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Advances in Monitoring and Management of Shock

Haifa Mtaweh, M.D.^{1,*}, Erin V. Trakas, M.D.^{1,*}, Erik Su, M.D.², Joseph A. Carcillo, M.D.¹, and Rajesh K. Aneja, M.D.¹

¹Departments of Critical Care Medicine and Pediatrics, University of Pittsburgh School of Medicine and Children's Hospital of Pittsburgh; Pittsburgh, PA

²Department of Anesthesia and Critical Care Medicine, Johns Hopkins Hospital; 1800 Orleans Street, Baltimore, MD 21287

Synopsis

Shock continues to be the proximate cause of death for many childhood diseases and imposes a significant burden. Early recognition and treatment of pediatric shock, regardless of etiology, decreases mortality and improves outcome. In addition to the conventional parameters (e.g., heart rate (HR), systolic blood pressure (SBP), urine output (UOP), and central venous pressure (CVP)), biomarkers and non-invasive methods of measuring cardiac output are now available to monitor and treat shock. In this article, we emphasize how fluid resuscitation is the cornerstone of shock resuscitation although the choice and amount of fluid may vary based on the etiology of shock. Other emerging treatments for shock i.e., temperature control, extracorporeal membrane oxygenation (ECMO)/Ventricular Assist Devices (VAD) are also discussed briefly in this article.

Keywords

Pediatric sepsis; septic shock; Cardiac output monitoring

Introduction

It has been estimated that 10 million young children die in the world every year. The common diagnoses that underlie this mortality include diarrhea, pneumonia, malaria, measles and neonatal causes (birth asphyxia, low birth weight)^{1,2}. The proximate cause of death in almost all of these conditions is shock due to hypovolemia, hypoxia, ischemia, infection and anemia. Historically, shock has been defined as a state of acute energy failure that stems from a decrease in adenosine triphosphate production, and subsequent failure to meet the metabolic demands of the body leading to anaerobic metabolism and cytotoxic metabolite accumulation. However, the clinical definition of shock relies on a constellation of signs and symptoms that include tachycardia, poor capillary perfusion, decreased urinary output and altered mental status. Because circulatory function is dependent on blood volume, cardiac function and vascular tone, shock can result from an alteration in any of

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Address for Correspondence: Rajesh K. Aneja, MD, Department of Critical Care Medicine, Children's Hospital of Pittsburgh, Children's Hospital Drive, 45th St. and Penn Ave, Pittsburgh, PA 15201, Telephone: (412) 692-5164, Fax: (412) 692-6076, anejar@upmc.edu.

*Both authors contributed equally to this manuscript

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these parameters, and a simple way to classify shock is as hypovolemic, cardiogenic and distributive shock.

While little has changed in the epidemiology and pathogenesis of the types of shock mentioned above, the emergence of multi-drug resistant (MDR) organisms has changed the treatment of septic shock. In addition, the pediatric intensive care unit (PICU) patient cohort has changed in recent years. There are a growing number of complex patients with a myriad of medical and surgical conditions, thereby increasing the burden of sepsis with MDR isolates. Three MDR organisms are increasingly responsible for morbidity and mortality in the PICU: methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant enterococci (VRE), and *Klebsiella pneumoniae* carbapenemases (KPC)—this has profound implications for the choice of empiric antibiotics for patients with severe sepsis and shock³⁻⁵ [ENREF 5](#).

Our understanding of the inflammatory pathways activated in shock has increased in the last few decades however, this has not led to new successful therapies for treatment of shock. For example, recombinant activated protein C has been used as a treatment in children with severe sepsis. Pediatric patients who received drotrecogin alfa (Drot AA) had more central nervous system bleeding during the infusion and 28-day study period. As a result of the adverse risk to benefit ratio, the use of Drot AA is not recommended in children with sepsis. It is hoped that as our understanding of the complex pathophysiology of inflammation accelerates, the search for novel treatments to improve outcomes and decrease mortality will increase. We have not included advances in basic science in this manuscript but instead have focused on the recent advances in monitoring and treatment of pediatric shock.

