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REVIEW

Pediatric Shock

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ABSTRACT

Millions of children die of shock due to various etiologies each year. Shock is a state of circulatory dysfunction where the metabolic demands of the tissue cannot be met by the circulation. Several different etiologies from hypovolemia to severe infection can result in shock. This review focuses on the definition of different types of shock seen in children and summarizes treatment strategies for the acute care practitioner based on pertinent recent literature. Early recognition and timely intervention are critical for successful treatment of pediatric shock. A strong index of suspicion by the treating clinician and early fluid resuscitation followed by ongoing assessment and timely transfer to a higher level of care can make the difference between life and death for the child who presents in shock.

Key words: shock, child, etiology, treatment

Introduction

More than 10 million children die each year in the world. The highest mortality rates are observed in children under five years in developing countries. Shock is the result of various etiologies and the leading causes of shock in children younger than 5 years of age are: pneumonia (19 %), diarrhea (18 %), malaria (8 %), neonatal pneumonia or sepsis (10 %), preterm delivery (10 %), and asphyxia at birth (8 %). (1) The early recognition of signs of shock and aggressive therapy to restore the intravascular volume and reverse the biochemical cascade is believed to improve outcome.

Pathophysiology

Shock ensues when systemic oxygen and nutrient supply become acutely inadequate to meet the metabolic demands of the body's organ systems. The true incidence of pediatric shock is not well documented in the literature. The most common cause of shock seen in pediatric patients is hypovolemic shock secondary dehydration.

The primary function of the cardiovascular system is to provide oxygen and other substrates to the cells as illustrated in figure 1. Oxygen content is defined as the total oxygen in whole blood and available to tissues. Oxygen content is an important consideration in the physiologic management of critically ill patients. Oxygen exists in two forms in the blood, dissolved and hemoglobin bound. The majority of oxygen stored in whole blood is bound to hemoglobin. The oxygen saturation (O_2 sats) is dependent on oxygen tension.

Cardiac output is the product of stroke volume and heart rate, stroke volume in turn is determined by ventricular filling volume and pressure (preload), myocardial contractility and the impedance to left ventricular output along with systemic vascular resistance (afterload).

In healthy individuals the oxygen consumption and demand are equal. Mixed venous oxygen saturations or central venous oxygen saturation can help to determine whether the cardi-

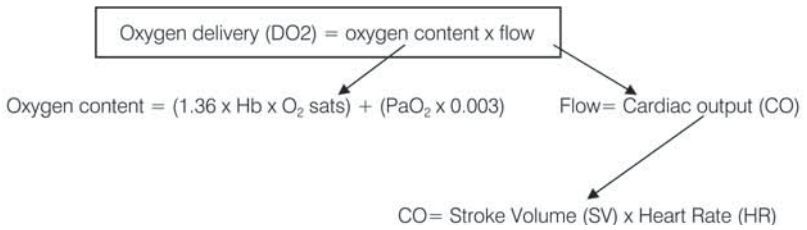

Figure 1. Role of cardiovascular system in oxygen delivery.

ac output and oxygen delivery is high enough to meet a patient's needs. The determinants of mixed venous oxygen saturation (SvO_2) include cardiac output, oxygen demand, hemoglobin level and arterial saturation. Normal SvO_2 is 5-7 % lower than central venous oxygen saturation. Any condition that disrupts this equilibrium and decreases oxygen delivery or increases oxygen demand may result in shock.

More explicitly, shock may be a consequence of several catastrophic conditions such as: 1) decreased blood oxygen carrying capacity with acute and profound decrease in hemoglobin (e.g. hemorrhagic shock, rapid hemolysis), 2) unavailability of oxygen with resulting severe hypoxemia (e.g. suffocation, CO poisoning) or 3) pumping or "plumbing" failure causing severe hypoperfusion or ischemia (e.g. cardiogenic and distributive shock, respectively). Depending on the underlying mechanism, tissue hypoxemia could be absolute as in hemorrhagic shock where supply is inadequate or relative as in septic shock where increasing demand cannot be met. Deprivation of tissues from oxygen leads to inadequate ATP production. In the absence of adequate oxygen, cells will revert to anaerobic metabolism which is almost 20-fold less efficient in terms of energy production compared to aerobic metabolism (2 ATP molecules produced anaerobically from 1 molecule of glucose vs. 36 ATPs produced aerobically). Anaerobic metabolism also produces large quantities of pyruvate which will be converted into lactate; prolonged hypoperfusion will lead to a build-up of hydrogen ions from lactic acid with ensuing metabolic acidosis. Circulatory insufficiency will also lead to a build-up of toxic metabolites that cannot be cleared away, contributing to microcirculatory dysfunction. Different types of shock meet in the final common pathway of tissue hypoxemia and energy uncoupling ultimately leading to death first at the cellular level as apoptosis and necrosis than leading to organ dysfunction and ultimately to demise of the patient. (2,3)

