2014 ACCM CLINICAL PRACTICE PARAMETERS FOR HEMODYNAMIC SUPPORT OF PEDIATRIC AND NEONATAL SEPTIC SHOCK

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Background: The American College of Critical Care Medicine (ACCM) provided 2002 and 2007 guidelines for hemodynamic support of newborn and pediatric septic shock.

Objective: 2014 update of the 2007 ACCM *Clinical Guidelines for Hemodynamic Support of Neonates and Children with Septic Shock*.

Participants: Society of Critical Care Medicine (SCCM) members were identified from general solicitation at SCCM Educational and Scientific Symposia (2006-2014).

Methods: The PUBMED/MEDLINE/EMBASE literature (2006-14) was searched by the SCCM librarian using the keywords: sepsis, septicemia, septic shock, endotoxemia, persistent pulmonary hypertension, nitric oxide, ECMO, and ACCM Guidelines. Using a modified Delphi method and the GRADE system, recommendations were developed with > 90% consensus.

Results: The 2002 and 2007 guidelines were widely disseminated, translated into Spanish and Portuguese, and incorporated into SCCM and AHA/PALS 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 the guidelines. Improved compliance reduced hospital mortality from 4-2%. 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.

In 1998 the Institute of Medicine called for establishment of best practice guidelines across medicine. In 2002 and 2007, the 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 to 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 updated 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 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 and grade the literature using the GRADE system. 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' grade recommendations was given 'letter' grades with A = to multiple randomized controlled trials and at least one metanalysis, B = one randomized controlled trial, C = cohort, case control studies, and D 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 literature was accrued by the SCCM librarian in part by searching PUBMED/MEDLINE/EMBASE using the following keywords: sepsis, septicemia, septic shock, endotoxemia, persistent pulmonary hypertension, nitric oxide, and ECMO. The search was narrowed to identify studies specifically relevant to children. Best Practice Outcomes were identified and described clinical practice in these centers was used as a model. A modified Delphi method was used attaining 90% compliance in recommendations made.

RESULTS

Evolution of 2002, 2007, and 2014 guidelines

Many studies have tested the observations and recommendations of the 2002 and 2007 guidelines. The findings have been mixed in the 'resource poor setting' where there is not access to mechanical ventilators, intravenous infusion pumps, inotrope medications and intensive care monitoring. Wills and colleagues (NEJM, 2005) demonstrated near 100% survival when fluid resuscitation was provided to children with dengue shock in the first hour.[10] In contrast, Maitland et al (NEJM 2011) found fluid boluses were harmful compared to maintenance intravenous fluid infusion and blood transfusion in severe malaria endemic sub-Saharan Africa.[11] The Maitland study included a large population of children with severe malaria and anemia, and excluded dehydrated children; whereas, the Wills study only included a population of children with Dengue Shock, with capillary leak, hemoconcentration, and dehydration . Importantly, neither of these studies actually tested fluid bolus use as recommended in the 2002 and 2007 ACCM guidelines because boluses were given without attention to the presence of of rales and hepatomegaly in the patients. The 2002 and 2007 ACCM guidelines specifically recommend against fluid boluses when rales or hepatomegly are present, and 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 hyper-volemic 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.

Studies in the resource rich setting where mechanical ventilators, intravenous infusion pumps, inotrope medications and intensive care monitoring (allowing for recognition of severe anemia, hypoproteinemia, and fluid overload/congestive sates) are available, have uniformly favored use of the ACCM/PALS guidelines. Han and colleagues 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%; NNT = 3.3). Every hour that went by without restoration of normal blood pressure for age and capillary refill < 3 seconds was associated with a two-fold increase in adjusted mortality odds ratio.[13] Ninis and colleagues 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 was attained.[12] Codreiro et al tested this 2007 recommendation in a randomized trial and found that use of peripheral adrenaline infusion reduced mortality to 7% compared to 20% with peripheral dopamine infusion.[14] de Oliveira 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 $ScvO_2$ > 70%, reduced mortality from 39% to 12% (NNT = 3.6) compared to therapy directed only to blood pressure and capillary refill.[15] Sankar et al, has now corroborated this finding in a cohort study in a population of Indian children showing that directing therapy to ScvO2 was associated with improved outcome with a number needed to treat = 5.[16] In a before and after study, Lin 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).[17] 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 recently 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.[18] Both of these centers also used high flux continuous renal replacement therapy (CRRT) and fresh frozen plasma infusion directed to the goal of normal INR (prothrombin time).

There is general consensus 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 USA 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 intravenous 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, 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 appears reasonable that each institution could locally develop their trigger tool while 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 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 intravenous access, 3) starting intravenous fluids and resuscitation as needed, 4) administering antibiotics, and 5) starting vasoactive agents if needed.[22] Achievement of 100% compliance required a number of human interaction interventions including use of time clocks set to have time going from 0-60 minutes rather than 60-0 minutes, that resulted in an increase in number of cases between death occurrence ($p < 0.05$) with an overall reduction in hospital mortality from 4.0% to 1.7%.

Han et al analyzed the international Global Sepsis Initiative data base 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.[25] The first hour/ emergency department three element bundle included 1) reversal of shock defined by normal blood pressure and capillary refill < 3 seconds, 2) provision of antibiotics, and 3) provision of D10 containing intravenous fluid infusion. The stabilization / PICU three element bundle included 1) reversal of shock defined by maintaining normal MAP-CVP for age and ScVO2 > 70%, 2) timely provision of the appropriate sensitive antibiotic and source control, and 3) maintenance of effective tidal volumes between 6-8 mL/kg in children mechanically ventilated with 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 which 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 $\leq$ 2 seconds with specific evalution 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 $ScvO_2$ > 70% and cardiac index 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 be addressed at the institutional level rather than only at the practitioner level. The new guidelines recommend that each institution implemented adopted or home-grown bundles that include the following 1) *Recognition Bundle* containing a the 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 (Figure 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 is usually maintained or increased by two mechanisms: tachycardia and ventricular dilation. Adults who do not develop this adaptive process to maintain cardiac output have a poor prognosis.[27,28] ***Pediatric septic shock*** is associated with severe hypovolemia, and children frequently respond well to aggressive volume resuscitation; however, the hemodynamic response of fluid resuscitated children appears diverse compared to adults. Contrary to the adult experience, low cardiac output, not low systemic vascular resistance, is associated with mortality in pediatric septic shock.[29-38] 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 in children.[31] Attainment of the therapeutic goal of oxygen consumption (VO_2) > 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 capillary wedge pressure)[30] were applied to children with septic shock.[38] Ceneviva et al reported 50 children with fluid-refractory (≥60 ml/kg in the first hour), dopamine-resistant shock.[38] The majority (58%) showed a low cardiac output/high systemic vascular resistance state, and 22% had low cardiac output 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 systemic vascular resistance state.[39-42] 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 to mortality in the 1985 study (58%),[30] in which aggressive fluid resuscitation was not used. More recently investigators in the UK confirmed these observations using Doppler ultrasound to measure cardiac output.[43,44] They found that previously healthy children with meningococcemia often had a low cardiac output with a high mortality rate, whereas cardiac output was high and mortality rate was low in septic shock related to catheter-associated blood stream infections.[43]

