Neonatal Septic Shock

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Rajesh K. Aneja, Ruby V. Aneja, Misty Good, and Joseph A. Carcillo

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R. K. Aneja (✉) · J. A. Carcillo
Departments of Critical Care Medicine and Pediatrics, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, Pittsburgh, PA, USA
e-mail: anejar@upmc.edu; carcilloja@ccm.upmc.edu

R. V. Aneja
Division of Neonatology, Temple University, West Penn Hospital, Pittsburgh, PA, USA
e-mail: rvarughese@pol.net

M. Good
Division of Neonatology, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, Pittsburgh, PA, USA
e-mail: goodml3@upmc.edu

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Abstract

Neonatal sepsis continues to be a major health problem in the world. Over the last decade, there has been an overall decrease in the incidence of neonatal sepsis. The institution of intrapartum Group B *Streptococcus* (GBS) prophylaxis has also led to a decrease in GBS early-onset disease. Early recognition and treatment of sepsis is essential to halt its progression to severe sepsis and septic shock. In this chapter, we compare the essential differences between the hemodynamic response to shock in neonates and older children. We also discuss various factors that make diagnosis and treatment of neonatal shock challenging. The American College of Critical Care Medicine recently published an update to their clinical practice parameters for the management of septic shock. We summarize these guidelines and briefly review thrombocytopenia-associated multiple organ failure in sepsis.

108.1 Salient Points

- Early recognition and treatment/resuscitation improve the outcome in sepsis and septic shock. Thrombotic microangiopathy responds to nonspecific and specific therapies.
- When sepsis is not recognized and treated early, septic shock becomes the predominant predictor of mortality and neurologic morbidity.
- Newborns and premature newborns in particular have a reduced ability to eradicate infection at almost all levels of immunity.
- Septic shock in neonates occurs primarily secondary to cardiac failure which is commonly associated with systemic pulmonary hypertension. Hence therapies that include volume resuscitation, inotropic support, and right ventricle afterload reduction are the mainstays of treatment. ECMO can be lifesaving for term newborns with refractory shock.

108.2 Introduction

Group B *Streptococcus* (GBS) continues to be a leading infectious cause of neonatal morbidity and mortality in the United States (Trends in perinatal group B streptococcal disease – United States 2009). Overall, the incidence of GBS early-onset disease (EOD) over the last three decades has decreased from 1.7 to 0.4 per 1,000 live births, which is a 70% reduction (Nandyal 2008). This success has largely been attributed to the institution of intrapartum prophylaxis. Since the implementation of Group B streptococcal (GBS) prophylaxis, there has been a reduction in GBS EOD from 5.9 to 1.7 per 1,000 live births of infants weighing 401–1,500 g but a concomitant increase in the rate of *Escherichia coli* sepsis from 3.2 to 6.8 per 1,000 live births (Fanaroff et al. 2007).

Investigators used hospital discharge data (from approximately one quarter of the US population) to estimate that 10% of infants and children with severe sepsis (bacterial or fungal infection + organ failure) died in 1995 (Watson et al. 2003; Angus et al. 2001). The incidence of sepsis in the neonatal population was 3.06 per 1,000 children. A decade later, in a follow-up study, the authors noted that the incidence of sepsis in the neonatal population had decreased to 2.22 per 1,000 children. Despite the decline in the overall incidence of sepsis, one cohort that demonstrated a significant increase in the incidence of sepsis was the very-low-birth-weight (VLBW) group, defined as less than 1,500 g (26.5% vs. 9.2% in 1995) (Hartman et al. 2008). Similar observations were made by Stoll and colleagues who published a series of epidemiologic evaluations of newborn sepsis/septicemia/septic shock using US Vital Statistics as well as the National Institute of

Child Health and Human Development sponsored newborn infection registry. Neonatal mortality steadily decreased over the past decade, but remained most prominent in low-birth-weight neonates, defined as less than 2,500 g (Stoll et al. 1998, 2002a, b). Low-birth-weight newborns with EOD are more likely to die than those without infection (37% vs. 13%). Twenty-one percent of low-birth-weight newborns also have one or more episodes of blood culture-positive late-onset disease (LOD) and are also more likely to die (18% vs. 7%). In VLBW newborns with LOD, the common causative organisms were Gram-positive (70%), followed by Gram-negative (17.6%) and fungal (12.2%) organisms. In the same study, mortality was higher in patients with Gram-negative organisms or fungal sepsis (Stoll et al. 2002b).