Shock is a dynamic process and progresses if not recognized and treated in a timely fashion. As the stage of shock increases so does mortality, with mortality rates increasing to over 10-fold in severe shock compared to early occult shock. (4) Since compensatory mechanisms may mask signs of tissue hypoperfusion especially in the young host, recognition in the early "cryptic" stages requires a high index of suspicion. Even with normal blood pressure, low cardiac index and low mixed venous pO_2 predict death from shock. (5,6) It is necessary to diagnose tissue hypoperfusion early to implement appropriate intervention.

Stages of shock

Early or Compensated Shock

In early compensated shock several compensatory mechanism are activated. In the face of impending hypoperfusion, sympathetic nervous system stimulation increases heart rate and systemic vascular resistance (SVR) through the release of catecholamines from adrenal glands. Renin-angiotensin-aldosterone system is also activated, contributing to vasoconstriction, maintenance of SVR, and fluid retention through concentration of urine.

In children, vascular tone is maintained in low flow states (7) of septic and cardiogenic shock. Therefore, children can often maintain their blood pressure until they are in profound shock. Compensatory vasoconstriction is often so pronounced that systemic blood pressure can be maintained within the normal range despite significant circulatory compromise. Hypotension is typically a late finding among children in shock. With vasoconstriction, blood flow is shunted away from the non-vital organs (skin and splanchnic bed) to brain, heart, and lungs. As a result, extremities are cold and mottled, capillary refill is prolonged, catecholamine-induced tachycardia occurs. If shock is left untreated, the compensatory mechanisms will fail and uncompensated shock develops. Failure of normalization of peripheral pulses, skin temp, and capillary refill with treatment predicts death from shock. (6)

Children are mostly dependent on their heart rate to increase cardiac output. Ability to increase contractility in response to catecholamine stimulation is limited due to insufficient muscle mass and "stiffness" of the young myocardium compared to the adult heart. (8) When the compensatory mechanisms are activated children become dependent on intravascular volume (preload) to maintain CO. (9) Since afterload is already increased in an effort to maintain SVR and BP, maintaining adequate intravascular volume is the key aspect of successful resuscitation.

Uncompensated shock

When the compensatory mechanisms fail to meet the increased metabolic demands at the tissue level uncompensated shock with hypotension will develop. Tissue hypoxemia and ischemia will trigger anaerobic metabolism resulting in lactate build-up and the development of metabolic acidosis. A number of other vasoactive metabolites such as adenosine, nitric oxide are also released and accumulate locally. Compensatory vasoconstriction fails as a result of hypoxia. Capillary blood flow becomes sluggish, leukocytes marginate, microthrombi form. The vasomotor paralysis and microcirculatory dysfunction escalate into end-organ hypoperfusion, organ dysfunction, and multi-organ failure. Organ hypoperfusion manifests itself as early organ dysfunction with altered mental status, tachypnea, tachycardia, lethargy, decreased or absent urine output, and mottled extremities. Once the blood pressure falls, the patient will progress into irreversible shock if the perfusion pressure to tissues is not restored. Irreversible shock, as the name implies, is the point of no return when the mortality rate is high irrespective of interventions.

Types of Shock

Several types of shock syndrome can be recognized based on the etiology. Table 1 summarizes the types of shock seen in pediatric patients and below is a brief description of each type.

Table 1. Types of shock seen in pediatric patients. CO = cardiac output, SVR= systemic vascular resistance, JVD = jugular venous distention. Adapted with changes from McKiernan CA, Lieberman SA. Pediatr Rev. 2005;26(12):451-60.

