Pediatric shock

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Pediatric shock accounts for significant mortality and morbidity worldwide, but remains incompletely understood in many ways, even today. Despite varied etiologies, the end result of pediatric shock is a state of energy failure and inadequate supply to meet the metabolic demands of the body. Although the mortality rate of septic shock is decreasing, the severity is on the rise. Changing epidemiology due to effective eradication programs has brought in new microorganisms. In the past, adult criteria had been used for the diagnosis and management of septic shock in pediatrics. These have been modified in recent times to suit the pediatric and neonatal population. In this article we review the pathophysiology, epidemiology and recent guidelines in the management of pediatric shock.

Keywords: cardiogenic, distributive, early goal-directed therapy, hypovolemic, infection, multiple-organ dysfunction, pediatric, sepsis, septic, shock, SIRS

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Shock is an acute syndrome in which the circulatory system is unable to provide adequate oxygen and nutrients to meet the metabolic demands of vital organs [1]. Due to the inadequate ATP production to support function, the cell reverts to anaerobic metabolism, causing acute energy failure [2]. This energy failure results in the cell being unable to maintain homeostasis, the disruption of ionic pumps, accumulation of intracellular sodium, efflux of potassium, accumulation of cytosolic calcium and eventual cell death. Widespread cell death results in multi-organ dysfunction.

Pathophysiology

Shock can result from lack of oxygen delivery, a lack of glucose delivery or mitochondrial dysfunction [2]. DO_2 is the amount of oxygen delivered to the tissues per minute, and is dependent on the amount of blood pumped by the heart per minute (cardiac output [CO]) and the oxygen content of that blood (CaO_2), that is:

$$DO_2 = CO \times CaO_2$$

Oxygen content is measured by the following formula:

$$CaO_2 = 1.36\ (\%\ \text{hemoglobin})\ (\%\ \text{oxygen saturation}) + 0.003\ (PaO_2)$$

Thus, oxygen delivery can be impaired by anemia (low hemoglobin), hypoxia (decreased oxygen saturation) or ischemia (decreased CO). Glucose delivery can be impaired during states of hypoglycemia or insulin resistance. Mitochondrial dysfunction results from the cellular hypoxia [2]. It is well known that mitochondria consume more than 90% of the total body oxygen consumption to generate ATP. It is postulated that in the face of prolonged systemic inflammatory insult, overproduction of cytokines, nitric oxide and other mediators, and in the face of hypoxia and tissue hypoperfusion, the body responds by turning off the most energy-consuming biophysiological process, namely the mitochondria [3].

In the initial stages of anemic and ischemic shock, compensation occurs by tachycardia, tachypnea and peripheral vasoconstriction, which maintains flow to the vital organs. However, when the shock state persists, hypotension occurs, and the shock becomes a decompensated one. In children, this occurs much later in the course. Anion gap acidosis occurs in the later stages due to reversion to anaerobic metabolism and conversion of pyruvate to lactate. An anion gap of greater than 16 mEq/l is a surrogate marker of ischemic shock [2].

Shock due to impaired glucose delivery presents as anion gap acidosis, and presence of hypoglycemia, euglycemia or hyperglycemia. In this case, the acidosis is due to the organic acids that are produced during catabolism of fat and protein as a result of the lack of glucose substrate [2].

Thus, clinical findings of shock are directly related to the abnormalities seen at the tissue, cellular and biochemical levels [1]. All types of shock have underlying maldistribution of capillary blood flow. Local sympathetic activity and circulating vasoactive and inflammatory mediators cause smooth muscle contraction in the precapillary sphincters and arterioles. Such mediators are released by the host in response to endotoxins and cell injury. Mechanical obstruction of the capillaries occurs due to blockage by debris that forms due to a fall in hydrostatic pressures,

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making it difficult for leukocytes to squeeze through the microvessels. Activation of the complement system causes further aggregation of platelets and granulocytes and damage to the endothelium.

The damaged endothelium promotes procoagulant activity, while superoxide radicals, metabolites of cells and cytokines of macrophages that the body produces to kill bacteria, add to the damage. The end result of all this is tissue ischemia, which is common to all types of shock.

This ischemia results in decreased ATP production (2 M of ATP per 1 M of glucose instead of the normal 38 M of ATP) and reversion to anaerobic metabolism. Glycogen stores are further depleted by the anaerobic metabolism, causing accumulation of lactate. Sodium and water enter the cell, resulting in cellular swelling and clinically apparent edema.

With prolonged states of low flow, thrombosis and hypofibrinolysis occur due to activation of the endothelium by systemic inflammation mediators [2]. The activated endothelium causes consumption of both procoagulant and anticoagulant proteins, thus explaining the presence of both bleeding and thrombosis in patients with severe shock. Prompt resuscitation with fluids, ionotropes and vasodilators reverses and prevents disseminated intravascular coagulation [2].

Cardiovascular physiology

Cardiac output is the volume of blood ejected by the heart per minute, and is a product of heart rate and stroke volume. In childhood, the heart rate is higher and the stroke volume is smaller than in adults. The stroke volume can be altered by conditions that affect ventricular preload, compliance, contractility and afterload [4].

Ventricular preload is the presystolic stretch of ventricular fibers, which, according to the Frank–Starling Law of the Heart, has a linear relationship with the tension generated by myocardial fibers (**Figure 1**) [4]. As the fiber length increases, the tension generated by the myocardial fibers, and hence the stroke volume, increase up to a point.

Since the length of the myocardial fiber cannot be measured clinically, right or left ventricular end-diastolic pressure (VEDP) is measured to help evaluate the ventricular preload. Increasing the VEDP causes increased stroke volume and CO. However, at one point, when the ventricle is overfilled, the stroke volume falls again. Central venous pressure (CVP) or right atrial pressure is equal to the RVEDP (provided there is no tricuspid valve stenosis) and can be easily assessed clinically. Similarly, in the absence of mitral valve disease, the pulmonary artery wedge pressure reflects the LVEDP. It is often not possible to evaluate the LVEDP by clinical assessment alone.

Compliance is the change in ventricular volume for a given change in pressure [4]. Thus, administration of fluids to a patient with a compliant ventricle may increase the stroke volume, while producing a minimal change in VEDP. Conversely, in a stiff ventricle, administration of even a small amount of fluid can cause a significant increase in VEDP, and hence judicious use of fluids with close monitoring is important [4].

Cardiac output is also defined by the following equation, where MAP is the mean arterial pressure, CVP is the central venous pressure and SVR is the systemic venous resistance:

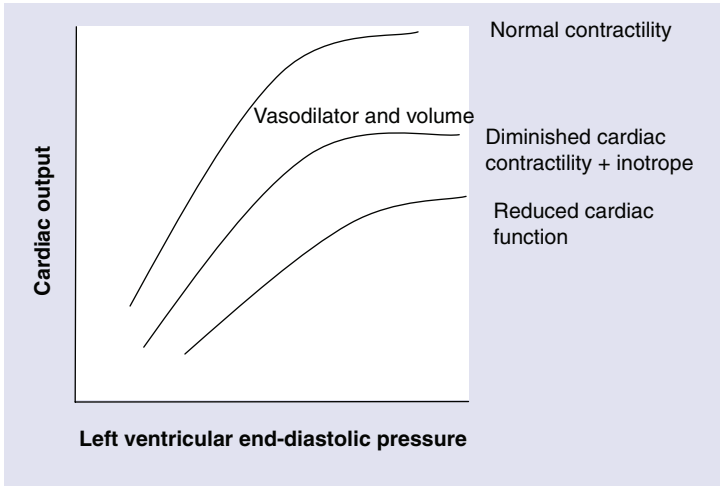
$$CO = MAP - CVP/SVR$$

This equation guides clinical management. During fluid resuscitation, the increase in MAP must be more than the increase in CVP, or the perfusion pressure would be reduced [2]. Hence, at this point, vasopressors would be indicated rather than fluids [2].

