

Shock in the neonate

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Abstract: Shock is a clinical challenge to neonatal intensivists and pediatricians alike. It occurs in critically ill babies for many reasons, but the main cause is sepsis that kills more than a million newborn globally every year.¹ This article is designed to help young doctors and trainees have a better understanding of shock in the neonatal period and its management. The paper reviews the basic pathophysiology, risk factors, clinical investigation, management, supportive care, and complications in the common types of shock seen in neonates. Treatment is governed largely by the underlying cause, with the ultimate goal of achieving adequate tissue perfusion with delivery of oxygen and substrates to the cells, and removal of toxic metabolic waste products. Intervention needs to be anticipatory and urgent to prevent progression to uncompensated and irreversible shock respectively. Early recognition and urgent effective management are crucial to successful outcomes.

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The attack rate for neonatal sepsis is variable (from <1% to >35% of live births) based on gestational age and time of onset (early<72 hours after birth) or late (>72 hours after birth).² Neonates with sepsis may present with or progress to septic shock, exemplified initially by cardiovascular dysfunction requiring fluid resuscitation or inotropic support.³ If the progression of infection cannot be stopped, end organ damage and death will ensue. While the true incidence is not known, a recent retrospective cohort study of 3800 neonates admitted to the NICU over a 6 year period reported septic shock in 1.3% with an associated mortality peaking at 71% for extremely low birth weight (ELBW) neonates <1000g⁷. There are few published data regarding the pathophysiology of septic shock in neonates.

Shock is a complex clinical syndrome characterized by acute failure of the circulatory system to maintain adequate tissue and organ perfusion. This leads to inadequate oxygen and nutrient substrate delivery to body tissues and compromised metabolic waste product removal. This results in cellular dysfunction that may eventually lead to cell death, organ failure and death of the entire organism itself.

Adequate tissue perfusion requires a combination of three major factors: (1) cardiac output; (2) integrity and maintenance of vasomotor tone of local arterial, venous, and capillary vascular beds, and (3) the ability of the blood to deliver oxygen and metabolic substrates, and remove metabolic wastes.

Cardiac output is the product of heart rate and stroke volume. In the neonate, cardiac output is more dependent on heart rate than stroke volume. Very rapid heart rates >180 beats per minute (bpm) and slow heart rates of <80 bpm are likely to compromise cardiac output if prolonged. However, not all infants with subnormal heart rates have impaired perfusion. At high rates, ventricular filling time and end-diastolic volume become compromised and myocardial oxygen consumption is increased. Because myocardial perfusion occurs during diastole, further acceleration in the heart rate may cause undesirable cardiac ischemia, leading to ventricular dysfunction.⁴ The other major determinant of cardiac output is stroke volume that is influenced by preload, afterload, and myocardial contractility.

Preload – correlates to the myocardial end-diastolic fiber length that is determined by the volume of blood filling the ventricles during diastole. Increase in preload increases stroke volume up to a peak value, beyond which stroke volume falls in accordance to Starling's law.

Afterload – is the force generated by the myocardium during ejection against systemic and pulmonary vascular resistance. Reduction in afterload will increase stroke volume, provided other variables remain constant.

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Contractility – is a semi-quantitative method of measuring ventricular function. An increase in contractility will increase the stroke volume provided preload and afterload remain unchanged. The main determinant is the percentage fractional shortening, which depends on the ventricular end-diastolic and end-systolic diameter.

Clinically significant alterations in preload, afterload and contractility may be achieved by vasoactive pharmacologic agents, inotropic agents, changes in blood volume, or a combination of these methods. Blood flow to tissues and organs is determined by their vascular beds that are under central and local auto vaso-regulation control. This enables the different organs to maintain internal blood flow despite wide arterial blood pressure fluctuations. When auto-regulation is lost, blood flow becomes pressure passive, with ischemic or hemorrhagic consequences. The biochemical mediators of vasomotor tone are different for each vascular bed, and their complex interactions are not well understood.