Type of shock	Mechanism of circulatory failure	Signs and symptoms	Interventions
Hypovolemic	Volume depletion absolute or relative, CO ↓, SVR ↑	Tachycardia, diminished pulses, sunken eyes and fontanels, oliguria, prolonged cap refill time	Crystalloid bolus 20 ml/kg until hemodynamics improve, reassess after each bolus, blood products in hemorrhagic shock
Cardiogenic	CO ↓, SVR ↑	Tachycardia, diminished pulses, hepatomegaly, JVD	Inotropic agents dopamine, dobutamine, epinephrine, milrinone Small volume boluses 5-10 ml/kg might be administered carefully while monitoring response Get echo early
Distributive			
Anaphylactic	CO ↑, then ↓, SVR ↓↓	Angioedema, respiratory distress, stridor, wheezing, early hypotension	Start adrenergic support while giving fluids, obtain vascular access early, supratherapeutic doses of inotropes might be required
Neurogenic	CO normal, SVR ↓	Hypotension in the absence of tachycardia	Support SVR with vasopressors, phenylephrine might be required, give fluids as necessary
Septic	"Warm shock" CO ↑, SVR↓ (20% of pediatric cases)	Tachycardia, bounding pulses, warm extremities with hypotension, hyperpnoea, altered mentation	Crytalloid boluses of 20 ml/kg repeat until hemodynamics stable, first choice agents vasopressors (dopamine or norepinephrine)
	"Cold shock" CO ↓, SVR ↑ (60% of pediatric cases)	Tachycardia, poor peripheral perfusion, diminished pulses, hyperpnoea, altered mentation	Crytalloid boluses of 20 ml/kg repeat until hemodynamics stable, early inotropic support with dopamine or epinephrine might be required, echocardiography might be useful to guide therapy
	CO ↓, SVR ↓	Tachycardia, diminished pulses, with hypotension, hyperpnoea, altered mentation	Crytalloid boluses of 20 ml/kg repeat until hemodynamics stable, early inotropic support with dopamine or epinephrine might be required, echocardiography might be useful to guide therapy
Obstructive	Preload ↓, CO ↓, SVR normal to ↑	Tachycardia, hypotension, JVD, tracheal deviation if pneumothorax, equalization of pressures with elevated CVP if invasive monitoring in place	Rapidly fatal if underlying process not recognized and reversed, fluid boluses should be given while preparation is made for emergent drainage

Table 2. Clinical signs of hemorrhagic shock in children with varying degrees of blood loss.

	Clinical Signs					
% blood loss	Heart rate	Blood Pressure	Capillary refill	Respiratory rate	Urine output	Mental status
< 15	Normal to slightly increased	Normal or increased	Normal	Normal	Normal	Anxious
15-25	Slightly increased	Might be decreased	Prolonged	Mildly tachypneic	Normal to slightly decreased	Anxious, might be agitated
25-40	Increased	Decreased	Prolonged	Moderately tachypneic	Decreased (<0.5 ml/kg/ hour)	Anxious, confused
> 40	Increased	Decreased	Prolonged	Severely tachypneic	Absent	Confused, lethargic, unresponsive

Table 3. Mechanisms of action, therapeutic effects and common doses of the most frequently used inotropic and vasoactive agents (mcg, micrograms, mU, miliunits).

Drug	Receptor	Action	Dose
Dopamine	Dopamine, ß,α	Chronotropy, inotropy, vasoconstriction	3-20 mcg/kg/min
Dobutamine	ß	Chronotropy, inotropy, vasodilatation	5-20 mcg/kg/min
Epinephrine	ß,α	Chronotropy, inotropy, vasoconstriction	0.05-0.2 mcg/kg/min
Norepinephrine	α,ß	Vasoconstriction, chronotropy, inotropy	0.01-2 mcg/kg/min
Milrinone	PDE inhibitor	Inotropy, lusitropy, vasodilatation	0.25-4 mcg/kg/min
Nitroprusside	NO donor, smooth muscle relaxation	Vasodilatation	0.5-10 mcg/kg/min
Vasopressin	V1 vascular receptors	vasoconstriction	0.3-4 mU/kg/min

Hypovolemic shock

This is by far the most common type of shock seen in pediatric patients. Hypovolemia may be absolute with actual fluid losses (severe dehydration with gastrointestinal losses, renal losses in diabetes mellitus, etc) or frank loss of blood as in hemorrhagic shock. Non-hemorrhagic hypovolemic shock is the most common type seen in the developing world. Findings of dehydration are present on physical exam with dry mucous membranes, sunken eyes and fontanels, diminished skin turgor (table 1). (10) Table 2 summarizes the varying presentation of hemorrhagic shock in children based on blood loss.

Distributive Shock

Volume loss could also be relative - sometimes referred to as distributive shock seen in anaphylaxis or spinal shock. The mechanism involved here is not an absolute loss of intravascular volume but pathological and inappropriate vasodilatation, endothelial dysfunction with capillary leak, loss of vascular tone or a combination of these factors. Based on the underlying etiology intravascular fluid volume is "maldistributed" and signs of shock will appear. In septic and anaphylactic shock, intravascular fluid leaks into the interstitial space augmenting the hypovolemic state.

