

Shock in children

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Abstract: Shock, a major cause of morbidity and mortality in children, is the the most anxiety-provoking emergency that needs to be addressed urgently and effectively by the attending paediatrician. It is a state where the metabolic demands of the tissue are not met due to circulatory dysfunction. Unlike adults, hypotension is a very late feature of shock in children. As the child's condition worsens, the clinical presentation of the different causes of shock become similar, and nullify any aetiological differences. Regardless of the type of shock, the final common pathway is inadequate tissue perfusion and oxygen supply to meet cellular demands. Delayed recognition and treatment result in progression from compensated reversible shock to uncompensated irreversible shock with widespread multiple system organ failure to death. This paper reviews the physiological basis, and pathophysiological classification of the various types of shock and their respective aetiologies. The clinical features of the different types of shock are described, and current diagnostic and therapeutic strategies are applied for the most effective and appropriate treatment for resuscitating the child in shock. A strong index of suspicion, early recognition, timely intervention and transfer to an intensive care unit are critical for successful outcomes in the management of paediatric shock.

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Epidemiology of shock

WHO determined during the years 2000–03, that six causes account for 73% of the 10.6 million yearly deaths in children younger than age 5 years. These are pneumonia (19%), diarrhoea (18%), malaria (8%), neonatal pneumonia or sepsis (10%), preterm delivery (10%), and asphyxia at birth (8%). These four listed communicable diseases accounted for more than half (54%) of all child deaths.¹ There is limited data on the incidence of shock in the general paediatric population;

most of the data is from paediatric intensive care units rather than the emergency departments. During a dengue epidemic in Thailand, the incidence of haemorrhagic shock syndrome was determined in children 15 years of age or less in the municipal area of Rayong, and its contiguous suburban villages. From 3,185 children randomly sampled in schools and households, 7 per 1000 developed dengue shock syndrome.² In a study from the United States, the national age adjusted annual incidence of paediatric sepsis in children admitted to hospitals in 7 states was 0.56 cases per 1000 children per year. It was highest among infants, particularly low and very low birth weight babies.³ The mortality rate was 10.3% from severe sepsis; half were in patients with chronic comorbidity.⁴ Multiple organ failure was found to occur early and simultaneously in critically ill children, and was associated with high mortality.⁵ An observational study of all emergency department (ED) patients with shock (excluding trauma) at University Medical Center, University of Nevada School of Medicine, between 1998 and 2006, identified 147 cases of shock. Septic shock accounted for 57%, hypovolemic shock due to gastroenteritis, metabolic disease, surgical emergencies, or haemorrhage for 24%, distributive shock for 14%, and cardiogenic shock for 5% of cases respectively. Clinical signs of shock developed in the ED after initially presenting without clinical signs of shock in 14% of study subjects. Mortality was 6% overall and 5% in septic shock patients.⁶ In the earlier 2 studies,^{3,4} gram-negative septic shock comprised 50% of total cases of culture-proven bacterial sepsis. Although gram-negative sepsis causes most of the deaths due to sepsis, there has been an increase in cases of gram-positive septic shock attributed to increased use of intravascular devices. Other factors contributing to the increase in sepsis are widespread use of corticosteroids, immunosuppressive agents, inflammatory diseases, patients living longer lives, surgical prostheses, home ventilator devices, percutaneous intravenous catheters and indiscriminate use of antibiotics.⁷

