Infection is a common complication in neonatal intensive care and is associated with significant morbidity and mortality. Risk factors include maternal factors that can facilitate vertical transmission and the development of early-onset sepsis (<72 hours after birth). Such factors include colonization with group B streptococcus (GBS), prolonged duration of ruptured membranes, and chorioamnionitis. Neonatal risk factors with horizontal transmission can cause late-onset sepsis (>72 hours after birth) and include prematurity, vascular catheterization, mechanical ventilation, and other invasive diagnostic and treatment modalities.

Infection starts with the presence of susceptibility to and invasion by a pathogen, which can be followed by a systemic inflammatory response with a complex series of molecular and cellular events. Neonates with infection may initially present with minimal signs and symptoms and then progress to sepsis, septic shock, and full-blown multiorgan failure.

To aid in the standardization of observational studies and evaluation of therapeutic interventions in clinical trials, Goldstein et al. presented consensus definitions of the pediatric sepsis continuum. Sepsis is defined as a systemic inflammatory response in the presence of a suspected or proven infection; septic shock is defined as sepsis with cardiovascular organ dysfunction. Details are provided for the clinical definition of a systemic inflammatory response, cardiovascular dysfunction, and
organ dysfunction, but it has been difficult to provide neonatal-specific definitions, especially for preterm infants. Indeed, the pediatric consensus definitions for sepsis are not accurate in neonates, which is most likely explained by the developmental differences in the systemic inflammatory, cardiovascular, and other organ systems' response to sepsis and the fact that many other common neonatal conditions can mimic sepsis.

The Hemodynamic Response to Sepsis

Adults

The hemodynamic response to sepsis is a continuum with different phases; to the clinician, this response will depend on the time of presentation and progress of the disease. In adults, septic shock is primarily a form of distributive shock, characterized by ineffective tissue oxygen delivery and extraction due to inappropriate vasodilatation with preserved or increased cardiac output. There is an absolute and/or relative decrease in central blood volume, with load-driven alterations in left and right ventricular function. However, the heart can also be directly affected by the host immune response or by pathogen toxins, especially in the advanced stages of sepsis. Indeed, a number of mediators and pathways have been shown to be associated with myocardial depression in sepsis, but the precise cause remains unclear. There is currently no evidence supporting global ischemia as an underlying cause of myocardial dysfunction in sepsis in adults.

Children

The presentation and hemodynamic response to sepsis in children is more variable compared with that in adults. In a prospective observational study, 30 children with suspected fluid-resistant septic shock were assessed within 4 hours after the onset of shock with a noninvasive cardiac output device. Fluid-resistant septic shock secondary to in-hospital acquired infection typically presented with high cardiac output and low systemic vascular resistance (SVR), or warm shock. However, in patients with community-acquired sepsis, a low cardiac output with a high SVR, or cold shock, was predominant. This finding might be explained by the longer interval to diagnosis for community-acquired sepsis and advanced disease progression at the time of admission to the pediatric intensive care unit (PICU). Both types evolved in a heterogeneous manner concerning the findings of cardiac output and SVR, needing frequent revision of the cardiovascular support therapy. Importantly, Raj et al. showed that cardiac dysfunction was common in children with septic shock. About one-third of the children had systolic dysfunction as measured by reduced ejection fraction (EF) or fractional shortening (SF) or diastolic dysfunction with an increased E/e’ ratio within 24 hours of admission. The E/e’ ratio represents the ratio of early mitral inflow velocity (E wave) and tissue Doppler–derived mitral annular early diastolic velocity (e’); it is used as an estimate of left ventricular filling pressure. Of note is that—because measures of myocardial function, especially EF and SF are load-dependent—caution should be used in interpreting these data.