108.3 Early Recognition and Treatment/Resuscitation Improves Outcome in Sepsis and Septic Shock

Clinical signs of apnea or tachypnea, poor feeding, and temperature instability should be considered as sepsis until proven otherwise, and the clinician should consider antibiotic therapy. In the nursery setting, fetal and neonatal tachycardia remain the most important early clinical predictors of sepsis and septic shock (Graves and Rhodes 1984; Paternoster and Laureti 1996). Prompt fluid and inotrope resuscitation to normalization of heart rate well before hypotension appears prudent in this population. Laboratory tests can also have a role in increasing early suspicion of newborn sepsis. Many investigators have demonstrated that measurement of cord or newborn blood quantitative levels of cytokines and proinflammatory markers including interleukin (IL) -6, procalcitonin, IL-1 receptor antagonist, IL-8,IL-10, tumor necrosis factor (TNF), and C-reactive protein (CRP) can attain over 95% sensitivity in diagnosis of EOD and LOD before blood culture results are available (Kuster et al. 1998; Silveira and Procianoy 1999; Janota et al. 2001; Ng et al. 1997; Rogers et al. 2002; Krueger et al. 2001; Romagnoli et al. 2001; Kashlan et al. 2000; Smulian et al. 1999). These author's believe that universal implementation of these clinical laboratory tests will allow more judicious use of antibiotic therapy than the present standard of care that do not utilize all of these biomarkers.

Shock remains the most prominent risk factor for death in neonatal sepsis (adjusted odds ratio 11.82: confidence interval 5.4–69.4). Best outcomes are attained with early reversal of shock in newborns using NRP/ACCM/PALS guidelines (see below) (Han et al. 2003). Aggressive, timely emergency department fluid and inotrope resuscitation directed to oxygen delivery/consumption goals has also been shown to improve outcome in pediatric septic shock. This preponderance of evidence suggests that early recognition is the key to survival in newborn sepsis and septic shock. Experimental and clinical literature show that early and aggressive fluid resuscitation with antibiotic therapy turns off inflammatory gene expression, prevents thrombosis, and results in 95% or greater survival. Delayed resuscitation on the other hand results in inflammatory gene expression, endothelial activation, thrombosis, the development of thrombocytopenia-associated multiple organ failure, and high mortality rates (Haque and Mohan 2003; Nguyen et al. 2001; Roman et al. 1992, 1993).

108.4 Neonatal Shock

108.4.1 Term Newborn

Term newborns and infants have a remarkably different cardiovascular response to septic shock than older children, and healthy newborns have higher resting heart rates. Therefore, (This change is being requested as there is another hence used one sentence later), in response to shock, newborns compensate by increasing systemic vasoconstriction. This vasoconstriction increases afterload and further impairs cardiac output. Hence, death in majority of newborns and infants with fluid-/dopamine-resistant shock is a result of cardiac failure, not vasoplegia.

Neonatal septic shock is often complicated by lack of the physiologic transition from fetal to