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Pathophysiology of shock

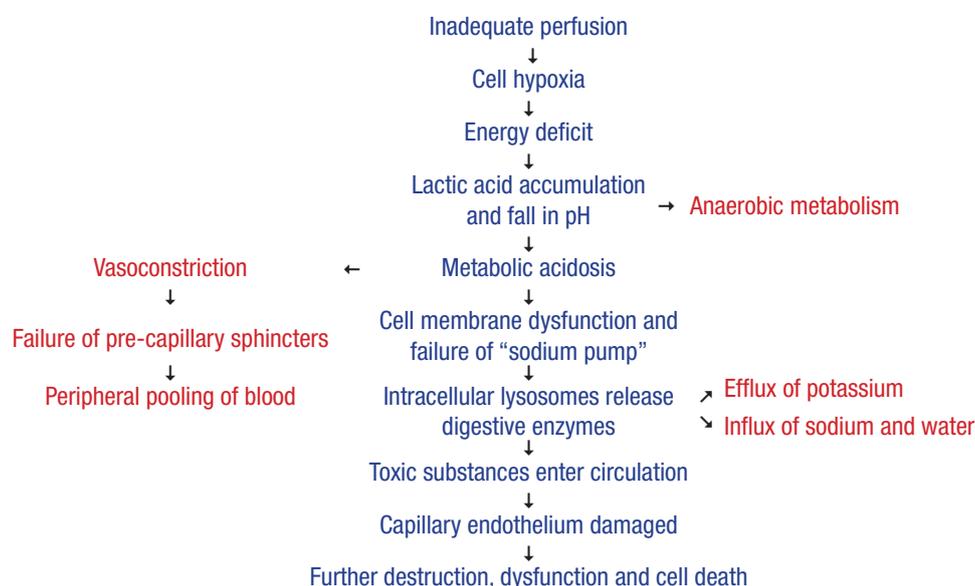
Definition of shock can be based either on the clinical presentation or at the cellular level. At the cellular level, shock is defined as a state of inadequate substrate for aerobic cellular respiration; the cardiopulmonary system is unable to supply the mitochondria with adequate glucose and oxygen for the manufacture of ATP (adenosine triphosphate) that is essential to energize the metabolic demands of the body. As oxygen delivery is normally dependent on the oxygen carrying capacity of the blood and the cardiac output, both the heart rate and stroke volume need to increase to maximize supply. When oxygen delivery fails, energy production switches to anaerobic metabolism that is 18-fold less efficient in terms of energy production compared to aerobic metabolism, and this results in the production of pyruvate that is converted to lactate with ensuing metabolic acidosis. Measures that would be helpful at this stage are rapid infusion of isotonic fluids to establish an adequate circulation, 100% inspired oxygen, and transfusion of packed red cells, if necessary, to ensure an adequate hematocrit level.

When the substrate deficit persists, the integrity of the cells becomes compromised, and the normal ionic

gradient across cell membranes is lost, with shift of fluid to the intracellular compartment. Cell death and organ dysfunction occur consequent to the cellular edema and energy deficit. Damage to the endothelial cells and vasculature results in release of cytokines and immune-modulators that leads to systemic inflammatory response syndrome in response to various insults, with hypothermia, tachycardia, tachypnea and abnormalities in white blood cell counts. The microcirculation becomes severely damaged compromising substrate delivery further; finally, multiple organ system failure results.⁷ The different types of shock end up in a final common pathway, of tissue hypoxemia and energy uncoupling that ultimately leads to death at the cellular level in the form of apoptosis and necrosis that, then, leads to organ dysfunction and ultimately the patient's demise.^{8,9}

Shock is a dynamic process that progresses if not recognized and treated timely; as the stage of shock advances so does mortality, with rates 10 fold higher in severe compared to early shock.¹⁰

Figure 1: Effects of inadequate tissue perfusion



Source: [http://en.wikipedia.org/wiki/Shock_\(circulatory\)](http://en.wikipedia.org/wiki/Shock_(circulatory)) accessed on 22 December 2011.

Types of shock

The tissues are supplied by a distribution network of blood vessels, primed with blood (intravascular compartment) that is pumped by the heart through its distribution network to the tissues. Delivery of adequate amounts of oxygen and substrate to the tissues is dependent upon a number of processes; failure at any one of these can result in shock. Based on the aetiology of the derangements that occur, there are five major types of shock:

Hypovolemic-shock

Loss of intravascular blood volume causing hypovolemic shock is by far the most common type of shock seen in children. This commonly results from severe dehydration with acute gastroenteritis, dengue shock syndrome, renal loss in diabetes mellitus, and blood loss from haemorrhage and sepsis. In sepsis, there is relative hypovolemia caused by disruption of capillary wall integrity, and leaking of fluid out from the intravascular compartment, resulting in 'third space' loss. The stages of hypovolemic shock, its mechanism, clinical features, and intervention are summarized in Tables 1 & 2, and Figure 2.

Cardiogenic shock

Cardiac shock is characterized by failure of the heart (pump) resulting in global hypoperfusion. Impaired contractility leads to decreased stroke volume (SV) and cardiac output (CO) resulting in decreased oxygen delivery (DO₂). The most common cause is congenital heart disease; others include myocarditis, arrhythmias, cardiomyopathies, toxins or poisons. Cardiogenic shock also presents in association with septic and poorly managed hypovolemic shock.

Clinical features of cardiogenic shock include;

- Hypotension
- Decreased urine output
- Altered mental status
- Rales
- Gallop rhythm
- Hepatomegaly

Successful outcome depends on recognizing the cause of the shock – whether it is purely cardiogenic or a complication of septic or hypovolemic shock, and managing accordingly. Needless to say, even pure cardiogenic shock may need adequate preload fluid therapy, administered judiciously with central venous pressure (CVP) monitoring, to achieve satisfactory response. Cardiogenic shock with adequate intravascular fluid should respond well to inotropes that improve contractility.