Neonates

Early newborn animal studies using rabbits, lambs, or piglets have shown that septic shock consistently presents with reduced cardiac output and increased systemic and pulmonary vascular resistance (PVR). Reduced cardiac contractility was found, often independent of a decrease in preload. Doppler echocardiography was only just being introduced in neonatal practice at the time of these studies; hence the experiments were not confirmed in neonates. Yet the clinical presentation of septic neonates fit with the findings of the animal studies. Neonates were
described as cold, mottled, and peripherally vasoconstricted, with hypoxia, oliguria, and evidence of organ ischemia—characteristic findings for cold shock.\textsuperscript{23-25} When echocardiography became more widely available, clinical studies revealed that cardiac output was often low in shocked hypotensive newborns.\textsuperscript{26-29} However, these cohorts described mostly infants with perinatal asphyxia or preterm transition, and the few included neonates with shock with sepsis were not described separately. Interestingly, more recent clinical echocardiography studies in neonates with sepsis have revealed, maybe unexpectedly, that almost all of the studied infants presented with warm shock. De Waal and Evans described a cohort of 20 preterm infants with suspected late-onset infection or necrotizing enterocolitis and at least two clinical signs of cardiovascular compromise. Of the 20 infants, 15 could be classified as having septic shock as they needed greater than 40 mL/kg of volume and/or vasopressor-inotrope support. The infants underwent echocardiography within 2 hours of presentation, which was repeated every 12 hours until clinical recovery or death.\textsuperscript{30} All infants presented with high cardiac output and low SVR, with the nonsurvivors showing a rapid decline in cardiac output and an increase in SVR during the first 12 hours of the clinical presentation (Figs. 27.1 and 27.2). This finding was later confirmed in a larger study of 52 preterm infants with

![Fig. 27.1](image1.png) Central blood flows in 20 preterm infants with late-onset sepsis at presentation at 12 hours and when clinically improved (survivors only). The upper limit of right ventricular output (RVO) and left ventricular output (LVO) in well preterm babies (using similar methodology) is estimated to be around 350 to 400 mL/kg/min. SVC flow, Superior vena cava flow. (From de Waal K, Evans N: Hemodynamics in preterm infants with late-onset sepsis. J Pediatr 156(6):918–922, 2010.)

![Fig. 27.2](image2.png) Systemic vascular resistance (SVR) in 20 preterm infants with late-onset sepsis at presentation at 12 hours and when clinically improved. The five nonsurviving infants (gray lines) showed a significant increase in SVR after initiation of the treatment within 12 hours after presentation. (From de Waal K, Evans N: Hemodynamics in preterm infants with late-onset sepsis. J Pediatr 156(6):918–922, 2010.)
late-onset sepsis or septic shock.\textsuperscript{31} Saini et al. also found higher left ventricular output (LVO) in the infants with septic shock but not those with celiac or cerebral blood flow.\textsuperscript{31} Using multisite near infrared spectroscopy and echocardiography, van der Laan et al. studied 24 preterm infants with clinically suspected sepsis.\textsuperscript{32} They also reported normal to high blood flows and mostly normal renal, cerebral, and intestinal fractional tissue oxygen extraction, indicating that oxygen delivery to the tissues matched cellular demand at the time of study. However, high intestinal fractional tissue oxygen extraction was correlated with low LVO and/or right ventricular output (RVO), suggesting that the intestinal perfusion is most at risk during periods of low cardiac output.\textsuperscript{32} Tomerak et al. studied 30 term and preterm newborns with sepsis within 24 hours of presentation and before the initiation of vasopressor-inotropes.\textsuperscript{33} EF was marginally increased, and the majority of infants showed diastolic dysfunction as measured by the EA ratio (the ratio between early diastolic and atrium contraction flow velocity) and myocardial performance index (MPI). In a study by Abdel Hady et al., 20 term infants with clinical and culture-proven sepsis were measured 1 to 4 days after presentation.\textsuperscript{34} Cardiac output was comparable to that in controls, but tissue Doppler revealed reduced systolic annular velocities and increased MPI, suggesting systolic and diastolic dysfunction.