Neonatal septic shock can be complicated by the physiologic transition from fetal to neonatal circulation. *In utero*, 85% of fetal circulation bypasses the lungs through the patent ductus arteriosus and foramen ovale. This flow pattern is maintained by 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 patent ductus arteriosus and foramen ovale complete this transition. Pulmonary vascular resistance and artery pressures can remain elevated and the ductus arteriosus can remain open for the first six weeks of life, while 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 (PFC). Neonatal septic shock with PPHN is associated with increased right ventricle work. Despite *in utero* conditioning, the thickened right ventricle may fail in the presence of systemic pulmonary artery pressures. Decompensated right ventricular failure can be clinically manifested by tricuspid regurgitation and hepatomegaly. Newborn animal models of Group B streptococcal and endotoxin shock have also documented reduced cardiac output, and increased pulmonary, mesenteric, and systemic vascular resistance.[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 infants with septic shock*** (<32 weeks gestation, <1000 gms) 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 'RDS' 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 to the low resistance placenta. Cardiac output 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, 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 one of life reduced the incidence of hypotension in this population,[66] and a seven-day course of hydrocortisone reduced the need for inotropes in very low birth weight (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 to 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 weeks 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 very low birth weight infants is the persistence of the patent ductus arteriosus. 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 ensuant 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 multi-center 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, shock should be diagnosed by clinical signs, which include hypothermia or hyperthermia, altered mental status, and peripheral vasodilation or vasoconstriction with capillary refill > 2 seconds (cold shock) before hypotension occurs. Threshold heart rates associated with increased mortality in critically ill (not necessarily septic) infants are a HR < 90 b.p.m. or > 160 b.p.m, and in children are a HR < 70 b.p.m. or > 150 b.p.m.[73] Emergency department therapies should be directed towards restoring normal mental status, threshold heart rates, peripheral perfusion (capillary refill < 3 seconds), palpable distal pulses, and blood pressure for age.[12] Orr and colleagues reported that specific hemodynamic abnormalities in the emergency department were associated with progressive increase in mortality (%): eucardia (1%) < tachycardia/bradycardia (3%) < hypotension with capillary refill less then 3 seconds (5%) < normotension with capillary refill greater than 3 seconds (7%) < hypotension with capillary refill greater 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 (mean arterial pressure minus central venous pressure or MAP-CVP) and cardiac output (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 (dP) and inversely with resistance (R). This is mathematically represented by $Q = dP/R$. For the systemic circulation this is represented by cardiac output (CO) = MAP – CVP / systemic vascular resistance (SVR). This relationship is important for organ perfusion. In the kidney, for example, renal blood flow (RBF) = mean renal arterial pressure (mRAP) – mean renal venous pressure (mRVP) / renal vascular resistance. Some organs (including the kidney and brain) have vasomotor auto-regulation, which maintains blood flow in low blood pressure (MAP or RAP) states. At some critical point, perfusion pressure is reduced below the ability of the organ to maintain blood flow.

One goal of shock treatment is to maintain perfusion pressure above the critical point below which blood flow can not be effectively maintained in individual organs. 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.[76] Producing a supranormal

MAP above this point is likely not of benefit[77] and may actually decrease cardiac output by increasing afterload above the capacity of the myocardium to compensate.

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 intra-bladder pressure) using diuretics and/or peritoneal drainage for IAP > 12 mmHg, and surgical decompression for > 30 mmHg, results in restoration of perfusion pressure and has been shown to improve renal function in children with burn shock.[78]

Normative blood pressure values in the very low birth weight (VLBW) newborn have been reassessed. A MAP < 30 mmHg 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 cardiac output, it is recommended that normal CO and/or superior vena cava (SVC) flow, measured by Doppler echocardiography, be a primary goal as well.[79-89]

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 cardiac output. Conversely, if ventricular function is reduced, the presence of normal blood pressure with high vascular resistance means that cardiac output is reduced. If the elevation in vascular resistance is marked, the reduction in blood flow results in shock. A cardiac index between 3.3-6.0 L/min/m^2 is associated with best outcomes in septic shock patients[30] compared to patients without septic shock for whom a cardiac index above 2.0 L/min/m^2 is sufficient.[90] Attainment of this cardiac output goal is often dependent on attaining threshold heart rates. However, if the heart rate is too high, then there is not enough time to fill the coronary arteries during diastole, and contractility and cardiac output will decrease. Coronary perfusion may be further reduced when an unfavorable transmural coronary artery filling pressure is caused by low diastolic blood pressure 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 stroke volume is low, or an inotrope if contractility is low. Because CO = heart rate (HR) x stroke volume (SV), therapies directed to increasing SV will often reflexively reduce HR and improve CO. This will be evident in improvement of the shock index (heart rate/systolic blood pressure, HR/SBP),[91] as well as CO. Children have limited heart rate reserve compared to adults because they are already starting with high basal heart rates. 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 b.p.m., but a baby cannot increase from 140 b.p.m to 280 b.p.m. Although tachycardia is an important method for maintaining cardiac output in infants and children, the younger the patient, the more likely this response will be inadequate and the cardiac output 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 diastolic blood pressure. 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 (ie, 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 x SV). This can be attained by using an inotrope that is also a chronotrope. In addition to threshold heart rates, attention must also be paid to diastolic blood pressure (DBP). If the DBP-CVP is too low then addition of a intrope/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 stroke volume by moving leftward on the over-filled 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.

Shock should also be assessed and treated according to oxygen utilization measures. Measurement of CO and O_2 consumption were proposed as being of benefit in patients with persistent shock because a cardiac index between 3.3 and 6.0 L/min/m^2 and O_2 consumption > 200 mL/min/m^2 are associated with improved survival.[30] 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 (cardiac index >3.3 and < 6 L/min/m^2) and found to have improved outcomes compared to historical reports.[38] Because low CO is associated with increased O_2 extraction,[31] $ScvO_2$ 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 arterial oxygen saturation of 100%, mixed venous saturation is > 70%. Assuming a hemoglobin concentration of 10 gm/dL and 100% arterial O_2 saturation then a cardiac index (CI) > 3.3 L/min/m^2 with a normal oxygen consumption of 150 mL/min/m^2 (O_2 consumption = CI x (arterial O_2 content – venous O_2 content) results in a mixed venous saturation of > 70%: 150 mL/min/m^2 = 3.3 L/min/m^2 x [1.36 x 10 gm/dL + paO2 x 0.003] x 10 x [1 -0.7]. In an emergency department study in adults with septic shock, maintenance of superior vena cava O_2 saturation > 70% by use of blood transfusion to a hemoglobin of 10 gm/dL and inotropic support to increase cardiac output, resulted in a 40% reduction in mortality compared with a group in whom MAP and CVP were maintained at usual target values without attention to superior vena cava O_2 saturation.[92] Since 2002, Oliveira and colleagues reproduced this finding in children with septic shock reducing mortality from 39% to 12% when directing therapy to the goal of $ScvO_2$ saturation > 70% (NNT 3.6).[15] Similarly, Sankar and colleagues demonstrated a mortality reduction from 54% to 33.3% (NNT 5) and lower organ dysfunction with a similar $ScvO_2$ saturation goal of > 70%.[16] In contrast, supranormal ScvO2 saturations > 80-85% that reflect a narrowed arterio-venous difference in O2 content ($AVDO_2$) may reflect either mitochondrial dysfunction, a high cardiac output state, or overly aggressive resuscitation.[93] 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 under- or over-estimate the true severity of illness, leading to either false reassurance and under- resuscitation or over-resuscitation. Multimodal monitoring refers to the use of multiple variables and their changes over time to better determine the underlying hemodynamic state. Shock index (heart rate / SBP)[91] and heart rate variability analysis[94] 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 and colleagues were able to titrate hemodynamic therapies more precisely and achieve equivalent mortality outcomes to PICUs using more invasive continuous cardiac output monitoring.[75]

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.[95-97] 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 appear to correlate with recovery.[98-102] 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.[103] 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.

In very low birth weight infants, superior vena cava (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 > 40 mL/kg/min is associated with improved neurologic outcomes and survival.[85-89] $ScvO_2$ saturation can be used in low birth weight infants but may be misleading in the presence of left to right shunting through the patent ductus arteriosus.