The ability of the blood to deliver oxygen and nutrients and remove metabolic excretory products relies mainly on adequate lung ventilation, oxygen-carrying capacity, tissue perfusion and oxygen extraction by the cells. Although each gram of hemoglobin binds 1.36mL of oxygen, fetal hemoglobin (HbF) binds oxygen more tightly than adult hemoglobin, but has a relatively reduced oxygen-unloading capacity at the tissue level. This leads to a shift of the oxygen-hemoglobin dissociation curve to the left. Other factors

that promote this shift are hypothermia and hypocarbia. Under these conditions, oxygen extraction by tissues may be decreased despite adequate delivery of oxygen.

The mean blood pressure, rather than systolic pressure is used to determine the normal blood pressure from an indwelling arterial line as it is more likely to be free of artifacts such as resonance, thrombi, and air bubbles. The lower limits of the mean blood pressure during the first day of life are numerically the same as the gestational age of the infant. Most prematures achieve a mean blood pressure of 30 mm Hg or greater by the third day of life. The presence of fetal shunts such as patent ductus arteriosus (PDA) and patent foramen ovale (PFO) further influence the systemic and pulmonary blood flow in premature babies. Large shunts can cause volume overloading of the left heart (PDA) and lead to cardiac failure and other complications like hypotension. Shock unresponsive to inotropes in the first few days of life in preterm babies can be caused by a large PDA. Estimations of blood pressure (mean and systolic) have poor correlation with cardiac output in babies with a PDA.³

Oxygen delivery to the tissue is influenced by cardiac output and blood flow more than blood pressure. Systolic, diastolic and mean arterial blood pressure readings that are usually considered abnormal may not necessarily be pathological. Likewise, hypotension is not synonymous with shock but is a feature that is emergent in the later stages of shock.

Determinants of cardiac function and oxygen delivery to tissues are shown in the algorithm (Figure 1) below:

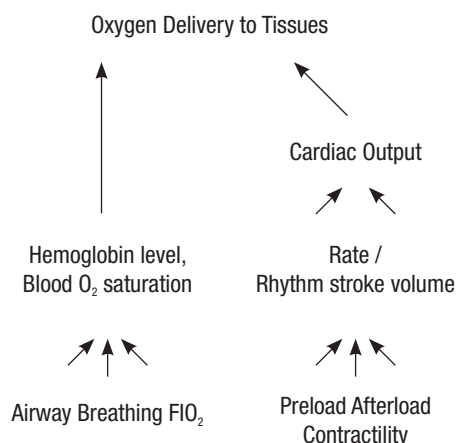


Figure1: Determinants of cardiac function and oxygen delivery to tissues. Adapted from Strange GR. APLS: The Pediatric Emergency Medicine Course. 3rd ed. Elk Grove Village, Ill: American Academy of Pediatrics; 1998:34.

1. Types of shock

The main types of neonatal shock and their causes are:

- Hypovolemic shock caused by acute blood or fluid and electrolyte loss.
- Cardiogenic shock caused by cardiomyopathy, myocardial ischemia, arrhythmias, and heart failure.
- Distributive shock caused by sepsis, vasodilation, myocardial depression, or endothelial injury.
- Obstructive shock from tension pneumothorax or cardiac tamponade
- Dissociative shock from severe anemia or methemoglobinemia

Hypovolemic shock

Hypovolemic shock is usually due to:

- antenatal haemorrhage (spotting during the third trimester, placenta previa, abruptio placenta, foeto-maternal transfusion, twin-to-twin transfusion, birth injuries, birth asphyxia or rupture of umbilical vessels, spleen or liver)
- post-natal blood loss - iatrogenic, or secondary to disseminated intravascular coagulation or vitamin K deficiency, or
- fluid and electrolyte loss in newborn secondary to gastrointestinal abnormalities, vomiting, diarrhea or heat stress .

The clinical signs of shock vary with the severity of intravascular volume depletion that ranges from 25% in compensated shock, to 25-40% in uncompensated shock, and 40% or more in irreversible shock. The normal blood volume in different age groups is shown in Table 1.