However, there are understandable limitations to these clinical studies. Not all of the included infants had culture-proven infection, and there were only a limited number of infants with early-onset sepsis. Accordingly, at the time of the first hemodynamic assessment, infants could be classified anywhere on the continuum of sepsis, from mild clinical signs to full-blown septic shock. Nevertheless, all currently available clinical data indicate that neonates most often present with warm rather than cold shock, as the early animal studies suggested.

**Approach to the Treatment of Neonates With Septic Shock**

Treatment of septic shock has seen significant changes over time. Early goal-directed therapy and the implementation of “sepsis bundles” have helped to reduce mortality in adults and children with sepsis.\textsuperscript{35–37} Guidelines are also available for neonates with septic shock. The 2012 international guidelines for the management of severe sepsis and septic shock provide recommendations for term newborns but exclude preterm infants.\textsuperscript{35} The 2007 clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock by the American College of Critical Care Medicine (ACCCM) do not specifically exclude preterm infants, but most thresholds, diagnostic interventions, and therapeutic end points are derived from the PICU environment.\textsuperscript{38}

Acknowledging these limitations, Wynn and Wong added an alternative flow diagram with suggestions for monitoring and treating preterm infants with septic shock (Fig. 27.3).\textsuperscript{4} For the treatment of septic shock in newborns, especially with early sepsis, it is important to recognize the variable hemodynamic conditions during the normal transition from fetus to newborn, as detailed in Chapter 1. If septic shock is likely, restoration of blood pressure, blood flow, hypoxia, and acidosis are generally accepted short-term therapeutic end points. The definitive goal when managing a neonate in shock is to restore blood flow and thus oxygen delivery to the tissues so that perfusion and aerobic cellular metabolism matching oxygen demand are restored and preserved. Suggestions for therapeutic end points in neonates include a capillary refill time of less than 2 seconds, normal pulses without differential between peripheral and central pulses, warm extremities, urine output greater than 1 mL/kg/h, low serum lactate, normal central blood flows (cardiac output between 200 and 400 mL/kg/min, superior vena cava [SVC] flow >40 mL/kg/ min), a central and mixed venous saturation of more than 70%, and normal mental status.\textsuperscript{38} Therapeutic end points in premature neonates have not been established, and some of the suggested hemodynamic measurements have not been validated in preterm infants.
Recognize decreased perfusion, cyanosis, and RDS. Maintain airway and establish access according to NRP guidelines.

**Initial resuscitation:**
- Push boluses of 10 cc/kg isotonic saline or colloid up to 60 cc/kg until perfusion improves, unless hepatomegaly develops.
- Correct hypoglycemia & hypocalcemia. Begin antibiotics. Begin prostanin if a ductal-dependent cardiac lesion is suspected and obtain comprehensive echocardiogram.

**Fluid refractory shock:**
- Titrated dopamine 5-9 mcg/kg/min.
- Add dobutamine up to 10 mcg/kg/min.

**Fluid refractory dopamine-resistant shock:**
- Titrated epinephrine 0.05 to 0.3 mcg/kg/min.

**Catecholamine-resistant shock:**
- Monitor CVP in NICU, attain normal MAP-CVP & ScvO2 > 70%.
- SVC flow > 40 mL/Kg/min or CI 3.3 L/m2/min

**Cold shock with normal blood pressure & evidence of poor LV function:**
- If ScvO2 > 70%, SVC flow > 40 mL/kg/min or CI < 3.3 L/min, add vasodilator (nitrovasodilators, milrinone) with volume loading.

**Cold shock with low blood pressure & evidence of RV dysfunction:**
- If PPHN with ScvO2 < 70%, SVC flow < 40 mL/kg/min or CI < 3.3 L/min, add inhaled nitric oxide, consider milrinone, consider inhaled Iloprost or IV adenosine.

**Warm shock with low blood pressure:**
- Consider vasopressin or terlipressin in conjunction with inotropes.

**Cold shock with normal blood pressure & evidence of poor LV function:**
- Consider milrinone (if normal renal function).