Intravascular Access Vascular access for fluid resuscitation and inotrope/vasopressor infusion is more difficult to attain in newborns and children compared with adults. 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 pediatric advanced life support (PALS) guidelines for emergency establishment of intravascular support.[104-107] Essential age-specific differences include use of umbilical artery (UAC) and umbilical venous (UVC) access in newborns, and rapid use of intraosseous (IO) access in children.[108-110] Ultrasound guidance may have a role in the placement of central lines in children.[110-116]

Fluid Therapy Several fluid resuscitation trials have been performed since 2002. For example, several randomized trials showed that when children with mostly Stage III (narrow pulse pressure/tachycardia) and some Stage IV (hypotension) WHO classification Dengue shock received fluid resuscitation in the emergency department there was near 100% survival regardless of the fluid composition used.[3,10,117,118] In a randomized controlled trial, Maitland and colleagues demonstrated a reduction in malaria septic shock mortality from 18% to 4% when albumin was used compared to crystalloid.[119] More recently Maitland et al demonstrated harm in the FEAST trial when fluid boluses were given rather than intravenous fluid at a maintenacce rate and blood transfusion contradicting this earlier underpowered study.**[11]** The adult SAFE trial that compared crystalloid versus albumin fluid resuscitation reported a trend towards improved outcome ($p < 0.1$) in septic shock patients who received albumin.[120] Preference for the exclusive use of colloid resuscitation was made based on a clinical practice position paper 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 minutes) and intubating all 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 to crystalloid.[121] 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.[122] Several new investigations examined both the feasibility of the 2002 guideline recommendation of rapid fluid resuscitation as well as the need for fluid removal in patients with subsequent oliguria following fluid resuscitation. The 2002 guideline recommended rapid 20 mL/kg fluid boluses over five 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 intravenous line.[123] Ranjit and colleagues 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.[124] In this regard, Foland and colleagues similarly reported that patients with multiple organ failure who received CRRT when they were < 10% fluid overloaded had better outcomes than those who were > 10% fluid overloaded.[125] 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.[4,18]

The use of blood as a volume expander was examined in two small pediatric studies, but no recommendations were given by the investigators.[126,127] In the previously mentioned study by Oliveira 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 > 70% (40% vs 7%).[15] Although the members of the taskforce use conservative goals for blood transfusion in routine critical illness (Hgb < 7 g/dL without cardiopulmonary compromise), the observation that patients who have septic shock with a ScvO2 < 70% and Hgb < 10g/dL had better outcomes when transfused to a goal Hgb > 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 cardiac output including heart rate, 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 requires 40 -60 ml/kg.[37, 122, 128-135] 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 cardiac output. Observation of little change in the CVP in response to a fluid bolus suggests that the venous capacitance system is not over-filled 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 acute respiratory distress syndrome [122,134] or cerebral edema.[122,135] Increased fluid requirements may be evident for several days secondary to loss of fluid from the intravascular compartment when there is profound capillary leak.[37] Routine fluid choices include crystalloids (normal saline or lactated ringers) and colloids (dextran, gelatin, or 5% albumin).[3,136-144,105-114] Fresh frozen plasma may be infused to correct abnormal PT and PTT values, but should not be pushed because it may produce acute hypotensive effects likely caused by vasoactive kinins and high citrate concentration. Since oxygen delivery depends on hemoglobin concentration, hemoglobin should be maintained at a minimum of 10 gm/dL.[15] Diuretics / peritoneal dialysis / CRRT are 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, ideally at least 40 to 60 ml/kg of either isotonic crystalloid or 5% albumin given rapidly, certainly 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 cannulae and other modes of non-invasive respiratory support may be appropriate for 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 must be impeccably timed: sedation, analgesia and positive-pressure ventilation associated with premature instrumentation of the airway, prior to adequate volume resuscitation, may cause profound drops in preload and precipitate severe hemodynamic instability or an arrest. Conversely, severe diastolic and systolic ventricular dysfunction may predispose the child to pulmonary edema and rapid desaturation during intubation, making the procedure more treacherous. Expertly performed intubation and mechanical ventilation eliminate work of breathing and improve oxygenation and organ perfusion, all of which are typically compromised in the septic child. The procedure should therefore be carefully planned and performed by the most experienced clinician available.[146-149]

Atropine increases the heart rate and protects against the deleterious effects of bradycardia, particularly in babies.[150] Atropine does not cause cardiac dysrhythmias, and is not contraindicated in children exhibiting tachycardia. Ketamine remains the agent of choice for intubation of pediatric patients with shock,[151] given its pharmacologic effects of dissociation while maintaining or augmenting systemic vascular resistance. Side effects may be minimized by administering intravenous boluses over 30 to 60 seconds. The use of ketamine with atropine pre-treatment should be considered as the sedative/induction regimen of choice to promote cardiovascular integrity.[152]

The use of etomidate is generally discouraged at this time, given its known effects on adrenal function,[153-155] despite some reports suggesting no direct effect on patient mortality.[156-157] 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 analogues 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. 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 to 2 micrograms per kilogram, given 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 systemic vascular resistance, 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 intensive care unit.

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 utilized as well, but there is concern regarding neuroapoptosis following exposure to ketamine in infants.[158,159] 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 Non-Invasive or Minimally Invasive Monitoring **M**inimal invasive monitoring is necessary in children with fluid-responsive shock; however, in children with fluid-refractory shock, physical signs of cold vs 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 and provides goals and therapeutic end points in shock resuscitation. Echocardiography is considered an appropriate non-invasive tool to rule out the presence of pericardial effusion, evaluate myocardial contractility and intravascular volume. Ranjit et al. 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. 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, Brierley et al, categorized the hemodynamic patterns of pediatric septic shock with the use of doppler ultrasounography and noted that the manifestation of central venous catheter (CVC) infection is cause dependent i.e., CVC infection presents with high cardiac output and low systemic vascular resistance, in comparison with community acquired infections.[43] Cardiac output > 3.3 L/min/m^2 < 6.0 L/min/m^2 are associated with improved survival and neurologic function.

Other non-invasive monitors undergoing evaluation in newborns and children include percutaneous venous oxygen saturation, aortic ultrasound, perfusion index (pulse–oximetry), near infra-red spectroscopy, sublingual pCO_2, and sublingual microvascular orthogonal polarization spectroscopy scanning. All show promise however none have been tested in goal-directed therapy trials.[160-168]

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.[47] Goal-directed therapy to achieve an $ScvO_2$ saturation > 70% is associated with improved outcome.[15] To gain accurate measures of $ScvO_2$, the tip of the catheter must be at the SVC-RA or IVC-RA junction.[169] A Pulmonary artery (PAC), PICCO, or femoral artery thermodilution (FATD) catheter can be used to measure CO in those who remain in shock despite therapies directed to clinical signs of perfusion, MAP-CVP, $ScvO_2$, and echocardiographic analyses.[170-174] The PAC measures the PAOP (pulmonary artery occlusion pressure) 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.[175,176]

Cardiovascular Drug Therapy When considering the use of cardiovascular agents in the management of infants and children with septic shock, several important points need emphasis. The first is that septic shock represents a dynamic process so that the agents selected and their infusion dose may have 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 systemic vascular resistance and pulmonary vascular resistance (i.e., vasodilators or vasopressors), contractility (i.e., inotropy) and heart rate (chronotropy). 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 alpha-adrenergic agonists that is mediated by excess nitric oxide production as well as alterations in the alpha-adrenergic receptor system. Similarly, cardiac beta-adrenergic responsiveness may be reduced by the effect of nitric oxide and other inflammatory cytokines.

Inotropes Epinephrine (0.05–0.5 μg/kg/min)[177-181] or dopamine (5–10 μg/kg/min)[182-193] if epinephrine is not available should be used as first-line inotropic support in pediatric fluid-refractory cold shock, while norepinephrine (0.05–0.5 μg/kg/min)[194-196] should be considered first-line vasoactive support in fluid-refractory warm shock. It is crucial to initiate these infusions as soon as possible preferably via a central line but administration via a peripheral or intraosseous line is acceptable to avoid delays while attempting to obtain central access. Even though a common perception, there is 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 subcutaneous infiltration with phentolamine, 1–5 mg diluted in 5 mL of normal saline.