Septic shock

Sepsis remains a major cause of mortality and morbidity for children. Although mortality from pediatric sepsis and sepsis shock has decreased from over 95% in 1960s to nearly 10% in 1990s, data from a recent US survey suggests that more than 4,300 children die each year from severe sepsis and septic shock

and the annual cost is approximately $ 2 billion. (11)

Definitions for pediatric systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock were standardized at the international consensus conference in 2002. (12) Children have specific physiological changes that occur as part of normal growth and development. Normal values for vital signs and laboratory values are also age dependant. Accordingly, for the purposes of diagnosing sepsis syndromes, pediatric patients are divided into six different age groups (neonate, newborn, toddler, child and adolescent). According to the international consensus criteria systemic inflammatory response syndrome (SIRS) is defined as tachycardia or tachypnea with fever or high leukocyte count. Sepsis is defined as SIRS in the presence of suspected or proven infection; and severe sepsis is defined as sepsis with accompanying organ dysfunction. When cardiovascular failure occurs in the setting of severe sepsis then it is classified as septic shock. The consensus definition also provides specific criteria for diagnosis of organ dysfunction (respiratory, cardiovascular, hematologic, neurologic, renal, and hepatic). In adults the classic picture of septic shock is one of high cardiac output and low SVR (warm shock). (13,14) However pediatric vascular tone is maintained in septic shock (6,7,15) and sepsis-induced myocardial dysfunction is more common. Therefore, pediatric septic shock can occur as low CO/high SVR, high CO/low SVR, or low CO/low SVR. In fact, in one study where cardiac index was measured, the majority (80%) of septic shock cases had low cardiac index and only about 20% presented in the typical "warm shock" (bounding peripheral pulses and flash capillary refill). (7) This has important therapeutic implications as children have more myocardial dysfunction in the setting of septic shock compared to adults and might benefit from early inotropic support and even in some instances afterload reduction. In adults the ability to increase oxygen consumption as oxygen delivery is enhanced by clinical interventions is associated with better survival in septic shock. (16) No evidence in pediatrics exists that oxygen extraction decreases in septic shock. In children with septic or cardiogenic shock, the major determinant for oxygen consumption is oxygen delivery, not oxygen extraction (15); therefore, efforts should be aimed at improving CO and oxygen delivery.

Cardiogenic shock

This type of shock is simply a pump failure. Myocardial failure may be primary as in myocarditis, congenital heart disease or secondary as in myocardial dysfunction in the setting of toxins, ischemia. Early use of echocardiography should be considered. Judicious fluid administration might still be indicated as many patients might still be on the hypovolemic side with room on theirs Starling curve. However, the mainstay of treatment is pharmacological support of the failing myocardium. Extracorporeal therapies are increasingly being used as a bridge to transportation or to "rest" the myocardium to allow recovery.

Obstructive shock

This is the setting of circulatory deficiency where venous blood return to the heart (preload) is "obstructed" usually as a result of an intrathoracic catastrophe such as tension pneumothorax or cardiac tamponade.

Diagnosis

It is important to reiterate that recognition of early shock in children could be difficult and requires maintaining a high index of suspicion by the clinician and a focused clinical exam. Physical exam should be directed at detecting signs of tissue hypoperfusion such as altered mental status, irritability, tachypnea, tachycardia, cold mottled extremities, prolonged capillary refill. For pediatric patients, a normal blood pressure in and by itself should not be used as a marker for adequate hemodynamics since hypotension is a sign of uncompensated shock and occurs late in the cascade.

While a focused clinical examination is a must, there are several aspects in the history that require special attention. Questions should be directed at preexisting chronic illnesses, current or recent use of medications (especially immunosuppressants such as steroids), use of illicit substances, prior and recent surgical procedures. The host factor is especially important in certain conditions of congenital or acquired immune deficiency, indwelling catheters, congenital heart disease all of which will require case-specific assessment and treatment.

Treatment

Early recognition and timely intervention are critical in treating shock and preventing progression of the shock cascade. Furthermore, early goal directed therapy has been shown to decrease mortality in adults and children. (17) In infants and children a 9 fold improvement in survival rate was achieved when aggressive resuscitation was initiated early by the emergency room physician. (4)

The goal of resuscitation is to reverse circulatory insufficiency and correct the hypoperfusion state. Animal studies have shown that early fluid resuscitation improves tissue ATP levels in burn shock. (18) Figure 2. summarize the clinical practice guidelines for management of children with septic shock developed by the American College of Critical Care Medicine Task Force on Pediatrics. These guidelines could essentially be applied to the management of all kinds of pediatric shock . (19) Neonates are considered separately since there are several unique clinical entities and physiological considerations like ductal-dependent congenital heart diseases and pulmonary hypertension that accompanies most shock states. The management guidelines for neonates are presented in Figure 3.