It is also important to note that CO can fall if the SVR increases, even in the presence of normal MAP – CVP. Perfusion pressure is maintained, even in the presence of low CO states, by increased SVR [2]. Hence, patients with a poor CO can have a normal blood pressure, as the systemic vascular tone is high. These patients may benefit from the addition of vasodilators and inotropes [2].

Ventricular contractility is the speed and force of ventricular contraction. With improved contractility, the speed of ejection improves, thus increasing the time for refill of the ventricles, and hence increasing the stroke volume. The contractility is best evaluated by an echocardiographic evaluation of the left ventricular shortening fraction (LVSP). The normal LVSP is approximately 28–44%, and a reduced LVSP is associated with reduced contractility. Other measures of the contractility include the ejection fraction and the rate of peak ventricular pressure development [4]. Patients with inadequate stroke volume despite adequate volume loading have reduced contractility and have a flat curve on the Frank–Starling curve [2]. Treatment with inotropes, vasodilators and volume in these patients moves the curve upwards and to the left.

Figure 1. Frank–Starling curve.



Afterload is the resistance or impedance to the ventricular ejection, and is determined by the ventricular lumen radius, thickness of the wall, and ventricular ejection pressure. As the afterload increases, the stroke volume decreases. Afterload reduction with vasodilators improves the stroke volume.

During any illness, there is a stress response that is due to central and sympathetic nervous system activation [2]. This causes release of adrenocorticotropic hormone (ACTH), cortisol, epinephrine and norepinephrine. The end result is an increase in heart rate, stroke volume and blood pressure, and release of glucagon to increase glucose delivery.

This stress response is exaggerated in shock, and catecholamine and cortisol levels are five- to ten-times higher than during stress response. The angiotensin and aldosterone pathways are also activated, resulting in oliguria. Although this shock response helps the patient survive for a short time, intervention is required at this time to ensure long-term survival.

Etiology

Shock can be hypovolemic, cardiogenic or distributive and further classification is based on the etiology (**Table 1**). Shock that results from inadequate intravascular volume relative to the vascular space is called hypovolemic shock [4]. Cardiogenic shock is due to the impaired myocardial function. Distributive shock is due to inappropriate distribution of blood flow, with increased capillary permeability. It is important to recognize that this classification may be inadequate, particularly when the patient in late shock is likely to show cardiac dysfunction, poor intravascular volume and maldistribution of blood flow.

Hypovolemic shock

Although hypovolemic shock can be caused by a variety of factors, the end result is decreased intravascular volume, decreased venous return to the heart and decreased stroke volume (**Box 1**) [5]. It is the leading cause of pediatric mortality in developing countries, and the WHO lists diarrhea as one of the leading causes of pediatric mortality. Due to aggressive fluid resuscitations and improved intensive-care medicine, mortality in the USA from diseases associated with hypovolemic shock has decreased by nearly tenfold in the past two decades [6].

Pathophysiology of hypovolemic shock

The common axiom that children are not little adults is particularly true with regards to the cardiovascular system of children and distribution of body fluids. Many of the physiologic factors are age related in children (e.g., heart rate and respiratory rate) and hence what is seen commonly in adults may not be applicable in children. Children often remain asymptomatic for prolonged periods of time, resulting in diagnostic and therapeutic delays.

Children have greater total body water (60–75%) and percentage of extracellular water (20–40%) when compared with adults (50–55% and 20–25%, respectively) leading to the assumption that they are protected against dehydration [5]. In reality, their higher resting metabolic rate, increased insensible water loss and decreased renal concentrating ability make them more susceptible to hypoperfusion of end organs [5,7]. It is also important to remember that compared with adults, the total amount of fluid loss required to produce shock is also less in a child [5].

Thus, early symptoms and signs of shock may be subtle in a child and get progressively worse as the disease progresses compared with an adult with a similar degree of hypovolemia.

The compensatory cardiovascular mechanisms in a child in response to decreases in volume and preload and impaired contractility also vary from adults. In children, the ability to improve myocardial contractility in response to catecholamines is limited due to insufficient muscle mass and stiffer myocardium when compared with adults. Hence, CO is more dependent on heart rate than on the stroke volume. Tachycardia is the primary response in children to decreasing preload or poor

Table 1. Types of shock, clinical features and management.

Type of shock	Pathophysiology	Clinical features	Management
Hypovolemic	↓CO, ↑SVR	↑heart rate, ↓pulses, prolonged cap refill, dry skin, sunken eyes	Bolus of crystalloids as 20 ml/kg and repeat as needed; blood for trauma
Septic	↓CO, ↑SVR (60% in children)	↑HR, hypotension (late), prolonged cap refill, ↓pulses, altered mentation	Bolus of crystalloids 20 ml/kg, maybe up to >60 ml/kg in the first hour Dopamine if fluid resistance Epineprine if dopamine and fluid resistant
	↑CO, ↓SVR (20% in children)	↑HR, ↓BP, ↑pulses, prolonged cap refill, altered mentation	Fluid bolus of 20 ml/kg up to >60 ml/kg in the first hour Dopamine if fluid refractory Norepinephrine if fluid and dopamine refractory
	↓CO, ↓SVR (20% in children)	↑HR, ↓BP, ↓pulses, prolonged cap refill, hyperpnea, altered mentation	Fluid bolus of 20 ml/kg up to >60 ml/kg in first hour Dopamine if fluid refractory Epinephrine if dopamine and fluid refractory
Distributive	Spinal cord injury: normal CO, ↓SVR	Normal HR, ↓BP, paralysis	Judicious fluids Norepinephrine or phenylephrine
	Anaphylaxis: ↑CO, ↓SVR	Angioedema, ↓BP, cardiovascular collapse, respiratory distress or arrest	Fluid boluses Epinephrine Norepinephrine or phenylepinephrine
Cardiogenic	↓CO, ↑HR, normal or ↑SVR	↑HR, ↓pulses, prolonged cap refill, hepatomegaly, rales, oliguria	Judicious fluids Dobutamine, dopamine or milrinone

BP: Blood pressure; CO: Cardiac output; HR: Heart rate; SVR: Systemic venous resistance.

contractility. As the resting heart rate in children is higher than in adults, any further increase in heart rate may be much higher than their normal percentiles, resulting in signs of hypoperfusion [5].

Since the vascular tone is maintained in children during periods of low flow, they also try to improve their CO by increasing the SVR by peripheral vasoconstriction, as discussed previously. Hence, blood pressure is maintained by this mechanism until late in the disease process. Once compensatory mechanisms are initiated, children become dependent on preload to maintain CO, and hence maintenance of intravascular volume is the key to a successful resuscitation.

Clinical features

Hypovolemic shock due to dehydration causes reduced intravascular and interstitial volume that in turn reduces the preload and the stroke volume. These patients present sunken eyes, sunken fontanelle, dry mucus membranes, decreased skin turgor, cool extremities, prolonged capillary refill and tachycardia. Hypotension may be a late finding and may not be seen until at least 30% of fluid loss has occurred.

The severity of signs and symptoms of hypovolemic shock depends on the degree of dehydration (**Box 2**).

In children with hypovolemic shock due to increased capillary permeability, such as that caused by burns or sepsis, although the intravascular volume is reduced, the interstitial volume may be normal or even increased. These patients may not exhibit the classic signs of hypovolemic shock. They may have features of end-organ hypoperfusion, such as altered mental status, oliguria and cool but swollen extremities, but be without other signs of dehydration. Care should be taken during resuscitation of these children, as aggressive fluid delivery may result in increased interstitial volume with continued intravascular hypovolemia.

Early recognition and treatment of hypovolemic shock is of paramount importance, as unrecognized and untreated hypovolemic shock can rapidly progress to cardiovascular collapse and arrest [5]. Children in hypovolemic shock may have an increased respiratory rate and work of breathing in response to the metabolic acidosis. Hence, a decreased respiratory rate or apnea

Box 1. Causes of hypovolemic shock.