neonatal circulation. In utero, 85% of fetal circulation bypasses the lungs through the patent ductus arteriosus and foramen ovale. This flow pattern is maintained by suprasystemic pulmonary artery pressures prenatally. At birth, inhalation of oxygen triggers a cascade of biochemical events that ultimately result in reduction in pulmonary artery pressure and transition from fetal to neonatal circulation with blood flow now being directed through the pulmonary circulation. Closure of the patent ductus arteriosus and foramen ovale completes this transition. Pulmonary artery pressures can remain elevated, and the ductus arteriosus can remain open for the first 6 weeks of life. Sepsis-induced acidosis and hypoxia increase pulmonary vascular resistance, subsequently increasing the pulmonary artery pressure leading to patent ductus arteriosus. This results in persistent pulmonary hypertension (PPHN) and persistent fetal circulation (PFC) in the newborn. Neonatal septic shock with PPHN is associated with increased right ventricle afterload. Despite in utero conditioning, the thickened right ventricle may fail in the presence of systemic pulmonary artery pressures. Decompensated right ventricle failure can be clinically manifested by tricuspid regurgitation and hepatomegaly. Newborn animal models of Group B streptococcal and endotoxin shock have also documented reduced cardiac output and increased pulmonary, mesenteric, and systemic vascular resistance. Therapies directed at reversal of right ventricle failure, through reduction of pulmonary artery pressures, are commonly needed in neonates with fluid refractory shock and PPHN. Newer therapies such as inhaled nitric oxide and ECMO have little to no role in adult septic shock, but are potentially lifesaving in newborns, infants, and children.

108.4.2 Preterm Newborns

The management of neonatal shock is challenging due to many factors outlined below. First, there is lack of consensus about the definition of hypotension in the extremely premature infants (Dempsey and Barrington 2009). The commonly used NICU criteria for mean arterial blood pressure (MAP) is that MAP should be maintained at or greater than the infant's gestational age in weeks (Dempsey and Barrington 2006; Report of working group of the British Association of Perinatal Medicine and Neonatal Nurses Association 1992). In the absence of a precise evidence-based definition, it is difficult to interpret the hemodynamic response to hypotension in preterm newborns. Pediatric data suggest that blood pressure cannot be used as a surrogate for adequate oxygen delivery in critically ill patients. Secondly, there is lack of data about the correlation of CVP with circulating blood volume in VLBW infants. Lastly, there is paucity of data regarding the use of lactate as a surrogate for inadequate tissue oxygen delivery in preterm infants. Serum lactate levels pose a unique challenge as neonates have high blood lactate concentrations at birth, which is normalized by 12 h after birth. Wardle and colleagues examined two groups of ventilated preterm infants with mean gestational age of 27 weeks. They found no difference in median lactate levels between normotensive and hypotensive preterm infants (1.20 vs.1.22 mmol/L). Despite the median lactate levels being similar in the two groups, persistent high lactate levels were associated with an adverse outcome (death or periventricular hemorrhage) (Wardle et al. 1999). Thus, recognition and treatment of shock in low-birth-weight infants should encompass clinical signs (peripheral pulses, perfusion, and urine output) along with biochemical values, i.e., serum lactate levels. Standard practices in resuscitation of premature infants in septic shock employ a more graded approach compared to resuscitation of term neonates and children. This more cautious approach is a response to reports that premature infants at risk for intraventricular hemorrhage (<30 weeks gestation) can develop hemorrhage after rapid shifts in blood pressure (Perry et al. 1990; Miall-Allen et al. 1987); however, some now question whether long-term neurologic outcomes are related to periventricular leukomalacia (a result of prolonged under perfusion) more than to the intraventricular hemorrhage itself. To summarize, while cerebral under perfusion is a setup for periventricular leukomalacia, aggressive resuscitation of critically ill VLBW can predispose them to intraventricular

hemorrhages. Hence the resuscitation of a VLBW neonate is challenging and needs to be studied further.

Several other developmental considerations influence therapies for shock. Relative initial deficiencies in the thyroid and parathyroid hormone axes have been appreciated and can result in the need for supplementation with thyroid hormone and/or calcium replacement. Adrenal insufficiency and the need for hydrocortisone have been documented in the preterm infant cohort as well (Soliman et al. 2004). In a double-blind, randomized, controlled study, 48 VLBW infants who had refractory hypotension and required dopamine (>10 μg/kg/min) were assigned to receive stress dose of hydrocortisone (1 mg/kg Q8H) for 5 days or placebo. A significantly higher number of hypotensive VLBW infants treated with hydrocortisone weaned off vasopressor support 72 h after starting treatment. There was decreased use of volume expanders and less cumulative dose of dopamine and dobutamine in steroid-treated patients as compared to control infants (Ng et al. 2006). Other factors that impact the neonate's response to shock include reduced glycogen stores and muscle mass. These are important for gluconeogenesis; hence attention should be paid to the maintenance of serum glucose in a critically ill neonate.