Table 1: Normal Blood Volume in Different Age Groups

Age Group	Blood Volume in ml/kg body weight
Preterm Infant	90 to 105
Newborn	83.3
6 months	86
1 year	80
6 years	80

(Geigy Scientific Tables, 7th Ed; 1971)

Although the circulating blood volume is relatively larger in neonates than adults, even small volume blood loss may result in shock in the neonate. The clinical features of hypovolemic shock are lethargy, mottling of the skin, cool peripheries, prolonged capillary refill – best tested by pressing on the skin of the chest, tachycardia, weak pulse, hypotension, and decreased urine output.

Cardiogenic shock

Cardiogenic shock in the neonate may be caused by:

1. Severe intra-partum asphyxia that is defined as metabolic acidemia at birth with pH < 7.00 and base deficit > /= 12 mmol/l. Neonatal complications of intrapartum asphyxia include multi-organ failure and neonatal encephalopathy. While the most severe consequences are death and neurological or sensorial impairment, moderate to severe neonatal encephalopathy is associated with a high risk of cerebral palsy (especially quadriplegic or dyskinetic type) and/or cognitive disorders. Prognosis of neonatal encephalopathy can be accurately assessed by MR imaging.
2. Primary structural heart disease like:
 - Hypoplastic left ventricle, tricuspid atresia, pulmonary atresia or arrhythmias
 - Myocardial ischemia that reduces myocardial contractility leading to papillary muscle dysfunction and secondary tricuspid valve insufficiency
 - Myocardial dysfunction from cardiomyopathy or cardiac arrhythmias
 - Shock of any cause
 - Mechanical reduction of cardiac function or venous return secondary to tension pneumothorax, diaphragmatic hernia or cardiac tamponade
3. Disturbance of transitional circulation due to persistent pulmonary hypertension in newborn, or patent ductus arteriosus in premature infants.

The four main clinical features of cardiogenic shock are tachycardia, tachypnea, hepatomegaly, and cardiomegaly. Other features are a heart murmur suggestive of tricuspid regurgitation, narrow pulse pressure, basal crackles, and decreased urine output. Peripheral edema and raised JVP are relatively uncommon in the neonate.

Septic shock

The commonest form of distributive shock is septic shock that is the major cause of mortality and morbidity in neonates. Although the cardiac output may be normal or even increased, it may still be far too inadequate to deliver sufficient oxygen and substrate to the tissues because of mal-distribution of blood flow in the microcirculation, leading to decreased tissue perfusion. In septic shock, cardiac function may be depressed in the left ventricle more than the right.⁶

The early phase of compensated septic shock is associated with increased cardiac output, decreased systemic vascular resistance, warm extremities, and wide pulse pressure. If effective therapy is delayed, cardiovascular performance deteriorates and cardiac output falls. It is to be noted that shock can ensue even with normal or increased cardiac output. Once the normal relationship between cardiac output and systemic vascular resistance breaks down, hypotension results from decreased vascular resistance.

Neonates with sepsis have limited cardiac reserve and often present with hypotension and cardiovascular collapse. Urgent clinical diagnosis and treatment are mandatory for good clinical outcomes. The critically ill infant represents a diagnostic and therapeutic challenge that needs to be anticipated and met immediately.

The common organisms that cause neonatal septic shock are shown in Table 2.

Table 2: Common organisms causing neonatal septic shock

Gram-negative organisms	Gram- positive organisms
• <i>E. coli</i>	• Group B <i>Streptococcus</i>
• <i>Klebsiella</i>	• <i>Staphylococcus</i>
• <i>Enterobacter</i>	• <i>Listeria</i>
• <i>Pseudomonas</i>	• <i>Enterococcus</i>
• <i>Proteus</i>	• Group A <i>Streptococcus</i>

2. Progression of shock/stages of shock

The clinical features of neonatal shock include weak cry, poor response to stimulation, lethargy, pallor or cyanosis, shallow respiration, cool extremities, sclerema neonatorum with hardening of skin over the extremities, poor capillary refill, hypothermia (core temperature), and hypotension. Infants with septic shock may have necrotic lesions around the mouth and mucus membranes of the mouth and nostrils, and bleeding into skin and other areas with onset of disseminated intravascular coagulation.