The first step in clinical management is always ABCs. Airway is the first priority and may need to be protected or a definitive airway established particularly in children with altered mental status.

Since functional residual capacity is smaller in pediatric patients compared to adults, early assisted ventilation might be required. In addition, endotracheal intubation may be indicated for hemodynamic instability alone since taking over the work of breathing will decrease oxygen consumption substantially. Care must be taken in selecting the appropriate induction agent for controlled pharmacological intubation to avoid hypotension and myocardial depression. While etomidate is not recommended in septic shock because of associated adrenal suppression, ketamine may be a reasonable choice in these cases. (20) Regardless of the agent used, initiation of positive pressure ventilation will decrease venous return and cause hypotension in the volume depleted patient. Therefore, aggressive fluid resuscitation should begin almost simultaneously with airway management. Following Frank-Starling mechanism, as left ventricular end diastolic volume increases stroke volume will increase proportionately. Fluid resuscitation is the first-line treatment in all shock syndromes. Mortality is significantly decreased when children with septic shock early liberal fluid resuscitated compared to those who were volume restricted. (21-23) Large bore intravenous or failing that intraosseous access should be established rapidly.

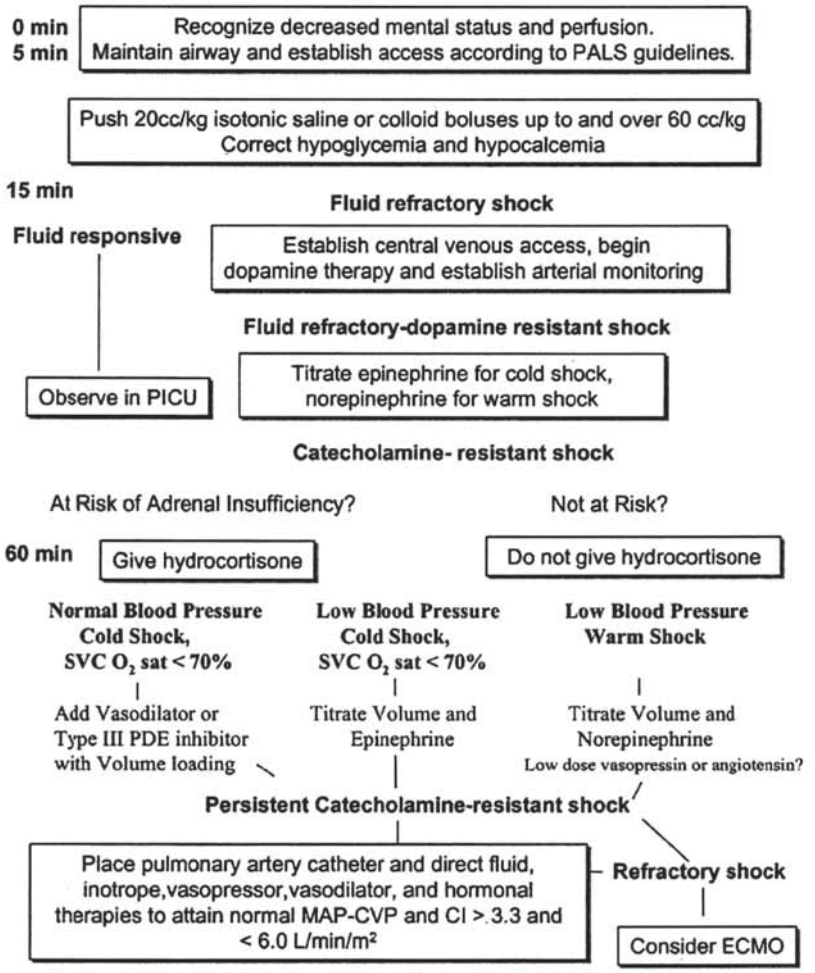

Figure 2. Recommendations for management of infants and children with septic shock (reprinted with permission). (19)