Monitoring in Shock

Clinical and Laboratory Parameters

Frequent and/or continuous monitoring is of utmost importance when treating shock. Parameters that must be monitored include heart rate (HR), systolic blood pressure (SBP), mean arterial pressure (MAP), urine output (UOP), central venous pressure (CVP), central venous (CvO₂) or mixed venous oxygenation saturations (SvO₂), lactate, and measures of cardiac output (CO). It is important to monitor the hemodynamic profile of the patient as treatment for shock is initiated. Normal heart rate and perfusion pressure for age should be the goals of resuscitation. The clinical effects of fluid resuscitation manifest as a decrease in the heart rate along with an increase in perfusion pressure (MAP – CVP). The shock index (HR/SBP) can be used to assess the effectiveness of fluid and inotrope therapy, and with resuscitation, the stroke volume (SV) along with SBP will increase and the HR will decrease, leading to a decrease in shock index. In patients with central venous catheters, CvO₂ of more than 70% should be used as a goal. The arterial-jugular venous oxygen difference (AVDO₂) can also be calculated with a hemodynamic goal of 3% to 5%. If it is wider than 5%, CO should be increased with therapy until the AVDO₂ returns to the normal range. The AVDO₂ is most accurate when the central venous catheter is located in the pulmonary artery.

In shock, the imbalance between oxygen delivery (DO₂) and oxygen consumption (VO₂) leads to an increase in oxygen extraction. At a critical juncture when the oxygen extraction can no longer keep up with the decreased DO₂, the VO₂ becomes dependent on DO₂. Mixed venous blood oxygen saturation (SvO₂) or CvO₂ reflects the balance between DO₂ and VO₂ as long as blood oxygen saturations (SaO₂) are normal (modified Fick equation: SvO₂= SaO₂ – [VO₂/DO₂]). Clinically, a decrease in SvO₂ of 5% from normal (70%) indicates a significant decrease in O₂ delivery and/or increase in O₂ demand.

Another marker to assess the degree of global tissue anoxia and anaerobic metabolism is blood lactate levels. Lactate is formed by reduction of pyruvic acid and is freely mobile through cell membranes. Lactate can be elevated by a number of conditions even in the absence of shock for example, metabolic disorders, lymphoproliferative disorders, and liver failure. Higher blood lactate levels are associated with increased severity of illness and worse outcomes in pediatric critical illness^{6,7}. Lactate is most useful in the setting of preoperative and postoperative cardiogenic shock and it has been suggested that the mortality risk increases as serum lactate levels rise above 2.0 mmol/L. Higher values portend an increase in mortality, therefore when used as a hemodynamic goal, a level of less than 2.0 mmol/L is the target.

Biomarkers

There has been considerable interest in developing biomarkers that can be used to diagnose, monitor and predict outcome in shock. Much of the work has been performed in patients with sepsis and the discussion below relates to severe sepsis/septic shock⁸. Biomarkers have been generally defined to have characteristics that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention⁹.

C-reactive protein (CRP) is an acute phase protein synthesized by the liver and increases 4-6 hours (hrs) after onset of inflammation or injury and peaks at 36-50 hrs¹⁰. CRP has been widely used in children to distinguish infection from inflammation, but it has become evident that it lacks the specificity to consistently discriminate between bacterial, viral and noninfectious inflammatory conditions.

Procalcitonin (PCT) is produced by the thyroid gland as a precursor to calcitonin, but other tissues can also produce procalcitonin during inflammation or sepsis. PCT has been found to be superior to CRP in distinguishing children with bacterial infections from those without¹¹⁻¹³. Furthermore, PCT increases with increasing severity of illness and clearance of PCT has been associated with improved outcome^{14,15}.

