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Pathophysiology and Treatment of Septic Shock in Neonates

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Keywords

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Introduction

Sepsis or serious infection within the first four weeks of life kills greater than 1 million newborns globally every year1. 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])2–5. Neonates with sepsis may present in or progress to septic shock, exemplified initially by cardiovascular dysfunction requiring fluid resuscitation or inotropic support6. If the progression of infection cannot be stopped, end organ damage and death become much more likely. 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. Previous clinical investigations into neonatal sepsis and shock have largely focused on diagnostic markers. Descriptions of septic shock are predominantly case reports on very small numbers, mixed populations with severe respiratory distress syndrome (RDS) and sepsis, or pediatric studies that included neonates that were not evaluated as a separate group8–24.

Definitions of the sepsis continuum

In 2005, definitions for pediatric infection, systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, and organ dysfunction were suggested that included *term* neonates (0– 7 days), newborns (1 week – 1 month) and infants (1 month – 1 year) [Box 1A/B][25]. Working definitions for the sepsis continuum specific for preterm neonates are needed to provide a uniform basis for clinicians and researchers to study and diagnose severe sepsis in this particularly vulnerable population. We have proposed modifications to the consensus definitions to incorporate preterm infants that are also presented in Box 1A/B.

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Why have definitions of sepsis and septic shock not been established for preterm neonates? These patients present diagnostic challenges that are clouded by immaturity of organ systems and transitional physiology. For example, normal blood pressure values for gestational and postnatal age have not been established, particularly in the very low birth weight neonate (VLBW, <1500g), largely because blood pressure alone cannot identify abnormal cardiac output, organ perfusion, and oxygen delivery[26]. In the absence of normative values, it is nearly impossible to establish parameters that are associated with poor outcome. Perhaps the most obvious limitation is the differences in monitoring capabilities between the preterm neonate and older, physically larger patients. For example, pulmonary artery catheterization may be used in children or adults to monitor the course of septic shock, but this is not feasible in small neonates.. For these reasons, the hemodynamic response to septic shock and optimum clinical interventions in preterm neonates are not well understood.

Risk factors for development of neonatal septic shock

Risk factors for a neonate developing sepsis have been well-described Though risk factors for septic shock will overlap with those for sepsis, specific antenatal and postnatal risks for the development of neonatal septic shock have not been described in depth.

Maternal factors contributing to the risk of neonatal sepsis are shown in Box 2 and include prematurity, low birth weight, rectovaginal colonization with group B streptococcus (GBS), prolonged rupture of membranes, maternal intrapartum fever, and chorioamnionitis [2, 3, 27–33].

Factors in the postnatal period associated with an increased risk of sepsis or septic shock include male gender, birth weight <1000 grams, hypogammaglobulinemia, intravenous alimentation, central venous catheters, use of steroids or drugs that decrease gastric acid acidity, and prolonged duration of mechanical ventilation. The development of severe necrotizing enterocolitis (NEC) is also associated with severe sepsis, shock, multi-organ system failure and death[34, 35]. Genetic evaluations in children and adults have identified a number of polymorphisms in cytokines and their receptors as well as other host defense proteins that may either increase or decrease risk for sepsis or poor outcome from sepsis [36–41]. However, gene polymorphism studies in neonates have not yielded consistent results due to relatively small sample sizes and a general lack of formal prospective validation studies[42–56].

Microbiology of sepsis and septic shock in neonates

A number of pathogens have been associated with sepsis in the neonatal period. The predominant agents are bacterial, but viruses including herpes simplex and enteroviruses have been associated fulminant neonatal sepsis with high mortality[57–59]. In one study, gram-negative infection accounted for 38% of cases of septic shock and 62.5% of sepsis mortality7. These results are similar to those from a previous study that showed Gram-negative infection was associated with 69% of cases of fulminant septic shock (death within 48 hours) [60]. Gram-positive etiologies of sepsis are dominated by GBS and coagulase-negative staphylococcus (CoNS)[3, 61]. While lethality and shock from GBS have been well described, mortality associated with CoNS is extremely low[3, 4] and septic shock is rare[60]. Fungi (primarily Candida albicans) may also lead to fulminant neonatal sepsis and predominantly affect ELBW infants[3, 62, 63]. It is important to note that studies of neonatal sepsis are confounded by the limitations of sensitivity of the current diagnostic “gold standard” blood culture. Sample volume constraints in newborns may undermine the identification of organisms causing shock, particularly in preterm infants64. For this reason, many studies combine the entities “culture-proven sepsis” and “clinical sepsis” (cultures negative but strong clinical suspicion leading to long-term antibiotic treatment). Improved techniques such as molecular

diagnostics, discussed in Chapter xx, may help to delineate which patients with "clinical sepsis" truly have sepsis versus other causes of clinical deterioration.

Pathophysiology of sepsis and shock:Molecular and cellular events

Molecular signaling: PRRs, PAMPs, and DAMPs

Pathogen recognition by local immune sentinel cells is the first step towards the development of an immune response once local barrier function has been compromised [Figure 1]. Recognition is initiated via the activation of pattern recognition receptors (PRRs)65 including Toll-like receptors (TLRs). There are 10 known TLRs in humans, and each receptor has a specific molecular activation trigger66, 67. TLRs, present on and within multiple cell types, recognize extracellular and intracellular pathogens by their signature microbial products known as pathogen associated molecular patterns (PAMPs). Lipopolysaccharide (LPS, endotoxin) on gram negative bacteria is the prototypic PAMP and a key mediator of systemic inflammation, septic shock, and multi-organ failure and death68. LPS signals primarily through TLR4 in conjunction with the cell surface adaptor proteins CD14 and MD265. Gram positive bacterial PAMPS such as lipoteichoic acid signal primarily through TLR2, while viral PAMPS such as double-stranded RNA signal through TLR3. Microorganisms often stimulate more than one TLR simultaneously allowing for initiation of a pathogen-specific host response67, 69. Ligandreceptor binding results in downstream production of cytokines and chemokines as well as activation of other antimicrobial effector mechanisms[66].

Intracellular non-TLR PRRs include NOD-like receptors (NLRs) and RIG-like receptors (RLRs). Nucleotide-binding oligomerization domain (a NLR) detects peptidoglycan of gram positive bacteria in the cytosol, and retinoic-acid-inducible protein I (RIG-I) detects viral double-stranded RNA and induce type I interferon production[67]. Once engaged by pathogens, these PRRs initiate an immune response including the production of proinflammatory cytokines via mitogen activated protein kinase (MAPK) and the transcription factor nuclear factor κB (NF-κB). To date, RLR and NLR function have not been examined in neonates with sepsis.

Since TLRs play an essential role in recognition and response to pathogens, alterations in their expression, structure, signaling pathways, and function can have consequences to host defense. Polymorphisms or mutations in TLRs are associated with increased risk for infection in adults[70–73] and in children74–76 but are less well characterized in neonates. Upregulation of TLR2 and TLR4 mRNA in leukocytes of neonates occurs during Gram-positive and Gram-negative infection, respectively, across gestational ages77. Dysregulation or overexpression of TLR4 is involved in the development of necrotizing enterocolitis in experimental animal models[78], demonstrating the importance of TLRs in the initial immune response to pathogens and their role in neonatal sepsis and septic shock. Mutations have been identified in NLRs that are involved in the pathogenesis of Neonatal-Onset Multisystem Inflammatory Disease (cryopyrin)[79]. Investigation for mutations in specific domains of NLRs has been performed to identify causes of abnormal inflammatory signaling leading to NEC, but no associations have been identified80. RLR mutations have been identified but are of unknown clinical significance81. The role that intracellular PRR play is of particular interest with respect to defense against *Listeria monocytogenes*, a pathogen particularly virulent in neonates, which can be recognized by NLRs[82].

Mutations or decreased expression of co-stimulatory molecules necessary for TLR activation are also associated with an increased risk for infection. For example, the lipopolysaccharide (LPS, endotoxin) co-receptor CD14 and LPS binding protein (LBP, which binds intravascular LPS and facilitates its attachment to CD14) are both increased during neonatal sepsis[83–85]. Genetic variations in these proteins have been associated with increased risk for sepsis in

adults47, 49, 50. Gene polymorphisms in myeloid differentiation-2 (MD-2), a small protein involved in LPS signaling through TLR4, increase the risk for organ dysfunction and sepsis in adults86 but the significance in neonates is unknown. Polymorphisms in select cytokines (IL-6 and IL-10) or their receptors (IL-4ra53), and constituents of their signaling pathways, may be associated with increased risk of infection42, 43, 46, 51, though there is not complete agreement on these findings44, 52, 54. Polymorphisms in post-TLR activation intracellular signaling molecules including myeloid differentiation factor 88(MyD88)87, IL-1-receptor-associated kinase 4(IRAK-4)88, and NF-κB essential modulator (NEMO)89 are associated with invasive bacterial infection in older populations. These genetic factors predisposing to sepsis are likely just the tip of the iceberg as evaluation of intracellular second messenger inflammatory signaling systems is a relatively new and active area of research.