The choice of resuscitation fluid–crystalloid vs. colloid- has been debated for many years. (24) Data from pediatric studies are scarce. Colloid solutions effectively restore blood pressure especially in young neonates (9); however, there is a concern over the potential adverse effects of using natural and synthetic colloids (disease transmission/exposure, allergic reactions). In adults a recent randomized controlled clinical trial (25) comparing crystalloid to colloid in resuscitation demonstrated no benefit or adverse effects of using either solution. In a recent pediatric open-label trial children with septic shock were randomized to receive either normal saline or gelatin polymer in saline. Both groups achieved hemodynamic stability and mortality and organ failure rates were similar in both groups. The colloid resuscitated group required 40% less volume compared to the saline resuscitated group. (26) In postoperative cardiac surgery patients where volume load is a concern, the use of hypertonic solutions might be beneficial. (27) The critical component seems to be not the type of fluid chosen but the time period of resuscitation. Early fluid resuscitation should always be liberal. In children with dengue fever shock, aggressive fluid resuscitation in the first hour targeting normalization of heart rate, hematocrite and resolution of narrow pulse pressure was associated with 100% survival regardless of the type of fluid used. (22,28) In general isotonic saline is efficacious, safe and more cost effective compared to colloids and should be the fluid of choice during the initial resuscitation. (25) The first fluid bolus should be 10-20 ml/kg and further fluid administration should be individualized based on continual assessment of the clinical presentation and response to treatment. (19,21,29)

As the fluid given as bolus is redistributed, only 25% of crystalloid solutions will remain in the intravascular compartment and 75% diffuses into the interstitial space. This excess fluid in the interstitial compartment will contribute to the development of edema and fluid overload which has been implicated as a mortality risk factor in certain popula-

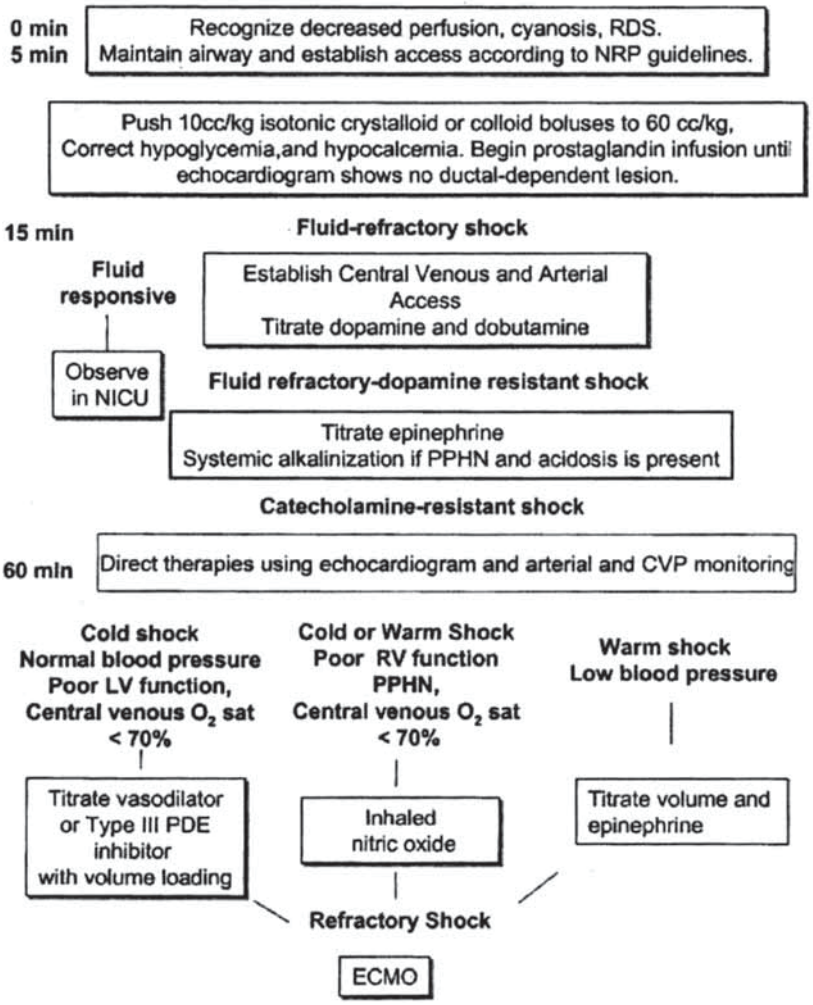

Figure 3. Recommendations for management of neonates with septic shock (reprinted with permission). (19)

tions of critically ill children. (30) The relatively short lifespan of intravascular crystalloids has led to investigating the use of hypertonic saline in trauma, hemorrhagic shock and traumatic brain injury. (31,32) There is circumstantial evidence that albumin administration in these cases is associated with increased mortality. (25,33,34)

Shock related mortality is independent of maintaining or normalizing the blood pressure alone, but is directly related to low cardiac index and low mixed venous oxygen saturations (21). Transfer to a tertiary care pediatric facility or a pediatric intensive care unit is strongly recommended for children in septic shock. (35)