Hemorrhage (blood loss)

- Trauma
  - External (e.g., lacerations)
  - Internal (e.g., solid-organ rupture, vascular injury)
  - Fractures
  - Gastrointestinal (e.g., bleeding ulcers)
  - Intracranial bleeding (especially in neonates)

Plasma loss

- Burns
- Sepsis or inflammation
- Nephrotic syndrome
- Third spacing as in peritonitis, intestinal obstruction, low protein

Fluid & electrolyte loss

- Vomiting
- Diarrhea
- Excessive sweating
- Heat stroke
- Water deprivation

Endocrine

- Diabetes insipidus
- Diabetes ketoacidosis
- Adrenal insufficiency
- Hypothyroidism

is an ominous sign of impending arrest. Similarly, irritability or obtundation are signs of cerebral hypoperfusion, and may progress quickly to coma if untreated [5]. Care must be taken to not depend on hypotension to guide fluid management, as it is a very late finding and significant fluid losses have occurred prior to this.

Infection, sepsis, systemic inflammatory response syndrome, severe sepsis & septic shock

The original definition of sepsis provided by Bone *et al.* was revisited at the 2001 International Sepsis Definitions Conference [8–10]. The group agreed that sepsis is infection plus presence of an inflammatory reaction, and included various criteria for the diagnosis of the inflammatory reaction [10].

Goldstein *et al.* point out that the definition used for adults may not be accurate for children whose physiological parameters at baseline vary from adults and with age [11]. They propose a modified definition of systemic inflammatory response syndrome (SIRS), severe sepsis and septic shock in children (**Box 3**).

They propose six different age groups for age-specific vitals and laboratory findings of SIRS:

- Newborn (0 days to 1 week)
- Neonate (1 week to 1 month)
- Infant (1 month to 1 year)
- Toddler and preschool (2–5 years)
- School-aged child (6–12 years)
- Adolescent and young adult (13–18 years)

Premature infants were not included.

They point out that major difference between adult and pediatric SIRS is that SIRS can not be diagnosed in children in the absence of changes in leukocyte counts or temperature. They also suggest modifying the numeric values in the earlier definition to account for different physiology. Finally, they point out that bradycardia can be used as evidence of SIRS in newborns, but not in older children, in whom it would be a near-terminal event.

Criteria used for septic shock include infection, with hypothermia or hyperthermia, tachycardia (may be absent with hypothermia) and altered mental status, in the presence of at least one or more of the following: decreased peripheral pulses, prolonged capillary refill of more than 2 s (indicating cold shock) or flash capillary refill (indicating warm shock), mottled or cool extremities (with cold shock) and decreased urine output (<1 cm^3/kg/h). Hypotension is suggestive of decompensated shock [12,13]. Multiple-organ dysfunction syndrome (MODS) is defined as failure of more than one organ. Several scoring systems exist in the literature for pediatric MODS and include Multiple Organ System Failure Score (MOSF), Pediatric Multiple Organ Dysfunction Score (PMOD), Pediatric Logistic Organ Dysfunction Score (PLOD) and Pediatric MOD [14–18]. Of these, only the PLOD has been validated in a multicenter study [16]. Based on the above, Goldstein *et al.* developed criteria for organ dysfunction [11].

Seven organs have been considered, including nervous system, respiratory, cardiovascular, gastrointestinal, hematological, renal and hepatic

Box 2. Clinical symptoms and signs of hypovolemic dehydration at different percentages of dehydration.

Mild (5%)

- Mild tachycardia, concentrated urine, normal capillary refill

Moderate (10%)

- Sunken eyes, flat fontanelle, irritable, decreased tears, dry mucus membranes, thirsty, increased respiratory rate, prolonged capillary refill of 2–3 s, oliguria, tachycardia, normal blood pressure

Severe (15%)

- Lethargic, sunken eyes and fontanelle, ashen appearance, very dry mucus membranes, absent tears, periods of apnea, capillary refill of more than 3 s, absent urine output, tachycardia, hypotension

Box 3. Definitions of SIRS, infection, sepsis, severe sepsis and septic shock.

- SIRS is defined as the presence of two of the four following criteria, one of which must be abnormal temperature or leukocyte count:
  - Core temperature of >38.5°C or <36°C
  - Tachycardia with heart rate >2 SD above what is normal for age in the absence of any other causes or bradycardia (in children <1 year of age) with heart rate <10th percentile in the absence of any other causes
  - Mean respiratory rate >2 SD above what is normal for age or mechanical ventilation not for general anesthesia or for a neuromuscular-related process
  - Elevated or depressed leukocyte count or >10% immature neutrophils
- Infection is defined as a suspected or proven infection (either by culture or tissue stain or PCR) caused by a pathogen or a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive clinical findings or laboratory tests or radiographs. Infection could be bacterial, viral, fungal or rickettsial in origin.
- Sepsis is SIRS in the presence of or as a result of proven or suspected infection.
- Severe sepsis is defined as sepsis plus one of the following: cardiovascular organ dysfunction or acute respiratory distress syndrome, or two or more other organ dysfunctions.
- Septic shock is sepsis and cardiovascular dysfunction.

SD: Standard deviation; SIRS: Systemic inflammatory response syndrome.
Adapted from [11].

(**Box 4**). For the purposes of enrolment in any severe sepsis study, they mandate the presence of both cardiovascular and respiratory organ dysfunction. They also recommend that a pediatric MOD scoring system should be used for any documentation of organ dysfunction.

It is generally agreed that mortality is higher when the number of organ failures is higher [19–23]. Leclerc *et al.* reported that children had a worse prognosis when MODS was present, irrespective of the diagnostic category of sepsis, and that there is a cumulative accrual of the risk of death with increasing severity of MODS and an increasing severity of the worst septic type (i.e., SIRS-sepsis, severe sepsis and septic shock) [24].

It should also be noted that MODS is usually seen in septic shock patients whose resuscitative measures were delayed, whose source of infection was inadequately controlled, or in children with an underlying primary or acquired immunodeficiency [12].

Epidemiology of pediatric sepsis & septic shock

The incidence of severe sepsis in the USA was reported by Watson *et al.* to be 0.56 per 1000 children each year [25]. The incidence was highest in infants (5.6/1000) and fell dramatically to 0.2/1000 in 10–14 year olds. The high rate among infants was primarily due to neonatal severe sepsis (69.7% of infants). Two-thirds of the neonates were low-birth-weight (LBW) infants and 50% of these were very-low-birth-weight infants (VLBW) [25]. The most common underlying conditions in infants were respiratory (19%), followed by cardiac (17.1%). Neuromuscular disorders were the most common underlying condition in older children between 1 and 10 years of age, while neoplasms were most common in children older than 10 years of age [25].

Sepsis mortality rates in reports from across the country have varied from 6 to 15% [26,27]. Mortality rates from sepsis have decreased steadily due to improved intensive-care techniques and aggressive resuscitation principles [28]. The use of vaccines against *Haemophilus* and the use of intra and peripartum Group B streptococcal prophylaxis has contributed to the lower rates in infants. The risk of death was shown to increase from 7% in those with one failed organ, to 53.1% in children with more than four failed organs [25]. Mortality rates in children with chronic underlying disease have been 12–15%, while in previously healthy children have ranged from 0 to 2% [12,27]. Although outcomes are improving per these reports, the burden of sepsis and septic shock is increasing in the USA, and the annual healthcare cost for it is estimated to be US$4 billion [29].

The infections causing sepsis were either respiratory (37.2%) or primary bacteremia (25%) in origin. The most common etiological organism causing sepsis and septic shock in children in the USA seems to be *Staphylococcus* (17.5%) [25]. While Group B *Streptococcus* and *Escherchia coli* infections are more common in neonates, *Staphylococcus* was also responsible for 25% of all neonatal infections. Fungal infections were more common in children with comorbidities. Bizzarro *et al.* reported a decrease in early-onset sepsis (EOS – defined as sepsis within 72 h after birth) per 1000 live births, and an increase in late-onset sepsis (LOS – defined as sepsis >72 h after delivery). The decrease in the EOS is proposed to be secondary to a decrease in Group B streptococcal infections following use of intrapartum antibiotics. The authors also report that although there was no change in the EOS due to *E. coli*, there was a significant increase in the incidence of both EOS and LOS of *E. coli* sepsis in the VLBW infants [30].

Box 4. Organ dysfunction criteria.