**Cold shock with low blood pressure & evidence of RV dysfunction:**
- If PPHN, add inhaled nitric oxide, consider milrinone (if normal renal function).

**Refractory shock:**
- Rule out & correct pericardial effusion, pneumothorax. Use hydrocortisone for absolute adrenal insufficiency and T3 for hypothyroidism. Begin pentoxifylline if VLBW newborn. Consider closing PDA if hemodynamically significant.

**ECMO**

**Emergency Department**
- Neonatal intensive care unit
- 0 min
- 5 min
- 15 min
- 30 min
- 60 min

**Pediatric Intensive care unit**
- Neonatal intensive care unit
- 0 min
- 5 min
- 15 min
- 30 min
- 60 min

**Term**

**Preterm**

**Fig. 27.3** American College of Critical Care Medicine consensus guidelines for the treatment of shock in term infants and suggested modifications for preterm infants. CI, Cardiac index; CVP, central venous pressure; ECMO, extracorporeal membrane oxygenation; IVIG, intravenous immunoglobulin; LV, left ventricular; MAP, mean arterial pressure; NRP, Neonatal Resuscitation Program; PDA, patent ductus arteriosus; PPHN, persistent pulmonary hypertension of the newborn; RDS, respiratory distress syndrome; RV, right ventricular; ScvO2, central venous oxygen saturation; SVC, superior vena cava; VLBW, very low birth weight. (From Wynn JL, Wong HR: Pathophysiology and treatment of septic shock in neonates. Clin Perinatol 37(2):439–479, 2010.)
As in the current ACCCM guideline, the following sections provide suggestions for a future update based on accumulated new evidence. Accordingly, initial resuscitation of septic shock starts with volume boluses of 10 to 20 mL/kg. Repeat boluses might be needed up to 60 mL/kg. The neonatal myocardium is very capable of increasing stroke volume with increasing preload, especially when the ductus arteriosus is open. Nevertheless, there are some concerns about early volume loading in septic children. Both early and acquired daily fluid overload were independently associated with mortality in children with severe sepsis. However, the available data for early volume resuscitation was heavily weighted by one well-conducted trial that enrolled a significant proportion of children with malaria in sub-Saharan Africa, sparking considerable controversy regarding the applicability of the results to different contexts and populations. Routine fluid administration in preterm infants with signs of poor perfusion or hypotension has not been reported to be associated with increased morbidity or mortality, but further trials are needed for the subgroup of neonates and especially preterm neonates with sepsis.

When fluid-refractory shock is present, a vasopressor-inotrope would be the first choice of vasoactive medication if no hemodynamic monitoring is available. Neonatologists are historically most familiar with dopamine, and it remains the most commonly used vasoactive medication in transitional hypotension and septic shock. Although dopamine is an effective vasopressor in neonates, there is accumulating evidence that dopamine in higher doses (>10 mcg/kg/min) might also increase PVR to the same or even a higher extent as the increase in SVR. Although these findings concern preterm neonates with preexisting increased pulmonary blood flow, such as patients with a large PDA with left-to-right shunting, there is no evidence that dopamine decreases PVR in patients with normal or decreased pulmonary blood flow. This is obviously a concern, as it can have possible negative effects on pulmonary blood flow and oxygenation. Dobutamine can be added when no echocardiography is available at this point or when low central blood flow is likely. A simple bedside assessment of high versus low cardiac output using Doppler flow velocity would provide the clinician with a targeted choice. Finally, epinephrine and norepinephrine have also been used as secondary or primary vasoactive drugs in neonates (see the following discussion).