Ferritin is an iron storage protein that plays a significant role in regulation of iron metabolism, it is also an acute phase reactant, and its elevation induces a reduction in available serum iron¹⁶. Serum ferritin levels are elevated in children with septic shock and are associated with poor outcomes¹⁷. Hyperferritinemia is one of the diagnostic criteria of hemophagocytic lymphohistiocytosis (HLH) and may alert the clinician to investigate further for the possibility of primary or secondary HLH and institute appropriate therapy¹⁸.

B-type natriuretic peptide (BNP) was first isolated from porcine brain and its gene is located on chromosome 1. BNP is synthesized in atrial and ventricular myocardium. Myocardial stretch resulting from an increased left ventricle end diastolic pressure and/or an increase in wall stress has been postulated to act as a major stimulus to increase BNP gene transcription¹⁹. The main properties of BNP include natriuretic and vasodilatory effects leading to decrease in preload and afterload²⁰. Serum BNP levels have been validated as a diagnostic marker for congestive heart failure in children^{21,22}. BNP has also been found to be elevated in pediatric patients with myocardial dysfunction from septic shock²³, but there are no published studies that document serum BNP levels in patients with cardiogenic shock. Although promising, more studies need to be conducted before serum BNP levels can be validated as a screening tool for myocardial dysfunction in pediatric shock.

Troponin T (cTnT) and I (cTnI) are cardiac specific proteins that are elevated with myocardial injury²⁴, acute coronary syndrome, myocarditis, tachycardia, cardiac trauma and

others. Elevated troponins can also be present in septic shock due to sepsis induced myocardial function. Troponin I levels decrease with resolution of myocardial injury.

Monitoring Cardiac Output

Low cardiac output is associated with increased mortality in pediatric septic shock²⁵⁻³⁰. Children with fluid-refractory, dopamine-resistant shock receiving goal-directed therapy (Cardiac Index (CI) >3.3 and <6 L/min/m²) were found to have improved outcomes compared with historical reports³⁰. Therefore, the American College of Critical Care Medicine (ACCM) clinical guidelines for hemodynamic support of neonates and children with septic shock (2007 update) recommends titration of therapy to a CI goal of $3.3 - 6.0$ L/min/m² in patients with persistent catecholamine resistant shock³¹. The guidelines recommend using CO monitoring in children who remain in shock despite therapies directed to improving perfusion and blood pressure. With decline in use of pulmonary artery catheters (PAC), the search continues for non-invasive cardiac output monitoring technologies. The ideal attributes of such a device are that it is safe, reliable, minimally invasive, cost-effective, and tracks rapid changes in hemodynamic status. In addition to cardiac index, other variables that are helpful in titrating therapy include stroke volume index, indexed systemic vascular resistance, pulmonary capillary wedge pressure (providing an indirect estimate of left atrial pressure), arterial oxygen content and oxygen delivery. Table 1 summarizes several hemodynamic variables in different types of shock³².

There are several non-invasive cardiac output monitoring devices that are currently available. A significant number of products can be further divided into calibrated and uncalibrated devices. Devices that rely on only one method are referred to as uncalibrated devices. Calibrated devices utilize a second CO determination with indicator dilution methods to establish current CO and therefore need to infer vessel compliance and resistance factors that affect the SVR.

Arterial Pulse Wave Analysis

One of the many techniques used for non-invasive cardiac output monitoring is arterial pulse wave analysis. It is a common bedside tool used by many intensivists for the estimation of cardiac preload by assessing the variation in the arterial line waveform^{33,34}.

Transpulmonary Thermodilution Technique (TPTD)