Fluid Refractory Shock-time for more support

Goal directed therapies target mixed venous or superior venous cava oxygen saturation of > 70 % and normal perfusion pressure. While perfusion pressure (CO= MAP-CVP/SVR) should be maintained in a normal range to ensures adequate organ function, continuous reassessment during fluid resuscitation is critical to avoid over resuscitation and evaluate responsiveness. In patients with inadequate or no response to fluids, fluid refractory shock (Figures 2, 3), pharmacological support using vasoactive amines is necessary. A comparison of ionotropes and vasopressor commonly used in the clinical setting is presented in table 3. The choice of appropriate agent depends on clinical findings such as cold or warm shock. However, warm shock (bounding peripheral pulses and flash capillary refill) is infrequent in pediatric septic shock. Children have progressive myocardial dysfunction and the majority of septic children is hypo dynamically unstable and requires inotropic support. (7) Central venous catheter access is usually recommended in these cases to gauge response to therapy and monitor central venous pressure.

Choice of pressors

The vasoactive agent of choice in pediatric patients is dopamine. For dopamine refractory cold shock, epinephrine is the recommended second line agent. (19) However, when low mixed venous oxygen saturation and myocardial dysfunction is suspected, dobutamine is more appropriate for improving cardiac index and decreasing afterload. (36) Dobutamine has also been suggested to reverse microcirculatory abnormalities that might persist despite normalization of blood pressure and achievement of stable hemodynamics. (37)

In adult septic shock, vasopression levels are low and this finding is thought to contribute to vasodilatation. (38) While this finding is not consistently noted in children (39,40), vasopressin has been shown to improve hemodynamics in neonates with post-cardiopulmonary bypass vasodilatatory shock. (41) Use of vasopressin in other types of shock is still controversial but might be considered as rescue therapy in refractory hypotension as an adjuvant to existing inotropes. (42)

For nonresponders to vasoactive agents, sepsis-related insensitivity to ß-adrenergic stimulation was described in adult sepsis. (43) Phosphodiesterase (PDE) inhibitors like milrinone and enoximone increase cAMP independent of the ß-receptor pathway by inhibiting break-down and thereby having inotropic, lusitropic and vasodilator properties. Milrinone particularly it has been

shown to be particularly useful in the setting of cardiogenic shock. In children with septic shock systolic function is decreased and afterload is increased. (8) Ventricular dilatation is not observed in pediatric septic shock compared to adult septic shock. With depressed myocardial contractility, compensation by increasing SVR is actually detrimental and overtaxes the already strained heart. In cases of low CO cold shock, afterload reduction with volume loading to maintain preload might improve CO and tissue perfusion. In children with cold septic shock (sepsis induced myocardial dysfunction) milrinone improved cardiac index, LVSWI, and oxygen delivery and decreased SVR and PVR. (44) In animal sepsis models, PDE inhibitors have been shown to decrease release of several proinflammatory mediators, decrease nitric oxide synthase activity and improve myocyte function. (44,45) Left ventricle failure complicates fluid refractory shock. (46) Therefore, another option in cold shock could be combination therapy with epinephrine to increase contractility and a vasodilator like nitroprusside to decrease SVR, however, this approach would require caution since nonselective venous vasodilatation caused by nitroprusside might lead to hypotension. In warm shock, the agent of choice will be norepinephrine. However caution should be exerted while using this potent agent in the setting of myocardial dysfunction since it does have some inotropic and chronotropic properties and might cause unwanted stress on the affected myocardium by causing endocardial ischemia.

For catecholamine refractory-shock the use of extracorporeal membrane oxygenation (ECMO) could be considered. Survival rates of over 60% are reported in catecholamine refractory pediatric septic shock with the use of ECMO. (47) However, for this complicated treatment that requires a team-effort to succeed, the particular center should be well-versed in ECMO with up-to-date trainings of all team members. In a recent pediatric report, dramatic improvement in survival rates was reported when rescue ECMO was used as extracardiac life support (ECLS) in in-house pediatric cardiac arrests. Other extracorporeal treatments like high-volume hemofiltration and plasmapheresis are suggested to improve hemodynamics and mortality by removing cytokines in adults (48,49), limited pediatric data exist but is promising in a subset of critically ill children with multi-organ dysfunction. (50)

Follow-up of response to treatment

The most sensitive indicator of adequate cardiac output in children is the heart rate. Treatment should be modified as necessary based on monitored vital signs, exam findings and laboratory values. The earliest sign of reversal of shock is usually a decline in heart rate followed by improved blood pressure and increased urine output. The goals should be normalization of capillary refill (< 2 seconds), normal peripheral pulses, warm extremities, adequate urine output of greater than 1ml/kg/hr, normal mental status. Blood pressure itself is not a reliable endpoint of resuscitation but an improvement in the HR/SBP ratio - also called the shock index- can be used as an indicator of improving perfusion. In an intubated patient with an indwelling arterial catheter for invasive blood pressure monitoring, intravascular volume depletion will manifest as respiratory variation in the arterial line tracing. With each positive pressure breath, intrathoracic pressure will increase; the venous return to the heart will decrease in turn decreasing the stroke volume. With volume loading, this variation will disappear.

