técnico de Acreditación de Establecimientos Sanitarios. Dr. Torres received funding from Abbott Point of Care (speaker).

He served as an expert witness for the defense paid for his time. Dr. Weiss received funding from honoraria to grand rounds lectures from ThermoFisher Scientific (but content of lecture was solely his own responsibility). He participates in AAP and Shock Society. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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Objectives: The American College of Critical Care Medicine provided 2002 and 2007 guidelines for hemodynamic support of newborn and pediatric septic shock. Provide the 2014 update of the 2007 American College of Critical Care Medicine "Clinical Guidelines for Hemodynamic Support of Neonates and Children with Septic Shock."

Design: Society of Critical Care Medicine members were identified from general solicitation at Society of Critical Care Medicine Educational and Scientific Symposia (2006–2014). The PubMed/Medline/Embase literature (2006–14) was searched by the Society of Critical Care Medicine librarian using the keywords: sepsis, septicemia, septic shock, endotoxemia, persistent pulmonary hypertension, nitric oxide, extracorporeal membrane oxygenation, and American College of Critical Care Medicine guidelines in the newborn and pediatric age groups.

Measurements and Main Results: The 2002 and 2007 guidelines were widely disseminated, translated into Spanish and Portuguese, and incorporated into Society of Critical Care Medicine and American Heart Association/Pediatric Advanced Life Support sanctioned recommendations. The review of new literature highlights two tertiary pediatric centers that implemented quality improvement initiatives to improve early septic shock recognition and first-hour compliance to these guidelines. Improved compliance reduced hospital mortality from 4% to 2%. Analysis of Global Sepsis Initiative data in resource rich developed and developing nations further showed improved hospital mortality with compliance to first-hour and stabilization guideline recommendations.

Conclusions: The major new recommendation in the 2014 update is consideration of institution–specific use of 1) a "recognition bundle" containing a trigger tool for rapid identification of patients with septic shock, 2) a "resuscitation and stabilization bundle" to help adherence to best practice principles, and 3) a "performance bundle" to identify and overcome perceived barriers to the pursuit of best practice principles. (*Crit Care Med* 2017; 45:1061–1093)

Key Words: hemodynamics; newborn; pediatric; septic shock

In 1998, the Institute of Medicine called for establishment of best practice guidelines across medicine. In 2002 and 2007, the American College of Critical Care Medicine (ACCM) Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Shock (1, 2) were published in part to replicate the reported outcomes associated with implementation of "best clinical practices" (mortality rates of 0–5% in previously healthy [3–5] and 10% in chronically ill children with septic shock [5]). Of note, neonatal and pediatric severe sepsis outcomes were already improving prior to 2002 with the advent of neonatal and pediatric intensive care (reduction in mortality from 97% to 9%) (6–9) and were markedly better than in adults (9% compared with 28% mortality) (8). There are two purposes served by this 2014 update of these 2002/2007 Clinical Practice Parameters. First, this 2014 update examines and grades new studies performed to test the utility and efficacy of the 2007 recommendations. Second, this 2014 update examines and grades relevant new treatment and outcome studies to determine to what degree, if any, the 2007 guidelines should be modified.

METHODS

Clinical investigators and clinicians affiliated with the Society of Critical Care Medicine (SCCM) who had special interest in hemodynamic support of pediatric patients with sepsis volunteered to be members of the update task force. Subcommittees were formed to review the literature and make recommendations using Grading of Recommendations Assessment, Development and Evaluation methodology. A strong recommendation received the "number" grade 1 and a weak recommendation received the number grade 2. The strength of the literature used to support these number recommendations was given "letter" grades with A equals to multiple randomized controlled trials and at least one meta-analysis, B equals to one randomized controlled trial, C equals to cohort, case control studies, and D equals to expert opinion and case reports. There is common discordance between strength of recommendation and strength of literature providing impetus to study most all recommendations made. The recommendations are largely based on opinion regarding the systematic review by a number of subcommittees, with editorial decision regarding content done initially by group leaders, and ultimately by the chairperson.

The PubMed/Medline/Embase literature (2006–2014) was searched by the SCCM librarian using the keywords: sepsis, septicemia, septic shock, endotoxemia, persistent pulmonary hypertension, nitric oxide, extracorporeal membrane oxygenation (ECMO), and ACCM guidelines in the newborn and pediatric age groups who identified 3,382 potential references. The search was refined by each of the subgroup leaders to identify studies specifically relevant to children and newborns ($n = 143$; see **supplement for CONSORT**, Supplemental Digital Content 1, http://links.lww.com/CCM/C598). The group members were asked to change the recommendations from 2007 in the new 2014 update only if there was new pediatric evidence since 2007 that warranted such change. The committee members graded all old and new recommendations (see above) because different systems had been used in the prior 2002 or 2007 documents. Due to the diverse, multidisciplinary, international composition of the SCCM membership, and the document's task force committee members, this update continues to follow the lead of the previous guidelines making recommendations on hemodynamic support medications which may or may not be approved by the U.S. Food and Drug Administration, but which are approved and used in other nations, such as levosimendan, terlipressin, and enoximone.

RESULTS

Evolution of the 2002, 2007, and 2014 Guidelines

Many studies have tested the observations and recommendations of the 2002 and 2007 guidelines (1, 2). Studies in the resource rich

setting, where mechanical ventilators, IV infusion pumps, inotrope medications, and intensive care monitoring are available, have uniformly favored use of the ACCM/Pediatric Advanced Life Support (PALS) guidelines. Han et al (10) showed an association between early use of practice consistent with the 2002 guidelines in the community hospital and improved outcomes in newborns and children (mortality rate 8% vs 38%; number needed to treat = 3.3). Every hour that went by without restoration of normal blood pressure for age and capillary refill less than 3 seconds was associated with a two-fold increase in adjusted mortality odds ratio (10). Ninis et al (11) similarly reported an association between delay in inotrope resuscitation and a 22.6-fold increased adjusted mortality odds ratio in meningococcal septic shock which led to the new guideline recommendation in 2007 that inotropes be started through peripheral infusion in children with fluid-refractory septic shock until central access is attained. Ventura et al (12) tested this 2007 recommendation in a randomized trial and found that use of peripheral adrenaline infusion reduced mortality to 7% compared with 20% with use of peripheral dopamine infusion until central access was attained. de Oliveira et al (13) reported in a randomized trial that use of the 2002 guidelines with continuous central venous oxygen saturation ($Scvo_2$) monitoring and therapy directed to maintenance of $Scvo_2$ greater than 70%, reduced mortality from 39% to 12% (NNT = 3.6) compared with therapy directed only to blood pressure and capillary refill. Sankar et al (14) corroborated this finding in a cohort study in a population of Indian children showing that directing therapy to $Scvo_2$ was associated with improved outcome with a number needed to treat equals to five. In a before and after study, Karapinar et al (15) reported that implementation of the 2002 guidelines in a U.S. tertiary center achieved best practice outcome with a fluid-refractory shock 28-day mortality of 3% and hospital mortality of 6% (3% in previously healthy children; 9% in chronically ill children). This outcome matched the "best practice outcomes" targeted by the 2002 guidelines (3–5). Similar to the experience of St. Mary's Hospital before 2002 (4), Sophia Children's Hospital in Rotterdam also reported a reduction in mortality rate from purpura and severe sepsis from 20% to 1% after implementation of 2002 guideline-based therapy in the referral center, transport system, and tertiary care settings (16). Both of these centers also used high flux continuous renal replacement therapy (CRRT) and fresh frozen plasma infusion directed to the goal of normal international normalized ratio (prothrombin time [PT]).

In contrast, the findings have been mixed in the "resource poor setting" where there is not access to mechanical ventilators, IV infusion pumps, inotrope medications, and intensive care monitoring. Wills et al (17) demonstrated near 100% survival when fluid resuscitation was provided to children with dengue shock in the first hour. In contrast, Maitland et al (18) (NEJM, 2011) found fluid boluses were harmful compared with maintenance IV fluid infusion and blood transfusion in severe malaria endemic sub-Saharan Africa. The Maitland study included a large population of children with severe malaria and anemia, and excluded cases with gastroenteritis or hypovolemia, whereas the Wills study only included a population of children with dengue shock, with capillary leak, hemoconcentration, and dehydration with gastroenteritis and hypovolemia. Importantly, neither of these studies formally tested fluid bolus use as recommended in the 2002 and 2007 ACCM guidelines because boluses were given without attention to the presence of rales and hepatomegaly in the patients, and without attention to electrolyte balance, or subsequent fluid removal as needed.

The 2002 and 2007 ACCM guidelines specifically recommend against fluid boluses when rales or hepatomegaly are present, instead recommend inotropic support for these patients (1, 2). The basic tenet of fluid resuscitation proposed in the ACCM guidelines is that "some do" and "some do not" require fluid resuscitation. Hypovolemic shock patients require fluid boluses, whereas euvolemic and hypervolemic patients do not. Severely anemic patients require blood transfusion, severely malnourished children require slow feeding, and patients with congestive heart failure or fluid overload require inotropes and diuretics, not fluid boluses.

There is general consensus among the committee members that these studies indirectly and directly support the utility and efficacy of implementation of the time-sensitive, goal-directed recommendations of the 2002 and 2007 ACCM/PALS guidelines in the "resource rich" setting. In this regard, since 2007 there has been a major effort in the United States to test the first-hour recommendations in pediatric academic centers in the American Academy of Pediatrics collaborative Septic Shock consortium which is dedicated to quality improvement in septic shock recognition and treatment. There have been four studies conducted in tertiary pediatric emergency departments that have examined adherence to ACCM/PALS guidelines for sepsis resuscitation in the first hour (19–22). Together, these studies demonstrated incomplete adherence to recommended goals for administration of IV fluids, antibiotics, and vasoactive agents. Subsequent quality-directed efforts from these studies showed improvement in both process metrics (e.g., decreased time to administration of IV fluids, antibiotics, and peripheral vasoactive agents) (19–22) and outcome metrics, including hospital and PICU length of stay and mortality (20–22). Importantly, all quality improvement studies were predicated on rapid identification of patients with suspected septic shock to trigger rapid clinician evaluation and implementation of appropriate resuscitation efforts. Multiple elements have been incorporated into trigger tools with success by several institutions (23, 24); however, there has been notable variation in the algorithms used at each institution, and none have sufficient evidence to fully endorse as a specific tool. Given the complexity of resource allocation and implementation, it seems reasonable that each institution could locally develop their trigger tool, whereas further studies refine the derivation and validation of an optimally sensitive and specific sepsis trigger tool (24).

From the best practice model standpoint, Paul et al (22) implemented a hospital-wide quality improvement initiative to improve compliance with all five elements of the ACCM/PALS guidelines first-hour recommendations: 1) recognition, 2) establishing IV access, 3) starting IV fluids and resuscitation as needed, 4) administering antibiotics, and 5) starting vasoactive agents if needed. Achievement of 100% compliance required a number of human interaction interventions including use of

time clocks set to have time going from 0 to 60 minutes rather than from 60 to 0 minutes that resulted in an increase in number of cases between death occurrences ($p < 0.05$) with an overall reduction in hospital mortality from 4.0% to 1.7%.

Han et al (25) analyzed the international Global Sepsis Initiative database which included children from resource rich settings in Europe, North America, and South America in order to derive "three-element" bundles associated with improved outcomes. The first-hour/emergency department three-element bundle included 1) reversal of shock defined by normal blood pressure and capillary refill less than 3 seconds, 2) provision of antibiotics, and 3) provision of D10 and sodium containing IV fluid infusion. The stabilization/PICU three-element bundle included 1) reversal of shock defined by maintaining normal mean arterial pressure (MAP)-central venous pressure (CVP) for age and $Scvo_2$ greater than 70%, 2) timely provision of the appropriate sensitive antibiotic and source control, and 3) maintenance of effective tidal volumes between 6 and 8 mL/kg in children mechanically ventilated with acute respiratory distress syndrome (ARDS). Reversal of shock was associated with use of the 2007 ACCM/PALS guidelines in both the resuscitation and stabilization bundles (2).

Major New Recommendations in the 2014 Update

Due to the success of the 2002 and 2007 guidelines (1, 2), the 2014 update compilation and discussion of the new literature were directed to the question of what changes, if any, should be implemented in the update. The members of the committee were asked whether there are clinical practices which the "best outcome practices" are using in 2014 that are not recommended in the 2002 and 2007 guidelines and should be recommended in the 2014 guidelines? "The changes recommended were few. Most importantly, there was no change in emphasis between the 2002 guidelines and the 2014 update. The continued emphasis is directed to 1) first-hour fluid resuscitation and inotrope therapy directed to goals of threshold heart rates, normal blood pressure, and capillary refill less than or equal to 2 seconds with specific evaluation after each bolus for signs of fluid overload, as well as first-hour antibiotic administration and 2) subsequent ICU hemodynamic support directed to goals of $Scvo_2$ greater than 70% and cardiac index (CI) 3.3–6.0 L/min/m^2 with appropriate antibiotic coverage and source control."

The major new recommendation in the 2014 update is that hemodynamic support of septic shock now be addressed at the institutional level rather than only at the practitioner level with well-planned coordination between the family, community, prehospital, emergency department, hospital, and ICU settings. The new guidelines recommend that each institution implements their own adopted or home-grown bundles that include the following:

1) Recognition bundle containing a trigger tool for rapid identification of patients with suspected septic shock at that institution,
2) Resuscitation and stabilization bundle to drive adherence to consensus best practice at that institution, and
3) Performance bundle to monitor, improve, and sustain adherence to that best practice.

The new 2014 guidelines provide examples of each bundle (**Fig. 1**) for consideration and review by each hospital's expert committee.