In addition to being activated by PAMPs, TLRs can be activated by DAMPs (damage or danger associated molecular patterns). such as intracellular proteins or mediators released by dying or damaged cells [Figure 1]. High mobility group box-1 (HMGB-1), an important DAMP, is involved in the progression of sepsis to septic shock68, 90. HMGB-1 is produced by macrophages or endothelial cells stimulated with LPS or TNF-α and signals through TLR2, TLR4, and receptor for advanced glycation end products (RAGE) 91. Important actions of HMGB-1 include cytokine production, activation of coagulation, and neutrophil recruitment90, 92. HMGB-1 mediates disruption of epithelial junctions within the gut via the induction of reactive nitrogen intermediates (RNI) leading to increased bacterial translocation93. The role of HMGB-1 and RAGE signaling in septic shock in human neonates has not been well studied, but has been linked to the pathophysiology of NEC in a preclinical model94.

Other DAMPs including heat shock proteins (Hsps) and uric acid may also contribute to the pathophysiology of septic shock. Hsps activate proinflammatory signaling through TLRs, regulate neutrophil function, are immune adjuvants, and are elevated in septic adults and children[95]. Elevated Hsp60 and Hsp70 measured within 24 hours of PICU admission was associated with pediatric septic shock and there was a strong trend towards a significant association with death96, 97. Hsp production in septic neonates has not been evaluated. Uric acid can increase cytokine production, PMN recruitment, and dendritic cell stimulation98 and may also serve as an antioxidant[99]. Uric acid is reduced in the serum of septic neonates as compared to control neonates[100]. The importance of DAMPs in neonatal sepsis and shock has yet to be determined.

Cytokines, Chemokines, and Adhesion molecules

Following PRR stimulation, production of cytokines and chemokines results in amplification of the innate response directed at the invading organisms [Figure 1]. Elevations of pro-inflammatory cytokines during sepsis and septic shock have been identified including interleukin (IL)-1β, IL-6, IL-8, IL-12, IL-18, interferon gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α)101. Compared to septic adults, septic neonates produce less IL-1β, TNF-α, IFN-γ, and IL-12102–107. The decreased cytokine production is due in part to decreased production of important intracellular mediators of TLR signaling including Myeloid Differentiation Factor 88 (MyD88), Interferon Regulatory Factor 5 (IRF5), and p38 which exhibit gestational age-specific diminution108. In a recent comprehensive study (>140 analytes) of serum from neonates evaluated for late-onset sepsis, IL-18 emerged as a predictive biomarker to differentiate infected from non-infected neonates 109, similar to data from adults with sepsis110. IL-18 reduces PMN apoptosis111, potentiates IFN-g production112, and induces production of TNF-α, IL-1β, and IL-8[113]. IL-18 primes PMNs for degranulation with production of reactive oxygen intermediates (ROI) on subsequent stimulation[114]. Dysregulation of many of these functions linked to IL-18 are seen in sepsis and septic shock.

Pro-inflammatory cytokine production leads to activation of endothelial cells including increased expression of cell adhesion molecules (CAMs) that facilitate leukocyte recruitment and diapedesis [Figure 2]. Upregulation of CAMs [soluble ICAM, VCAM, L, P, and E-selectins, and CD11b/CD18] during sepsis facilitates rolling and extravascular migration of leukocytes[115–118]. Decreased neonatal PMN and monocyte L-selectin and MAC-1 expression impairs accumulation at sites of inflammation[119, 120]. Chemokine gradients produced by endothelial cells and local macrophages are necessary in addition to CAM interactions for effective and specific leukocyte attraction and accumulation. Without adequate leukocyte recruitment, there is increased risk for propagation from a local to a systemic infection. Although poor cellular chemotaxis in the neonate has been observed, it is not likely a result of reduced serum concentrations of chemokines.[121]. Suboptimal chemotaxis may be related to other mechanisms such as poor complement receptor upregulation following stimulation[122], deficiencies in another downstream signaling process[123], or inhibition by bacterial products[124].

A wide variety of chemokines are increased during sepsis including IP-10, CCL5 (RANTES), MCP-1, MIP-1, and IL-8[125]. Other chemo-attractive molecules are also increased in sepsis including complement proteins C3a and C5a, host defense proteins or peptides such as cathelicidins and defensins, and components of invading bacteria themselves[101, 109]. The role of chemoattractive substances in the pathogenesis of severe sepsis is highlighted by recent studies showing IL-8 can be used a stratifying factor for survival.in children[126] and C5a is implicated in sepsis-associated organ dysfunction in adults[68]. Studies of chemokines in neonates with sepsis have shown that IP-10 is a sensitive early marker of infection [125], and decreased levels of CCL5 help predict development of DIC[127].

Anti-inflammatory Response

If inflammatory homeostasis is not restored, the consequences can include a systemic inflammatory response syndrome (SIRS) associated with multi-organ failure and death [Figure 3]. The careful interplay between anti and pro-inflammatory stimuli serves to govern the immune response to allow local pathogen containment but prevent systemic activation leading to excessive inflammatory damage though SIRS[128]. To this end, near simultaneous increases in anti-inflammatory cytokine production occurs during infection, with TGF-β, IL-4, IL-10, IL-11, and IL-13 countering the actions of pro-inflammatory cytokines [101, 129, 130] [Figure 2]. These mediators blunt the activation of phagocytic cells, block fever, modify coagulation factor expression, and decrease production of ROI/RNI, NO, and other vasoactive mediators[131–135]. In addition to the anti-inflammatory cytokines, specific soluble cytokines and receptor antagonists produced during sepsis modulate pro-inflammatory mediator action, including TNFR2 (which regulates the concentration of TNF-α), sIL-6R, sIL2, and IL-1ra. Elevations of these inhibitors have been documented in neonatal sepsis with resolution following effective treatment[130, 136, 137]. The role of these regulatory cytokine inhibitors in the immune response to neonatal sepsis and septic shock has been incompletely characterized. Soluble RAGE (sRAGE) competes with cell-bound RAGE for the binding of HMGB-1 and other RAGE ligands[138], reduces the intensity of the inflammatory response, and is elevated in adults during sepsis[139]. In addition, administration of exogenous sRAGE improved survival and reduced inflammation in infected adult rodents[140].

Role of complement in host defense and sepsis pathophysiology

Complement is an extraordinarily important component of early innate immunity that facilitates killing of bacteria through opsonization and direct microbicidal activity. Complement components also possess chemotactic or anaphylactic activity that increases leukocyte aggregation and local vascular permeability at the site of invasion. In addition, complement components reciprocally activate a number of other important processes such as

coagulation, proinflammatory cytokine production, and leukocyte activation [Figure 3][68]. Dysregulation of complement activation may participate in the untoward effects seen in neonates with severe sepsis or septic shock. Neonates, particularly the very premature, exhibit decreased basal levels of complement proteins and function for both the alternative and classic pathways[141, 142]. Additionally, complement-mediated opsonization is poor in premature neonates and limited in term neonates[143, 144].

Complement-mediated activation of leukocytes during sepsis occurs via upregulated cell surface receptors (CR1 [CD35], CR3 [Mac-1, CD11b/CD18])145, 146. For example, stimulation of CR1 and C5aR, the receptors for C3b and C5a respectively, facilitate opsonization (CR1-C3b), redistribution of blood flow, increased inflammation, platelet aggregation, and release of ROI (C5a–C5aR)147, 148. Additionally, activation of the multifunctional CR3 facilitates leukocyte adhesion, phagocytosis, migration and activation, as well as recognition of a broad range of microbial products149. Upregulation of CR3 on neutrophils following stimulation is blunted in neonates compared to adults and is believed to play a significant role in diminished chemotaxis and transmigration122. Similar to the effects of TLR stimulation, C5a–mediated local leukocyte activation also results in increased cytokine production with subsequent upregulation of adhesion molecules on vascular endothelium allowing for increased cell recruitment to the site of infection[150]. Deficiencies in C5aR found in term neonates as compared to adults may limit the ability to respond to C5a and therefore increase the likelihood of infection[151]. The expression of C5aR on neutrophils of preterm infants has not been quantified.

Complement regulatory proteins modify the effects of complement and prevent potential damage due to over-activation. In particular, CD59 blocks formation of C9 polymerization and target lysis, CD55 destabilizes CR1 and C3 and C5 convertases, and CD35 (CR1) accelerates the deactivation of C3b[152]. The role of these regulators in the neonatal response to sepsis and septic shock is presently unknown. Dysregulation of complement activation can lead to a vicious activation cycle that results in excessive cellular stimulation, cytokine production, endothelial cell activation, and local tissue damage. Dysregulation likely contributes to the development of SIRS and shock [Figure 3][153].

Data in adults link elevated C5a levels with multiple facets of sepsis-associated pathology such as the development of disseminated intravascular coagulation (DIC) via increased tissue factor expression, cardiomyopathy, increased pro-inflammatory cytokine levels and the development of SIRS, adrenal insufficiency, and neutrophil dysfunction[68]. Whether or not C5a or other complement proteins play a role in the development of these phenomena in septic neonates remains to be determined.