Studies of therapies specifically directed at premature VLBW infants with septic shock are needed. A single-center randomized controlled trial reported improved outcome with use of daily 6 h pentoxifylline infusions (a systemic vasodilator) in very premature infants with sepsis. The Cochrane analysis agrees that the smaller trials are promising but suggests that larger multicenter trials would be helpful (Haque and Mohan 2003; Pammi and Haque 2015).

The American College of Critical Care Medicine (ACCM) sets a priority to establish clinical practice parameters and guidelines for the management of septic shock (Table 1). As a follow-up to their revised guidelines published in 2007 (Brierley et al. 2008; Carcillo and Fields 2002), recently the "2014 update of the 2007 ACCM *Clinical Guidelines for Hemodynamic Support of Neonates and Children with Septic Shock*" was formulated. The major new recommendation is that hemodynamic support of septic shock is addressed at the institutional level rather than only at the practitioner level. The new guidelines recommend that each institution implement their own adopted or homegrown bundles that include the following: (1) *recognition bundle* containing a trigger tool for rapid identification of patients with suspected septic shock at that institution, (2) *resuscitation and stabilization bundle* to drive adherence to consensus best practice at that institution, and (3) *performance bundle* to monitor, improve, and sustain adherence to that best practice. These guidelines should be reviewed by every hospital's expert committee (Fig. 1).

Table 1 Clinical definition of sepsis and septic shock

Sepsis	Clinical suspicion of infection with the following signs: tachycardia, tachypnea or apnea, poor feeding, temperature instability
Septic shock	Clinical suspicion of infection with the following signs: tachycardia or bradycardia, tachypnea or apnea, prolonged capillary refill >2 s, decreased urine output[a] [a]Hypotension is considered a late confirmatory sign

Although the intent was to develop guidelines for the management of premature as well as term newborns, the literature review on septic shock in the premature was relatively sparse. The evidence and expert opinion-based document found age-specific differences in both pathophysiology and response to therapies. Early recognition and rapid fluid resuscitation are the hallmark of therapy. It should be implemented when newborns are in compensated shock and directed to reversal of tachycardia. Newborns with fluid refractory shock can have any hemodynamic state. Some have the classic adult form of septic shock with high cardiac output and low vascular resistance; however, majority have a low cardiac output state commonly associated with elevated, not reduced vascular resistance. If there is heightened concern for a ductal dependent heart lesion, all newborns with shock should be started on prostaglandin E. Newborns have an age-specific resistance to dopamine and dobutamine; hence, epinephrine (cold shock)