Epinephrine is more commonly used in children than in adults. Some members of the committee recommend use of low-dose epinephrine (<0.5 μg/kg/min) as a first-line choice for cold hypodynamic shock. 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 (<0.5 μ/kg/min) epinephrine has greater beta-2-adrenergic effects in the peripheral vasculature with little alpha-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,[181] 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 the 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.

Observational studies in adults in shock raised the concern of increased mortality with use of dopamine. Possible explanations include the action of a dopamine infusion to reduce the release of hormones from the anterior pituitary gland, such as prolactin, through stimulation of the DA_2 receptor, which can have important immunoprotective effects, and inhibition of thyrotropin releasing hormone release. More recent studies have not supported these observations. Codreiro et al demonstrated in a randomized trial that children with fluid refractory septic shock treated with an epinephrine infusion had a decreased mortality (7%) compared to those treated with a dopamine infusion. The Dopamine arm experienced a delay in time to resolution of shock, and an increased incidence of secondary infection compared to the epinephrine arm.[14] Dopamine remains as a first line agent in septic shock, in situations where epinephrine or norepinephrine infusion are not readily available.

Dobutamine may be used when there is a low CO state with adequate or increased SVR.[197-208] However, milrinone if preferred in this situation if available. Dobutamine is a synthetic catecholamine which causes chronotropy and increase in myocardial oxygen demand, while milrinone is a phosphodiesterase III inhibitor which does not exerts its pharmacologic effects via adrenergic stimulation and therefore does not increase the myocardial consumption of oxygen.

Vasodilators When pediatric patients are normotensive with a low cardiac output and high systemic vascular resistance, initial treatment of fluid-refractory patients consists of the use of an inotropic agent such as epinephrine or dobutamine. The addition of the inodilator milrinone [a type III phosphodiesterase inhibitor (PDEI)] to epinephrine may also be considered to improve cardiac contractility and lower systemic vascular resistance in selected normotensive patients with clinical evidence of poor oxygen tissue delivery. This class of agents has a synergistic effect with beta-adrenergic agonists since the latter agents stimulate intracellular cAMP production while the PDE inhibitors increase intracellular cAMP by blocking its hydrolysis. [209-215]

Since the PDE inhibitors do not depend on a receptor mechanism, they maintain their action even when the beta-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) Fluid boluses are likely to be required if milrinone is administered with full loading doses. Because milrinone has a long half-life (1 -10 hours depending on organ function) it can take 3 to 30 hours to reach 90% of steady state. Although recommended in the literature some individuals in the committee choose not to use boluses of milrinone. This group administers the drugs as a continuous infusion only. Other members divide the bolus in 5 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 systemic vascular resistance. 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 $ß_2$ receptor.

A short-acting vasodilator may be added in selected patients, such as sodium nitroprusside or nitroglycerin to recruit microcirculation.[216-222] Orthogonal polarizing spectroscopy showed that addition of systemic IV nitroglycerin to dopamine/norepinephrine infusion restored tongue microvascular blood flow during adult septic shock.[222] 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.[222-228]

Rescue from refractory shock has been described in case reports and series using two medications with Type III phosphodiesterase activity. Levosimendan is a promising new medication that increases Ca^{++} / actin / tropomyosin complex binding sensitivity and also has some Type III PDEI and ATP-sensitive K^+ channel activity. Because one of the pathogenic mechanisms of endotoxin-induced heart dysfunction is desensitization of Ca^{++} / actin / tropomyosin complex.binding,[1229-234] this drug allows treatment at this fundamental level of signal transduction overcoming the loss of contractility that characterizes septic shock. Enoximone is a Type III PDEI with 10 times more β_1 cAMP hydrolysis inhibition than β_2 cAMP hydrolysis inhibition.[235-237] Hence it can be used to increase cardiac performance with less risk of undesired hypotension.

Vasopressors There is evidence that shows the benefits of applying pediatric guidelines for the treatment of septic shock includes the use of vasopressors.[21,38] Vasopressors can be titrated to end points of perfusion pressure (mean arterial pressure [MAP]-central venous pressure [CVP]) or systemic vascular resistance (SVR) that promote optimum urine output and creatinine clearance,[195,196,230] 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 one specific vasoactive drug over another (dopamine >15 ug/kg/min, epinephrine >0.3 ug/kg/min or norepinephrine). Havel et al [239] in a Cochrane Database systematic review for adult patients concludes that there is not sufficient evidence of any difference between six vasopressors that were examined. Independently of the vasopressor choice, the most important point is not to delay the vasoactive infusion in fluid refractory septic shock.

When epinephrine is administrated in doses greater than 0.3 ug/kg/min or dopamine in doses greater than 10 ug/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. Dopamine has been used as the first-line vasopressor for fluid-refractory hypotensive shock in the setting of low systemic vascular resistance (SVR). However, there is some evidence that adult patients treated with dopamine have worse outcomes than those treated without dopamine[240] and that norepinephrine, when used exclusively in this setting, leads to adequate outcomes.[241] Dopamine-resistant shock commonly responds to norepinephrine or high-dose epinephrine.[195,196,242]

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 systemic vascular resistance (SVR) (e.g. wide pulse pressure with diastolic blood pressure that is less than one-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.[243,244] Vasu et al [245] report, in a systematic review of randomized control trials comparing dopamine with norepinephrine in critically ill adult patients with septic shock, a better outcome in 28 day mortality, however the difference is statistically marginal (RR 0.91, CI 0.83-0.99). Oba et al [246] in recent meta-analyses found that the use of norepinephrine, with or without low dose vasopressin, as the first line vasopressor therapy in adult septic shock was associated with reduced mortality compared with dopamine.

The infusion of norepinephrine is suggested as the initial vasoactive drug in patients with warm shock, with vasodilatation and low systemic vascular resistance (SVR). A study using a non-invasive ultrasound cardiac output monitor device (USCOM) 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. Children with initial warm shock were commenced on norepinephrine. Despite an initial good response, four patients developed low CI and needed epinephrine.[44]

When the use of vasopressor drugs is needed, it must be started as soon as possible but within 60 minutes of resuscitation, using peripheral or intraosseus access, while central venous access is obtained. Lampin et al, describe in a retrospective study the use of norepinephrine in 144 children over a 10 year period (10); 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 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.[21,22]

Vasopressin has been shown to increase mean arterial pressure (MAP), systemic vascular resistance (SVR), and urine output in patients with vasodilatory septic shock and hyporesponsiveness to catecholamines .[247-261] Vasopressin's action is independent of catecholamine receptor stimulation, and therefore its efficacy is not affected by alpha-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 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 end point.[262] The results of another randomized control trial evaluating the use of low doses of vasopressin as an adjunctive therapy in hyperdynamic pediatric septic shock failed to show benefits.[31]

Vasopressin or terlipressin can be considered as rescue therapy in patients in vasodilatory shock who don't 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.[250,252,255-270] Administered as a continuous infusion or in bolus, it increases BP and urine output in pediatric patients with refractory septic shock. Decreased CO or distal necrosis has been reported as possible adverse events.[271,272] Yildizdas et al evaluated the effect of continuous infusion of terlipressin in a randomized control trial in pediatric patients with septic shock and high catecholamine requirement. Although terlipressin infusion had no effect on mortality, it significantly increased mean arterial pressure, $PaO2/FIO2$, and survival time in nonsurvivors.[273]

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.[274] Phenylephrine is another pure vasopressor with no beta adrenergic activity.[275] Its clinical role is also limited. NO inhibitors and methylene blue are considered investigational therapies.[276-279] Studies have shown an increased mortality with nonselective NO synthase inhibitors suggesting that simply increasing blood pressure through excessive vasoconstriction has adverse effects.