Cardiovascular dysfunction

Despite administration of >40 ml/kg of fluids in 1 h:

- Hypotension (less than the 5th percentile for age or 2 SD below normal for age) **OR**
- Requirement for vasoactive drugs **OR**
- Two of the following:
  - Unexplained metabolic acidosis
  - Increased lactate (>two-times normal)
  - Oliguria
  - Prolonged capillary refill
  - Difference between core and peripheral temperature >3°C

Respiratory dysfunction. Any one of the following:

- PaO_2 <300 in absence of other causes such as congenital heart disease
- $PaCO_2$ >65 torr or 20 mmHG above baseline
- Need for >50% FiO_2 to maintain oxygen saturation above 92%
- Need for mechanical ventilation

Neurologic dysfunction. Any one of the following:

- GCS of <11
- Change in GCS of >3 from baseline

Hematologic dysfunction. Any one of the following:

- Thrombocytopenia
- International Normalized Ratio >2

Renal dysfunction

- Elevated creatinine (>two-times normal)

Hepatic dysfunction. Any one of the following:

- Elevated bilirubin (>4 mg/dl) (excluding newborns)
- Elevated ALT (>two-times normal)

ALT: Alanine aminotransferase; FiO_2: Fraction of inspired oxygen; GCS: Glasgow Coma Score; $PaCO_2$: Partial pressure of carbon dioxide; PaO_2: Partial pressure of oxygen; SD: Standard deviation.
Adapted from [11].

Some of the predisposing conditions associated with sepsis and septic shock include age (prematurity, newborns <1 year), underlying malignancies, treatment with immunosuppressives, primary and acquired immunedeficiencies, neutropenia, cardiac disorders, malnutrition and indwelling invasive catheters [12]. Boys are more commonly associated with severe sepsis than girls [31].

Pathophysiology

When the body is invaded by a microorganism, it responds with a controlled immune cell response to the endotoxin and glycoprotein of the organism. However, when this is ineffective in killing the infection or clearing it, the inflammation becomes uncontrolled, resulting in organ injury, bleeding and thrombotic states [12]. After a review of autopsies of children who died from sepsis and multiple organ failure at the Children's Hospital of Pittsburgh (PA, USA), Amoo-Lamptey *et al.* demonstrated that there was an 80% incidence of thrombosis and bleeding, with a 30% incidence of adrenal pathology and an 80% incidence of persistent infection in these children [32]. These findings suggest that there is uncontrolled inflammation that contributes to organ failure in septic shock, which in turn causes systemic thrombosis and adrenal dysfunction. The uncontrolled inflammation also suggests untreated or persistent infection. All of this is further affected by any underlying disease processes and the genetic make-up of the child [12].

Physiologically, in contrast to adults, low CO and not low systemic vascular resistance is associated with mortality in pediatric septic shock [33,34]. The majority of children with fluid-refractory and dopamine-resistant shock in a study by Ceneviva *et al.* demonstrated a low CO and high systemic vascular resistance state [35].

In addition, unlike adults, oxygen delivery, and not extraction, is the major determinant of oxygen consumption in children [34].

Clinical findings

Septic shock can be recognized in a child who has a suspected infection by a clinical triad of hypothermia or hyperthermia, altered mental status and peripheral vasodilatation with bounding pulses (warm shock) or cool extremities with prolonged capillary refill and mottled appearance (cold shock) [32]. Decreased urine output of less than 1 ml/kg/h may be seen. Hypotension is not required for the diagnosis, although its presence confirms the shock state [32]. Other findings may include tachycardia, hyperpnea and edema [6].

Cardiogenic shock

Cardiogenic shock in children occurs due to impaired myocardial function that results in decreased CO. This may be a result of impaired contractility, arrhythmias or redirected blood flow due to congenital heart disease [6]. Congenital heart diseases that result in shock are usually those with left ventricle outflow tract obstruction (hypoplastic left heart, severe aortic stenosis, hypoplastic right ventricle). Other conditions include cardiomyopathy, myocarditis, drugs, acid–base imbalance, electrolyte imbalance, ischemic heart disease or cardiovascular surgery. Myocardial dysfunction can be present in any form of shock, and often may be the final common pathway of any type of shock.

Pathophysiology

In cardiogenic shock, myocardial dysfunction limits the CO. In the early stages, compensatory

mechanisms are activated and maintain intravascular volume and perfusion of vital organs. But these adrenergic responses increase myocardial oxygen consumption. Decreased renal perfusion results in sodium and water retention. This may contribute to relative hypervolemia. With progression of the myocardial depression, CO and blood pressure fall.

Clinical findings

Children with cardiogenic shock may show signs of inadequate perfusion, despite adequate intravascular volume or even hypervolemia. This is generally a low CO shock. Hence, there may be normal to increased heart rate, thready pulses, prolonged capillary refill and cool extremities with a mottled appearance, jugular venous distension, periorbital edema, hepatomegaly and oliguria. Pulmonary edema may be present, and the heart may appear enlarged on a chest radiograph. In severe cases, pulsus alternans may be present, and a fall in mixed venous saturation may be seen. Blood pressure is again maintained until late in the course.

Distributive shock

This type of shock occurs due to a fall in systemic vascular resistance, causing abnormal redistribution of blood flow in the microcirculation, resulting in a functional hypovolemia [7]. Although the cardiac contractility and output increase initially, an eventual fall in CO due to decreased preload occurs. Causes include anaphylaxis and spinal injury (neurogenic).

Anaphylaxis

This is a life-threatening reaction, usually as a result of exposure to an allergen, such as bee sting or fish protein, which results in an IgE-mediated hypersensitivity reaction, causing massive release of inflammatory mediators such as cytokines from mast cells. These patients present with angioedema, respiratory failure or arrest, hypotension, cardiovascular collapse and even arrest. There is loss of vascular tone and third spacing of intravascular volume.

Neurogenic (spinal shock)

This can develop after spinal cord injury that causes loss of sympathetic vascular tone and autonomic tone, resulting in relative hypovolemia. Cardiac contractility is preserved despite the fall in output due to decreased venous return. This type of shock should be considered in a child after spinal cord injury if hypotension persists in the absence of tachycardia despite adequate volume resuscitation, and further blood loss has been ruled out [7].

Laboratory signs of shock

Shock is largely a clinical and physiological diagnosis. The use of laboratory findings to prove or predict the presence of shock has not been supported in the literature. Teach *et al.* found that blood urea nitrogen:creatinine ratio, total serum CO_2, uric acid, serum anion gap, urine anion gap, pH, venous base deficit, urine-specific gravity and fractional excretion of sodium were all poor laboratory predictors of fluid deficits [36]. However, certain ancillary data may aid in therapy and predicting prognosis. Lactic acid is a sensitive indicator of inadequate systemic perfusion. In a study of critically ill children, Hatherill *et al.* found that an admission lactate of more than 6 mmol/l had optimum predictive value for complications, and found no association with the magnitude of metabolic acidosis, as quantified by the base excess and mortality [37]. Recently, several authors have reported the usefulness of procalcitonin in predicting severity and poor outcome of shock over white count or C-reactive protein [38–42]. Other studies have found antithrombin III and protein C levels to be the most reliable marker of severity of sepsis [43,44]. Although these tests are theoretically attractive in terms of feasibility and possible early prediction of shock, further studies are needed to establish their usefulness.

Although a positive blood culture, urine culture, joint-fluid culture or cerebrospinal-fluid culture aids in the diagnosis and management and should be performed, a negative culture does not rule out the presence of sepsis or shock. Coagulation studies, including platelet counts, hemoglobin, prothrombin time, partial thromboplastin time, fibrinogen, fibrin split products and D-dimer, should be obtained and may help guide therapy. Blood typing and screening may help with transfusions later. A chest radiograph will help determine cardiac size and the presence of pulmonary edema. An arterial blood gas can help with identification of acidosis and diffusion and ventilation problems. Electrocardiogram and echocardiography Doppler should be performed selectively to evaluate for arrhythmias and cardiac function.