LITERATURE AND BEST PRACTICE REVIEW

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 (26). Adults have myocardial dysfunction manifested as a decreased ejection fraction; however, cardiac output (CO) is usually maintained or increased by two mechanisms: tachycardia and ventricular dilation. Adults who do not develop this adaptive process to maintain CO have a poor prognosis (27, 28). "Pediatric septic shock" is typically associated with severe hypovolemia, and children frequently respond well to aggressive volume resuscitation; however, the hemodynamic response of fluid resuscitated children seems diverse compared with adults. Contrary to the adult experience, low CO, not low systemic vascular resistance (SVR), is associated with mortality in pediatric septic shock (29–40). Attainment of the therapeutic goal of CI 3.3–6.0 L/min/m^2 may result in improved survival (30, 38). Also contrary to adults, a reduction in oxygen delivery rather than a defect in oxygen extraction is the major determinant of oxygen consumption (Vo_2) in children (31). Attainment of the therapeutic goal of Vo_2 greater

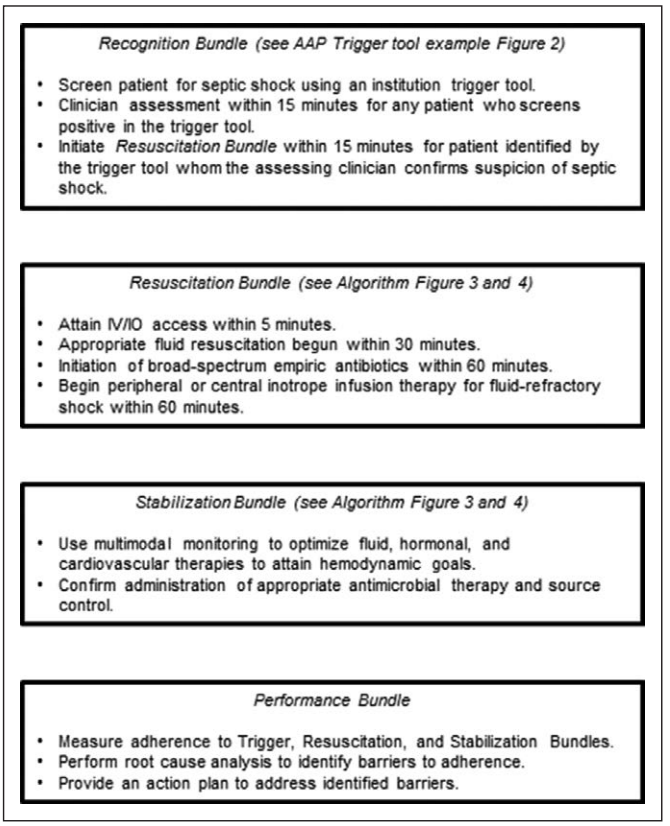

Figure 1. Examples of recognition, resuscitation, stabilization, and performance bundles.

than 200 mL/min/m^2 may also be associated with improved outcome (30).

It was not until 1998 that investigators reported patient outcome when aggressive volume resuscitation (60 mL/kg fluid in the first hour) and goal-directed therapies (goal = CI, 3.3–6.0 L/min/m^2 and normal pulmonary artery occlusion pressure [PAOP]) were applied to children with septic shock (38). Ceneviva et al (38) reported 50 children with fluid-refractory (≥ 60 mL/kg in the first hour), dopamine-resistant shock. The majority (58%) showed a low CO/high SVR state, and 22% had low CO and low vascular resistance. Hemodynamic states frequently progressed and changed over the first 48 hours. 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/low SVR state (41–44). Inotropes, vasopressors, and vasodilators were directed to maintain normal CI and SVR in the patients. Mortality from fluid-refractory, dopamine-resistant septic shock in this study (18%) was markedly reduced compared with mortality in the 1985 study (58%) (30), in which aggressive fluid resuscitation could not be accomplished in part because intraosseous vascular access was not yet commonly used and attainment of intravascular access in the resuscitation bay was difficult. More recently investigators in the United Kingdom confirmed these observations using Doppler ultrasound to measure CO (39, 40). They found that previously healthy children with community-acquired sepsis often had a low CO with a higher mortality rate, whereas CO was high and mortality rate was low in septic shock related to catheter-associated blood stream infections (39).

"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 (PDA) and foramen ovale. This flow pattern is maintained by supra systemic pulmonary vascular resistance in the prenatal period. At birth, inhalation of oxygen triggers a cascade of biochemical events that ultimately result in reduction in pulmonary vascular resistance and artery pressure and transition from fetal to neonatal circulation with blood flow now being directed through the pulmonary circulation. Closure of the PDA and foramen ovale (that can occur much later) complete this transition. Pulmonary vascular resistance and artery pressures can remain elevated and the ductus arteriosus can remain open for the first 6 weeks of life, whereas the foramen ovale may remain probe patent for years. Sepsis-induced acidosis and hypoxia can increase pulmonary vascular resistance and 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 CO, and increased pulmonary, mesenteric, and SVR (45–48). 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 birth weight (VLBW) infants with septic shock (< 32-wk gestation, < 1,000 gm) is least understood. Most hemodynamic information is derived only from echocardiographic evaluation, and there are few septic shock studies in this population. Neonatology investigators often fold septic shock patients into "respiratory distress syndrome" and "shock" studies rather than conduct septic shock studies alone. Hence, the available clinical evidence on the hemodynamic response in premature infants for the most part is in babies with respiratory distress syndrome or shock of undescribed etiology. In the first 24 hours after birth during the "transitional phase," the neonatal heart must rapidly adjust to a high vascular resistance state compared with the low resistance placenta. CO and blood pressure may decrease when vascular resistance is increased (49). However, the literature indicates that premature infants with shock can respond to volume and inotropic therapies with improvements in stroke volume (SV), contractility, and blood pressure (50–63).

Several other developmental considerations influence shock therapy in the premature infant. Relative initial deficiencies in the thyroid and parathyroid hormone axes have been reported and can result in the need for thyroid hormone and/or calcium replacement (64, 65). Hydrocortisone has been examined in this population as well. Since 2002, randomized controlled trials showed that prophylactic use of hydrocortisone on day 1 of life reduced the proportion of patients with hypotension in this population (66), and a 7-day course of hydrocortisone reduced the need for inotropes in VLBW infants with septic shock (67–69). Immature mechanisms of thermogenesis require attention to external warming. Reduced glycogen stores and muscle mass for gluconeogenesis require attention to maintenance of serum glucose concentration. Standard practices in resuscitation of preterm infants in septic shock employ a more graded approach to volume resuscitation and vasopressor therapy compared with resuscitation of term neonates and children. This more cautious approach is a response to anecdotal reports that preterm infants at risk for intraventricular hemorrhage (< 30-wk 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 under perfusion) more than to intraventricular hemorrhage. Another complicating factor in VLBW infants is the persistence of the PDA. This can occur because immature muscle is less able to constrict. The majority of infants with this condition are treated medically with indomethacin, or in some circumstances with surgical ligation. Rapid administration of fluid may further increase left to right shunting through the ductus with resultant pulmonary edema.

One single-center, randomized control trial reported improved outcome with use of daily 6-hour pentoxyfilline

infusions in very premature infants with sepsis (70, 71). This compound is both a vasodilator and an anti-inflammatory agent. A Cochrane analysis agrees that this promising therapy deserves evaluation in the multicenter trial setting (72).

What Clinical Signs and Hemodynamic Variables Can Be Used to Direct Treatment of Newborn and Pediatric Shock?

Shock can be defined by clinical variables, hemodynamic variables, oxygen utilization variables, and/or cellular variables. However, after review of the literature, the committee continues to choose to define septic shock by clinical, hemodynamic, and oxygen utilization variables only.

Ideally, septic shock should be diagnosed by clinical signs, which include hypothermia or hyperthermia, altered mental status, and peripheral vasodilation (warm shock) or vasoconstriction with capillary refill greater than 2 seconds (cold shock) before hypotension occurs. Threshold heart rates (HRs) associated with increased mortality in critically ill (not necessarily septic) infants are a HR less than 90 or greater than 160 beats/min, and in children are a HR less than 70 or greater than 150 beats/min (73). Emergency department therapies should be directed toward restoring normal mental status, threshold HRs, peripheral perfusion (capillary refill < 3 s), palpable distal pulses, and blood pressure for age (10). Carcillo et al (74) reported that specific hemodynamic abnormalities in the emergency department were associated with progressive increase in mortality (%): eucardia (1%) less than tachycardia/bradycardia (3%) less than hypotension with capillary refill less than 3 seconds (5%) less than normotension with capillary refill longer than 3 seconds (7%) less than hypotension with capillary refill longer than 3 seconds (33%). Reversal of these hemodynamic abnormalities using ACCM/PALS recommended therapy was associated with a 40% reduction in mortality odds ratio regardless of the stage of hemodynamic abnormality at the time of presentation (74).

In both neonates and children, shock should be further evaluated and resuscitation treatment guided by hemodynamic variables including perfusion pressure (MAP – CVP) and CO. Invasive blood pressure monitoring provides more accurate reflection of vasomotor state. Shock has historically been divided into warm and cold based on clinical examination, inferring vasodilation or vasoconstriction based on warm and cold phenotypes, respectively. This categorization has been demonstrated to be fraught with errors. Indeed, as many as 66% of children judged by experienced clinicians to be in "cold shock" were noted to be vasodilated on invasive monitoring (75). Blood flow (Q) varies directly with perfusion pressure (ΔP) and inversely with resistance (R). This is mathematically represented by $Q = \Delta P/R$. For the systemic circulation, this is represented by CO = MAP – CVP/SVR. This relationship is important for organ perfusion. In the kidney, for example, renal blood flow = mean renal arterial pressure (mRAP) – mean renal venous pressure/renal vascular resistance. Some organs (including the kidney and brain) have vasomotor autoregulation, which maintains blood flow in low blood pressure (MAP or RAP) states; however, at some critical point, perfusion pressure is reduced below the ability of the organ to maintain blood flow.

Therefore, the goal of shock treatment is to maintain perfusion pressure above the critical point below which blood flow cannot be effectively maintained in individual organs. Kumar et al (76) demonstrated in children with severe CNS infections and sepsis that therapies targeted to preservation of a minimum cerebral perfusion pressure (CPP) rather than to intracranial pressure (ICP) reduced mortality from 38.2% in the ICP control group to 18.2% in the CPP preservation group. The mean blood pressure in the CPP targeted group was the 90th percentile for age supporting targeting a mean blood pressure greater than 50th percentile for age (76). The kidney receives the second highest blood flow relative to its mass of any organ in the body, and measurement of urine output (with the exception of patients with hyperosmolar states such as hyperglycemia which leads to osmotic diuresis) and creatinine clearance can be used as an indicator of adequate perfusion pressure. Maintenance of MAP with norepinephrine has been shown to improve urine output and creatinine clearance in hyperdynamic sepsis (77, 78). Producing a supranormal MAP above this point is likely not of benefit (78) and may actually decrease CO by increasing afterload above the capacity of the myocardium to compensate.

In addition, reduction in perfusion pressure below the critical point necessary for adequate splanchnic organ perfusion can also occur in disease states with increased intra-abdominal pressure (IAP) such as bowel wall edema, ascites, or abdominal compartment syndrome. If this increased IAP is not compensated for by an increase in MAP, then splanchnic perfusion pressure is decreased. Therapeutic reduction of IAP (measured by intrabladder pressure) using diuretics and/or peritoneal drainage for IAP greater than 12 mm Hg, and surgical decompression for greater than 30 mm Hg, results in restoration of perfusion pressure and has been shown to improve renal function in children with burn shock (79).

Normative blood pressure values in the VLBW newborn have been reassessed. A MAP less than 30 mm Hg is associated with poor neurologic outcome and survival and is considered the absolute minimum tolerable blood pressure in the extremely premature infant (51). Since blood pressure does not necessarily reflect CO, it is recommended that normal CO and/or superior vena cava (SVC) flow, measured by Doppler echocardiography, be a primary goal as well (80–90).

Although perfusion pressure is used as a surrogate marker of adequate flow, the previous equation shows that organ blood flow (Q) correlates directly with perfusion pressure but indirectly with vascular resistance. If the ventricle is healthy, an elevation of SVR results in hypertension with maintenance of CO. Conversely, if ventricular function is reduced, the presence of normal blood pressure with high vascular resistance means that CO is reduced. If the elevation in vascular resistance is marked, the reduction in blood flow results in shock. A CI between 3.3 and 6.0 L/min/m^2 is associated with best outcomes in septic shock patients (29, 39, 40) compared to patients without septic shock for whom a CI above

2.0 L/min/m^2 is sufficient (91). Attainment of this CO goal is often dependent on attaining threshold HRs. However, if the HR is too high, then there is not enough time to fill the coronary arteries during diastole, and contractility and CO will decrease. Coronary perfusion may be further reduced when an unfavorable transmural coronary artery filling pressure is caused by low diastolic blood pressure (DBP) and/or high end-diastolic ventricular pressure. In this scenario, efforts should be made to improve coronary perfusion pressure and reverse the tachycardia by giving volume if the end-diastolic volume is low, or an inotrope if contractility is low. Because CO = HR × SV, therapies directed to increasing SV will often reflexively reduce HR and improve CO. This will be evident in improvement of the shock index (HR/systolic blood pressure [SBP]) (92), as well as CO. Children have limited HR reserve compared with adults because they are already starting with high basal HRs. For example, if SV is reduced due to endotoxin-induced cardiac dysfunction, an adult can compensate for the fall in SV by increasing HR two-fold from 70 to 140 beats/min, but a baby cannot increase from 140 to 280 beats/min. Although tachycardia is an important method for maintaining CO in infants and children, the younger the patient, the more likely this response will be inadequate and the CO will fall. In this setting, the compensatory response to falling SV and contractility is to vasoconstrict to maintain blood pressure. Increased vascular resistance is clinically identified by absent or weak distal pulses, cool extremities, prolonged capillary refill, and narrow pulse pressure with relatively increased DBP. The effective approach for these children is vasodilator therapy with additional volume loading as vascular capacity is expanded. Vasodilator therapy reduces afterload and increases vascular capacitance. This shifts the venous compliance curve so that more volume can exist in the right and left ventricle at a lower pressure. In this setting, giving volume to restore filling pressure results in a net increase in end-diastolic volume (i.e., preload) and a higher CO at the same or lower filling pressures. Effective use of this approach results in a decreased HR and improved perfusion.