Glucose, Calcium, Thyroid, and Hydrocortisone Replacement Hypoglycemia has been associated with worse short-term outcomes in critically ill children.[280,281] Therefore, hypoglycemia must be rapidly diagnosed and promptly treated. Causation has not been established. Hyperglycemia in non-diabetic children with sepsis has been associated with worse outcomes.[282,283] Branco et al.[282] reported a greater risk of death with hyperglycemia ($\geq$178 mg/dl) in 57 children with septic shock. Day et al. [283] reported hyperglycemia (>180 mg/dl) negatively correlated with ventilator free days at 30 days in a retrospective review of 97 children with meningococcal sepsis. Hyperglycemia and hypoglycemia during critical illness may simply represent epiphenomena. In contrast, Mesotten et al.[285] reported that brief hypoglycemia ($\leq$ 40 mg/dl) caused by tight glycemic control in a pediatric randomized controlled trial was <u>not</u> associated with worse neurocognitive outcome approximately four years later.

Randomized controlled trials of tight glycemic control have been conducted primarily in post-cardiac surgery children.[286-289] Results are conflicting, with one study showing a reduction in PICU length of stay and inflammatory markers[288] and the other three not showing an improvement in mortality or morbidity.[286,287,289] 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.[290,291]

Calcium replacement should be directed to normalize ionized calcium concentration, however it's safety and efficacy has 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.[292-309] Hypothyroidism is relatively common in children with Trisomy 21 and children with central nervous system 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 Tri-iodothyronine may be beneficial in postoperative congenital heart disease patients but has yet to be studied in children with septic shock.

Multiple studies suggest sepsis induced changes in the HPA axis [310,311] glucocorticoid receptor changes, [312] and changes in cortisol metabolism during sepsis).[313] A possible rationale for the use of corticosteroids in sepsis is its pharmacologic effect on the cardiovascular system and anti-inflammatory properties.[296,314-316] 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 mcg/dl after administration of low dose (1 mcg) adrenocorticotropic hormone (ACTH).[310] The prevalence of relative adrenal insufficiency reported in other studies is widely variable depending on the diagnostic criteria used.[317] Low or high serum cortisol concentrations have been associated with increased mortality.[318] A cutoff of < 25 mcg/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 > 36 mcg/dl and a lack in response to ACTH stimulation may predict a failure to respond to exogenous corticosteroid administration.[319] 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 mcg/dl versus 16.7 mcg/dl, $p < 0.001$).[310]

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.[320] 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.[313] The role of free cortisol in the diagnosis of adrenal insufficiency determination has not been sufficiently elucidated. Administration of etomidate[321] , megestrol [322], and ketoconazole[323] have been identified as iatrogenic causes of adrenal insufficiency due to their interference with cortisol production.

Non-survivors have exceedingly high ACTH/cortisol ratios within the first eight hours of meningococcal shock.[324] The lack of increase in serum cortisol concentration (<9 mcg/dl) in patients undergoing an ACTH stimulation test with baseline cortisol concentrations >18 mcg/dl was associated with catcholamine refractory shock, but not mortality. [301,317,319] The value of ACTH stimulation test in the diagnosis and treatment of relative adrenal insufficiency and CIRCI “critical illness–related corticosteroid insufficiency” in children remains unclear.[310] No gold standard has been established in the diagnosis of adrenal insufficiency in critical illness. Absolute adrenal insufficiency has been defined as a basal serum cortisol concentration of < 7 mcg/dl and peak serum cortisol of < 18 mcg/dl after stimulation.[317] Others suggested a basal serum cortisol of < 5 [310](Menon 2010) or < 9 mcg/dl and use the same peak cutoff after ACTH stimulation of < 18 mcg/dl for the definition of absolute adrenal insufficiency. Relative adrenal insufficiency has been proposed as a basal serum cortisol concentration of < 20 mcg/dl and < 9 delta after ACTH stimulation. [325]

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-Friedrichson 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 menigococcemia.[326] The administration of fludrocortisone in addition to hydrocortisone has been suggested in septic shock [327] 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 per day (equivalent to about 100 mg/m^2/day) when given to adults.[328] Hydrocortisone's mineralocorticoid activity is deemed to be equivalent to 150mcg/m^2/day of 9α-fludrocortisone when a total daily dose of 20-50 mg of hydrocortisone is reached [329, 330].

Treatment with low dose hydrocortisone for relative adrenal insufficiency has gained interest since the first RCT in adults with septic shock was published in 2002, proving a mortality benefit.[292] A subsequent RCT in adults did not confirm a mortality advantage for the treatment with stress doses of hydrocortisone, leaving us with conflicting results [331]. The pediatric literature lacks large RCTs evaluating the benefit of corticosteroids specifically in septic shock and refractory septic shock and a pediatric metanalysis evaluating the role of corticosteroids in shock did not demonstrate benefit.[319] 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.[292,327,331-334]

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. [331, 335, 336] Steroid use was linked to disseminated candidiasis in a case report, [337] however infectious complications were not found to be increased by the administration of corticosteroids in children and adults with shock in other studies.[314, 319] Other side effects in patients receiving corticosteroids have been described, including hyperglycemia[314, 338] and bleeding [319]. Concerns regarding the development of myopathy in association with corticosteroid therapy have been raised, but not confirmed in either the adult [314] or pediatric population with shock [315]. A rise in sodium during corticosteroid administration was observed in several studies and self-resolves after discontinuation.[314]

Analysis of data obtained during the RESOLVE Trial did not reveal treatment benefit associated with the administration of corticosteroids,[339] but the concerns for higher mortality associated with corticosteroid administration raised by the analysis of the PHIS database were not corroborated. Studies in patients with serious infectious illnesses, i.e. meningococcal meningitis, have shown cortisol production rates between 4-15 times the normal daily production rate of 5.7mg/m[293,340,341] to 12.5mg/m^2 [293,294,342,343] 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 0.18mg/kg/hour of hydrocortisone (about 4 mg/kg/day) shorten the time to cessation of vasopressor support *(median time 2 days vs 7 days in the placebo group)* without improving mortality in adults.[344] In a single center study of term neonates, the administration of 45mg/m^2/day of hydrocortisone resulted in similar complication rates compare to historical controls and resulted in a statistically significant increase in blood pressure at 2, 6, 12 and 24 hours after initiation.[334]

Cortisol levels in adults after intravenous 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.[328] These levels are well above what has been described during physiologic response to septic shock or meningococcal meningitis and has led several authors to question higher corticosteroid dosing schedules.[320, 345]

Persistent Pulmonary Artery Hypertension (PPHN) of the Newborn Therapy Inhaled nitric oxide therapy is the treatment of choice for uncomplicated PPHN.[346,347] However, metabolic alkalinization remains an important initial resuscitative strategy during shock because PPHN can reverse when acidosis is corrected.[275] For centers with access to inhaled nitric oxide, this is the only selective pulmonary vasodilator reported to be effective in reversal of PPHN.[346-354] Milrinone may be added to improve heart function as tolerated.[335-357] ECMO remains the therapy of choice for patients with refractory PPHN and sepsis.[358-361] Investigations support use of inhaled iloprost (synthetic analog of prostacyclin) or adenosine infusion as modes of therapy for PPHN.[362-367]

Extracorporeal therapies ECMO is now used in adults after being pioneered at the University of Michigan).[385] ECMO is a viable therapy for refractory septic shock in neonates[359] and children because neonates (approximate 80% survival) and children (approximate 50% survival)[368-371] have the same outcomes whether the indication for ECMO is refractory respiratory failure or refractory shock from sepsis or not. It is also effective in adult Hantavirus victims with low CO/high SVR shock.[372,373] Although ECMO survival is similar in pediatric patients with and without sepsis, thrombotic complications can be more common in sepsis. Efforts are warranted to reduce ECMO induced hemolysis because free heme scavenges nitric oxide, adenosine, and ADAM TS 13 (vWF cleaving protease) leading to microvascular thrombosis, reversal of portal blood flow and multiple organ failure.[374, 375] Nitroglycerin (NO donor), adenosine, and FFP (ADAM TS 13) can be infused to attempt to neutralize these effects. Hemolysis can be avoided in part by using the proper sized cannula for age and limiting ECMO total blood flow to no greater than 110 mL/kg/min (2.2 L/min/m^2). Additional cardiac output can be attained using inotrope/vasodilator therapies.