Other host defense proteins, acute phase reactants, and opsonins—In addition to the initial inflammatory response and complement activation following pathogen recognition, presence of microbes result in increases in other innate proteins that possess valuable immune function[154]. These components serve to reduce bacterial load and include collectins (e.g. surfactant proteins A and D), lactoferrin, cathelicidins, bacteriocidal permeability increasing protein (BPI), and phospholipase $A_2$155. Acute phase reactant proteins such as CRP (opsonin), haptoglobin and lactoferrin (reduce available iron/antimicrobial peptidelactoferricin), serum amyloid A (cellular recruitment), procalcitonin (unknown function), and others increase during sepsis and provide useful ancillary immune functions101. Neutrophils from term neonates are deficient in BPI, potentially contributing to the increased risk for infection156. Polymorphisms in BPI increase the risk for Gram-negative sepsis in children157, although the impact of these polymorphisms in neonates is unknown. Sepsis results in an increase in other serum components with opsoninic function including fibronectin and natural antibodies (predominantly IgM) produced by circulating B1

lymphocytes158–160. Despite these increases, neonatal plasma has significantly impaired opsonizing activity compared to adults that increases the likelihood of progression to systemic infection161.

Role of dysregulated coagulation in severe sepsis: Development of a pro-coagulant state in the microvasculature surrounding a focal site of infection is a natural host defense mechanism, trapping invading pathogens and preventing further dissemination [Figure 2]. However, like the inflammatory response, if the pro-coagulant response to infection escalates unchecked, it can lead to disseminated intravascular coagulation (DIC) resulting in severe tissue and organ damage. [Figure 3] (DIC)[162]. Neonates with early elevated ratios of serum inflammatory to anti-inflammatory cytokines during sepsis have an increased risk of developing DIC127. This finding is consistent with the elevated serum levels of IL-659 and high frequency of DIC seen with disseminated HSV infection163.

Initiation of coagulation cascades during infection may begin with activated neutrophils, monocytes, or endothelium, which express increased tissue factor apoprotein164, 165.Activation of tissue factor leads to increased clotting proteins including thrombin-antithrombin complex (TAT), plasminogen activator inhibitor (PAI), and plasmin-α2-antiplasmin complex[166]. There is also a shift towards inactivation of protein S and depletion of anticoagulant proteins including antithrombin III (ATIII) and protein C167, 168. A small study demonstrated low protein C levels in preterm neonates with sepsis predicted death169. In DIC, platelets are consumed in microthrombi creating a state of thrombocytopenia; a very common finding in infected neonates170. The longest duration and lowest initial and nadir platelet levels have been noted during neonatal Gram-negative and fungal infections[171], and this thrombocytopenia may or may not be associated with DIC. Decreased platelet function in preterm neonates with sepsis further increases the risk for bleeding[172]. In ELBW infants, platelets are hyporeactive for the first few days after birth, complicating the ability of the immune system to contain a microbiological threat and increasing the risk for hemorrhage[173].

Role of the neutrophil in septic shock

The most important means of early innate cellular defense against bacterial invasion in neonates is the neutrophil or polymorphonuclear leukocyte (PMN). Neonatal PMNs exhibit quantitative and qualitative deficits as compared to adult cells[174, 175]. A complete discussion of these deficits is presented within chapter XXXX in this issue. Three aspects of PMN function with particular relevance to neonatal severe sepsis and septic shock deserve brief mention: neutropenia, decreased deformability, and delayed apoptosis.

Rapid depletion of neonatal marrow PMN reserves during infection176 can lead to neutropenia with consequent impaired antimicrobial defenses and significantly increased risk for death177. Neutropenia is particularly common in Gram-negative sepsis in neonates[178]. Release of immature neutrophil forms (bands) which have even greater dysfunction than mature neonatal neutrophils[179] can further predispose to adverse outcomes. PMN respiratory burst activity is also suppressed during sepsis and may contribute to poor microbicidal activity180–182.

PMNs of neonates have reduced deformability compared to PMNs of adults, which, combined with the low blood pressure/flow state associated with septic shock, increases the risk of microvascular occlusion[174, 183]. Irreversible aggregation of newborn PMNs in the vascular space leads to decreased diapedesis, rapid depletion of bone marrow reserves, vascular crowding[183], and increased likelihood of compromised tissue perfusion [184] leading to organ dysfunction.

Neutrophils, while essential for combating pathogens, can also cause significant tissue damage and thus play a role in progression from sepsis to multi-organ system dysfunction. Reactive oxygen and nitrogen intermediates and proteolytic enzymes produced by PMNs can be released extracellularly, via activation of membrane associated-NADPH oxidase. Extracellular release of these reactive intermediates and enzymes can lead to destruction of non-phagocytized bacteria but also can cause local tissue destruction185. Increased levels of neutrophil elastase as well as the neutrophil activators urokinase plasminogen activator, and urokinase plasminogen activator receptor have been described in infected neonates109. Compared to adult PMNs, neonatal PMNs exhibit delayed apoptosis186, 187 as well as sustained capacity for activation (CD11b upregulation) and cytotoxic function (ROI production) that contributes to tissue damage188. Neutrophil-mediated damage may include endothelial and lung injury (including surfactant inactivation189) [Figure 2] in addition to other organ dysfunction [Figure 3].

Other innate cellular contributions to sepsis

Many other cells besides neutrophils are involved in the development of an immune response to infection, but the role that these cells play in the development of neonatal septic shock is incompletely characterized. Monocytes, macrophages, and dendritic cells amplify cellular recruitment through production of inflammatory mediators, phagocytosis and killing of pathogens, and antigen presentation to cells of the adaptive immune system. Important substances produced by stimulated monocytes that may contribute to septic shock include complement components, cytokines (both pro and anti-inflammatory), coagulation factors, and extracellular matrix proteins [Figure 1][190]. The role of NK cells in neonatal bacterial sepsis is incompletely defined. Despite activation[191], NK cytotoxicity is deficient in both sepsis and recurrent infections[192, 193]. Circulating NK cells are decreased with neonatal shock[194]. Further studies are necessary to more clearly define the role of NK cells in neonatal sepsis and shock.

Mast cells play a role in the response to pathogen invasion via production of histamines (which promote vasodilation and upregulation of P-selectin) and cytokines (TNF-α, IL-1α/β), and by promoting neutrophil recruitment, direct bacterial phagocytosis, and antigen presentation[195]. The production of histamine by mast cells likely contributes to the vasodilation associated with septic shock. Like eosinophils and PMNs, mast cells of adults are also capable of bacterial killing via generation of extracellular traps, like the neutrophil NETS described previously 196. This means of immune protection has not been investigated in neonates. Mast cells may also alter adaptive immune function by patterning the T_H2 immunosuppressive phenotype seen in the neonate and therefore contribute to the increased risk of infection. Immature dendritic cells exposed to histamine and LPS during maturation exhibit altered T-cell polarizing activity with predominance of T_H2 phenotype via increased production of IL-10 and decreased production of IL-12[197]. Furthermore, compared to mast cells of adults[198] stimulated mast cells from neonates secrete significantly more histamine which may contribute to vasodilation and the development of shock[199].

Role of the endothelium and vasoactive mediators in septic shock—Vascular endothelium has not historically been considered part of the innate cellular defenses, but recent studies have shown the importance of these sentinel cells in the early recognition and containment of microbial invasion. The endothelium can be a two-edged sword, however, as excessive activation can lead to vascular dilation and leak which are a driving forces behind the severe consequences of septic shock [Figure 3] [124,200].

Expression of TLRs allows endothelium to become activated in the presence of microbial components, leading to production of cytokines, chemokines, and adhesion molecules which attract circulating leukocytes and facilitate adherence[124]. Vasoactive substances released from

activated leukocytes, platelets, and endothelial cells are shown in Figure 2 and include platelet-activating factor (PAF), thromboxane (TBX), leukotrienes (LTE), nitric oxide (NO), histamine, bradykinin, and prostaglandins (PGE)[201, 202]. Activated PMNs produce phospholipase A2 (PLA_2), which is elevated in the serum of neonates with sepsis[203] and leads to generation of vasoactive substances including PGE and LTE. Thromboxane produced by activated platelets and endothelin produced by activated endothelium [204] are potent vasoconstrictors that participate in the development of PPHN[205–208]. Systemic overproduction of cytokines and vasoactive substances is associated with circulatory alterations and organ failure seen in severe sepsis and septic shock [Figure 3][25, 209–212]. For example, the balance of NO and endothelin-1 (ET-1) may be disrupted with endothelial damage, favoring the constrictive effects of ET-1 leading to ischemia and injury. This may explain in part why NO inhibitors increased mortality in adults with septic shock[213].

Activated or damaged endothelium establishes a prothrombotic environment that can result in local microvascular occlusion[165] or progress to DIC214. Endothelial cell apoptosis, detachment from the lamina, and alterations in vascular tone combine to promote capillary leak of proteins and fluid leading to hypovolemia and shock215. The role of endothelial activation during sepsis and septic shock in neonates, particularly in the premature infant, has not been thoroughly investigated. Adhesion molecules E and P selectin, expressed and secreted by activated endothelium, are increased in the serum of septic neonates109 and likely reflect significant endothelial activation. Toxins from GBS have been shown to damage pulmonary endothelium[216] and likely participate in pulmonary complications associated with GBS pneumonia such as ARDS and pulmonary hypertension (PPHN)[217]. Using transgenic mice, it was recently shown that pulmonary endothelial cells sense bloodborne bacteria and their products124 while alveolar macrophages patrol the airspaces for pathogens218. These data help to explain in part the occurrence of ARDS and PPHN associated with severe sepsis in the absence of a primary pulmonary infectious focus.