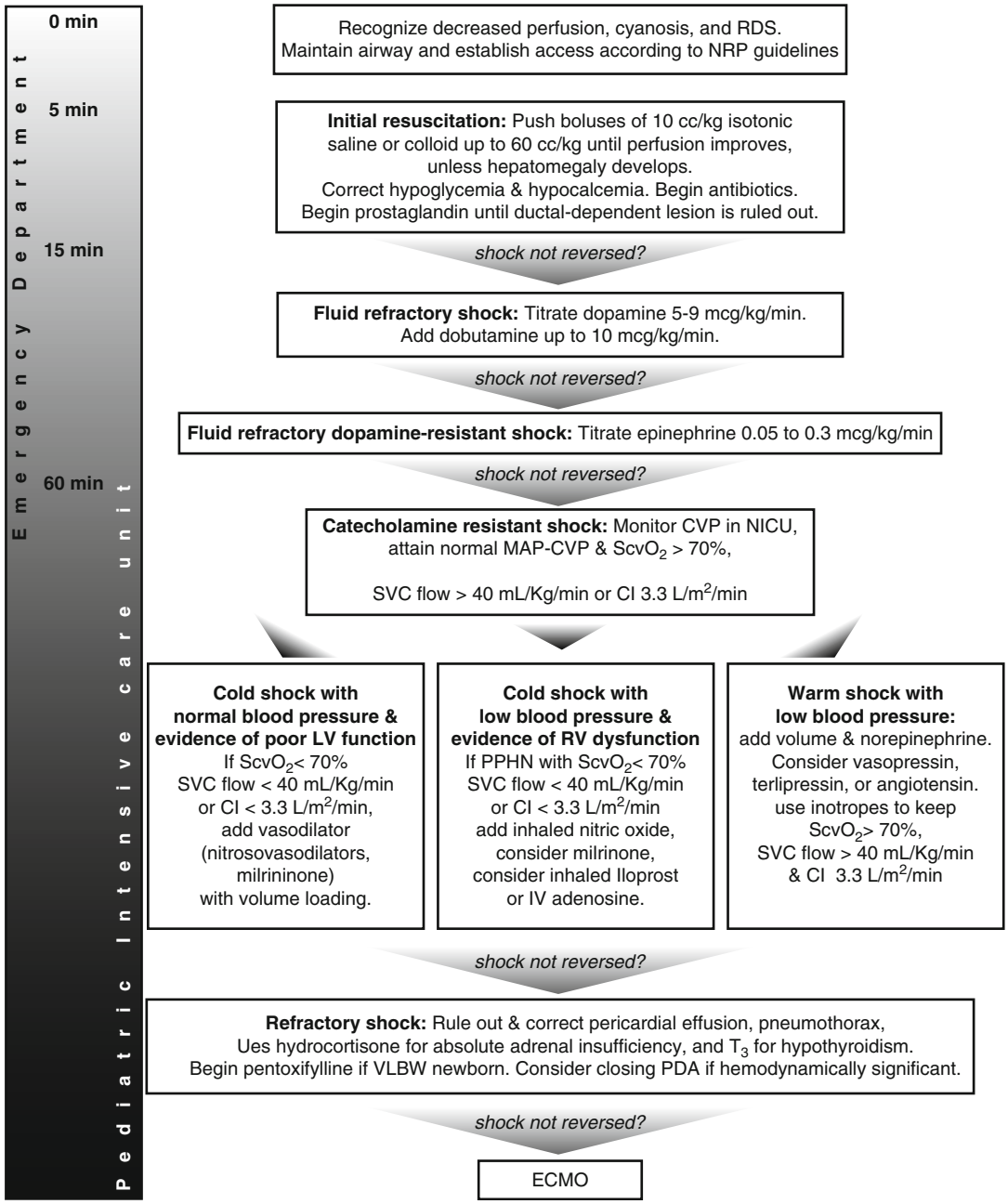

Fig. 1 Algorithm for time-sensitive, goal-directed stepwise management of hemodynamic support in newborns. Proceed to the next step if shock persists. (1) First hour goals – restore and maintain heart rate thresholds, capillary refill $\leq$2 s, and normal blood pressure in the first hour. (2) Subsequent intensive care unit goals – restore normal perfusion pressure (mean arterial pressure [*MAP*]-central venous pressure [*CVP*]), preductal and postductal O_2 saturation difference <5%, and either central venous O_2 saturation (*ScvO2*) >70%, superior vena cava (*SVC*) flow >40 ml/kg/min, or cardiac index (*CI*) >3.3 L/min/m^2 in neonatal intensive care unit (*NICU*). *RDS* respiratory distress syndrome, *NRP* Neonatal Resuscitation Program, *PDA* patent ductus arteriosus, *ECMO* extracorporeal membrane oxygenation

can be more commonly required. Newborns with septic shock have a higher incidence of true adrenal insufficiency cortisol <18 mg/dL when requiring epinephrine, and as such these patients may benefit from hydrocortisone therapy. In patients with low cardiac output and elevated systemic vascular resistance, vasodilators are effective in reversing shock. Additionally, ECMO is lifesaving for refractory newborn septic shock. Inhaled nitric oxide decreases the use of ECMO, but does not improve outcome in ECMO centers. ECMO is recommended for term infants with refractory shock.