The time to evaluate outcomes of the initial resuscitation with fluids and first-line vasoactive drug administration is set at 60 minutes in early goal-directed guidelines. It is unclear if this time line is feasible and/or appropriate in neonates. Particularly for infants with very low birth weight, infusion rates are low and dead space in a newly inserted central venous line (either umbilical or central venous) can be significant. Manual flushing of vasoactive drugs is not recommended, as this could lead to large fluctuations in blood pressure. Cerebral hyperperfusion following cerebral hypoperfusion is fundamental to the hemodynamic basis of periventricular intraventricular hemorrhage in preterm infants, and rapid changes in blood pressure and flow should be avoided if possible. However, careful priming of the infusion line and the use of higher vasoactive drug infusion rates can mitigate some of these concerns.

If shock is resistant to dopamine and/or dobutamine, adding hydrocortisone early in the course of treatment for shock can reduce the duration of vasopressor-inotrope or inotrope use in term and preterm infants (see Chapter 30 for further details). Neonates with septic shock often have blood cortisol levels within the normal and not appropriately elevated range, but with increased levels of cortisol precursors suggesting inadequate cortisol synthesis. Epinephrine is recommended in cold shock and norepinephrine in warm shock if shock remains resistant to first-line therapies, although there is limited evidence to support either therapy in neonates. Heckman et al. showed that epinephrine improved blood pressure in a cohort of 22 shocked very low birth weight infants. Most infants were considered as having an infection, but only 10% had a culture-proven infection. Epinephrine was started 3 days (median) after birth as first- or second-line...
vasoactive therapy. Cardiac output was not studied, but the authors classified the infants as having cold shock with probable depressed myocardial function and poor organ perfusion. Daga et al. describe nine term and late preterm infants with fluid-refractory septic shock where epinephrine improved the immediate hemodynamic compromise.\textsuperscript{57} Tourneux et al. studied 22 term newborns with fluid-refractory and dopamine/dobutamine-resistant early-onset septic shock.\textsuperscript{58} Norepinephrine (mean starting dose 0.4 mcg/kg/min) improved blood pressure in all; there was also a suggestion of improved tissue oxygenation as indicated by an increase in urine output and a decrease in blood lactate concentration. Rowcliff et al. presented a cohort of 48 preterm infants with shock.\textsuperscript{59} Two-thirds had early- or late-onset septic shock, and most infants received additional vasoactive medications before norepinephrine was started. Normotension was achieved at a median of 1 hour in all but one infant at a median dose of 0.5 mcg/kg/min.

In most studies the infants were treated with a combination of two or three catecholamines. The addition of potent vasoactive drugs like epinephrine or norepinephrine led to an average 10% increase in heart rate. Neonates, and in particular preterm infants, have stiff ventricles with intrinsic poor diastolic function. A further shortening of the ventricular filling time can lead to reduced stroke volume and organ blood flow. It is also possible that catecholamine overload with high SVR contributes to cardiovascular failure and early mortality during sepsis, as seen in a cohort of preterm infants with late-onset sepsis.\textsuperscript{30} In a patient with severe shock, an unplanned discontinuation of all four running catecholamines prompted a reduction in heart rate and an acute improvement in oxygenation and blood flow (de Waal, unpublished data). Therefore the targeted increase in SVR in septic neonates with warm shock must be matched with the ability of the myocardium to pump against the increased resistance. This is a delicate balance and can only be achieved with careful and thorough monitoring of blood flow, blood pressure, and tissue oxygenation. The risk of an unwanted increase in SVR beyond the targeted range is especially high when very high doses of vasoactive medications are used, the patient has been started on hydrocortisone and/or starts improving, and cardiovascular adrenergic receptor expression is enhanced. Therefore careful titration of these medications is a fundamental requirement to decrease the chances of side effects and enhance drug effectiveness. The risk of tachycardia might also be reduced by appropriate titration resulting in decreased dose and by replacing one vasopressor-inotrope for another (epinephrine for dopamine or norepinephrine for epinephrine) instead of adding them all together, thus preventing catecholamine overload from occurring.\textsuperscript{60,61}