Pathophysiology of septic shock: Cardiovascular and other organ effects

Cardiovascular effects

The hemodynamic response to sepsis has been less well characterized in premature and term neonates compared with children and adults, and the hemodynamic abnormalities are significantly more variable219. Factors contributing to developmental differences in hemodynamic responses include altered structure and function of cardiomyocytes, limited ability to increase stroke volume and contractility, and contributions of the transition from fetal to neonatal circulation[220]. A patent ductus arteriosus (PDA) and the presence of PPHN are significant modifying factors for the management of hypotension and hypoxia. In preterm infants with a PDA, aggressive volume administration to treat low blood pressure may lead to fluid overload, pulmonary edema, or heart failure. In the term infant with severe PPHN, on the other hand, aggressive volume and vasoactive medication administration to maintain a normal blood pressure may be beneficial by reducing right to left shunting and improving oxygenation. Although cardiomyopathy and heart failure may occasionally complicate sepsis in neonates, underlying coronary artery disease or other chronic cardiac conditions often present in septic adults do not complicate septic shock in the neonate.

In adults, septic shock is most commonly characterized by reduced systemic vascular resistance and elevated cardiac index[221]. In children, a nonhyperdynamic state with reduced cardiac output and increased systemic vascular resistance is most common[219, 222–224]. The hemodynamic presentation in neonates is much more variable219 and complicated by an unclear association between a “normal” blood pressure and adequate systemic blood flow[225, 226]. Abnormal peripheral vasoregulation with or with out myocardial dysfunction are the primary mechanisms for the hypotension accompanying septic shock in the

neonate[227]. Neonates with sepsis may present with tachycardia, poor perfusion and “normal” blood pressure (high SVR) or with hypotension and either adequate perfusion (warm shock, vasodilation) or inadequate perfusion (cold shock, vasoconstriction). These distinctions may be important for directing appropriate therapy to restore tissue perfusion, as discussed later.

Multi-organ dysfunction syndrome

Septic shock that leads to multi-organ failure or MODS carries a dismal prognosis. Poor cardiac output and microcirculatory failure, sometimes combined with formation of microthrombi and DIC, can lead to compromised perfusion to the kidney[228, 229], liver[230], gut[231], and CNS[232] Figure 3][59, 210, 233, 234] Recent studies suggest that the mechanism of organ failure in sepsis may relate to decreased oxygen utilization associated with mitochondrial dysfunction rather than or in addition to poor oxygen delivery to tissues[235, 236]. Many other organ systems can be compromised in the setting of septic shock. Pulmonary complications include acute respiratory distress syndrome[237], secondary surfactant deficiency[238], pulmonary edema, pneumonia[23], and PPHN, [220, 237]. Endocrine abnormalities may include adrenal insufficiency associated with refractory hypotension[239] and altered thyroid function[240]. Lymphocyte loss secondary to thymic involution and splenocyte apoptosis may also be present and may lead to a state of immune compromise following the acute phase of sepsis[241–246]. The importance of this finding has been shown in infected adults[247–249], but the impact in neonates in whom adaptive immune function is immature is unknown. In a transgenic mouse model, neonatal animals lacking an adaptive immune system showed no difference in survival with polymicrobial sepsis compared to wild-type controls. This is in stark contrast to findings in adult mice[250]. Hematologic findings during severe sepsis may include thrombocytopenia[170], neutropenia[177], and coagulation abnormalities including disseminated intravascular coagulation[162]. Finally, sepsis can lead to metabolic and nutritional consequences. Increased energy expenditure and oxygen consumption[251] and decreased mitochondrial oxidative function precipitated by hypoxia and the presence of damaging free radicals may lead to impaired growth and energy failure[252, 253]. The importance of providing optimum nutritional support in septic adults and children is increasingly recognized and should be considered in septic neonates as well.

Treatment of sepsis and septic shock

Initial resuscitation

Treatment guidelines for the management of severe sepsis and septic shock have been established for adults[254] children and term neonates[255], but no such consensus guidelines exist for preterm neonates. We have attempted to incorporate the special circumstances related to premature physiology into the framework of treatment guidelines for term infants [Figure 4]. Development, testing, and acceptance of consensus guidelines for classification and management of preterm neonates with sepsis and septic shock are urgently needed in order to more systematically assess, diagnose, and treat these conditions.

As with all emergencies in neonatology, management of septic shock begins with airway, breathing, and circulation. Septic neonates often present with apnea or severe respiratory distress and may require intubation[3, 4]. Following establishment of a secure airway and maintenance of lung volume for adequate gas exchange, administration of antibiotics and continuing assessment for cardiovascular dysfunction is critical. Shortly after birth, an umbilical vein catheter can be used for resuscitation but beyond this time, other peripheral or central venous access is essential for volume resuscitation, antibiotic administration, and pressor therapy. Timely therapy, including rapid restoration of adequate tissue perfusion, has been shown to improve outcomes in adults and children with sepsis and should be the goal in neonates as well.

Therapeutic Endpoints

In absence of widely available or well-tested methods for quantifying hemodynamic compromise in septic shock in neonates, clinicians generally rely on vital signs and physical examination for decisions about therapy. Although mean arterial pressure (MAP) may not reflect systemic blood flow, monitoring blood pressure and other measures such as capillary refill time and urine output provide indirect information on the adequacy of organ blood flow. Suggestions for cardiovascular therapeutic endpoints in term neonates include a capillary refill time of < 2 seconds, normal pulses without differential between peripheral and central pulses, warm extremities, urine output greater than 1ml/kg/hr, low serum lactate, and mixed venous saturation of >70%[256]. Therapeutic endpoints in premature neonates have not been established but the goals for term infants seem reasonable. ELBW infants present the greatest challenge for determination of therapeutic endpoints in septic shock. Assessment of mean arterial pressure, urine output and capillary refill may not be particularly useful determinates of systemic blood flow in ELBW infants, particularly in the first 72 hours of life257. In addition, the contribution of fetal hemoglobin may complicate accurate determination of central venous oxygen saturation ($ScvO_2$) in neonates. $ScvO_2$ obtained using hemoglobin A calibration is 4–7% higher compared to $ScvO_2$ that accounts for fetal hemoglobin[258] implying that perhaps the goal ScvO2 should be different in neonates than in older patients for optimum tissue oxygen delivery.

In the future, monitoring techniques such as functional echocardiography (FE) and near-infrared spectroscopy (NIRS) may provide physiologic data to optimize management of septic shock. FE provides a bedside means to assess cardiac output, peripheral vascular resistance, and organ blood flow in response to volume, colloid, and vasoactive medications259, 260. FE can also be used to assess superior vena cava (SVC) flow, which has been suggested as a surrogate marker for cerebral blood flow261 and should be maintained ≥40ml/kg/min262. Prolonged decreases in SVC flow are associated with impaired neurodevelopmental outcome in very preterm neonates263. In the absence of FE to monitor SVC flow, A capillary refill time of >4 seconds combined with a serum lactate concentration of >4 mmol/L had a specificity of 97% for identifying VLBW infants with a low SVC flow state on the first day of life264. NIRS can be used to monitor end organ perfusion non-invasively265 and is used often in neonates with congenital heart disease[266]. A combination of FE and NIRS, in conjunction with traditional measures (MAP, SpO2, capillary refill, urine output) as well as intermittent laboratory evaluations of tissue perfusion such as pH, mixed venous saturation, lactate, and base deficit would be ideal for monitoring severity of septic shock and response to therapy.

Management of hypotension and cardiovascular support

An algorithm for time-sensitive, goal-directed stepwise management of hemodynamic support for the term newborn with septic shock has been established and should be followed[255]. Preterm neonates require specific caveats to this algorithm due to their unique physiology and risk for complications [Figure 4].

In contrast to term neonates, the definition of hypotension and shock in preterm neonates is less clear, particularly in the immediate newborn period26. Blood pressure may be a poor indicator of systemic blood flow in preterm neonates225, yet objective measures of adequacy of tissue perfusion and oxygenation delivery are lacking. Another confounding variable in the management of neonatal shock is that inotrope use (dopamine, dobutamine) in hypotensive preterm neonates has not been shown to significantly improve short or long-term outcomes227, 267, 268. These considerations notwithstanding, and in absence of evidence of harm, some neonatologists advocate treating hypotension in preterm neonates to achieve a mean arterial pressure (MAP) of greater than or equal to 30mm Hg. This goal MAP is based in part on a small study showing improved cerebral blood flow autoregulation above this

threshold269. However, a gestational age-based cutoff for "normal" blood pressure (goal MAP > GA) is used at many tertiary centers, especially in the first 3 days after birth. Clearly, more studies are required to determine whether targeting a specific blood pressure improves outcomes in preterm infants.