The transpulmonary thermodilution technique (TPTD) has been validated as a reliable technique to assess cardiac preload and output and has remained in use for the last two decades. Calculation of the cardiac output is based on the Stewart-Hamilton principle — the area under the change in temperature-time curve is inversely proportional to the cardiac output. A TPTD continuous cardiac output system automatically calibrates its continuous system every time a thermodilution based calculation is performed; hence the cardiac output obtained by the pulse contour analysis is compared with the cardiac output obtained by the thermodilution technique. Fakler et al, demonstrated a variation of 5.2% between the three repeated measurements of TPTD and demonstrated a strong correlation between thermodilution and continuous contour analysis cardiac indices (Pearson correlation coefficient $r = 0.93$; coefficient of determination $r^2 = 0.86$)³⁵. While this study excluded patients with intra cardiac shunts, another study performed by Mahajan et al, included patients with intra-cardiac shunt. The pulse contour analysis was noted to be less reliable in the study patients even after shunt correction (correlation coefficient $r = 0.72$)³⁶. In contrast, Tibby et al validated TPTD cardiac output measurement by comparing it to Fick principle using metabolic VO_2 monitoring, and demonstrated strong correlation (correlation coefficient $r = 0.99$)³⁷. Similarly, bias and precision for TPTD are good when compared to direct Fick, pulmonary artery thermodilution, and lithium ion dilution methods³⁷⁻³⁹.

Carbon dioxide rebreathing techniques

Other methodologies calculate CO using the Fick equation in the carbon dioxide rebreathing technique. This noninvasive technique uses expiratory carbon dioxide as an indicator for CO, reflected in the changing ratio of end-tidal carbon dioxide in normal respiration to that measured after a brief period of rebreathing⁴⁰.

Ultrasound continuous wave Doppler CO

Ultrasound continuous wave Doppler CO monitoring utilizes transaortic (transducer placed at suprasternal notch) or transpulmonary (transducer placed at the left midsternal edge) Doppler ultrasound flow to obtain a flow profile (velocity-time plot) across the aorta or main pulmonary artery respectively. CO is then determined by multiplying the cross-sectional area of the target vessel by the area under the flow-time tracing during systolic ejection (velocity-time integral, VTI)⁴¹. A precise measurement of VTI necessitates good flow signal and correct interpretation. These are both dependent on the subject and the operator⁴² and therefore, this method does not always produce the most accurate measurement of CO.

Thoracic impedance

Some monitors measure the bioreactance (phase shift) in voltage across the thorax between electrodes placed on the chest. It determines the CO measurement signal from each side of the body and averages the two signals. In adults it has been shown to highly correlate with CO measured by thermodilution and pulse contour analysis, unlike the other two non-invasive methods for measuring CO⁴³⁻⁴⁵.

Bedside echocardiography

Bedside echocardiography performed by intensivists is gaining increasing popularity as a way to determine volume status. With appropriate training, the intensivist can use respiratory variation in inferior vena cava (IVC) diameter or VTI in the aorta or left ventricular outflow tract, as well as qualitative assessments of left ventricle size and motion to help identify preload-dependent patients⁴⁶. With more advanced training, the intensivist can use respiratory variation of SV determined by Doppler echocardiography and changes in SV after the passive leg maneuver to identify volume responsiveness⁴⁶.

Near-infrared cerebral oximetry

Cerebral oximetry, based on near-infrared spectroscopy (NIRS) is a noninvasive technology that serves as a surrogate for index of global cerebral perfusion. This technology utilizes near infrared wavelength to measure regional venous oxygen saturation and thereby provide an estimate of adequate oxygen delivery. There is widespread interest to use NIRS to prevent or predict a cerebral catastrophic event and have a positive effect on clinical outcome. In a study by Marimon et al, a statistically significant correlation between NIRS cerebral values and S_{VO_2} values measured within the superior vena cava was demonstrated⁴⁷. Further study must be completed to demonstrate such a correlation in pediatric shock.

Treatment of Shock

Cruz et al, demonstrated that the institution of a protocol to identify children with sepsis in the emergency department allowed earlier recognition and treatment of shock⁴⁸. Furthermore, early recognition and aggressive resuscitation can reverse the clinical signs of shock and improve outcomes in children⁴⁹. The supportive therapy for shock includes supplemental oxygen (to enhance oxygen delivery to compromised organs), and airway

management. In addition, acute circulatory shock should be treated with fluids and/or blood, when needed, to optimize intravascular volume prior to addition of vasoactive agents.