Table 3 : Comparison of the main cardiovascular features of 3 more common types of shock in the neonate

CVS Features	Hypovolemic	Cardiogenic	Early septic (warm)	Late septic (cold)
Arterial BP	Low	Low	Low	Low
Central venous pressure	Low	Low	Normal	High
Pulse pressure	Decreased	Decreased	Normal	Decreased
Total peripheral resistance	High	High	Low	High
Cardiac output	Low	Low	Normal/High	Low
Core & peripheral skin temperature difference	Increased	Increased	Normal / Decreased	Increased

Adapted from Shock in the newborn. G.S. Levin⁷
www.ttuhsc.edu/.../documents/lectures/shockinthenewborn.ppt - accessed 6 November 2012.

It is seen from the Table 3 that the cardiovascular features are similar between late septic shock and cardiogenic shock. The features differ little between hypovolemic and cardiogenic shock except for high CVP in cardiogenic shock and low CVP in hypovolemic

shock. In early septic (warm) shock, the cardiovascular features appear normal except for low CVP, low total peripheral resistance, high or normal cardiac output and normal or increased core to skin temperature.

Shock, if not managed competently, progresses through 3 phases: compensated, uncompensated, and irreversible, each with its own characteristic clinico-pathological features and outcome. Distinguishing between them may be impossible.

More important is the need to initiate prompt, aggressive treatment as soon as shock is anticipated or suspected.

Compensated shock

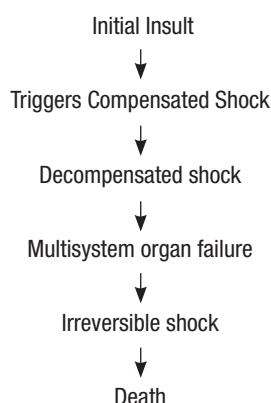
In compensated shock, perfusion of the vital organs – the brain, heart, kidneys, adrenals, and liver are maintained. Alterations in vital signs, such as heart rate, respiratory rate, blood pressure, and temperature, are either absent or minimal. Angiotensin and vasopressin secretions are increased to enhance salt and water conservation by the kidneys. Myocardial contractility is increased by catecholamine release. Reduction in spontaneous activity decreases oxygen consumption by the body.

Uncompensated shock

Once the compensatory homeostatic mechanisms are exhausted, the clinical signs of pallor, tachycardia, cool peripheries, and prolonged capillary refill time will emerge as uncompensated shock ensues. Blood flow in the small blood vessels become sluggish, leading to platelet adhesion, activation of the coagulation cascade, bleeding and volume depletion. As the blood pressure falls, metabolic acidosis leads to rapid breathing, and oliguria or anuria as the kidneys start to fail with hypotension and poor organ perfusion. If urgent treatment is not forthcoming or is ineffective, progression to irreversible shock will ensue. As delivery of oxygen and nutrients becomes insufficient to meet tissue demands, anaerobic metabolism becomes the

major source of energy production with excessive production of lactic acid that leads to metabolic acidosis, reduced myocardial contractility and impaired response to catecholamines. Chemical mediators, cytokines, histamines, xanthine oxidase, platelet aggregating factors and bacterial toxins are released in cases of septic shock causing reduction in tissue perfusion and oxidative phosphorylation. The sodium–potassium pump fails, the capillary endothelial integrity is disrupted and plasma proteins leak, with resultant loss of oncotic pressure and shift of intravascular fluids to the extravascular space. The algorithm of decompensated shock is shown in Figure 2.

Figure 2: Algorithm of decompensated shock



Irreversible shock

Early recognition of neonatal shock and appropriate intervention are vital to saving lives. Shock should be diagnosed and treated appropriately before hypotension occurs.⁹ If reversible shock is not successfully treated, it will progress and cause multiple end-organ damage to the kidneys, liver, heart and brain that are sensitive to hypoxic-ischemic injury. It is not possible to identify the exact point of no return beyond which death is inevitable irrespective of the intensiveness of resuscitative measures and success in restoration of circulation. The diagnosis of irreversible shock is a retrospective one. Those who recover from uncompensated shock

may have varying degrees of persistent multi-organ damage during and following recovery that needs to be identified and managed. These include acute tubular necrosis, and compromised myocardial contractility from prior inadequate myocardial perfusion. Liver and bowel compromise during shock may lead to GI bleeding from necrotizing enterocolitis especially in premature infants.