At the other end of the spectrum, a threshold minimum HR is also needed because if the HR is too low, then CO will be too low (CO = HR × SV). This can be attained by using an inotrope that is also a chronotrope. In addition to threshold HRs, attention must also be paid to DBP. If the DBP-CVP is too low, then addition of an inotrope/vasopressor agent such as norepinephrine will be required to improve diastolic coronary blood flow. Conversely, if wall stress is too high due to an increased end-diastolic ventricular pressure secondary to fluid overload, then a diuretic may be required to improve SV by moving leftward on the overfilled Starling function curve. The effectiveness of these maneuvers will similarly be evidenced by improvement in the HR/SBP shock index, CO, and SVR along with improved distal pulses, skin temperature, and capillary refill.

In addition, shock should be treated according to oxygen utilization measures. Measurement of CO and oxygen consumption was 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 greater than 200 mL/min/m^2 is associated with improved survival (29). Low CO is associated with mortality in pediatric septic shock (29–38). In one study, children with fluid-refractory, dopamine-resistant shock were treated with goal-directed therapy (CI, > 3.3 and < 6 L/min/m^2) and found to have improved outcomes compared with historical reports (38). Because low CO is associated with increased oxygen extraction (30), $Scvo_2$ saturation can be used as an indirect indicator of whether CO is adequate to meet tissue metabolic demand. If tissue oxygen delivery is adequate, then assuming a normal Sao_2 of 100%, mixed venous saturation is greater than 70%. Assuming a hemoglobin concentration of 10 g/dL and 100% arterial oxygen saturation, then a CI greater than 3.3 L/min/m^2 with a normal Vo_2 of 150 mL/min/m^2 (oxygen consumption = CI × [arterial oxygen content – venous oxygen content]) results in a mixed venous saturation of greater than 70%: 150 mL/min/m^2 = 3.3 L/min/m^2 × (1.36 × 10 g/dL + Pao_2 × 0.003) × 10 × (1–0.7). Since 2002, de Oliveira et al (13) performed a randomized controlled trial in children with septic shock showing a reduction in mortality from 39% to 12% when directing therapy to the goal of $Scvo_2$ saturation greater than 70% (NNT, 3.6) (93). Sankar et al (14) observed an association with reduced mortality from 54% to 33.3% (NNT, 5) and lower organ dysfunction with a similar $Scvo_2$ saturation goal of greater than 70%. In contrast, supranormal $Scvo_2$ saturations greater than 80–85% that reflect a narrowed arteriovenous difference in oxygen ($AVDo_2$) content may reflect either mitochondrial dysfunction, a high CO state, or overly aggressive resuscitation (94). In this narrow $AVDo_2$ shock state, practitioners should incorporate in their serial patient assessments other markers of adequate tissue oxygen delivery and utilization and organ perfusion such as serum lactate and urine output.

In isolation, any one of the above clinical or hemodynamic parameters may underestimate or overestimate the true severity of illness, leading to either false reassurance and underresuscitation or overresuscitation. Multimodal monitoring refers to the use of multiple variables and their changes over time to better determine the underlying hemodynamic state. Shock index (HR/SBP) (92) and HR variability analysis (95) both leverage the added value of evaluating combinations of variables and their trends over time and have been suggested as being superior to any individual parameter alone for diagnosing septic shock and assessing response to therapy. By combining information from clinical signs, invasive arterial monitoring, and serial bedside echocardiograms, Ranjit et al (75) were able to titrate hemodynamic therapies more precisely and achieve equivalent mortality outcomes to PICUs using more invasive continuous CO monitoring.

Laboratory markers of cardiac function and oxygen delivery:utilization balance include troponin and lactate. Blood troponin concentrations correlate well with poor cardiac function and response to inotropic support in children with septic shock (96–98). Lactate is recommended in adult septic shock laboratory testing bundles for both diagnosis and subsequent

monitoring of therapeutic responses. However, most adult literature continues to define shock by hypotension and recommends using lactate concentration to identify shock in normotensive adults. In pediatric studies, initial elevated lactate levels have correlated with increased mortality, and decreasing lactate trends over time seem to correlate with recovery (99–103). However, each of these studies has been limited by small numbers. Lactate elevation for reasons other than cellular hypoxia further clouds the utility of using lactate to either predict outcome or track response to therapy (104). For now, the committee recommends early recognition of pediatric septic shock using clinical examination, not biochemical tests. Nevertheless, given the broad adoption of lactate in the adult guidelines and the suggestive data in small pediatric studies, lactate measurements if high on initial measurement may be useful to judge resolution of shock. Early elevated lactate (from a free flowing sample) may grab a clinician's attention, when clinical signs are difficult to decipher—it is inexpensive, readily available, and over time performed well as an indicator of shock and its resolution. Because clinical signs of compensated and decompensated shock are always present in children whereas high lactate is commonly not (12, 13), we stress early recognition with clinical signs, not lactate.

In VLBW infants, ultrasound-derived SVC blood flow measurement was reportedly useful in assessing the effectiveness of shock therapies. The SVC flow approximates blood flow from the brain. A value greater than 40 mL/kg/min is associated with improved neurologic outcomes and survival (86–90). $Scvo_2$ saturation can be used in low birth weight infants but may be misleading in the presence of left to right shunting through the PDA.

Intravascular Access

Vascular access for fluid resuscitation and inotrope/vasopressor infusion is more difficult to attain in newborns and children compared with adults. Portable near-infrared imaging devices may assist with placement of peripheral vascular access (105, 106). To facilitate a rapid approach to vascular access in critically ill infants and children, the American Heart Association and the American Academy of Pediatrics developed Neonatal Resuscitation Program (NRP) and PALS guidelines for emergency establishment of intravascular support (107–110). Essential age-specific differences include use of umbilical artery catheter (UAC) and umbilical venous catheter access in newborns and rapid use of intraosseous access in children (108–114). Ultrasound guidance facilitates placement of central catheters in children but is technologist dependent (113–119).

Fluid Therapy

Fluid resuscitation trials have been performed since 2002. Several randomized trials showed that when children with mostly stage III (narrow pulse pressure/tachycardia) and some stage IV (hypotension) World Health Organization classification dengue shock received fluid resuscitation in the emergency department, there was near 100% survival regardless of the fluid composition used (3, 17, 120, 121). In a randomized controlled trial, Maitland et al (122) demonstrated a reduction in malaria septic shock mortality from 18% to 4% when albumin was used compared with crystalloid. In contrast, Maitland et al (18) subsequently demonstrated harm in the Fluid Expansion as Supportive Therapy (FEAST) trial when fluid boluses were given rather than IV fluid at a maintenance rate and blood transfusion contradicting this earlier study. The adult Saline versus Albumin Fluid Evaluation (SAFE) trial that compared crystalloid versus albumin fluid resuscitation reported a hypothesis generating trend toward improved outcome ($p < 0.1$) in septic shock patients who received albumin (123). Preference was given for exclusive use of colloid resuscitation in a clinical practice position article from a group who reported outstanding clinical results in resuscitation of meningococcal septic shock (5% mortality) both using 4% albumin exclusively (20 mL/kg boluses over 5–10 min) and intubating patients who required greater than 40 mL/kg (4). In an Indian trial of fluid resuscitation of pediatric septic shock, there was no difference in outcome with gelatin compared with crystalloid (124). In the initial clinical case series that popularized the use of aggressive volume resuscitation for reversal of pediatric septic shock, a combination of crystalloid and colloid therapies was used (125). Several new investigations examined both the feasibility of the 2002 guideline recommendation of rapid fluid resuscitation and the need for fluid removal in patients with subsequent oliguria following fluid resuscitation. The 2002 guideline recommended rapid 20 mL/kg fluid boluses over 5 minutes followed by assessment for improved perfusion or fluid overload as evidenced by new onset rales, increased work of breathing and hypoxemia from pulmonary edema, hepatomegaly, or a diminishing MAP-CVP. Emergency medicine investigators reported that 20 mL/kg of crystalloid or colloid can be pushed over 5 minutes, or administered via a pressure bag over 5 minutes through a peripheral and/or central IV catheter (126). Ranjit et al (127) reported improved outcome from dengue and bacterial septic shock when they implemented a protocol of aggressive fluid resuscitation followed by fluid removal using diuretics and/or peritoneal dialysis if oliguria ensued. In this regard, Foland et al (128) similarly reported that patients with multiple organ failure who received CRRT when they were less than 10% fluid overloaded had better outcomes than those who were greater than 10% fluid overloaded. Similarly, two best outcome practices reported routine use of CRRT to prevent fluid overload while correcting prolonged INR with plasma infusion in patients with purpura and septic shock (4, 16).

The use of blood as a volume expander was examined in two small pediatric studies, but no recommendations were given by the investigators (129, 130). In the previously mentioned study by de Oliveira et al (13) reporting improved outcome with use of the 2002 ACCM guidelines and continuous $Scvo_2$ saturation monitoring, the treatment group received more blood transfusions directed to improvement of $Scvo_2$ saturation to greater than 70% (40% vs 7%). Although the members of the task force use conservative goals for blood transfusion in stable critical illness (Hgb > 7 g/dL without cardiopulmonary compromise) (131), the observation that patients who have septic shock with a $Scvo_2$ less than 70% and Hgb less than 10 g/dL had

better outcomes when transfused to a goal Hgb greater than 10 g/dL supports a higher hemoglobin goal in this population.

Fluid infusion is best initiated with boluses of 20 mL/kg, titrated to assuring an adequate blood pressure and clinical monitors of CO including HR, quality of peripheral pulses, capillary refill, level of consciousness, and urine output. Initial volume resuscitation requirements may be 0 mL/kg if rales or hepatomegaly are present but commonly are 40–60 mL/kg (41, 125, 132–138). Patients who do not respond rapidly to initial fluid boluses, or those with insufficient physiologic reserve, should be considered for invasive hemodynamic monitoring. Monitoring filling pressures can be helpful to optimize preload and thus CO. Observation of little change in the CVP in response to a fluid bolus suggests that the venous capacitance system is not overfilled and that more fluid is indicated. Observation that an increasing CVP is met with reduced MAP-CVP suggests that too much fluid has been given. Large volumes of fluid for acute stabilization in children have not been shown to increase the incidence of the ARDS or cerebral edema (13, 138). Increased fluid requirements may be evident for several days secondary to loss of fluid from the intravascular compartment when there is profound capillary leak (17). Fluid choices include crystalloids (normal saline or lactated Ringers solution) and colloids (dextran, gelatin, or 5% albumin) (139–144). Fresh frozen plasma may be infused to correct abnormal PT and partial thromboplastin time values. Since oxygen delivery depends on hemoglobin concentration, hemoglobin can be maintained at a minimum of 10 g/dL during the initial resuscitation phase with good results (13). Diuretics/peritoneal dialysis/CRRT is indicated for patients who develop signs and symptoms of fluid overload.

Sedation for Invasive Procedures or Intubation

Supplemental oxygen and optimal airway positioning should be provided at presentation for all patients with shock, consistent with PALS guidelines. Although patients presenting with hypopnea or frank apnea may need immediate intubation, in most instances, there is time for fluid resuscitation, at least 20 mL/kg of either isotonic crystalloid or 5% albumin, and starting a peripheral epinephrine infusion within the first hour of presentation. Children with persistent or worsening shock, as manifested by failure to approximate normal vital signs for age and inadequate perfusion, should be considered to be at high risk for deterioration and should receive ventilatory support. High-flow nasal cannula and other modes of noninvasive respiratory support can be evaluated in selected patients (145). Patients with shock of any etiology are particularly vulnerable to the hemodynamic effects of sedatives and analgesics, emphasizing the importance of prompt appropriate fluid resuscitation and inotrope infusion (peripheral or central) prior to airway instrumentation in spontaneously breathing patients.

Intubation for controlled ventilation plays an important role in the management of neonates and children with septic shock, and timing and should be thoughtfully considered. Sedation, analgesia and positive-pressure ventilation prior to adequate volume resuscitation (146-148), may cause profound drops in preload and precipitate severe hemodynamic instability during intubation. Also, severe diastolic and systolic ventricular dysfunction may predispose the child to pulmonary edema and rapid desaturation during intubation, providing rationale for considering peripheral epinephrine infusion before intubation. Mechanical ventilation can eliminate work of breathing and improve oxygenation and organ perfusion, all of which are typically compromised in the septic child (149–152).

Atropine increases the HR and protects against the deleterious effects of bradycardia, particularly in babies (153). Atropine does not cause cardiac dysrhythmias and is not contraindicated in children exhibiting tachycardia. Ketamine remains an important agent for intubation of pediatric patients with shock (154, 155), given its pharmacologic effects of dissociation while maintaining or augmenting SVR. Side effects may be minimized by administering IV boluses over 30–60 seconds.

The use of ketamine with atropine pretreatment is considered to be the sedative/induction regimen which best promotes cardiovascular integrity (155). The use of etomidate is generally discouraged at this time, given its known effects on adrenal function (156, 157), despite some reports suggesting no direct effect on patient mortality (158–160). Etomidate can be considered in the presence of profound shock if ketamine is unavailable. The role of hydrocortisone supplementation in this setting is unclear. It is possible that etomidate analogs currently in development may have a role in urgent pediatric airway management.

Other options to consider for intubation of neonates and children include the opioids fentanyl and remifentanil (161, 162). These agents should be used instead of morphine, when available, because they have fewer hemodynamic effects. Opioids such as fentanyl should be given in titrated aliquots of 1–2 μg/kg, administered over 60 seconds. Although chest wall rigidity is usually associated with larger doses given as a bolus, this complication and altered hemodynamics can also occur with smaller doses. Benzodiazepines, if used, should be likewise carefully titrated to effect, using small doses.

Pentobarbital and other barbiturates are direct myocardial depressants and decrease SVR, commonly causing hemodynamic instability. These drugs are also devoid of intrinsic analgesic effects, making them unsuitable for tracheal intubation of patients with shock. Inhalational agents are not appropriate for isolated airway instrumentation in shock. Propofol commonly causes hypotension and should be avoided during intubation or sedation in the presence of shock, particularly during transport and before admission to the ICU.