108.5 Thrombocytopenia-Associated Multiple Organ Failure; A Thrombotic Microangiopathy Which Responds to Nonspecific and Specific Therapies

Thrombocytopenia, platelet count <100,000 mm^3, is an independent risk factor for the development of multiple organ failure and death in critical illness, in part because it is a recognizable clinical sign of endotheliopathy with platelet thrombi (Nguyen et al. 2001). This syndrome is accounted for by variations on two "prototype" thrombotic microangiopathies. The consumptive coagulopathy (reduced fibrinogen levels) occurs when tissue factor complexes with factor VII and initiates coagulation factor consumption cascade. This is commonly called disseminated intravascular coagulation (DIC). Roman and colleagues have documented that newborns with sepsis/septic shock have a prothrombotic/anti-fibrinolytic state with excessive thrombosis – procoagulant (Factors II, VII), and anticoagulant factors (i.e., protein C and antithrombin III) are both consumed. This leads to a paradoxical observation, overwhelming thrombosis (when the anticoagulant factors are depleted), and then overwhelming bleeding (when the procoagulant factors are consumed). Newborns have lower protein C levels than children. Activated protein C (APC) has 40 times the fibrinolytic activity as protein C concentrate, and it is associated with intracranial bleeding. The pediatric arm of the "Extended Evaluation of Recombinant Activated Protein C" (ENHANCE) trial noted increased incidence of significant bleeding in 27% of the patients enrolled, and 3% had a central nervous system bleeding (Goldstein et al. 2006). Due to the adverse risk to benefit ratio associated with use of APC, it is not being used by most practitioners.

The second prototype is a nonconsumptive coagulopathy (normal or increased fibrinogen levels) which is characterized by low ADAM TS 13 activity leading to platelet thrombi. Newborns have lower ADAM TS 13 activity than children and adults. This condition has been named infection-associated thrombotic thrombocytopenic purpura. It responds to daily centrifugation-based plasma exchange therapy for a median of 14 days. Plasma exchange machines are not approved for infants under 5 kg so their use is limited in the newborn period. Nevertheless, newborns have reduced ADAM TS 13 activity and increased circulating ultra large vWF multimers (thrombogenic multimers), which puts the newborn at risk for nonconsumptive coagulopathy. The use of fresh frozen plasma remains a standard approach to both forms of coagulopathy in newborns. Some have reported improved outcome with whole blood exchange, but not blood component exchange therapy (Sadana et al. 1997; Togari et al. 1983).

108.6 Why Do Newborns Have Difficulty Eradicating Infection?

108.6.1 Hypogammaglobulinemia

Newborns and premature newborns in particular have a reduced ability to eradicate infection at almost all levels of immunity. Most notorious is the common deficiency of IgG levels in the VLBW infant. Prophylaxis with IVIG therapy has not reduced late-onset sepsis in this group of patients, but IVIG therapy in newborns with hypogammaglobulinemia and septic shock has been thought to be of benefit. A meta-analysis previously demonstrated that the use of immunoglobulin preparation rich in IgG, IgA, and IgM reduces the mortality in neonatal sepsis or septic shock by 50% (Kreymann et al. 2007). Hence, IVIG therapy should be considered in newborns with

Table 2 Suggested treatments to reverse immune insufficiency and/or to prevent nosocomial infection and sepsis in term infants

Sepsis/MODS	Neutropenia	Prolonged lymphopenia ALC $<1{,}000/mm^3$ for 7 days, or IgG <500 mg/dl	Monocyte deactivation HLA-DR <30% or 8,000 molecules >5 days
Give GM-CSF	Yes		Yes?
Give IVIG		Yes if IgG <500	
Consider empiric and prophylactic antibiotic/ protozoal fungal strategies	Yes	Yes	Yes?

hypogammaglobulinemic septic shock or toxic shock (Stiehm 1997; Jenson and Pollock 1998; Cawley et al. 1999; Despond et al. 2001). However, a recent Cochrane meta-analysis demonstrated no reduction in mortality, death, or major disability in infants with infection with IGM-enriched IVIG. Hence, routine IVIG therapy in neonatal sepsis is not recommended {Ohlsson 2015 #243}.