Once a decision is made to treat hypotension with or without shock in a neonate, the recommended initial step is a fluid bolus (crystalloid). Though there is less data in neonates to support this intervention, it remains the accepted clinical practice to treat and monitor closely for signs of intravascular volume depletion227. In term infants or older preterm infants, aggressive volume expansion (20–40 ml/kg) should be considered. In contrast to outcomes with early aggressive fluid resuscitation in older populations270, there is insufficient evidence to support early volume expansion in very preterm neonates271 and there is a significant risk of intracranial hemorrhage associated with rapid volume expansion in the first few days after birth272. In hypotensive preterm neonates, it is recommended that a single bolus of saline (10–20ml/kg over 30–60 minutes) be given and if further intervention is necessary to begin vasoactive medications268. In cases of obvious acute volume loss in preterm infants, more volume may be needed.

Dopamine is generally the first line vasoactive drug, with a starting dose of 5–10μg/kg/minute227 and dose escalation as needed. For neonates with shock, which is unresolved with volume resuscitation and dopamine, several possibilities exist for additional therapy, including glucocorticoids (see below), other catecholamines, and inotropes/vasodilators. Epinephrine or norepinephrine infusions for refractory shock in neonates have been studied to a very limited extent. Neonates with vasodilatory shock may have a positive response to the alpha-adrenergic vasoconstrictive effect of these agents. A recent report in term neonates showed the addition of noradrenaline to existing therapy (after fluid loading and dopamine or dobutamine infusion) resulted in increased blood pressure and decreased tissue lactate18. In another study, low-dose epinephrine was found as effective as low/moderate-dose dopamine for increasing blood pressure, cerebral blood volume, and cerebral oxygen delivery in VLBW infants273. Patients with depressed myocardial function may benefit from infusion of dobutamine for both inotropy and vasodilation. In a study of 42 preterm neonates with low systemic blood flow (as determined by low superior vena cava flow262) in the first 24h after birth, dobutamine treatment improved and maintained systemic blood flow better than dopamine274, 275. As a caution, dobutamine, particularly in high doses, can increase myocardial oxygen demand due to β1 adrenergic stimulation. Dobutamine also has chronotropic actions and severe tachycardia may lead to decreased cardiac output that may be corrected by decreasing the dose. Milrinone, a phosphodiesterase inhibitor and inodilator, has not been studied in neonatal septic shock but has been used in pediatric patients with septic shock276 277. In a study of patients aged 9 months-15 years with volume-resuscitated catecholamine-resistant nonhyperdynamic septic shock milrinone increased cardiac index, stroke volume, and oxygen delivery and decreased systemic vascular resistance without increasing heart rate or blood pressure[276]. Another alternative agent for treating septic shock is the vasoconstrictor arginine-vasopressin (AVP) or its longer half-life analogue terlipressin[278]. In a report of six ELBW infants, AVP improved MAP and urine output in patients with septic shock but not in those with non-septic shock279.

Hydrocortisone treatment in neonatal septic shock

Induced by proinflammatory cytokines, endogenous cortisol attenuates the intensity of the systemic inflammatory response associated with severe sepsis and septic shock[280]. Studies in adults have shown that high-dose glucocorticoid therapy does not impact sepsis mortality while low-dose therapy may be beneficial[254]. In one randomized clinical trial, low-dose cortisol treatment in conjunction with standard of care measures was associated with a reduction in

mortality in adults with septic shock and adrenal insufficiency[281]. In another study in adults, cortisol treatment sped the reversal of septic shock but had no effect on mortality[282].

Cortisol production in the neonate is significantly increased early in septic shock[283]. However, very preterm neonates can have relative adrenal insufficiency that may contribute to hemodynamic instability and hypotension. In many clinical practices, hydrocortisone is the third-line agent in treatment of neonatal shock after volume resuscitation and dopamine[227, 268, 284]. In addition to its cytokine-suppressing effects, hydrocortisone has been shown to increase the sensitivity of the cardiovascular system to endogenous or exogenous catecholamines, resulting in improvements in myocardial contractility, stroke volume, effective circulating blood volume, systemic vascular resistance, and urine output. Hydrocortisone has not been evaluated in prospective randomized clinical trials for the treatment of septic shock in the neonate, but it has been shown to increase blood pressure, decrease heart rate and decrease vasoactive medication requirements in preterm and term neonates[284, 285]. If hydrocortisone treatment is considered, obtaining a pre-treatment serum cortisol level is prudent in order to differentiate contributing causes of hypotension. The reader is referred to a recent review on the diagnosis and treatment of adrenal insufficiency in the premature neonate[286].

Pulmonary support

Increased inspired oxygen may be necessary in the setting of neonatal septic shock to maximize tissue oxygen delivery. Decreased pulmonary function (RDS) and/or respiratory failure (apnea) in conjunction with increased tissue demand (increased respiratory and metabolic activity associated with acidosis) contribute to tissue hypoxia. Mechanical ventilation can improve gas exchange through maintenance of lung volume and decreased work of breathing. Administration of exogenous surfactant to neonates with severe pneumonia has been shown to improve oxygenation and gas exchange and reduce the need for ECMO 238.In extremely sick neonates, consideration should be given to maintaining a normal or near-normal pH and oxygen saturations in the 90's rather than allowing permissive hypercapnia and lower saturations which is standard practice in healthy preterm neonates. Normalizing pH and arterial oxygen content may improve cardiac contractility and improve tissue oxygen content, thus decreasing the risk of multiorgan dysfunction and the risk of pulmonary hypertension. Infants with sepsis and PPHN may require inhaled nitric oxide (iNO) in addition to optimized ventilation strategies such as high frequency oscillatory ventilation287. If oxygenation or tissue perfusion remain severely compromised despite optimal medical management, extracorporeal membrane oxygenation (ECMO) should be considered in neonates >2 kg without contraindications such as presence of or high risk for acute hemorrhage 288, 289.

Other supportive care of neonates with septic shock

Avoidance of hypothermia and hypoglycemia is important in neonates with septic shock. With the exception of patients with acute perinatal hypoxic ischemic encephalopathy[290], normothermia should be maintained on a radiant warmer. Use of a 10% glucose solution delivering 4–6 mg/kg/min of glucose combined with frequent monitoring to ensure normoglycemia is recommended. Correction of a significant coagulopathy and anemia (hemoglobin ≤10 g/dL) through the transfusion of fresh frozen plasma or packed red blood cells may also serve to improve blood pressure[291] and oxygen delivery. The importance of providing adequate protein and calories to the infant with sepsis and septic shock cannot be overstated. Increased energy demands promote catabolism if adequate nutrition is not provided. Premature neonates have decreased muscles mass and energy reserves as well as higher baseline nutritional requirements as compared to term neonates292. Elevation of serum triglycerides during sepsis293 and increased serum oxygen-derived free radicals associated with infusions of lipid have prompted some clinicians to withhold or decrease intralipid

infusions. A recent study showed concurrent administration of intralipids in neonates with infection is not associated with hypertriglyceridemia in the absence of liver dysfunction or fetal growth restriction294. It is suggested that intralipid infusions during sepsis or septic shock in neonates be accompanied by careful monitoring of serum triglycerides to avoid hypertriglyceridemia. Maintenance of a carbohydrate to lipid ratio of ~3:1 increases fat utilization and decreases production of oxygen-derived free radicals to levels seen with fat exclusion[295]. Protein intakes of 2–3g/kg/day are generally not associated with azotemia, hyperammonemia, or metabolic acidosis[296] in the setting of sepsis, but monitoring of blood urea nitrogen is recommended. Monitoring liver and renal function is important for assessing the effectiveness of therapies to improve tissue perfusion and for making decisions about dosing medications that require modification for elimination.

Alternative immunologic and pharmacotherapies for neonatal sepsis/shock

There have been many attempts directed at improving outcomes of sepsis and septic shock in neonates via immunomodulation. A complete review of adjunct immunologic therapies in neonatal sepsis is provided in Chapter xxxx.

Outcomes with sepsis and septic shock

The outcome of septic shock in the neonate is dismal. One study reported death or severe sequelae in 52% of infants, with only 28% of infants < 1000grams alive and free of disability at 18 months of age[7]. Variables predictive of mortality include cardiac dysfunction manifested as refractory shock, acute renal failure, neutropenia, increased prothrombin time, excessive bleeding, metabolic acidosis, and hypothermia[231, 297].

Neurodevelopmental outcomes following neonatal sepsis, without stratification for shock, have been studied in some detail and demonstrate significant risk for impairment, particularly in the most premature neonates[298]. VLBW infants with sepsis, compared with those without, have been reported to have significantly increased mortality (21% vs. 9%), longer hospital stay (98 vs. 58 days) and a higher risk of chronic lung disease[31]. ELBW infants are at especially high risk for sepsis-associated adverse neurodevelopmental outcomes, including deafness, cerebral palsy, lower mental and psychomotor development scores, and vision impairment299, 300. In a study of preterm infants, white matter abnormality on MRI at term corrected age predicted neurodevelopmental impairment in those with sepsis compared to those without301. Surgical NEC, which is often accompanied by SIRS or shock, has been associated with significant growth delay and adverse neurodevelopmental outcomes at 18–22 months[302]. A study of ELBW infants with systemic Candidiasis found that 73% died or developed a neurodevelopmental impairment[63] including retinopathy[303]. These data show that the toll of neonatal sepsis and septic shock reaches far beyond the acute complications of organ dysfunction and mortality.