Neuromuscular blocking agents such as rocuronium, or succinylcholine (absent a contraindication), may facilitate intubation by qualified providers. Hypotension may occur even in children who have received appropriate volume resuscitation and pharmacotherapy for intubation. It is advisable, therefore, to have additional isotonic crystalloid and vasoactive infusions available for immediate use during or following the procedure. Additional vascular access should be obtained as soon as practical. Sedation and analgesia may be maintained in ventilated patients requiring transport using agents such as fentanyl and midazolam, supplemented by neuromuscular

blockade. Ketamine infusions may be used as well, but there is concern regarding neuroapoptosis following exposure to ketamine in infants (161, 162). Unplanned extubation may occur as the child recovers from shock. The endotracheal tube should be carefully secured once adequate placement is achieved. Appropriately titrated analgesia and sedation are essential for safe transport. Neuromuscular blockade and physical restraints may be appropriate under some circumstances, always in the presence of adequate analgesia and sedation.

Intravascular Catheters and Noninvasive or Minimally Invasive Monitoring

Minimal invasive monitoring is necessary in children with fluid-responsive shock; however, in children with fluid-refractory shock, physical signs of cold versus warm shock may be unreliable, and central venous access and arterial pressure monitoring is recommended. Intensivists have long used the ultrasound for central venous catheter placement in children, but its role is now expanding to direct resuscitation goals and therapeutic endpoints in shock resuscitation. Echocardiography is considered an appropriate noninvasive tool to rule out the presence of pericardial effusion, evaluate myocardial contractility and intravascular volume. Ranjit et al (75) incorporated the use of echocardiography in their usual practice to categorize the hemodynamics in 48 patients with fluid-refractory septic shock. Based on their findings on the echocardiogram and invasive blood pressure monitoring, fluid and inotrope/vasopressor therapy was changed in almost 88% of the patients (75). Early placement of invasive arterial catheters helped in the identification and subsequent management of a cohort of patients who presented with cold shock but had wide pulse pressure with low diastolic pressure (75). Similarly, Brierly et al (39) categorized the hemodynamic patterns of pediatric septic shock with the use of Doppler ultrasonography and observed that the manifestation of hemodynamics was cause dependent, that is, CVC-associated sepsis presented with high CO and low SVR, whereas community-acquired infections sepsis presented with low CO. A CO greater than 3.3 less than 6.0 L/min/m^2 is associated with improved survival and neurologic function. Other noninvasive monitors undergoing evaluation in newborns and children include percutaneous venous oxygen saturation, aortic ultrasound, perfusion index (pulse oximetry), near-infrared spectroscopy, sublingual P_{CO_2}, and sublingual microvascular orthogonal polarization spectroscopy scanning. All show promise; however, none has been tested in goal-directed therapy trials (163–166).

Maintenance of perfusion pressure (MAP – CVP), or (MAP – IAP) if the abdomen is tense secondary to bowel edema or ascitic fluid, is considered necessary for organ perfusion (79). Goal-directed therapy to achieve an Scv_{O_2} saturation greater than 70% is associated with improved outcome (13, 14). To gain accurate measures of Scv_{O_2}, the tip of the catheter must be at the superior vena cava-right atrium or inferior vena cava-right atrium junction (164). A pulmonary artery catheter (PAC), pulse index contour CO (PiCCO) (165, 166), or femoral artery thermodilution catheter can be used to measure CO in those who remain in shock despite therapies directed to clinical signs of perfusion, MAP-CVP, Scv_{O_2}, and echocardiographic analyses (165–172). The PAC measures the PAOP to help identify selective left ventricular dysfunction and can be used to determine the relative contribution of right and left ventricle work. A less invasive PiCCO catheter estimates global end-diastolic volume in the heart (both chambers) and extra vascular lung water and can be used to assess whether preload is adequate. This measure of intravascular volume by global end-diastolic volume has been demonstrated in both children and adults to be more predictive than either CVP or PAOP for changes in CO associated with volume challenge.

Cardiovascular Drug Therapy

When considering the use of cardiovascular agents in the management of infants and children with septic shock, several important points need to be emphasized. The first is that septic shock represents a dynamic process so that the agents selected and their infusion dose may need to be changed over time based on the need to maintain adequate organ perfusion. It is also important to recognize that the vasoactive agents are characterized by varying effects on SVR and pulmonary vascular resistance (i.e., vasodilators or vasopressors), contractility (i.e., inotropy), HR (chronotropy), and lusotropy (ventricle relaxation). These pharmacologic effects are determined by the pharmacokinetics of the agent and the pharmacodynamics of the patient's response to the agent. In critically ill septic children, perfusion of the liver and kidney is often altered leading to changes in the pharmacokinetics of these drugs with higher concentrations observed than anticipated. Thus, the infusion doses quoted in many textbooks are approximations of starting rates and should be adjusted based on the patient's response. "We recommend frequent reevaluation of hemodynamic parameters when a patient requires the use of vasopressors, especially in relation to CO, SVR, and peripheral perfusion so as to choose the appropriate combination with inotropic or vasodilator drugs ± fluids."

The latter is also determined by the pharmacodynamic response to the agent, which is commonly altered in septic patients. For example, patients with sepsis have a well-recognized reduced response to α-adrenergic agonists that is mediated by excess nitric oxide production and alterations in the α-adrenergic receptor system. Similarly, cardiac β-adrenergic responsiveness may be reduced by the effect of nitric oxide and other inflammatory cytokines.

Inotropes

Dopamine (5–9 μg/kg/min), dobutamine, or epinephrine (0.05–0.3 μg/kg/min) can be used as first-line inotropic support. Dobutamine may be used when there is a low CO state with adequate or increased SVR (38, 173–201). Dobutamine or mid-dosage dopamine can be used as the first line of inotropic support if supported by clinical and objective data (e.g., assessment of contractility by echocardiogram) when one of the initial goals is to increase cardiac contractility in patients with normal blood pressure. However, children less than 12 months may be less responsive (195).

Dobutamine- or dopamine-refractory low CO shock may be reversed with epinephrine infusion (12, 38, 173, 174, 176). 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 (12). It is clear that epinephrine has potent inotropic and chronotropic effects, but its effects on peripheral vascular resistance and the endocrine stress response may result in additional problems. At lower infusion doses (≤ 0.3 μg/kg/min), epinephrine has greater β_2-adrenergic effects in the peripheral vasculature with little α-adrenergic effect so that SVR falls, particularly in the skeletal musculature and skin. This may redirect blood flow away from the splanchnic circulation even though blood pressure and CO increases. This effect of epinephrine likely explains the observation that epinephrine transiently reduces gastric intramucosal pH in adults and animals with hyperdynamic sepsis (177), but there are no data available to evaluate whether gut injury does or does not occur with epinephrine use in children. Epinephrine stimulates gluconeogenesis and glycogenolysis, and inhibits the action of insulin, leading to increased blood glucose concentrations. In addition, as part of the stimulation of gluconeogenesis, epinephrine increases the shuttle of lactate to liver as a substrate for glucose production (the Cori cycle). Thus, patients on epinephrine infusion have increased plasma lactate concentrations independent of changes in organ perfusion, making this parameter somewhat more difficult to interpret in children with septic shock.

Ideally, epinephrine should be administered by a secure central venous route, but in an emergency, it may be infused through a peripheral IV route or through an intraosseous needle while attaining central access (12). The AHA/PALS guidelines for children recommend the initial use of epinephrine by peripheral IV or intraosseous for CPR or post CPR shock, and by the subcutaneous or intramuscular route for anaphylaxis. Even though a common perception, there are no data clarifying if the peripheral infiltration of epinephrine produces more local damage than observed with dopamine. The severity of local symptoms likely depends on the concentration of the vasoactive drug infusion and the duration of the peripheral infiltration before being discovered. If peripheral infiltration occurs with any catecholamine, its adverse effects may be antagonized by local infiltration with phentolamine, 1–5 mg diluted in 5 mL of normal saline.

Vasodilators

When pediatric patients are normotensive with a low CO and high SVR, initial treatment of fluid-refractory patients consists of the use of an inotropic agent such as epinephrine or dobutamine that tends to lower SVR. In addition, a short-acting vasodilator may be added, such as sodium nitroprusside or nitroglycerin to recruit microcirculation (202–208). Orthogonal polarizing spectroscopy showed that addition of systemic IV nitroglycerin to dopamine/norepinephrine infusion restored tongue microvascular blood flow during adult septic shock (208). Nitrovasodilators can be titrated to the desired effect, but use of nitroprusside is limited if there is reduced renal function secondary to the accumulation of sodium thiocyanate. Use of nitroglycerin may also have limited utility over time through the depletion of tissue thiols that are important for its vasodilating effect. Other vasodilators that have been used in children include prostacyclin, pentoxyfilline, dopexamine, and fenoldapam (209–214).

An alternative approach to improve cardiac contractility and lower SVR is based on the use of type III phosphodiesterase inhibitors (PDEIs) (206, 207, 215, 216). This class of agents, which includes milrinone and inamrinone (formerly amrinone, but the name was changed to avoid confusion with amiodarone), has a synergistic effect with β-adrenergic agonists because the latter agents stimulate intracellular cyclic adenylate mono phosphate (cAMP) production while the PDEIs increase intracellular cAMP by blocking its hydrolysis. Since the PDEIs do not depend on a receptor mechanism, they maintain their action even when the β-adrenergic receptors are down-regulated or have reduced functional responsiveness. The main limitation of these agents is their need for normal renal function (for milrinone clearance) and liver function (for inamrinone clearance). Inamrinone and milrinone are rarely used in adults with septic shock because catecholamine refractory low CO and high vascular resistance are uncommon; however, this hemodynamic state represents a major proportion of children with fluid-refractory, dopamine-resistant shock. Fluid boluses are likely to be required if inamrinone or milrinone is administered with full loading doses. Because milrinone and inamrinone have long half-lifes (1–10 hr depending on organ function), it can take 3–30 hours to reach 90% of steady state. Although recommended in the literature, some individuals in the committee choose not to use boluses of inamrinone or milrinone. This group administers the drugs as a continuous infusion only. Other members divide the bolus into five equal aliquots administering each aliquot over 10 minutes if blood pressure remains within an acceptable range. If blood pressure falls, it is typically because of the desired vasodilation and can be reversed by titrated (e.g., 5 mL/kg) boluses of isotonic crystalloid or colloid. Because of the long elimination half-life, these drugs should be discontinued at the first sign of arrhythmia, or hypotension caused by excessively diminished SVR. Hypotension-related toxicity can also be potentially overcome by beginning norepinephrine. Norepinephrine counteracts the effects of increased cyclic adenosine monophosphate in vascular tissue by stimulating the alpha receptor resulting in vasoconstriction. Norepinephrine has little effect at the vascular β_2 receptor.

Rescue from refractory shock has been described in case reports and series using two medications with type III phosphodiesterase activity. Levosimendan is a promising medication that increases Ca^{++}/actin/tropomyosin complex binding sensitivity and also has some type III PDEI and adenosine triphosphate–sensitive K^+ channel activity. Because one of the pathogenic mechanisms of endotoxin-induced heart dysfunction is desensitization of Ca^{++}/actin/tropomyosin complex binding, this drug allows treatment at this fundamental level of signal transduction overcoming the loss of contractility that

characterizes septic shock (217–222). Enoximone is a type III PDEI with 10 times more β_1 cAMP hydrolysis inhibition than β_2 cAMP hydrolysis inhibition (223–225). Hence, it can be used to increase cardiac performance with less risk of undesired hypotension.

Vasopressors

Vasopressors may also be beneficial in the treatment of pediatric septic shock when applied according to the guideline algorithm. Vasopressors can be titrated to endpoints of perfusion pressure (MAP-CVP) or SVR that promote optimum urine output and creatinine clearance, but excessive vasoconstriction compromising microcirculatory flow should be avoided. Vasopressor effect can be obtained with different sympathicomimetic drugs. There is no clear evidence that supports the use of one specific vasoactive drug over another (dopamine > 15 μg/kg/min, epinephrine > 0.3 μg/kg/min, or norepinephrine) (77, 179, 226–231). When epinephrine is administrated in doses greater than 0.3 μg/kg/min or dopamine in doses greater than 10 μg/kg/min, there is a vasopressor effect additional to their inotropic action. However, if the patient has ongoing shock and/or shows findings consistent with warm shock (flash capillary refill, warm extremities, low diastolic pressure, and bounding pulses), the additional use of norepinephrine is suggested (231). Some committee members advocate the use of low-dose norepinephrine as a first-line agent for fluid-refractory hypotensive hyperdynamic shock. Based on experimental and clinical data, norepinephrine is recommended as the first-line agent in adults with fluid-refractory shock. If the patient's clinical state is characterized by low SVR (e.g., wide pulse pressure with DBP that is < half the systolic pressure), norepinephrine is recommended alone. Other experts have recommended combining norepinephrine with dobutamine, recognizing that dobutamine is a potent inotrope that has intrinsic vasodilating action that may be helpful to counteract excessive vasoconstriction from norepinephrine. Higher norepinephrine doses than those usually suggested in the literature have been described to reverse hypotension and hypoperfusion without inducing significant adverse effects (230, 231).

The infusion of norepinephrine is suggested as the initial vasoactive drug in patients with warm shock, vasodilatation, and low SVR. A study using a noninvasive ultrasound CO monitor device to measure serial hemodynamics showed that patients could present with cold or warm shock and that both types evolved in a heterogeneous manner needing frequent revision of cardiovascular support therapy (40). Children with initial warm shock were commenced on norepinephrine. Despite an initial good response, four patients developed low CI and needed epinephrine (40).

When the use of vasopressor drugs is needed, it must be started as soon as possible but within 60 minutes of resuscitation, using intraosseus access, while central venous access is obtained. Lampin et al (230) describe in a retrospective study the use of norepinephrine in 144 children over a 10-year period; it was used as the first-choice drug in 22% of the patients, and in 19% of the cases, it was used either by peripheral or intraosseus route. Paul et al (21, 22) describe delay in the initiation of vasoactive drugs in 65% of the cases and associate this with an increase in length of stay in intensive care.