In severe form of cardiogenic shock, a vasodilator maybe needed to improve the afterload and SV. The reduction in afterload (by the vasodilator) may cause a drop in preload, necessitating more fluid therapy. The reduction in afterload, though it favourably improves SV, can cause a significant drop in aortic pressures that may impair coronary perfusion that is vitally required to supply adequate blood to the myocardium. Fluid therapy, inotropes (dobutamine, epinephrine), vasodilators and inodilators used appropriately will improve outcome, but should fluid overload develop, fluids should be stopped and inotropes started early. Dopamine is indicated when blood pressure is low, and dobutamine when the blood pressure is normal or high. In the event of resistance to dopamine/dobutamine, afterload reducing agents (vasodilators) can be used. Correction of acidosis, hypoglycaemia, hypocalcaemia etc. helps improve myocardial contractility.

Distributive shock

This form of shock is seen in anaphylaxis, neurological injury (spinal shock), sepsis, and following administration of certain group of drugs (vasodilators in excess). The mechanism involved is not an absolute loss of intravascular volume, but inappropriate vasodilatation, endothelial dysfunction with capillary leak, and loss of vascular tone, or a combination of all three factors. In septic shock and anaphylaxis, the leakage of intravascular fluid into the interstitial space and vasodilation causing increase in intravascular capacity

aggravate the hypovolemic status, thus “reducing the preload”. Shock occurs because of maldistribution of the intravascular fluid volume resulting in interruption of DO₂.

Septic shock

Systemic inflammatory response syndrome (SIRS) is characterized by tachycardia, tachypnoea and hyperthermia (or hypothermia) or high leukocyte count. If SIRS is identified and reversed early, the subsequent inflammatory cascade can often be avoided. However, if the damage is too extensive and the host immune response is too great, this can result in increased cardiac output, peripheral vasodilation, increased tissue oxygen consumption, and a hyper-metabolic state (i.e., warm shock).¹¹ Sepsis is defined as SIRS in the presence of suspected or proven infection; and severe sepsis as sepsis with accompanying organ dysfunction (respiratory, cardiovascular, haematological, neurological, renal, and hepatic). Septic shock is defined as cardiovascular failure occurring in the setting of severe sepsis.¹²

While the classic picture of septic shock in adults is one of high CO and low systemic vascular resistance (SVR) (warm shock), in children two forms of septic shock manifest: 20% occur as (early) warm shock with high CO/low SVR, and 80% as (late) cold shock with low CO/high SVR.¹³ Sepsis-induced myocardial dysfunction is more common in children, suggesting that early inotropic support would be more beneficial for them than adults. Efforts should be aimed at improving CO and oxygen delivery early.¹⁴ Septic shock includes features of all 3 types of shock: hypovolemic, cardiogenic and distributive shock.

Obstructive shock

In this form of shock, there is either obstruction to outflow of blood, as in, obstructive congenital heart disease like coarctation of aorta; acquired heart disease like hypertrophic cardiomyopathy, or impedence to venous return, as in, tension pneumothorax or cardiac

tamponade. The resultant reduced cardiac output state acts along the common pathway of other forms of shock affecting the perfusion of tissues and DO₂.

Stages of shock

Early or compensated shock

In early shock with impending hypoperfusion, the compensatory mechanism in the sympathetic nervous system is activated through the release of catecholamines from the adrenals with resultant increase in heart rate and (SVR). Stimulation of the renin-angiotensin-aldosterone system causes vasoconstriction, and maintenance of SVR and fluid retention through concentration of urine. Children are able to maintain their vascular tone and blood pressure in low flow states of septic and cardiogenic shock until their shock is profound because of their remarkable compensatory vasoconstriction mechanism. The blood is shunted from the non-vital organs to the brain, heart and lungs, leaving the extremities cold and mottled, and capillary refill prolonged. Blood flow to vital organs i.e. heart and brain is maintained at the expense of non-essential organs. Hypotension should be considered a late sign in children that becomes evident at stage 3 shock (see Table 1 and References 15, 16). Children are dependent on tachycardia to increase cardiac output, as they are unable to increase contractility of the heart in response to catecholamine stimulation, as their myocardium is lacking in both muscle mass and “stiffness” compared to adults.¹⁷ They depend on intravascular volume (preload) to maintain cardiac output since after load is already increased to maintain SVR and blood pressure (BP) when compensatory mechanisms are activated. Untreated, the compensatory mechanism will fail and uncompensated shock will result. Maintaining an adequate intravascular volume is the key to successful resuscitation in children.¹⁸