Factors that suggest irreversibility of shock are:

- Ongoing fluid/blood requirement despite control of hemorrhage
- Persistent hypotension despite restoration of intravascular volume
- No improvement in parameters (cardiac output/ blood pressure) despite inotropic support
- Futile cycle of uncorrectable hypothermia, hypoperfusion, acidosis, and coagulopathy

Laboratory tests

Although a large array of laboratory tests is available, most lack specificity and practical utility. The suspected cause should guide what diagnostic tests are required. The tests should determine:

- Type of shock
- Cause of shock
- Severity of shock - whether end organ damage is present
- Presence of other complications
- Type of management and prognosis

The following tests should be considered:

- Complete blood count to determine anaemia and blood loss; total and differential white blood cell counts for infection. Although both elevated WBC and low neutrophil counts can be predictive of neonatal sepsis, neutropenia is a better marker because of its greater specificity; few conditions other than sepsis and pre-eclampsia depress the

neutrophil count of neonates¹⁰. When defining neutropenia, one needs to bear in mind that neutrophil counts vary depending on gestational age, type of delivery, site of sampling and even altitude.

- Coagulation tests for DIC, liver failure and hypocoagulability states.
- Electrolytes, BUN/creatinine and urinalysis; and hepatic function tests to assess renal and liver function respectively.
- Chest x-ray, EKG, cardiogenic - cardiac enzymes and echocardiogram; obstructive - CT or V/Q scan (PE), echo (tamponade). An echocardiogram (heart ultrasound) or right heart (Swan-Ganz) catheterization may show low cardiac output (pumping action), confirming shock, and may also help to differentiate hypovolemic from cardiogenic shock
- Serum lactate - to gauge the degree of hypoperfusion
- Pro-inflammatory cytokines such as IL-18 a predictive marker that differentiates infected and non-infected neonates
- Increase in the chemokine IP-10 is a sensitive early marker of infection in neonates
- More invasive testing is often required: arterial blood gas for O₂/pH; central venous oxygen measurement, systemic vascular resistance, and cardiac output may be measured through special central venous catheters.
- Central venous oxygen saturation (ScvO₂) >70%
- Arterial blood gases (especially the pH and base excess (BE))
- Mixed venous saturation
- If septic shock is suspected, blood, urine, umbilical or wound cultures are advocated with head CT and lumbar puncture. Targeted imaging (US/CT) tests may help determine site and cause of volume depletion, and can include a CT scan or an X-ray of suspected areas.

- Endoscopy may be performed in cases of bleeding in the gastrointestinal tract.
- Newer non- invasive tools such as functional echocardiography (FE) and near infrared spectroscopy (NIRS) may be used more regularly in future. FE provides a bedside means of measuring cardiac output, peripheral vascular resistance and organ blood flow in response to fluid and drug therapy. NIRS allows non- invasive monitoring of the end-organ perfusion.

Table 4: Tests recommended for septic shock

Tests specific for septic shock	Expected results
blood culture	positive
WBC	<4000 or >30,000 (depends on age of neonate)
I/T Ratio	> 0.2
CRP	>2 mg/dl (EOS)
CRP	> 2 ng/ml
PCT	> 2 ng/ml
IL-8	> 70 pg/ml
PCR	16SrRNA??
sTREM-1	> 60 nanogram/ml
CD 64 and combination tests	I/T ratio + CRP
	PCT + CRP
	IL-8 + CRP

- **Urine Examination:** Because of difficulties with collection of clean samples, and risks of catheterisation and supra-pubic aspiration, this investigation is often not done. The low rate of urinary tract infection in the new born has led to recommendations against routine urine culture to diagnose sepsis. Urine bacterial antigens are no substitutes as their accuracy and reliability is very poor and their routine use should be abandoned.
- **Cerebrospinal Fluid (CSF)**
There is controversy as to whether CSF examination should be a routine at each sepsis work-up.