Some neonatal units have changed the choice of first-line vasoactive drug for septic shock from dopamine to epinephrine or norepinephrine depending on the findings on echocardiography. In preterm animal models, the distribution of adrenergic receptor subtypes in the myocardium and vasculature is strikingly different from that seen in older animals, and the cardiovascular actions of dopamine and dobutamine might not be adequate at moments of significant hemodynamic compromise.\textsuperscript{62,63} Two recent randomized trials in pediatric patients with fluid-refractory septic shock showed that early administration of epinephrine as a first-line drug was associated with increased survival or improved organ function compared with dopamine.\textsuperscript{64,65} As detailed earlier, however, neonates show a similar hemodynamic response to sepsis as seen in adults (primarily warm shock) rather than children (primarily cold shock). Indeed, as most neonatal cases with septic shock present while the infant is still in hospital, it would be reasonable to direct the first-line treatment at warm shock. Norepinephrine is superior to dopamine when used to treat septic shock in adults.\textsuperscript{66} Furthermore, norepinephrine has additional advantages over dopamine, with an improved SVR:PVR ratio, and can thus be used if sepsis is accompanied by pulmonary hypertension.\textsuperscript{47,67,68} However, more data are needed to satisfactorily settle the issue as to whether norepinephrine is superior to epinephrine in neonatal septic shock. Finally, due to norepinephrine’s very potent systemic vasoconstrictive effects, careful but effective titration of the medication to the optimum hemodynamic
response (improved systemic blood pressure, systemic blood flow, and tissue oxygenation) is of great clinical relevance, since significant and sudden swings in systemic blood pressure and organ blood flow (particularly to the brain) are harmful in neonates, especially in preterm infants.

These changes can simplify the flow diagram for early- and late-onset sepsis in neonates (see Fig. 27.3). A main concern remains the clinician’s limited ability to confirm the presence of sepsis early on. Other more common neonatal illnesses, especially those eliciting a nonspecific inflammatory response, can present with hypotension and signs of shock, and it is not clear if aggressive treatment improves long-term outcomes in those situations.69

**Catecholamine-Resistant Septic Shock (see Chapter 30)**

If catecholamine-resistant shock develops, it will be increasingly difficult to manage without information on central blood flow, cardiac shunts, and the presence of pulmonary hypertension. The 2007 guideline suggests central venous pressure monitoring, central or mixed venous saturation measurements, and/or echocardiography to collect the necessary hemodynamic practice parameters. In neonatology and especially for preterm infants, ultrasound remains the most frequently used noninvasive tool to provide the information needed. However, there are other emerging monitoring tools, such as electrical impedance velocimetry, that can be used noninvasively and continuously and do not require the sophistication needed for the use and interpretation of echocardiography (see Chapter 14). In addition, use of the recently developed comprehensive monitoring systems described in Chapter 21 has the potential to provide information on most aspects of neonatal hemodynamics. However, it must be kept in mind that all of the diagnostic tools have their limitations and should only be used with a full understanding of their potentials and pitfalls.

Fluid responsiveness (preload reserve) remains difficult to assess in neonates. Several echocardiographic parameters can reliably be used as a proxy for fluid responsiveness in adults, but they can only be assessed when the patient is on ventilator support and without spontaneous respiratory effort (i.e., during neuromuscular blockade).70,71 In addition, the normal range of central venous pressure is too variable in neonates and is also dependent on mean airway pressure. Central venous pressure is not a good predictor of fluid responsiveness even in adults and should probably no longer be recommended.72–74 Central venous oxygen saturation is an invasive measurement but is being replaced by the use of tissue oxygen saturation measurements using near infrared spectroscopy, although much more needs to be understood and more comprehensive clinical information needs to be collected before routine use in patients with septic shock can be recommended.75,76

Suggestions for the treatment of catecholamine-resistant shock are mainly unchanged from the 2007 ACCCM guideline. Vasopressin has been well studied in adults with warm shock and is increasingly studied in children and neonates with catecholamine-resistant shock.77 Neonates with septic shock responded well to vasopressin, but mortality in these cohorts remained high.