Uncompensated shock

This occurs when compensatory mechanisms fail

to maintain blood pressure, and meet the metabolic demands of the tissues. Hypoperfusion leads to tissue hypoxemia and ischemia, triggering anaerobic metabolism with pyruvate being converted to lactic acid by the enzyme lactate dehydrogenase (LDH) resulting in metabolic acidosis. Vasoactive metabolites such as adenosine, nitric oxide accumulate locally, and capillary blood flow becomes sluggish. The capillaries become leaky, plasma flows out from the vascular compartment, white cells marginate, and hemostasis becomes deranged, leading to microvascular thrombosis. Multi-organ hypoperfusion leads to clinical shock with hypotension, rapid shallow breathing, altered mental status, absent urine output, and mottled extremities.

Irreversible (refractory) shock

If hypoperfusion of the organs and tissues persists, patient will progress into irreversible shock – the point of no return – that is associated with failure of vital organs and inability to recover irrespective of intervention. With brain damage and cell death, death

will be imminent. Most of the cellular ATP would have been degraded into adenosine that leaks out into the extracellular fluid, further aggravating capillary vasodilatation, and is then transformed into uric acid. As the cells can only regenerate adenosine at 2% of the cell's total need per hour, administration of oxygen would be futile at this point as there is no adenosine to phosphorylate into ATP.¹⁹

Shock versus dehydration

Shock refers to an acute reduction in the circulating blood volume with the fluid loss mainly from the intravascular compartment. Eventually this deficit is shared by the other compartments in a bid to maintain the physiologic fluid equilibrium in the body. In dehydration, however, the fluid loss is more gradual, prolonged, and shared by all fluid compartments. Electrolyte disturbance that commonly presents with dehydration, and that can lead to shock if prolonged or severe, is unusual in early shock.

Table 1: Stages of hypovolemic shock^{13,14}

Stage	% blood volume loss	BP	Capillary refill	Clinical features
1	Up to 15	Maintained	Normal	Normal mental state, respiratory rate, UO
2	15-25	Systolic maintained, diastolic increased, pulse pressure decreased	Delayed	Anxious sweaty, increased HR, RR. Reduced UO
3	25-40	Systolic falls	Delayed	Tachycardia, tachypnea, altered mental state, sweating, cool pale skin, reduced UO
4	>40	Systolic significantly decreased	Absent	Marked tachycardia, tachypnea, weak pulse, sweaty cool, pale skin, decreased consciousness – coma, negligible UO

BP: blood pressure; HR: heart rate; RR respiratory rate; UO: urine output

Figure 2: Stages of shock, pulse, blood pressure, serum bicarbonate and lactic acid levels.

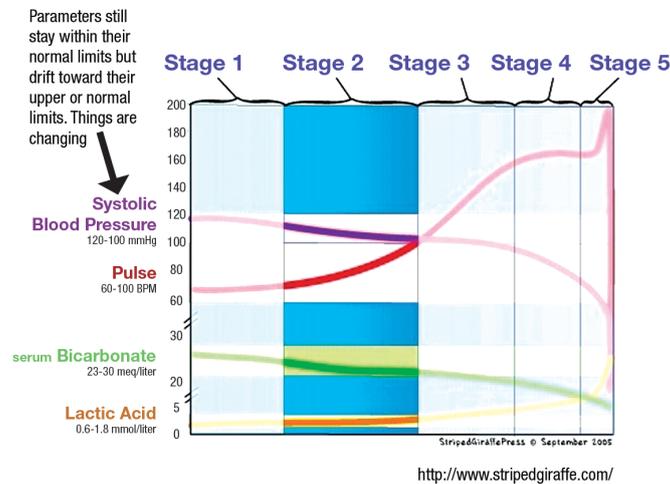


Table 2: Types of paediatric shock, mechanism, clinical features, and intervention