Therapy

Studies have shown that delay in recognition and inadequate resuscitation is associated with poor outcome. Investigators from the UK reported a reduction in mortality from meningococcal septic

shock from 23 to 2% after development of a specialized transport team and a program dedicated to early recognition and appropriate resuscitation [45]. Han *et al.* reported that every hour of hypotension or prolonged capillary refill of greater than 2 s was associated with a severity-of-illness-adjusted odds ratio of mortality from MOD of 2.0 in children with septic shock [46]. A reduction in mortality from adult septic shock was reported by Rivers *et al.* following the use of early perfusion pressure and oxygen use goal-directed therapies [47]. The patients who received therapy guided by superior vena cava O_2 saturation had a reduction in prothrombin time and improved survival, thus supporting the hypothesis that increased CO decreases thrombosis and disseminated intravascular coagulation.

Evidence-based treatment guidelines for the hemodynamic support of pediatric septic shock were published by the International Surviving Sepsis Campaign Guidelines Committee in 2004 and were updated in 2008 (**Figures 2 & 3**) [13,48].

The Committee used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system to guide assessment of quality of evidence from high (A) to very low (D) to determine the strength of recommendation. A strong recommendation (1) means that an intervention's desirable effects clearly outweigh its undesirable effects or clearly do not. Weak recommendation (2) indicates that this trade off between desirable and undesirable effects is less clear. The grade of strong or weak is considered to be of greater clinical importance than the letter indicating the level of quality of evidence [48].

Goals of therapy

Clinical

A urine output of more than 1 ml/kg/h, normal mentation, normal pulse and blood pressure and a capillary refill of less than 2 s should be the goal of therapy [2].

Hemodynamic

Normal heart rate for age and normal perfusion pressure for age should be the hemodynamic goal during therapy. The shock index (heart rate/systolic blood pressure) has been suggested as an indicator of adequacy of resuscitation [2]. The shock index is a sensitive indicator of left ventricular dysfunction. The normal ranges from 0.5 to 0.7. If the resuscitation is adequate, the heart rate will fall and the systolic pressure will increase – hence, the shock index will decrease. The shock index will not decrease if the stroke volume does not improve [2].

In a study comparing three different fluid solutions for resuscitation in Dengue shock syndrome, Wills *et al.* defined cardiac stability by a pulse pressure (difference between systolic and diastolic pressures) of 25 mmHg or higher [49]. However, it should be noted that Dengue is unusual in that the leak occurs over a period of days, giving time for compensatory mechanisms to operate and narrow the pulse pressure.

Biochemical

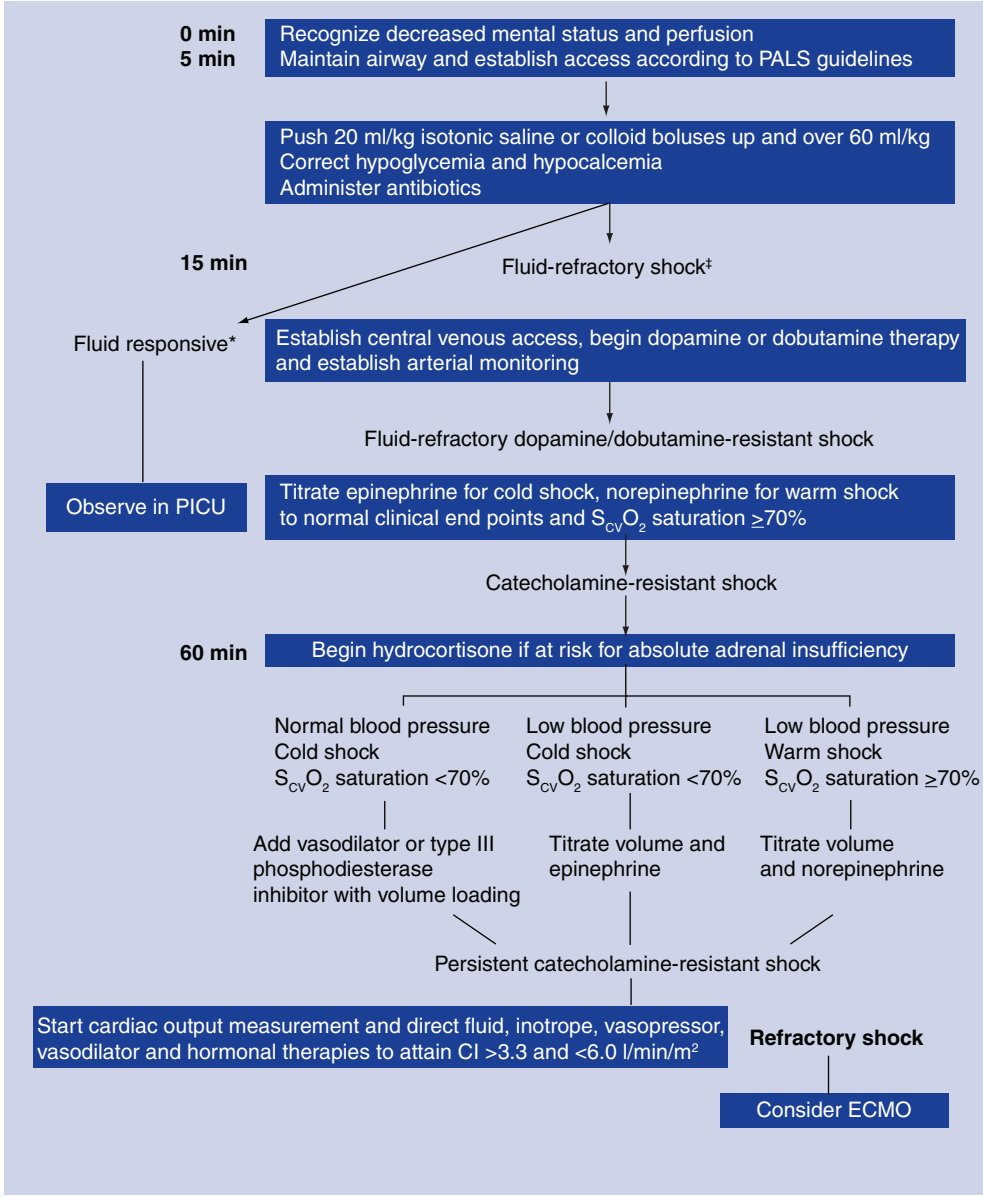
It must be remembered that although lactate could imply reversion to anaerobic metabolism, it can be elevated in the absence of shock, in other conditions such as liver failure, inborn errors of metabolism, diabetes, renal failure, bowel ischemia and thiamine deficiency, and when taking drugs like salicylates. Lactate is most useful in the setting of pre- and post-operative cardiogenic shock states. In these cases, a lactate level of less than 2 mmol/l should be the goal. Anion gap of less than 16 mmol/l should be targeted. Creatinine clearance can be used as a therapeutic marker.

First hour of resuscitation

Airway & breathing

Airway and breathing should be addressed as per Pediatric Advanced Life Support (PALS) guidelines. All children in shock should be provided with 100% oxygen delivered via a non-rebreather mask, and if necessary intubation and mechanical ventilation should be performed. The need for intubation should be based on the clinical evaluation guidelines of PALS and the Neonatal Resuscitation Program (NRP), and not on blood gas analysis or other laboratory results. Since functional residual capacity is smaller in children when compared with adults, early assisted ventilation may be required. Additionally, taking over the breathing earlier can help reduce the oxygen consumption. Generally, increased work of breathing, altered sensorium or hypoventilation or apnea are indications for intubation. The Surviving Sepsis Committee recommends the same lung-protective strategies in children as used in adults with acute respiratory distress syndrome (tidal volume of 6 ml/kg of predicted body weight and a plateau pressure of ≤30 cm of water), but this may need to be altered on an individual basis. Sedation is required along with neuromuscular blockade for intubation of patients in shock. Etomidate and ketamine are sedative hypnotics that are often used for induction for intubation of children with cardiovascu-