Vasopressin and terlipressin have been shown to increase MAP, SVR, and urine output in patients with vasodilatory septic shock and hyporesponsiveness to catecholamines (232–258). Vasopressin's action is independent of catecholamine receptor stimulation, and therefore, its efficacy is not affected by α-adrenergic receptor down-regulation often seen in septic shock. Low-dose infusion of vasopressin should not be used as routine adjunctive therapy but may be considered as rescue therapy in patients with catecholamine and steroid resistant hypotension. The adult Vasopressin and Septic Shock Trial, a randomized, controlled clinical trial that compared low-dose arginine vasopressin with norepinephrine in adults with septic shock, showed no difference between regimens in the 28-day mortality primary endpoint (247). The results of another randomized control trial evaluating the use of low doses of vasopressin as an adjunctive therapy in vasodilated pediatric septic shock also failed to show benefits (248).

Both vasopressin and terlipressin can be considered as rescue therapy in patients in vasodilatory shock who do not respond to high doses of norepinephrine or other sympathicomimetics. Terlipressin, a long acting form of vasopressin, has been reported to reverse vasodilated shock as well. Administered as a continuous infusion or in bolus, it increases blood pressure and urine output in pediatric patients with refractory septic shock. Decreased CO or distal necrosis has been reported as possible adverse events. Yildizdas et al (258) evaluated the effect of continuous infusion of terlipressin in a randomized control trial in pediatric patients with septic shock and high catecholamine requirement. Terlipressin infusion had no effect on mortality.

Angiotensin can also be used to increase blood pressure in patients who are refractory to norepinephrine; however, its clinical role is not as well defined (259). Phenylephrine is another pure vasopressor with no β-adrenergic activity (260). Its clinical role is also limited. Nitric oxide (NO) inhibitors and methylene blue are considered investigational therapies (261–264). Studies have shown an increased mortality with nonselective NO synthase inhibitors suggesting that increasing blood pressure through excessive vasoconstriction can have adverse effects (261).

Glucose, Calcium, Thyroid, and Hydrocortisone Replacement

Hypoglycemia, hyperglycemia, and glycemic variability have been associated with worse short-term outcomes in critically ill children (265–268). Hypoglycemia must be rapidly diagnosed and promptly treated. Hyperglycemia in nondiabetic children with sepsis has been associated with worse outcomes (266–268). Branco et al (267) reported a greater risk of death with hyperglycemia (≥ 178 mg/dL) in 57 children with septic shock. Day et al (268) reported hyperglycemia (> 180 mg/dL) negatively correlated with ventilator-free days at 30 days in a retrospective review of 97 children with meningococcal sepsis.

Hyperglycemia and hypoglycemia during critical illness may simply represent epiphenomena. In contrast, Mesotten et al (269) reported that brief hypoglycemia (≤ 40 mg/dL) caused by tight glycemic control in a pediatric randomized controlled trial was not associated with worse neurocognitive outcome approximately 4 years later.

Randomized controlled trials of tight glycemic control have been conducted primarily in postcardiac surgery children (270–273). Results are conflicting, with one study showing a reduction in PICU length of stay and inflammatory markers (272) and the other three not showing an improvement in mortality or morbidity (270, 271, 273). Hyperglycemia in children with meningococcal sepsis has been partially attributed to the suppression of insulin production by proinflammatory mediators rather than insulin resistance as seen in other critical illnesses (274, 275).

Calcium replacement should be directed to normalize ionized calcium concentration; however, its safety and efficacy have not been established in septic shock. Replacement with thyroid and/or hydrocortisone can also be lifesaving in children with thyroid and/or adrenal insufficiency and catecholamine-resistant shock (64, 276–291). Hypothyroidism is relatively common in children with trisomy 21 and children with CNS pathology, (e.g., pituitary abnormality). Hypothyroidism may manifest clinically after the administration of corticosteroids for adrenal insufficiency and needs to be recognized and treated promptly. Infusion therapy with triiodothyronine may be beneficial in postoperative congenital heart disease patients but has yet to be studied in children with septic shock.

Multiple studies suggest changes in the hypopituitary adrenal axis (292–294), glucocorticoid receptor changes (295), and changes in cortisol metabolism during sepsis (296, 297). Possible rationales for the use of corticosteroids in sepsis are beneficial pharmacologic effect on the cardiovascular system and anti-inflammatory properties (276, 298, 299). A recent prospective study of critically ill children reported a prevalence of relative adrenal insufficiency in critically ill children of 30.2% on the first day of admission and 19.8% on the second day of admission as defined by an increase in cortisol of less than 9 μg/dL after administration of low dose (1 μg) adrenocorticotropic hormone (ACTH) (300). The prevalence of relative adrenal insufficiency reported in other studies is widely variable depending on the diagnostic criteria used and remains somewhat arbitrary. Low or high serum cortisol concentrations have been associated with increased sepsis mortality (301). A cutoff of less than 25 μg/dL in adults with septic shock has been described as useful to predict hemodynamic response to cortisol administration. In children, a serum cortisol concentration of greater than 36 μg/dL and a lack in response to ACTH stimulation may predict a failure to respond to exogenous corticosteroid administration (302). Several factors contribute to the diagnostic controversy. In one study, patients with relative adrenal insufficiency had higher basal cortisol concentrations than those without relative adrenal insufficiency (28.6 vs 16.7 μg/dL; $p < 0.001$) (302). A study of total and free cortisol concentrations among critically ill children found a high incidence of biochemical adrenal insufficiency using various definitions but no evidence of corresponding clinical adrenal insufficiency (303).

Hypoproteinemia decreases total cortisol concentrations, but free cortisol concentrations have been observed to be high in patients with serum albumin concentrations less than 2.5 mg/dL despite a low total serum cortisol concentration in nearly 40% of adults tested (304). Reduced cortisol metabolism in critically ill adults suggests a 50% decrease in clearance of corticosteroids due to suppression of activity or expression of metabolizing enzymes. Furthermore, the authors observed a dissociation of cortisol concentrations after ACTH stimulation. In patients with elevated serum cortisol concentrations due to reduced clearance, ACTH concentrations were found to be lower suggesting negative feedback on the HPA axis. Mortality is correlated with a higher degree of suppression of corticosteroid metabolism in adults (296). The role of free cortisol in the diagnosis of adrenal insufficiency determination has not been sufficiently elucidated (303, 304). Administration of etomidate (305), megestrol (306), and ketoconazole (307) have been identified as iatrogenic causes of adrenal insufficiency due to their interference with cortisol production.

Nonsurvivors have exceedingly high ACTH/cortisol ratios within the first 8 hours of meningococcal shock (277–279, 290, 292, 308). The lack of increase in serum cortisol concentration (< 9 μg/dL) in patients undergoing an ACTH stimulation test with baseline cortisol concentrations greater than 18 μg/dL was associated with catecholamine refractory shock but not mortality (309, 310). The value of ACTH stimulation test in the diagnosis and treatment of relative adrenal insufficiency and critical illness-related corticosteroid insufficiency in children and adults remains unclear. No gold standard has been established for the diagnosis of adrenal insufficiency in critical illness. Absolute adrenal insufficiency has been defined as a basal serum cortisol concentration of less than 7 μg/dL and peak serum cortisol of less than 18 μg/dL after stimulation. Others suggested a basal serum cortisol of less than 5 or less than 9 μg/dL and use the same peak cutoff after ACTH stimulation of less than 18 μg/dL for the definition of absolute adrenal insufficiency. Relative adrenal insufficiency has been proposed as a basal serum cortisol concentration of less than 20 μg/dL and Δ less than 9 after ACTH stimulation, or a basal total cortisol less than 10, Δ total cortisol less than 9 or free cortisol less than 2.

Patients at risk of inadequate cortisol/aldosterone production due to absolute adrenal insufficiency in the setting of shock include children with purpura fulminans and Waterhouse-Friderichsen syndrome, children who previously received steroid therapies for chronic illness, and children with pituitary or adrenal abnormalities. These patients may benefit from stress doses of hydrocortisone early in the course of their illness, in the presence of sepsis without shock. The need for separate mineralocorticoid replacement during critical illness is unclear. Serum aldosterone concentrations are markedly depressed in meningococcemia (311). The administration of fludrocortisone in addition to hydrocortisone has been suggested in septic shock (312) with the benefit of shortening

the duration of norepinephrine administration in the septic subgroup, over hydrocortisone administration alone. The mineralocorticoid activity of hydrocortisone alone, however, may be sufficient and should not exceed 200 mg/d (equivalent to about 100 mg/m^2/d) when given to adults (313–316). Hydrocortisone's mineralocorticoid activity is deemed to be equivalent to 150 μg/m^2/d of 9α-fludrocortisone when a total daily dose of 20–50 mg of hydrocortisone is reached.

Treatment with low-dose hydrocortisone for relative adrenal insufficiency has gained interest since the first randomized controlled trial (RCT) in adults with septic shock was published in 2002, proving a mortality benefit (276). A subsequent RCT in adults did not confirm a mortality advantage for the treatment with stress doses of hydrocortisone, leaving us with conflicting results (316). The pediatric literature lacks large RCTs evaluating the benefit of corticosteroids specifically in septic shock and refractory septic shock, and a pediatric meta-analysis evaluating the role of corticosteroids in shock did not demonstrate benefit (302). Trials in premature newborns, and other studies in children and adults have repeatedly shown a positive effect on the cardiovascular system by decreasing the duration and/or amount of catecholamines administered (2, 67, 284, 287, 317, 318).

Very high-dose corticosteroid administration in septic shock has previously been associated with higher infection rates. Several studies published since 2006 point to the possibility of infectious complications as a result of corticosteroid administration in adults and children. Steroid use was linked to disseminated candidiasis in a case report (319); however, infectious complications were not found to be increased by the administration of corticosteroids in children and adults with shock in other studies. Other side effects in patients receiving corticosteroids have been described, including hyperglycemia and bleeding. Concerns regarding the development of myopathy in association with corticosteroid therapy have been raised but not confirmed in either the adult or pediatric population with shock. A rise in sodium during corticosteroid administration was observed in several studies and self-resolves after discontinuation. Pediatric septic shock is associated with suppression of all aspects of adaptive immunity, and steroid use was associated with further depression of peripheral blood mononuclear cell adaptive immunity messenger RNA expression (320, 321).

Analysis of data obtained during the RESOLVE trial did not reveal treatment benefit associated with the administration of corticosteroids, but the concerns for higher mortality associated with corticosteroid administration raised by the analysis of the Pediatric Health Information System database were not corroborated (321). Studies in patients with serious infectious illnesses, that is, meningococcal meningitis, have shown cortisol production rates between 4 and 15 times the normal daily production rate of 5.7–12.5 mg/m^2 (277–279, 290, 322–325) of cortisol. Effects on the cardiovascular system in shock have been shown at the lower end of the stress dose range. Administration of stress doses as low as 0.18 mg/kg/hr of hydrocortisone (about 4 mg/kg/d) shorten the time to cessation of vasopressor support (median time 2 vs 7 d in the placebo group) without improving mortality in adults (326). In a single-center study of term neonates, the administration of 45 mg/m^2/d of hydrocortisone resulted in similar complication rates compared with historical controls and resulted in a statistically significant increase in blood pressure at 2, 6, 12, and 24 hours after initiation (67). Cortisol levels in adults after IV boluses of 50 mg of hydrocortisone given 6 hourly showed peak plasma cortisol levels over 100 μg/dL, and nadir levels remained elevated at 40–50 μg/dL (326). Among children, only those with fluid-refractory shock were found to have adrenal insufficiency (327).

Persistent Pulmonary Artery Hypertension (PPHN) of the Newborn Therapy

Inhaled nitric oxide therapy is the treatment of choice for uncomplicated PPHN (328, 329). However, metabolic alkalinization remains an important initial resuscitative strategy during shock because PPHN can reverse when acidosis is corrected (330). For centers with access to inhaled nitric oxide, this is the only selective pulmonary vasodilator reported to be effective in reversal of PPHN (331–336). Milrinone may be added to improve heart function as tolerated (337, 338). Investigations support use of inhaled iloprost (synthetic analog of prostacyclin) or adenosine infusion as modes of therapy for PPHN (339–345). ECMO remains the therapy of choice for patients with refractory PPHN and sepsis (346–349).

Extracorporeal Therapies

Various extracorporeal therapies such as ECMO, CRRT, and blood purification (hemofiltration, hemoperfusion, and therapeutic plasma exchange [TPE]) have been reported with various successes in the management of pediatric sepsis and septic shock. ECMO is a viable therapy for refractory septic shock in neonates and children (346–359). Neonates have comparably good outcomes (80% + survival) whether the indication for ECMO is refractory respiratory failure or refractory shock from sepsis. Pediatric and adult patients with sepsis have lower survival (historically ≤ 50%) than neonates, but experienced ECMO centers are now reporting survival rates approaching 75% (356–358) for refractory shock and 90% for refractory pneumonia (359). Although ECMO survival is similar in pediatric patients with and without sepsis, thrombotic complications are common in sepsis. Efforts are warranted to reduce ECMO-induced hemolysis because free heme scavenges nitric oxide, adenosine, and a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (a.k.a. von Willebrand factor-cleaving protease) leading to microvascular thrombosis, reversal of portal blood flow, and multiple organ failure (360–364). Severe hemolysis (plasma Hgb > 1 g/L) is associated with longer ECMO runs, more blood product administration, and increased mortality (362). Independent risk factors for hemolysis on ECMO include very negative inlet pressures, higher pump speeds, kinked or narrowed cannulae, and nonpediatric oxygenators (362). The risk of hemolysis can be mitigated by using the proper sized cannulas for age, avoiding excessive pump speeds, and maintaining the negative inlet pressure close to the specified pressure drop given by the manufacturer for the flow rate and never greater than –100 mm Hg (363, 364).