Pulmonary hypertension is commonly described in animal models of septic shock. Sepsis-induced acidosis and hypoxia can increase PVR and thus pulmonary artery pressure, with increased right ventricular work. As early animal studies also showed low cardiac output, treatments targeted to provide systemic and pulmonary vasodilatation was tried but with variable results.78 Inhaled nitric oxide (iNO) is currently the treatment of choice in sepsis-induced pulmonary hypertension during the transitional period, especially when pulmonary blood flow is low. We strongly recommend echocardiography evaluation before starting iNO, as clinical signs of pulmonary hypertension such as a pre- and postductal saturation difference can also become apparent in severe systemic hypotension without high pulmonary pressures. iNO was not effective in adult patients with sepsis and adult respiratory distress syndrome, and it is not known if iNO for sepsis-induced pulmonary hypertension after the transitional period is effective in neonates.79,80
In preterm infants with septic shock, the presence of a large patent ductus arteriosus can complicate hemodynamics. Closure with nonsteroidal anti-inflammatory drugs can be attempted if renal function allows and PVR is not elevated, although animal studies could not show benefits from early treatment with prostaglandin synthesis inhibitors in sepsis.\textsuperscript{81,82}

Some neonates present with cold shock or change from a high to low cardiac output phenotype during the course of their disease. If these changes are recognized, careful weaning off the vasopressor-inotrope support and replacement with inotropes (dobutamine) and/or lusitropes (milrinone) with appropriate titration of these medications has the potential to reduce the SVR and should be the drugs of choice.

When available, extracorporeal membrane oxygenation (ECMO) should be considered as a final therapeutic option. Although success rates are high, early studies showed a high rate of bleeding complications (especially intraventricular hemorrhage) has earlier been reported in neonates with intractable septic shock.\textsuperscript{83} However, ECMO technology has changed over time, and there has been a move from venoarterial to venovenous ECMO, with superior efficacy in infants with sepsis and with lower complication rates. Survival in the studies in neonates and children with sepsis requiring ECMO support varies from 50% to 100%, with neonates showing higher survival as compared with older children.\textsuperscript{84–86} Indications to initiate ECMO are not always clear from the publications, but they have included catecholamine-resistant shock and/or respiratory failure with sepsis.

**Hypovolemic Shock in Neonates**

True hypovolemic shock is rare in neonates and is mostly seen early after birth. Causes include peripartum bleeding from the fetal side of the placenta, fetomaternal hemorrhage, fetofetal hemorrhage, or a postpartum neonatal hemorrhage. With ongoing bleeding, the autonomic sympathetic system is activated with inhibition of the parasympathetic system leading to increased heart rate, cardiac contractility, and arterial and venous tone. Blood volume from the nonvital organs and the venous system will be recruited to help preserve blood flow to the brain, heart, and adrenal glands. The decreased perfusion pressure and increased sympathetic tone associated with epinephrine and norepinephrine release activate the renin-angiotensin-aldosterone system in the juxtaglomerular apparatus of the kidneys. If the bleeding cannot be stopped, severe hypovolemia will finally lead to severe acidosis and myocardial dysfunction, organ failure, and death.

The optimal approach to hemorrhagic hypovolemia in neonates has not been well studied. Most of what is known about physiology and management has been extrapolated from animal and adult data. First-line resuscitation of hemorrhagic shock starts with volume, and the limited available clinical evidence would suggest isotonic saline.\textsuperscript{87,88} A second step would be replacing the type of volume lost, in this case blood. Neonates with severe bleeding or anemia may require a massive transfusion with blood products. The definition of a massive transfusion in pediatric patients varies. According to one suggestion, a transfusion of greater than 50% of total blood volume in 3 hours, replacement of greater than 100% of total blood volume in 24 hours, or transfusion to replace an ongoing blood loss of greater than 10% of the total blood volume per minute would qualify as a massive transfusion.\textsuperscript{89} Most massive transfusion protocols for adults employ a physiologic 1:1:1 transfusion ratio of red blood cells, plasma, and platelets, but there are limited neonatal data to make recommendations. Importantly, the availability of an institute-specific massive transfusion protocol has the potential to improve outcomes.\textsuperscript{90} Neonates in particular are at risk for metabolic derangements and/or coagulopathy after a massive transfusion and should be monitored closely for hypocalcemia, hypomagnesemia, and fluctuations in potassium, glucose, and pH as well as for signs of oozing or bleeding.\textsuperscript{91}