Future considerations

The field of neonatal sepsis is wide open for translational and clinical research. Definitions for the sepsis continuum and treatment algorithms specific for preterm infants should be developed to improve the quality of clinical trials and facilitate metaanalyses of prophylactic and therapeutic interventions. Systems biology and genomic and proteomic studies have yielded important data on septic shock in older populations[304–312] and the utilization of these modern techniques in the study of neonatal inflammation and response to pathogen challenge has begun [109, 138, 313]. With further research, real-time sampling using only microliters of blood will allow rapid identification of highest-risk patients, pathogen-specific responses, and sepsis-staging biomarkers.314. Immaturities of immune function and physiology in the neonate necessitate developmental stage-specific evaluations of sepsis pathophysiology and treatment. Exploration of adjuvant treatments including LPS binding proteins (rBPI315, sCD14 or anti-

CD14316), anti-inflammatory therapies (pentoxifylline317, nicotinic stimulation318, statins319), synthetic host defense peptides (rhSP-D320, lactoferrin321, 322), combination therapies323 (i.e. IVIg and colony stimulating factor), and innate immune priming using TLR agonists[250] may yield improved outcomes. Advances in these areas are urgently needed and are likely to substantially improve long-term outcomes.

Summary

Neonatal septic shock is a devastating condition associated with high morbidity and mortality, Definitions for the sepsis continuum and treatment algorithms specific for premature neonates are needed to improve studies of septic shock and assess benefit from clinical interventions. Unique features of the immature immune system and pathophysiologic responses to sepsis, particularly those of extremely preterm infants, necessitate that clinical trials consider them as a separate group. Keen clinical suspicion and knowledge of risk factors will help to identify those neonates at greatest risk for development of septic shock. Genomic and proteomic approaches, particularly those that utilize very small sample volumes, will increase our understanding of the pathophysiology and direct the development of novel agents for prevention and treatment of severe sepsis and shock in the neonate. Although at present antimicrobial therapy and supportive care remain the foundation of treatment, in the future immunomodulatory agents are likely to improve outcomes for this vulnerable population.

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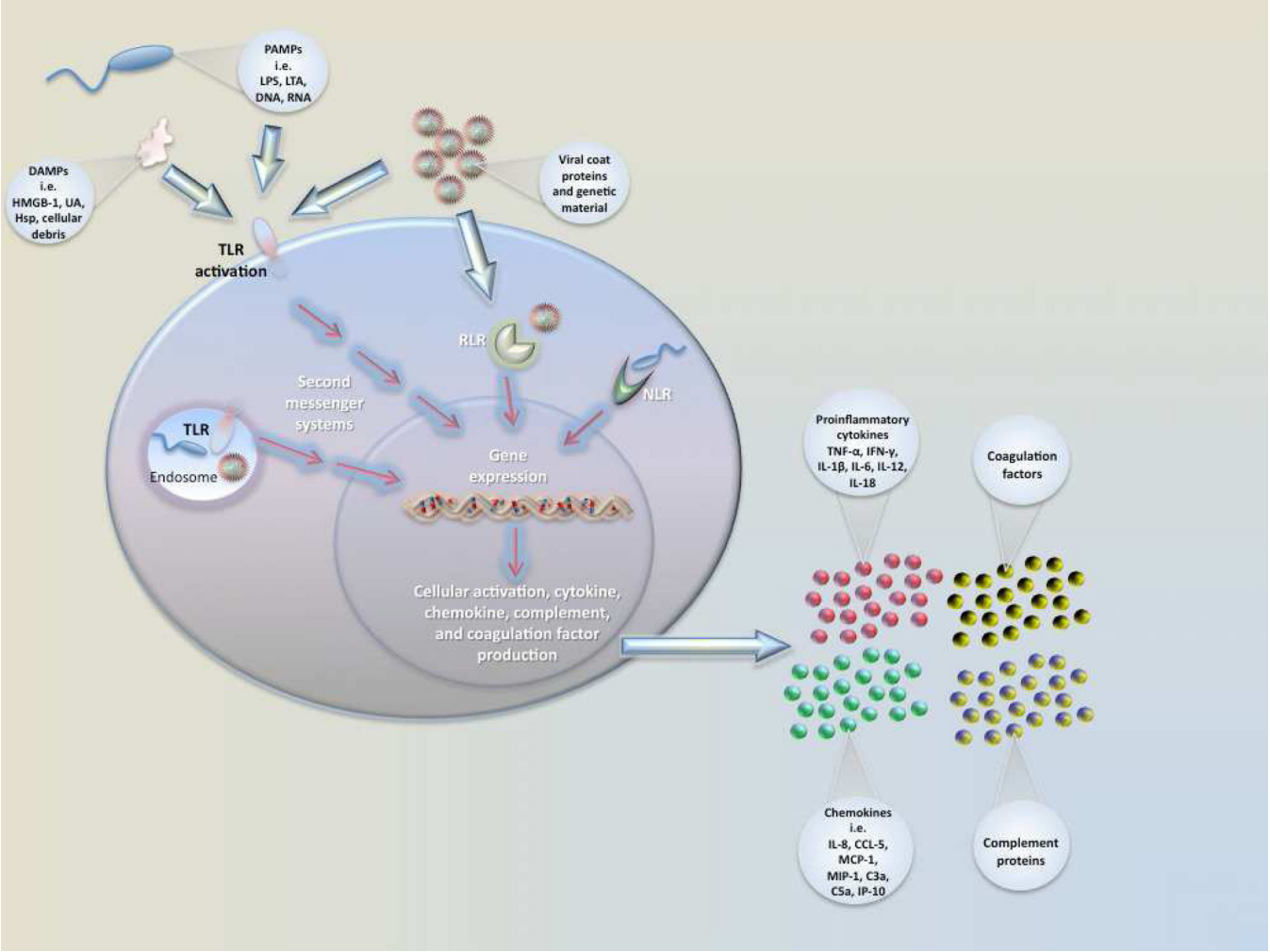

Figure 1. Activation of sentinel immune cells

Sentinel cells (e.g.. monocyte, macrophage) sense pathogens via PAMPs or DAMPs binding to PRRs. Pathogen recognition receptors (PRRs) include TLRs (Toll-like receptor), RLRs (Rig-1-like receptors), and NLRs (NOD-like receptors). Pathogen associated molecular patterns (PAMPs) include LPS (lipopolysaccharide), LTA (lipotechoic acid), DNA, and RNA. Damage/Danger associated molecular patterns (DAMPs) can also be sensed through TLRs and include uric acid (UA), heat shock proteins (Hsp), and HMGB-1. Signaling occurs through a series of second messengers and results in transcription and translation of cytokines and chemokines that amplify the immune response.