Outcome benefits of CRRT, either alone or in tandem with ECMO, are uncertain in pediatric sepsis. Theoretical benefits of CRRT in sepsis could include prevention or management of fluid overload, management of acute kidney injury, clearance of lactate and organic acids, binding of inflammatory mediators, reversal of coagulopathy, or some combination of these actions (365, 366). Mortality in children receiving CRRT in sepsis ranges from 39% to 59%, likely reflecting severity of illness of patient selection for CRRT use. The best documented association of CRRT and outcome is related to fluid overload. In general, use of CRRT earlier in the course of multiple organ dysfunction syndrome (MODS), including septic patients, has been associated with decreased mortality in children, even when adjusted for severity of illness (128, 367, 368). No specific randomized trials of CRRT use in pediatric sepsis have been performed. In adults, use of higher CRRT flux rates (> 35 mL/kg/hr filtration-dialysis flux), while initially encouraging, has not shown overall mortality benefit in subsequent randomized trials and meta-analysis (369, 370). Investigators in pediatric settings have reported that the use of high flux flow rate CRRT, with concomitant fresh frozen plasma, antithrombotic protein C infusion, or in combination with plasma exchange on ECMO has been associated with reduced inotrope/vasopressor requirements in children with refractory septic shock and purpura (4, 371–376).

Investigators have reported more experiences with blood purification for pediatric sepsis since the last update. In 2010, guided by the evidence-based adult and pediatric literature, the American Society of Apheresis gives a category III recommendation, which is "Optimum role of apheresis therapy is not established. Decision-making should be individualized," for the use of TPE for sepsis with multiple organ failure (377). Meta-analysis of adult randomized trials reports survival benefit with the use of blood purification for sepsis by hemoperfusion or TPE but not by hemofiltration (378). In this regard, pediatric case series and small trials have reported survival benefits with the use of TPE for sepsis-induced MODS, and in particular, patients with significant coagulopathy (379–387). These studies use TPE as a strategy to reverse MODS and not for shock resuscitation. As for other blood purification techniques for pediatric sepsis, a large RCT testing plasma filtration was stopped due to poor recruitment and showed no benefit of plasmafiltration for severe sepsis (388), and hemoperfusion experience had been very limited (389–391).

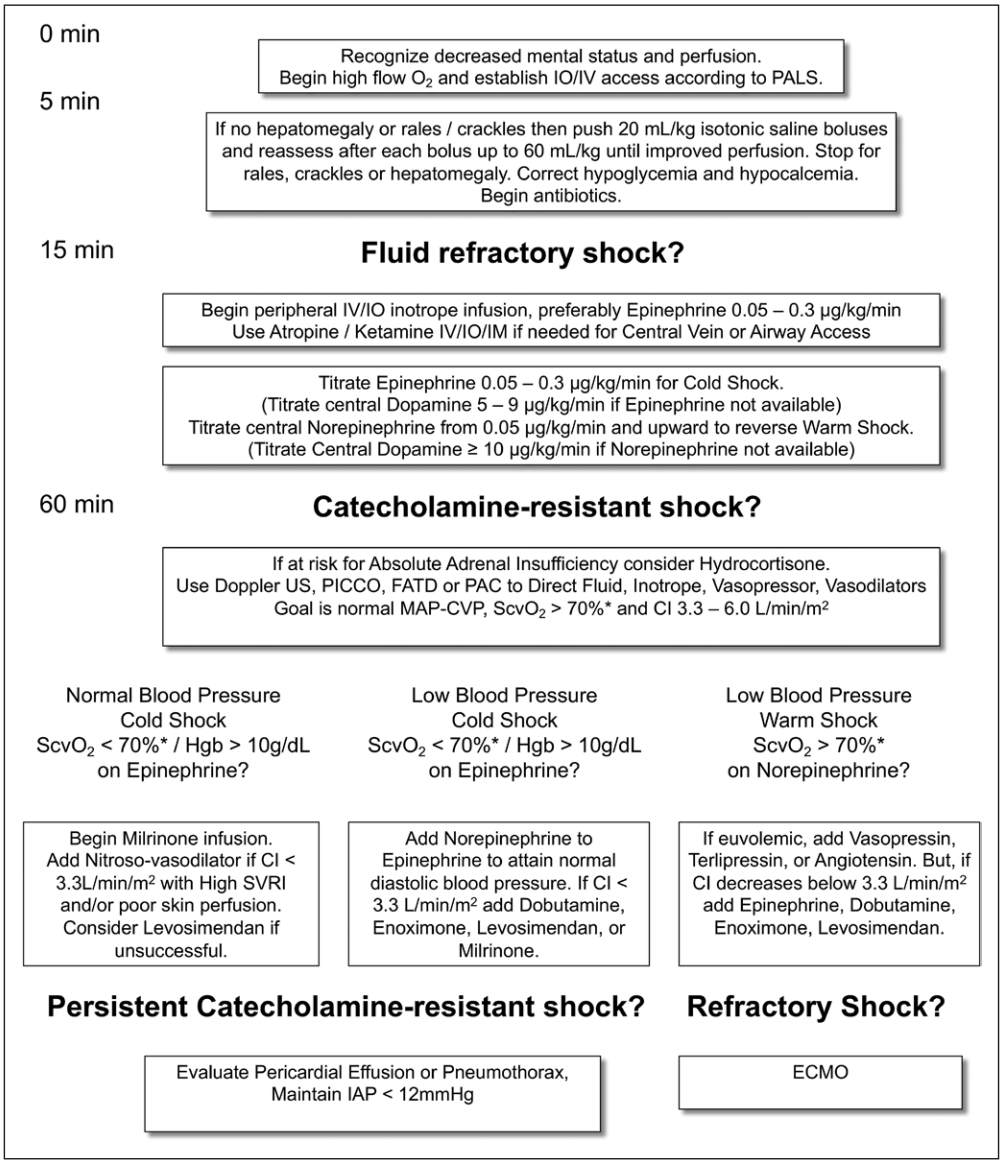

Figure 2. American College of Critical Care Medicine algorithm for time-sensitive, goal-directed stepwise management of hemodynamic support in infants and children. Proceed to next step if shock persists. 1) First-hour goals—restore and maintain heart rate thresholds, capillary refill ≤ 2 s, and normal blood pressure in the first hour/emergency department. 2) Subsequent ICU goals—if shock not reversed proceed to restore and maintain normal perfusion pressure (MAP – CVP) for age, $Scvo_2$ > 70% (* except congenital heart patients with mixing lesions), and cardiac index > 3.3 < 6.0 L/min/m² in PICU.

OVERALL RECOMMENDATIONS

Pediatric Septic Shock

Diagnosis. The inflammatory triad of fever, tachycardia, and vasodilation is common in children with benign infections (**Fig. 2**). Septic shock is suspected when children with this triad have a change in mental

status manifested as irritability, inappropriate crying, drowsiness, confusion, poor interaction with parents, lethargy, or becoming unarousable. The clinical diagnosis of septic shock is made in children who 1) have a suspected infection manifested by hypothermia or hyperthermia and 2) have clinical signs of inadequate tissue perfusion including any of the following: decreased or altered mental status, prolonged capillary refill greater than 2 seconds, diminished pulses, mottled cool extremities, or flash capillary refill, bounding peripheral pulses and wide pulse pressure or decreased urine output less than 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.

We recommend that each institution develop a recognition bundle (Fig. 1) to optimize identification of patients at risk for septic shock that is based on vital sign abnormalities and high-risk criteria (1C).

The recognition bundle should contain:

1) A trigger tool. Elements that are recommended for use in a trigger tool include vital signs, physical examination, and at-risk populations (an example trigger tool is located in **Fig. 3**).
2) Rapid clinician assessment within 15 minutes for any patient that is identified by the trigger tool.
3) Activation of a sepsis resuscitation bundle within 15 minutes for patients with suspected septic shock. We recommend that each institution also develop or adopt a first-hour resuscitation and stabilization bundle (Fig. 1) to optimize time to completion of first hour and stabilization tasks when a patient with suspected septic shock is identified (1C).

The resuscitation bundle may contain:

1) Intraosseous or IV access within 5 minutes
2) Appropriate fluid resuscitation initiated within 30 minutes
3) Initiation of broad spectrum antibiotics within 60 minutes
4) Blood culture if it does not delay antibiotic administration
5) Appropriate use of peripheral or central inotrope within 60 minutes

The stabilization bundle may contain:

1) Multimodal monitoring to guide fluid, hormonal, and cardiovascular therapies to attain a normal MAP-CVP for age ($55 + 1.5 \times$ age in yr), and $ScvO_2$ greater than 70% and/or CI 3.3–6.0 L/min/m^2
2) Administration of appropriate antibiotic therapy and source control. We recommend that each institution develop or adopt a performance bundle (Fig. 1) to identify barriers to attaining the recognition, resuscitation, and stabilization bundle goals (1C).

The performance bundle should contain:

1) Measurement of adherence as well as achievement of goals and individual components.
2) Assessment of barriers as well as unintended consequences such as inappropriate antibiotic duration or fluid overresuscitation.

ABCs: The First Hour of Resuscitation (Emergency Department Resuscitation)

Goals: (Level 1C)

- Maintain or restore airway, oxygenation, and ventilation
- Maintain or restore circulation, defined as normal perfusion and blood pressure
- Maintain or restore threshold HR.

Therapeutic Endpoints (Level 1C). Capillary refill less than or equal to 2 seconds, normal pulses with no differential between the quality of peripheral and central pulses, warm extremities, urine output greater than 1 mL/kg/hr, normal mental status, normal blood pressure for age (only reliable when pulses palpable), normal glucose concentration, normal ionized calcium concentration.

Monitoring (Level 1C)

- Pulse oximeter
- Continuous electrocardiogram (ECG)
- Blood pressure and pulse pressure
- Temperature
- Urine output
- Glucose, ionized calcium

Airway and Breathing (Level 1C). Airway and breathing should be rigorously monitored and maintained. Supplemental oxygen or high-flow nasal cannula oxygen is titrated as initial therapy to avoid hypoxia and hyperoxia (SpO_2 100%). Lung compliance and work of breathing may change precipitously. In early sepsis, patients often have a respiratory alkalosis from centrally mediated hyperventilation. As sepsis progresses, patients may have hypoxemia as well as metabolic acidosis and are at high risk to develop respiratory acidosis secondary to a combination of parenchymal lung disease and/or inadequate respiratory effort due to altered mental status. The decision to intubate and ventilate is based on clinical assessment of increased work of breathing, hypoventilation, or impaired mental status. Waiting for confirmatory laboratory tests is discouraged. If possible, volume loading and peripheral or central inotropic/vasoactive drug support is recommended before and during intubation because of relative or absolute hypovolemia, cardiac dysfunction, and the risk of suppressing endogenous stress hormone response with agents that facilitate intubation. Etomidate is not recommended. Ketamine with atropine pretreatment should be considered the induction combination of choice during intubation, to promote cardiovascular integrity during the procedure. A short-acting neuromuscular blocking agent can facilitate intubation if the provider is confident and skilled.

Circulation (Level 1C). Vascular access should be rapidly attained. In addition to direct visualization and/or palpation, portable near-infrared imaging devices may assist in peripheral vascular access. Establish intraosseous access if reliable peripheral intravenous line (PIV) access cannot be attained in minutes. Powered intraosseous devices (i.e., intraosseous drill) can facilitate successful intraosseous placement but should

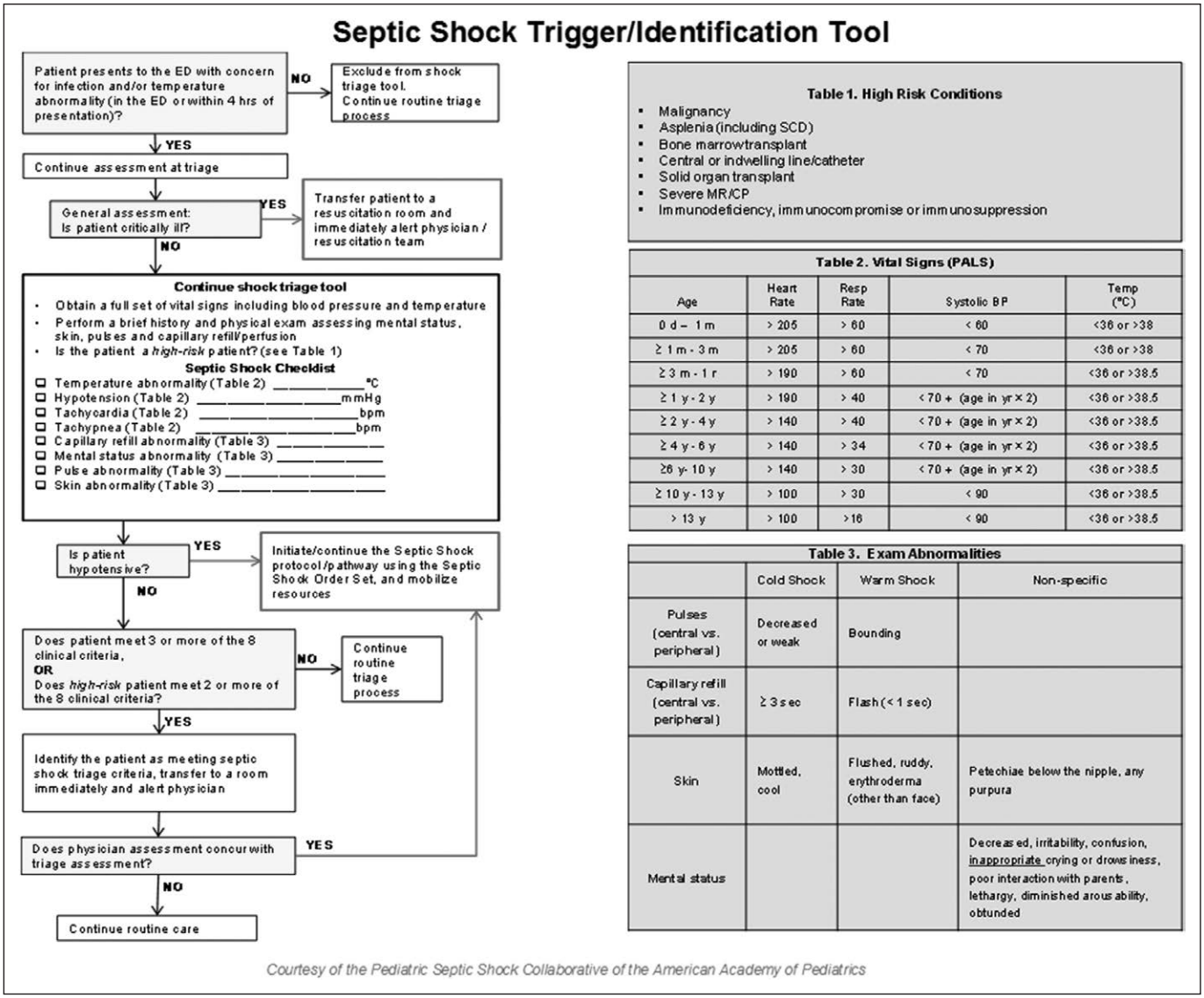

Figure 3. American Academy of Pediatrics trigger tool for early septic shock recognition.

be reserved for use in children greater than 3 kg (device not approved below this size). Fluid resuscitation should commence immediately unless hepatomegaly, rales, or a cardiac gallop are present. In the fluid-refractory patient, begin a peripheral inotrope if a second PIV/intraosseous is in place, while establishing a central venous catheter. When administered through a PIV/intraosseous, the inotrope should be infused either as a dilute solution (peripheral epinephrine dilution may be 10 × central) or with a second carrier solution running at a flow rate to assure that it reaches the heart in a timely fashion. Care must be taken to reduce dosage if evidence of peripheral infiltration/ischemia occurs as α-adrenergic receptor mediated effects occur at higher concentrations for epinephrine and dopamine. Central dopamine, epinephrine, or norepinephrine can be administered as a first-line drug as indicated by hemodynamic state when a central line is in place. It is generally appropriate to begin central venous infusion and wait until a pharmacologic effect is observed before stopping the peripheral infusion. Establishing a central venous catheter during the initial resuscitation may be dependent upon the availability of skilled personnel and appropriate equipment and should not delay or compromise ongoing resuscitation efforts. Utilization of bedside vascular imaging modalities such as ultrasound guidance can facilitate successful central venous access for skilled personnel familiar with such technologies. High frequency (7.5–13 MHz) probes should be used for infants and children, with higher frequencies yielding better resolution for the smallest patients (< 15 kg).