The 2012 AAP clinical report (www.pediatrics.org/cgi/doi/10.1542/peds.2012.0541) recommends that LP be performed for an infant with any of the following clinical conditions:

- A positive blood culture
- Clinical findings that are highly suggestive of sepsis
- Laboratory data strongly suggestive of sepsis
- Worsening clinical status while on antibiotic therapy

Shock index

The shock index is easily calculated (heart rate divided by systolic blood pressure) and can provide clues to the severity of the patient's condition. A normal index ranges from 0.5-0.7; repeated values >1.0 indicate decreased left ventricular function and are associated with higher mortality.

Management

Shock should be diagnosed and managed before onset of hypotension. Absence of hypotension does not preclude shock that is mainly related to blood flow rather than blood pressure; the mean blood pressure may be in the normal range due to compensatory mechanisms.¹¹⁻¹² In the evaluation of blood pressure, physiological variability with age and gestational age should be taken in account.¹² Thirty mmHg is the absolute minimum tolerable in extremely premature infants.¹³ In critically

ill prematures, refractory hypotension may be related to patent ductus arteriosus, intraventricular haemorrhage and poor prognosis,¹⁴ while in healthy prematures, lower mean blood pressure levels may be accepted as being associated with appropriate cerebral perfusion and normal cardiac output. In septic shock hypotension is not permissive and needs therapeutical intervention. There are many well-defined algorithmic management guidelines available with large practice variability in the treatment of neonatal septic shock. However, early and aggressive management of septic shock is vital right from the onset, because each hour of delay increases the risk of death 2-fold.

The immediate aim of management is to optimize perfusion and delivery of oxygen and nutrients to the tissues. The American College of Critical Care Medicine estimates that 60 min is the average time needed to provide adequate circulatory support and block the development of shock.¹⁵ The first step in managing shock in the newborn during the first 5 minutes is to recognize cyanosis, respiratory distress and decreased perfusion⁷. This should be followed immediately by airway access and ventilation to optimise oxygenation. Rapid peripheral, central venous, or intraosseous access is of primary importance in the initial management of the newborn in shock. Any baby with shock and hepatomegaly, cyanosis or a pressure gap between upper and lower limbs should be treated with prostaglandin within 10 min of birth until congenital heart disease is excluded.¹⁴⁻¹⁵

Table 5: Recommended management of neonatal shock

A. Early detection	Early recognition and intervention are crucial for favourable outcomes.
B. Aggressive fluid therapy	Mortality is significantly reduced if hemodynamic function is optimized early. ¹⁶ There is no advantage in using crystalloids instead of colloids in septic shock. ¹⁷ Intraventricular haemorrhage and infection transmission is lower with crystalloids. The incidence of pulmonary edema is less with 5% albumin. ¹⁸ Bolus resuscitation as a life-saving intervention in shock without hypotension is challenged. Infants who do not diurese after adequate fluids may need diuretics to prevent fluid overload. ¹⁴
C. Antibiotics	Blood cultures, biochemical markers for sepsis, blood glucose and ionized calcium should be taken before initiating antibiotics for suspected sepsis. ¹⁹ Ampicillin plus gentamycin is more effective than cefotaxime plus gentamycin. ²⁰ Cefotaxime is preferred for meningitis.
D. Respiratory support	Respiratory failure accompanying shock requires elective ventilation. Anoxia and over-distension of alveoli- a potent IL-6 inducer should be avoided
E. Metabolic support	There is no consensus on ideal blood sugar but it should not be lower than 30 mg/dL. ²¹ Level of 175 mg/dL or more has a 2.5X increased mortality; same in ELBW babies with level above 150 mg/dL. Insulin should be used only when sugar level exceeds 180mg/dL in refractory shock and unfavourable response newborn. ²² There is no evidence to support bicarbonate therapy in acidemia of septic shock. Hypocalcemia is a reversible cause of cardiac dysfunction; it should be normalized. Corticosteroids often used in septic shock when volume expansion and inotropes are unable to raise BP, appear to increase mortality in a subset of patients. ²³ Consequently, corticosteroids are recommended for refractory shock when adrenal insufficiency is suspected. ²⁴
F. Nutrition	In infants with poor muscle mass and energy reserves, metabolic requirements increase due to hypercatabolic state in sepsis. Appropriate enteral feeding to reduce bacterial translocation from gut mucosa and preserve gut mucosal function is advocated.
G. Cardiovascular support	Inotropes like dopamine, dobutamine, epinephrine and norepinephrine are indicated via iv or io route before central access is achieved when myocardial contractility remains poor despite adequate volume replacement. Delay increases mortality 20-fold. ²⁵ Epinephrine and norepinephrine raise mean arterial pressure but epinephrine causes adverse hyperglycemia requiring insulin, increased plasma lactate and inadequate gastric mucosa perfusion. ²⁶ Dopamine is the first line drug although dobutamine raises systemic blood flow more effectively. ²⁷ It reduces TSH release making hypothyroidism diagnosis difficult. The best vasoactive drug schedule for premature transition shock is low dose dopamine and dobutamine, Epinephrine is a potent inotrope and chronotrope, and a systemic and pulmonary vasodilator. Norepinephrine is indicated for “warm” shock in neonates.