There has been a paradigm shift in the approach toward major bleeding in adults. Observational data have shown that aggressive fluid resuscitation increases the risk of mortality, probably by promoting dilution coagulopathy and delayed clot formation due, at least in part, to increased arterial pressure.\textsuperscript{92} The currently recommended approach is low-volume fluid resuscitation while maintaining an acceptable level of tissue perfusion with permissive hypotension. Noradrenaline is the first-line...
vasopressor-inotrope used in adults, as it induces significant vasoconstriction as well at the level of the splanchnic circulation in particular. This increases the pressure in capacitance vessels and actively shifts splanchnic blood volume to the systemic circulation.\[93\] The effect of dopamine on the splanchnic circulation is complex, and the information in the literature is controversial.\[94\] However, in newborn animal models, dopamine was the most effective vasoactive drug in increasing gut blood flow; it might therefore be considered an alternative to norepinephrine.\[46,95\] The effect of catecholamines administered during hypovolemia depends to a large extent on the volume of blood in the splanchnic reservoir. When hypovolemia is severe, the physiologic responses to maintain volume and pressure have already emptied the splanchnic reservoir. The use of exogenous catecholamines should thus be limited to a brief period and should not be viewed as a substitute for the immediate replacement of blood volume.

The use of vasopressin may be beneficial in the management of fluid- and transfusion-resistant uncontrolled bleeding. Vasopressin not only restores the depleted intrinsic vasopressin production but also seems to be more effective in maintaining vascular tone compared with catecholamines in a hypovolemic and acidotic environment.\[96,97\] However, in an infant animal model of hypovolemic shock, the addition of terlipressin did not improve cardiac output or blood pressure 90 minutes after resuscitation.\[98\] Thus more data are needed before routine vasopressin administration in hypovolemic neonatal shock can be recommended.

Echocardiography can be effectively used to monitor systemic perfusion during hypovolemic shock in neonates. Biventricular low cardiac output, small ventricular internal dimensions in diastole, and increased collapsibility of the large veins (SVC and inferior vena cava) are all indicators of hypovolemia in the early phase of hypovolemic shock. In addition, respiratory variation in aortic blood flow peak velocity remains an important predictor of fluid responsiveness in mechanically ventilated children.\[99\] However, this parameter has not been validated in neonates. Myocardial dysfunction, independent of the loading condition, is not uncommon with persistent hypovolemia and can be supported with the addition of dobutamine. In addition, monitoring tissue oxygen saturation by the use of near infrared spectroscopy may add important information on organ blood flow distribution and tissue oxygen delivery in neonates with hypovolemic shock.

Finally, the effects of physiologic cord clamping on hemodynamic transition and the volume status of the neonate is discussed in detail in Chapters 4 and 5.

Conclusion

Contrary to what is seen in children, neonatal septic shock is mostly diagnosed in its earlier phases as warm, distributive shock. Accordingly, the cardiovascular pathophysiologically targeted first-line management approach includes aggressive fluid resuscitation and the use of a vasopressor-inotrope. Recent data suggest the consideration of careful use of effectively titrated norepinephrine as the potential first choice of a vasopressor-inotrope. In hypovolemic shock of the neonate, rapid replacement of the type of the fluid lost, most frequently whole blood, is the key approach, along with appropriate supportive measures and, if available, use of more sophisticated hemodynamic monitoring to follow the patient’s response to the treatment.

REFERENCES