Fluid resuscitation

Fluid resuscitation is the cornerstone of shock resuscitation in hypovolemic infants and children. Repleting the intravascular volume with fluids improves cardiac output and has been shown to reduce mortality. Han et al examined early goal-directed therapy for neonatal and pediatric septic shock in community hospital emergency departments. They noted that when community physicians implemented therapies that resulted in successful shock reversal (within a median time of 75 minutes), almost all of the infants and children who presented with septic shock survived⁴⁹. Similarly, adults and children who received early goal directed therapy targeting MAP, CVP, UOP, and $S_{cv}O_2$ had improved survival in comparison to patients who received standard therapy^{50,51}.

The 2007 ACCM pediatric sepsis guidelines recommend fluid resuscitation in 20 ml/kg increments up to 60 ml/kg or shock reversal as long as the child does not have hepatomegaly or rales on lung exam³¹. The amount of fluid needed depends on the etiology of shock. Patients in septic shock often require more fluid resuscitation in comparison to patients with hemorrhagic shock who require more blood products. Excessive fluids can lead to worsening heart failure and subsequent deterioration in children with cardiogenic shock or severe chronic anemia with cardiac failure⁵².

The choice of fluid for resuscitation continues to be a subject of ongoing debate. The conflicting results of various meta-analyses and clinical trials have left many clinicians unsure about the effect of albumin-containing fluids on survival in critically ill patients. One of the most widely published trials is the Saline versus Albumin Fluid Evaluation (SAFE) Study in 16 ICUs in Australia and New Zealand. The authors tested the hypothesis that when 4 percent albumin is compared with 0.9 percent sodium chloride (normal saline) for intravascular-fluid resuscitation in patients in the ICU, there is no difference in the overall 28-day rate of death⁵³. However, the subgroup analysis of the SAFE trial noted a treatment effect favoring albumin in patients with severe sepsis and crystalloid fluids were helpful in traumatic shock. In the pediatric literature, children with dengue shock syndrome showed no difference in resuscitation efficacy with either colloid or crystalloid solutions. The authors noticed no clear benefit to the use of a colloid in children with moderately severe shock due to vascular-leak syndrome⁵⁴. In addition, a recent Cochrane review showed that resuscitation with colloids does not reduce the risk of death, compared to resuscitation with crystalloids in patients with trauma, burns or following surgery⁵⁵.

The fluid management is different in patients with cardiogenic shock; rather than the usual resuscitation with 20 ml/kg fluid bolus, one should use a fluid bolus that is 5-10 ml/kg and monitor for signs of worsening heart failure i.e., worsening of hepatomegaly, jugular venous distention, and pulmonary edema. After initial stabilization, diuresis may have to be initiated in fluid overloaded cardiogenic shock patients.

In hemorrhagic shock, the primary etiology is loss of intravascular blood volume. Depending upon the degree of hemodynamic instability, fluid resuscitation can be started with crystalloids including normal saline and lactated ringer's solution. The definitive treatment includes achieving hemostasis and blood transfusion. Packed red blood cells (pRBC) will be needed, along with platelets and fresh frozen plasma to restore the blood loss⁵⁶. In shock associated with acute-on-chronic anemia, crystalloid or colloid boluses can also be harmful and blood resuscitation is needed. Under these circumstance, crystalloid at maintenance along with blood transfusions for hemoglobin <5 gm/dl should be given⁵². Careful attention should be paid to signs of volume overload and heart failure.