Investigators also reported that the use of high flux CRRT (> 35 mL/kg/h filtration-dialysis flux), with concomitant FFP or anti-thrombotic protein C infusion to reverse prolonged INR without causing fluid overload, reduced inotrope/vasopressor requirements in children with refractory septic shock and purpura.[4, 18 303-308] The basis of this beneficial effect remains unknown. It could result from prevention of fluid overload, clearance of lactate and organic acids, binding of inflammatory mediators, reversal of coagulopathy or some combination of these actions.

RECOMMENDATIONS

PEDIATRIC SEPTIC SHOCK (FIGURE 3)

Diagnosis The inflammatory triad of fever, tachycardia, and vasodilation is common in children with benign infections. Septic shock is suspected when children with this triad have a change in mental status manifested as 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 > 2 seconds, diminished pulses, mottled cool extremities, or flash capillary refill, bounding peripheral pulses and wide pulse pressure or decreased urine output < 1 ml/kg/h. 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 (see Figure 2)* 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 exam, and at-risk populations. (An example trigger tool is located in Figure 1)
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 develop or adopt a first hour *Resuscitation and Stabilization Bundle (see Figure 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* should contain:

1) IV/IO access within 5 minutes
2) Appropriate fluid resuscitation within 30-60 minutes
3) Initial broad-spectrum empiric antibiotics within 60 minutes
4) Inotrope therapy (peripheral if central not available) for fluid-refractory shock within 60 minutes

The *Stabilization Bundle* should contain

1) Multimodal monitoring to guide fluid, hormonal; and cardiovascular therapies to reverse shock in the ICU (see ACCM algorithms Figure 3)
2) Timely administration of sensitive antibiotic therapy and source control

We recommend that each institution develop or adopt a *Performance Bundle (see Figure 2)* 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.

ABCs: The first hour of Resuscitation (Emergency Room 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 heart rate

Therapeutic Endpoints (Level 1C)

Capillary refill $\leq$ 2 seconds, normal pulses with no differential between the quality of peripheral and central pulses, warm extremities, urine output > 1 ml/kg/h, 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 EKG

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. High flow nasal cannula oxygen is recommended as initial therapy. 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 pre-treatment 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. Analgesia and sedation may be achieved with opioids such as fentanyl and benzodiazepines such as midazolam, carefully titrated to effect.

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 IO access if reliable PIV access cannot be attained in minutes. Powered IO devices (i.e. “IO drill”) can facilitate successful IO placement but should be reserved for use in children >3kg. Fluid resuscitation should commence immediately unless hepatomegaly / rales are present. In the fluid-refractory patient, begin a peripheral inotrope (low dose dopamine or epinephrine) if a second PIV / IO is in place, while establishing a central venous line. When administered through a PIV / IO, the inotrope should be infused either as a dilute solution 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 alpha adrenergic receptor mediated effects occur at higher concentrations for epinephrine and dopamine. Establishing a central venous line 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 (<15kg). 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 the vasoactive infusion(s) centrally and wait until a pharmacologic effect is observed before stopping the peripheral infusion. Although not an immediate concern when trying to establish emergency central venous access, heparin-bonded central venous catheters (CVCs) and antibiotic-coated CVCs have both been associated with reduced catheter-associated blood stream infections (CA-BSIs), and the operator may consider preferential insertion of these modified CVCs, if available.

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 (ie, the development of increased work of breathing, rales, gallop rhythm, or hepatomegaly). In the absence of these clinical findings, children commonly 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 D10% containing isotonic IV solution can be run at maintenance intravenous fluid rates to provide age appropriate glucose delivery and to prevent hypoglycemia.

Hemodynamic Support (Level IC)

Central dopamine may be titrated to a maximum of 10 mcg/kg/min through central access. If the child has ***fluid refractory/dopamine resistant shock*** then central epinephrine can be started for ***cold shock*** (0.05-0.3 mcg/kg/min) or norepinephrine can be titrated for ***warm shock*** to restore normal perfusion and blood pressure.

Hydrocortisone Therapy (Level IC)

If a child is ***at risk of absolute adrenal insufficiency or adrenal pituitary axis failure*** (eg purpura fulminans, congenital adrenal hyperplasia, prior steroid exposure, hypothalamic/pituitary abnormality) 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. Hydrocortisone may be administered as an intermittent or continuous infusion at a dosage which may range from 1-2 mg/kg/day for stress coverage to 50 mg/kg/day titrated to reversal of shock titrated to pharmacodynamic effect.

STABILIZATION: Beyond the first hour (PICU hemodynamic support).

Goals: (Level 1C)

Normal perfusion, capillary refill $\leq$ 2 secs, threshold heart rates

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

$ScvO_2 > 70\%$

Cardiac index > 3.3 $L/min/m^2$ and < 6.0 $L/min/m^2$

Therapeutic Endpoints: (Level 1C)

Capillary refill $\leq$ 2 seconds, threshold heart rates, normal pulses with no differential between the quality of the peripheral and central pulses, warm extremities, urine output > 1 ml/kg/h, normal mental status, CI > 3.3 and < 6.0 L/min/m^2 with normal perfusion pressure (MAP-CVP, or MAP-IAP) for age (Table 1), $ScvO_2$ >70 %. Maximize preload in order to maximize CI, MAP – CVP. Normal INR, anion gap and lactate.

Monitoring (Level 1C)

Pulse oximetry

Continuous ECG

Continuous Intra-arterial Blood Pressure

Temperature (core)

Urine Output

Central Venous Pressure/ O_2 saturation and/or

Pulmonary Artery Pressure/ O_2 saturation

Cardiac Output

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, pulmonary capillary wedge pressure/EDV (when available), and cardiac output. Crystalloid is the fluid of choice in patients with Hgb > 10 g/dL. Red blood cell transfusion can be given to children with Hgb < 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 continuous renal replacement therapy (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 $\geq$ 10 g/dL and cardiac output > 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 $\leq$ 150 mg/dL) and hypoglycemia (keep glucose concentration $\leq$ 80 mg/dL). The use of lesser glucose infusion rates (eg D5% or lower volumes of D10%) will not meet not provide glucose delivery requirements.

Hemodynamic support (Level 1C)

Hemodynamic support can be required for days in children with ***fluid-refractory/dopamine resistant shock***. Children with ***catecholamine resistant shock*** can present with low cardiac output/high systemic vascular resistance, high cardiac output /low systemic vascular resistance, or low cardiac output/low systemic vascular resistance 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, heart rate, 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 cardiac output may be warranted. Many modalities for cardiac output assessment currently exist and include, pulmonary artery, PICCO, femoral artery or thermodilution catheters, and/or cardiac output 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/$ScvO_2$ > 70%, CI > 3.3 $L/min/m^2$ < 6.0 $L/min/m^2$, and a normal perfusion pressure for age (MAP-CVP).

Milrinone is considered by the authors to be the first line inodilator in patients with epinephrine-resistant shock and normal blood pressure. Nitroprusside or nitroglycerin maybe considered as second line vasodilators. If cyanide or isothiocyanate toxicity develops from nitroprusside, or methemoglobin toxicity develops from nitroglycerin, or there is a continued low cardiac output state, then the clinician should substitute milrinone. 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 or vasopressin infusion. Additional volume loading may be necessary to prevent hypotension when loading doses are used. Levosimendan and enoximone may have a role in recalcitrant low cardiac output syndrome. Thyroid replacement with tri-iodothyronine is warranted for thyroid insufficiency, and hydrocortisone replacement can be warranted for adrenal or HPA axis insufficiency.