<p>H. Adjunctive treatments</p>	<p>Nitric Oxide is used in PPH (persistent pulmonary hypertension).²⁸</p> <p>Triiodothyronine is an effective inotrope in newborns with thyroid insufficiency.²⁹</p> <p>Phosphodiesterase inhibitors are used if cardiac output does not improve and high systemic vascular resistance persists.</p> <p>Milrinone, an inodilator (inotrope/vasodilator), and selective phosphodiesterase type III inhibitor improves myocardial contractility and relaxation by effects on calcium.² In the vasculature it relaxes arterial and venous smooth muscle. It is advocated in “cold shock” with high peripheral resistance. Limited data is available on use of milrinone in preterm infants.</p> <p>Arginine-vasopressin (AVP)³⁰: Endogenous AVP, released in response to hypovolemia and hypotension, shows a biphasic response in septic shock, with initial high levels followed by inappropriately low levels in later stages. This justifies exogenous administration to correct hypotension in vasodilatory shock in children and also in extremely-low-birth weight infants.</p> <p>Terlipressin (TP) is a synthetic AVP analogue with prolonged action; it has higher affinity for vascular receptors than vasopressin.² It is an effective rescue treatment for refractory vasodilatory septic shock.³¹ It is advocated as a last resort when septic patients remain hypotensive despite fluid resuscitation and high doses of catecholamine.³²</p> <p>Levosimendan (LS) is an inodilator that has cardio-protective and anti-inflammatory effects.² It is a calcium-sensitizing agent that acts by binding to myocardial troponin C, allowing more efficient contraction. In peripheral vascular beds, LS causes vascular relaxation which reduces cardiac afterload and promotes coronary vasodilation. LS's potential utility is due to a number of reasons; it can be used with conventional inotropic agents, it has a simple dosing regimen and does not worsen the diastolic dysfunction often present in structural heart disease. Clinical experience confirms the potential beneficial effects of LS infusion in restoring hemodynamics in infants with low cardiac output septic shock resistant to catecholamines.³³</p> <p>Granulocyte and granulocyte-macrophage colony stimulating factors (G-CSF, GM-CSF) increase the number of circulating white cells but do not reduce mortality from neonatal sepsis or septic shock.³⁴</p> <p>Pentoxifylline is a carbonic anhydrase inhibitor that improves white cell function. One RCT in pretermes shows significantly reduced multi-organ failure, mortality and coagulopathy with improved BP blood.³⁵</p> <p>Intravenous immunoglobulin (IVIG): Polyclonal and IgM-enriched IVIG reduces mortality from sepsis in the newborn. Tumour necrosis factor can be blocked by various antagonists. Generally immunomodulators have shown frustrating results in newborn septic shock management.³⁶</p> <p>Protein C. Low PC plasma activity correlates with adverse outcomes, such as multiple organ failure and mortality.^{37,38} It is a useful predictor of organ failure in severe sepsis and an important factor of high diagnostic and negative prognostic significance.^{39,40} It is successfully used in term neonates and preterms at high-risk of haemorrhage with sepsis-induced coagulopathy.^{41,42}</p>
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