Serum pH, lactate, base deficit and bicarbonate are well demonstrated surrogate markers of tissue perfusion that correlate with severity of shock and adequacy of resuscitation in adult patients and are proven to be even more useful than estimated blood loss, heart rate and blood pressure (conventionally recorded hemodynamic measurements). (51,52) Serum glucose and calcium levels should be checked and abnormalities should be corrected. Normalization of serum bicarbonate and lactate are associated with patient recovery in pediatric septic shock. (53) Successful resuscitation should be accompanied by a decreasing anion gap, decreasing lactate and improving base excess. In patients with fluid refractory shock a central line in a central venous pressure monitor position should be in place and a mixed venous oxygen saturation or central venous oxygen saturations of > 70% should be targeted. Because children with septic shock die of low oxygen delivery and cardiac output, the superior vena cava or mixed venous saturation is suggested as the fifth vital sign of intensive care. (54,55) Low venous saturations can be corrected by increasing hemoglobin concentration or by increasing cardiac output.

Can we give too much fluid?

Continuous assessment and close bedside monitoring and intervention are the key to successful resuscitation in pediatric shock. For example, when hemodynamic parameters are worse with fluid resuscitation and signs of congestive heart failure become apparent the addition of inotropic agents may be warranted. In a study of over 35 children, Carcillo et al did not find a difference in the occurrence of ARDS between groups with restricted fluid resuscitation compared to those who received liberal fluid resuscitation. Complications from over resuscitation could be abdominal compartment syndrome, ARDS, and organ failure. However, in a study of over 35 children, Carcillo et al did not find a difference in the occurrence of ARDS between groups with limited resuscitation vs. those with a liberal fluid regimen. Therapy should be guided not by the absolute numbers of volume of fluid administered but by improving physical exam findings. While early aggressive treatment is warranted, there is evidence that fluid overload is a mortality predictor independent of severity of illness in critically ill children. Early institution of renal replacement therapies should be considered after the initial instability resolves to ensure

metabolic control and allow for adequate nutrient delivery. (54)

Antibiotics and Infection Source Control

Surviving Sepsis Guidelines proposed by an international consensus of critical care organizations to raise awareness about and improve outcomes from sepsis, recommend commencing early broad-spectrum antibiotic therapy as soon as appropriate cultures are obtained in suspected sepsis. (56) Early administration of antibiotics has been shown to improve survival in multiple trials. (57,58) The choice of the initial antibiotic combination should be directed by specific host factors, underlying illnesses and site of suspected infection as well as antibiotic resistance patterns in the community and ICU. Antibiotics should be reevaluated as soon as culture results and susceptibilities are available in order to narrow the spectrum in an attempt to avoid emergence of multiple-drug resistance. In some cases of localized infection such as deep tissue abscess or intra abdominal infections, sole reliance on antibiotic treatment is not enough and measures should be directed early to control source of infection. The methods involved might range from minimally-invasive abscess drainage by interventional radiology to open surgery.

Steroid Use in Pediatric Shock

Relative adrenal insufficiency is common in the PICU, occurring in over 75% of patients in septic shock. (59) Nonresponders -patients who fail to increase serum cortisol levels in response to test-dose corticotrophin - have 60% mortality compared to responders. There is evidence in adult patients with septic shock that low-dose steroids shorten shock duration. (60) No supporting data is available for the pediatric population. The recent CORTICUS study found that in adult critically ill patients treatment with steroids did not have a survival benefit and was associated with increased incidence of nosocomial infections. (20) In the light of these findings, routine treatment of pediatric patients with steroids cannot be recommended. However in children with catecholamine-refractory shock or in the presence of risk factors such as history of chronic or recent high dose steroid treatment, steroid administration should be considered. (19)

Conclusion

Pediatric shock syndrome is treatable if recognized early. Successful management requires early aggressive fluid resuscitation followed by treatment individualization based on bedside assessment. Support should escalate rapidly following American College of Critical Care task force guidelines. Life saving interventions do not require state-of-the-art medical technology, can be instituted by primary care physicians and lead to dramatic improvement in survival.

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