Shock with Low Cardiac Index, Normal Blood Pressure and High Systemic Vascular Resistance (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 or vasopressin infusion. Additional volume loading may be necessary to prevent hypotension when loading doses are used. Nitroprusside or nitroglycerin maybe considered as second line vasodilators. Monitoring is needed to avoid cyanide or isothiocyanate toxicity. Levosimendan and enoximone may have a role in recalcitrant low cardiac output syndrome. Thyroid replacement with tri-iodothyronine is warranted for thyroid insufficiency, and hydrocortisone replacement can be warranted for adrenal or HPA axis insufficiency

Shock with Low Cardiac Index, Low Blood Pressure, and Low SystemicVascular Resistance (Level 1D)

Norepinephrine can be added to/or substituted for epinephrine to increase diastolic blood pressure and systemic vascular resistance. Once an adequate blood pressure is achieved, Dobutamine, Type III PDE inhibitors such as milrinone or enoximone, (which is more cardio-selective than milrinone), or Levosimendan can be added to norepinephrine to improve cardiac index and $ScvO_2$. Thyroid replacement with tri-iodothyronine is warranted for thyroid insufficiency, and hydrocortisone replacement is warranted for adrenal or HPA axis insufficiency.

Shock with High Cardiac Index and Low Systemic Vascular Resistance (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 cardiac output, 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 1C)

Children with refractory shock must be suspected to have unrecognized morbidities (treatment in parenthesis), including pericardial effusion (pericardiocentesis), pneumothorax (thoracentesis), hypoadrenalism (adrenal hormone replacement), hypothyroidism (thyroid hormone replacement), ongoing blood loss (blood replacement/hemostasis), increased intra-abdominal pressure (peritoneal catheter, or abdominal release), necrotic tissue (nidus removal), inappropriate source control of infection (remove nidus and use antibiotics with the lowest MIC possible, preferably < 1, use IVIG for toxic shock), excessive immunosuppression (wean immunesuppressants), or immune compromise (restore immune function; eg, white cell growth factors/transfusion for neutropenic sepsis). When these potentially reversible causes are addressed, ECMO becomes an important alternative to consider. Currently, however, the expected survival with ECMO is no greater than 50%. If the clinician suspects that outcome will be better with ECMO, flows which induce hemolysis should be discouraged . Measure free hemoglobin and maintain concentration < 10 mg/dL by using adequate catheter, circuit and oxygenator sizes for age. Calcium concentration should be normalized in the red blood cell pump prime (usually requires 300 mg $CaCl_2$ per unit of pRBCs). Additional venous access may be required if ECMO flow is < 110 mL/kg/min with a negative pressure less than - 25 mmHg. This may require the addition of intrathoracic drainage as well. Indeed best outcomes occurred with use of central cannulation which allows attainment of higher flows with less hemolysis. Cannula placement should be checked using both chest x-ray and ultrasound guidance. High flux CRRT (> 35 ml/kg/h) should also be considered, particularly in patients at risk for fluid overload, with septic shock and purpura. This extracorporeal therapy can reduce inotrope/vasopressor needs within six hours of use. It allows replacement of plasma products in patients with disseminated intravascular coagulation without inducing fluid overload.

NEWBORN SEPTIC SHOCK (FIGURE 4)

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. It is important to distinguish newborn septic shock from cardiogenic shock caused by closure of the patent ductus arteriosus in newborns with ductal-dependent complex congenital heart disease. Any newborn with shock and hepatomegaly, cyanosis, a cardiac murmur, or differential upper and lower extremity blood pressures or pulses should be started on prostaglandin 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. Persistent pulmonary hypertension (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 heart rates

Therapeutic Endpoints: (Level 1C)

Capillary refill $\leq$ 2 seconds, normal pulses with no differential in quality between peripheral and central pulses, warm extremities, urine output > 1 ml/kg/h, normal mental status, normal blood pressure for age, normal glucose and calcium concentrations.

Difference in pre- and post-ductal O_2 saturation < 5%

95 % arterial oxygen saturation

Monitoring: (Level 1C)

Temperature

Pre- and Post-Ductal 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 ID)

Airway patency and adequate oxygenation and ventilation should be rigorously monitored and maintained. 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 is 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 and sedation, which can be accomplished in many cases with small doses of fentanyl, given slowly as 1 – 2 microgram/kg aliquots. The use of NMDA-receptor antagonists such as ketamine is discouraged by many experts, given concerns regarding neurotoxicity. Etomidate is associated with adrenal suppression, and is generally discouraged, although the agent has been used successfully by some experts in this setting. 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 guidelines. Placement of an umbilical arterial and venous line 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 mcg/kg/min) and dobutamine (up to10 mcg/kg/min) is initially recommended. If the patient does not adequately respond to these interventions, then epinephrine (0.05 to 0.3 mcg/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 iNO is available. Mild hyperventilation to produce a respiratory alkalosis can also be instituted until 100% O_2 saturation and < 5% difference in pre- and post-ductal 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 heart rate.

Maintain normal perfusion and blood pressure.

Maintain neonatal circulation.

$ScvO_2 > 70\%$

CI > 3.3 L/min /m^2

SVC flow > 40 mL/kg/min

Therapeutic Endpoints (Level 1C)

Capillary refill $\leq$ 2 seconds, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output > 1 ml/kg/h, normal mental status, normal blood pressure for age

> 95% arterial oxygen saturation

< 5% difference in pre- and post- ductal arterial oxygen saturation

$ScvO_2$ > 70%

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

Normal glucose and ionized calcium concentrations

SVC flow > 40 mL/kg/min

CI > 3.3 $L/min/m^2$

Normal INR

Normal anion gap, and lactate

Fluid overload < 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

Central Venous Pressure/ O_2 saturation

Cardiac Output

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 central venous pressure. Crystalloid is the fluid of choice in patients with Hgb > 12 g/dL. Packed red blood cells can be transfused in newborns with Hgb < 12 g/dL. Diuretics or CRRT 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, six- hour per day 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 phosphodiesterase inhibitors to epinephrine (0.05-0.3 mcg/kg/min) can be effective but must be monitored for toxicities. It is important to volume load based on clinical exam and blood pressure changes when using these systemic vasodilators. Tri-iodothyronine is an effective inotrope in newborns with thyroid insufficiency. Norepinephrine can be effective for refractory hypotension but $ScvO_2$ should be maintained > 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 mcg/dL, or basal cortisol < 18 mg/dL, or basal cortisol < 18 An additional inotrope therapy should be added if warranted. Hydrocortisone or terlipressin, or angiotensin can be considered in the presence of adequate CO, SVC flow, and/or $ScvO_2$ monitoring.

The total duration of umbilical catheterization should not exceed 5 days for an umbilical artery catheter 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 umbilical arterial catheters. 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.

ECMO and CRRT therapy for Refractory Shock (Level 1C)

Newborns with refractory shock must be suspected to have unrecognized morbidities (requiring specific treatment) including pericardial effusion (pericardiocentesis), pneumothorax (thoracentesis), ongoing blood loss (blood replacement/hemostasis), hypoadrenalism (hydrocortisone), hypothyroidism (tri-iodothyronine), inborn errors of metabolism (responsive to glucose & insulin infusion or ammonia scavengers), and/or cyanotic or obstructive heart disease (responsive to PGE1), or a critically large PDA (PDA closure). 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 $PaO_2 < 40$ mm Hg after maximal therapy to be sufficient indication for ECMO support. ECMO flows greater than 110 ml/kg should be discouraged because hemolysis can ensue. When on veno-venous ECMO, persistent hypotension and/or shock should be treated with dopamine / dobutamine or epinephrine. Inotrope requirements frequently diminish when veno-arterial ECMO is used nut not always. Calcium concentration should be normalized in the red blood cell 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.