108.6.2 Neutropenia

Neutropenia is commonly seen in newborns with sepsis/septic shock. Some have defined it as an absolute neutrophil count $<1{,}500/mm^3$. GM-CSF therapy at 5 μg/kg/day over 12 h for 7 days has been reported to improve outcome in newborns with neutropenic septic shock (Bilgin et al. 2001). G-CSF has also been studied in newborns with non-neutropenic sepsis and was found to be associated with a shortened length of stay (Kucukoduk et al. 2002). In a multicenter trial in United Kingdom, 280 small for gestational age neonates of ≤31 weeks gestation were randomized within 72 h of birth to receive GM-CSF 10 μg/kg per day subcutaneously for 5 days or standard management. The primary outcome was sepsis-free survival to 14 days from trial entry. The investigators found that neutrophil counts increased significantly more rapidly in infants treated with GM-CSF than in control infants during the first 11 days; however, there was no significant difference in sepsis-free survival for all infants (Carr et al. 2009). Hence, GM-CSF can be used to increase the neutrophil count but may not provide any survival benefit in septic neonates (Parravicini et al. 2002; Bedford Russell et al. 2001; La Gamma and De Castro 2002; Banerjea and Speer 2002; Goldman et al. 1998) (Table 2).

108.6.3 Prolonged Monocyte Deactivation and Immune Paralysis

Monocyte deactivation (<30% HLA-DR expression or 8,000 HLA-DR molecules, or ex vivo whole blood TNF response <200 pg/ml for >5 days) is associated with immune paralysis and increased risk of late-onset sepsis from a secondary infection in children (Volk et al. 1996). Hallwirth and colleagues have reported that cord monocyte deactivation is a reliable parameter for predicting EOD in VLBW infants (Hallwirth et al. 2002). The anti-inflammatory cytokine, IL-10, and the reactive oxygen species, nitric oxide, and peroxynitrite radicals both deactivate monocytes. This common response becomes pathogenic when it lasts for more than 5 days. GM-CSF and interferon reverse this process ex vivo (Table 2).

108.6.4 Prolonged Lymphopenia and Lymphoid Depletion Syndrome

Lymphopenia ($<1{,}000/mm^3$ for >7 days) is associated with the development of secondary infection, unresolving multiple organ failure, and the finding of lymphoid depletion at autopsy in children (Hotchkiss et al. 2001). Gurevitch et al. examined autopsies from low-birth-weight newborns with sepsis similarly reported lymphoid depletion

(Gurevich et al. 1995). At present prophylactic and empiric antifungal/antiviral strategies may be appropriately considered in these patients as per the clinical experience with patients with low CD4 counts from other immunodeficiency diseases. IVIG therapy should be considered if B-cell numbers are substantially depleted along with hypogammaglobulinemia (IgG level <500 mg/dl) (Table 2).

108.6.5 Antibiotic Prophylaxis, Empiric Therapy, and Antibiotic Resistance

Because EOD is commonly caused by GBS and LOD is commonly caused by *Staphylococcus epidermidis*, antibiotic prophylaxis therapies have been considered. Antepartum and intrapartum antibiotic use has markedly reduced the incidence of GBS EOD, but, not surprisingly, has led to increased incidence of neonatal sepsis caused by resistant organisms. Vancomycin and teicoplanin prophylaxes are both effective in reducing LOD with *Staphylococcus* species (Moller et al. 1997), but routine prophylaxis is not yet recommended because of concern for emergence of resistant organisms (Moller et al. 1997). Fluconazole prophylaxis has been very effective in preventing Candida sepsis in VLBW infants and is recommended (Kaufman 2004). Empirical antifungal therapy should be strongly considered for infants with gestational age <25 weeks, thrombocytopenia, history of third-generation cephalosporin, or carbapenem exposure for 7 days (Benjamin et al. 2003). Empiric use of amphotericin for VLBW babies with risk factors for fungal infection has also been recommended (Brian Smith et al. 2005; Chapman 2003).