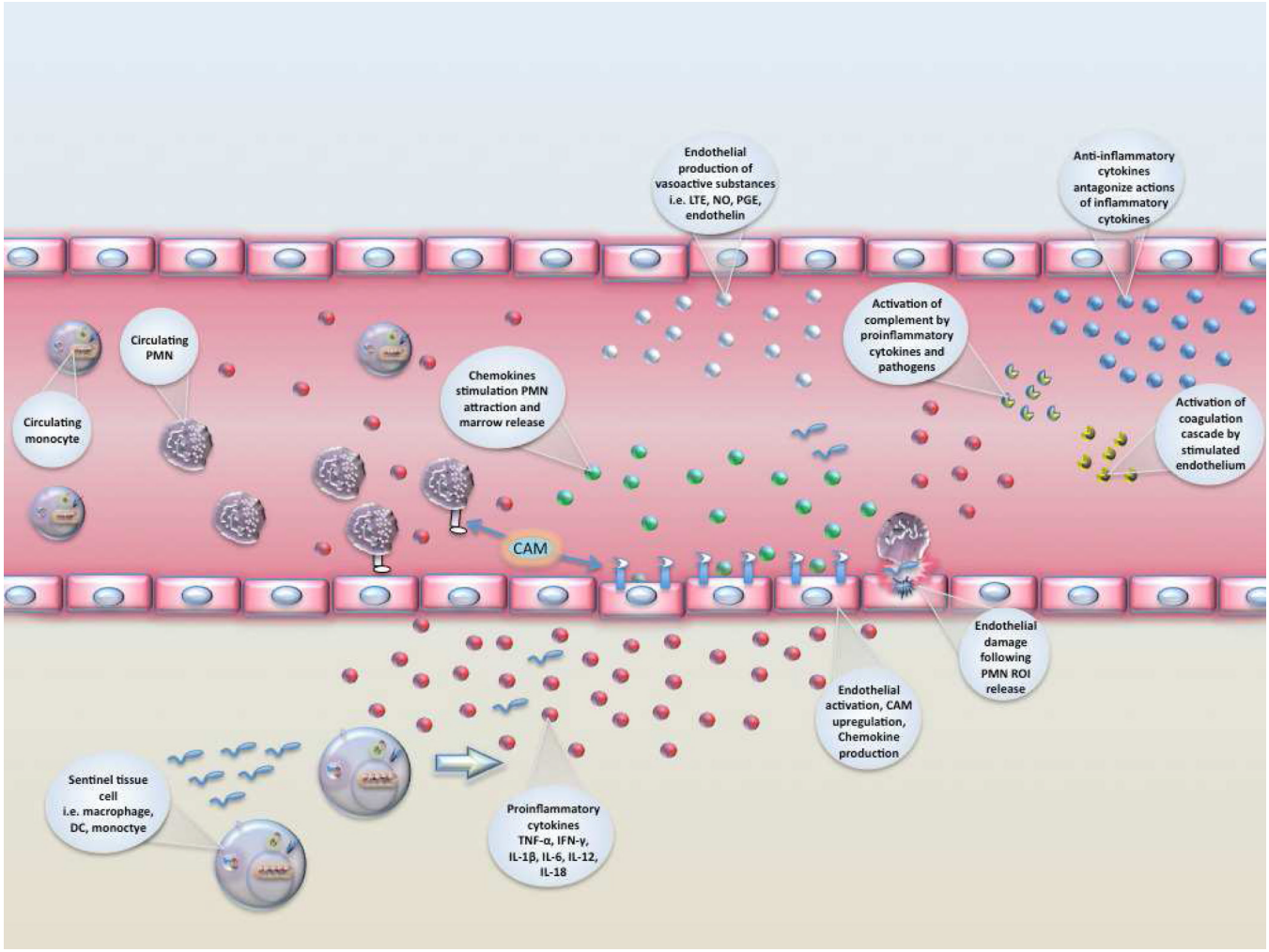

Figure 2. Cellular recruitment and endothelial activation following pathogen detection

Pathogen-stimulated tissue/blood monocytes, dendritic cells (DC), and macrophages release proinflammatory cytokines that activate the surrounding endothelium. Endothelial activation results in upregulation of cell adhesion molecules (CAM), production of chemokines and vasoactive substances, activation of complement, and development of a procoagulant state. Recruitment of PMNs occurs along the chemokine gradient surrounding the area of inflammation. Anti-inflammatory cytokines counter the actions of proinflammatory cytokines to prevent excessive cellular activation and recruitment that can result in tissue damage and systemic inflammation. Endothelium can be damaged when PMNs release reactive oxygen intermediates (ROI). LTE-leukotriene, NO-nitric oxide, PMN-neutrophil.

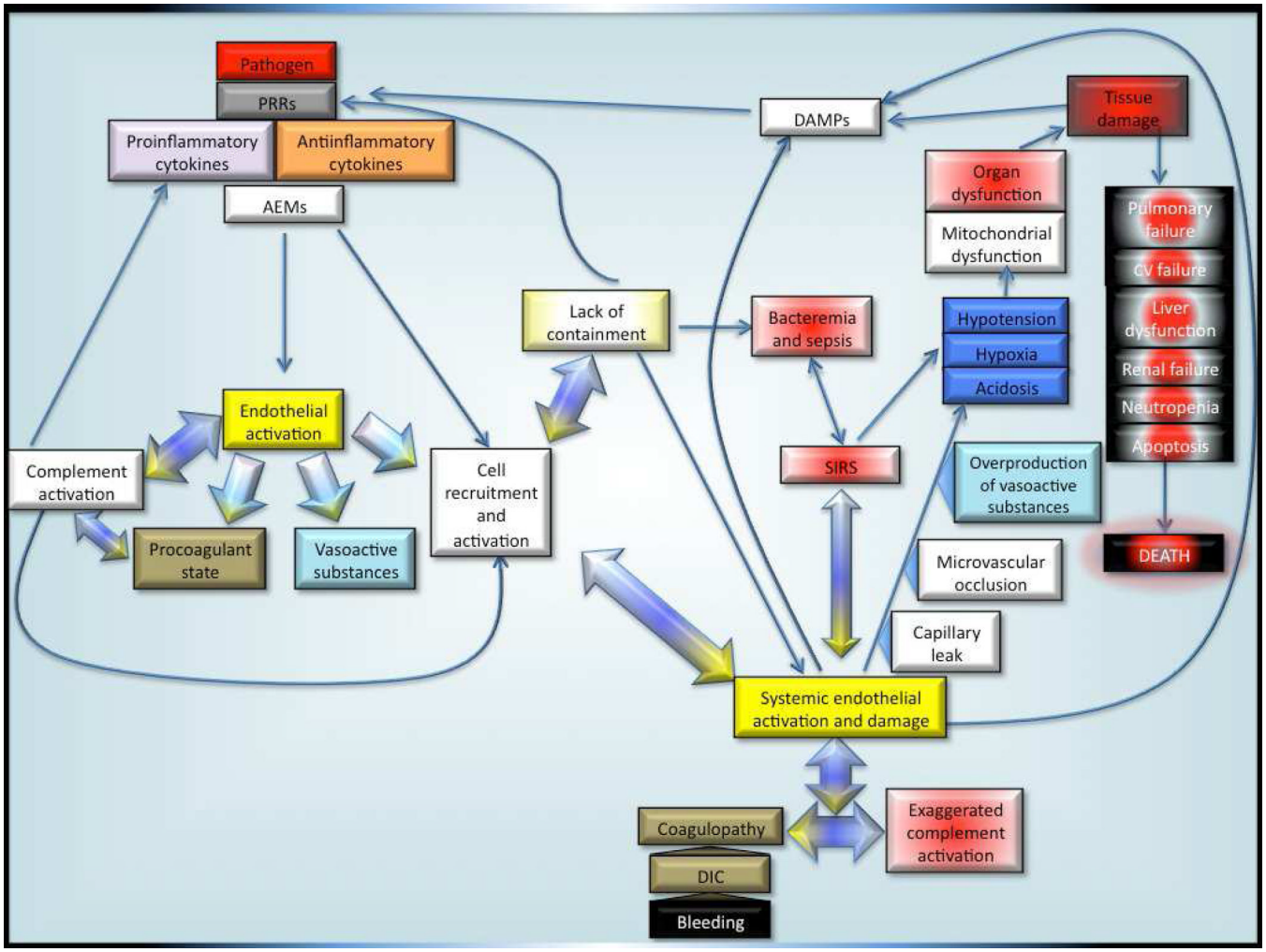

Figure 3. Pathophysiology of neonatal sepsis and septic shock

PRR-Pattern recognition receptors; AEM-antimicrobial effector mechanisms; DAMP-Danger/damage-associated molecular patterns; SIRS-Systemic inflammatory response syndrome; DIC-disseminated intravascular coagulation; CV-cardiovascular.