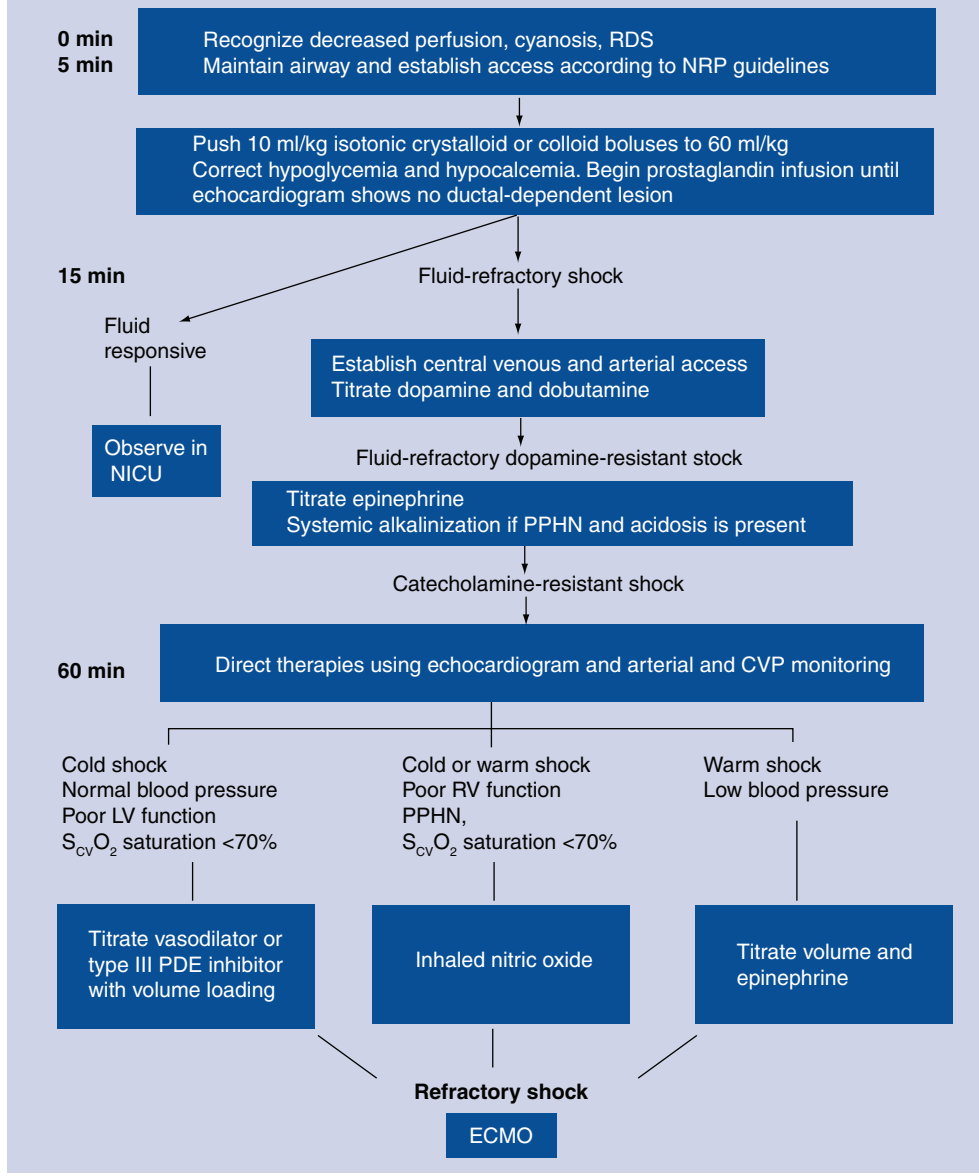
Figure 2. Approach to pediatric shock.



*Normalization of blood pressure and tissue perfusion.
‡Hypotension, abnormal capillary refill or extremity coolness.
CI: Cardiac index; ECMO: Extracorporeal membrane oxygenation; PALS: Pediatric Advanced Life Support; PICU: Pediatric intensive-care unit: $S_{CV}O_2$: Superior vena cava oxygen.
Reproduced with permission from [48].

lar compromise, as both of these drugs cause very little or no change on circulatory parameters. Etomidate is an imidiazole with hypnotic effects that was widely used by emergency physicians for intubations due to it's rapid onset and short duration of action, excellent hemodynamic profile, cerebroprotection with reduction of intracranial pressure and maintenance of cerebral perfusion pressure. However, etomidate inhibits adrenal synthesis of cortisol by blocking 11-β-hydroxylase and hence currently it is not recommended for use in children with septic shock [50]. Ketamine is an inovasopressor that turns off interleukin 6 production and induces endogenous release of norepinephrine by central sympathetic stimulation and inhibition of neuronal catecholamine uptake. The net result in a healthy individual is increased heart rate, blood pressure

Figure 3. Recommendations for stepwise management of hemodynamic support in term newborns.



Recommendations with goals of normal perfusion and perfusion pressure (mean arterial pressure – central venous pressure) and preductal and postductal oxygen saturation difference of less than 5%.
Proceed to next step if shock persists.
CVP: Central venous pressure; ECMO: Extracorporeal membrane oxygenation; LV: Left ventricular; NICU: Neonatal intensive-care unit; NRP: Neonatal resuscitation program; PDE: Phosphodiesterase; PPHN: Pulmonary hypertension of the newborn; RDS: Respiratory distress syndrome; RV: Right ventricular; $S_{CV}O_2$: Superior vena cava oxygen.
Reproduced with permission from [33].

and cardiac output. In experimental studies, ketamine improved survival from septic shock by reversing myocardial suppression and turning off systemic inflammation [2]. Ketamine infusions in adults undergoing cardiac bypass surgery have been shown to decrease inflammation and improve cardiac function [51]. Hence, ketamine can be used as an induction agent during intubation in children with shock. However, a failing myocardium has a decreased ability to contract in response to the ketamine, even in the presence of increased β-adrenergic stimulation. Therefore, in

critically ill patients with a catecholamine depletion, the negative inotropic and vasodilating effects of ketamine may be unmasked, resulting in cardiovascular collapse [52,53].

Propofol is not recommended for long-term sedation due to the association with fatal metabolic acidosis [48]. Atropine may also be added in young children to reduce bronchorrhea and vagus-induced bradycardia during intubation [2].

Volume resuscitation

Early fluid resuscitation is recognized widely as the frontline treatment of septic shock [54–56]. Venous access must be established immediately and if unable to do so, an intraosseous line should be established. The 2008 guidelines call for initial resuscitation to begin with 20 ml/kg of crystalloids over 5–10 min titrated to clinical monitors of CO, such as heart rate, capillary refill, urine output and level of consciousness (level 2C recommendation). They reiterate that since blood pressure is maintained until much later, it is not a reliable end point for assessing adequacy of resuscitation [48].

Carcillo *et al.* demonstrated that rapid fluid resuscitation in excess of 40 ml/kg in the first hour following emergency department presentation was associated with improved survival, decreased occurrence of persistent hypovolemia and no increase in the risk of cadiogenic pulmonary edema. Such rapid boluses seem to restore the volume and reduce inflammation [2]. Some patients may even require higher volumes and up to 200 ml/kg in the first hour. If the liver edge is palpable, if rales are heard in the lungs, or if the perfusion pressure (mean arterial pressure – central venous pressure) is decreased, the administration of more fluids is not advised [12]. Neonates may need more judicious fluid resuscitation, as excess fluids may have deleterious consequences. Boluses should be started in neonates at 10 ml/kg, and then advanced as necessary. Although colloids have been shown to be superior to crystalloids in adults, in a study on children with dengue shock, crystalloids and colloids performed equally well, although a longer time to recovery was seen with lactated ringers [57]. The Cochrane Collaboration found no difference between the different colloid solutions [58]. Shock that persists beyond the first hour of resuscitation should be treated with vasopressors.

Children with cardiogenic shock may be euvolemic, hyper or hypovolemic, and hence it is important that a careful assessment of the fluid status be done both by clinical examination and echocardiogram. Judicious use of fluids (5–10 ml/kg) should be carried out in these children while monitoring the response. However, pharmacological therapy is the mainstay of treatment in these children.