108.7 Supporting Organs During Multiple Organ Failure: What's New?

Acute respiratory distress syndrome – Overdistention of alveoli results in systemic inflammation with systemic release of inflammatory cytokines and depression of immunity. Lung protection ventilation strategies which limit volutrauma are prudent (The Acute Respiratory Distress Syndrome 2000).

Acute renal failure – Investigators have demonstrated the efficacy of continuous veno-venous hemofiltration in children with meningococcal septic shock (Smith et al. 1997). A recent randomized controlled adult study showed survival benefit with daily dialysis compared to intermittent dialysis therapy in patients with acute renal failure in the ICU (Schiffl et al. 2002). Peritoneal dialysis/hemofiltration, continuous veno-venous hemofiltration, or continuous arteriovenous hemofiltration can be successfully performed in newborns (Schroder et al. 1992).

Steroid and drug metabolism – Reactive oxygen species impair cytochrome P450 activity. This leads to reduction of cortisol and aldosterone synthesis and reduced drug metabolism during sepsis and multiple organ failure. Newborns have an age-specific reduced cortisol synthesis for a given substrate (17-OH progesterone), as well as reduced drug metabolism due to an immature cytochrome P450 system (Carcillo et al. 2003). Hydrocortisone has reversed epinephrine-resistant septic shock in premature infants with adrenal insufficiency. In a retrospective observational study, 117 infants treated with hydrocortisone for refractory hypotension were reviewed. Refractory hypotension was defined as a mean arterial pressure (MAP) less than the gestational age (GA) despite a total inotrope dose of 20 μg/kg/min. Patients treated with hydrocortisone demonstrated improved hemodynamics and decreased inotropic dose at 6, 12, and 24 h. The incidence of side effects, i.e., intraventricular hemorrhage, periventricular leukomalacia, sepsis, and spontaneous intestinal perforation, was similar to institutional historic controls (Baker et al. 2008).

108.8 Summary

Newborn sepsis remains a major international health-care problem, particularly in low-birthweight infants. It is a significant cause of mortality and neurologic morbidity including cerebral palsy. As with all major health-care problems, resources should be invested in prevention and early intervention programs. Antepartum GBS

prophylaxis has been successful in reducing incidence and mortality. Early clinical signs of sepsis include tachycardia, apnea or tachypnea, poor feeding, and temperature instability. While no one biomarker can diagnose sepsis early, biomarker panel including IL-6, procalcitonin, IL-1 receptor antagonist, IL-8, IL-10, TNF, and CRP might be a better diagnostic tool. Early clinical diagnosis and therapy are the keys to these improved outcomes. However, because antibiotics ultimately are met with the development of resistant organisms, a commitment to the development of specific maternal immunizations (e.g., GBS) in the developed world and the use of heterologous newborn immunizations (e.g., BCG) in the developing world is recommended.

When sepsis is not recognized and treated early, septic shock becomes the predominant predictor of mortality and neurologic morbidity. In contrast to older children, septic shock in neonates occurs primarily secondary to cardiac failure, not vascular failure. This state of cardiac failure is commonly associated with systemic pulmonary hypertension. Hence therapies including volume resuscitation, inotropic support, and right ventricle afterload reduction are the mainstays of treatment. ECMO can be lifesaving for term newborns with refractory shock. At present no specific therapies have been approved for thrombotic complications (DIC or TTP/HUS) in newborns; hence plasma therapies remain the mainstay.

Sepsis is all too common in very-low-birthweight newborns (20–30% of the neonatal population) with a predominant late (after 72 h) rather than early onset. Development of early diagnostic tests, infection prevention practices, and immunostimulant therapies is urgently needed for this population not only to improve survival but to reduce periventricular leukomalacia.

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