Table 1. Threshold heart rates and perfusion pressure MAP-CVP or MAP-IAP for age, (modified from The Harriet Lane Handbook, *Thirteenth Edition* and National Heart, Lung, and Blood Institute, Bethesda. MD: Report of the second taskforce on blood pressure control in children-1987).

	Heart Rate (b.p.m.)	MAP-CVP (mmHg)
Threshold rates		
Term Newborn	120-180 b.p.m.	55
Up to 1 year	120-180 b.p.m.	60
Up to 2 years	120-160 b.p.m.	65
Up to 7 years	100-140 b.p.m.	65
Up to 15 years	90-140 b.p.m.	65

Figure 1   Examples of Recognition, Resuscitation, Stabilization Bundles

Recognition Bundle – Goal is early recognition of patient with septic shock

- A trigger tool. (An example of trigger tool is located in Figure 2 - AAP Septic Shock Identification Tool).
- Rapid clinician assessment and activation of Resuscitation bundle within 15 minutes for any patient that screens positive.

Resuscitation Bundle – Goal is Capillary Refill < 3 secs and normal Blood Pressure

- IV/IO access within 5 minutes Appropriate fluid resuscitation within 30-60 minutes
- Begin glucose containing intravenous fluid maintenance and appropriate isotonic fluid boluses in first 30 minutes
- Initial broad-spectrum empiric antibiotics within 60 minutes
- Inotrope therapy for fluid-refractory shock within 60 minutes

Stabilization Bundle- Goal is normal perfusion pressure (MAP - CVP), SCVO2 > 70%. and Cardiac index between 3.3 and 6.0 LPM/m^2

- Multimodal monitoring to direct fluid, hormonal, and cardiovascular therapies to attain hemodynamic goals (see algorithm)
- Timely administration of ‘sensitive’ antibiotic therapy with source control

Performance Bundle- Goal to identify barrierst to bundle implementation

- Measurement of adherence to the *Recognition, Resuscitation, and Stabilization Bundles* as well as achievement of goals and individual components.

Figure 2 AAP trigger tool for Early Septic Shock Recognition

Septic Shock
Identification Tool.pd

Figure 3

0 min

5 min

Recognize decreased mental status and perfusion.
Begin high flow nasal cannul O_2 and establish IO/IV access according to PALS

If no hepatomegaly or rales then push 20 mL/kg isotonic saline boluses and reassess up to 60 mL/kg until improved perfusion but stop if rales / hepatomegaly develop. Correct hypoglycemia and hypocalcemia. Begin Antibiotics.

15 min

Fluid refractory shock?

Begin PIV/IO Inotrope infusion preferably epinephrine 0.05-0.5 mcg/kg/min
Use Atropine/Ketamine PIV/IO/IM if needed for Central Vein or Airway Access

When central access available titrate central Epinephrine 0.05 -0.5 μg/kg/min to reverse Cold Shock (titrate central Dopamine 5-10 μg/kg/min if Epinephrine not available)
Titrate central Norepinephrine 0.05-0.3 μg/kg/min to reverse Warm Shock (central Dopamine if Norepinephrine is not available)

Catecholamine- resistant shock?

60 min

If at risk for Absolute Adrenal Insufficiency begin Hydrocortisone Infusion

Attain normal MAP- CVP and $ScvO_2 > 70\%$ and CI 3.3-6.0 L/min/m^2

Use Doppler US, PICCO, FATD, or PAC to Direct Fluid, Inotrope, Vasopressor, Vasodilato

Normal Blood Pressure **Cold Shock** **$ScvO_2 < 70\%$/Hgb > 10 g/dl** **on Epinephrine?**	**Low Blood Pressure** **Cold Shock** **$ScvO_2 < 70\%$/Hgb > 10 g/dL** **on Epinephrine?**	**Low Blood Pressu** **Warm Shock** **$ScvO_2 > 70\%$** **on Norepinephrine?**
Begin Milrinone infusion Add Nitroso-vasodilator if CI index < 3.3 L/min/m^2 with High SVRI and /or poor skin perfusion. Consider Levosimendan if unsuccessful	Add Norepinephrine to epinephrine to attain normal diastolic blood pressure. If CI < 3.3 L/ min/m^2 add dobutamine, enoximone, levosimendan, or milrinone	If euvolemic, add vasopressin, terlipressin o angiotensin but if CI decreases below 3.3 add epinephrine, dobutamine, enoximone, levosimendan

Persistent Catecholamine- resistant shock?

Remove Pericardial effusion or Pneumothorax,
Maintain IAP < 12 mm/Hg.

Refractory Shock?

ECMO
CRRT 35mL/kg/hr
When Stable

Figure 4

0 min
5 min

Recognize decreased perfusion, cyanosis, RDS.
Maintain airway and establish access according to NRP guidelines.

Push 10 mL/kg isotonic crystalloid or colloid boluses to 60 mL/kg
until improved perfusion or unless hepatomegaly.
Correct hypoglycemia and hypocalcemia. Begin antibiotics.
Begin prostaglandin infusion until r/o ductal - dependent lesion.

Fluid-refractory shock?

15 min

Infuse Dopamine (< 10 μg/kg/min)
+/- Dobutamine

Fluid refractory-dopamine resistant shock?

Titrate Epinephrine 0.05 -0.3 μg/kg/min

60 min

Catecholamine-resistant shock?

ATTAIN
Normal MAP-CVP + $ScvO_2$ >70 %, SVC flow>40 mL/kg/min or CI > 3.3 $L/m^2/min$

Cold Shock
Normal Blood Pressure
Poor LV function
$ScvO_2$ < 70, Hgb ≥ 12 g/dL
SVC flow < 40 mL/kg/min
or CI < 3.3 $L/m^2/min$?

Add Nitrosovasodilator
Milrinone/Imrinone
with volume loading

Cold Shock
Poor RV function
PPHN
$ScvO_2$ < 70%
SVC flow < 40 mL/min
or CI < 3.3 $L/m^2/min$?

Inhaled Nitric Oxide
Inhaled Iloprost/ IV Adenosine
IV milrinone/amrinone

Warm Shock
Low Blood Pressure?

Titrate Volume
Add Norepinephrine
? Vaso/Terli pressin
? Angiotensin
Keep $ScvO_2$ >70%,
SVC flow > 40 mL/kg/min,
or CI > 3.3 $L/m^2/min$
with Inotropic Support

Refractory Shock?

Evacuate pneumothoraces and pericardial effusion. Give Hydrocortisone if Absolute Adrenal Insufficiency and T_3 if Hypothyroid. Begin Pentoxifylline if VLBW newborn. Consider Closing PDA if hemodynamically significant.

ECMO
(110 mL/kg/min)

FIGURE LEGENDS

Figure 1 Examples of Recognition, Resuscitation, and Stabilization Bundles

Figure 2 American Academy of Pediatrics trigger tool for Early Septic Shock Recognition

Figure 3 ACCM 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 seconds, 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, $ScvO_2 > 70\%$, and $CI > 3.3 < 6.0$ L/min/m^2 in PICU.

Figure 4 ACCM 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 seconds, and normal blood pressure in the (first hour), and

2) ***Subsequent ICU goals*** – restore normal perfusion pressure (MAP-CVP), pre and post-ductal O_2 saturation difference < 5%, and either $ScvO_2 > 70\%$, SVC flow > 40 ml/kg/min or $CI > 3.3$ L/min/m^2 in NICU.

Abbreviations - MAP – CVP = mean arterial pressure – central venous pressure; ScvO2 = central venous oxygen saturation at right atrial / vena cava junction level; IAP = intra-abdominal pressure; US = Doppler ultra sound; PICCO = pulse index contour cardiac output catheter; FATD = femoral artery thermodilution catheter; PAC = pulmonary artery catheter; ECMO = extracorporeal membrane oxygenator; CRRT = continuous renal replacement therapy; CI = cardiac index; SVC = superior vena cava flow; T3 = tri-idothyronine; VLBW = very low birth weight; PDA = patent ductus arteriosus

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