Inotrope therapy

Inotropes, or a combination of inotropes and vasodilators, should be started if there is fluid-refractory shock. The 2008 guidelines recommend dopamine as the first inotrope of choice for as child with shock that is refractory to fluids (grade 2C recommendation) [48,59]. Dose should be started at 5–10 µg/kg/min intravenously. The committee also points out that children with septic shock may have a low CO with high systemic vascular resistance, high CO with low SVR or low CO with low SVR. A child may move, at various stages, from one hemodynamic state to another, and hence vasopressor therapy should be used according to the clinical state [48].

It should be noted that dopamine insensitivity in very young children (less than 6 months) has been documented, and is believed to be due to poor development of the sympathetic vesicles on which the dopamine acts to release norepinephrine [60,61]. Dopamine-resistant shock usually responds to epinephrine (cold shock) or norepinephrine (warm shock) [35]. Children with low CO states and elevated SVR (cool extremities, prolonged capillary refill, decreased urine output, but normal blood pressure after fluids) should be given dobutamine (grade 2C recommendation) [48].

Vasodilators

Vasodilators can reverse shock in children who remain hemodynamically unstable with a high SVR, despite fluids and inotropes. Vasodilators help reduce the pulmonary or systemic vascular resistance in these patients and improve CO. Nitrosovasodilators with a very short half-life, such as nitroprusside or nitroglycerin, are used as first-line therapy in children with epinephrine-resistant low CO and increased SVR shock [59]. Inhaled nitric oxide is a selective pulmonary vasodilator that has been shown to be useful in neonates with persistent pulmonary artery hypertension and sepsis [59]. Prostaglandins are vasodilators that increase cyclic adenosine monophosphate levels, and are helpful in keeping the ductus open in ductal-dependent congenital heart disease.

Inodilators

Phosphodiesterase inhibitors mediate inotropy and vasodilation by inhibition of hydrolysis of cAMP and include milrinone, amrinone and pentoxyfilline. When used alone, they improve contractility and cause systemic and pulmonary vasodilatation. When used in combination with epinephrine, they may help reduce the vasoconstriction seen with epinephrine. Current recommendations are if a child remains in a low CO and high SVR state despite epinephrine and nitrosovasodilator therapy, phosphodiesterase inhibitor should be added [48,59,62]. In one study, pentoxifylline improved outcome in premature babies with sepsis [63]. Hoffman *et al.* compared low- and high-dose milrinone with placebo in preventing development of low cardiac-output syndrome in infants and children after corrective surgery for congenital heart disease. They concluded that high-dose milrinone significantly reduced the development of low cardiac-output syndrome in these children [64].

Vasopressors

Recently there has been a renewed interest in using vasopressin and angiotensin. Angiotensin causes vasoconstriction through the phospholipase C system, but has no inotropic effect. Vasopressin works like angiotensin, but also causes increased cortisol production by causing release of adrenocorticotropic hormone. It has been used in some cases of extreme low SVR, despite norepinephrine use [65]. It can reduce CO in children with poor cardiac function [2]. At this time, the 2008 guidelines do not recommend the use of vasopressin for pediatric sepsis [48].

Steroids

Studies have demonstrated that septic shock is associated with relative adrenal insufficiency or resistance to glucocorticoids. The role of steroids in shock remains controversial. Patients who are at risk for adrenal insufficiency include children with severe septic shock and purpura, chronic use of steroids and children with pituitary or adrenal abnormalities [66,67]. Adrenal insufficiency in pediatric severe sepsis is associated with poor prognosis [66]. A total cortisol level of less than 18 µg/dl is considered to be adrenal insufficiency in a child with catecholamine-resistant septic shock [59]. A post 30- or 60-min ACTH stimulation test increase in cortisol of 9 µg/dl or less has been used to define relative adrenal insufficiency [48]. Markovitz *et al.,* in a large retrospective study, reported that the use of any steroids in children with severe sepsis was associated with increased mortality, and use of steroids was an independent predictor of mortality in a multivariate analysis [68].

The current guidelines suggest that steroid therapy be reserved for children with catecholamine resistance and suspected or proven adrenal insufficiency or those with the above risk factors (grade 2C recommendation). Dose recommendation is 50 mg/m^2/24 h for empirical stress–dose therapy of hydrocortisone [48]. Steroids should not be used in children who do not meet the minimum criteria for adrenal insufficiency [48].

Electrolyte abnormalities

Infants are at risk for hypoglycemia when dependent on intravenous fluids. Untreated hypoglycemia can result in serious neurological outcome, due to already depleted glucose stores. Hence, serum glucose should be monitored, and any hypoglycemia corrected promptly. Infants should be on a maintenance fluid of D10W with 0.45% sodium chloride [59].

Recent studies have reported associations of hyperglycemia and glucose variability with increased length of stay and mortality [69,70]. There are no studies in children about the use of insulin for hyperglycemic states [59]. While a level of glucose of less than 150 mg/dl is preferred, the optimum level of glucose in children is unknown [48].

Calcium levels are frequently low in critically ill children and can worsen myocardial dysfunction. Hence, any hypocalcemia should be corrected promptly. There is no support in the literature for use of bicarbonate to reverse any metabolic acidosis, as this was not associated with improved hemodynamic states.

Antibiotics

Antibiotic choice should be empiric and of a broad spectrum for septic shock. The choice of antibiotic should be based on the organism and sensitivity, the site of infection, host factors and whether the infection is community or hospital acquired. It has been shown that uncontrolled infection is associated with uncontrolled inflammation in septic shock, and of the pediatric deaths studied, 80% had an unrecognized or untreated infection [32]. Hence, it is recommended that an antibiotic or antifungal agent that has the lowest minimum inhibitory concentration should be used. Double coverage should be considered if no antibiotic has a minimum inhibitory concentration of less than 1 [12]. The 2008 surviving sepsis

guidelines recommend that antibiotics be administered within 1 h of the identification of severe sepsis after appropriate cultures have been obtained (grade 1D) [48]. Antibiotics should never be delayed for obtaining cultures.

Protein C & activated protein C

Protein C concentration reaches adult levels only by 3 years of age, and hence young children may be deficient in protein C. Some studies have shown improvement in sepsis-induced coagulation disturbances by using protein C preparations [71,72]. However, these studies were not powered to show effect on mortality rates. One randomized, controlled study of recombinant human activated protein C (rhAPC) in pediatric severe sepsis patients was stopped by recommendation of the Data Monitoring Committee for futility after enrollment of 399 children. Due to the increased risk of bleeding and lack of proof of efficacy, the 2008 guidelines recommend against the use of rhAPC in children (Grade 1B).

Granulocyte macrophage colony-stimulating factor

Studies have shown improved outcomes in neonates with sepsis and neutropenia with use of granulocyte colony-stimulating factor (GCSF) [73]. However, a study by Stephens *et al.* on the use of GCSF in adults with septic shock demonstrated no improvement in outcome [74]. Increased hepatic dysfunction and higher troponin levels were reported in the group that was given the GCSF. A very recent study by Cirioni *et al.* reports that combination of GCSF and LL-37, an antimicrobial peptide, was very effective in protecting neutropenic mice from the onset of sepsis with *Pseudomonas* infection [75].

Blood products

It was recommended that the hemoglobin be maintained above 10 g/dl in children with septic shock and severe sepsis [59]. However, there are no graded recommendations for the use of blood products in critically ill children in the 2008 guidelines for pediatric septic shock [48].

Administration of polyclonal intravenous immunoglobin has been reported to reduce mortality rates in neonates with severe sepsis. A recent study of polyclonal immunoglobins in pediatric patients reported a significant reduction in mortality, length of stay and progression to complications [76]. At this time, the 2008 guidelines recommended that immunoglobins be considered in severe sepsis (grade 2C) [48].

Immunotherapy

Since sepsis is characterized by release of proinflammatory cytokines such as TNF, interleukins and interferon, there has been a lot interest lately in the use of antibodies or antagonists to these mediators. However, reviews have not indicated any benefit or reduction in mortality from the use of these drugs.