Blood Transfusions

The primary goal of pRBC transfusion is to increase oxygen delivery with subsequent improvement in tissue oxygen utilization. While there is little debate about the role of blood transfusion in hemorrhagic shock resuscitation, there is significant variation in the practice of administering blood transfusion in other critically ill patients⁵⁷. The ACCM guidelines for treatment of pediatric septic shock recommend blood transfusions for Hgb <10 g/dL and $S_{cv}O_2$ <70%³¹. Lacroix et al. compared liberal transfusion strategy (target hemoglobin level, 10.0 to 12.0 g per deciliter, with a transfusion trigger of 10.0 g per deciliter) to a restrictive transfusion strategy (target hemoglobin level, 7.0 to 9.0 g per deciliter, with a transfusion trigger of 7.0 g per deciliter) in a pediatric general medical and surgical setting. With a restrictive strategy they demonstrated a 96% reduction in the number of patients who had any transfusion exposure and a 44% decrease in the number of red-cell transfusions administered. Furthermore, there was no increase in the incidence of new or progressive multiple organ dysfunctions in critically ill children^{58,59}. Due to the exclusion criteria of the study, these results cannot be applied to premature infants, or children with severe hypoxemia, hemodynamic instability, active blood loss, or cyanotic heart disease, which constitutes a big cohort of the PICU population. The results of this study were different from smaller trials in pediatric subpopulation where complications like poor neurodevelopmental outcome, intraparenchymal brain hemorrhage, periventricular leukomalacia, and apnea were higher in the restrictive-strategy group^{60,61}. It may be pointed out that these differences in outcomes were not designated *a priori* and were not confirmed in a subsequent larger trial⁶².

In summary, while RBC transfusion is indicated for critically ill hemodynamically unstable with low hemoglobin concentrations, the current evidence does not support the unrestricted use of red-cell transfusion in critically ill patients.

Vasopressor and Inotropic Support

The next tier of therapy is vasopressors and/or inotrope administration, and is largely dictated by the etiology of shock. For example, for children with septic shock, dopamine (5-9 μ g/kg/min), dobutamine, or epinephrine (0.05-0.3 μ g/kg/min) can be used as first-line inotropic support³¹. Recent adult data raises the concern of increased mortality with the use of dopamine⁶³. There is no clear explanation for these observations, but they may be related to the action of dopamine infusion to reduce the release of hormones from the anterior pituitary gland (prolactin and thyrotropin releasing hormone release). Therefore many centers are now routinely using epinephrine as a first line inotropic agent.

Critically ill children who are normotensive with a low CO and high SVR, often require a short-acting vasodilator e.g., sodium nitroprusside, nitroglycerin or type III phosphodiesterase inhibitors to lower SVR. In contrast, the use of low-dose norepinephrine has been recommended as a first-line agent for fluid-refractory hypotensive hyperdynamic shock (low CO, low SVR).

In cardiogenic shock, afterload reduction improves blood flow by reducing ventricular afterload and increasing ventricular emptying. In children with cardiogenic shock a combination of low dose epinephrine and milrinone can be used for inotropy and afterload reduction.

We have briefly summarized the mechanism of action of different inotropic and vasopressor medications that are used in treatment of shock (Table 2)⁶⁴.

Dopamine is an endogenous catecholamine and binds α_1 -, β_1 -, β_2 -, and dopaminergic (D_1 and D_2) receptors. Similar to the β_1 receptors, the D_1 -receptors activate adenylate cyclase through G_s protein coupling, resulting in vasodilation. Dopamine stimulates β_1 -receptors

and α_1 -receptor in the myocardium resulting in increased inotropy, chronotropy and vascular smooth muscle contraction.

Dobutamine is a synthetic catecholamine that acts on α - and β -adrenergic receptors. It increases cardiac output, and vascular smooth muscle relaxation. In the treatment of pediatric postoperative cardiac surgery patients, dobutamine increases cardiac output by increasing heart rate, and significant tachycardia may prompt discontinuation of use of the drug⁶⁵. The ACCM guidelines consider dobutamine an alternative to dopamine for septic shock patients with adequate or increased SVR.

Epinephrine is a hormone produced in the adrenal medulla and stimulates α -, β_1 -, β_2 -receptors. At low infusion rates, the β_1 - and β_2 -receptor effects predominate leading to myocardial contraction, increased oxygen consumption along with a decrease in SVR. Higher infusion rates cause systemic and pulmonary vasoconstriction through α -receptor stimulation.