Fluid Resuscitation (Level 1C). Rapid fluid boluses of 20 mL/kg (isotonic crystalloid or 5% albumin) can be administered by push or rapid infusion device (pressure bag) while observing for signs of fluid overload (i.e., the development of increased work of breathing, rales, cardiac gallop rhythm, or hepatomegaly). In the absence of these clinical findings, children can require 40–60 mL/kg in the first hour. Fluid can be pushed with the goal of attaining normal perfusion and blood

pressure. Hypoglycemia and hypocalcemia should be corrected. A 10% dextrose containing isotonic IV solution can be run at maintenance IV fluid rates to provide age appropriate glucose delivery and to prevent hypoglycemia.

Hemodynamic Support (Level 1C). Central dopamine can be titrated to a maximum of 10 μg/kg/min through central access; however, epinephrine or norepinephrine is more likely to be beneficial. Central epinephrine can be started for "cold shock" (0.05–0.3 μg/kg/min) or norepinephrine can be titrated for "warm shock" to restore normal perfusion and blood pressure.

Hydrocortisone Therapy (Level 1C). If a child is "at risk of absolute adrenal insufficiency or adrenal pituitary axis failure" (e.g., purpura fulminans, congenital adrenal hyperplasia, prior steroid exposure, hypothalamic/pituitary abnormality, intubation with etomidate induction) and remains in shock despite epinephrine or norepinephrine infusion, then hydrocortisone can be administered ideally after attaining a blood sample for subsequent determination of baseline cortisol concentration.

Stabilization: Beyond the First Hour (PICU Hemodynamic Support)

Goals: (Level 1C)

- Normal perfusion, capillary refill less than or equal to 2 seconds, threshold HRs
- Perfusion pressure (MAP-CVP or MAP-IAP) appropriate for age. $Scvo_2$ greater than 70%
- CI greater than 3.3 and less than 6.0 L/min/m^2

Therapeutic Endpoints: (Level 1C). Capillary refill less than or equal to 2 seconds, threshold HRs, normal pulses with no differential between the quality of the peripheral and central pulses, warm extremities, urine output greater than 1 mL/kg/hr, normal mental status, CI greater than 3.3 and less than 6.0 L/min/m^2 with normal perfusion pressure (MAP-CVP, or MAP-IAP) for age (**Table 1**), $Scvo_2$ greater than 70%. Maximize preload in order to maximize CI, MAP-CVP. Normal INR, anion gap, and lactate.

TABLE 1. Threshold Heart Rates and Perfusion Pressure (Mean Arterial Pressure-Central Venous Pressure or Mean Arterial Pressure-Intra-Abdominal Pressure for Age)

		Perfusion Pressure
	Heart Rate (beats/min)[a]	Mean Arterial Pressure – Central Venous Pressure (mm Hg)[b]
Newborn	110–160	(55 + age ×1.5) = 55
Infant (2 yr)	90–160	(55 + age × 1.5) = 58
Child (7 yr)	70–150	(55 + age × 1.5) = 65

[a]The "good risk" heart rates are as defined in the Pediatric Risk of Mortality Scoring System (73).

[b]The mean arterial pressure (MAP) goal is based on the estimated formula for 50th percentile MAP for a child with 50th percentile height in the healthy population with an expected central venous pressure (CVP) = 0 mm Hg (76, 392). When the CVP > 0, then the goal MAP should be adjusted accordingly to achieve adequate perfusion pressure.

Monitoring (Level 1C)

- Pulse oximetry
- Continuous ECG
- Continuous intra-arterial blood pressure
- Temperature (core) urine output
- CVP/oxygen saturation and/or pulmonary artery pressure/oxygen saturation CO
- Serial limited echocardiogram
- Glucose and calcium
- INR
- Lactate, anion gap

Fluid Resuscitation (Level 1C). Fluid losses and persistent hypovolemia secondary to diffuse capillary leak can continue for days. Ongoing fluid replacement should be directed at clinical endpoints including perfusion, PAOP/global end-diastolic volume (when available), and CO. Crystalloid is the fluid of choice in patients with Hgb greater than 10 g/dL. RBC transfusion can be given to children with Hgb less than 10 g/dL. FFP is recommended for patients with prolonged INR but as an infusion, not a bolus. Following shock resuscitation, diuretics/peritoneal dialysis/high flux CRRT can be used to remove fluid in patients who are 10% fluid overloaded and unable to maintain fluid balance with native urine output/extra-renal losses.

Elevated lactate concentration and anion gap measurements can be treated by assuring both adequate oxygen delivery and glucose utilization. Adequate oxygen delivery (indicated by a $Scvo_2$ > 70%) can be achieved by attaining Hgb greater than 10 g/dL and CO greater than 3.3 L/min/m^2 using adequate volume loading and inotrope/vasodilator support when needed (as described below). Appropriate glucose delivery can be attained by giving a D10% containing isotonic IV solution at fluid maintenance rate. Appropriate glucose uptake can be attained in subsequently hyperglycemic patients by titrating a glucose/insulin infusion to prevent hyperglycemia (keep glucose concentration ≤ 150 mg/dL) and hypoglycemia (keep glucose concentration > 80 mg/dL). The use of lesser glucose infusion rates (e.g., D5% or lower volumes of D10%) will not provide glucose delivery requirements.

Hemodynamic Support (Level 1C). Hemodynamic support can be required for days. Children with "catecholamine-resistant shock" can present with low CO/high SVR, high CO/low SVR, or low CO/low SVR shock. Although children with persistent shock commonly have worsening cardiac failure, hemodynamic states may completely change with time. Titration of vasoactive infusion(s) may be guided by clinical examination (blood pressure, HR, and capillary refill/skin perfusion analysis) and laboratory data (arterial blood gas and $Scvo_2$ analysis). For patients with persistent shock (reduced urine output, poor perfusion, metabolic/lactic acidosis, or hypotension), a more accurate assessment of CO may be warranted. Many modalities for CO assessment currently exist and include pulmonary artery, PiCCO, femoral artery or thermodilution catheters,

and/or CO estimated by Doppler ultrasound. These additional data may justify further changes in the vasoactive regimen with resolution of shock. Therapies should be directed to maintain mixed venous/$Scvo_2$ greater than 70%, CI greater than 3.3 less than 6.0 L/min/m^2, and a normal perfusion pressure for age (MAP-CVP).

Shock With Low CI, Normal Blood Pressure, and High SVR (Level 1D). Milrinone is considered by the authors to be the first-line inodilator in patients with epinephrine-resistant shock and normal blood pressure. As noted above, the long elimination half-life of these drugs can lead to slowly reversible toxicities (hypotension, tachyarrhythmias, or both) particularly if abnormal renal or liver function exists. Such toxicities can be reversed in part with norepinephrine infusion. Additional volume loading may be necessary to prevent hypotension when loading doses are used. Nitroprusside or nitroglycerin may be considered as second-line vasodilators. Monitoring is needed to avoid cyanide or isothiocyanate toxicity. Levosimendan and enoximone may have a role in recalcitrant low CO syndrome. Thyroid replacement with triiodothyronine is warranted for thyroid insufficiency, and hydrocortisone replacement can be warranted for adrenal or HPA axis insufficiency.

Shock With Low CI, Low Blood Pressure, and Low SVR (Level 1D). Norepinephrine can be added to/or substituted for epinephrine to increase DBP and SVR. Once an adequate blood pressure is achieved, dobutamine, type III PDEIs such as milrinone or enoximone (which is more cardioselective than milrinone) or levosimendan can be added to norepinephrine to improve CI and $Scvo_2$. Thyroid replacement with triiodothyronine is warranted for thyroid insufficiency, and hydrocortisone replacement is warranted for adrenal or HPA axis insufficiency.

Shock With High CI and Low SVR (Level 1D). When titration of norepinephrine and fluid does not resolve hypotension, then low-dose vasopressin, angiotensin, or terlipressin can be helpful in restoring blood pressure; however, these potent vasoconstrictors can reduce CO, therefore it is recommended that "these drugs are used with CO/$Scvo_2$ monitoring." In this situation, additional inotropic therapies will be required such as low-dose epinephrine or dobutamine. Terlipressin is a longer acting drug than angiotensin or vasopressin, so toxicities are more long-acting. As with other forms of severe shock, thyroid hormone or adrenocortical replacement therapy may be added for appropriate indications. We recommend frequent reevaluation of hemodynamic parameters when a patient requires the use of vasopressors, especially in relation to CO, SVR, and peripheral perfusion so as to choose the appropriate combination with inotropic or vasodilator drugs ± fluids.

Refractory Shock (Level 2C). Children with refractory shock must be suspected to have unrecognized morbidities (treatment in parenthesis), including inappropriate source control of infection (remove nidus and use antibiotics with the lowest minimum inhibitory concentration possible, preferably < 1, use IV immunoglobulin for toxic shock), pericardial effusion (pericardiocentesis), pneumothorax (thoracentesis), hypoadrenalism (adrenal hormone replacement), hypothyroidism (thyroid hormone replacement), ongoing blood loss (blood replacement/hemostasis), increased IAP (peritoneal catheter or abdominal release), necrotic tissue (nidus removal), excessive immunosuppression (wean immunosuppressants), or immunocompromise (restore immune function; e.g., white cell growth factors/transfusion for neutropenic sepsis). When these potentially reversible causes are addressed, ECMO becomes an important alternative to consider. The expected survival with ECMO for septic shock is no greater than 50% in children, although some centers have recently reported survival rates as high as 75% by using high flow, goal-directed central ECMO where the right atrium and ascending aorta are cannulated directly. This approach mitigates any differential cyanosis and allows the highest possible flow rates, which may facilitate faster resolution of shock. If high flow rates are necessary to resolve shock, it is important to monitor for, and prevent, hemolysis. Maintaining plasma free hemoglobin concentration less than 0.05 g/L by using adequate catheter, circuit, and oxygenator sizes for age. Monitor the inlet pressure as close to the patient as possible (at the connection between the venous cannula and the tubing) and maintain this pressure between zero and the expected pressure drop for the cannula size and the pump flow that is employed. At pressures below these points, there is an increased risk for creating negative pressure in the vessel leading to vessel damage. Thus, the cannula size should be chosen to stay below this limit at the peak expected flow. If these limits are approached, the pump speed should be temporarily reduced while the cause is urgently sought out and corrected. Aside from unnecessarily high circuit flow targets, causes of extremely negative inlet pressures include hypovolemia, inadequate cannula size, partial cannula obstruction or kinking, or high intrathoracic pressure (e.g., cardiac tamponade, excessive positive end-expiratory pressure, pneumothorax, abdominal compartment syndrome). Adequate cannula placement can be confirmed using both chest x-ray and ultrasound guidance. Use of CRRT should be considered for management of potential or actual fluid overload and in patients with purpura. CRRT dosing of 20–25 mL/kg/hr is adequate. High flux CRRT dosing (> 35 mL/kg/hr) can be used, but benefits are theoretical. Consideration should be given to use of CRRT on ECMO primarily for improvement of fluid balance. TPE should not be used during the initial septic shock resuscitation. Once shock resuscitation is addressed, TPE could be considered as a strategy to reverse MODS, especially in patients with significant coagulopathy. Titration of medications will be needed during the procedure to prevent hemodynamic changes because TPE will also remove inotropes, vasopressors, and sedatives. Citrate, a calcium chelator, is used as an anticoagulant for the TPE circuit; therefore, calcium levels will need to be monitored and replenished during the procedure.

TERM NEWBORN SEPTIC SHOCK

Diagnosis

Septic shock should be suspected in any newborn with tachycardia, respiratory distress, poor feeding, poor tone,

poor color, tachypnea, diarrhea, or reduced perfusion, particularly in the presence of a maternal history of chorioamnionitis or prolonged rupture of membranes (**Fig. 4**). It is important to distinguish newborn septic shock from cardiogenic shock caused by closure of the PDA 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 infusion until complex congenital heart disease is ruled out by echocardiographic analysis. Inborn errors of metabolism resulting in hyperammonemia or hypoglycemia may simulate septic shock, and appropriate laboratory tests should be obtained to rule out these conditions. Newborn septic shock is typically accompanied by increased pulmonary vascular resistance and artery pressures. PPHN can cause right ventricle failure with right-to-left shunting at the atrial/ductal levels causing cyanosis.