Deep-vein thrombosis prophylaxis

Most deep-vein thromboses (DVTs) in children are secondary to central venous catheters. DVT occurs in approximately 25% of children with femoral vein catheters. Pierce *et al.* reported that heparin-bonded catheters may decrease the incidence of DVT [77]. However, at this time there are no data on the efficacy of low-molecular-weight heparin prophylaxis for preventing DVT occurrence [48].

The new guidelines call for use of DVT prophylaxis in postpubertal children with severe sepsis (grade 2C) [48].

Stress ulcer prophylaxis

The incidence of clinically important gastrointestinal bleeding and the risk of coagulopathy and mechanical ventilation to cause gastrointestinal bleeding are similar in children and adults [78]. Although stress ulcer prophylaxis with H2 blockers is commonly used in intensive care units, the efficacy is unknown. Hence, there are no graded recommendations regarding this in the 2008 guidelines [48].

Renal replacement therapy

Continous veno–venous hemofiltration (CVVH) may be useful in children with anuria and fluid overload [48]. Foland *et al.* reported that less fluid overload before CVVH improved survival in children with multiple organ dysfunction, thus indicating that CVVH should be instituted before significant fluid overload occurs [79]. However, there have been no large controlled studies comparing CVVH with intermittent dialysis. Hence, at this time, there are no graded recommendations in the new guidelines regarding this.

Extracorporeal membrane oxygenation

The impact of extracorporeal membrane oxygenation (ECMO) on children with septic shock is not very clear. In a small study of 12 children with meningococcemia on ECMO, Goldman *et al.* reported survival and complete neurological recovery in eight of them [80]. The current

recommendations advise the use of ECMO only in children with refractory septic shock and/or respiratory failure that can not be supported by conventional means (grade 2C) [48].

Therapeutic end points

Therapeutic end points for treatment of shock should be capillary refill of more than 2 s, normal pulses with no differential between peripheral and central pulses, normal heart rate, warm limbs, urine output of more than 1 ml/kg/h and normal mental status (grade 2C) [48].

Other parameters used in adults that may be applicable in children include: improved base deficit, decreased lactate and superior vena cava oxygen saturation ($S_{CV}O_2$) of more than 70% or $S_{CV}O_2$ of 65% or more and central venous pressure of 8–12 mmHg [48,58]. A recent study by de Oliveira *et al.*, in which children and adolescents with severe sepsis or fluid-refractory septic shock were randomly assigned to receive American College of Critical Care Medicine/PALS-guided resuscitation with or without $S_{CV}O_2$ goal-directed therapy, showed that the $S_{CV}O_2$-directed therapy had lesser mortality and improved outcome [81]. In children with cardiogenic shock, arterial venous oxygen content difference is a better marker than mixed venous hemoglobin saturation. If a pulmonary artery catheter has been inserted, therapeutic end points are a cardiac index of more than 3.3 and less than 6.0 l/min/m^2, with a normal coronary perfusion pressure (MAP minus CVP) for age [59]. Blood pressure by itself is not reliable as an end point to resuscitation.

In the initial stages of management, the treatment of hypovolemic shock is not different from any other kind of shock. However, the management of hypo- or hyper-natremic dehydration after the initial stabilization requires attention to the specific type of deficit.

Future perspective

The optimum treatment of shock and septic shock is a dynamic and evolving process. At this time, early-goal therapy has become the front line of management of shock. We believe the future holds promise particularly in early diagnostic and prognostic markers such as procalcitonin. Recent studies in children with septic shock with endotoxin-neutralizing therapies reported reduction in mortality with recombinant human bactericidal proteolytic increasing factor and HA-1A antibody. A multicenter trial with use of recombinant human bactericidal proteolytic increasing factor may bring favorable results and remains to be seen. Terlipressin, a long acting vasopressin analog, stimulates vascular V1a receptors, resulting in vasoconstriction. A recent study reported improved hemodynamic indices and renal function in critically ill children [82]. However, larger studies are needed to assess the safety profile of this drug in children.

Recently, there has been an interest in gene-expression studies of septic shock. Translational genome-level studies are currently being conducted in pediatric septic shock [83,84]. These studies have provided a list of potential biomarkers associated with poor outcome in septic shock. Initial results have shown downregulation of large numbers of genes, especially those that involve zinc homeostasis and T-lymphocyte function. The future may involve studies into these two new areas, namely zinc homeostasis and lymphocyte dysfunction [85].

Executive summary

Definition

- Shock is defined as an acute syndrome where the circulatory system is unable to provide adequate nutrients to meet the metabolic demands.

Classification

- Based on etiology, shock is classified into hypovolemic, septic, cardiogenic and distributive types.

Pathophysiology

- Shock results from a lack of oxygen delivery, lack of glucose delivery or mitochondrial dysfunction, and the end result is tissue ischemia.
- Uncontrolled inflammation, thrombosis and persistent infection occurs.
- The majority of children with septic shock present with low cardiac output and high systemic vascular resistance states.

Epidemiology of septic shock

- Although the mortality from sepsis and septic shock has decreased, the severity of sepsis has increased recently.
- Septic shock is commonly seen in low-birth-weight infants.
- *Staphylococcus* is currently the most common infection associated with sepsis, followed by fungal infections in children.

Executive summary

Defintions of SIRS, sepsis, severe sepsis, septic shock & multi-organ dysfunction

- The original definitions were revised for children to accommodate their special physiological features.
- Systemic inflammatory response syndrome (SIRS): defined by the presence of two of the following four criteria, one of which must be temperature or leukocyte abnormalities:
  – Temperature of more than 38.5°C or less than 36°C
  – Heart rate 2 SD above or less than the 10th percentile for the age
  – Mean respiratory rate of more than 2 SD for age
  – Elevated leukocyte count or more than 10% immature neutrophils.
- Sepsis: SIRS plus the presence of, or suspected, infection.
- Severe sepsis: sepsis plus one of the following: cardiovascular dysfunction or acute respiratory distress syndrome or two other organ dysfunctions.
- Septic shock: criteria include infection with hypo- or hyper-thermia, altered mental status and tachycardia with one of the following: decreased pulses, prolonged capillary refill or flash refill, cool mottled extremities or decreased urine output. Hypotension is not required for the diagnosis.
- Multiple organ dysfunction: failure of more than one organ.
- Mortality increases with increasing number of organ failures.

Management

- Every hour of prolonged capillary refill of more than 2 s or hypotension increases mortality by an odds ratio of 2.
- Early fluid resuscitation is the front-line of therapy for septic shock.
- Use of >40 ml/kg in the first hour in the emergency department in septic shock results in increased survival.
- In early oxygen therapy, ketamine is used for sedation for intubations.
- Etomidate should be avoided in septic shock due to risk of adrenal suppression.
- Dopamine is the first drug of choice for fluid-resistant septic shock.
- Dopamine-resistant shock may respond to epinephrine or norepinephrine.
- Vasodilators are used in epinephrine-resistant, low cardiac output, increased systemic vascular resistance shock.
- Inhaled nitric oxide has been shown to be useful in neonates with pulmonary hypertension and shock.
- The role of steroids in septic shock is controversial, and primarily reserved for catecholamine-resistant and suspected or proven adrenal-insufficiency states.
- Hypoglycemia and hypocalcemia should be corrected.
- Antibiotics with the lowest minimum inhibitory concentration should be used in septic shock and should be administered within 1 h of presentation.
- Immunoglobulins may be considered in severe sepsis.
- Deep-vein thrombosis prophylaxis are indicated in older children with severe sepsis.
- There are no graded recommendations in the 2008 guidelines for renal replacement, blood and stress ulcer prophylaxis.
- Recombinant activated protein C is not recommended in children due to increased risk of bleeding.

Future perspective

- Future multicenter studies on immunotherapy and terlipressin (a long-acting vasopressin) may help establish efficacy and safety.
- A randomized trial of bactericidal permeability-increasing protein in children is being planned.
- There has been recent interest in gene-expression studies of septic shock.
- Preliminary studies reveal downregulation of genes involving zinc homeostasis and lymphocyte function, and future studies may involve these two areas.

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