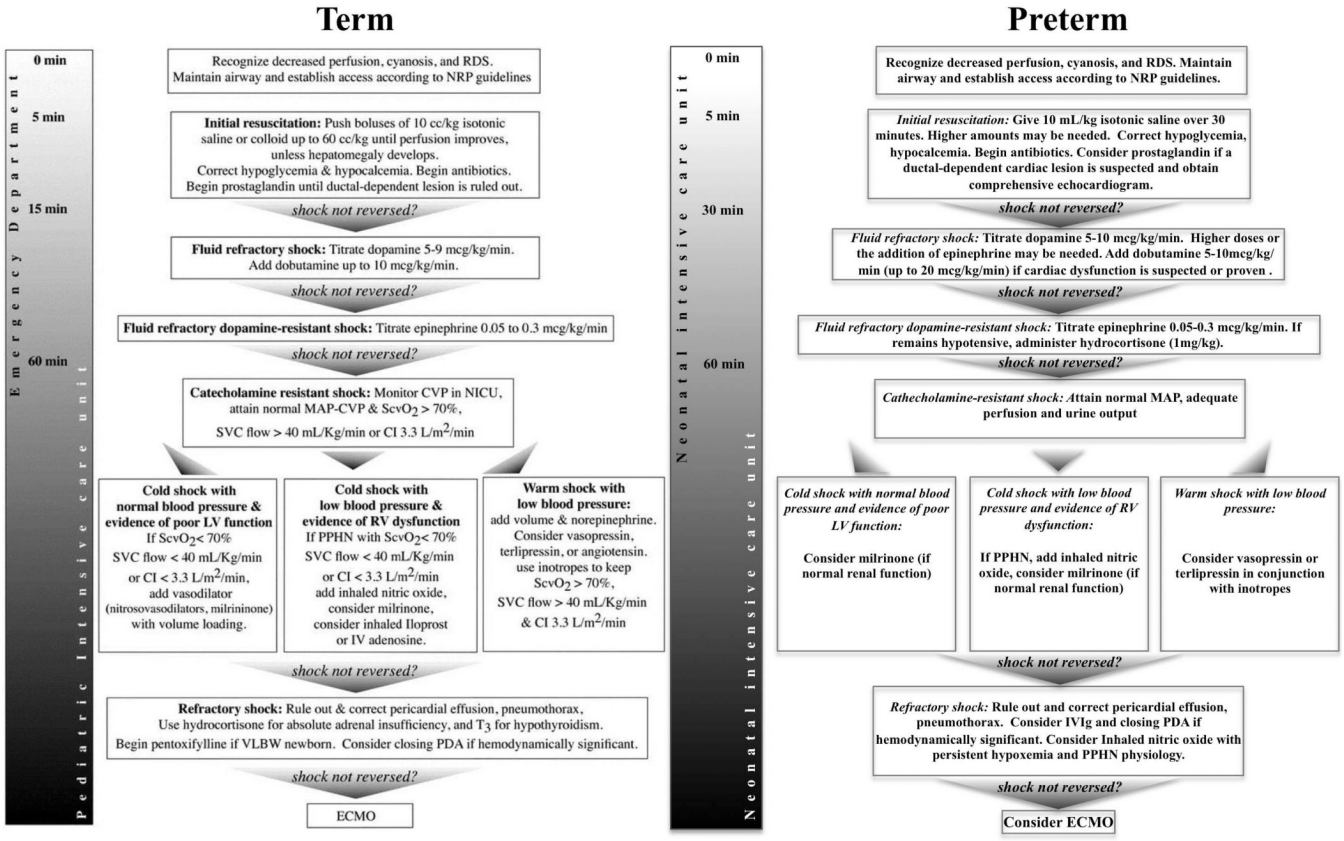

Figure 4. ACCCM consensus guidelines for treatment of shock in term infants and suggested modifications for preterm infants

RDS-respiratory distress syndrome, NRP-Neonatal Resuscitation Program, CVP-central venous pressure, MAP-mean arterial pressure, ScvO2-central venous oxygen saturation, SVC-superior vena cava, CI-cardiac index, VLBWvery low birth weight, PDA-patent ductus arteriosus, PPHN-persistent pulmonary hypertension of the newborn.

Box 1

Box 1A: Definition of systemic inflammatory response syndrome (SIRS), infection, sepsis, severe sepsis, and septic shock.

Consensus definitions	Suggested modifications for premature infants
SIRS The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:	**SIRS** The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:
• Core* temperature of >38.5°C or <36°C.	• Core temperature of >38.0°C[1] or <36°C.
• Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-hr time period OR for children <1yr old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, β blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-hr time period.	• Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-hr time period OR bradycardia, defined as a mean heart rate <10th percentile for age in the absence of β-blocker drugs or congenital heart disease[2]; or otherwise unexplained persistent bradycardia[3]
• Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.	• Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.
• Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or >10% immature neutrophils.	• Leukocyte count elevated or depressed for age or >20% immature to total neutrophil ratio[4] or C-reactive protein > 10mg/dL.
Infection A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans)	**No change suggested**
Sepsis SIRS in the presence of or as a result of suspected or proven infection.	**No change suggested**
Severe sepsis Sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions.	**No change suggested**
Septic shock Sepsis and cardiovascular organ dysfunction.	**No change suggested**

Box 1B: Definitions of organ dysfunction.

Consensus definitions of organ dysfunction[25]	Suggested modifications for premature infants
Cardiovascular dysfunction	**Cardiovascular dysfunction**
Despite administration of isotonic intravenous fluid bolus >40 mL/kg in 1 hr	Despite administration of isotonic intravenous fluid bolus >40 mL/kg in 1 hr (>10ml/kg in infants less than 32 weeks)[1]
• Decrease in BP (hypotension) <5th percentile for age or systolic BP >2 SD below normal for age	• Decrease in BP (hypotension) <5th percentile for age or systolic BP >2 SD below normal for age or MAP < 30mm Hg with poor capillary refill time (>4 seconds)[2]
OR	OR
• Need for vasoactive drug to maintain BP in normal range (dopamine >5 mcg/kg/min or dobutamine, epinephrine, or	• Need for vasoactive drug to maintain BP in normal range (dopamine

Box 1B: Definitions of organ dysfunction.

Consensus definitions of organ dysfunction[25]	Suggested modifications for premature infants
norepinephrine at any dose)	>5 mcg/kg/min or dobutamine, or epinephrine at any dose)[3]
OR	OR
• Two of the following:	• Two of the following:
-Unexplained metabolic acidosis: base deficit >5.0 mEq/L	-Unexplained metabolic acidosis: base deficit >5.0 mEq/L
-Increased arterial lactate >2 times upper limit of normal	-Increased arterial lactate >2 times upper limit of normal
-Oliguria: urine output <0.5 mL/kg/hr	-Oliguria: urine output <0.5 mL/kg/hr
-Prolonged capillary refill: >5 secs	-Prolonged capillary refill: >4 sec[4]
-Core to peripheral temperature gap >3°C	-Simultaneous measurement of core and peripheral temperature not common in premature neonates
Pulmonary[a]	**Pulmonary**
• PaO2/FIO2 <300 in absence of cyanotic heart disease or preexisting lung disease	• Excessive oxygen should be limited to avoid complications including retinopathy of prematurity
OR	
• PaCO2 >65 torr or 20 mm Hg over baseline PaCO2	• PaCO2 >65 torr or 20 mm Hg over baseline PaCO2
OR	OR
• Proven need[b] for >50% FIO2 to maintain saturation >92%	• Proven need for >50% FIO2 to maintain saturation >92% (88% for <32 weeks)
OR	OR
• Need for non-elective invasive or noninvasive mechanical ventilation[c]	• Need for non-elective invasive or noninvasive mechanical ventilation
Neurologic	**Neurologic**
• Glasgow Coma Score >11	• Acute change in mental status[5]
OR	
• Acute change in mental status with a decrease in Glasgow Coma Score >3 points from abnormal baseline	
Hematologic	**Hematologic**
• Platelet count <80,000/mm3 or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients)	• Platelet count <80,000/mm3 or a decline of 50% in platelet count from highest value recorded over the past 3 days[6]
OR	OR
• International normalized ratio >2	• International normalized ratio >2
Renal	**Renal**
• Serum creatinine >2 times upper limit of normal for age or 2-fold increase in baseline creatinine	• Serum creatinine >2 times upper limit of normal for age or 2-fold increase in baseline creatinine
Hepatic	**Hepatic**
• Total bilirubin >4 mg/dL (not applicable for newborn)	• Alanine transaminase 2 times upper limit of normal for age[7] or 50% increase over patient's baseline[8]
OR	
• ALT 2 times upper limit of normal for age	

* core temperature must be measured by rectal, bladder, oral, or central catheter probe

1) Neonatal fever is considered greater than 38°C;

2) External vagal stimulus use is very uncommon in preterm infants;

3) Infrequent self-resolving bradycardic episodes can be common in premature neonates in the absence of sepsis;

4) more commonly accepted ratio is greater than 20% immature to total ratio and chemotherapy-induced leukopenia is uncommon in premature infants.

From Goldstein et al. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005 Jan;6(1):2–8, with permission.

BP, blood pressure; ALT, alanine transaminase.

a) acute respiratory distress syndrome must include a PaO2/FIO2 ratio ≤200 mm Hg, bilateral infiltrates, acute onset, and no evidence of left heart failure. Acute lung injury is defined identically except the PaO2/FIO2 ratio must be ≥300 mm Hg;

b) proven need assumes oxygen requirement was tested by decreasing flow with subsequent increase in flow if required;

c) in postoperative patients, this requirement can be met if the patient has developed an acute inflammatory or infectious process in the lungs that prevents him or her from being extubated.

1) Rapid large volume expansion can be associated with intraventricular hemorrhage;

2) 30mm Hg suggested as minimum MAP;

3) Norepinephrine not commonly used in premature neonates;

4) Greater than 4 seconds may reflect a low systemic blood flow[264];

5) Glasgow Coma Score not applicable to term or preterm neonates;

6) Neonates not frequently chronic hematology-oncology patients;

7) Indirect hyperbilirubinemia is common in newborn.

8) Transaminases are commonly elevated in preterm neonates on long-term intravenous hyperalimentation

From Goldstein et al. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005 Jan;6(1):2–8, with permission.

Box 2

Risk factors for the development of neonatal sepsis and septic shock

Maternal factors

- Maternal age (>30years)
- Lack of prenatal care
- High gravidity
- Premature or prolonged (>6 hours) rupture of membrane (PROM)
- Meconium stained amniotic fluid
- Foul smelling amniotic fluid
- Premature labor
- Chorioamnionitis
- Group B streptococcal (GBS) rectovaginal colonization
- Urinary tract infection
- Intrapartum fever
- Multiple courses of prenatal steroids or tocolytic agents
- Prolonged duration of internal monitoring

Delivery room

- Prematurity <37 weeks
- Low birth weight</= 2500g
- 5-minute Apgar score <5
- Resuscitation in DR
- Male gender

Neonatal

- Vascular catheterization
- Mechanical ventilation (CPAP or ETT)
- Lack of enteral feeding
- Gastrointestinal tract pathology
- Medications (H2 blockers, proton pump inhibitors; post-natal steroids, cephalosporins)
- Neutropenia
- Decreased baseline serum IgG concentrations
- Hyperalimentation
- Prolonged hospital stay
- Delay in time to regain birth weight