Norepinephrine is a central nervous system neurotransmitter with strong α - and β_1 -agonist with little β_2 -agonist activity. It is a second-line vasopressor after dopamine for warm shock in the ACCM guideline. Stroke volume increases and cardiac output changes little. The myocardial oxygen supply-demand relationship is neutral or favorably affected⁶⁵. Clinical use of norepinephrine centers on treatment of hypotensive and distributive forms of shock, such as warm septic shock.

Vasopressin is a nonapeptide hormone that stimulates 3 receptor subtypes (V_1 , V_2 , and V_3) that are G-protein coupled to intracellular modulators. Vasopressin increases SVR and blood pressure with no inotropy and reduces the need for catecholamine support in shock patients. Vasopressin has been shown to lower cardiac index and adversely affect outcome in cardiogenic shock⁶⁵. The safety and efficacy of low-dose vasopressin was investigated in pediatric patients with vasodilatory shock and it did not demonstrate any beneficial effects^{66,67}.

Milrinone, a bipyridine, is a nonsympathomimetic inotropic agent that is a selective inhibitor of phosphodiesterase III. It increases cardiac output, reduces SVR and demonstrates no chronotropic effect. Milrinone has been the drug of choice for afterload reduction in post-operative pediatric cardiac patients and results in slight decrease in SBP, increased CI, decreased SVR and pulmonary vascular resistance (PVR). Milrinone has been investigated in children with nonhyperdynamic septic shock (low to normal CI and normal to high SVR) and it resulted in increased CI and oxygen delivery and decreased SVR⁶⁵.

Corticosteroids

Adrenal insufficiency can be classified as absolute or relative. Absolute adrenal insufficiency is baseline cortisol level <5 g/dl or stressed cortisol level <20 g/dl. As for relative adrenal insufficiency, it is diagnosed if basal cortisol level is >20 g/dl and ACTH response increment increase in cortisol 9 g/dl⁶⁸. It should be suspected in patients with refractory shock and history of trauma (head or abdominal), sepsis, central nervous system disease, Waterhouse-Friedrickson syndrome, treatment with etomidate, or steroid use in the 6 months prior to presentation⁶⁹. In a cohort analysis by Zimmerman et al, children who received corticosteroids had no improvement in mortality, days of vasoactive-inotropic infusion, days of mechanical ventilation, change in pediatric overall performance category score, PICU and hospital length of stay⁷⁰. The current recommendations are to use steroids in absolute adrenal insufficiency in presence of catecholamine resistant shock. As for the recommended dosage, stress-shock dose has been considered to be $2 - 50$ mg/kg/day⁷¹. Clinicians have extrapolated these recommendations to other types of shock.

Antibiotics

Current guidelines recommend initiation of antibiotics within one hour of presentation of severe sepsis and septic shock³¹. In a study by Kumar et al examining the duration of hypotension in adult septic patients and administration of effective antimicrobial therapy, each hour delay over the first six hours was associated with a mean decrease in survival of 7.6%⁷². These results were validated in another recent study by Gaieski who noted that mortality was significantly decreased when time from triage to appropriate antibiotic administration was ≤ 1 hour⁷³.

Temperature Control

In a recent multicenter randomized controlled trial, febrile patients with septic shock who needed vasopressors, mechanical ventilation, and sedation were allocated to achieve normothermia with external cooling (36.5 – 37 °C) or no external cooling. The authors demonstrated shock reversal and decrease in early mortality with normothermia⁷⁴.

The use of hypothermia in refractory shock and impending cardiac arrest situations has increased in the last few years largely due to its role in neuroprotection. A study by Schmidt-Schweda investigated use of moderate hypothermia (33°C) in patients with cardiogenic shock (50% of patients were post cardiac arrest)—they demonstrated a decrease in HR, increase in SV and CI without any major adverse effects⁷⁵. Further studies are warranted to identify the patient cohort that is most likely to benefit from use of hypothermia in shock.