ABCs: The First Hour of Resuscitation (Delivery Room Resuscitation)

Goals: (Level 1C)

- Maintain airway, oxygenation, and ventilation
- Restore and maintain circulation, defined as normal perfusion and blood pressure
- Maintain neonatal circulation
- Maintain threshold HRs.

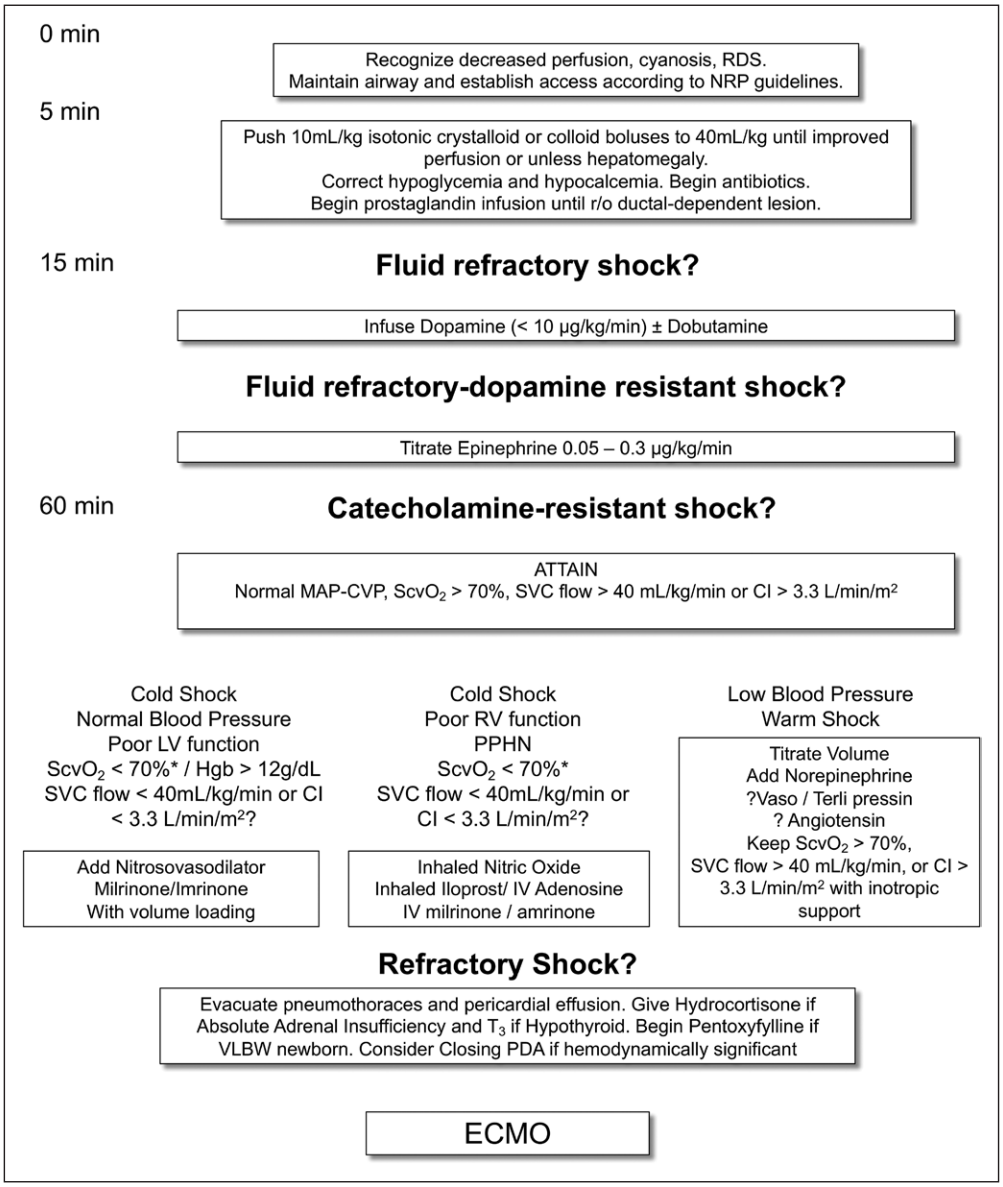

Figure 4. American College of Critical Care Medicine algorithm for time-sensitive, goal-directed stepwise management of hemodynamic support in newborns. Proceed to next step if shock persists. 1) First-hour goals—restore and maintain heart rate thresholds, capillary refill ≤ 2 s, and normal blood pressure in the (first hour). 2) Subsequent ICU goals—restore normal perfusion pressure (mean arterial pressure – central venous pressure), preductal and postductal oxygen saturation difference < 5%, and either $Scvo_2$ > 70% (* except congenital heart patinets with mixing lesions), superior vena cava flow > 40 mL/kg/min, or cardiac index > 3.3 L/min/m^2 in NICU.

Therapeutic Endpoints: (Level 1C)

- Capillary refill less than or equal to 2 seconds, normal pulses with no differential in quality between peripheral and central pulses, warm extremities, urine output greater than 1 mL/kg/hr, normal mental status, normal blood pressure for age, normal glucose, and calcium concentrations.
- Difference in preductal and postductal oxygen saturation less than 5%
- 95% Sao_2

Monitoring: (Level 1C)

- Temperature
- Preductal and postductal pulse oximetry
- Intra-arterial (umbilical or peripheral) blood pressure
- Continuous ECG
- Blood pressure
- Arterial pH
- Urine output
- Glucose, ionized calcium concentration

Airway and Breathing (Level 1D). Airway patency and adequate oxygenation and ventilation should be rigorously monitored and maintained. Supplemental or high-flow nasal cannula oxygen is the first choice for respiratory support. The decision to intubate and ventilate is based on clinical diagnosis of increased work of

breathing or inadequate respiratory effort or marked hypoxemia. Volume loading and inotrope infusion are often necessary prior to intubation and ventilation because analgesia, sedation, and positive-pressure ventilation can reduce preload, precipitating severe hemodynamic instability or arrest. Critically ill neonates may have rapid decline in systolic and diastolic ventricular function, which implies the need for close reassessment as resuscitation progresses. Expertly timed and performed intubation and mechanical ventilation will enhance physiologic performance at all levels by obviating work of breathing and ensuring the best possible oxygenation and perfusion. Pharmacologic management of intubation includes, in addition to adequate fluid resuscitation, the use of atropine to prevent hemodynamically significant bradycardia, and judicious analgesia, which can be accomplished in many cases with small doses of fentanyl, given slowly as 1–2 μg/kg aliquots. The use of NMDA-receptor antagonists such as ketamine is discouraged by many experts, given concerns regarding neurotoxicity despite it being the only hemodynamically stable drug. Etomidate is associated with adrenal suppression and is generally discouraged, although the agent has been used successfully by some experts in this setting with adjunctive hydrocortisone. Morphine, propofol, barbiturates, high-dose benzodiazepines, and dexmedetomidine are likely to cause hemodynamic instability in the septic neonate and should not be used as first-line agents to secure the airway in this setting.

Circulation (Level 1D). Vascular access can be rapidly attained according to NRP/PALS guidelines. Placement of an umbilical arterial and venous catheter is preferred. Intraosseous access, particularly in preterm newborns, is not the preferred route of drug administration.

Fluid Resuscitation (Level 1C). Fluid boluses of 10 mL/kg can be administered, observing for the development of hepatomegaly and increased work of breathing. Up to 60 mL/kg may be required in the first hour. Fluid should be infused with a goal of attaining normal perfusion and blood pressure. A D10 containing isotonic IV solution run at maintenance rate will provide age appropriate glucose delivery to prevent hypoglycemia.

Hemodynamic Support (Level 1C). Patients with severe shock uniformly require cardiovascular support during fluid resuscitation. Although dopamine can be used as the first-line agent, its effect on pulmonary vascular resistance should be considered. A combination of dopamine at low dosage (< 8 μg/kg/min) and dobutamine (up to 10 μg/kg/min) is initially recommended. If the patient does not adequately respond to these interventions, then epinephrine (0.05–0.3 μg/kg/min) can be infused to restore normal blood pressure and perfusion.

PPHN Therapy (Level 1B). Hyperoxygenate initially with 100% oxygen and institute metabolic alkalinization (up to pH 7.50) with $NaHCO_3$ or tromethamine unless and until inhaled NO is available. Mild hyperventilation to produce a respiratory alkalosis can also be instituted until 100% oxygen saturation and less than 5% difference in preductal and postductal saturations are obtained. Inhaled nitric oxide should be administered as the first treatment when available. Back-up therapies include milrinone and inhaled iloprost.

Stabilization: Beyond the First Hour (NICU Hemodynamic Support)

Goals: (Level 1C)

- Restore and maintain threshold HR.
- Maintain normal perfusion and blood pressure.
- Maintain neonatal circulation.
- $ScvO_2$ greater than 70%
- CI greater than 3.3 L/min/m^2
- SVC flow greater than 40 mL/kg/min

Therapeutic Endpoints (Level 1C)

- Capillary refill less than or equal to 2 seconds, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output greater than 1 mL/kg/hr, normal mental status, and normal blood pressure for age
- greater than 95% SaO_2
- less than 5% difference in preductal and postductal SaO_2
- $ScvO_2$ greater than 70%
- Absence of right-to-left shunting, tricuspid regurgitation, or right ventricular failure on echocardiographic analysis.
- Normal glucose and ionized calcium concentrations
- SVC flow greater than 40 mL/kg/min
- CI greater than 3.3 L/min/m^2
- Normal INR
- Normal anion gap, and lactate Fluid overload less than 10%

Monitoring (Level 1C)

- Pulse oximetry
- Arterial pH Continuous ECG
- Continuous intra-arterial blood pressure
- Temperature
- Glucose and calcium concentration
- Ins and outs, urine output
- CVP/oxygen saturation
- CO
- SVC flow
- INR
- Anion gap and lactate

Fluid Resuscitation (Level 1C). Fluid losses and persistent hypovolemia secondary to diffuse capillary leak can continue for days. Ongoing fluid replacement should be directed at clinical endpoints, including perfusion and CVP. Crystalloid is the fluid of choice in patients with Hgb greater than 12 g/dL. Packed RBCs can be transfused in newborns with Hgb less than 12 g/dL. Diuretics are recommended in newborns who are 10% fluid overloaded and unable to attain fluid balance with native urine output/extra-renal losses. A D10% containing isotonic IV solution run at maintenance rate can provide age appropriate glucose delivery to prevent hypoglycemia. Insulin infusion can be used to correct hyperglycemia. Diuretics are indicated in hypervolemic patients to prevent fluid overload.

Hemodynamic Support (Level 1C). A 5-day, 6 hour/d course of IV pentoxifylline can be used to reverse septic shock in VLBW babies. In term newborns with PPHN, inhaled nitric oxide is often effective. Its greatest effect is usually observed at

20 ppm. In newborns with poor left ventricle function and normal blood pressure, the addition of nitrosovasodilators or type III PDEIs to epinephrine (0.05–0.3 µg/kg/min) can be effective but must be monitored for toxicities. It is important to volume load based on clinical examination and blood pressure changes when using these systemic vasodilators. Triiodothyronine is an effective inotrope in newborns with thyroid insufficiency. Norepinephrine can be effective for refractory hypotension, but $Scvo_2$ should be maintained greater than 70%. An additional inotrope therapy should be added if warranted. Hydrocortisone therapy can be added if the newborn has adrenal insufficiency (defined by a peak cortisol after ACTH < 18 µg/dL, or basal cortisol < 4 mg/dL, or basal cortisol < 18 with the need for inotropic support). An additional inotrope therapy should be added if warranted.

The total duration of umbilical catheterization should not exceed 5 days for an UAC or 14 days for an umbilical vein catheter. Low doses of heparin (0.25–1.0 U/mL) should be added to the fluid infused through UACs. Prophylactic use of heparin for peripherally inserted silastic percutaneous central venous catheters increases the likelihood that they will complete their intended use (complete therapy) and reduces catheter occlusion.

Refractory Shock (Level 1C). Newborns with refractory shock must be suspected to have unrecognized morbidities (requiring specific treatment) including cyanotic or obstructive heart disease (responsive to prostaglandin E1), a critically large PDA (PDA closure), inborn errors of metabolism (responsive to glucose and insulin infusion or ammonia scavengers), pericardial effusion (pericardiocentesis), pneumothorax (thoracentesis), ongoing blood loss (blood replacement/hemostasis), hypoadrenalism (hydrocortisone), and/or hypothyroidism (triiodothyronine). When these causes have been excluded, ECMO becomes an important therapy to consider in term newborns. The current ECMO survival rate for newborn sepsis is 80%. Most centers accept refractory shock or a Pao_2 less than 40 mm Hg after maximal therapy to be sufficient indication for ECMO support. When on venovenous ECMO, persistent hypotension and/or shock should be treated with inotropic and/or vasopressor therapy, or conversion to venoarterial support. For newborns with refractory shock related to PPHN-induced right ventricular failure, venovenous ECMO can unload the right ventricle, reduce septal bowing, and improve left ventricle output. However, for newborns with primary left ventricle or biventricular failure refractory to inotropic and vasodilator support, venoarterial ECMO is required to reverse shock. Inotrope requirements can diminish when venoarterial ECMO is used but may persist. Calcium concentration should be normalized in the RBC pump prime (usually requires 300 mg $CaCl_2$ per unit of pRBCs). In newborns with inadequate urine output and 10% fluid overload despite diuretics, CRRT is best performed while on the ECMO circuit. No specific recommendations for CRRT can be made in neonatal sepsis. Venous access for CRRT in neonates can be problematic, but in patients on ECMO, CRRT can be provided in tandem. It is a technical challenge to perform TPE in a neonate weighing less than 5 kg. TPE should not be used during the initial septic shock resuscitation. Once the shock resuscitation is addressed, TPE could be considered as a strategy to reverse MODS, especially in patients with significant coagulopathy. Titration of medications and calcium replenishment will be needed during the procedure to prevent hemodynamic changes.

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