Type of shock	Mechanism	Clinical features	Intervention
Hypovolemic (absolute or relative depletion of blood volume)	CO: decreased, SVR: increased	Tachycardia, weak pulse, sunken eyes/ fontanel, oliguria, capillary refill prolonged.	Oxygen. Immediate venous access. Arrest haemorrhage or fluid loss in burns by cling-film. Crystalloid bolus 20 ml/kg over 20 min.; reassess & repeat 2X if indicated. Blood products for haemorrhagic shock. Assess CVP to avoid over-transfusion & pulmonary oedema.
Cardiogenic	CO: decreased SVR: increased	Arrhythmia, often tachycardia, weak or absent pulse, hepatomegaly, raised JVP.	Dopamine, dobutamine, epinephrine, milrinone. May give small fluid boluses 5-10 ml/kg under close monitoring. Urgent ECHO assessment.
Distributive Anaphylactic Neurogenic	CO increased, then decreased SVR greatly decreased CO normal, SVR decreased	Angioedema, respiratory distress due to narrowing of airways, stridor, wheezing, early hypotension, weak rapid pulse.	Adrenergic & fluid support, supra-therapeutic doses of inotropes if required. Support SVR with vasopressors, phenylephrine.
Septic Warm shock	CO normal SVR decreased	Warm extremities, tachycardia, bounding pulse, wide pulse pressure, hypotension, hyperpnoea, altered senses.	Crystalloid bolus 20 ml/kg, repeat till stable. Consider albumin bolus. Drugs: dopamine or norepinephrine/adrenaline
Cold shock	CO decreased SVR increased	Cold extremities, tachycardia, poor peripheral perfusion, diminished pulses, hyperpnoea, altered senses.	Stabilise with crystalloid as above. Consider early dopamine/epinephrine under ECHO guidance.
Obstructive	Preload decreased CO decreased SVR normal/raised	Tachycardia, hypotension, distended JVP, tracheal deviation if pneumothorax present, pulsus paradoxus in case of tamponade.	Rapidly fatal if underlying process not recognized. Give fluid boluses while preparing for emergent drainage.

CO: cardiac output, SVR: systemic venous resistance, JVP: jugular venous pressure; ECHO: echocardiography

(Adapted from Arkin AA, Citak A. Pediatric shock. Signa Vitae 2008; 3(1): 13-23.)¹⁴

Table 3: Drugs used for treating shock

Drug	Receptor	Mode of action				Dosage mcg/kg/min
		Chronotropy	Inotropy	Vasodilatation	Vasoconstriction	
Dopamine	Dopamine, B, alpha	+	+		+	3-20
Dobutamine	B	+	+	+		5-20
Ephedrine	B, alpha	+	+	+	+	0.05-0.2
Adrenaline	B alpha,	+	+	+ (low doses)	+	0.05-0.3
Norephedrine	Alpha, B	+	+		+	0.01-2
Milrinone	PDE inhibitor	(lusitropy)	+	+		0.25-4
Nitroprusside	NO donor, smooth muscle relaxation			+		0.5-10
Vasopressin	VI vascular receptors				+	0.3-4 mU/kg/min

Management strategies

Goal-directed therapy, with clinical, hemodynamic, and biochemical status monitoring serving as a guide, appears to be more effective in the management of patients with shock.²⁰ Depending on the type of shock, fluids, blood, inotropes, vasodilators, inodilators, vasopressors, corticosteroids and insulin for glycemic control are used as outlined in Tables 2 and 3 above.

Other adjunctive therapies that are used in septic shock include the following:

1. Inhaled nitric oxide, ECMO (extracorporeal membrane oxygenation), corticosteroids, IV immunoglobulins may be needed.¹¹
2. Pentoxifylline, a phosphodiesterase inhibitor that modulates inflammation may improve outcome when used along with antibiotics especially in late onset sepsis.²¹
3. Terlipressin (TP) is a synthetic analogue of vasopressin (AVP) with a similar pharmacodynamic profile, but with a significantly longer half-life. It has shown promise in some case reports of adult patients in refractory shock²² but not in children.
4. Activated Protein C (aPC) is not recommended in children, unlike in adult sepsis, as there has been no significant statistical proof of improved outcome in sepsis.²³
5. Newer agents such as milrinone, a phosphodiesterase inhibitor have shown some benefit in low CO states as has levosimendan, a calcium sensitiser (experimental sepsis).²³

In summary, fluid therapy given timely and adequately, towards the goal of improving stroke volume, improves the outcome of resuscitation. The clinical targets of improved stroke volume would be: normal heart

rate, capillary refill of less than 2s, good peripheral pulses, blood pressure, correction of haemoglobin and superior vena cava saturation of > 70%. Patients who do not respond to fluid therapy, perhaps due to myocardial suppression, tend to benefit from inotropes. Consideration must be given to adrenal insufficiency, when necessary, and treated with IV hydrocortisone.¹⁹ In paediatric patients, fluid therapy is very important as the initial management of shock; good outcomes can be expected if this is initiated early.

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