Extracorporeal membrane oxygenation (ECMO)/Ventricular Assist Device (VAD)

ECMO was considered the last resort in refractory shock of any etiology, and its use has increased in the last few years to provide hemodynamic support. Clinicians have been encouraged by the survival data in patients who were placed on ECMO during CPR (ECPR). In a study drawn from the ELSO registry, 682 patients less than 18 years old received ECPR⁷⁶; underlying cardiac disease was present in 73%, sepsis in 8%, and respiratory failure in 5%. The survival to discharge in this cohort was 38%. The neurologic outcomes of these patients were not available in this study. Similarly, a single institution study demonstrated a survival to discharge rate of 33%⁷⁷. Another ELSO registry report stated that 40% of cannulated patients who had cardiogenic shock survived to discharge from the hospital. Approximately a third of the survivors had neurological morbidity, with significant deficits in approximately 10%⁷⁸. In shock arrest, central cannulation appears to be beneficial in cardiogenic and septic shock⁷⁹. Therefore, while these data support the use of ECMO in shock, efforts must be made to improve survival and long-term outcome in these patients.

Historically, ECMO has been the mainstay of pediatric circulatory support after unresponsiveness to inotropic/vasopressor support and VAD support have been used in children for circulatory support after cardiogenic shock from myocarditis, cardiomyopathy, and congenital heart disease. In a single institution retrospective study, the authors report the use of pulsatile VADs in 14 children with refractory cardiogenic shock with 79% survival, and 29% neurologic morbidity⁸⁰.

Conclusion

Shock is the proximate cause of death for many childhood diseases that cause significant mortality in the world. Clinicians have always targeted vital signs to treat shock but new biomarkers and non-invasive cardiac output monitors are being increasingly used to diagnose, monitor and predict outcome in pediatric shock. Early recognition and aggressive resuscitation has been shown to improve outcomes in pediatric shock. The choice of inotropes and/or vasopressor is largely dictated by the type of shock. The role of emerging

therapies like hypothermia and ventricular assist devices needs to be delineated and the patient population they are likely to help needs to be identified further.

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- Shock is the proximate cause of death for many childhood diseases that cause significant mortality in the world.
- Clinicians have always targeted vital signs to treat shock but new biomarkers and non-invasive cardiac output monitors are being increasingly used to diagnose, monitor and predict outcome in pediatric shock.
- Early recognition and aggressive resuscitation has been shown to improve outcomes in pediatric shock.
- The choice of inotropes and/or vasopressor is largely dictated by the type of shock. The role of emerging therapies like hypothermia and ventricular assist devices needs to be delineated and the patient population they are likely to help needs to be identified further.

Table 1

Hemodynamic Variables and Shock States

Type of shock	Cardiac Output	Systemic Vascular Resistance	Mean Arterial Pressure	Capillary Wedge Pressure	Central Venous Pressure
Hypovolemic	↓	↑	< > or ↓	↓↓↓	↓↓↓
Cardiogenic: Systolic	↓	↑↑↑	< > or ↓	↑↑	↑↑
Cardiogenic: Diastolic	< >	↑↑	< >	↑↑	↑
Distributive	↑↑	↓↓↓	< > or ↓	< > or ↓	< > or ↓
Septic: Early	↓↓↓	↑↑↑	< > or ↓	↓	↓

Adapted from Nelson Textbook of Pediatrics⁷⁷

Table 2

Receptor Affinity of Different Inotropes and Vasopressors

Drug	Alpha (α)	Beta ₁ (β_1)	Beta ₂ (β_2)	Dopamine	Vasopressin
Dobutamine	+	+++	+		
Dopamine	++	+++	+	++	
Epinephrine	+++	+++	+++		
Norepinephrine	+++	+			
Vasopressin					++

Adapted from Shekerdemian L.S. Redington A. Cardiovascular pharmacology, In: Chang AC, Hanley F, Wernovsky G, Wessel DL, eds. Pediatric Cardiac Intensive Care. Baltimore, MD: Williams, & Wilkins; 1998:48⁵⁴